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Review

Dietary approaches for exploiting metabolic vulnerabilities in cancer

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ABSTRACT

Renewed interest in tumor metabolism sparked an enthusiasm for dietary interventions to prevent and treat cancer. Changes in diet impact circulating nutrient levels in the plasma and the tumor microenvironment, and preclinical studies suggest that dietary approaches, including caloric and nutrient restrictions, can modulate tumor initiation, progression, and metastasis. Cancers are heterogeneous in their metabolic dependencies and preferred energy sources and can be addicted to glucose, fructose, amino acids, or lipids for survival and growth. This dependence is influenced by tumor type, anatomical location, tissue of origin, aberrant signaling, and the microenvironment.

This review summarizes nutrient dependencies and the related signaling pathway activations that provide targets for nutritional interventions. We examine popular dietary approaches used as adjuvants to anticancer therapies, encompassing caloric restrictions, including time-restricted feeding, intermittent fasting, fasting-mimicking diets (FMDs), and nutrient restrictions, notably the ketogenic diet. Despite promising results, much of the knowledge on dietary restrictions comes from in vitro and animal studies, which may not accurately reflect real-life situations. Further research is needed to determine the optimal duration, timing, safety, and efficacy of dietary restrictions for different cancers and treatments. In addition, well-designed human trials are necessary to establish the link between specific metabolic vulnerabilities and targeted dietary interventions. However, low patient compliance in clinical trials remains a significant challenge.

1. Introduction

In recent decades, tumor metabolism has sparked renewed interest in cancer prevention and treatment. Altered metabolism is one of the well-described hallmarks of cancer [1]. Tumor cells increase their nutrient uptake and metabolic processes to provide energy for uncontrolled growth and proliferation. They also use different strategies to reprogram their metabolism to improve their survival in a harsh microenvironment [2]. Nevertheless, their remarkable adaptability also creates potentially exploitable vulnerabilities for dietary and pharmacological interventions [3].

Cancers are highly heterogeneous in their **metabolic dependencies** and preferred energy sources [3]. Tumor type, anatomical location, tissue of origin, aberrant signaling, and microenvironment all modulate metabolic requirements. The distinct microenvironment is further potentiated by the abnormal and dysfunctional tumor vasculature [3,4]. The complex interplay between genomic losses in cancer and immediate nutrient availability may facilitate particular „nutrient addictions" that profoundly determine signaling pathway activations, cellular growth, and drug sensitivity [5]. The tumor's addiction to glucose, fructose, amino acids, or lipids can be explored for therapeutic purposes [6]. As a result, metabolic enzymes are attractive targets in oncology [7]. Nevertheless, few metabolic drugs have been translated from the bench to the bedside [7].

Dietary and lifestyle habits are associated with the onset and outcome of several cancers [8]. Excess body weight is linked to an increased risk of cancer in at least 13 anatomic sites, and the cancer burden attributable to obesity can be as high as 11.9% in men and 13.1% in women [9]. In the United States, obesity is estimated to account for 14–20% of all cancer-related mortality. A large-scale prospective analysis identified a >50% increase in cancer-related death among those with the highest body mass index. Emerging data suggest that higher body fat percentage during childhood and adolescence is associated with an increased risk of malignancy at an older age, underscoring the importance of preventing childhood obesity [9]. The link between systemic metabolic alterations and cancer-risk/cancer-related death

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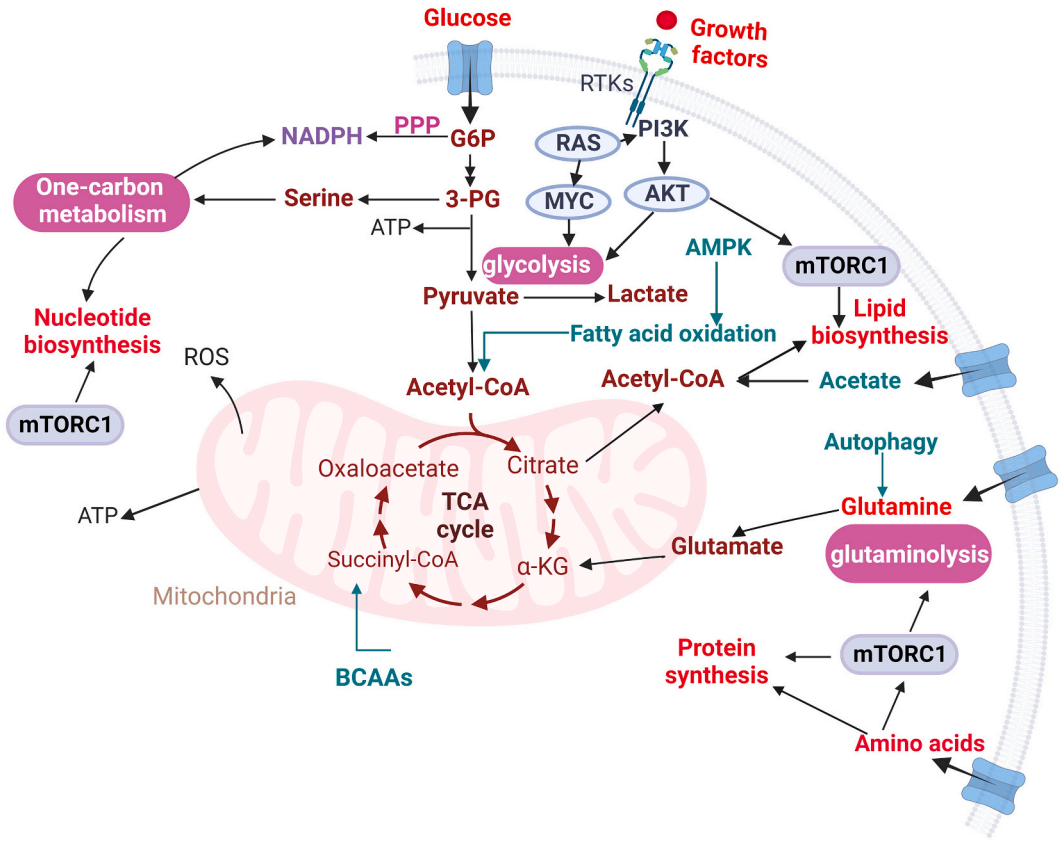

Fig. 1. Signaling pathways of tumor metabolism. Nutrient-replete conditions in cancer cells induce anabolic processes, synthesizing nucleotides, proteins, and lipids (anabolic processes are labeled red). The aberrant signaling pathways (e.g., PI3K/AKT), abnormal activation of mTORC1, the loss of tumor suppressors, or the activation of oncogenes further amplify cellular growth via the transcriptional control of genes associated with metabolism. In contrast, diminished accessibility to nutrients induces alternative forms of metabolism including oxidation of fatty acids, BCAAs, and macromolecular degradation through autophagy to support cell viability (green labels). (Abbreviations: G6P, glucose-6-phosphate; 3-PG, 3-phosphoglycerate; PPP, pentose phosphate pathway; ATP, adenosine 5′-triphosphate; mTORC1, mTOR complex 1; α-KG, α-ketoglutarate; RTK, receptor tyrosine kinase.) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

suggests that a large proportion of malignancies are preventable by an altered lifestyle [10,11].

One straightforward way to modulate nutrient availability is to alter the diet composition, timing, or volume. **Dietary modifications** affect the circulating nutrient levels in the plasma and the tumor microenvironment [3]. Most preclinical studies suggest that dietary restrictions can modulate tumor initiation, progression, and metastasis [12]. Combining dietary restrictions may alleviate the adverse effects of chemotherapies or may enhance their efficacy [13,14]. Following the success of preclinical experiments, translational studies are under development.

This review summarizes nutrient addictions of cancers, signaling pathways behind metabolic reprogramming, and discusses approaches to target metabolic vulnerabilities by dietary restrictions. We do not attempt to provide a complete summary for each discussed topic; instead, we aim to synthesize nutritional dependencies and interventions. Additional reviews offer profound insight into particular metabolic preferences of cancers [15–21].

There is no one-size-fits-all dietary solution for all cancer types. Routine clinical application of dietary alterations requires a better understanding of context-dependent metabolic preferences and signaling pathway limitations. Our summary highlights the need to carefully evaluate each cancer's unique metabolic requirements and signaling pathway activations for personalized nutrient modifications, especially when combined with systemic anticancer therapies.

2. Rewiring the energy metabolism

The altered energy metabolism of cancer cells evoked interest in the nineteenth century. However, the German physiologist Otto Warburg was the first to systematically investigate the altered tumor cell metabolism nearly 100 years ago [22]. Unfortunately, Warburg's initial observations went to oblivion for decades. However, the resurrection of the study of cancer metabolism in the past 25 years initiated intense research [23]. It led to an expanding field focusing on metabolic alterations initiating and fueling malignant transformation [20,24,25]. Most hallmarks of cancer, including unlimited proliferation, self-sustained growth signals, continuous angiogenesis, resistance to apoptosis, insensitivity to anti-growth signals, and invasion and metastasis, increase the demand for energy and the amount of material needed for the production of daughter cells [1]. **Metabolic reprogramming** includes not only a shift from oxidative phosphorylation to aerobic glycolysis but also altered amino acid metabolism, increased glutamine uptake and glutaminolysis, altered flux through the pentose phosphate pathway and the tricarboxylic acid (TCA) cycle for macromolecule generation; increased lipid uptake, lipogenesis, and cholesterol synthesis; altered one-carbon metabolism for the production of (NADH) /NADPH, nucleotides, and glutathione, and leads to the utilization of alternative substrates, including lactate and acetate [26] (Fig. 1). Below, we elaborate on the critical substrates affected by these changes, including glucose, fructose, amino acids, and lipids.

2.1. Glucose

A major distinguishing hallmark of tumor cells is their heightened demand for glucose. Cancerous cells undergo a metabolic transition from oxidative phosphorylation to "fermentation," metabolizing increased amounts of glucose into lactic acid even when sufficient oxygen is available. This phenomenon is referred to as aerobic glycolysis. The observed differences in the ratio of "fermentation" to respiration in cancer cells have been known as the Warburg effect [22]. Fermentation is a seemingly inefficient energy production method yet remains a principal metabolic pathway of cancer cells. With aerobic glycolysis, only two ATP molecules are derived from a single glucose molecule versus 30–32 ATPs during oxidative phosphorylation. However, converting glucose to lactate occurs 10–100 times faster as the complete oxidation of glucose in the mitochondria [27], and malignant cells enhance their glucose uptake by 10-fold, diverting the extra energy to biosynthetic pathways to support their rapid proliferation and long-term maintenance [25]. The "Warburg effect" is used for synthesizing anabolic macromolecules and is no longer viewed as solely a means of energy production [25,28]. **Rapid glucose metabolism** provides substrates for non-mitochondrial pathways, including the pentose-phosphate pathway, the hexosamine pathway, serine– glycine– and one-carbon metabolism, and glycerol synthesis [28]. Notably, **lactate**, previously identified as a waste product of glycolysis, is now recognized as a major circulating carbohydrate fuel for both tumors and healthy tissues [29]. Lactate becomes incorporated into the TCA cycle; in fact, its incorporation in the TCA cycle surpasses that of glucose in all tissues except the central nervous system [30].

Glycolysis is the most frequently up- or dysregulated metabolic process in most cancer types [31]. However, the intensity of the Warburg effect is not universal among proliferating cancer cells: an eight-fold range was discovered in the rate of glucose utilization within a panel of 80 NSCLC cell lines [32]. Transformation of glucose metabolism is also significantly heterogeneous across tumor types and within the tumor microenvironment [33]. Upregulation of glycolysis-related genes have been identified in several cancers, including pancreatic thyroid, renal, and colon cancers. In contrast, genes participating in oxidative phosphorylation were more upregulated in lymphomas, leukemias, lung and ovarian cancers [33,34].

Warburg originally thought that aerobic glycolysis stems from impaired mitochondria unable to perform oxidative phosphorylation, causing malignant transformation [35]. However, oxidative metabolism persists in the mitochondria even during increased glucose consumption. The presence of aerobic glycolysis is not equivalent to the loss of oxidative phosphorylation in tumors [28]. It has recently been established that elevated glucose uptake, glycolysis, and rewired metabolism are not restricted to tumors but are also present in normal proliferating immune cells [36].

2.2. The multifaceted role of lactate in the tumor microenvironment

The Warburg effect results in elevated lactate production, contributing to the unique features of the tumor microenvironment and influencing multiple aspects of cancer progression. Lactate not only serves as an energy substrate but as an oncometabolite, modulates intracellular and extracellular signaling pathways, and affects the differentiation, metabolism, and function of innate and adaptive tumor-infiltrating immune cells [37,38]. Lactate concentrations in tumor tissues are approximately 100 times higher than in the blood: intratumoral lactate levels can reach up to 30 mM, while concentrations within the tumor microenvironment range from 5 to 20 mM [37,39]. Elevated lactate concentrations in biopsies of colorectal, cervical, breast, lung, head and neck cancers were linked to unfavorable prognosis and increased risk of metastasis [37]. The low-pH tumor microenvironment created by high lactate concentrations can activate HIF-1α and NF-κB independent of hypoxia, promote cancer aggressiveness and metastasis, stimulate angiogenesis, and increase resistance to anti-cancer therapies [38,40–42].

Lactate cannot cross the plasma membrane by free diffusion, but proton-like monocarboxylate transporters (MCTs) assist the transmembrane lactate trafficking [43]. MCTs 1–4 are frequently overexpressed in tumors with high metabolic rates. MCT upregulation has been linked to worse disease outcomes in numerous cancers and is also implicated in the process of metastasis [37,44–48]. Additionally, lactate exerts different effects on metabolically diverse tumor regions. Cells in well-oxygenated regions exhibit high lactate uptake through MCT1. In contrast, cells in hypoxic tumor regions show low lactate uptake mediated by MCT4, which creates a metabolic symbiosis where cells in nutritionally rich areas support the growth of hypoxic tumor cells in a rapidly proliferating tumor [37].

The inter-conversion between pyruvate and lactate is mediated by the lactate dehydrogenase (LDH) enzymes. Out of their multiple isoforms, LDHA is found predominantly in the skeletal muscle and preferentially reduces pyruvate to lactate while transforming NADH to NAD^+. High LDHA expression has been described in multiple cancers and correlates with malignant progression, lower survival rates, and resistance to chemotherapy [37,49]. Extracellular lactate impacts various cell types within the tumor microenvironment (TME), including immune and endothelial cells, cancer-associated fibroblasts (CAFs), and non-cancer stroma cells [50]. Lactate may promote tumor immune escape through PD-L1 upregulation and the transformation of M1 macrophages to an M2-like phenotype [51]. GPR81 receptor-mediated, lactate-induced PD-L1 upregulation depends on the presence of LDHA: knockdown of LDHA significantly decreases glucose-induced PD-L1 overexpression; thus, elevated glycolysis and the subsequent lactate production plays a pivotal role in inducing PD-L1 in the tumor microenvironment [52]. Lactate may also activate GPR81 on non-cancerous cells of the tumor microenvironment, including macrophages and dendritic cells [53].

There is a potential interdependence between glycolysis and glutamine catabolism pathways: lactate stabilizes HIF-2α and activates c-Myc, which increases the expression of glutamine transporter SLC1A5/ASCT2 and the enzyme glutaminase 1 (GLS1), resulting in upregulated glutamine uptake and catabolism. A glutamine catabolite, α-ketoglutaric acid (α-KG), is eventually converted to pyruvate and lactate by LDHA [54]. Thus, the diverse role of lactate in different aspects of tumor biology and the tumor microenvironment offers promising opportunities for developing innovative anticancer strategies [38].

2.2.1. Genetic reprogramming of glucose metabolism

During metabolic stress, cancer cells frequently exhibit a decreased expression of tumor suppressor genes and increased expression of oncogenes as part of their adaptive response [55]. Increased activity of the protein kinase B (PKB/AKT), phosphoinositide 3-kinase (PI3K), RAS, and Von Hippel-Lindau (VHL) lead to the non-hypoxic activation of the **hypoxia-inducible factor 1α (HIF-1α).** Conversely, HIF-1α upregulates glucose transporter 1 (GLUT1) and hexokinase 2 (HK2), the first rate-limiting enzyme of glycolysis, that catalyzes the conversion of glucose to glucose-6-phosphate [56,57].

High AKT and mTOR activity promote the expression of HIF-1α even in the presence of oxygen, leading to persistent activation of glycolysis. The expression of mTOR-induced HIF-1α facilitates the upregulation of additional glycolytic enzymes, such as pyruvate kinase type M2 (PKM2) and phosphoglyceric acid mutase-1 (PGAM1) [58,59]. PKM2 catalyzes the final and rate-limiting step in tumor glycolysis, resulting in pyruvate production and ATP generation [60]. High PKM2 expression has been associated with poor prognosis in multiple myeloma patients, reduced survival and resistance to chemotherapy in esophageal squamous cell carcinoma, and progression in prostate cancer [61–63]. Moreover, PKM2 knockdown increased the radiosensitivity of non-small cell lung cancer (NSCLC) cells, and PKM2 inhibition significantly reduced clonogenic survival in prostate cancer cell lines [64]. PKM2 exists in

catalytically distinct tetrameric and dimeric states that control the balance between ATP synthesis and energy production versus the production of glycolytic intermediates for other metabolic pathways [65]. Thus, PKM2 is a multifaceted protein with numerous cellular functions that require further investigation [66].

PKM2 enhances the phosphorylation of PGAM1, another pivotal glycolytic enzyme, that facilitates the bidirectional transformation of 2-phosphoglycerate to 3-phosphoglycerate [67]. Elevated PGAM1 has been observed in gliomas, breast, pancreatic, lung, liver, colon, prostate, kidney, and urothelial bladder cancers, and substantial evidence suggests that overexpression of PGAM1 is involved in cancer progression [68,69].

Other oncogenic pathways promote aerobic glycolysis independently of HIF-1α, including the activation of MYC, RAS, AKT, or the loss of TP53. Two major classes of glucose transporters have been linked to cancer: glucose transporter GLUTs and sodium-glucose co-transporters SGLTs, among which GLUT1 and GLUT3 are most frequently overexpressed in cancers [70]. MYC upregulation, just like HIF-1α, directly controls the expression of GLUT and HK2 [71]. Loss of TP53 also upregulates GLUT expression [72]. Increased **GLUT1 expression** has been described in triple-negative breast cancer (TNBC), especially in the basal-like subtype, exhibiting a glycolytic phenotype. HIF-1α, IGF-1, and MIF upregulation were also identified in HER-2-positive breast cancer samples [73]. Elevated GLUT1 expression has been described in glioblastomas and astrocytomas, ovarian, endometrial, and cervical cancers, prostate and lung cancers, colorectal, pancreatic, and gastric cancers, and hematologic malignancies such as acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) [74–76]. Elevated expression of GLUT1 has been linked to worse disease outcomes, poor prognosis, and low poor overall survival (OS) in most solid cancers [75].

Although preclinical studies have demonstrated the effectiveness of numerous therapies targeting glucose metabolism and the process of glycolysis, their clinical translation has remained limited due to low selectivity, high toxicity, and various off-target and side effects [74,77,78].

2.3. Fructose

Fructose, frequently consumed as high-fructose corn syrup in the Western diet, has been linked to an increased prevalence of metabolic syndrome. The small intestine mainly metabolizes small concentrations of fructose; however, higher doses reach the circulation and the liver [79]. In the liver, fructose induces de novo lipid synthesis and contributes to the development of obesity, metabolic dysfunction-associated fatty liver disease (MAFLD – formerly known as non-alcoholic fatty liver disease), and type 2 diabetes [80]. Fructose diverges from glucose in its stimulation of the glycolytic pathway. Initially phosphorylated to fructose-1-phosphate by fructokinase, fructose is subsequently transformed to dihydroxyacetone phosphate and glyceraldehyde. These intermediates are converted to triose phosphates, participating in purine nucleotide synthesis and transforming into uric acid [81]. Fructose-induced serum uric acid elevation has been implicated in multiple pathological conditions associated with altered metabolic processes, including endothelial dysfunction, insulin resistance, inflammation, cardiovascular risk, and chronic renal disease [82–84].

Fructose could be an **important alternative energy source** for malignant tissues, supported by the observation that many cancers upregulate the fructose-specific transporter GLUT5 [85,86]. Acute myeloid leukemia (AML) cells prefer to utilize fructose with an upregulated fructose transporter GLUT5, and in AML patients, elevated transcription of the GLUT5-encoding gene *SLC2A5* is associated with poor disease outcomes [87]. Dietary fructose enhances the hypoxic cell survival of intestinal cells and promotes nutrient absorption, weight gain, and fat accumulation in mice by increasing the intestinal surface area, providing a compelling explanation for fructose-promoted tumor growth [88]. Even physiological doses of fructose can promote cancer growth: in APC mutant mice predisposed to develop intestinal tumors, moderate fructose consumption increases tumorigenesis [89]. Fructose, as a critical metabolic substrate, enhances the growth and aggressiveness of prostate cancer cells both in vitro and in vivo [85]. Metastatic cells in the liver upregulate the enzyme aldolase B (ALDOB), which enhances fructose metabolism and fuels major proliferation pathways [90].

2.4. Amino acids

Amino acids are indispensable building blocks of anabolic processes, and the addiction of tumor cells to amino acids has started to receive greater attention. The altered amino acid metabolism of cancers offers potential avenues for nutritional modifications. Although dietary interventions can deplete amino acid levels in the tumor microenvironment, it is not as straightforward as glucose deprivation [91]. Restriction of essential amino acids may induce systemic adaptive responses, such as muscle atrophy, causing an increase in the levels of non-deprived amino acids in the blood [92].

2.4.1. Glutamine

Glutamine, the most abundant amino acid in blood and muscle, is **the second most frequent growth-supporting substrate** after glucose. Cancer cells' high demand is not limited to the essential amino acids, as restricting non-essential amino acids can be lethal to specific tumor cells.

Glutaminolysis is a versatile metabolic pathway that occurs primarily in the mitochondria and can support both aerobic and anaerobic energy production as well as various biosynthetic processes [93]. Glutamine, whether acquired externally or produced internally, enters cells through specific transporters and is subsequently transported to the mitochondria. The glutaminase enzyme converts it to glutamate, an important intermediate, in the mitochondrial matrix. Glutamate can be transaminated with oxaloacetate to produce aspartate or can be converted to α ketoglutarate, a key metabolite in the TCA cycle, where it is further oxidized to produce ATP [93].

In some cases, excess glutamate may be exported from the mitochondria to the cytosol, where it can participate in various cellular processes, including neurotransmitter synthesis and ammonia detoxification.

Abnormal mitochondrial number, pathological ultrastructure, and function have been documented in numerous cancers [94]. On the submicroscopic level, these ultrastructural abnormalities in mitochondria and mitochondria-associated membranes may explain abnormal cancer metabolism [95] and lead to greater reliance on substrate-level phosphorylation than on OxPhos for energy production. Substrate-level phosphorylation involves the transfer of a phosphate from a metabolic substrate to form ATP, which yields high-energy phosphates in the absence of oxygen and partially compensates for reduced ATP synthesis through both OxPhos and glycolysis [94]. Glutamine metabolism has been rewired to adapt to mitochondrial dysfunction [96]. During glutaminolysis, the enzyme succinyl-CoA synthetase may convert α-ketoglutarate to succinyl CoA. Succinyl CoA is converted to succinate by succinate-CoA ligase, and the produced ATP provides energetic advantages to cancer cells [94].

Glutamine metabolism modulates multiple signaling pathways, including mTORC1 [97]. mTORC1 (mammalian target of rapamycin complex 1) is a multiprotein complex part of the mTOR (mammalian target of rapamycin) signaling pathway. Its primary role is to maintain a dynamic equilibrium between anabolic and catabolic processes in response to environmental cues, thereby governing cellular functions such as growth, metabolism, protein-, lipid-, nucleotide-synthesis, and autophagy [98]. Glutamine impairs autophagy through the negative regulation of the ULK1 complex, one key regulator of autophagosome formation and also by eliminating ROS by glutathione and NADPH [99,100].

The metabolic sensor, AMP-activated protein kinase (AMPK), regulates various metabolic processes, including pyruvate kinase expression, glycolytic enzyme modulation, mitochondrial biogenesis, and fatty acid metabolism, ensuring metabolic balance and cellular survival [101,102]. Under glucose-deprived conditions, tumor cells increase the expression of AMPK to maintain energy homeostasis. AMPK activates FOXO3a, which upregulates hematopoietic PBX1-interacting protein (HPIP), identified as a proto-oncogene. HPIP, in turn, rewires and enhances cellular glutamine import by upregulating the expression of glutamine transporter SLC1A5/ASCT2 and glutaminase genes to replenish TCA intermediates and restore the ATP pool [103]. However, under prolonged glucose stress, HPIP undergoes ubiquitination by the E3-Ub ligase RNF2, leading to its degradation through the proteasome-mediated pathway, ultimately promoting apoptosis. Clinical analyses reinforced the correlation between elevated HPIP levels and AMPK activation in breast cancer, highlighting the pivotal role of HPIP as a signal coordinator during metabolic stress [103].

In summary, the classification of glutaminolysis as an anaerobic or aerobic pathway depends on the specific metabolic needs of the cell. Excess glutaminolysis is often a hallmark of cancer metabolism and is regulated by oncogenes, tumor suppressors, and tumor microenvironments [93]. Glutamine thus participates in many fundamental cellular functions, including energy regulation, cellular signaling, redox homeostasis, and the biosynthesis of essential molecules (amino acids, fatty acids, purines, and pyrimidines) [93,104].

Some cancers, including non-small cell lung cancer (NSCLC), TNBC, clear cell renal cell carcinoma, pancreatic cancer, myeloma and brain tumors, display a **high dependency on glutamine** for their growth and survival [97,105–108]. Glioblastoma cells consume high amounts of glutamine, exceeding the nitrogen demand required for nucleotide synthesis or maintenance of the amino acid pools [109,110]. Mutations in IDH1 and IDH2 in about 70% of malignant gliomas are linked to altered glutamine metabolism [111,112]. A frequent feature of glutamine-addicted cancers is the upregulated expression of the glutamine transporter SLC1A5 (also known as ASCT2) [104,113]. Moreover, cancers harboring the KRAS oncogene are frequently addicted to glutamine for growth and survival. For example, PDAC cells are dependent on the transportation of glutamine-derived aspartate into the cytoplasm, where it is converted into oxaloacetate, then into malate and pyruvate, increasing the NADPH/NADP+ ratio to maintain the cellular redox state. Glutamine deprivation in PDAC cells increases reactive oxygen species and reduces glutathione [114]. Mutations of BRAF, KRAS, and HRAS have also been identified in TNBC, suggesting the glutamine dependence of these cancers [115]. In the lung, breast, and pancreatic cancer cell lines harboring KRAS mutations, glutamine deprivation resulted in an S- and G2/M-phase cell cycle arrest, suggesting the potential utility of cell cycle phase-specific cytotoxic drugs [116]. Similar to KRAS, deregulated expression of MYC induces glutamine addiction, which has been demonstrated in a variety of cancer cell lines [117,118]. Glutamine metabolism may be reprogrammed by additional cancer mutations involving the TP53, LKB1-AMPK, and phosphatidylinositol 3-kinase (PI3K) pathways [104,119]. STK11 (LKB1) is the second most commonly altered tumor suppressor in NSCLC, and the loss of the serine/threonine kinase LKB1 frequently cooccurs with KRAS alterations. KRAS mutant NSCLCs bearing LKB1 loss with additional activation of the KEAP1/NRF2 pathway are particularly dependent on glutamine metabolism, making them specifically sensitive to glutaminase inhibition [120].

2.5. Targeting glutamine metabolism

Glutamine and glutamine-related enzymes provide valuable opportunities for developing novel diagnostic approaches and targeted therapies against cancer cells [7,121–123]. For example, depleting the serum from asparagine and glutamine is universally used in treating childhood acute lymphoblastic leukemia with manageable adverse effects, suggesting that normal cells can adapt to the limited amino acid supply [124].

However, depriving tumors of glutamine through diet is not a viable approach. The availability of glutamine in the tumor environment is often limited, reflecting the metabolic plasticity of cancer cells to use other carbon sources to fuel the TCA cycle when glutamine is not accessible [125]. Moreover, co-existing cells in the tumor microenvironment, such as stromal cells, fibroblasts, and macrophages, support tumor cells by de-novo glutamine synthesis [126,127].

The current metabolic approaches focus on glutamine depletion, glutaminase inhibition, and inhibition of membrane glutamine transporters with pharmacological agents, and excellent summaries discuss the mechanisms underlying cancer cell resistance to drugs designed to target glutamine metabolism [128,129]. Combining glutamine deprivation with other anti-cancer therapies to enhance the overall effectiveness of cancer treatment is an active area of research [105,130]. Simultaneous targeting of glycolysis and glutaminolysis emerges as a promising strategy for cancer treatment. Notably, treatment with aminooxyacetate (AOA) synergistically increased sensitivity to 2-deoxyglucose, inhibiting cell growth in ovarian cancer cell lines [131]. Metformin combined with a selective glutaminase inhibitor, BPTES, encapsulated in nanoparticles, demonstrated more significant inhibition of growth in pancreatic tumor cell lines than individual treatments, highlighting the potential of targeting multiple metabolic pathways [132].

Nevertheless, further research and clinical trials are needed to determine the safety, efficacy, and optimal combinations for targeting glutamine metabolism and other metabolic pathways.

2.5.1. Methionin

Some cancers are heavily dependent on **methionine**. Methionine restriction inhibits one-carbon metabolism and nucleotide synthesis in mice and humans and confers several metabolic benefits [6]. Methionine depletion has been linked to enhanced cancer treatment in several malignancies, including sarcomas, gliomas, where methionine-cystine double deprivation inhibited proliferation [133], prostate cancers, where reduced methionine consumption reduced development of the TRansgenic Adenocarcinoma of the Mouse Prostate (TRAMP) model [134], melanomas, where methionine deficient diet substantially potentiated the effects of radiotherapy and diminished the tumors' metastatic potential [135], and breast cancers. In triple-negative BC models, dietary methionine deprivation enhanced the antitumor effects of lexatumumab [136]. It suppressed the metastatic potential of cells both in vitro and in vivo [137]. Dietary methionine restriction yielded positive therapeutic outcomes in two patient-derived xenograft models of chemotherapy-resistant colorectal cancer driven by RAS mutations. It also showed efficacy in a mouse model of radiation-resistant soft-tissue sarcoma, characterized by a KRAS G12D mutation and p53 knockout [91]. In a well-controlled and well-tolerated dietary study involving human subjects, restricting methionine had systemic metabolic effects that closely paralleled those observed in mice [91]. Thus, methionine restriction confers potential possibilities to be considered in anticancer therapies. Nevertheless, the restriction of methionine and cysteine has pro-angiogenic effects, pointing to careful consideration of diet alterations before advising patients [138].

2.5.2. Serine

In some cancers, extracellular **serine** supports cellular proliferation, whereas other malignancies require de novo serine synthesis, even in abundant serine supplementation. Recent studies shed new light on active serine synthesis in cancer, suggesting its role in amino acid transport, nucleotide synthesis, folate metabolism, and redox homeostasis [139]. Anaplerotic reactions are metabolic pathways used to replenish intermediates of the citric acid cycle extracted for biosynthesis to maintain adequate levels of ATP so that cellular respiration can carry on uninterrupted. The enhanced serine synthesis pathway could

significantly contribute (~50%) to the anaplerosis of glutamine into the mitochondrial TCA cycle [140]. The enzyme phosphoglycerate dehydrogenase (PHGDH) catalyzes the first step in the serine biosynthesis pathway. Protein levels of PHGDH are elevated in 70% of estrogen receptor (ER)-negative breast cancers, associated with increased serine synthesis flux, suggesting that certain breast cancers depend upon increased serine metabolism [140]. Deprivation of dietary serine was harmful to tp53-deficient colon tumors because the cells failed to induce G1 arrest in vivo. Moreover, these cells failed to channel the residual serine for glutathione production and used it for nucleotide synthesis, resulting in oxidative stress [141]. Simultaneous deprivation of serine and glycine reduced tumor growth and increased survival in genetically engineered mouse models of intestinal cancer (driven by APC inactivation) and lymphomas (driven by MYC activation) [142].

Dietary restriction of amino acids may synergize with anticancer therapies. The absence of exogenous serine and glycine sensitized colorectal, breast, and pancreatic cancer cell lines, patient-derived organoids, and syngeneic mouse tumor models to radiotherapy. The comprehensive metabolomic and transcriptomic analysis revealed that amino acid restriction impacted antioxidant response nucleotide synthesis and inhibited the TCA cycle [143]. Thus, dietary deprivation of serine, or serine and glycine, is promising, but additional studies are needed in combination cancer therapies.

One early-phase exploratory clinical trial currently explores the effects of Non Essential Amino Acid Restricted medical food (NEAAR) for patients diagnosed with metastatic pancreatic cancer (NCT05078775). Moreover, the MACS (NCT04469296) trial analyzes the feasibility of restricted proteins or ketogenic diet modifications before breast cancer surgery for patients with early luminal breast cancer (Table 2).

2.5.3. Branched-chain amino acids (BCAAs)

Branched-chain amino acids (BCAAs: leucine, isoleucine, and valine) are essential amino acids acquired mainly from the diet and regulate protein metabolism via multiple pathways, including mTOR signaling [144]. Cancer cells require elevated nutrient uptake for increased biomass production, and elevated BCAA uptake and BCAA catabolism have been observed in various cancers [145]. In chronic myeloid leukemia (CML), BCAT1, a cytosolic aminotransferase for BCAAs, was aberrantly upregulated and linked to progression and disease outcome [146]. In human pancreatic ductal adenocarcinomas (PDAC), BCAAs provide a carbon source for fatty-acid biosynthesis, while elevated BCAA uptake was linked to disease progression [147].

Based on the metabolomes and consumption profiles of the NCI-60 cancer cell lines representing nine human cancers, leucine is the most heavily used amino acid in the human proteome [148]. Leucine also acts as a signaling molecule activating mTORC1 signaling through sestrin-2, a cytosolic leucine sensor [149]. Due to the low activity of BCAA aminotransferase, BCAAs, including leucine, do not undergo primary catabolism in the liver; therefore, leucine concentration increases rapidly after a meal in the circulation, indicating the potential for dietary restrictions targeting these amino acids [150]. Leucine deprivation inhibited proliferation and induced apoptosis in breast cancer models by reducing the expression of fatty acid synthase, although the effects were relatively modest [151]. In a mouse model of CRC, dysregulated amino acid sensing involving the expression of the genes Sesn2, Wdr24, or Depdc5 induced mTORC1 activation, leading to chemotherapy (5FU) resistance. Drug resistance could be reverted by limiting amino acids in the diet, particularly by depriving the leucine content [152].

2.6. Lipids

Lipids represent a class of molecules with enormous structural complexity and equally diverse functions in cellular physiology as essential structural components of biological membranes, secondary messengers in signal transduction pathways, and fuel sources for energy production. Fatty acids are obtained from the diet or can be synthesized de novo from carbohydrate precursors and are stored in the body as triglycerides.

Energy production in normal conditions primarily relies on pathways involving stored carbohydrates or non-carbohydrate compounds. Under these typical physiological circumstances, the liver continually synthesizes a minimal quantity of ketones for utilization as an energy source [153]. The conversion of fatty acids into ketone bodies is upregulated in the liver when insulin levels are low, glucagon levels rise, and fatty acid concentrations are elevated, as typically observed during fasting, starvation, or adherence to a low-carbohydrate diet. The liver oxidizes fatty acids to ketone bodies β-hydroxybutyrate, acetone, and acetoacetate, which are then used by the TCA cycle in other tissues [154,155].

Obesity and associated metabolic alterations augment cancer risk and worsen the prognosis [156]. In obese individuals, adipocyte accumulation in locations not classically associated with adipose tissue has systemic effects by altering the steroid hormone homeostasis and insulin sensitivity, causing low-grade inflammation [156]. Fat accumulation also alters the cellular composition of the tumor microenvironment, especially in tumors close to adipose tissue, such as breast, ovary, or colon tumors [157].

Cancer cells are able to reprogram their lipid metabolism by upregulating enzymes to increase **de novo cholesterin synthesis** or exogenous uptake of fatty acids [158,159]. Several studies found associations between altered lipid metabolism and cell migration, invasion, and angiogenesis, the essential steps toward forming metastases [156]. Increased expression of lipogenic enzymes such as fatty acid synthase, responsible for the terminal catalytic step in fatty acid synthesis, is a long-recognized metabolic feature of tumors [160].

Hypoxia, driven by the activity of hypoxia-inducible factors (HIFs), enhances lipogenesis by modulating proteins involved in various aspects of fatty acid metabolism, including uptake, hydrolysis, synthesis, storage, and usage and promotes lipid storage by the formation of lipid droplets [161,162]. Under hypoxic conditions, HIF-1 stimulates the upregulation of Lipin 1, a crucial protein involved in the biosynthesis of triglycerides, which are the primary constituents of lipid droplets [161]. The increase in lipid uptake under hypoxia may seem counterintuitive, given that fatty acid oxidation typically requires oxygen. However, it represents an adaptive response to challenging environmental conditions, as lipid droplets provide an energy reserve for when oxygen becomes available again. Lipid droplets may also sustain tumor cells during nutrient scarcity or metabolic stress. Importantly, this energy generation process occurs through beta-oxidation, which does not rely on oxygen [162]. This flexibility in energy utilization helps cancer cells survive and proliferate under the dynamic and often harsh conditions within the tumor microenvironment [163].

Some tumors progress rapidly in the presence of fat as the primary energy source in the diet [164]. For example, in some models of breast cancer, metabolic stress or MYC-overexpression activates fatty acid oxidation for ATP production [164,165]. Whole transcriptome profiling of breast tissues before and after tumor diagnosis revealed a significant upregulation of genes involved in fatty acid uptake/transport, lipolysis, and lipid peroxidation in the susceptible breast epithelium [166]. Glioblastomas, prostate cancers, and diffuse B-cell lymphomas are also actively uptaking and oxidizing fatty acids, especially during metastasis and cellular stress [167]. These findings suggest that the increasingly popular high-fat ketogenic diet might have adverse, tumor-promoting effects in some malignancies.

In summary, cancers are highly heterogeneous in their metabolic dependencies and preferred energy sources [2]. Although the **tissue of origin profoundly determines metabolic pathways** and the preference for metabolites, cancer metabolism is remarkably dynamic [168]. While much has been learned about cancer metabolism, much remains to be uncovered and understood about the complex metabolic processes involved in cancer initiation and progression. Nevertheless, adjusting therapy selection to particular metabolic demands and pathway activations of cancers may lead to the next level of precision medicine

[169].

3. Systemic therapies targeting the tumor metabolism

3.1. Anti-metabolite pharmaceutics

We briefly cover the pharmacologic targeting of metabolic enzymes. Anti-metabolites **disrupting a cellular function essential for cellular division** have been used in anticancer therapy for decades. The earliest example was the anti-folate aminopterin in children with acute lymphocytic leukemia (ALL), which changed the course of a previously fatal disease. Methotrexate, another folate antagonist with L-asparaginase, is still used to treat childhood ALL. More recently, the discovery of mutations in isocitrate dehydrogenase (IDH) in gliomas and acute myeloid leukemias producing the oncometabolite d-2-hydroxyglutarate [170,171], led to the approval of ivosidenib and enasidenib, inhibitors of the mutated IDH1 and IDH2, respectively, for relapsed/refractory IDH-mutated AML [172]. The discovery of IDH mutations allowed the precise targeting of particular metabolic pathways, starting a promising new era in metabolic cancer therapy. Overall, only a few metabolism-based drugs have been translated from the bench to the bedside [7].

Clinical translation of metabolic derangements in tumor cells is challenging for several reasons. On the one hand, tumor metabolic pathways frequently overlap with the metabolism of healthy cells, narrowing the therapeutic window. Moreover, the same pathways are used by antitumor cells in the tumor microenvironment: numerous metabolic similarities exist between tumors and cells of the immune system, particularly in immune cells that transition from a resting stage to activated effector cells (G. Andrejeva & J. C. Rathmell, 2017). Several promising substances in clinical trials target metabolic pathways in malignancies; however, many are in the early phase (Lemberg et al., 2022). Due to the high toxicity of antimetabolites, combination therapies that block multiple metabolic pathways at lower concentrations may be superior to single-agent therapies.

3.2. Dietary alterations influence cancer development and progression

The relationship between diet and cancer is a complex and evolving field of study. While systemic nutrient content impacts tumor growth, the extent to which diet plays a role in tumor initiation and progression is only beginning to be understood.

Diet modifications may take different forms: some interventions manipulate the content by supplementing or restricting certain nutrients, while other approaches control calories, timing, and feeding frequency. There are distinctions between dietary restrictions, caloric restrictions, and nutrient restrictions. **Dietary restrictions** refer to limitations or modifications encompassing various aspects of a person's overall diet, including types of food, meal timing, and portion sizes. In the context of cancer, dietary restrictions may involve avoiding foods believed to promote cancer growth or adhering to specific dietary patterns known for their cancer-fighting properties. This paper discusses two specific dietary restrictions: **caloric restriction** focuses on reducing the total calories consumed while maintaining adequate nutrition to extend lifespan, improve metabolic health, and potentially reduce the risk of age-related diseases, including cancer. **Nutrient restriction** is a more focused form of dietary restriction that involves limiting specific nutrients in the diet linked to the growth of cancer cells, such as glucose or specific amino acids.

Restriction of specific nutrients or the overall calorie content can have an anti-tumorigenic effect through several mechanisms, including i) deprivation of tumors from essential nutrients they became addicted to, ii) the enhancement of anticancer therapies, and iii) activation of the anticancer immune response. In the rest of the paper, we focus on the effects of **caloric restriction and glucose deprivation,** as the effects of supplementations on cancer progression are summarized in various excellent papers [6,173].

3.3. Nutrient restrictions: dietary deprivation of carbohydrates, the ketogenic diet

3.3.1. Types of the ketogenic diet

The ketogenic diet (KD), developed in the 1920s for treating refractory epilepsy [174], soon attracted interest in slowing the progression of certain malignancies. The German physician Wilhelm Brünings started experimenting with hypoglycemic treatments, including insulin administration and KD, to treat head and neck cancers as early as 1943 with encouraging short-term results [175].

Traditional KD consists mainly of fat (90%) with a minimal carbohydrate (2%) and protein (8%) content, with a ratio by weight of fat to protein plus carbohydrate of 4:1 (or 3:1, or 2:1, where more protein is required for rapid growth, such as in children and adolescents). Besides macronutrient composition, other factors are increasingly recognized for long-term adherence and efficacy [176]. Modifications to the traditional bland and restrictive KD include increasing the fat proportion or supplementing KD with medium-chain triglycerides (MCTs), omega-3 fatty acids, or ketone esters to enhance the anti-tumor effects [177–180]. Medium-chain triglycerides (MCT) are liquid fats and more ketogenic than the long-chain fats of the traditional KD. MTCs are swiftly absorbed into the bloodstream and readily oxidized for energy due to their ability to diffuse through membranes [181], stimulating the synthesis of ketone bodies in the liver [182], although high concentrations may cause gastrointestinal distress. **An MCT-supplemented KD** was first introduced into cancer research in 1987, reversing the cachectic process and reducing the tumor weight in a colon adenocarcinoma model [183]. With an 8:1 ratio comprising 25% MCTs and 75% long-chain triglycerides (LCTs), the modified KD decelerated tumor growth more effectively than the KD consisting solely of LCTs [177].

Other alternatives to KD include the **Atkins diet**, developed in the 1970s for weight loss, which promotes a low carbohydrate, high-fat diet without calorie or protein restriction. The **modified Atkins diet (MAD)** is more restrictive, allowing 15–20 g/day of carbohydrates (10 g/day in children) and encouraging high-fat food without fluid, caloric, and energy restrictions [184]. The **low glycemic index diet**, as a ketogenic-like diet, encourages the consumption of carbohydrates with low glycemic index, which could be as effective but more palatable than the traditional KD [185].

The **paleolithic KD**, developed by the gastroenterologist Voegtlin, consists of at least 70% animal-based food with a fat: protein ratio of approximately 2:1 in grams, with a preference for fatty red meats over lean meats, including liver, brain, and marrow [186]. The diet restricts the consumption of dairy, milk, grains, cereals, legumes, oilseeds, nightshades, all plant oils, refined sugars, artificial sweeteners, and foods with additives. The classic version of the KD has been associated with various early-onset complications, including hypomagnesemia as one of the most well-known side effects [187]. The paleolithic KD ensures adequate magnesium levels, moreover, it does not predispose to vitamin C deficiency [188,189]. The efficiency of the various KD approaches underscores the importance of optimizing diet composition to inhibit tumor growth more effectively.

3.3.2. Mechanisms behind the KD

KD mimicks a chronic fasting state by suppressing the feeding-induced insulin spike and inducing persistently elevated circulating ketone bodies, offering alternative approaches to fasting-mimicking diets [190]. KD slightly decreases body weight and increases whole-body oxygen consumption and energy expenditure [154].

When carbohydrate intake is insufficient due to caloric restriction, prolonged fasting, high-fat, low-carbohydrate KD, or endurance exercise, hepatic ketogenesis increases, and oxidation of fatty acids intensifies. In the liver, circulating fatty acids are transformed into ketone bodies, mainly β-hydroxybutyrate, acetone, and acetoacetate, increasing the circulating levels of ketones, which are then exported to other tissues [155]. In healthy adults, total ketone body concentrations exhibit

circadian oscillations between 100 and 250 μM. Ketosis is achieved when blood β-hydroxybutyrate reaches 0.5 mmol/L concentrations [191]. After prolonged exercise or 24 h of fasting, ketone concentrations rise to ~1 mM but can reach 20 mM in pathological states like diabetic ketoacidosis [192]. The daily 300 g of ketone bodies produced by the liver supply about 5–20% of energy requirements, depending on fed, fasted, or starved states [193,194].

Among the ketone bodies, β-hydroxybutyrate and acetoacetate are more abundant than acetone, and their generation and utilization are regulated on several levels. Ketogenesis occurs in the mitochondrial matrix through a series of enzymatic reactions, assisted by a rate-limiting ketogenic enzyme 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2), abundantly expressed in the hepatocytes [195]. In the liver, the lack of metabolic enzyme succinyl-CoA:3-ketoacid CoA transferase (SCOT) prevents liver cells from using ketone bodies for energy; therefore, β-hydroxybutyrate and acetoacetate enter the bloodstream to be distributed to different body tissues with the help of monocarboxylate transporters [196]. Ketone bodies are primarily used by the heart and the brain and in smaller amounts by other organs, where they are oxidized into acetyl-CoA. Acetyl-CoA enters the TCA cycle, or lipogenesis, or is excreted by the urine [155].

In the brain, which does not effectively take up fatty acids, β-hydroxybutyrate and acetoacetate are widely assumed to be the major fuels during ketosis and are metabolized mainly via mitochondria to produce adenosine triphosphate (ATP). An isotope tracing of circulating nutrients comparing high-carbohydrate-rich diets and KD showed that glucose remained the largest TCA substrate of the brain along with lactate [154]. Nevertheless, during a short-term (4 days) high-fat KD, ketone bodies supplied as much as 33% of brain energy requirements and were utilized at a rate inversely proportional to glucose [197]. During prolonged starvation, a more pronounced shift was reported toward ketone bodies as a fuel supply for the brain [192]. Moreover, β-hydroxybutyrate was capable of supplying all basal (housekeeping) energy requirements of the brain and around half of the energy needs of neuronal activity if the blood concentration of β-hydroxybutyrate was high enough [198,199]. In addition to functioning as an alternative energy source during energy stress, β-hydroxybutyrate also operates as a signaling molecule affecting a broad range of physiological processes at cellular and systemic levels, affecting stress response, orchestrating an antioxidant defense program and exerting a neuroprotective role [200,201].

Some tumors cannot efficiently utilize ketone bodies for energy during glucose withdrawal. Ketone bodies are metabolized exclusively in mitochondria, but widespread defects in mitochondrial structure and function in cancer cells impair the tumor's reliance on ketones [202]. Also, many tumors do not express the SCOT enzyme necessary to utilize ketone bodies [203].

Ketone bodies possess several additional characteristics that impair cancer cell proliferation and survival: in normal cells, ketones decrease mitochondrial ROS production and enhance endogenous antioxidant defenses, but not in cancer cells [204], ketones decrease the rate of glycolysis, reducing energy resources of tumors [205,206], and β-hydroxybutyrate may act as an endogenous HDAC inhibitor [207], thus by controlling the cancer epigenome ketones may alter the expression of oncogenes and tumor suppressors [200,208,209].

3.3.3. KD in preclinical studies

A growing number of **preclinical studies** suggest some effectiveness of KD in anticancer therapy, leading to increased survival and decreased tumor growth [210–213]. Nevertheless, the effectiveness of KD monotherapy widely varies across tumor models and depends on timing and particular aspects of the diet [214].

Delayed tumor growth and reduced inflammation were reported in mice inoculated by mouse colon or human gastric cancer cell lines and fed by KD [179,215]. KD has also been linked to prolonged survival in mouse models of malignant glioma, explained by both direct tumor growth inhibition and suppression of the pro-inflammatory microenvironment [216]. In mice with astrocytomas, a restricted standard diet and KD reduced tumor growth and plasma levels of IGF-1 [217]. KD-fed mice also showed increased innate and adaptive immune responses, including increased cytokine production and CD4 infiltration, suggesting an adjuvant immunologic role of the diet [218]. Ketone administration elicited anticancer effects in vitro and in vivo independent of glucose levels or calorie restriction: in vitro ketone supplementation, even in the presence of high glucose concentration in the culture media, decreased cellular viability and proliferation of VM-M3 cells. Dietary ketone supplementation with 1,3-butanediol or a ketone ester, which are metabolized to the ketone bodies β-hydroxybutyrate and acetoacetate, prolonged survival in VM-M3 mice with metastatic cancer by 51 and 69% [202].

Meta-analyses and systematic reviews provide beneficial insight into the field's current state. Eight studies out of nine exploring the relationship between carbohydrate restriction and cancer supported the protective role of KD in involving prostate, brain, gastric, and metastatic cancers on murine models [12]. In a systematic review, 72% of animal studies yielded evidence of the antitumor effects of KD [219]. Pooled results of 17 animal studies indicated significantly prolonged survival time and reduced tumor weight and tumor volume after KD monotherapy in certain tumor types [212]. A recent and more robust meta-analysis reporting on 65 mouse experiments corroborated the survival-prolonging effect of KD monotherapy [211].

There is evidence of synergy between KD and anti-cancer therapies in preclinical studies: for example, KD enhanced survival when combined with whole-brain radiation in mice [220]. KD has also been suggested to have implications in treating malignancies with altered PI3K signaling. PI3K inhibitors induce insulin feedback that reactivates the PI3K–mTOR signaling axis in tumors, compromising treatment effectiveness. KD reduced the systemic insulin response in model tumors in mice and, combined with PI3K inhibitors, widened their efficacy in a wide range of tumors [221]. A meta-analysis reported that KD combined with radiotherapy and targeted therapy, based on the results of four and ten experiments, increased survival in murine models of cancers. However, the same study could not identify a synergy between KD and chemotherapy [211].

Nevertheless, in a neuroblastoma xenograft model, metronomic cyclophosphamide combined with MCT-supported KD suppressed tumor growth and reduced tumor blood vessel density [177]. In mice bearing NCI-H292 and A549 lung cancer xenografts, KD slowed tumor growth when combined with radiation therapy or radiation-carboplatin treatment by a mechanism that may involve increased oxidative stress [222]. KD also synergized with the anti-programmed cell death 1 (PD-1) immunotherapy in animal models of RET melanoma, renal cell carcinoma, and lung cancer [223]. Additionally, KD improved overall survival when combined with anti-cytotoxic T lymphocyte-associated protein-4 (CTLA-4) immunotherapy in mouse tumor models and enhanced the efficacy in breast and colon cancer cells [224].

3.3.4. KD in clinical studies

Data are slowly accumulating from clinical studies suggesting the safety, feasibility, and some beneficial effects of KDs during cancer therapy. According to a systematic meta-analysis of fifteen studies on isocaloric KD in cancer patients, 37% of the participating 177 patients could adhere to the dietary recommendations. However, the overall antitumor effect of the KD was not significant. Nevertheless, the studies utilized different types of KD, with inconsistent and inadequately described protocols, complicating the direct comparisons [225]. In another systematic review, four studies showed beneficial effects of KDs on overall- and progression-free survival across 13 individual clinical studies. However, most trials were plagued by severe weaknesses, including small sample sizes, low compliance, or lack of controls [214].

During a four-week pilot study of ten patients with advanced and progressive cancers, the extent of ketosis but not calorie deficit or weight

loss was associated with stable disease or partial remission in five participants [226]. A prospective clinical trial from Japan investigated the effects of an MCT-supplemented KD on response rates in stage IV colon cancer patients receiving chemotherapy. The trial identified an overall response rate of 60% in the KD group and 21% in the control group, indicating a synergistic effect between KD and chemotherapy. However, the conclusions are based on a relatively low number of patients, with ten participants in the KD and 14 in the control group [227]. A randomized trial investigated the effects of MCT-based KD on breast cancer patients with locally advanced or metastatic disease. Fasting blood sugar decreased while serum levels of ketone bodies increased in the KD group, and among patients treated with neoadjuvant chemotherapy, the overall survival was higher in the intervention group ($p < 0.04$) [228]. In a retrospective study, 44 patients with stage IV metastatic NSCLC were treated with a combination of metabolically administered chemotherapy, KD, hyperbaric oxygen, and hyperthermia. Despite the large percentage of patients with unfavorable prognostic factors, the treatment combination resulted in a higher-than-expected overall and progression-free survival compared to values from the literature [229].

In a study involving tumor patients in primary care clinics, of the four palliative patients who adhered to a strict KD, one patient with metastatic breast cancer experienced complete remission of bone and lung metastases, and another with ovarian cancer experienced stable disease [230]. The expression of transketolase-like-1 (TKTL1), a marker associated with aerobic glycolysis, was correlated with tumor status, and adherence to the strict KD was associated with reduced TKTL1 levels [230]. In a case study involving a patient with a myoepithelial tumor of the soft palate, not treated by conventional treatment, the paleolithic KD resulted in a halted progression of the tumor, with lasting effect at the 20-month follow-up [231].

Regardless of the survival outcomes, several reports support that patients who adhere to the KD diet tend to retain higher portions of skeletal muscle mass and more favorable body composition than the controls [214].

3.3.5. *Factors influencing the efficacy of KD*

The efficacy of KD is influenced by multiple factors, including the cancer type, subtype, genetic and metabolic background: while KD showed some efficacy in gliomas, glioblastomas, and neuroblastomas, there were little or no effects in other brain tumors [232,233]. In IL-6-producing cancers, such as colon or pancreatic tumors, IL-6 reduces the hepatic ketogenic potential and impairs the response to the KD, while caloric deficiency triggers a rise in glucocorticoid levels, ultimately resulting in cancer cachexia [234,235]. Thus, unfortunately, accelerated cachexia will shorten survival in IL-6-producing cancers despite the decreased tumor growth. The phenomenon results from the interaction of two NADPH-dependent pathways: increased lipid peroxidation and saturation of the glutathione (GSH) system lead to the ferroptotic death of cancer cells, and at the same time, redox imbalance and NADPH depletion impair corticosterone biosynthesis [236]. Dexamethasone administration to mice increased food intake, normalized glucose levels, delayed cachexia, and extended the survival of tumor-bearing mice fed KD while maintaining reduced tumor growth [236]. In addition, despite renal cell carcinomas (RCC) displaying similar energetic features as neuroblastomas, KD dramatically decreased the survival of mice with RCC due to massive weight loss, potentially also affected by the associated hepatic dysfunction [237].

Thus, a **few cancers progress rapidly when fat is the primary energy source** in the diet [164], including some AML models, where KD also accelerates disease progression [221]. For example, breast cancer cells undergoing metabolic stress upon loss of attachment activated fatty acid oxidation for ATP production [164], and reliance on dysregulated fatty acid oxidation has also been identified in an MYC-driven model of triple-negative breast cancer [165]. Additionally, a high-fat diet enhanced the stemness and tumorigenicity of LGR5(+) intestinal stem cells and progenitor cells and allowed aberrant proliferation in vivo and colony formation in vitro [238]. Therefore, it is essential to study the metabolic preferences of each tumor with careful evaluation for every type and subtype before adopting any dietary recommendations for patients.

3.3.6. *Current clinical trials on KD*

While KD may have some potential benefits in preclinical studies, it is not recommended as a standalone treatment for cancer; however, it can only be used under the guidance of a healthcare provider. It may not be appropriate for all individuals due to its side effects, such as nausea, fatigue, and constipation. More randomized studies with clear, standard protocols and strict compliance monitoring are needed for definitive conclusions.

Currently (as of September 2023), 32 clinical trials are recruiting, will be recruiting, or are active but not recruiting participants for various **cancer therapies complemented by KD** (www.clinicaltrials.gov) (Table 2). Most focus on gliomas, glioblastomas, and recurrent or metastatic brain tumors (12 out of 32), and five studies are designed to study the effects of KD on breast cancer patients (Table 2). Hopefully, the results will address the limitations of previous research and provide more precise insights into its clinical feasibility.

3.4. *Caloric restriction*

Caloric restriction (CR) is based on a **reduced energy intake (by 15–40%) for an extended period** with a balanced ratio of macronutrients and has been linked to enhanced health and longevity in obese, overweight, or normal-weight individuals [239]. In the CALERIE phase II clinical study, two years of 25% CR on healthy humans persistently reduced blood pressure, insulin sensitivity, cholesterol levels, and metabolic syndrome score, decreasing the 10-year risk of cardiovascular disease by 30% [240,241]. In addition, the intervention improved several liver biomarkers [242], and reduced whole-body inflammation [243]. Moreover, sustained caloric restriction slowed the effects of aging [244–246]. Increased inflammation, aging, and metabolic imbalance are associated with cancer initiation and progression; therefore, it is unsurprising that a solid rationale can explain the beneficial anticancer effects of CR in preclinical animal studies [12]. For instance, in a 20-year-long longitudinal study involving rhesus monkeys, a 30% caloric restriction (CR) regimen delayed the onset of age-associated pathologies and reduced the incidence of neoplasia by 50% compared to the control group. Among the control animals, 37% succumbed to age-related causes, whereas only 13% of the CR group met the same fate. Furthermore, none of the animals on CR exhibited impaired glucose metabolism [247]. In a seemingly parallel study conducted by the National Institute on Aging (NIA), the CR regimen implemented in both young and older rhesus monkeys did not lead to improved survival outcomes despite an overall enhancement in health. Several factors may account for the disparate results observed between the two studies, including variations in diet composition, vitamin and mineral supplementation, access to food in the control groups (either ad libitum or *near* ad lib), and the genetic diversity of the two animal populations [248]. Despite these distinctions, the significantly improved cancer incidence rates and the reinforced immune response observed in the young-onset CR group in the NIA study affirm the effectiveness of caloric restriction in preserving health.

However, adherence to CR regimens, especially in cancer patients, is not feasible in clinical settings due to the potential danger of muscle loss [249]. Another concern is the anti-inflammatory effect of CR, especially in immunodeficient patients due to illness or therapy [250].

Alternative diets are being developed to **mimic the effects of CR** without its adverse side effects. There is a wide variation across feeding protocols, and the categories may not be mutually exclusive. Experimental designs belong to several major types: i) short-term fasting or periodic water-only fasting when 3–4 days or more extended periods of low-calorie intake are followed by regular feeding for weeks or months;

ii) intermittent fasting, in which usually cyclical short periods (1–2 days) of fasting or low caloric intake are interspersed between 1 and 5 days of ad libitum (AL) feeding bouts; iii) time-restricted feeding (TRF), which limits food intake into a daily 4–12 h window, but can be isocaloric in compositions; and iv) fasting mimicking diets (FMD), based on a cyclically administered, plant-based, calorie, sugar, and protein-restricted composition. It is important to note that various feeding models may have different synergistic effects with anticancer therapies.

Also, many early publications on caloric restriction did not distinguish between expressions of fasting and starvation, but there is a major physiological distinction between the two processes. Fasting is a voluntary and controlled, often short-term practice, where an individual deliberately abstains from consuming food or caloric beverages for a specified period, and when practiced safely and appropriately, it may have health benefits. On the other hand, starvation is an involuntary and uncontrolled condition when an individual lacks access to essential nutrients, including macronutrients and micronutrients, resulting in severe health consequences, such as malnutrition and dehydration. The majority of the findings in this paper refer to fasting, and all exceptions are otherwise stated and explained.

3.5. Types of caloric restrictions

3.5.1. Intermittent fasting (IF)

Intermittent fasting (IF) is an eating pattern involving alternating fasting periods with periods of a regular diet. It has many forms, most frequently based on alternate-day fasting (ADF), also called every-other-day (EOD) feeding, or periodic prolonged fasting (PF) when fasting lasts up to 24 h once or twice a week. There is a wide variation in fasting protocols, with some allowing calorie intake on fast days while others do not [251]. Strictly speaking, time-restricted feeding (TRF) is also a form of IF, but we discuss TRF separately.

In mice, EOD feeding extends the average lifespan by 12–27% [252,253], explained by a delay in the development of malignant disorders [254]. On a particular strain (OF1) of middle-aged mice, alternate-day fasting decreased the production of mitochondrial reactive oxygen species and the incidence of age-associated lymphoma [255]. The effect of IF is related mainly to the metabolic conversion to use ketone bodies instead of glucose as an energy source, and the reduced levels of glucose, insulin, and IGF1 are accompanied by cell death. However, the refeeding cycles during IF may increase proliferative activity in the affected tissues driven by the replenishment of growth factors that may contribute to the initiation of malignant transformation. In rats treated with a subnecrogenic dose of the carcinogen diethylnitrosamine (DENA) 24 h post-refeeding, no focal lesions developed in the ad libitum group, while a significant number of focal lesions were identified in animals kept on IF diets [256]. Additionally, in SCID mice, twice weekly 24-h fasts (IF) followed by ad libitum feeding did not delay prostate xenograft tumor growth nor improve survival [257]. A systematic meta-analysis found that 37.5% of studies on IF did not show preventative effects against cancer development, highlighting the need for further research.

3.5.2. Time-restricted feeding (TRF)

During TRF, the timing and distribution of meals and the duration of fasting play a crucial role. The circadian system, with master pacemaker neurons in the central nervous system and peripheral clocks, regulates gene expression in various organs and coordinates the activity of hormones and enzymes involved in metabolism [258]. Prolonged fasting during sleeping is associated with increased hepatic gluconeogenesis and a rise in plasma-free fatty acids, ghrelin, and growth hormones [259]. The misalignment between fasting-feeding and sleep-wake cycles has implications for metabolic processes. Nocturnal mice fed high-fat diets during the 12 h light phase gained significantly more weight than mice fed during the 12 h dark phase [260]. The alignment of time-restricted feeding of high-fat diets with daily activity prevented the development of fatty liver disease and obesity in mice [261]. Meal timing similarly impacts human health [262]. **Limiting food intake to the beginning or the middle of the day** improved metabolic markers, decreased body fat and insulin resistance, and resulted in weight loss without calorie counting [263–266]. Bigger breakfasts and smaller dinners positively affected the cardiac autonomic nervous system and lipid metabolism [267]. Consuming meals before 3 p.m. during a 6-h window in prediabetic men ameliorated markers of diabetes by improving insulin sensitivity, β cell responsiveness, blood pressure, and oxidative stress without weight loss [268]. Nevertheless, based on a smartphone app to monitor daily eating patterns, half of the monitored adult human population displayed an erratic eating and fasting pattern [264].

Hyperglycemia has been identified as one of the critical pathogenic metabolic components linked to increased cancer risk. An analysis of 14 studies found a positive relationship between glycosylated hemoglobin (HbA1c), a marker of hyperglycemia, and the incidence of numerous cancers independent of diabetes [269]. Accordingly, low-baseline glycemia is linked to increased survival in triple-negative breast cancer [270], while high fasting blood glucose is an independent risk factor for breast cancer development both in pre-and postmenopausal women [271], and for cancer death in estrogen receptor-positive breast cancer patients [272]. In addition, a study based on data from over 2000 women found an association between nighttime fasting and glycemic regulation: an increase in nighttime fasting duration was associated with reduced elevated HbA1c, and mean fasting durations of over 13 h resulted in decreased recurrence of breast cancer [273,274].

3.5.3. Fasting-mimicking diet (FMD)

Compliance with prolonged water-only fasting or restricted food intake is challenging for humans and has potential adverse effects, such as exacerbation of malnourishment in frail subjects, including cancer patients. Longo and colleagues have developed an alternative dietary intervention, called a fasting-mimicking diet (FMD), to emulate the physiological effects of prolonged fasting without complete food deprivation. The **low-protein, low-carb plant-based diet** comprising roughly 200–1100 kcal per day is based on soup, herbal tea, energy bars, nuts, and supplements and is administered for 3–5 days, often repeated in cycles every couple of weeks [275–277]. FMD maintains a physiologic fasting-like state without actual fasting: in a clinical trial, the FMD regimen for five days reduced median blood glucose, insulin, and IGF1 concentration by 18.6%, 50.7%, and 30.3%, respectively, reaching levels comparable to water-only fasting [276], while minimizing loss of lean body mass [275]. Nevertheless, in 4 T1 murine metastatic models of breast cancer, mild levels of daily caloric restriction (20%) produced a more robust antitumor response than caloric cycling by FMD [278]. The relatively short-term and low-level CR did not reduce lean body mass in mice; thus, daily CR could be evaluated as a short-term adjuvant intervention when coupled with existing therapies.

3.5.4. An alternative option: Caloric restriction mimetics (CRM)

Patients, particularly cancer patients, have difficulties adhering to fasting, and in most clinical trials, compliance with caloric restrictions is problematic. Caloric restriction mimetics (CRMs) can recapitulate some metabolic effects of fasting, particularly by eliciting pharmacological autophagy by reducing cellular protein acetylation [279]. Injections with **hydroxycitrate**, a CRM, reduced the bioavailability of IGF-I in vivo and mimicked the physiological effects of fasting without significant weight loss. CRM treatments improved the outcome of various malignancies treated with simultaneous methotrexate chemotherapy. The tumor-reducing and survival-improving effects diminished when CD8+ T lymphocytes were depleted from the system, suggesting that the synergistic effects between CRMs and chemotherapy depend on an adaptive cellular immune response [280]. Autophagy-deficient cells could escape immunosurveillance by attracting Tregs into the tumor bed; hence, both fasting and CRMs improved the efficacy of

chemotherapy via immunological mechanisms that reduce intratumoral Treg infiltration [280].

3.6. Systemic responses to caloric restrictions

Fasting in mammals alters the circulating level of numerous hormones and metabolites in a tissue-specific manner: the stress of food shortage induces **ketogenesis in the liver**, lipolysis in adipose tissue, and ketone consumption in various organs. In the initial phase of fasting, insulin levels fall while glucagon increases as the liver's glycogen storage is broken down to glucose. Altered insulin and glucagon also trigger the transformation of triglycerides into fatty acids and glycerol. Fasting also reduces insulin-like growth factor I (IGF1) levels, in part by increasing the concentration of insulin-like growth factor-binding protein 1 (IGFBP1) [275]. Also, growth hormone (GH) resistance of the liver caused by low insulin levels inhibits hepatic IGF1 production [281,282]. Fatty acids provide the primary energy source for most tissues during fasting, while the brain primarily utilizes glucose. By the second or third day of fasting, during the ketogenic phase, the rising levels of ketone bodies and fat-derived glycerol and amino acids contribute to gluconeogenesis to maintain stable glucose levels. Fasting also lowers leptin, an adipocyte-secreted hormone that reduces hunger [283], and increases adiponectin production to break down fatty acids [284]. Glucocorticoids and adrenalin also play a role in maintaining blood sugar by increasing lipolysis [285]. Altogether, reduced glucose, insulin, leptin, and IGF1 levels and increased IGFBP1, ketone bodies, and adiponectin concentration are hallmarks of the mammalian systemic response to fasting.

3.6.1. Signaling pathways affected by glucose or caloric restriction

The **IGF1 signaling cascade** plays a crucial role in mediating the systemic effects of nutrient availability. Under normal nutrition and protein consumption, IGF-1R binds to IRS1, which then transmits signals through the phosphatidyl-inositol-3 kinase (PI3K)-AKT1-mammalian target of rapamycin (mTOR) pathway and through the mitogen-activated protein kinase (MAPK) pathway. Increased IGF1 levels stimulate AKT and mTOR activity, boost protein synthesis, and inactivate the pro-apoptotic protein BAD. Insulin/IGF balances cell growth (PI3K) with proliferation (MAPK); the crosstalk between these signaling cascades is essential for normal development.

Insulin and **insulin-like growth factor 1** (IGF1) levels decrease during fasting, downregulating PI3K, AKT, and PDK1 phosphorylation and inducing the expression of the tumor suppressor PTEN [286]. The reduced IGF1 and insulin-like growth factor 1 receptor (IGF1R) levels decrease the AKT-mediated inhibition of mammalian FOXO transcription factors, activating enzymes with antioxidant properties and protective effects such as heme oxygenase 1 (HO-1), superoxide dismutase, and catalase.

Reduced glucose levels inhibit the activity of protein kinase A (PKA) and increase the activity of the master intracellular energy sensor **AMPK** [287]. AMPK plays a vital role in controlling mitochondrial respiration, nutrient transport, autophagy, longevity, differentiation, and cell polarity [288]. AMPK activation suppresses anabolic pathways, such as protein and lipid synthesis, promotes catabolic processes, such as glucose uptake and fatty acid oxidation, and activates autophagy, which helps the cells recycle cellular components to maintain energy levels during starvation.

AMPK activation during fasting inhibits the **mammalian target of rapamycin (mTOR),** an autophagy inhibitor often called the master regulator of cell growth. This serine/threonine protein kinase is a central molecular connection between nutrient signals and cellular anabolic processes, on which many nutrient sensing and pro-growth oncogenic pathways converge, and dysregulation of the mTOR pathway underlies various human diseases, including cancer [289]. Reduced mTOR pathway activity warns the cells about the nutrient shortage and induces metabolic reprogramming by switching toward available nutrient sources, such as fatty acids.

Nutrient availability fluctuates significantly through tumor evolution, and growing tumors with increasing anabolic requirements must tune their metabolic responses to the available supplies. Deprivation of glucose, lipids, oxygen, or amino acids affects complex gene expression programs [290], and influences various families of **transcription factors,** including the expression of HIFs, SREBPs, and ATF4, which have a central role in nutrient sensing [291].

Activating transcription factor 4 (ATF4) is at the core of an adaptive pathway integrating diverse stress stimuli, including endoplasmic reticulum stress, viral infections, or amino acid deprivation [292]. ATF4 is also one of the master regulators of the stress response that promotes cellular adaptation to limited nutrients [291,293,294]. Proliferating tumor cells require a great demand of proteins, and ATF4 levels rapidly increase upon depletion of intracellular amino acids, while glucose deprivation or hypoxia also activates ATF4 expression [291,294]. ATF4-mediated synthesis of amino acids (e.g., asparagine or serine), antioxidants (glutathione), and regulation of autophagy play an essential role in cancer cell survival and treatment resistance [291,293–296]. The induction of transcriptional factors, such as HIFs or ATF4, likely helps cancer cells to compete in a nutritionally scarce environment.

The **hypoxia-inducible factor (HIF)** proteins are activated by limiting oxygen levels, facilitating tumor growth and survival in hypoxic areas. HIF upregulation is linked to a cell-intrinsic increase in glucose uptake and glycolysis, corresponding attenuation of mitochondrial oxidative metabolism, allowing cells to maintain energy production under low oxygen. HIF1α and HIF2α exert opposite effects over tumor metabolism in some cancer settings, and HIF1α subunit accumulation has been associated with poor prognosis in various cancers [290,291].

Sterol regulatory element-binding proteins (SREBPs) constitute a family of transcription factors with distinctive physiological roles in cellular lipid homeostasis. During energy abundance, insulin and growth factors activate the PI3K–AKT–mTOR–SREBP signaling axis, a primary pathway in anabolic metabolism [297]. Upon lipid depletion, SREBPs induce a complex program to restore lipid levels by the activation of enzymes for de novo synthesis of fatty acids and sterol lipids. SREBs are often upregulated in human cancers, and their activation has been implicated in tumor progression and poor disease outcomes [291,298].

In a nutrient-rich environment, mTORC1 promotes protein synthesis and biosynthesis of macromolecules, including lipids and nucleotides, and increases the expression of HIFs, SREBPs, and ATF4. However, during nutrient depletion, HIF1α, SREBP, and ATF4 activation results in mTORC1 inhibition, blocking anabolic processes and growth [291].

3.6.2. Differential stress resistance and differential stress sensitization

Reduced glucose levels induce cell-cycle arrest, force healthy cells to slow division, and enter a protected mode by activating cell maintenance and repair [299,300]. **Switching from growth to repair** enhances resistance to toxic insults such as chemotherapy and radiotherapy [13,14].

This physiologic cellular switch is not observed in cancer cells. In rapidly proliferating tumors, the constant growth resulting from gain-of-function mutations affecting proliferation-inducing oncogenes such as AKT, mTOR, RAS, and/or loss of tumor suppressors, such as TP53, Rb, or PTEN abrogates the tumor cells' ability to adapt to the changing nutrient levels [1]. Without cell-cycle arrest, cancer cells are more prone to chemotherapy-mediated DNA damage.

Moreover, cancer cells, unlike normal cells, are often metabolically inflexible and heavily reliant on glucose for energy. When exposed to a ketogenic state induced by fasting or a KD, cancer cells may struggle to adapt, which may augment sensitivity to chemotherapy by various mechanisms [206,301,302].

Fasting and KD, therefore, increase healthy cells' resistance to stressors, also known as differential stress resistance (DSR), while increasing cancer cells' sensitivity to chemotherapeutic agents, which is

known as differential stress sensitization (DSS) [13,14,303,304].

3.7. The synergy between fasting-like conditions and chemotherapy

3.7.1. Preclinical studies

The efficacy of fasting in augmenting chemotherapy is twofold: fasting protects from the toxic effects of high-dose chemotherapy in preclinical and clinical studies while simultaneously **sensitizing malignant cells to chemotherapeutic drugs**. An unusually high concentration (80 mg/kg) of etoposide, a chemotherapeutic causing DNA double-strand breaks, was significantly less toxic in mice fasted for 48 or 60 h before treatment. In neuroblastoma-bearing mice, high doses of etoposide led to 50% mortality in ad libitum-fed animals, while 48 h fasting before treatment protected animals without compromising tumor-specific toxicity [14]. Effects of fasting were mediated through stem cell populations: in mice fasting for 24 h before etoposide chemotherapy, the structure and function of small intestinal crypt stem cells were preserved. While in normally fed mice, nearly all small intestinal stem cells were lost, stem cell populations marked by Lgr5, Bmi1, or Hopx contributed to fasting-induced survival [305].

A 72-h fast in melanoma-bearing mice protected the animals from the toxicity of doxorubicin: 60% of fasted mice achieved long-term survival, while all control animals died. Fasting achieved a 70–80% reduction of circulating IGF-1 levels, but restoring IGF-1 reversed the protective effects of fasting. Conversely, genetically modified mice with reduced IGF-1 expression were protected from the toxicity of doxorubicin [306]. Similarly, a 24-h fast before and after chemotherapy protected mice from oxaliplatin- or doxorubicin-induced multi-organ toxicity. A shorter fasting time (12 h before and after therapy administration) did not result in the same level of protection compared to the 48 h of extended fasting [307]. Cancer cell lines supplemented with the serum of fasted mice were more susceptible to doxorubicin and cyclophosphamide than cells cultured with the serum of ad libitum-fed animals [13]. Intermittent fasting also retarded the growth of subcutaneous xenografts: two cycles of 48 h fast were sufficient to reduce tumor growth, and more significant effects were achieved when fasting was combined with chemotherapy [13]. Short-term fasting in cancer-bearing dogs reduced doxorubicin-induced nausea and vomiting [308].

A three-day fast before treatment protected against the side effects of irinotecan, a highly toxic topoisomerase-I inhibitor in FabplCre; Apc (15lox/+) mice with spontaneous intestinal tumors. Although fasting did not enhance the treatment's antitumor activity, it reduced diarrhea and leukopenia [309]. One of the potential benefits of fasting prior to treatment is the reduction in side effects; as a result, tolerating higher doses of therapeutic agents could increase treatment efficacy.

Some anticancer drugs, including dexamethasone and the pharmacological inhibitor of mTOR, rapamycin, are hyperglycemic, and the elevated glucose levels sensitized cardiomyocytes and mice to the effects of doxorubicin. **Reducing circulating glucose** levels by fasting or insulin can alleviate such toxicity. The effects are mediated through decreased expression of PKA, leading to increased AMPK and EGFR1 signaling [287]. In preclinical models of colorectal carcinoma, treatment with rapamycin synergized with FMD and inhibited in vitro cellular proliferation and in vivo cancer progression. Fasting upregulated the expression of the farnesyl-diphosphate farnesyltransferase 1 gene (FDFT1), encoding an enzyme participating in cholesterin biosynthesis. Increasing FDFT1 levels suppressed the proliferation of CRC cells by inhibiting the AKT-mTOR-HIF1α pathway and impairing aerobic glycolysis. Downregulation of FDFTP1 correlated with poor prognosis in CRC patients [310].

Recently, short-term fasting increased the anti-tumor activities of tamoxifen and fulvestrant in hormone-receptor-positive, HER2 receptor-negative breast cancer cell lines, and periodic fasting in mice bearing MCF7 xenografts reverted acquired resistance to treatment [311].

3.7.2. Human trials investigating caloric restriction

Short-term fasting is well tolerated in non-cancer patients [312,313]. A series of case reports of 10 volunteer cancer patients undergoing fasting prior to (48–140 h) and after (5–56 h) various chemotherapy treatments reported tolerability and only mild side effects, demonstrating the feasibility of fasting in cancer patients [314]. A subsequent study on HER2-negative, stage II/III breast cancer patients confirmed the previous findings, as 24 h fast prior and after docetaxel/doxorubicin/cyclophosphamide therapy was tolerable and reduced hematological toxicity: patients in the fasting arm had higher erythrocyte- and thrombocyte counts and less DNA damage in CD45 + CD3- cells [315].

A clinical trial with a dose-escalation protocol investigated water-only fasting for 24, 48 h prior to, or 72 h around platinum-based chemotherapy (48 h before and 24 h after therapy). Fasting was linked to reduced DNA damage in leucocytes in subjects fasting for at least 48 h, with a non-significant trend toward reduced grade 3 and 4 neutropenia [316]. IGF-1 decrease was most substantial in the 24-h fasting group, although there was no improvement upon fasting in this group. In an individually randomized cross-over trial, 34 patients with gynecological cancers fasted for 36 h before and 24 h after chemotherapy and reported improved quality of life and less fatigue [317].

In the randomized phase II DIRECT trial on HER2-negative stage II/III breast patients (NCT02126449), cyclic FMD was administered three days before and during standard anthracycline-taxane preoperative chemotherapy. The maximum number of required FMD cycles was eight. The study was prematurely interrupted due to lower-than-anticipated pCR rates and low participant compliance, which might have affected the results. Despite the lack of adherence to the experimental diet, FMD eliminated the need for dexamethasone and significantly curtailed chemotherapy-induced DNA damage in T-lymphocytes. The treatment somewhat improved the frequency of radiologically complete- or partial response but failed to reduce chemotherapy-related adverse effects [318]. Notably, the compliant patients had significantly higher rates of pathological tumor responses [318,319].

The subsequent NCT03340935 clinical trial enrolling 101 patients with different tumor types demonstrated the safety and feasibility of cyclic FMD combined with standard-of-care antitumor therapies, with a much higher compliance rate (91.8%) compared to the DIRECT trial [276]. The five-day fast followed by 16–23 days of refeeding resulted in a 12.9% incidence of G3/G4 adverse effects and improved the patients' antitumor immune response and general metabolic status. Moreover, a sub-analysis of the NCT03340935 trial data revealed that out of the 69 patients with advanced solid neoplasms, five patients achieved complete and long-lasting tumor remission, where FMD might have significantly contributed to the exceptional therapy response [320].

3.8. Molecular mechanisms underlying differential stress resistance and differential stress sensitization

The possible mechanisms by which fasting protects normal but not cancer cells from toxic agents are likely mediated by immune-dependent and immune-independent mechanisms [14,306].

IGF-1 downregulation is one of the fundamental mechanisms promoting chemotherapy tolerance and minimizing significant adverse effects in healthy cells. In mice, a 72 h fast **downregulated circulating IGF-1 levels** by 70%, simultaneously increasing the IGF-1 inhibitor IGFBP-1 levels by eleven-fold. IGF-1 deficiency was sufficient to protect LID mice from chemotherapy, and restoring IGF-1 levels abrogated the protective effects of fasting on normal cells [306]. Furthermore, decreased IGF-1 levels reduced the activity of mTOR, and inhibition of the mTOR pathway increased the sensitivity of many cancer cells to chemotherapy [321]. Fasting also upregulated the expression of the farnesyl-diphosphate farnesyltransferase-1 gene (FDFT1), which inhibits aerobic glycolysis and the AKT-mTOR-HIF1α pathway [310].

As short-term fasting down-regulates aerobic glycolysis and reduces glutaminolysis, cancer cells are forced to rely more on oxidative

phosphorylation. Despite increased oxygen consumption, tumor cells fail to generate ATP in the oxidative chain, accumulating toxic **reactive oxygen species** (ROS), a phenomenon termed the anti-Warburg effect. Upon chemotherapeutic insult, the resulting ROS sensitizes cancer cells to apoptosis [286]. Moreover, many antitumor agents, including vinblastine, cisplatin, doxorubicin, and camptothecin, induce oxidative stress by increasing the formation of reactive oxygen species that lead to single and double-strand DNA breaks and cell death [322]. Findings from in vivo studies suggest that fasting in combination with chemotherapy is beneficial in reducing DNA damage: short-term fasting prior to chemotherapy reduced DNA damage in subjects who fasted for ≥48 h, evaluated in leukocytes using the COMET assay, although no effects were observed when fasting lasted for 24 h only [316].

The stress-responsive enzyme **heme-oxygenase-1 (HO-1)** is a major antioxidative enzyme of tumors and another critical mediator of differential stress sensitization: FMD caused the reduction of HO-1 in cancer cells but not in normal cells. In addition, activation of HO-1 in mice rendered FMD ineffective in inducing an immune-based attack of cancer cells. However, pharmacological inhibition of HO-1 was sufficient to reduce tumor progression in the absence of FMD treatment [323].

Fasting also modulates apoptosis and prevents apoptosis-mediated damage to normal cells. Rat pups were allocated into normal size, large, and extremely large litters to restrict breast milk access and induce underweight. The resulting moderate dietary restriction in large, but not in extremely large, litters protected against neurovascular injury after hypoxic ischemia. The intervention inhibited the apoptotic machinery by suppressing p53 to increase neuronal survival in the brain [324]. In addition, fasting cycles augmented the effectiveness of chemotherapeutic drugs in breast cancer cell lines by increasing their sensitivity to apoptotic cell death. In contrast, fasting-induced cell cycle arrest protected normal cells from the same drugs [13].

Autophagy is a protective housekeeping process that uses a lysosome-dependent controlled mechanism to degrade malfunctioning cellular components from the cytoplasm for later reuse. Autophagy allows cells to react to stress and has been linked to both carcinogenic and anticarcinogenic processes [325]. Caloric restriction and fasting trigger **autophagy** in various tissues and organs, regulated by the AMPK, mTOR, and PI3K pathways [326]. Fasting-induced upregulation of autophagy before exposure to chemotherapeutics may be protective against damage to organelles but may also have a pro-survival function in some cancer cells, affecting therapy resistance [327,328].

The extent of fasting-induced protection is also associated with changes in erythrocyte membrane fatty acids and gene expression in peripheral blood mononuclear cells (PMBC) [307]. Short-term fasting in mice (and humans) altered the composition of cell membranes, enriching them with polyunsaturated fatty acids. Biomarkers of lipid homeostasis directly correlated with the extent of fasting-mediated protection from chemotherapy in mice: animals with a less dramatic change in their insulin-responding genes and membrane fatty acid composition (milder decreased in monounsaturated fatty acids and a reduced increase of polyunsaturated fatty acids) were more strongly protected from chemotherapy toxicity. Consequently, individuals with the best basal metabolic status displayed a milder response to fasting and were most protected from chemotherapy [307].

The periodically reduced IGF-1 levels during fasting affected the regeneration of hematopoietic cells: 48 h fasting cycles dramatically reduced white blood cells. However, refeeding bouts induced a coordinated self-renewal proliferation of stem cells in mice, indicating a potent mechanism to regenerate the hematopoietic system [329]. Similarly, in chemotherapy-treated cancer patients, 72 h fasting (but 24 h fasting was not) was associated with normal lymphocyte counts and maintenance of normal lineage balance among white blood cells. The observed effects were linked to reduced protein kinase A (PKA) activity downstream of IGF-1. Thus, fasting promotes IGF-1/PKA-dependent **hematopoietic regeneration** and reverses chemotherapy-induced immunosuppression [329].

Ample evidence supports that the synergistic effect between fasting and chemotherapy relies on the **antitumor immune response**. Combining low-calorie and low-protein FMD with chemotherapy enhanced tumor immunogenicity by increasing the level of common lymphoid progenitor cells and cytotoxic CD8+ tumor-infiltrating lymphocytes, delaying melanoma and breast cancer progression [323]. Similarly, a five-day cycling FMD coupled with standard-of-care chemotherapy downregulated peripheral blood immunosuppressive myeloid cells while boosting cytotoxic T lymphocytes and cytolytic NK cells. FMD also affected the tumor microenvironment by switching it toward a more favorable phenotype: in a subcohort of breast cancer patients, FMD increased CD8+ T cells, NK cells, activated dendritic cells, and central and effector memory CD4+ and CD8+ T cells. In post-FMD tumors, fasting enriched the IFNγ-activating signature associated with favorable outcomes, and some of these effects were present even 40 days after the treatment [276].

Immune checkpoint inhibitors, including monoclonal antibodies against PD-1 and PD-L1, are inefficient in a significant portion of patients. Mechanisms in the tumor microenvironment preventing the infiltration and activation of cytotoxic T cells may be overcome by **combining immune checkpoint inhibitors with short-term fasting.** Accordingly, 3-day-long complete fasting combined with the anti-PD-1 antibody RMP1–14 significantly reduced the growth of KRAS-driven adenocarcinomas, with a complete response in four out of eight mice [330]. Mice that exhibited complete response were protected from tumor re-challenge. Consistent with previous findings, the combined treatment significantly increased the tumor-infiltrating CD8+ and NK cells, reducing the proportion of CD4+ and B cells and Treg in the tumors. The effects of the combined therapy were mediated by the downregulation of the IGF-1/IGF-1R axis, indicating that IGF-1/IGF-1R may contribute to primary resistance toward PD-1 blockade. Conversely, in NSCLC patients, the circulating IGF-1 levels in plasma samples were inversely associated with the efficacy of the anti-PD-1/PD-L1 therapy. Inhibition of IGF-1R synergized with the PD-1 blockade and restored antitumor immunity, significantly reducing tumor growth and increasing survival in mice [330].

Ketone bodies produced during fasting are increasingly recognized as essential in modulating differential stress response and stress sensitization. Ketones, such as β-hydroxybutyrate, can provide an alternative energy source for normal cells, particularly in the brain and heart. Patients on a ketogenic diet or those naturally in ketosis may experience reduced side effects like cognitive impairment (chemo brain) and cardiac complications during chemotherapy, as normal brain and heart cells become more resistant to stress. The protective effects of ketone bodies on normal cells are based on a **controlled increase of oxidative stress within the mitochondria** that activate crucial regulators, including the nuclear factor erythroid 2-related factor 2 (Nrf2), sirtuins, and AMP-activated kinase. These regulators enhance the cells' ability to defend against damage, improve mitochondria function and growth, aid DNA repair, and promote autophagy [331]. Thus, the seemingly counterintuitive oxidative stress triggers a protective response in normal cells and increases their stress tolerance. Furthermore, caloric restriction and KD can bolster **DNA repair mechanisms** in normal tissues by increasing SIRT1 activity and decreasing PI3K-Akt signaling [332].

In contrast to normal cells, cancer cells are often **metabolically inflexible** and heavily reliant on glucose for energy. Numerous studies have demonstrated that many tumor cells exhibit inefficiencies in utilizing ketone bodies, often attributed to mitochondrial dysfunction and inadequate levels of ketolytic enzymes [333]. This metabolic vulnerability can render cancer cells more susceptible to the cytotoxic effects of chemotherapy [222]. However, cancer cells with lower levels of the ketolytic enzymes BDH1 and OXCT1 demonstrated heightened responsiveness to beta-hydroxybutyrate in both in vitro and in vivo settings [334].

Ketone bodies may elevate **cancer cells' reactive oxygen species**

Table 1
Clinical studies focusing on the effects of special diets administered to cancer patients. The 38 recruiting or soon-to-be-active interventional clinical trials involve dietary interventions incorporating fasting-mimicking diets, caloric restriction, and time-restricted feeding.

Status	NCT Number	Phase	Acronym	Conditions	Interventions	Control	#patients	Study Designs
active, not recruiting	NCT03162289	N/A	FIT2	breast and ovarian cancer	intermittent fasting of 72–84 h parallel to the application of the chemotherapy (CT): (36–48 h before and 24 h after CT): 350-400 kcal per day with vegetable juices during the first four cycles of CT.	60–72 h vegan diet with sugar restriction (36–48 h before and 24 h after CT) during the first four cycles of CT.	150	randomized
active, not recruiting	NCT02827370	N/A		breast cancer	behavioral, dietary intervention: during chemotherapy: patients will receive dietary counseling based on the molecular pathways driving their specific breast cancers found through genetic testing	N/A	26	single group assignment
recruiting	NCT03131024	N/A	CREATE	breast cancer	50% caloric restriction for 48 h prior to each anthracycline treatment.	normal diet	56	randomized
recruiting	NCT05113485	N/A		breast cancer	diabetes prevention program-based lifestyle change intervention (DPP): DPP-based lessons on how to lose excess body fat through calorie restriction and increased physical activity.	Highly microbiota-accessible foods (HMAFs) intervention: 6 daily instances of minimally processed, fiber-rich food sources, drawn from all four of the My Plate.gov categories: vegetables, fruits, whole grains, and plant-based protein-rich foods (e.g., legumes, nuts, and seeds).	30	randomized
recruiting	NCT05259410	N/A		breast cancer	8-h time-restricted eating combined with chemotherapy: all food is eaten between 10:00–18:00, water fasting the remaining hours of the day	eat enough calories, standard of care	40	randomized
not yet recruiting	NCT05432856	N/A	IMPACT-Women	breast cancer	time-restricted eating, nutrition education, and sedentary time reduction strategies, plus standard chemotherapy treatment	standard of care and nutritional education	65	randomized
recruiting	NCT04959474	II		breast cancer, early stage (stage 0-3c, triple negative, ductal carcinoma in situ)	reduced calorie intake by 25% for 6–12 weeks while undergoing stereotactic ablative radiation therapy	standard diet while undergoing stereotactic ablative radiation therapy	80	randomized
recruiting	NCT04079270	II		breast cancer, early stage, hormone receptor-positive	algorithm-based arm in which patients will receive personally tailored dietary recommendations, based on their microbiome, and other clinical data, such as blood tests and lifestyle features	Mediterranean-style low-fat diet	200	randomized
recruiting	NCT04298086	II		breast cancer, primary hormone receptor-positive	calorie-restricted plant-based diet plus a structured exercise treatment	nutrition counseling	62	randomized
active, not recruiting	NCT04248998	II	BREAKFAST	breast cancer, triple-negative	chemotherapy plus fasting-mimicking diet: cyclic, 5-day, calorie-restricted (600 KCal on day 1; 300 KCal on days 2–5), low-carbohydrate, low protein diet every three weeks	chemotherapy plus fasting-mimicking diet: cyclic, 5-day, calorie-restricted (600 KCal on day 1; 300 KCal on days 2–5), low-carbohydrate, low protein diet every three weeks plus metformin	30	randomized
recruiting	NCT01802346	II		breast cancer, hormone-resistant prostate cancer, recurrent prostate cancer	low-calorie diet during three days before chemotherapy, 12 weeks of chemotherapy, and 24 h after chemotherapy.	regular diet	120	randomized
not yet recruiting	NCT05023967	II		breast cancer, invasive or ductal carcinoma in situ (DCIS)	time-restricted eating and metformin	usual dietary pattern	120	randomized
active, not recruiting	NCT04243512	pilot, feasibility		cancer survivorship	time-restricted eating for 14 days in a 10-h window	N/A	40	single group assignment
recruiting	NCT04722341	N/A		colorectal cancer	time-restricted eating: 8-h daily eating period, starting 1–3 h after waking up	More than equal to a 12-h daily eating period	300	randomized
recruiting	NCT04753359	N/A	Bridge CRC	colorectal cancer	daily calorie restriction (−500–750 kcal/day) OR a Mediterranean diet	no intervention	192	randomized
not yet recruiting	NCT05384444	N/A	FCRC22	colorectal cancer	perioperative fasting-mimicking diet (FMD) for 5 days. At least 4 cyclic FMDs will be performed after the operation.	regular diet	602	randomized

(*continued on next page*)

Table 1 (*continued*)

Status	NCT Number	Phase	Acronym	Conditions	Interventions	Control	#patients	Study Designs
recruiting	NCT05114798	N/A		elevated CRC risk and prediabetic or insulin resistance	time-restricted eating ad libitum from 12:00 pm - 8:00 pm OR caloric restriction (25%)	normal diet	255	randomized
recruiting	NCT04763902	N/A	TIMESPAN	endometrial cancer	time-restricted eating within an 8 to a 10-h period for eight weeks	no restriction	30	randomized
recruiting	NCT04783467	N/A	TREND	endometrial cancer	time-restricted eating within 8 to 10 h for six weeks	no restriction	15	randomized
recruiting	NCT05082519	II	IDEAL2	leukemia, B-cell acute lymphoblastic	15% daily calory deficit. Fat intake will make up <25%, carbohydrate <55% of daily calories consisting of "low" glycemic load foods (<100/2000 kcal adjusted for daily calories). Protein will make up ≥ 20% of daily calories.	standard of care: one-time education on diet and exercise	240	randomized
recruiting	NCT03709147	II		lung adenocarcinoma, advanced, LKB-1-inactive	standard of care chemoimmunotherapy (platinum salt + pemetrexed + pembrolizumab), with metformin plus cyclic fasting-mimicking diet (FMD)	standard of care chemoimmunotherapy with metformin	64	non-randomized parallel assignment
not yet recruiting	NCT05703997	II	FASTIMMUNE	lung, small cell carcinoma	cyclic, 5-day calorie restriction (plant-based, low-protein, low-carbohydrate diet) with atezolizumab maintenance	N/A	20	single group assignment
recruiting	NCT05376709	N/A		lymphoma, B-cell	short-term calorie reduction: water fast 24 h before (day 0) and during the first day of chemotherapy. On day 2, they will resume normal calorie intake until the day before the next cycle of chemotherapy. Most patients will receive a total of 6–8 cycles over four to six months.	standard care	200	randomized
not yet recruiting	NCT05433805	N/A	MDS-LIME	myelodysplastic syndromes	fasting-mimicking diet (FMD) then physiotherapy: FMD is a diet held monthly for five days with the restriction of calories to <1000 kcal, glucose, and proteins.	physiotherapy, then a fasting-mimicking diet (FMD)	36	randomized
recruiting	NCT04538482	N/A	DINING	neoplasm	calorie-restricted DASH diet (25% fat; 57% carbohydrate; 18% protein; 34 g fiber)	calorie-restricted standard American diet (35% fat; 51% carbohydrate; %15 protein; 14 g fiber)	112	randomized
recruiting	NCT05356182	N/A		neoplasm	immunotherapy plus intervention low-protein diet (10% protein content)	immunotherapy plus a control protein diet (20% protein content)	30	randomized
recruiting	NCT05359848	pilot, feasibility		neoplasm	intermittent caloric restriction and a plant-based diet combined with standard chemotherapy	N/A	30	single group assignment
recruiting	NCT05256888	N/A		neoplasm - fatigue	12 weeks of time-restricted eating (10-h window)	normal diet	30	randomized
recruiting	NCT05126199	N/A	TimeMAP	polycystic ovarian syndrome	time-restricted eating on an 18:6 basis (18 h fasting, 6 h eating window) for 12 weeks	Normal ad libitum **diet**	20	randomized
active, not recruiting	NCT03792282	N/A	TRF-PCOS	polycystic ovary syndrome	time-restricted eating: a diet of 1200-1500 kcal/d and be instructed to eat only during a window of 8 h	general lifestyle counseling	76	randomized
not yet recruiting	NCT05629858	N/A		polycystic ovary syndrome	6-h time-restricted eating: Ad libitum food intake from 1 to 7 pm every day. Fasting from 7 to 1 pm every day (18-h fast). OR calorie restriction: 25% energy restriction every day	usual diet	300	randomized
not yet recruiting	NCT05702905	IV		polycystic ovary syndrome	metformin hydrochloride 500 mg or semaglutide, 1.34 mg/m or semaglutide, 1.34 mg/ml and metformin hydrochloride 500 mg and calorie-restricted diet, physical exercise		75	randomized
recruiting	NCT03679260	II		prostate cancer	carbohydrate-restricted diet: 20 g total carbs/day	normal diet	40	randomized
not yet recruiting	NCT05990426	N/A	FAST	endometrial cancer, ovarian cancer, uterine cancer	alternate day fasting during chemotherapy for a total of 6 weeks	usual diet	30	randomized

Table 2
Clinical trials that are currently recruiting, will be recruiting in the future, or are active but not recruiting participants for various cancer therapies complemented by the ketogenic diet.

Status	NCT Number	Acronym	Conditions	Interventions	Phases	Enrollment
Not yet recruiting	NCT05234502		breast cancer	ketogenic diet program (6%, protein:19%, fat:75%) simultaneously with taxane treatment OR adequate and balanced healthy diet program (45–60%, protein:10–20%, fat:20–35%) with standard neoadjuvant treatment	N/A	56
Recruiting	NCT04469296	MACS	breast cancer	isocaloric ketogenic diet OR protein-restricted diet	N/A	75
Recruiting	NCT03962647		breast cancer, estrogen receptor-positive	dietary supplement: 2-week ketogenic diet in combination with letrozole	Early Phase 1	36
Recruiting	NCT05090358		breast cancer, stage iv, metastatic breast cancer	ketogenic diet in combination with endocrine therapy (fulvestrant) and PI3K inhibition (alpelisib) OR Low Carbohydrate Diet therapy each in combination with SOC endocrine therapy (fulvestrant) and PI3K inhibition (alpelisib) OR Canagliflozin with endocrine therapy (fulvestrant) and PI3K inhibition (alpelisib). Canagliflozin is an inhibitor of SGLT2, the transporter responsible for reabsorbing the majority of glucose	Phase 2	106
Not yet recruiting	NCT06046755	NUTOBREST	breast cancer	very low-calorie ketogenic diet: 600–800 kcal/day, carbohydrates <50 g daily from vegetables and only 10 g of olive oil per day OR balanced hypocaloric diet	N/A	220
Recruiting	NCT05708716		cognitive impairment, hematologic malignancy	modified ketogenic diet using an exogenous ketogenic formula OR behavioral online cognitive training	N/A	80
Active, not recruiting	NCT03285152		endometrial cancer	ketogenic diet with a 3:1 fat to net carbohydrate ratio OR standard diet during the presurgical window	N/A	19
Recruiting	NCT04750941		follicular lymphoma, endometrial cancer	ketogenic diet combined with copanlisib	Phase 2	42
Recruiting	NCT05564949		brain cancer	the classic ketogenic diet for three months with a possible extension depending on their compliance with the diet	N/A	15
Recruiting	NCT05428852		brain metastases, adult	standard of care + ketogenic diet	N/A	24
Not yet recruiting	NCT03955068		brain tumor, childhood, recurrent	strict classic ketogenic diet administered from a 2:1 to 4:1 ratio; 2 to 4 parts of fat to 1 part of a protein	N/A	24
Active, not recruiting	NCT01535911	Ketones	glioblastoma	energy-restricted ketogenic diet	N/A	16
Active, not recruiting	NCT03278249		glioblastoma	modified Atkins ketogenic diet in combination with Temodar and radiation	N/A	11
Recruiting	NCT04730869		glioblastoma	standard treatment plus metabolic therapy program: 6 weeks of chemoradiation - two 5-day fasts during chemoradiation followed by a 5-day fast during each adjuvant chemotherapy cycle, with a time-restricted modified ketogenic diet between fasts. OR 3 weeks of chemoradiation - one 5-day fast during chemoradiation followed by a 5-day fast during each adjuvant chemotherapy cycle, with a time-restricted modified ketogenic diet between fasts.	N/A	22
Active, not recruiting	NCT03451799		glioblastoma	16-week-long ketogenic diet in combination with standard-of-care radiation and standard-of-care temozolomide	Phase 1	21
Recruiting	NCT04691960		glioblastoma	ketogenic diet and metformin	Phase 2	36
Not yet recruiting	NCT05708352		glioblastoma	an intensive, 18-week ketogenic diet	Phase 2	170
Recruiting	NCT05183204		glioblastoma	paxalisib, metformin, and a ketogenic diet	Phase 2	33
Not yet recruiting	NCT05373381		glioma	supplemental high-fat low carbohydrate (sHFLC) + KetoPhyt	N/A	10
Recruiting	NCT04461938	ERGO3	glioma, mixed	one fasting cycle of 72 h prior to biopsy/resection	N/A	30
Recruiting	NCT04231734		mantle cell lymphoma	Prepared ketogenic meals, 3 per day for up to 12 weeks	N/A	8
Recruiting	NCT03950635		melanoma	high-fat, low-carbohydrate (ketogenic) diet or a fiber-rich diet for 6 weeks.	N/A	20
Recruiting	NCT04631445		pancreatic ductal adenocarcinoma, metastatic	ketogenic with triplet chemotherapy or non-ketogenic diet with triplet chemotherapy	N/A	40
Recruiting	NCT03510429		pancreaticobiliary cancer	postoperative nutritional supplement, a newly developed ketogenic drink: NDKD	N/A	40
Not yet recruiting	NCT04175964		polycystic ovary syndrome	ketogenic diet OR caloric diet with metformin OR caloric diet only	N/A	240
Recruiting	NCT05348967		polycystic ovary syndrome	ketogenic diet plus a food supplement containing an association of d-chiro-inositol and alpha-lactalbumin (TECADRIOL)	N/A	44
Recruiting	NCT04228055	CLIPP2	prostate cancer	24-week lifestyle modification intervention: diabetes prevention program and comprehensive lifestyle improvement program with an emphasis on a low carbohydrate and keto diet, physical activity, sleep optimization, and stress management.	N/A	36
Recruiting	NCT03679260		prostate cancer	carbohydrate-restricted diet and phone counseling with a dietitian. After six months, patients will crossover to a non-restricted diet.	Phase 2	40
Recruiting	NCT04316520	CETOREIN	renal cancer, metastatic	ketogenic diet plus standard of care	N/A	20
Not yet recruiting	NCT05119010	KETOREIN	renal cell carcinoma, metastatic	continuous ketogenic diet OR discontinuous ketogenic diet OR beta-hydroxybutyrate (BHB) supplementation	N/A	60
Not yet recruiting	NCT05938322	KOMPARC	rectal cancer	ketogenic eating plan to be followed throughout the treatment period (carbohydrates <30 g/day, 1.2 g–1.5 g protein/kg/day, and	N/A	194

(*continued on next page*)

Table 2 (*continued*)

Status	NCT Number	Acronym	Conditions	Interventions	Phases	Enrollment
Not yet recruiting	NCT05884723		liver metastasis of colon cancer, liver steatoses	lipids >65%) OR Mediterranean diet: carbohydrates 45–55%, protein 15–20% and lipids 30–35% 4-week preoperative very low carbohydrate isocaloric diet consisting of 50 g net daily carbohydrates and 1.5 g/kg protein with the remaining energy needs consisting of primarily mono- and polyunsaturated fats OR 4-week standard diet	N/A	124

(ROS) levels. In glioma-stem-like cells and the CT26+ colon cancer model, KD and β-hydroxybutyrate reduced cell proliferation and induced apoptosis by generating ROS, potentially enhancing the effectiveness of conventional oxidative therapies like radiation and chemotherapy [335]. Moreover, KD in mouse models augmented the **anti-angiogenic** effectiveness of anti-cancer therapies [177]. KD also affects the immune system and inflammatory processes, potentially enhancing the overall response to anti-cancer therapy and contributing to cancer prevention [336]. Combining cancer therapy with KD **reduced the expression of pro-inflammatory factors** like COX-2 and cytokines such as tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and interleukins, including IL-1β, attributed to the inhibition of NF-κB [337]. Additional findings suggest that KD can **ameliorate the immunosuppressive tumor microenvironment**, enhancing the anti-tumor effects of immunotherapies [338].

4. Outlook

4.1. Ongoing clinical trials investigating nutrient and caloric restrictions

We searched the database clinicaltrials.gov for studies adopting caloric restrictions with the keywords"cancer" and"caloric restriction" (Table 1), and we conducted a separate search with the keywords"cancer" and"ketogenic diet" (Table 2) in September of 2023. The search was also extended to synonyms of keywords, including tumor, oncology, and neoplasm. We selected only recruiting, completed, and active but not recruiting studies. Currently, 35 recruiting or soon-to-be-active interventional clinical trials incorporate caloric restriction such as fasting mimicking diets and time-restricted feeding (Table 1) in therapies for glucose-dependent cancers. Most of these clinical trials (12 studies) focus on various molecular types and stages of female breast cancers.

The CREATE trial (NCT03131024) will test 50% caloric restriction for 48 h before each anthracycline treatment cycle in 56 breast cancer patients, while in the phase II NCT04959474 trial, calorie intake will be reduced by 25% for 6–12 weeks while undergoing stereotactic ablative radiation therapy. In the phase II NCT01802346 trial, a low-calorie diet will be combined with chemotherapy. In the randomized BREAKFAST trial (NCT04248998), 30 triple-negative breast cancer patients will receive chemotherapy while on a cyclic fasting-mimicking diet every three weeks, either with or without metformin. The NCT04079270 trial tests a more targeted approach for early-stage, hormone-positive breast cancer patients with personally tailored dietary recommendations based on their microbiome and other clinical data, such as blood tests and lifestyle features. A similar personalized approach is applied in the NCT02827370 trial, in which breast cancer patients undergoing chemotherapy will receive dietary counseling based on tumor-driving molecular pathways identified through genetic testing.

Altogether, out of the 35 trials, four studies focus on colorectal carcinomas, while two prostate cancer, three endometrial cancer, and two lung cancer trials are being planned (Table 1). The NCT03709147 trial represents a novel, genuinely personalized approach considering the disease's genetic background and metabolic vulnerabilities. LKB1-inactive lung adenocarcinomas are particularly aggressive, with poor response to immune checkpoint inhibitors. However, they also show an exquisite vulnerability to energy deprivation, such as glucose reduction or metformin, which inhibits mitochondrial metabolism and reduces the intracellular concentration of ATP. The trial will combine chemo-immunotherapy (platinum with pemetrexed and pembrolizumab) with metformin, plus a low-calorie, low-carbohydrate, low-protein fasting-mimicking diet or metformin alone.

4.2. Future questions

The study of cancer metabolism opened up novel possibilities in cancer therapy. Caloric and nutrient restrictions are being explored in human clinical trials as adjuvants to current cancer treatments. In addition, recent trials started to consider **subtype-specific metabolic vulnerabilities**, such as loss of LKB1 activity in lung cancers, moving toward more targeted approaches (e.g., NCT03709147) (**Tables 1 and 2**). Nevertheless, additional studies are needed to clarify actual metabolic dependencies because cellular metabolic changes and limiting nutrients frequently depend on the circumstances of the investigation [3]. For example, in vitro studies suggest that PDAC cells consume large quantities of glucose, glutamine [114,339], and branched-chain amino acids [340]. Contrarily, in vivo investigation of PDAC cells found depleted arginine in the microenvironment, potentially affecting the activation of T lymphocytes in this highly immunosuppressive cancer type [3].

Moreover, most preclinical studies on fasting involve mouse models, but there are significant **divergences in fasting responses** between mice and humans. Both humans and mice show similar blood levels of the ketone body β-hydroxybutyrate (β-HB) and similarly reduced glucose levels after short-term fast [307]. Nevertheless, comparing the body weight after 24 h and 48 h of fasting, humans lost about 1.3% or 5% of their body weight, respectively, while mice lost 13.5 and 18.8% [307]. Also, short-term (24 h) fasting altered the fatty acid composition of erythrocyte lipid membranes more profoundly in mice compared to humans. In humans, changes in membrane fatty acids correlated very closely with levels of cell-free circulating miRNA, particularly of miR-29b-3p and miR-100-5p, but not in mice, reflecting different regulations between the two species [307]. Furthermore, the basal metabolic rate of the mouse is seven to eight-fold higher than that of humans, and this difference could cause human tumor cells to grow much slower in xenografts due to competition for metabolites [341]. The divergent metabolic rate might be responsible for the low incidence of metastases in xenograft models implanted with human metastatic samples [342].

Lastly, dietary modifications, including caloric restriction and a KD, may inhibit tumor growth and progression, but low patient compliance not only in clinical trials but also in real-life situations still poses a significant challenge [6]. Due to the lack of coherent scientific data, **evidence-based recommendations regarding the optimal diet during cancer and its effect on cancer growth cannot be made**.

In conclusion, the role of dietary factors in tumor initiation and progression is an area of active investigation, and ongoing research continues to shed light on the complex interplay between systemic nutrient content and tumor growth. While the potential for dietary interventions to impact tumor growth has been recognized, our understanding of the underlying mechanisms remains limited. The future will undoubtedly embrace **personalized dietary modifications,** which

must consider each cancer's unique metabolic requirements and signaling pathway activations, especially when combined with pharmacological interventions. Ongoing clinical trials will hopefully provide further clarification on practical and targeted cancer-specific approaches.

Declaration of Competing Interest

None.

Data availability

No data was used for the research described in the article.

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References

[1] D. Hanahan, Robert A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.
[2] S.R. Taylor, J.N. Falcone, L.C. Cantley, M.D. Goncalves, Developing dietary interventions as therapy for cancer, Nat. Rev. Cancer 22 (2022) 452–466.
[3] M.R. Sullivan, L.V. Danai, C.A. Lewis, S.H. Chan, D.Y. Gui, T. Kunchok, E. A. Dennstedt, M.G. Vander Heiden, A. Muir, Quantification of microenvironmental metabolites in murine cancers reveals determinants of tumor nutrient availability, Elife 8 (2019).
[4] D.T. Fisher, J.B. Muhitch, M. Kim, K.C. Doyen, P.N. Bogner, S.S. Evans, J. J. Skitzki, Intraoperative intravital microscopy permits the study of human tumour vessels, Nat. Commun. 7 (2016) 10684.
[5] A. Muir, L.V. Danai, M.G. Vander Heiden, Microenvironmental regulation of cancer cell metabolism: implications for experimental design and translational studies, Dis. Model. Mech. 11 (2018).
[6] N. Kanarek, B. Petrova, D.M. Sabatini, Dietary modifications for enhanced cancer therapy, Nature 579 (2020) 507–517.
[7] K.M. Lemberg, S.S. Gori, T. Tsukamoto, R. Rais, B.S. Slusher, Clinical development of metabolic inhibitors for oncology, J. Clin. Invest. 132 (2022).
[8] J. Kerr, C. Anderson, S.M. Lippman, Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence, the lancet, Oncology 18 (2017) e457–e471.
[9] K.I. Avgerinos, N. Spyrou, C.S. Mantzoros, M. Dalamaga, Obesity and cancer risk: emerging biological mechanisms and perspectives, Metabolism 92 (2019) 121–135.
[10] J.W. Choi, T.N.M. Hua, Impact of lifestyle behaviors on cancer risk and prevention, J. Lifestyle Med. 11 (2021) 1–7.
[11] M. Song, E. Giovannucci, Preventable incidence and mortality of carcinoma associated with lifestyle factors among White adults in the United States, JAMA Oncol. 2 (2016) 1154–1161.
[12] M. Lv, X. Zhu, H. Wang, F. Wang, W. Guan, Roles of caloric restriction, ketogenic diet and intermittent fasting during initiation, progression and metastasis of cancer in animal models: a systematic review and meta-analysis, PLoS One 9 (2014) e115147.
[13] C. Lee, L. Raffaghello, S. Brandhorst, F.M. Safdie, G. Bianchi, A. Martin-Montalvo, V. Pistoia, M. Wei, S. Hwang, A. Merlino, L. Emionite, R. de Cabo, V.D. Longo, Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy, Sci. Transl. Med. 4 (2012), 124ra127.
[14] L. Raffaghello, C. Lee, F.M. Safdie, M. Wei, F. Madia, G. Bianchi, V.D. Longo, Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 8215–8220.
[15] G. Bergers, S.-M. Fendt, The metabolism of cancer cells during metastasis, Nat. Rev. Cancer 21 (2021) 162–180.
[16] R.J. DeBerardinis, N.S. Chandel, Fundamentals of cancer metabolism, Sci. Adv. 2 (2016) e1600200.
[17] P. Dey, A.C. Kimmelman, R.A. DePinho, Metabolic Codependencies in the tumor microenvironment, Cancer Discov. 11 (2021) 1067–1081.
[18] B. Faubert, A. Solmonson, R.J. DeBerardinis, Metabolic reprogramming and cancer progression, Science (New York, N.Y.) (2020) 368.
[19] G. Hoxhaj, B.D. Manning, The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism, Nat. Rev. Cancer 20 (2020) 74–88.
[20] I. Martínez-Reyes, N.S. Chandel, Cancer metabolism: looking forward, Nat. Rev. Cancer 21 (2021) 669–680.
[21] M. Tajan, K.H. Vousden, Dietary approaches to Cancer therapy, Cancer Cell 37 (2020) 767–785.
[22] O. Warburg, The metabolism of carcinoma Cells1, J. Cancer Res. 9 (1925) 148–163.
[23] M.V. Liberti, J.W. Locasale, The Warburg effect: how does it benefit Cancer cells? Trends Biochem. Sci. 41 (2016) 211–218.
[24] N.N. Pavlova, C.B. Thompson, The emerging hallmarks of cancer metabolism, Cell Metab. 23 (2016) 27–47.
[25] M.G. Vander Heiden, L.C. Cantley, C.B. Thompson, Understanding the Warburg effect: the metabolic requirements of cell proliferation, Science (New York, N.Y.) 324 (2009) 1029–1033.
[26] C. Schiliro, B.L. Firestein, Mechanisms of metabolic reprogramming in cancer cells supporting enhanced growth and proliferation, Cells 10 (2021).
[27] A.A. Shestov, X. Liu, Z. Ser, A.A. Cluntun, Y.P. Hung, L. Huang, D. Kim, A. Le, G. Yellen, J.G. Albeck, J.W. Locasale, Quantitative determinants of aerobic glycolysis identify flux through the enzyme GAPDH as a limiting step, eLife 3 (2014) e03342.
[28] R.J. DeBerardinis, N.S. Chandel, We need to talk about the Warburg effect, Nat. Metab. 2 (2020) 127–129.
[29] S. Hui, J.M. Ghergurovich, R.J. Morscher, C. Jang, X. Teng, W. Lu, L.A. Esparza, T. Reya, Z. Le, J. Yanxiang Guo, E. White, J.D. Rabinowitz, Glucose feeds the TCA cycle via circulating lactate, Nature 551 (2017) 115–118.
[30] J.D. Rabinowitz, S. Enerbäck, Lactate: the ugly duckling of energy metabolism, Nat. Metab. 2 (2020) 566–571.
[31] S.R. Rosario, M.D. Long, H.C. Affronti, A.M. Rowsam, K.H. Eng, D.J. Smiraglia, Pan-cancer analysis of transcriptional metabolic dysregulation using the Cancer genome atlas, Nat. Commun. 9 (2018) 5330.
[32] P.H. Chen, L. Cai, K. Huffman, C. Yang, J. Kim, B. Faubert, L. Boroughs, B. Ko, J. Sudderth, E.A. McMillan, L. Girard, D. Chen, M. Peyton, M.D. Shields, B. Yao, D.S. Shames, H.S. Kim, B. Timmons, I. Sekine, R. Britt, S. Weber, L.A. Byers, J. V. Heymach, J. Chen, M.A. White, J.D. Minna, G. Xiao, R.J. DeBerardinis, Metabolic diversity in human non-small cell lung cancer cells, Mol. Cell 76 (2019) 838–851.e835.
[33] S. Bose, C. Zhang, A. Le, Glucose metabolism in cancer: the Warburg effect and beyond, in: A. Le (Ed.), The Heterogeneity of Cancer Metabolism, Springer International Publishing, Place Published, 2021, pp. 3–15.
[34] F. Camelo, A. Le, The intricate metabolism of pancreatic cancers, Adv. Exp. Med. Biol. 1063 (2018) 73–81.
[35] O. Warburg, On the origin of cancer cells, Science (New York, N.Y.) 123 (1956) 309–314.
[36] L.A.J. O'Neill, R.J. Kishton, J. Rathmell, A guide to immunometabolism for immunologists, Nat. Rev. Immunol. 16 (2016) 553–565.
[37] K.G. de la Cruz-López, L.J. Castro-Muñoz, D.O. Reyes-Hernández, A. García-Carrancá, J. Manzo-Merino, Lactate in the regulation of tumor microenvironment and therapeutic approaches, Front. Oncol. 9 (2019) 1143.
[38] Z. Li, Q. Wang, X. Huang, M. Yang, S. Zhou, Z. Li, Z. Fang, Y. Tang, Q. Chen, H. Hou, L. Li, F. Fei, Q. Wang, Y. Wu, A. Gong, Lactate in the tumor microenvironment: a rising star for targeted tumor therapy, Front. Nutr. 10 (2023).
[39] B. Faubert, K.Y. Li, L. Cai, C.T. Hensley, J. Kim, L.G. Zacharias, C. Yang, Q.N. Do, S. Doucette, D. Burguete, H. Li, G. Huet, Q. Yuan, T. Wigal, Y. Butt, M. Ni, J. Torrealba, D. Oliver, R.E. Lenkinski, C.R. Malloy, J.W. Wachsmann, J.D. Young, K. Kernstine, R.J. DeBerardinis, Lactate metabolism in human lung tumors, Cell 171 (2017), 358–371.e359.
[40] C. Corbet, O. Feron, Tumour acidosis: from the passenger to the driver's seat, Nat. Rev. Cancer 17 (2017) 577–593.
[41] F. Hirschhaeuser, U.G. Sattler, W. Mueller-Klieser, Lactate: a metabolic key player in cancer, Cancer Res. 71 (2011) 6921–6925.
[42] F. Végran, R. Boidot, C. Michiels, P. Sonveaux, O. Feron, Lactate influx through the endothelial cell monocarboxylate transporter MCT1 supports an NF-κB/IL-8 pathway that drives tumor angiogenesis, Cancer Res. 71 (2011) 2550–2560.
[43] V.L. Payen, E. Mina, V.F. Van Hée, P.E. Porporato, P. Sonveaux, Monocarboxylate transporters in cancer, Molecul. Metabol. 33 (2020) 48–66.
[44] J.M. Curry, M. Tuluc, D. Whitaker-Menezes, J.A. Ames, A. Anantharaman, A. Butera, B. Leiby, D.M. Cognetti, F. Sotgia, M.P. Lisanti, U.E. Martinez-Outschoorn, Cancer metabolism, stemness and tumor recurrence: MCT1 and MCT4 are functional biomarkers of metabolic symbiosis in head and neck cancer, Cell Cycle (Georgetown, Tex.) 12 (2013) 1371–1384.
[45] J. Fang, Q.J. Quinones, T.L. Holman, M.J. Morowitz, Q. Wang, H. Zhao, F. Sivo, J. M. Maris, M.L. Wahl, The H+-linked monocarboxylate transporter (MCT1/SLC16A1): a potential therapeutic target for high-risk neuroblastoma, Mol. Pharmacol. 70 (2006) 2108–2115.
[46] Y. Kim, J.W. Choi, J.H. Lee, Y.S. Kim, Expression of lactate/H^+ symporters MCT1 and MCT4 and their chaperone CD147 predicts tumor progression in clear cell renal cell carcinoma: immunohistochemical and the Cancer genome atlas data analyses, Hum. Pathol. 46 (2015) 104–112.
[47] J. Pérez-Escuredo, R.K. Dadhich, S. Dhup, A. Cacace, V.F. Van Hée, C.J. De Saedeleer, M. Sboarina, F. Rodriguez, M.J. Fontenille, L. Brisson, P.E. Porporato, P. Sonveaux, Lactate promotes glutamine uptake and metabolism in oxidative cancer cells, Cell Cycle (Georgetown, Tex.) 15 (2016) 72–83.
[48] G. Zhang, Y. Zhang, D. Dong, F. Wang, X. Ma, F. Guan, L. Sun, MCT1 regulates aggressive and metabolic phenotypes in bladder cancer, J. Cancer 9 (2018) 2492–2501.
[49] Y. Feng, Y. Xiong, T. Qiao, X. Li, L. Jia, Y. Han, Lactate dehydrogenase a: a key player in carcinogenesis and potential target in cancer therapy, Cancer Med. 7 (2018) 6124–6136.

[50] C.A. Lyssiotis, A.C. Kimmelman, Metabolic interactions in the tumor microenvironment, Trends Cell Biol. 27 (2017) 863–875.
[51] T. Shan, S. Chen, X. Chen, T. Wu, Y. Yang, S. Li, J. Ma, J. Zhao, W. Lin, W. Li, X. Cui, Y. Kang, M2-TAM subsets altered by lactic acid promote T-cell apoptosis through the PD-L1/PD-1 pathway, Oncol. Rep. 44 (2020) 1885–1894.
[52] J. Feng, H. Yang, Y. Zhang, H. Wei, Z. Zhu, B. Zhu, M. Yang, W. Cao, L. Wang, Z. Wu, Tumor cell-derived lactate induces TAZ-dependent upregulation of PD-L1 through GPR81 in human lung cancer cells, Oncogene 36 (2017) 5829–5839.
[53] P. Ranganathan, A. Shanmugam, D. Swafford, A. Suryawanshi, P. Bhattacharjee, M.S. Hussein, P.A. Koni, P.D. Prasad, Z.B. Kurago, M. Thangaraju, V. Ganapathy, S. Manicassamy, GPR81, a cell-surface receptor for lactate, regulates intestinal homeostasis and protects mice from experimental colitis, J. Immunol. (Baltimore, Md.: 1950) 200 (2018) 1781–1789.
[54] C. Damiani, R. Colombo, D. Gaglio, F. Mastroianni, D. Pescini, H.V. Westerhoff, G. Mauri, M. Vanoni, L. Alberghina, A metabolic core model elucidates how enhanced utilization of glucose and glutamine, with enhanced glutamine-dependent lactate production, promotes cancer cell growth: the WarburQ effect, PLoS Comput. Biol. 13 (2017) e1005758.
[55] R.G. Jones, C.B. Thompson, Tumor suppressors and cell metabolism: a recipe for cancer growth, Genes Dev. 23 (2009) 537–548.
[56] A.J. Levine, A.M. Puzio-Kuter, The control of the metabolic switch in cancers by oncogenes and tumor suppressor genes, Science (New York, N.Y.) 330 (2010) 1340–1344.
[57] S. Rodríguez-Enríquez, A. Marín-Hernández, J.C. Gallardo-Pérez, R. Moreno-Sánchez, Kinetics of transport and phosphorylation of glucose in cancer cells, J. Cell. Physiol. 221 (2009) 552–559.
[58] Q. Sun, X. Chen, J. Ma, H. Peng, F. Wang, X. Zha, Y. Wang, Y. Jing, H. Yang, R. Chen, L. Chang, Y. Zhang, J. Goto, H. Onda, T. Chen, M.R. Wang, Y. Lu, H. You, D. Kwiatkowski, H. Zhang, Mammalian target of rapamycin up-regulation of pyruvate kinase isoenzyme type M2 is critical for aerobic glycolysis and tumor growth, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 4129–4134.
[59] Q. Sun, S. Li, Y. Wang, H. Peng, X. Zhang, Y. Zheng, C. Li, L. Li, R. Chen, X. Chen, W. Bai, X. Jiang, L. Liu, F. Wei, B. Wang, Y. Zhang, H. Li, X. Ren, H. Zhang, Phosphoglyceric acid mutase-1 contributes to oncogenic mTOR-mediated tumor growth and confers non-small cell lung cancer patients with poor prognosis, Cell Death Differ. 25 (2018) 1160–1173.
[60] T.H. Witney, M.L. James, B. Shen, E. Chang, C. Pohling, N. Arksey, A. Hoehne, A. Shuhendler, J.H. Park, D. Bodapati, J. Weber, G. Gowrishankar, J. Rao, F. T. Chin, S.S. Gambhir, PET imaging of tumor glycolysis downstream of hexokinase through noninvasive measurement of pyruvate kinase M2, Sci. Transl. Med. 7 (2015), 310ra169.
[61] S. Fukuda, H. Miyata, Y. Miyazaki, T. Makino, T. Takahashi, Y. Kurokawa, M. Yamasaki, K. Nakajima, S. Takiguchi, M. Mori, Y. Doki, Pyruvate kinase M2 modulates esophageal squamous cell carcinoma chemotherapy response by regulating the pentose phosphate pathway, Ann. Surg. Oncol. 22 (Suppl. 3) (2015). S1461–1468.
[62] S. Panchabhai, I. Schlam, S. Sebastian, R. Fonseca, PKM2 and other key regulators of Warburg effect positively correlate with CD147 (EMMPRIN) gene expression and predict survival in multiple myeloma, Leukemia 31 (2017) 991–994.
[63] N. Wong, J. Yan, D. Ojo, J. De Melo, J.C. Cutz, D. Tang, Changes in PKM2 associate with prostate cancer progression, Cancer Investig. 32 (2014) 330–338.
[64] D. Hasan, E. Gamen, N. Abu Tarboush, Y. Ismail, O. Pak, B. Azab, PKM2 and HIF-1α regulation in prostate cancer cell lines, PLoS One 13 (2018) e0203745.
[65] G. Dong, Q. Mao, W. Xia, Y. Xu, J. Wang, L. Xu, F. Jiang, PKM2 and cancer: the function of PKM2 beyond glycolysis (review), Oncol. Lett. 11 (2016) 1980–1986.
[66] K. Zahra, T. Dey, S.P. Ashish, U. Pandey Mishra, Pyruvate kinase M2 and cancer: the role of PKM2 in promoting tumorigenesis, Front. Oncol. 10 (2020).
[67] M.G. Vander Heiden, J.W. Locasale, K.D. Swanson, H. Sharfi, G.J. Heffron, D. Amador-Noguez, H.R. Christofk, G. Wagner, J.D. Rabinowitz, J.M. Asara, L. C. Cantley, Evidence for an alternative glycolytic pathway in rapidly proliferating cells, Science (New York, N.Y.) 329 (2010) 1492–1499.
[68] F. Sharif, A. Rasul, A. Ashraf, G. Hussain, T. Younis, I. Sarfraz, M.A. Chaudhry, S. A. Bukhari, X.Y. Ji, Z. Selamoglu, M. Ali, Phosphoglycerate mutase 1 in cancer: a promising target for diagnosis and therapy, IUBMB Life 71 (2019) 1418–1427.
[69] G.-J. Yang, F. Tao, H.-J. Zhong, C. Yang, J. Chen, Targeting PGAM1 in cancer: an emerging therapeutic opportunity, Eur. J. Med. Chem. 244 (2022) 114798.
[70] C.A. Martinez, C. Scafoglio, Heterogeneity of glucose transport in lung Cancer, Biomolecules 10 (2020).
[71] S.P. Mathupala, A. Rempel, P.L. Pedersen, Glucose catabolism in cancer cells: identification and characterization of a marked activation response of the type II hexokinase gene to hypoxic conditions, J. Biol. Chem. 276 (2001) 43407–43412.
[72] F. Schwartzenberg-Bar-Yoseph, M. Armoni, E. Karnieli, The tumor suppressor p53 down-regulates glucose transporters GLUT1 and GLUT4 gene expression, Cancer Res. 64 (2004) 2627–2633.
[73] J. Choi, W.H. Jung, J.S. Koo, Metabolism-related proteins are differentially expressed according to the molecular subtype of invasive breast cancer defined by surrogate immunohistochemistry, Pathobiol.: J. Immunopathol. Mol. Cell. Biol. 80 (2013) 41–52.
[74] M. Pliszka, L. Szablewski, Glucose transporters as a target for anticancer therapy, Cancers 13 (2021).
[75] J. Wang, C. Ye, C. Chen, H. Xiong, B. Xie, J. Zhou, Y. Chen, S. Zheng, L. Wang, Glucose transporter GLUT1 expression and clinical outcome in solid tumors: a systematic review and meta-analysis, Oncotarget 8 (2017) 16875–16886.
[76] A. Zambrano, M. Molt, E. Uribe, M. Salas, Glut 1 in cancer cells and the inhibitory action of resveratrol as a potential therapeutic strategy, Int. J. Mol. Sci. 20 (2019) 3374.
[77] Z.E. Stine, Z.T. Schug, J.M. Salvino, C.V. Dang, Targeting cancer metabolism in the era of precision oncology, Nat. Rev. Drug Discov. 21 (2022) 141–162.
[78] Y. Zhang, Q. Li, Z. Huang, B. Li, E.C. Nice, C. Huang, L. Wei, B. Zou, Targeting glucose metabolism enzymes in cancer treatment: current and emerging strategies, Cancers 14 (2022).
[79] C. Jang, S. Hui, W. Lu, A.J. Cowan, R.J. Morscher, G. Lee, W. Liu, G.J. Tesz, M. J. Birnbaum, J.D. Rabinowitz, The small intestine converts dietary fructose into glucose and organic acids, Cell Metab. 27 (2018) 351–361.e353.
[80] B.H. Mai, L.J. Yan, The negative and detrimental effects of high fructose on the liver, with special reference to metabolic disorders, Diabetes, Metabol. Syndr. Obesity: Target Therpy 12 (2019) 821–826.
[81] T. Nakagawa, K.R. Tuttle, R.A. Short, R.J. Johnson, Hypothesis: fructose-induced hyperuricemia as a causal mechanism for the epidemic of the metabolic syndrome, nature clinical practice, Nephrology 1 (2005) 80–86.
[82] T. Nakagawa, M.A. Lanaspa, I.S. Millan, M. Fini, C.J. Rivard, L.G. Sanchez-Lozada, A. Andres-Hernando, D.R. Tolan, R.J. Johnson, Fructose contributes to the Warburg effect for cancer growth, Cancer & Metabol. 8 (2020) 16.
[83] T. Nakagawa, R.J. Johnson, A. Andres-Hernando, C. Roncal-Jimenez, L. G. Sanchez-Lozada, D.R. Tolan, M.A. Lanaspa, Fructose production and metabolism in the kidney, J. Am. Soc. Nephrol.: JASN 31 (2020) 898–906.
[84] E. Russo, G. Leoncini, P. Esposito, G. Garibotto, R. Pontremoli, F. Viazzi, Fructose and uric acid: major mediators of cardiovascular disease risk starting at pediatric age, Int. J. Mol. Sci. 21 (2020).
[85] D.V. Carreño, N.B. Corro, J.F. Cerda-Infante, C.E. Echeverría, C.A. Asencio-Barría, V.A. Torres-Estay, G.A. Mayorga-Weber, P.A. Rojas, L.P. Véliz, P.A. Cisternas, V. P. Montecinos, I.F. San Francisco, M.A. Varas-Godoy, P.C. Sotomayor, M. A. Castro, F.J. Nualart, N.C. Inestrosa, A.S. Godoy, Dietary fructose promotes prostate cancer growth, Cancer Res. 81 (2021) 2824–2832.
[86] V. Douard, R.P. Ferraris, The role of fructose transporters in diseases linked to excessive fructose intake, J. Physiol. 591 (2013) 401–414.
[87] W.L. Chen, Y.Y. Wang, A. Zhao, L. Xia, G. Xie, M. Su, L. Zhao, J. Liu, C. Qu, R. Wei, C. Rajani, Y. Ni, Z. Cheng, Z. Chen, S.J. Chen, W. Jia, Enhanced fructose utilization mediated by SLC2A5 is a unique metabolic feature of acute myeloid leukemia with therapeutic potential, Cancer Cell 30 (2016) 779–791.
[88] S.R. Taylor, S. Ramsamooj, R.J. Liang, A. Katti, R. Pozovskiy, N. Vasan, S.-K. Hwang, N. Nahiyaan, N.J. Francoeur, E.M. Schatoff, J.L. Johnson, M.A. Shah, A.J. Dannenberg, R.P. Sebra, L.E. Dow, L.C. Cantley, K.Y. Rhee, M.D. Goncalves, Dietary fructose improves intestinal cell survival and nutrient absorption, Nature 597 (2021) 263–267.
[89] M.D. Goncalves, C. Lu, J. Tutnauer, T.E. Hartman, S.K. Hwang, C.J. Murphy, C. Pauli, R. Morris, S. Taylor, K. Bosch, S. Yang, Y. Wang, J. Van Riper, H. C. Lekaye, J. Roper, Y. Kim, Q. Chen, S.S. Gross, K.Y. Rhee, L.C. Cantley, J. Yun, High-fructose corn syrup enhances intestinal tumor growth in mice, Science (New York, N.Y.) 363 (2019) 1345–1349.
[90] P. Bu, K.Y. Chen, K. Xiang, C. Johnson, S.B. Crown, N. Rakhilin, Y. Ai, L. Wang, R. Xi, I. Astapova, Y. Han, J. Li, B.B. Barth, M. Lu, Z. Gao, R. Mines, L. Zhang, M. Herman, D. Hsu, G.F. Zhang, X. Shen, Aldolase B-mediated fructose metabolism drives metabolic reprogramming of colon cancer liver metastasis, Cell Metab. 27 (2018) 1249–1262.e1244.
[91] X. Gao, S.M. Sanderson, Z. Dai, M.A. Reid, D.E. Cooper, M. Lu, J.P. Richie, A. Ciccarella, A. Calcagnotto, P.G. Mikhael, S.J. Mentch, J. Liu, G. Ables, D. G. Kirsch, D.S. Hsu, S.N. Nichenametla, J.W. Locasale, Dietary methionine influences therapy in mouse cancer models and alters human metabolism, Nature 572 (2019) 397–401.
[92] S. Kamata, J. Yamamoto, K. Kamijo, T. Ochiai, T. Morita, Y. Yoshitomi, Y. Hagiya, M. Kubota, R. Ohkubo, M. Kawaguchi, T. Himi, T. Kasahara, I. Ishii, Dietary deprivation of each essential amino acid induces differential systemic adaptive responses in mice, Mol. Nutr. Food Res. 58 (2014) 1309–1321.
[93] L. Yang, S. Venneti, D. Nagrath, Glutaminolysis: a Hallmark of cancer metabolism, Annu. Rev. Biomed. Eng. 19 (2017) 163–194.
[94] T.N. Seyfried, G. Arismendi-Morillo, P. Mukherjee, C. Chinopoulos, On the origin of ATP synthesis in cancer, iScience 23 (2020) 101761.
[95] G. Arismendi-Morillo, A. Castellano-Ramírez, T.N. Seyfried, Ultrastructural characterization of the mitochondria-associated membranes abnormalities in human astrocytomas: functional and therapeutics implications, Ultrastruct. Pathol. 41 (2017) 234–244.
[96] Q. Chen, K. Kirk, Y.I. Shurubor, D. Zhao, A.J. Arreguin, I. Shahi, F. Valsecchi, G. Primiano, E.L. Calder, V. Carelli, T.T. Denton, M.F. Beal, S.S. Gross, G. Manfredi, M. D'Aurelio, Rewiring of glutamine metabolism is a bioenergetic adaptation of human cells with mitochondrial DNA mutations, Cell Metab. 27 (2018) 1007–1025.e1005.
[97] M. van Geldermalsen, Q. Wang, R. Nagarajah, A.D. Marshall, A. Thoeng, D. Gao, W. Ritchie, Y. Feng, C.G. Bailey, N. Deng, K. Harvey, J.M. Beith, C.I. Selinger, S. A. O'Toole, J.E. Rasko, J. Holst, ASCT2/SLC1A5 controls glutamine uptake and tumour growth in triple-negative basal-like breast cancer, Oncogene 35 (2016) 3201–3208.
[98] R.A. Saxton, D.M. Sabatini, mTOR signaling in growth, metabolism, and disease, Cell 168 (2017) 960–976.
[99] F. Nazio, F. Strappazzon, M. Antonioli, P. Bielli, V. Cianfanelli, M. Bordi, C. Gretzmeier, J. Dengjel, M. Piacentini, G.M. Fimia, F. Cecconi, mTOR inhibits autophagy by controlling ULK1 ubiquitylation, self-association and function through AMBRA1 and TRAF6, Nat. Cell Biol. 15 (2013) 406–416.
[100] M. Dewaele, H. Maes, P. Agostinis, ROS-mediated mechanisms of autophagy stimulation and their relevance in cancer therapy, Autophagy 6 (2010) 838–854.

[101] Y. Angin, C. Beauloye, S. Horman, L. Bertrand, Regulation of carbohydrate metabolism, Lipid Metabol. Protein Metabol.AMPK 107 (2016) (2012) 23–43. Experientia supplementum.
[102] C.K. Keerthana, T.P. Rayginia, S.C. Shifana, N.P. Anto, K. Kalimuthu, N. Isakov, R. J. Anto, The role of AMPK in cancer metabolism and its impact on the immunomodulation of the tumor microenvironment, Front. Immunol. 14 (2023) 1114582.
[103] V. Penugurti, S.S. Khumukcham, C. Padala, A. Dwivedi, K.R. Kamireddy, S. Mukta, T. Bhopal, B. Manavathi, HPIP protooncogene differentially regulates metabolic adaptation and cell fate in breast cancer cells under glucose stress via AMPK and RNF2 dependent pathways, Cancer Lett. 518 (2021) 243–255.
[104] Y.K. Choi, K.G. Park, Targeting glutamine metabolism for cancer treatment, Biomol. Ther. 26 (2018) 19–28.
[105] Y.-A. Shen, C.-L. Chen, Y.-H. Huang, E.E. Evans, C.-C. Cheng, Y.-J. Chuang, C. Zhang, A. Le, Inhibition of glutaminolysis in combination with other therapies to improve cancer treatment, Curr. Opin. Chem. Biol. 62 (2021) 64–81.
[106] J. Márquez, F.J. Alonso, J.M. Matés, J.A. Segura, M. Martín-Rufián, J.A. Campos-Sandoval, Glutamine addiction in gliomas, Neurochem. Res. 42 (2017) 1735–1746.
[107] A. Mohamed, X. Deng, F.R. Khuri, T.K. Owonikoko, Altered glutamine metabolism and therapeutic opportunities for lung cancer, Clin. Lung Cancer 15 (2014) 7–15.
[108] D.R. Wise, C.B. Thompson, Glutamine addiction: a new therapeutic target in cancer, Trends Biochem. Sci. 35 (2010) 427–433.
[109] R.J. DeBerardinis, A. Mancuso, E. Daikhin, I. Nissim, M. Yudkoff, S. Wehrli, C. B. Thompson, Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis, Proc. Natl. Acad. Sci. 104 (2007) 19345–19350.
[110] P. Mukherjee, Z.M. Augur, M. Li, C. Hill, B. Greenwood, M.A. Domin, G. Kondakci, N.R. Narain, M.A. Kiebish, R.T. Bronson, G. Arismendi-Morillo, C. Chinopoulos, T.N. Seyfried, Therapeutic benefit of combining calorie-restricted ketogenic diet and glutamine targeting in late-stage experimental glioblastoma, Commun. Biol. 2 (2019) 200.
[111] H. Yan, D.W. Parsons, G. Jin, R. McLendon, B.A. Rasheed, W. Yuan, I. Kos, I. Batinic-Haberle, S. Jones, G.J. Riggins, H. Friedman, A. Friedman, D. Reardon, J. Herndon, K.W. Kinzler, V.E. Velculescu, B. Vogelstein, D.D. Bigner, IDH1 and IDH2 mutations in gliomas, N. Engl. J. Med. 360 (2009) 765–773.
[112] J. Bi, S. Chowdhry, S. Wu, W. Zhang, K. Masui, P.S. Mischel, Altered cellular metabolism in gliomas — an emerging landscape of actionable co-dependency targets, Nat. Rev. Cancer 20 (2020) 57–70.
[113] Y.D. Bhutia, E. Babu, S. Ramachandran, V. Ganapathy, Amino acid transporters in cancer and their relevance to "glutamine addiction": novel targets for the design of a new class of anticancer drugs, Cancer Res. 75 (2015) 1782–1788.
[114] J. Son, C.A. Lyssiotis, H. Ying, X. Wang, S. Hua, M. Ligorio, R.M. Perera, C. R. Ferrone, E. Mullarky, N. Shyh-Chang, Y.A. Kang, J.B. Fleming, N. Bardeesy, J. M. Asara, M.C. Haigis, R.A. DePinho, L.C. Cantley, A.C. Kimmelman, Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway, Nature 496 (2013) 101–105.
[115] X. Hu, H.M. Stern, L. Ge, C. O'Brien, L. Haydu, C.D. Honchell, P.M. Haverty, B. A. Peters, T.D. Wu, L.C. Amler, J. Chant, D. Stokoe, M.R. Lackner, G. Cavet, Genetic alterations and oncogenic pathways associated with breast cancer subtypes, Molecul. Cancer Res.: MCR 7 (2009) 511–522.
[116] M. Saqcena, S. Mukhopadhyay, C. Hosny, A. Alhamed, A. Chatterjee, D.A. Foster, Blocking anaplerotic entry of glutamine into the TCA cycle sensitizes K-Ras mutant cancer cells to cytotoxic drugs, Oncogene 34 (2015) 2672–2680.
[117] M. Yuneva, N. Zamboni, P. Oefner, R. Sachidanandam, Y. Lazebnik, Deficiency in glutamine but not glucose induces MYC-dependent apoptosis in human cells, J. Cell Biol. 178 (2007) 93–105.
[118] V. Tambay, V.A. Raymond, M. Bilodeau, M.Y.C. Rules, Leading glutamine metabolism toward a distinct cancer cell phenotype, Cancers 13 (2021).
[119] R. Rais, K.M. Lemberg, L. Tenora, M.L. Arwood, A. Pal, J. Alt, Y. Wu, J. Lam, J.M. H. Aguilar, L. Zhao, D.E. Peters, C. Tallon, R. Pandey, A.G. Thomas, R.P. Dash, T. Seiwert, P. Majer, R.D. Leone, J.D. Powell, B.S. Slusher, Discovery of DRP-104, a tumor-targeted metabolic inhibitor prodrug, Sci. Adv. 8 (2022) eabq5925.
[120] A. Galan-Cobo, P. Sitthideatphaiboon, X. Qu, A. Poteete, M.A. Pisegna, P. Tong, P.-H. Chen, L.K. Boroughs, M.L.M. Rodriguez, W. Zhang, F. Parlati, J. Wang, V. Gandhi, F. Skoulidis, R.J. DeBerardinis, J.D. Minna, J.V. Heymach, LKB1 and KEAP1/NRF2 pathways cooperatively promote metabolic reprogramming with enhanced glutamine dependence in KRAS-mutant lung adenocarcinoma, Cancer Res. 79 (2019) 3251–3267.
[121] A. Halama, K. Suhre, Advancing cancer treatment by targeting glutamine metabolism—a roadmap, Cancers 14 (2022) 553.
[122] J.M. Matés, J.A. Campos-Sandoval, J. Márquez, Glutaminase isoenzymes in the metabolic therapy of cancer, Biochim. Biophys. Acta Rev. Cancer 2018 (1870) 158–164.
[123] J.M. Matés, F.J. Di Paola, J.A. Campos-Sandoval, S. Mazurek, J. Márquez, Therapeutic targeting of glutaminolysis as an essential strategy to combat cancer, Semin. Cell Dev. Biol. 98 (2020) 34–43.
[124] R. Pieters, S.P. Hunger, J. Boos, C. Rizzari, L. Silverman, A. Baruchel, N. Goekbuget, M. Schrappe, C.H. Pui, L-asparaginase treatment in acute lymphoblastic leukemia: a focus on Erwinia asparaginase, Cancer 117 (2011) 238–249.
[125] J. Márquez, F. Sánchez-Jiménez, M.A. Medina, A.R. Quesada, I. Núñez de Castro, Nitrogen metabolism in tumor bearing mice, Arch. Biochem. Biophys. 268 (1989) 667–675.
[126] R. Mishra, S. Haldar, V. Placencio, A. Madhav, K. Rohena-Rivera, P. Agarwal, F. Duong, B. Angara, M. Tripathi, Z. Liu, R.A. Gottlieb, S. Wagner, E.M. Posadas, N.A. Bhowmick, Stromal epigenetic alterations drive metabolic and neuroendocrine prostate cancer reprogramming, J. Clin. Invest. 128 (2018) 4472–4484.
[127] L. Yang, A. Achreja, T.L. Yeung, L.S. Mangala, D. Jiang, C. Han, J. Baddour, J. C. Marini, J. Ni, R. Nakahara, S. Wahlig, L. Chiba, S.H. Kim, J. Morse, S. Pradeep, A.S. Nagaraja, M. Haemmerle, N. Kyunghee, M. Derichsweiler, T. Plackemeier, I. Mercado-Uribe, G. Lopez-Berestein, T. Moss, P.T. Ram, J. Liu, X. Lu, S.C. Mok, A.K. Sood, D. Nagrath, Targeting stromal glutamine Synthetase in tumors disrupts tumor microenvironment-regulated cancer cell growth, Cell Metab. 24 (2016) 685–700.
[128] M.K.L. Fung, G.C.-F. Chan, Drug-induced amino acid deprivation as strategy for cancer therapy, J. Hematol. Oncol. 10 (2017) 144.
[129] J. Jin, J.-K. Byun, Y.-K. Choi, K.-G. Park, Targeting glutamine metabolism as a therapeutic strategy for cancer, Exp. Mol. Med. 55 (2023) 706–715.
[130] F. Lengauer, F. Geisslinger, A. Gabriel, K. von Schwarzenberg, A.M. Vollmar, K. Bartel, A metabolic shift toward glycolysis enables cancer cells to maintain survival upon concomitant glutamine deprivation and V-ATPase inhibition, Front. Nutr. 10 (2023).
[131] L. Sun, Y. Yin, L.H. Clark, W. Sun, S.A. Sullivan, A.Q. Tran, J. Han, L. Zhang, H. Guo, E. Madugu, T. Pan, A.L. Jackson, J. Kilgore, H.M. Jones, T.P. Gilliam, C. Zhou, V.L. Bae-Jump, Dual inhibition of glycolysis and glutaminolysis as a therapeutic strategy in the treatment of ovarian cancer, Oncotarget 8 (2017) 63551–63561.
[132] A. Elgogary, Q. Xu, B. Poore, J. Alt, S.C. Zimmermann, L. Zhao, J. Fu, B. Chen, S. Xia, Y. Liu, M. Neisser, C. Nguyen, R. Lee, J.K. Park, J. Reyes, T. Hartung, C. Rojas, R. Rais, T. Tsukamoto, G.L. Semenza, J. Hanes, B.S. Slusher, A. Le, Combination therapy with BPTES nanoparticles and metformin targets the metabolic heterogeneity of pancreatic cancer, Proc. Natl. Acad. Sci. 113 (2016) E5328–E5336.
[133] H. Liu, W. Zhang, K. Wang, X. Wang, F. Yin, C. Li, C. Wang, B. Zhao, C. Zhong, J. Zhang, F. Peng, Y. Bi, C. Shen, X. Hou, D. Zhang, Y. Liu, J. Ai, S. Zhao, Methionine and cystine double deprivation stress suppresses glioma proliferation via inducing ROS/autophagy, Toxicol. Lett. 232 (2015) 349–355.
[134] R. Sinha, T.K. Cooper, C.J. Rogers, I. Sinha, W.J. Turbitt, A. Calcagnotto, C. E. Perrone, J.P. Richie Jr., Dietary methionine restriction inhibits prostatic intraepithelial neoplasia in TRAMP mice, Prostate 74 (2014) 1663–1673.
[135] I.R. Miousse, J. Tobacyk, C.M. Quick, A. Jamshidi-Parsian, C.M. Skinner, R. Kore, S.B. Melnyk, K.R. Kutanzi, F. Xia, R.J. Griffin, I. Koturbash, Modulation of dietary methionine intake elicits potent, yet distinct, anticancer effects on primary versus metastatic tumors, Carcinogenesis 39 (2018) 1117–1126.
[136] E. Strekalova, D. Malin, D.M. Good, V.L. Cryns, Methionine deprivation induces a targetable vulnerability in triple-negative breast CANCER cells by enhancing TRAIL receptor-2 expression, Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 21 (2015) 2780–2791.
[137] H. Jeon, J.H. Kim, E. Lee, Y.J. Jang, J.E. Son, J.Y. Kwon, T.G. Lim, S. Kim, J. H. Park, J.E. Kim, K.W. Lee, Methionine deprivation suppresses triple-negative breast cancer metastasis in vitro and in vivo, Oncotarget 7 (2016) 67223–67234.
[138] A. Longchamp, T. Mirabella, A. Arduini, M.R. MacArthur, A. Das, J.H. Treviño-Villarreal, C. Hine, I. Ben-Sahra, N.H. Knudsen, L.E. Brace, J. Reynolds, P. Mejia, M. Tao, G. Sharma, R. Wang, J.M. Corpataux, J.A. Haefliger, K.H. Ahn, C.H. Lee, B.D. Manning, D.A. Sinclair, C.S. Chen, C.K. Ozaki, J.R. Mitchell, Amino acid restriction triggers angiogenesis via GCN2/ATF4 regulation of VEGF and H(2)S production, Cell 173 (2018) 117–129.e114.
[139] K.R. Mattaini, M.R. Sullivan, M.G. Vander Heiden, The importance of serine metabolism in cancer, J. Cell Biol. 214 (2016) 249–257.
[140] R. Possemato, K.M. Marks, Y.D. Shaul, M.E. Pacold, D. Kim, K. Birsoy, S. Sethumadhavan, H.-K. Woo, H.G. Jang, A.K. Jha, W.W. Chen, F.G. Barrett, N. Stransky, Z.-Y. Tsun, G.S. Cowley, J. Barretina, N.Y. Kalaany, P.P. Hsu, K. Ottina, A.M. Chan, B. Yuan, L.A. Garraway, D.E. Root, M. Mino-Kenudson, E. F. Brachtel, E.M. Driggers, D.M. Sabatini, Functional genomics reveal that the serine synthesis pathway is essential in breast cancer, Nature 476 (2011) 346–350.
[141] O.D.K. Maddocks, C.R. Berkers, S.M. Mason, L. Zheng, K. Blyth, E. Gottlieb, K. H. Vousden, Serine starvation induces stress and p53-dependent metabolic remodelling in cancer cells, Nature 493 (2013) 542–546.
[142] O.D.K. Maddocks, D. Athineos, E.C. Cheung, P. Lee, T. Zhang, N.J.F. van den Broek, G.M. Mackay, C.F. Labuschagne, D. Gay, F. Kruiswijk, J. Blagih, D. F. Vincent, K.J. Campbell, F. Ceteci, O.J. Sansom, K. Blyth, K.H. Vousden, Modulating the therapeutic response of tumours to dietary serine and glycine starvation, Nature 544 (2017) 372–376.
[143] M. Falcone, A.H. Uribe, V. Papalazarou, A.C. Newman, D. Athineos, K. Stevenson, C.G. Sauvé, Y. Gao, J.K. Kim, M. Del Latto, M. Kierstead, C. Wu, J.J. Smith, P. B. Romesser, A.J. Chalmers, K. Blyth, O.D.K. Maddocks, Sensitisation of cancer cells to radiotherapy by serine and glycine starvation, Br. J. Cancer 127 (2022) 1773–1786.
[144] D.R. Bolster, L.S. Jefferson, S.R. Kimball, Regulation of protein synthesis associated with skeletal muscle hypertrophy by insulin-, amino acid- and exercise-induced signalling, Proc. Nutr. Soc. 63 (2004) 351–356.
[145] M.K. Jung, A.P. Okekunle, J.E. Lee, M.K. Sung, Y.J. Lim, Role of branched-chain amino acid metabolism in tumor development and progression, J. Cancer Preven. 26 (2021) 237–243.
[146] A. Hattori, M. Tsunoda, T. Konuma, M. Kobayashi, T. Nagy, J. Glushka, F. Tayyari, D. McSkimming, N. Kannan, A. Tojo, A.S. Edison, T. Ito, Cancer

progression by reprogrammed BCAA metabolism in myeloid leukaemia, Nature 545 (2017) 500–504.
[147] J.H. Lee, Y.-R. Cho, J.H. Kim, J. Kim, H.Y. Nam, S.W. Kim, J. Son, Branched-chain amino acids sustain pancreatic cancer growth by regulating lipid metabolism, Exp. Mol. Med. 51 (2019) 1–11.
[148] J.-S. Kang, Dietary restriction of amino acids for Cancer therapy, Nutrit. Metabol. 17 (2020) 20.
[149] R.L. Wolfson, L. Chantranupong, R.A. Saxton, K. Shen, S.M. Scaria, J.R. Cantor, D. M. Sabatini, Sestrin2 is a leucine sensor for the mTORC1 pathway, Science (New York, N.Y.) 351 (2016) 43–48.
[150] M. Holeček, Branched-chain amino acids in health and disease: metabolism, alterations in blood plasma, and as supplements, Nutrit. Metabol. 15 (2018) 33.
[151] F. Xiao, C. Wang, H. Yin, J. Yu, S. Chen, J. Fang, F. Guo, Leucine deprivation inhibits proliferation and induces apoptosis of human breast cancer cells via fatty acid synthase, Oncotarget 7 (2016) 63679–63689.
[152] S. Solanki, K. Sanchez, V. Ponnusamy, V. Kota, H.N. Bell, C.S. Cho, A. H. Kowalsky, M. Green, J.H. Lee, Y.M. Shah, Dysregulated amino acid sensing drives colorectal cancer growth and metabolic reprogramming leading to chemoresistance, Gastroenterology 164 (3) (2023) 376–391.e13.
[153] K.K. Dhillon, S. Gupta, Biochemistry, Ketogenesis, StatPearls, StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC, 2023. Place Published.
[154] S. Hui, A.J. Cowan, X. Zeng, L. Yang, T. TeSlaa, X. Li, C. Bartman, Z. Zhang, C. Jang, L. Wang, W. Lu, J. Rojas, J. Baur, J.D. Rabinowitz, Quantitative Fluxomics of circulating metabolites, Cell Metab. 32 (2020) 676–688.e674.
[155] R.G.R. Mooli, S.K. Ramakrishnan, Emerging role of hepatic Ketogenesis in fatty liver disease, Front. Physiol. 13 (2022).
[156] L.P. Fernández, M. Gómez de Cedrón, A. Ramírez de Molina, Alterations of lipid metabolism in cancer: implications in prognosis and treatment, Front. Oncol. 10 (2020) 577420.
[157] M. Gómez de Cedrón, A. Ramírez de Molina, Chapter 28 - precision nutrition to target lipid metabolism alterations in cancer, in: J. Faintuch, S. Faintuch (Eds.), Precision Medicine for Investigators, Academic Press, Place Published, Practitioners and Providers, 2020, pp. 291–299.
[158] N. Koundouros, G. Poulogiannis, Reprogramming of fatty acid metabolism in cancer, Br. J. Cancer 122 (2020) 4–22.
[159] F. Röhrig, A. Schulze, The multifaceted roles of fatty acid synthesis in cancer, Nat. Rev. Cancer 16 (2016) 732–749.
[160] J.A. Menendez, R. Lupu, Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis, Nat. Rev. Cancer 7 (2007) 763–777.
[161] I. Mylonis, G. Simos, E. Paraskeva, Hypoxia-inducible factors and the regulation of lipid metabolism, Cells 8 (2019).
[162] K. Bensaad, E. Favaro, C.A. Lewis, B. Peck, S. Lord, J.M. Collins, K.E. Pinnick, S. Wigfield, F.M. Buffa, J.L. Li, Q. Zhang, M.J.O. Wakelam, F. Karpe, A. Schulze, A.L. Harris, Fatty acid uptake and lipid storage induced by HIF-1α contribute to cell growth and survival after hypoxia-reoxygenation, Cell Rep. 9 (2014) 349–365.
[163] L. Tirinato, F. Pagliari, T. Limongi, M. Marini, A. Falqui, J. Seco, P. Candeloro, C. Liberale, E. Di Fabrizio, An overview of lipid droplets in Cancer and Cancer stem cells, Stem Cells Int. 2017 (2017) 1656053.
[164] A. Carracedo, L.C. Cantley, P.P. Pandolfi, Cancer metabolism: fatty acid oxidation in the limelight, Nat. Rev. Cancer 13 (2013) 227–232.
[165] R. Camarda, A.Y. Zhou, R.A. Kohnz, S. Balakrishnan, C. Mahieu, B. Anderton, H. Eyob, S. Kajimura, A. Tward, G. Krings, D.K. Nomura, A. Goga, Inhibition of fatty acid oxidation as a therapy for MYC-overexpressing triple-negative breast cancer, Nat. Med. 22 (2016) 427–432.
[166] N. Marino, R. German, X. Rao, E. Simpson, S. Liu, J. Wan, Y. Liu, G. Sandusky, M. Jacobsen, M. Stoval, S. Cao, A.M.V. Storniolo, Upregulation of lipid metabolism genes in the breast prior to cancer diagnosis, npj, Breast Cancer 6 (2020) 50.
[167] G. Andrejeva, J.C. Rathmell, Similarities and distinctions of Cancer and immune metabolism in inflammation and tumors, Cell Metab. 26 (2017) 49–70.
[168] E. Reznik, A. Luna, B.A. Aksoy, E.M. Liu, K. La, I. Ostrovnaya, C.J. Creighton, A. A. Hakimi, C. Sander, A landscape of metabolic variation across tumor types, Cell Syst. 6 (2018) 301–313.e303.
[169] J.H. Joly, B.T.L. Chew, N.A. Graham, The landscape of metabolic pathway dependencies in cancer cell lines, PLoS Comput. Biol. 17 (2021) e1008942.
[170] D.W. Parsons, S. Jones, X. Zhang, J.C. Lin, R.J. Leary, P. Angenendt, P. Mankoo, H. Carter, I.M. Siu, G.L. Gallia, A. Olivi, R. McLendon, B.A. Rasheed, S. Keir, T. Nikolskaya, Y. Nikolsky, D.A. Busam, H. Tekleab, L.A. Diaz Jr., J. Hartigan, D. R. Smith, R.L. Strausberg, S.K. Marie, S.M. Shinjo, H. Yan, G.J. Riggins, D. D. Bigner, R. Karchin, N. Papadopoulos, G. Parmigiani, B. Vogelstein, V. E. Velculescu, K.W. Kinzler, An integrated genomic analysis of human glioblastoma multiforme, Science (New York, N.Y.) 321 (2008) 1807–1812.
[171] P.S. Ward, J. Patel, D.R. Wise, O. Abdel-Wahab, B.D. Bennett, H.A. Coller, J. R. Cross, V.R. Fantin, C.V. Hedvat, A.E. Perl, J.D. Rabinowitz, M. Carroll, S.M. Su, K.A. Sharp, R.L. Levine, C.B. Thompson, The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate, Cancer Cell 17 (2010) 225–234.
[172] D. Golub, N. Iyengar, S. Dogra, T. Wong, D. Bready, K. Tang, A.S. Modrek, D. G. Placantonakis, Mutant Isocitrate dehydrogenase inhibitors as targeted Cancer therapeutics, Front. Oncol. 9 (2019) 417.
[173] M. Harvie, Nutritional supplements and cancer: potential benefits and proven harms, American Society of Clinical Oncology educational book, Proc. Am. Soc. Clin. Oncol. 34 (2014) e478–e486. Annual Meeting.
[174] I. D'Andrea Meira, T.T. Romão, H.J. Pires do Prado, L.T. Krüger, M.E.P. Pires, P. O. da Conceição, Ketogenic diet and epilepsy: what we know so far, Front. Neurosci. 13 (2019) 5.
[175] R.J. Klement, Wilhelm Brünings' forgotten contribution to the metabolic treatment of cancer utilizing hypoglycemia and a very low carbohydrate (ketogenic) diet, J. Tradit. Complement. Med. 9 (2019) 192–200.
[176] E.H. Kossoff, B.A. Zupec-Kania, S. Auvin, K.R. Ballaban-Gil, A.G. Christina Bergqvist, R. Blackford, J.R. Buchhalter, R.H. Caraballo, J.H. Cross, M.G. Dahlin, E.J. Donner, O. Guzel, R.S. Jehle, J. Klepper, H.C. Kang, D.A. Lambrechts, Y.M. C. Liu, J.K. Nathan, D.R. Nordli Jr., H.H. Pfeifer, J.M. Rho, I.E. Scheffer, S. Sharma, C.E. Stafstrom, E.A. Thiele, Z. Turner, M.M. Vaccarezza, E. van der Louw, P. Veggiotti, J.W. Wheless, E.C. Wirrell, Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the international ketogenic diet study group, Epilepsia Open 3 (2018) 175–192.
[177] S. Aminzadeh-Gohari, R.G. Feichtinger, S. Vidali, F. Locker, T. Rutherford, M. O'Donnel, A. Stöger-Kleiber, J.A. Mayr, W. Sperl, B. Kofler, A ketogenic diet supplemented with medium-chain triglycerides enhances the anti-tumor and anti-angiogenic efficacy of chemotherapy on neuroblastoma xenografts in a CD1-nu mouse model, Oncotarget 8 (2017) 64728–64744.
[178] G.W. Hao, Y.S. Chen, D.M. He, H.Y. Wang, G.H. Wu, B. Zhang, Growth of human colon cancer cells in nude mice is delayed by ketogenic diet with or without omega-3 fatty acids and medium-chain triglycerides, Asian Pac. J. Cancer Prev. 16 (2015) 2061–2068.
[179] C. Otto, U. Kaemmerer, B. Illert, B. Muehling, N. Pfetzer, R. Wittig, H.U. Voelker, A. Thiede, J.F. Coy, Growth of human gastric cancer cells in nude mice is delayed by a ketogenic diet supplemented with omega-3 fatty acids and medium-chain triglycerides, BMC Cancer 8 (2008) 122.
[180] A.M. Poff, N. Ward, T.N. Seyfried, P. Arnold, D.P. D'Agostino, Non-toxic metabolic management of metastatic cancer in VM mice: novel combination of ketogenic diet, ketone supplementation, and hyperbaric oxygen therapy, PLoS One 10 (2015) e0127407.
[181] N.D. Shah, The Use of Medium-Chain Triglycerides in Gastrointestinal Disorders, 2017.
[182] K.A. Page, A. Williamson, N. Yu, E.C. McNay, J. Dzuira, R.J. McCrimmon, R. S. Sherwin, Medium-chain fatty acids improve cognitive function in intensively treated type 1 diabetic patients and support in vitro synaptic transmission during acute hypoglycemia, Diabetes 58 (2009) 1237–1244.
[183] M.J. Tisdale, R.A. Brennan, K.C. Fearon, Reduction of weight loss and tumour size in a cachexia model by a high fat diet, Br. J. Cancer 56 (1987) 39–43.
[184] E.H. Kossoff, J.L. Dorward, The modified Atkins diet, Epilepsia 49 (Suppl. 8) (2008) 37–41.
[185] J.M. Freeman, E.H. Kossoff, Ketosis and the ketogenic diet, 2010: advances in treating epilepsy and other disorders, Adv. Pediatr. Infect. Dis. 57 (2010) 315–329.
[186] W. Voegtlin, The Stone Age Diet: Based on in-Depth Studies of Human Ecology and the Diet of Man, Vantage Press, Place Published, 1975.
[187] H.C. Kang, D.E. Chung, D.W. Kim, H.D. Kim, Early- and late-onset complications of the ketogenic diet for intractable epilepsy, Epilepsia 45 (2004) 1116–1123.
[188] Z. Clemens, A. Dabóczi, C. Csiba-Tóth, The paleolithic ketogenic diet may ensure adequate serum magnesium levels, J. Evolut. Health 2 (2018).
[189] Z. Clemens, C. Csiba-Tóth, Vitamin C and disease: insights from the evolutionary perspective, J. Evolut. Health 1 (2016).
[190] M.N. Roberts, M.A. Wallace, A.A. Tomilov, Z. Zhou, G.R. Marcotte, D. Tran, G. Perez, E. Gutierrez-Casado, S. Koike, T.A. Knotts, D.M. Imai, S.M. Griffey, K. Kim, K. Hagopian, M.Z. McMackin, F.G. Haj, K. Baar, G.A. Cortopassi, J. J. Ramsey, J.A. Lopez-Dominguez, A ketogenic diet extends longevity and Healthspan in adult mice, Cell Metab. 26 (2017) 539–546.e535.
[191] C.G.J. Saris, S. Timmers, Ketogenic diets and ketone suplementation: a strategy for therapeutic intervention, Front. Nutr. 9 (2022) 947567.
[192] J. George, F. Cahill, Fuel metabolism in starvation, Annu. Rev. Nutr. 26 (2006) 1–22.
[193] E.O. Balasse, F. Féry, Ketone body production and disposal: effects of fasting, diabetes, and exercise, Diabetes Metab. Rev. 5 (1989) 247–270.
[194] P.J. Cox, T. Kirk, T. Ashmore, K. Willerton, R. Evans, A. Smith, A.J. Murray, B. Stubbs, J. West, S.W. McLure, M.T. King, M.S. Dodd, C. Holloway, S. Neubauer, S. Drawer, R.L. Veech, J.L. Griffin, K. Clarke, Nutritional ketosis alters fuel preference and thereby endurance performance in athletes, Cell Metab. 24 (2016) 256–268.
[195] F.G. Hegardt, Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase: a control enzyme in ketogenesis, Biochem. J. 338 (Pt 3) (1999) 569–582.
[196] S.J. Koppel, R.H. Swerdlow, Neuroketotherapeutics: a modern review of a century-old therapy, Neurochem. Int. 117 (2018) 114–125.
[197] A. Courchesne-Loyer, E. Croteau, C.A. Castellano, V. St-Pierre, M. Hennebelle, S. C. Cunnane, Inverse relationship between brain glucose and ketone metabolism in adults during short-term moderate dietary ketosis: a dual tracer quantitative positron emission tomography study, J. Cerebr. Blood Flow Metabol.: Off. J. Intern. Soc. Cerebr. Blood Flow Metabol. 37 (2017) 2485–2493.
[198] G.M. Chowdhury, L. Jiang, D.L. Rothman, K.L. Behar, The contribution of ketone bodies to basal and activity-dependent neuronal oxidation in vivo, J. Cerebr. Blood Flow Metabol.: Off. J. Intern. Soc. Cerebr. Blood Flow Metabol. 34 (2014) 1233–1242.
[199] L.B. Achanta, C.D. Rae, β-Hydroxybutyrate in the brain: one molecule, multiple mechanisms, Neurochem. Res. 42 (2017) 35–49.
[200] P. Rojas-Morales, J. Pedraza-Chaverri, E. Tapia, Ketone bodies, stress response, and redox homeostasis, Redox Biol. 29 (2020) 101395.

[201] M. Rahman, S. Muhammad, M.A. Khan, H. Chen, D.A. Ridder, H. Müller-Fielitz, B. Pokorná, T. Vollbrandt, I. Stölting, R. Nadrowitz, J.G. Okun, S. Offermanns, M. Schwaninger, The β-hydroxybutyrate receptor HCA2 activates a neuroprotective subset of macrophages, Nat. Commun. 5 (2014) 3944.
[202] A.M. Poff, C. Ari, P. Arnold, T.N. Seyfried, D.P. D'Agostino, Ketone supplementation decreases tumor cell viability and prolongs survival of mice with metastatic cancer, Int. J. Cancer 135 (2014) 1711–1720.
[203] M.J. Tisdale, R.A. Brennan, Loss of acetoacetate coenzyme a transferase activity in tumours of peripheral tissues, Br. J. Cancer 47 (1983) 293–297.
[204] R.L. Veech, B. Chance, Y. Kashiwaya, H.A. Lardy, G.F. Cahill Jr., Ketone bodies, potential therapeutic uses, IUBMB Life 51 (2001) 241–247.
[205] G.Y. Wu, J.R. Thompson, The effect of ketone bodies on alanine and glutamine metabolism in isolated skeletal muscle from the fasted chick, Biochem. J. 255 (1988) 139–144.
[206] L. Yang, T. TeSlaa, S. Ng, M. Nofal, L. Wang, T. Lan, X. Zeng, A. Cowan, M. McBride, W. Lu, S. Davidson, G. Liang, T.G. Oh, M. Downes, R. Evans, D. Von Hoff, J.Y. Guo, H. Han, J.D. Rabinowitz, Ketogenic diet and chemotherapy combine to disrupt pancreatic cancer metabolism and growth, Med 3 (2022) 119–136.e118.
[207] T. Shimazu, M.D. Hirschey, J. Newman, W. He, K. Shirakawa, N. Le Moan, C. A. Grueter, H. Lim, L.R. Saunders, R.D. Stevens, C.B. Newgard, R.V. Farese Jr., R. de Cabo, S. Ulrich, K. Akassoglou, E. Verdin, Suppression of oxidative stress by β-hydroxybutyrate, an endogenous histone deacetylase inhibitor, Science (New York, N.Y.) 339 (2013) 211–214.
[208] N. Gensous, C. Franceschi, A. Santoro, M. Milazzo, P. Garagnani, M.G. Bacalini, The impact of caloric restriction on the epigenetic signatures of aging, Int. J. Mol. Sci. 20 (2019).
[209] S. Ropero, M. Esteller, The role of histone deacetylases (HDACs) in human cancer, Mol. Oncol. 1 (2007) 19–25.
[210] R.J. Klement, Fasting, fats, and physics: combining ketogenic and radiation therapy against cancer, Complement. Med. Res. 25 (2018) 102–113.
[211] R.J. Klement, Anti-tumor effects of ketogenic diets and their synergism with other treatments in mice: Bayesian evidence synthesis of 1755 individual mouse survival data, Biom. J. (2023 May 26) 100609.
[212] J. Li, H. Zhang, Z. Dai, Cancer treatment with the ketogenic diet: a systematic review and Meta-analysis of animal studies, Front. Nutr. 8 (2021).
[213] D.D. Weber, S. Aminzadeh-Gohari, J. Tulipan, L. Catalano, R.G. Feichtinger, B. Kofler, Ketogenic diet in the treatment of cancer - where do we stand? Molecul. Metabol. 33 (2020) 102–121.
[214] R.J. Klement, N. Brehm, R.A. Sweeney, Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes, Med. Oncol. (Northwood, London, England) 37 (2020) 14.
[215] K. Nakamura, H. Tonouchi, A. Sasayama, K. Ashida, A ketogenic formula prevents tumor progression and cancer Cachexia by attenuating systemic inflammation in Colon 26 tumor-bearing mice, Nutrients 10 (2018).
[216] E.C. Woolf, K.L. Curley, Q. Liu, G.H. Turner, J.A. Charlton, M.C. Preul, A. C. Scheck, The ketogenic diet alters the hypoxic response and affects expression of proteins associated with angiogenesis, invasive potential and vascular permeability in a mouse glioma model, PLoS One 10 (2015) e0130357.
[217] T.N. Seyfried, T.M. Sanderson, M.M. El-Abbadi, R. McGowan, P. Mukherjee, Role of glucose and ketone bodies in the metabolic control of experimental brain cancer, Br. J. Cancer 89 (2003) 1375–1382.
[218] D.M. Lussier, E.C. Woolf, J.L. Johnson, K.S. Brooks, J.N. Blattman, A.C. Scheck, Enhanced immunity in a mouse model of malignant glioma is mediated by a therapeutic ketogenic diet, BMC Cancer 16 (2016) 310.
[219] R.J. Klement, Beneficial effects of ketogenic diets for cancer patients: a realist review with focus on evidence and confirmation, Med. Oncol. (Northwood, Lond., Engl.) 34 (2017) 132.
[220] M.G. Abdelwahab, K.E. Fenton, M.C. Preul, J.M. Rho, A. Lynch, P. Stafford, A. C. Scheck, The ketogenic diet is an effective adjuvant to radiation therapy for the treatment of malignant glioma, PLoS One 7 (2012) e36197.
[221] B.D. Hopkins, C. Pauli, X. Du, D.G. Wang, X. Li, D. Wu, S.C. Amadiume, M. D. Goncalves, C. Hodakoski, M.R. Lundquist, R. Bareja, Y. Ma, E.M. Harris, A. Sboner, H. Beltran, M.A. Rubin, S. Mukherjee, L.C. Cantley, Suppression of insulin feedback enhances the efficacy of PI3K inhibitors, Nature 560 (2018) 499–503.
[222] B.G. Allen, S.K. Bhatia, J.M. Buatti, K.E. Brandt, K.E. Lindholm, A.M. Button, L. I. Szweda, B.J. Smith, D.R. Spitz, M.A. Fath, Ketogenic diets enhance oxidative stress and radio-chemo-therapy responses in lung cancer xenografts, Clin. Cancer Res.: Off. J. Am. Assoc. Cancer Res. 19 (2013) 3905–3913.
[223] G. Ferrere, M. Tidjani Alou, P. Liu, A.G. Goubet, M. Fidelle, O. Kepp, S. Durand, V. Iebba, A. Fluckiger, R. Daillère, C. Thelemaque, C. Grajeda-Iglesias, C. Alves Costa Silva, F. Aprahamian, D. Lefevre, L. Zhao, B. Ryffel, E. Colomba, M. Arnedos, D. Drubay, C. Rauber, D. Raoult, F. Asnicar, T. Spector, N. Segata, L. Derosa, G. Kroemer, L. Zitvogel, Ketogenic diet and ketone bodies enhance the anticancer effects of PD-1 blockade, JCI Insight 6 (2021).
[224] X. Dai, X. Bu, Y. Gao, J. Guo, J. Hu, C. Jiang, Z. Zhang, K. Xu, J. Duan, S. He, J. Zhang, L. Wan, T. Liu, X. Zhou, M.C. Hung, G.J. Freeman, W. Wei, Energy status dictates PD-L1 protein abundance and anti-tumor immunity to enable checkpoint blockade, Mol. Cell 81 (2021) 2317–2331.e2316.
[225] N. Erickson, A. Boscheri, B. Linke, J. Huebner, Systematic review: isocaloric ketogenic dietary regimes for cancer patients, Med. Oncol. (Northw., Lond., Engl.) 34 (2017) 72.
[226] E.J. Fine, C.J. Segal-Isaacson, R.D. Feinman, S. Herszkopf, M.C. Romano, N. Tomuta, A.F. Bontempo, A. Negassa, J.A. Sparano, Targeting insulin inhibition as a metabolic therapy in advanced cancer: a pilot safety and feasibility dietary trial in 10 patients, Nutrition (Burbank, Los Angeles County, Calif.) 28 (2012) 1028–1035.
[227] K. Furukawa, K. Shigematus, Y. Iwase, W. Mikami, H. Hoshi, T. Nishiyama, A. Ohtuka, H. Abe, Clinical effects of one year of chemotherapy with a modified medium-chain triglyceride ketogenic diet on the recurrence of stage IV colon cancer, J. Clin. Oncol. 36 (2018) e15709.
[228] A. Khodabakhshi, M.E. Akbari, H.R. Mirzaei, H. Mehrad-Majd, M. Kalamian, S. H. Davoodi, Feasibility, safety, and beneficial effects of MCT-based ketogenic diet for breast cancer treatment: a randomized controlled trial study, Nutr. Cancer 72 (2020) 627–634.
[229] M.S. Iyikesici, Feasibility study of metabolically supported chemotherapy with weekly carboplatin/paclitaxel combined with ketogenic diet, hyperthermia and hyperbaric oxygen therapy in metastatic non-small cell lung cancer, Intern. J. Hypertherm.: Off. J. Eur. Soc. Hypertherm. Oncol. North Am. Hypertherm. Group 36 (2019) 446–455.
[230] N. Jansen, H. Walach, The development of tumours under a ketogenic diet in association with the novel tumour marker TKTL1: a case series in general practice, Oncol. Lett. 11 (2016) 584–592.
[231] C. Csiba-Tóth, Z. Clemens, Halted progression of soft palate cancer in a patient treated with the paleolithic ketogenic diet alone: a 20-months follow-up, Am. J. Med. Case Reports 4 (2016) 288–292.
[232] K. Schwartz, H.T. Chang, M. Nikolai, J. Pernicone, S. Rhee, K. Olson, P. C. Kurniali, N.G. Hord, M. Noel, Treatment of glioma patients with ketogenic diets: report of two cases treated with an IRB-approved energy-restricted ketogenic diet protocol and review of the literature, Cancer Metab. 3 (2015) 3.
[233] D.D. Weber, S. Aminazdeh-Gohari, B. Kofler, Ketogenic diet in cancer therapy, Aging 10 (2018) 164–165.
[234] T.R. Flint, T. Janowitz, C.M. Connell, E.W. Roberts, A.E. Denton, A.P. Coll, D. I. Jodrell, D.T. Fearon, Tumor-induced IL-6 reprograms host metabolism to suppress anti-tumor immunity, Cell Metab. 24 (2016) 672–684.
[235] M.D. Goncalves, S.K. Hwang, C. Pauli, C.J. Murphy, Z. Cheng, B.D. Hopkins, D. Wu, R.M. Loughran, B.M. Emerling, G. Zhang, D.T. Fearon, L.C. Cantley, Fenofibrate prevents skeletal muscle loss in mice with lung cancer, Proc. Natl. Acad. Sci. U. S. A. 115 (2018) E743–e752.
[236] M. Ferrer, N. Mourikis, E.E. Davidson, S.O. Kleeman, M. Zaccaria, J. Habel, R. Rubino, Q. Gao, T.R. Flint, L. Young, C.M. Connell, M.J. Lukey, M. D. Goncalves, E.P. White, A.R. Venkitaraman, T. Janowitz, Ketogenic diet promotes tumor ferroptosis but induces relative corticosterone deficiency that accelerates cachexia, Cell Metab 35 (2023) 1147–1162, e7.
[237] S. Vidali, S. Aminzadeh-Gohari, R.G. Feichtinger, R. Vatrinet, A. Koller, F. Sternberg, T. Rutherford, M. O'Donnell, A. Stöger-Kleiber, B. Lambert, T. K. Felder, W. Sperl, B. Kofler, The ketogenic diet is not feasible as a therapy in a CD-1 nu/nu mouse model of renal cell carcinoma with features of Stauffer's syndrome, Oncotarget 8 (2017).
[238] S. Beyaz, M.D. Mana, J. Roper, D. Kedrin, A. Saadatpour, S.J. Hong, K.E. Bauer-Rowe, M.E. Xifaras, A. Akkad, E. Arias, L. Pinello, Y. Katz, S. Shinagare, M. Abu-Remaileh, M.M. Mihaylova, D.W. Lamming, R. Dogum, G. Guo, G.W. Bell, M. Selig, G.P. Nielsen, N. Gupta, C.R. Ferrone, V. Deshpande, G.C. Yuan, S. H. Orkin, D.M. Sabatini, H. Yilmazö, High-fat diet enhances stemness and tumorigenicity of intestinal progenitors, Nature 531 (2016) 53–58.
[239] L.K. Heilbronn, L. de Jonge, M.I. Frisard, J.P. DeLany, D.E. Larson-Meyer, J. Rood, T. Nguyen, C.K. Martin, J. Volaufova, M.M. Most, F.L. Greenway, S.R. Smith, W. A. Deutsch, D.A. Williamson, E. Ravussin, Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial, Jama 295 (2006) 1539–1548.
[240] W.E. Kraus, M. Bhapkar, K.M. Huffman, C.F. Pieper, S. Krupa Das, L.M. Redman, D.T. Villareal, J. Rochon, S.B. Roberts, E. Ravussin, J.O. Holloszy, L. Fontana, 2 years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicentre, phase 2, randomised controlled trial, the lancet, Diabetes & Endocrinol. 7 (2019) 673–683.
[241] J. Most, L.A. Gilmore, S.R. Smith, H. Han, E. Ravussin, L.M. Redman, Significant improvement in cardiometabolic health in healthy nonobese individuals during caloric restriction-induced weight loss and weight loss maintenance, Am. J. Physiol. Endocrinol. Metab. 314 (2018) E396–e405.
[242] J.L. Dorling, E. Ravussin, L.M. Redman, M. Bhapkar, K.M. Huffman, S.B. Racette, S.K. Das, J.W. Apolzan, W.E. Kraus, C. Höchsmann, C.K. Martin, Effect of 2 years of calorie restriction on liver biomarkers: results from the CALERIE phase 2 randomized controlled trial, Eur. J. Nutr. 60 (2021) 1633–1643.
[243] E. Ravussin, L.M. Redman, J. Rochon, S.K. Das, L. Fontana, W.E. Kraus, S. Romashkan, D.A. Williamson, S.N. Meydani, D.T. Villareal, S.R. Smith, R. I. Stein, T.M. Scott, T.M. Stewart, E. Saltzman, S. Klein, M. Bhapkar, C.K. Martin, C.H. Gilhooly, J.O. Holloszy, E.C. Hadley, S.B. Roberts, A 2-year randomized controlled trial of human caloric restriction: feasibility and effects on predictors of health span and longevity, J. Gerontol. Series A, Biolog. Sci. Med. Sci. 70 (2015) 1097–1104.
[244] D.W. Belsky, K.M. Huffman, C.F. Pieper, I. Shalev, W.E. Kraus, Change in the rate of biological aging in response to caloric restriction: CALERIE biobank analysis, J. Gerontol. Series A, Biol. Sci. Med. Sci. 73 (2017) 4–10.
[245] D. Il'yasova, L. Fontana, M. Bhapkar, C.F. Pieper, I. Spasojevic, L.M. Redman, S. K. Das, K.M. Huffman, W.E. Kraus, Effects of 2 years of caloric restriction on oxidative status assessed by urinary F2-isoprostanes: the CALERIE 2 randomized clinical trial, Aging Cell 17 (2018).
[246] L.M. Redman, S.R. Smith, J.H. Burton, C.K. Martin, D. Il'yasova, E. Ravussin, Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging, Cell Metab. 27 (2018) 805–815.e804.

[247] R.J. Colman, R.M. Anderson, S.C. Johnson, E.K. Kastman, K.J. Kosmatka, T. M. Beasley, D.B. Allison, C. Cruzen, H.A. Simmons, J.W. Kemnitz, R. Weindruch, Caloric restriction delays disease onset and mortality in rhesus monkeys, Science (New York, N.Y.) 325 (2009) 201–204.
[248] J.A. Mattison, G.S. Roth, T.M. Beasley, E.M. Tilmont, A.M. Handy, R.L. Herbert, D.L. Longo, D.B. Allison, J.E. Young, M. Bryant, D. Barnard, W.F. Ward, W. Qi, D. K. Ingram, R. de Cabo, Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study, Nature 489 (2012) 318–321.
[249] C. Doyle, L.H. Kushi, T. Byers, K.S. Courneya, W. Demark-Wahnefried, B. Grant, A. McTiernan, C.L. Rock, C. Thompson, T. Gansler, K.S. Andrews, Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices, CA Cancer J. Clin. 56 (2006) 323–353.
[250] E.M. Ibrahim, M.H. Al-Foheidi, M.M. Al-Mansour, Energy and caloric restriction, and fasting and cancer: a narrative review, Support Care Cancer 29 (2021) 2299–2304.
[251] M.-C. Stockman, D. Thomas, J. Burke, C.M. Apovian, Intermittent fasting: is the wait worth the weight? Curr. Obes. Rep. 7 (2018) 172–185.
[252] R. Weindruch, R.S. Sohal, Seminars in medicine of the Beth Israel Deaconess Medical Center. Caloric intake and aging, N. Engl. J. Med. 337 (1997) 986–994.
[253] C.L. Goodrick, D.K. Ingram, M.A. Reynolds, J.R. Freeman, N. Cider, Effects of intermittent feeding upon body weight and lifespan in inbred mice: interaction of genotype and age, Mech. Ageing Dev. 55 (1990) 69–87.
[254] K. Xie, F. Neff, A. Markert, J. Rozman, J.A. Aguilar-Pimentel, O.V. Amarie, L. Becker, R. Brommage, L. Garrett, K.S. Henzel, S.M. Hölter, D. Janik, I. Lehmann, K. Moreth, B.L. Pearson, I. Racz, B. Rathkolb, D.P. Ryan, S. Schröder, I. Treise, R. Bekeredjian, D.H. Busch, J. Graw, G. Ehninger, M. Klingenspor, T. Klopstock, M. Ollert, M. Sandholzer, C. Schmidt-Weber, M. Weiergräber, E. Wolf, W. Wurst, A. Zimmer, V. Gailus-Durner, H. Fuchs, M. Hrabě de Angelis, D. Ehninger, Every-other-day feeding extends lifespan but fails to delay many symptoms of aging in mice, Nat. Commun. 8 (2017) 155.
[255] O. Descamps, J. Riondel, V. Ducros, A.M. Roussel, Mitochondrial production of reactive oxygen species and incidence of age-associated lymphoma in OF1 mice: effect OF alternate-day fasting, Mech. Ageing Dev. 126 (2005) 1185–1191.
[256] L. Tessitore, C. Tomasi, M. Greco, E. Sesca, E. Laconi, O. Maccioni, R. Ramo, P. Pani, A subnecrogenic dose of diethylnitrosamine is able to initiate hepatocarcinogenesis in the rat when coupled with fasting/refeeding, Carcinogenesis 17 (1996) 289–292.
[257] J.A. Thomas 2nd, J.A. Antonelli, J.C. Lloyd, E.M. Masko, S.H. Poulton, T. E. Phillips, M. Pollak, S.J. Freedland, Effect of intermittent fasting on prostate cancer tumor growth in a mouse model, Prostate Cancer Prostatic Dis. 13 (2010) 350–355.
[258] J. Bass, M.A. Lazar, Circadian time signatures of fitness and disease, Science (New York, N.Y.) 354 (2016) 994–999.
[259] H. Nørrelund, The metabolic role of growth hormone in humans with particular reference to fasting, Growth Hormon. IGF Res. 15 (2005) 95–122.
[260] D.M. Arble, J. Bass, A.D. Laposky, M.H. Vitaterna, F.W. Turek, Circadian timing of food intake contributes to weight gain, Obesity (Silver Spring, Md.) 17 (2009) 2100–2102.
[261] M. Hatori, C. Vollmers, A. Zarrinpar, L. DiTacchio, E.A. Bushong, S. Gill, M. Leblanc, A. Chaix, M. Joens, J.A. Fitzpatrick, M.H. Ellisman, S. Panda, Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet, Cell Metab. 15 (2012) 848–860.
[262] D. Jakubowicz, O. Froy, J. Wainstein, M. Boaz, Meal timing and composition influence ghrelin levels, appetite scores and weight loss maintenance in overweight and obese adults, Steroids 77 (2012) 323–331.
[263] K. Gabel, K.K. Hoddy, N. Haggerty, J. Song, C.M. Kroeger, J.F. Trepanowski, S. Panda, K.A. Varady, Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: a pilot study, Nutrit. Healthy Aging 4 (2018) 345–353.
[264] S. Gill, S. Panda, A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits, Cell Metab. 22 (2015) 789–798.
[265] T. Moro, G. Tinsley, A. Bianco, G. Marcolin, Q.F. Pacelli, G. Battaglia, A. Palma, P. Gentil, M. Neri, A. Paoli, Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males, J. Transl. Med. 14 (2016) 290.
[266] G.M. Tinsley, J.S. Forsse, N.K. Butler, A. Paoli, A.A. Bane, P.M. La Bounty, G. B. Morgan, P.W. Grandjean, Time-restricted feeding in young men performing resistance training: a randomized controlled trial, Eur. J. Sport Sci. 17 (2017) 200–207.
[267] T. Yoshizaki, Y. Tada, A. Hida, A. Sunami, Y. Yokoyama, J. Yasuda, A. Nakai, F. Togo, Y. Kawano, Effects of feeding schedule changes on the circadian phase of the cardiac autonomic nervous system and serum lipid levels, Eur. J. Appl. Physiol. 113 (2013) 2603–2611.
[268] E.F. Sutton, R. Beyl, K.S. Early, W.T. Cefalu, E. Ravussin, C.M. Peterson, Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes, Cell Metab. 27 (2018) 1212–1221.e1213.
[269] J.C. de Beer, L. Liebenberg, Does cancer risk increase with HbA1c, independent of diabetes? Br. J. Cancer 110 (2014) 2361–2368.
[270] G. Salvadori, F. Zanardi, F. Iannelli, R. Lobefaro, C. Vernieri, V.D. Longo, Fasting-mimicking diet blocks triple-negative breast cancer and cancer stem cell escape, Cell Metab. 33 (2021), 2247–2259.e2246.
[271] S. Sieri, P. Muti, A. Claudia, F. Berrino, V. Pala, S. Grioni, C.A. Abagnato, G. Blandino, P. Contiero, H.J. Schunemann, V. Krogh, Prospective study on the role of glucose metabolism in breast cancer occurrence, Int. J. Cancer 130 (2012) 921–929.
[272] P. Minicozzi, F. Berrino, F. Sebastiani, F. Falcini, R. Vattiato, F. Cioccoloni, G. Calagreti, M. Fusco, M.F. Vitale, R. Tumino, A. Sigona, M. Budroni, R. Cesaraccio, G. Candela, T. Scuderi, M. Zarcone, I. Campisi, M. Sant, High fasting blood glucose and obesity significantly and independently increase risk of breast cancer death in hormone receptor-positive disease, Eur. J. Cancer 49 (2013) 3881–3888.
[273] C.R. Marinac, L. Natarajan, D.D. Sears, L.C. Gallo, S.J. Hartman, E. Arredondo, R. E. Patterson, Prolonged nightly fasting and breast cancer risk: findings from NHANES (2009-2010), cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive, Oncology 24 (2015) 783–789.
[274] C.R. Marinac, S.H. Nelson, C.I. Breen, S.J. Hartman, L. Natarajan, J.P. Pierce, S. W. Flatt, D.D. Sears, R.E. Patterson, Prolonged nightly fasting and breast cancer prognosis, JAMA Oncol. 2 (2016) 1049–1055.
[275] S. Brandhorst, I.Y. Choi, M. Wei, C.W. Cheng, S. Sedrakyan, G. Navarrete, L. Dubeau, L.P. Yap, R. Park, M. Vinciguerra, S. Di Biase, H. Mirzaei, M. G. Mirisola, P. Childress, L. Ji, S. Groshen, F. Penna, P. Odetti, L. Perin, P.S. Conti, Y. Ikeno, B.K. Kennedy, P. Cohen, T.E. Morgan, T.B. Dorff, V.D. Longo, A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and Healthspan, Cell Metab. 22 (2015) 86–99.
[276] C. Vernieri, G. Fucà, F. Ligorio, V. Huber, A. Vingiani, F. Iannelli, A. Raimondi, D. Rinchai, G. Frigè, A. Belfiore, L. Lalli, C. Chiodoni, V. Cancila, F. Zanardi, A. Ajazi, S. Cortellino, V. Vallacchi, P. Squarcina, A. Cova, S. Pesce, P. Frati, R. Mall, P.A. Corsetto, A.M. Rizzo, C. Ferraris, S. Folli, M.C. Garassino, G. Capri, G. Bianchi, M.P. Colombo, S. Minucci, M. Foiani, V.D. Longo, G. Apolone, V. Torri, G. Pruneri, D. Bedognetti, L. Rivoltini, F. de Braud, Fasting-mimicking diet is safe and reshapes metabolism and antitumor immunity in patients with cancer, Cancer Discov. 12 (2022) 90–107.
[277] M. Wei, S. Brandhorst, M. Shelehchi, H. Mirzaei, C.W. Cheng, J. Budniak, S. Groshen, W.J. Mack, E. Guen, S. Di Biase, P. Cohen, T.E. Morgan, T. Dorff, K. Hong, A. Michalsen, A. Laviano, V.D. Longo, Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease, Sci. Transl. Med. 9 (2017).
[278] L.C.D. Pomatto-Watson, M. Bodogai, O. Bosompra, J. Kato, S. Wong, M. Carpenter, E. Duregon, D. Chowdhury, P. Krishna, S. Ng, E. Ragonnaud, R. Salgado, P. Gonzalez Ericsson, A. Diaz-Ruiz, M. Bernier, N.L. Price, A. Biragyn, V.D. Longo, R. de Cabo, Daily caloric restriction limits tumor growth more effectively than caloric cycling regardless of dietary composition, Nat. Commun. 12 (2021) 6201.
[279] F. Madeo, F. Pietrocola, T. Eisenberg, G. Kroemer, Caloric restriction mimetics: towards a molecular definition, Nat. Rev. Drug Discov. 13 (2014) 727–740.
[280] F. Pietrocola, J. Pol, E. Vacchelli, S. Rao, David P. Enot, Elisa E. Baracco, S. Levesque, F. Castoldi, N. Jacquelot, T. Yamazaki, L. Senovilla, G. Marino, F. Aranda, S. Durand, V. Sica, A. Chery, S. Lachkar, V. Sigl, N. Bloy, A. Buque, S. Falzoni, B. Ryffel, L. Apetoh, F. Di Virgilio, F. Madeo, Maria C. Maiuri, L. Zitvogel, B. Levine, Josef M. Penninger, G. Kroemer, Caloric restriction mimetics enhance anticancer immunosurveillance, Cancer Cell 30 (2016) 147–160.
[281] V. Beauloye, B. Willems, V. de Coninck, S.J. Frank, M. Edery, J.P. Thissen, Impairment of liver GH receptor signaling by fasting, Endocrinology 143 (2002) 792–800.
[282] K.C. Leung, N. Doyle, M. Ballesteros, M.J. Waters, K.K. Ho, Insulin regulation of human hepatic growth hormone receptors: divergent effects on biosynthesis and surface translocation, J. Clin. Endocrinol. Metab. 85 (2000) 4712–4720.
[283] A.M. Brennan, C.S. Mantzoros, Drug insight: the role of leptin in human physiology and pathophysiology–emerging clinical applications, Nat. Clin. Pract. Endocrinol. Metab. 2 (2006) 318–327.
[284] N. Kubota, W. Yano, T. Kubota, T. Yamauchi, S. Itoh, H. Kumagai, H. Kozono, I. Takamoto, S. Okamoto, T. Shiuchi, R. Suzuki, H. Satoh, A. Tsuchida, M. Moroi, K. Sugi, T. Noda, H. Ebinuma, Y. Ueta, T. Kondo, E. Araki, O. Ezaki, R. Nagai, K. Tobe, Y. Terauchi, K. Ueki, Y. Minokoshi, T. Kadowaki, Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake, Cell Metab. 6 (2007) 55–68.
[285] J.E. Campbell, A.J. Peckett, M. D'Souza A, T.J. Hawke, M.C. Riddell, Adipogenic and lipolytic effects of chronic glucocorticoid exposure, Am. J. Physiol. Cell Physiol. 300 (2011) C198–C209.
[286] G. Bianchi, R. Martella, S. Ravera, C. Marini, S. Capitanio, A. Orengo, L. Emionite, C. Lavarello, A. Amaro, A. Petretto, U. Pfeffer, G. Sambuceti, V. Pistoia, L. Raffaghello, V.D. Longo, Fasting induces anti-Warburg effect that increases respiration but reduces ATP-synthesis to promote apoptosis in colon cancer models, Oncotarget 6 (2015) 11806–11819.
[287] S. Di Biase, H.S. Shim, K.H. Kim, M. Vinciguerra, F. Rappa, M. Wei, S. Brandhorst, F. Cappello, H. Mirzaei, C. Lee, V.D. Longo, Fasting regulates EGR1 and protects from glucose- and dexamethasone-dependent sensitization to chemotherapy, PLoS Biol. 15 (2017) e2001951.
[288] M.M. Mihaylova, R.J. Shaw, The AMPK signalling pathway coordinates cell growth, autophagy and metabolism, Nat. Cell Biol. 13 (2011) 1016–1023.
[289] D.A. Guertin, D.M. Sabatini, Defining the role of mTOR in cancer, Cancer Cell 12 (2007) 9–22.
[290] M.S. Nakazawa, B. Keith, M.C. Simon, Oxygen availability and metabolic adaptations, Nat. Rev. Cancer 16 (2016) 663–673.
[291] M.E. Torrence, B.D. Manning, Nutrient sensing in cancer, Ann. Rev. Cancer Biol. 2 (2018) 251–269.

[292] K. Pakos-Zebrucka, I. Koryga, K. Mnich, M. Ljujic, A. Samali, A.M. Gorman, The integrated stress response, EMBO Rep. 17 (2016) 1374–1395.
[293] M. Wang, Y. Lu, H. Wang, Y. Wu, X. Xu, Y. Li, High ATF4 expression is associated with poor prognosis, amino acid metabolism, and autophagy in gastric cancer, Front. Oncol. 11 (2021).
[294] I.M.N. Wortel, L.T. van der Meer, M.S. Kilberg, F.N. van Leeuwen, Surviving stress: modulation of ATF4-mediated stress responses in normal and malignant cells, Trends Endocrinol. Metab. 28 (2017) 794–806.
[295] X. Bai, J. Ni, J. Beretov, V.C. Wasinger, S. Wang, Y. Zhu, P. Graham, Y. Li, Activation of the eIF2α/ATF4 axis drives triple-negative breast cancer radioresistance by promoting glutathione biosynthesis, Redox Biol. 43 (2021) 101993.
[296] M.E. Torrence, M.R. MacArthur, A.M. Hosios, A.J. Valvezan, J.M. Asara, J. R. Mitchell, B.D. Manning, The mTORC1-mediated activation of ATF4 promotes protein and glutathione synthesis downstream of growth signals, eLife 10 (2021) e63326.
[297] H. Shimano, R. Sato, SREBP-regulated lipid metabolism: convergent physiology — divergent pathophysiology, nature reviews, Endocrinology 13 (2017) 710–730.
[298] C.A. Lewis, C. Brault, B. Peck, K. Bensaad, B. Griffiths, R. Mitter, P. Chakravarty, P. East, B. Dankworth, D. Alibhai, A.L. Harris, A. Schulze, SREBP maintains lipid biosynthesis and viability of cancer cells under lipid- and oxygen-deprived conditions and defines a gene signature associated with poor survival in glioblastoma multiforme, Oncogene 34 (2015) 5128–5140.
[299] N.A. Bishop, L. Guarente, Genetic links between diet and lifespan: shared mechanisms from yeast to humans, Nat. Rev. Genet. 8 (2007) 835–844.
[300] L. Fontana, L. Partridge, V.D. Longo, Extending healthy life span–from yeast to humans, Science (New York, N.Y.) 328 (2010) 321–326.
[301] M.A. Badgley, D.M. Kremer, H.C. Maurer, K.E. DelGiorno, H.-J. Lee, V. Purohit, I. R. Sagalovskiy, A. Ma, J. Kapilian, C.E.M. Firl, A.R. Decker, S.A. Sastra, C. F. Palermo, L.R. Andrade, P. Sajjakulnukit, L. Zhang, Z.P. Tolstyka, T. Hirschhorn, C. Lamb, T. Liu, W. Gu, E.S. Seeley, E. Stone, G. Georgiou, U. Manor, A. Iuga, G. M. Wahl, B.R. Stockwell, C.A. Lyssiotis, K.P. Olive, Cysteine depletion induces pancreatic tumor ferroptosis in mice, Science (New York, N.Y.) 368 (2020) 85–89.
[302] P. Puchalska, P.A. Crawford, Multi-dimensional roles of ketone bodies in fuel metabolism, signaling, and therapeutics, Cell Metab. 25 (2017) 262–284.
[303] S. de Groot, H. Pijl, J.J.M. van der Hoeven, J.R. Kroep, Effects of short-term fasting on cancer treatment, J. Experiment. Clin. Cancer Res.: CR 38 (2019) 209.
[304] V.D. Longo, M.P. Mattson, Fasting: molecular mechanisms and clinical applications, Cell Metab. 19 (2014) 181–192.
[305] K.L. Tinkum, K.M. Stemler, L.S. White, A.J. Loza, S. Jeter-Jones, B.M. Michalski, C. Kuzmicki, R. Pless, T.S. Stappenbeck, D. Piwnica-Worms, H. Piwnica-Worms, Fasting protects mice from lethal DNA damage by promoting small intestinal epithelial stem cell survival, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) E7148–E7154.
[306] C. Lee, F.M. Safdie, L. Raffaghello, M. Wei, F. Madia, E. Parrella, D. Hwang, P. Cohen, G. Bianchi, V.D. Longo, Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index, Cancer Res. 70 (2010) 1564–1572.
[307] M. Barradas, A. Plaza, G. Colmenarejo, I. Lázaro, L.F. Costa-Machado, R. Martín-Hernández, V. Micó, J.L. López-Aceituno, J. Herranz, C. Pantoja, H. Tejero, A. Diaz-Ruiz, F. Al-Shahrour, L. Daimiel, V. Loria-Kohen, A.R. de Molina, A. Efeyan, M. Serrano, O.J. Pozo, A. Sala-Vila, P.J. Fernandez-Marcos, Fatty acids homeostasis during fasting predicts protection from chemotherapy toxicity, Nat. Commun. 13 (2022) 5677.
[308] S.S. Withers, P.H. Kass, C.O. Rodriguez Jr., K.A. Skorupski, D. O'Brien, T. A. Guerrero, K.D. Sein, R.B. Rebhun, Fasting reduces the incidence of delayed-type vomiting associated with doxorubicin treatment in dogs with lymphoma, Transl. Oncol. 7 (2014) 377–383.
[309] S.A. Huisman, W. Bijman-Lagcher, I.J. JN, R. Smits, R.W. de Bruin, Fasting protects against the side effects of irinotecan but preserves its anti-tumor effect in Apc15lox mutant mice, Cell Cycle (Georgetown, Tex.) 14 (2015) 2333–2339.
[310] M.-L. Weng, W.-K. Chen, X.-Y. Chen, H. Lu, Z.-R. Sun, Q. Yu, P.-F. Sun, Y.-J. Xu, M.-M. Zhu, N. Jiang, J. Zhang, J.-P. Zhang, Y.-L. Song, D. Ma, X.-P. Zhang, C.-H. Miao, Fasting inhibits aerobic glycolysis and proliferation in colorectal cancer via the Fdft1-mediated AKT/mTOR/HIF1α pathway suppression, Nat. Commun. 11 (2020) 1869.
[311] I. Caffa, V. Spagnolo, C. Vernieri, F. Valdemarin, P. Becherini, M. Wei, S. Brandhorst, C. Zucal, E. Driehuis, L. Ferrando, F. Piacente, A. Tagliafico, M. Cilli, L. Mastracci, V.G. Vellone, S. Piazza, A.L. Cremonini, R. Gradaschi, C. Mantero, M. Passalacqua, A. Ballestrero, G. Zoppoli, M. Cea, A. Arrighi, P. Odetti, F. Monacelli, G. Salvadori, S. Cortellino, H. Clevers, F. De Braud, S. G. Sukkar, A. Provenzani, V.D. Longo, A. Nencioni, Fasting-mimicking diet and hormone therapy induce breast cancer regression, Nature 583 (2020) 620–624.
[312] M. Maccario, G. Aimaretti, S. Grottoli, C. Gauna, F. Tassone, G. Corneli, R. Rossetto, Z. Wu, C.J. Strasburger, E. Ghigo, Effects of 36 hour fasting on GH/IGF-I axis and metabolic parameters in patients with simple obesity. Comparison with normal subjects and hypopituitary patients with severe GH deficiency, Intern. J. Obesity Relat. Metabol. Disord.: J. Internat. Assoc. Study Obesity 25 (2001) 1233–1239.
[313] M.A. Wijngaarden, G.C. van der Zon, K.W. van Dijk, H. Pijl, B. Guigas, Effects of prolonged fasting on AMPK signaling, gene expression, and mitochondrial respiratory chain content in skeletal muscle from lean and obese individuals, Am. J. Physiol. Endocrinol. Metab. 304 (2013) E1012–E1021.
[314] F.M. Safdie, T. Dorff, D. Quinn, L. Fontana, M. Wei, C. Lee, P. Cohen, V.D. Longo, Fasting and cancer treatment in humans: a case series report, Aging 1 (2009) 988–1007.
[315] S. de Groot, M.P. Vreeswijk, M.J. Welters, G. Gravesteijn, J.J. Boei, A. Jochems, D. Houtsma, H. Putter, J.J. van der Hoeven, J.W. Nortier, H. Pijl, J.R. Kroep, The effects of short-term fasting on tolerance to (neo) adjuvant chemotherapy in HER2-negative breast cancer patients: a randomized pilot study, BMC Cancer 15 (2015) 652.
[316] T.B. Dorff, S. Groshen, A. Garcia, M. Shah, D. Tsao-Wei, H. Pham, C.-W. Cheng, S. Brandhorst, P. Cohen, M. Wei, V. Longo, D.I. Quinn, Safety and feasibility of fasting in combination with platinum-based chemotherapy, BMC Cancer 16 (2016) 360.
[317] S.P. Bauersfeld, C.S. Kessler, M. Wischnewsky, A. Jaensch, N. Steckhan, R. Stange, B. Kunz, B. Brückner, J. Sehouli, A. Michalsen, The effects of short-term fasting on quality of life and tolerance to chemotherapy in patients with breast and ovarian cancer: a randomized cross-over pilot study, BMC Cancer 18 (2018) 476.
[318] S. de Groot, R.T. Lugtenberg, D. Cohen, M.J.P. Welters, I. Ehsan, M.P. G. Vreeswijk, V. Smit, H. de Graaf, J.B. Heijns, J.E.A. Portielje, A.J. van de Wouw, A.L.T. Imholz, L.W. Kessels, S. Vrijaldenhoven, A. Baars, E.M. Kranenbarg, M. D. Carpentier, H. Putter, J.J.M. van der Hoeven, J.W.R. Nortier, V.D. Longo, H. Pijl, J.R. Kroep, Fasting mimicking diet as an adjunct toneoadjuvant chemotherapy for breast cancer in the multicentre randomized phase 2 DIRECT trial, Nat. Commun. 11 (2020) 3083.
[319] C. Vernieri, F. Ligorio, E. Zattarin, L. Rivoltini, F. de Braud, Fasting-mimicking diet plus chemotherapy in breast cancer treatment, Nat. Commun. 11 (2020) 4274.
[320] F. Ligorio, G. Fucà, L. Provenzano, R. Lobefaro, L. Zanenga, A. Vingiani, A. Belfiore, A. Lorenzoni, A. Alessi, G. Pruneri, F. de Braud, C. Vernieri, Exceptional tumour responses to fasting-mimicking diet combined with standard anticancer therapies: a sub-analysis of the NCT03340935 trial, Eur. J. Cancer (Oxford Engl.: 1990) 172 (2022) 300–310.
[321] M. Shimobayashi, M.N. Hall, Making new contacts: the mTOR network in metabolism and signalling crosstalk, Nat. Rev. Mol. Cell Biol. 15 (2014) 155–162.
[322] J. Fang, H. Nakamura, A.K. Iyer, Tumor-targeted induction of oxystress for cancer therapy, J. Drug Target. 15 (2007) 475–486.
[323] S. Di Biase, C. Lee, S. Brandhorst, B. Manes, R. Buono, C.W. Cheng, M. Cacciottolo, A. Martin-Montalvo, R. de Cabo, M. Wei, T.E. Morgan, V. D. Longo, Fasting-mimicking diet reduces HO-1 to promote T cell-mediated tumor cytotoxicity, Cancer Cell 30 (2016) 136–146.
[324] Y.-F. Tu, P.-J. Lu, C.-C. Huang, C.-J. Ho, Y.-P. Chou, Moderate dietary restriction reduces p53-mediated neurovascular damage and microglia activation after hypoxic ischemia in neonatal brain, Stroke 43 (2012) 491–498.
[325] N. Mizushima, B. Levine, Autophagy in human diseases, N. Engl. J. Med. 383 (2020) 1564–1576.
[326] M. Bagherniya, A.E. Butler, G.E. Barreto, A. Sahebkar, The effect of fasting or calorie restriction on autophagy induction: a review of the literature, Ageing Res. Rev. 47 (2018) 183–197.
[327] M. Sadeghian, S. Rahmani, S. Khalesi, E. Hejazi, A review of fasting effects on the response of cancer to chemotherapy, Clin. Nutr. 40 (2021) 1669–1681.
[328] S. Zhou, A. Starkov, M.K. Froberg, R.L. Leino, K.B. Wallace, Cumulative and irreversible cardiac mitochondrial dysfunction induced by doxorubicin, Cancer Res. 61 (2001) 771–777.
[329] C.W. Cheng, G.B. Adams, L. Perin, M. Wei, X. Zhou, B.S. Lam, S. Da Sacco, M. Mirisola, D.I. Quinn, T.B. Dorff, J.J. Kopchick, V.D. Longo, Prolonged fasting reduces IGF-1/PKA to promote hematopoietic-stem-cell-based regeneration and reverse immunosuppression, Cell Stem Cell 14 (2014) 810–823.
[330] D. Ajona, S. Ortiz-Espinosa, T. Lozano, F. Exposito, A. Calvo, K. Valencia, M. Redrado, A. Remírez, F. Lecanda, D. Alignani, J.J. Lasarte, I. Macaya, Y. Senent, C. Bértolo, C. Sainz, I. Gil-Bazo, I. Eguren-Santamaría, J.M. Lopez-Picazo, A. Gonzalez, J.L. Perez-Gracia, C.E. de Andrea, S. Vicent, M.F. Sanmamed, L.M. Montuenga, R. Pio, Short-term starvation reduces IGF-1 levels to sensitize lung tumors to PD-1 immune checkpoint blockade, Nat. Can. 1 (2020) 75–85.
[331] H. Kolb, K. Kempf, M. Röhling, M. Lenzen-Schulte, N.C. Schloot, S. Martin, Ketone bodies: from enemy to friend and guardian angel, BMC Med. 19 (2021) 313.
[332] R.J. Klement, C.E. Champ, Calories, carbohydrates, and cancer therapy with radiation: exploiting the five R's through dietary manipulation, Cancer Metastasis Rev. 33 (2014) 217–229.
[333] C.Y. Hwang, W. Choe, K.S. Yoon, J. Ha, S.S. Kim, E.J. Yeo, I. Kang, Molecular mechanisms for ketone body metabolism, signaling functions, and therapeutic potential in cancer, Nutrients 14 (2022).
[334] J. Zhang, P.P. Jia, Q.L. Liu, M.H. Cong, Y. Gao, H.P. Shi, W.N. Yu, M.Y. Miao, Low ketolytic enzyme levels in tumors predict ketogenic diet responses in cancer cell lines in vitro and in vivo, J. Lipid Res. 59 (2018) 625–634.
[335] C.C. Ji, Y.Y. Hu, G. Cheng, L. Liang, B. Gao, Y.P. Ren, J.T. Liu, X.L. Cao, M. H. Zheng, S.Z. Li, F. Wan, H. Han, Z. Fei, A ketogenic diet attenuates proliferation and stemness of glioma stem-like cells by altering metabolism resulting in increased ROS production, Int. J. Oncol. 56 (2020) 606–617.
[336] W.H. Talib, A.I. Mahmod, A. Kamal, H.M. Rashid, A.M.D. Alashqar, S. Khater, D. Jamal, M. Waly, Ketogenic diet in cancer prevention and therapy: molecular targets and therapeutic opportunities, Curr. Issues Mol. Biol. 43 (2021) 558–589.
[337] A. Khodabakhshi, M.E. Akbari, H.R. Mirzaei, T.N. Seyfried, M. Kalamian, S. H. Davoodi, Effects of ketogenic metabolic therapy on patients with breast cancer: a randomized controlled clinical trial, Clin. Nutrit. (Edinbur., Scotl.) 40 (2021) 751–758.
[338] R. Wei, Y. Zhou, C. Li, P. Rychahou, S. Zhang, W.B. Titlow, G. Bauman, Y. Wu, J. Liu, C. Wang, H.L. Weiss, B.M. Evers, Q. Wang, Ketogenesis attenuates KLF5-

dependent production of CXCL12 to overcome the immunosuppressive tumor microenvironment in colorectal cancer, Cancer Res. 82 (2022) 1575–1588.
[339] H. Ying, A.C. Kimmelman, C.A. Lyssiotis, S. Hua, G.C. Chu, E. Fletcher-Sananikone, J.W. Locasale, J. Son, H. Zhang, J.L. Coloff, H. Yan, W. Wang, S. Chen, A. Viale, H. Zheng, J.H. Paik, C. Lim, A.R. Guimaraes, E.S. Martin, J. Chang, A.F. Hezel, S.R. Perry, J. Hu, B. Gan, Y. Xiao, J.M. Asara, R. Weissleder, Y.A. Wang, L. Chin, L.C. Cantley, R.A. DePinho, Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism, Cell 149 (2012) 656–670.
[340] N. Grankvist, J.D. Watrous, K.A. Lagerborg, Y. Lyutvinskiy, M. Jain, R. Nilsson, Profiling the metabolism of human cells by deep (13)C labeling, Cell Chem. Biol. 25 (2018) 1419–1427.e1414.
[341] L.B. Mahoney, C.A. Denny, T.N. Seyfried, Caloric restriction in C57BL/6J mice mimics therapeutic fasting in humans, Lipids Health Dis. 5 (2006) 13.
[342] T.N. Seyfried, R.E. Flores, A.M. Poff, D.P. D'Agostino, Cancer as a metabolic disease: implications for novel therapeutics, Carcinogenesis 35 (2014) 515–527.