Chapter 23

Transient Receptor Potential (TRP) channels in cancer: Implications for drug discovery and development

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Background and general aspects

In the last decade, many studies have shown the expression of different ion channels in human cancers and suggested their role in several cellular processes, including proliferation, migration, and invasion. Cellular responses induced by Ca^{2+} influx are context-specific and dependent on both the amplitude and pattern of the responses and the presence of specific regulatory signals and/or partner proteins [1−3]. Transient receptor potential (TRP) channels have recently emerged as potential targets in cancer therapy. They are expressed in a broad range of mammalian tissues and cells, and they are of special interest as they play key roles in regulating Ca^{2+}, Na^{+}, and Mg^{2+} ions [4]. Therefore, they have been directly linked to the hallmarks of cancer pathophysiology. Besides being expressed by several types of cancer cells, the tumor microenvironment contains TRP channels such as Canonical 1 and 6 (TRPC1, TRPC6), Melastatin 1, 2, 4, 7, and 8 (TRPM1, TRPM2, TRPM4, TRPM7, TRPM8), Vanilloid 1 (TRPV1, TRPV4), and Ankyrin 1 (TRPA1) mainly expressed by cancer cells and by immune, vascular endothelial smooth muscle, stromal cells, and sensory nerve endings that can influence the cancer characteristics by complex sensory−vascular−immune−tumor interactions and feedback mechanisms [5,6]. Previously, TRP-channel-targeted drug discovery focused only on pain-related conditions, but as our knowledge has grown about the role and function of these channels, these efforts expanded into new clinical indications such as cancer growth, metastatic features, and cancer-related pain. Studies looking into different type of cancers have demonstrated that tumor progression is often associated with altered expression of the TRP channels. Some TRP channels are functionally linked to different cellular events and structures that are important for cell migration and invasion, such as focal adhesion and actin cytoskeleton [7]. These findings suggest that TRP channels might be potential targets for drug developmental purposes in cancer therapy. This chapter summarizes the current literature data regarding the expression and potential function of several TRP channels in different types of cancer tissues and cell lines.

The TRPC channel family

The TRPC channel family consists of seven members (TRPC1−7), but TRPC2 is a pseudogene not expressed in humans [8]. TRPCs possess two coiled-coil domains, one in the N terminus and the other in the C terminus, four ankyrin domains in the N terminus, a TRP domain, a calmodulin, and IP3R-binding site in the C terminus. These highly conserved regions within the TRPC family are shown to be involved in protein interactions and regulation of their functions [9,10]. TRPC channels participate in both receptor-operated calcium entry (ROCE) and store-operated Ca^{2+} entry (SOCE) together with

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TRP Channels as Therapeutic Targets. https://doi.org/10.1016/B978-0-443-18653-0.00003-4
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Orai1 and STIM1 proteins [11]. The role of TRPC channels in tumor proliferation, migration, invasion, and neovascularization has been studied in a wide range of malignancies. Reports on critical role of the calcineurin pathway or other downstream targets such as the Na^+/Ca^{2+} exchanger or chlorine channels suggest possible pathways underlying their cancer-related roles [12]. Both up- and downregulation of TRPC proteins were shown to be associated with different phases of tumor progression in several types of human cancers. To date, research exploring the role of TRPC channels in cancer mainly focuses on TRPC1 and TRPC6, while TRPC2 and TRPC7 have not yet been investigated. High expression of TRPC1 in breast cancer [13,14], TRPC3 in glioblastoma [15], TRPC5 in colon cancer [16], and TRPC6 in prostate cancer (PCa) [17] and esophageal squamous cell carcinoma samples [18] have been linked to poor prognosis or bad therapeutic response. In addition, it was reported that TRPC1, TRPC4, and TRPC5 may mediate cancer cell resistance to certain chemotherapeutics and contribute to the adverse effects caused by some anticancer treatments [12,19–23].

TRPC1

Both in vitro and in vivo studies have demonstrated the expression levels of TRPC1 in different types of cancers. In breast cancer, TRPC1 expression is different depending on the type of tumor. TRPC1 was found to be overexpressed in human breast ductal adenocarcinoma compared with the normal tissues, and this overexpression strongly correlated with proliferation, tumor size, and prognosis [24]. Low expression of TRPC1 in basal-like and triple-negative breast cancer was associated with better prognosis, while in cases of luminal breast cancer patients, high expression of TRPC1 resulted in better outcomes [13] (Table 23.1). It was also shown that blocking TRPC1 can reduces cancer cell proliferation. TRPC1 knockdown in ML-1 thyroid cancer cells [25], in human hepatocellular carcinoma Huh7 cell line [26], in non-small-cell lung carcinoma (NSCLC) cell lines [27] remarkably attenuated cancer cell proliferation. Disruption of TRPC1 by shRNA knockdown approach caused incomplete cytokinesis and slowed malignant glioma growth in a flank tumor mouse model [28]. TRPC1 overexpression promoted colorectal tumor growth and progression both in vitro and in vivo by activating calmodulin-mediated phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway [29]. In addition, TRPC1 activation inhibited the proliferation and migration of estrogen receptor-positive breast cancer and improved the prognosis by inhibiting the PI3K/AKT pathway [30]. Other studies have employed different pharmacological modulators to determine the role of TRPC1 in ROCE and SOCE pathways related to cancer. For example, the selective TRP channel inhibitor 2-APB, the SOCE pathway inhibitor MRS1845, and the multitarget (SOCE, TRPC channels, and voltage-gated K^+ and Ca^{2+} channels) inhibitor SKF96365 were used [31]. Suppression of the SOCE pathways using 2-APB and La^{3+} reduced cytosolic Ca^{2+} entry induced by tumor growth factor-β (TGFβ), a key modulator of epithelial−mesenchymal transition through TRPC1 [32]. Knockdown of TRPC1 or treatment with 2-APB reversed TGFβ-induced pancreatic cancer cell motility [31]. Moreover, 2-APB, SKF96365, and MRS1845 largely reduced Ca^{2+} influx, proliferation, and the formation of multinucleated cells in D54MG malignant glioma cell as well as disrupted cells migration. To confirm the selective role of TRPC1 in SOCE, its function was blocked by a polyclonal antibody, which decreased the Ca^{2+} entry, reduced proliferation of enlarged multinucleated cells, whereas no effect was observed with TRPC5 inhibitors [28]. Blocking TRPC1 channels by 2-APB or a specific antibody inhibited proliferation of A549 human NSCLC [33]. Furthermore, TRPC1 was shown to be involved in regulating migration and invasion both in vivo and in vitro as it is an important component of a Ca^{2+}-dependent phosphorylation and activation of epidermal growth factor (EGF)-evoked cell proliferation and migration. TRPC1 also activates PI3K/AKT and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK, Ras-Raf-MEK-ERK pathway) signaling pathway [34]. Therefore, TRPC1 acts as a key player in both normal and cancer cell functions and might be a potential diagnostic and/or therapeutic target for cancer.

TRPC6

TRPC6 membrane expression and activation are regulated by receptor tyrosine kinases and diacylglycerol generated by G-protein-coupled receptors. Consequent Ca^{2+} influx leads to activation of intracellular pathways involved in pathological cell proliferation and human malignancies [35,95]. TRPC6 was shown to be overexpressed at both mRNA and protein levels in human esophageal cancer specimen [18] and gastric cancer cells compared with the healthy epithelium [35]. The expression of TRPC6 in human head and neck squamous cell carcinomas was also greatly upregulated, and knockdown of TRPC6 in these tumors significantly attenuated invasion [36]. TRPC6 expression was higher in isolated human hepatoma cells compared with healthy hepatocytes [37]. TRPC6 was overexpressed in human glioma cells and found to be highly important in Notch-driven glioblastoma invasiveness and growth by regulating G2/M phase transition [38,39]. Cell proliferation and invasion were increased in TRPC6-overexpressing A549 human NSCLC, and its knockdown decreased invasion and suppressed the expression of the adhesion protein fibronectin and the tight junction protein ZO-1 [40].

TABLE 23.1 TRP channels function in different types of cancer cells.

Channel	Cancer type	Cell line/Tissue	Function	References
TRPC1	Thyroid cancer	ML-1	Proliferation, migration, invasion	[25]
	Hepatocellular carcinoma	Huh7	Proliferation	[26]
	Lung cancer	NSCLC A549	Proliferation, invasion	[27,33]
	Breast cancer	MCF-7, MDA-MB-468, MDA-MB-23 /Tissue	Tumor growth, proliferation, migration, invasion	[13,24,30]
	Glioma	Tissue	Tumor growth	[28]
	Colorectal cancer	SW620, HT29/Tissue	Tumor growth	[29]
TRPC6	Esophageal cancer	KYSE30, KYSE140, KYSE180, KYSE 410, KYSE510, KYSE520, HKESC1, EC9706/ Tissue	Tumor growth and proliferation	[18]
	Gastric adenocarcinoma	AGS and MKN45/Tissue	Tumor growth and proliferation	[35]
	Head and neck cancer	SCC2, SCC40, SCC38, SCC42b /Tissue	Invasion	[36]
	Liver cancer	Huh7/Tissue	Proliferation	[37]
	Glioblastoma	U373MG, HMEC-1	Proliferation, invasion, angiogenesis	[38,39]
	Lung cancer	NSCLC A549	Proliferation, invasion	[40]
	Breast cancer	MCF-7 and MDA-MB-231	Proliferation, migration, invasion	[41]
TRPM2	Neuroblastoma	Neuroblastoma tumor cells and xenograft mouse model	Proliferation	[42,43]
	Acute myeloid leukemia	Human AML cell line	Proliferation	[44]
	Prostate cancer	PCa, PC3	Tumor growth	[45,46]
	Breast cancer	MDA-MB-231, MCF-7	Tumor growth, proliferation	[47,48]
TRPM4	Prostate cancer	PCa, DU145, PEC	Proliferation	[49]
	Breast cancer	4T1, T47D	Contractility, migration	[50]
	Leukemia	MLL-gene-rearranged leukemia cells	Proliferation	[51]
	Endometrial cancer	Tissue	Pathogenesis	[52,53]
TRPM7	Pancreatic ductal adenocarcinoma (PDAC)	Human PDAC, PANC-1 and MIA PaCa-2	Progression, invasion	[54,55]
	Prostate cancer	PCa, DU145, PC3	Proliferation, migration, invasion	[56,57]
	Breast cancer	MDA-MB-435	Migration, invasion	[58,59]
	Urinary bladder cancer	UMUC3, T24, xenograft mouse model	Proliferation, motility, migration, invasion, colony-formation	[60,61]
	Lung cancer	A549, 95D	Proliferation	[62,63]
	Glioblastoma	U87	Tumor growth, proliferation, migration,	[64]
	Hepatocellular carcinoma	HCC	Tumor growth, proliferation	[65]

Continued

TABLE 23.1 TRP channels function in different types of cancer cells.—cont'd

Channel	Cancer type	Cell line/Tissue	Function	References
TRPM8	Oral squamous cell carcinoma	HSC3 and HSC4	Migration, invasion	[66]
	Prostate cancer	LNCaP, PC3, DU145, xenograft mouse model	Tumor growth, proliferation	[67–73]
	Pancreatic adenocarcinoma	PANC-1, BxPC-3	Tumor growth, proliferation	[74]
	Glioblastoma	GBM, U251, T98G, U-87MG	Migration, proliferation	[75,76]
	Osteosarcoma	MG-63, U2OS,143B, HOS, xenograft mouse model	Tumor growth, proliferation	[77,78]
TRPV1	Breast cancer	MCF-7, BT-20	Tumor growth and progression	[79,80]
	Human papillary thyroid carcinoma	Thyroid cancer BCPAP cells	Tumor growth and progression	[81]
	Prostate cancer	LNCaP, PC-3	Tumor growth, proliferation	[82,83]
	Glioma	U373, U87, FC1 and FLS	Pro-apoptotic activity, tumor growth and progression	[84,85]
	Gastric cancer	MKN45, SGC7901, AGS, MGC803, BGC823, GES-1/ Tissue	Progression, proliferation, and migration	[86,87]
TRPA1	Pancreatic adenocarcinoma	Panc-1, MIA Paca-2, BxPC-3	Migration, cell cycle progression	[88]
	Hepatocellular carcinoma	HepG2	DNA damage, viability, migration	[89]
	Breast tumor	Breast tumor derived spheroids and endothelial cells, SUM149PT	ROS induced malignant transformation, migration,	[90,91]
	Bladder cancer	T24	Cell proliferation, cell morphology	[92]
	Cervix cancer	HeLa	Viability, apoptosis	[93]
	Lung cancer	Lung tumor derived spheroids, SCLC NCI—H146/SCLC tissue	ROS induced malignant transformation, cell survival, antiapoptotic effect	[90,94]

Furthermore, TRPC6 upregulation has been found in MCF-7 and MDA-MB-231 breast adenocarcinoma cell lines compared with normal breast epithelial MCF10A cells, which enhanced proliferation, migration, and invasion of these cells [41] (Table 23.1). The majority of studies suggest this critical role to be through Ca^{2+}-related cell cycle modulation in these cells [34]. In this context, blocking TRPC6 activity may be a novel strategy to arrest cancer cells at G2/M phase rendering them responsive for radiotherapy. For example, it was demonstrated that inhibition of TRPC6 arrests human umbilical vein endothelial cells (HUVECs) at G2/M phase and attenuate vascular endothelial growth factor-induced HUVEC proliferation [96]. Blocking TRPC6 channels in human esophageal cancer cells depleted intracellular Ca^{2+} concentration and suppressed the activation of cyclin-dependent kinase 1 leading to cell cycle arrest and attenuation of tumor cell growth both in vitro and in vivo [97]. Moreover, in renal cell carcinoma, TRPC6 blockage prolonged the transition through G2/M phase and reduced tumor cell proliferation [98]. Based on that, targeting TRPC6 channel function may bring benefit to the treatment of different diseases, including cancers. Due to the highly conserved sequence among

TRPC channels, very few selective TRPC6 inhibitors have been developed and shown strong growth-inhibitory effects on cancer. Interestingly, vitamin D greatly reduced Ca^{2+}-mediated prostate tumorigenesis by suppressing calcium sensing receptor and TRPC6 both in vitro and in vivo [99]. SKF96365 inhibited Ca^{2+} elevation mediated by TRPC6 channels and supported the results from siRNA silencing to arrest the cell cycle in G2/M phase and suppress growth of gastric cancer cells and tumor formation in a mouse xenograft model [35,100]. Several other TRPC6 antagonists were reported, but very few of them were employed in vivo because they showed poor selectivity, low potency, or low oral bioavailability. Recently, some pyrazolo[1,5-a] pyrimidine-based selective TRPC6 inhibitors [100] and benzothiazole amides [101] effectively inhibited gastric cancer cell growth in cultures and mouse xenograft models. Based on these data, it is suggested that TRPC6 antagonists offer anticancer therapeutic potential, which needs further studies to confirm.

The TRPM channel family

TRPM channels represent the most diverse TRP receptor family consisting of eight members. TRPMs are activated by Ca^{2+}, Mn^{2+}, Na^{+}, K^{+}, Ba^{2+}, Cs^{+}, and Mg^{2+} ions, voltages, temperatures, and lipid compounds [102]. Some TRPM channels compose cytoskeletal complexes, which regulate ion homeostasis. Recent observations highlight the role of TRPMs in autophagy, cancer metabolic reprogramming, and tumor epithelial mesenchymal transition leading to cancer cell growth, survival, or death.

TRPM1

TRPM1 has been implicated in malignant skin diseases such as cutaneous melanoma, dysplastic and benign nevi [103]. Its reduced expression was found in more advanced melanomas [104]. The increase in miR-211 expression reduces the gene expression of the growth factor receptors IGF2R and TGFBR2, as well as the nuclear factor of activated T cells 5, thus the invasion of malignant melanoma cell lines [105].

TRPM2

Pathological processes triggering oxidative stress activate TRPM2 [42,106,107], which increase intracellular Ca^{2+} concentration leading to cell death [108–110]. In contrast, there are also data that Ca^{2+} entry can play a protective role in damaged cells [111]. TRPM2 activation modulates both antioxidant responses and ROS production in neuroblastoma cells and xenograft mouse models leading to cell survival and proliferation through transcription factors and kinases [42,43]. Inhibition of TRPM2 induces mitochondrial dysfunction and increased ROS generation, while depletion of antioxidants results in cell death. A mechanism of action similar to that observed in neuroblastoma is seen in *in vitro* and in vivo models of acute myeloid leukemia. Deletion of TRPM2 in cells causes decreased Ca^{2+} uptake, along with reduced antioxidant response. These effects inhibit leukemia proliferation and at the same time increase sensitivity to doxorubicin [44]. TRPM2 expression is increased in PCa cells [45]. In PC3 PCa cells, H_2O_2 increases intracellular Ca^{2+} levels, decreases levels of the autophagy marker LC3-II, and leads to apoptotic cell death [46]. TRPM2 was also detected in human breast cancer (MDA-MB-231 and MCF-7 cells), and tumor cell proliferation could be reduced with an inhibitor (2-APB) or RNAi gene silencing. TRPM2 inhibition led to cell death after treatment with doxorubicin or N-methyl-N′-nitro-N-nitrosoguanidine in MDA-MB-231 cells, and in both MDA-MB-231 and MCF-7 cells, TRPM2 silencing increased both tamoxifen- and doxorubicin-induced cell death [47,48] (Table 23.1).

TRPM4

The TRPM4 channel has been identified as a protective prognostic gene in endometrial cancer (EC) [52,53]. TRPM4 silencing downregulates the p53 and PI3K/AKT signaling pathways, which are involved in the pathogenesis of EC. Low TRPM4 expression in EC patient tissues is associated with worse recurrence-free and overall survival [53]. TRPM4 is one of the leading genes in nonhormonal PCa. Its increased expression has been detected in PCa and prostatic intraepithelial neoplastic tissues [49]. TRPM4 knockdown significantly increased SOCE in normal prostate epithelial cells and the DU145 PCa cells, which is a human cell line with epithelial morphology. TRPM4 and K^{+} channel tetramerization domain

5 protein are overexpressed in breast cancer, which increases the Ca^{2+} sensitivity of the channel and promotes cell contractility and migration [50] (Table 23.1). TRPM4 knockdown arrested the cell cycle at the G0/G1 phase in mixed-lineage leukemia rearranged (MLL-r) leukemia cells, therefore decreased tumor proliferation. TRPM4 has been described to be involved in the regulation of the AKT/GLI1/Cyclin D1 pathway, therefore in the pathogenesis of this type of leukemia [51].

TRPM7

TRPM7 was found to be essential for pancreatic progression and invasion of ductal adenocarcinoma via inducing Mg^{2+} entry [54], therefore silencing TRPM7 reduced cancer cell invasion [55]. TRPM7 was overexpressed in PCa cells and tissues leading to poor survival [56], and its activation leads to increased serum Ca^{2+}/Mg^{2+} ratio and cell proliferation in PCa [57]. Knockdown of TRPM7 in androgen-independent DU145 and PC3 PCa cells suppressed migration and invasion [56]. Increased expression level of TRPM7 reduced survival in luminal A breast cancer patients, deadhesion of cell−matrix interactions and myosin−II−based cell strains are TRPM7-dependent [58]. TRPM7 also had a role in the migration and invasion of MDA-MB-435 breast cancer cells through the regulation of the Src and MAPK pathways [59]. TRPM7 upregulation was described in urinary bladder cancer proliferation, motility, and apoptosis [60,61]. Its silencing decreased c-Jun N-terminal kinase, Akt and Src phosphorylation, therefore the migration and invasion ability of the human epithelial urinary bladder cancer UMUC3 and T24 cells. In addition, the TRPM7 antagonist oridonin inhibited the T24 cell proliferation, migration, and colony formation [60]. Another TRPM7 inhibitor, carvacrol, diminished the bladder tumor size in a xenograft mouse model [61]. TRPM7 is overexpressed in the most commonly used A549 human NSCLC after EGF stimulation [62]. The lipid raft constituent Cav-1 overexpressed in lung adenocarcinoma is decreased by TRPM7 inhibition [63]. In U87 glioblastoma cells, the TRPM7 agonist, naltriben, evoked Ca^{2+}-related MAPK/ERK signaling pathway activation. In addition, carvacrol induced apoptosis and diminished cell growth, cell viability, migration, and matrix metalloprotease 2 protein expression in these glioblastoma cells [64]. In hepatocellular carcinoma, inhibition of the TRPM7/myocardin-related transcription factors A and B inhibited cell growth. TRPM7 blockade arrested cell cycle in G1 phase. Meanwhile, TRPM7 activation induced Mg^{2+} influx too, which is required for kinase activity resulting in TRPM7-Ras homolog family member A (RhoA) interaction and myocardin-related transcription factor transcriptional activity [65].

TRPM8

TRPM8 was reported to be overexpressed in oral squamous cell carcinoma (SCC) cells, and the TRPM8 antagonist RQ-00203078 reduced migration and invasion capability of HSC3 and HSC4 SCC cell lines [66]. TRPM8 was also upregulated in several prostate cancer types. In prostate epithelial cells, the TRPM8 gene promoter activation was found to be androgen receptor activation-dependent [67,68]. Overexpression of TRPM8 transcript has been described in the androgen-responsive LNCaP PCa cells [69], in which TRPM8 silencing or capsazepine blockade decreased cell viability and induced apoptosis [67]. Other TRPM8 blockers BCTC, AMT, and JNJ41876666 decreased cell proliferation in both the androgen-responsive LNCaP and the androgen-unresponsive PC3 and DU145 cell lines. TRPM8 silencing in different prostatic tumor cells arrested cells in the G0/G1 phases [70] TRPM8 depletion increased p38 MAPK and c-Jun N-terminal kinase (JNK) phosphorylation and inhibited cell proliferation in LNCaP and PC3 cells [71]. The TRPM8 agonist menthol induced antiproliferative effect in PC3 cells and in a Pca xenograft mouse model [72]. A novel, selective tetrahydroisoquinoline-based TRPM8 antagonist had strong antiproliferative effect in LNCaP cells [73]. Pancreatic adenocarcinoma cell lines also overexpressed TRPM8 channels, and its silencing decreased cell proliferation and arrested the cell cycle in the G1 in PANC-1 and BxPC-3 cell lines [54]. The TRPM8 agonists menthol and icilin increased glioblastoma cell migration rate [75] and increased proliferation of U251 glioblastoma cells [76]. Icilin also increased migration speed in T98G and U-87MG glioblastoma cell lines through the activation of the large-conductance Ca^{2+-}activated K^+ membrane ion channels (BK) [75]. TRPM8 was found upregulated in human osteosarcoma cancer cell lines MG-63 and U2OS leading to increased proliferation [77]. TRPM8 silencing arrested cell cycle in G0/G1 through decreased p-GSK-3β and p-Akt expressions. TRPM8 silencing not only negatively influences the cell proliferation and metastasis but also increases epirubicin-evoked cell apoptosis [112]. The TRPM8 antagonist AMTB resulted in suppressed proliferation and apoptosis induction in 43B, U2OS, HOS, and MG-63 osteosarcoma cells. In nude mice xenograft model, AMTB repressed the activation of TGFβ signaling and increased the sensitivity of tumor cells to cisplatin [78] (Table 23.1).

The TRPV channel family

TRPV receptors are structurally similar to the other TRP channels, but they contain additional three to five ankyrin repeat domains in the N-terminus. TRPV family members are related to specific activation mechanisms and physiological functions [1]. They are activated by multiple stimuli (noxious heat, protons, vanilloids such as capsaicin) and participate in the activation of several downstream cascades [113].

Based on their homology, the six members of the TRPV subfamily can be classified into four groups: TRPV1/TRPV2, TRPV3, TRPV4, and TRPV5/TRPV6 [114]. Among these, TRPV1 is the most thoroughly investigated member in relation to pain, inflammation, neural functions, and cancer.

TRPV1

TRPV1 is expressed in a wide range of tissues, most importantly on the capsaicin-sensitive sensory neurons, but also in the skin, airways, GI tract, immune cells, pancreatic B cells, and urinary epithelial cells [115]. Noxious heat (>43°C), protons, capsaicin and other vanilloids, and bacterial toxins such as lipopolysaccharide activate this channel [116,117], TRPV1 was originally associated with thermosensation, nociception, and pain. It can also be sensitized by inflammatory molecules, such as bradykinin, through G-protein-coupled receptors and substance-P, which generate second messengers such as phosphatidylinositol-4,5-biphosphate, inositol triphosphate, and diacylglycerol [118]. The TRPV1 agonists capsaicin and resiniferatoxin, as well as antagonists such as capsazepine, BCTC, SB-705,498, NEO6860 were investigated to manage migraine, osteoarthritis, bladder, dermatitis, and neuropathic pain. Activation of TRPV1 receptors can be associated with antiinflammatory and anticancer effects [119].

Different studies indicated TRPV1 to be a potential as a drug target for cancer genesis and development. Functional expression of TRPV1 was demonstrated in several tumor types such as human breast cancer MCF-7 and BT-20 cells, human papillary thyroid carcinoma BCPAP cells, LNCaP and PC-3 prostate adenocarcinoma cells, urothelial cancer cells, and glioma [79,81,82,84]. The role of TRPV1 in tumorigenesis is not clear. Its capsaicin-induced activation was shown to significantly reduce proliferation and induce apoptosis of aggressive triple-negative breast cancer SUM149PT cells [79]. Increased TRPV1 expression was shown in high-grade astrocytoma, and its stimulation induced tumor cell death through activating the transcription factor-3 [120]. On the other hand, studies showed that despite the presence of TRPV1 in breast (MCF7, MDA-MB- 231, BT-474) and prostate carcinoma (PC-3, Du 145, LNCaP) cell lines, capsaicin administration at high concentration (50 μM) did not exhibit cytotoxic effect [80]. TRPV1 uniquely extinguished gastric cancer development through a novel Ca^{2+}/calmodulin-dependent protein kinase kinase/adenosine 5'monophosphate-activated protein kinase (Ca^{2+}/CaMKKβ/AMPK) pathway, and its downregulation relates to poor survival of gastric cancer patients [86] (Table 23.1).

TRPV1 channels play unique role in the pathogenesis of lung adenocarcinoma. Hyperexpression of TRPV1 increased the proliferation and migration of tumor cells through the nuclear accumulation of the hypoxia-inducible factor 1α and Nitric oxide synthase 1 (NOS1−NO) pathway in multiple lung cancer cells, including A549 cells and clinical tissue samples from lung cancer patients. Newly discovered mechanism, which photothermal nanoparticles (CuS-TRPV1 mAb) targeted to TRPV1, may kill tumor cells with TRPV1 overexpression, causes inhibited tumor proliferation and metastasis [121].

TRPA1

TRPA1 is the sole member of the TRP ankyrin family expressed in a wide range of human and animal cell types. TRPA1 is a promiscuous channel activated by numerous exogenous (cinnamaldehyde, allyl-isothiocyanate- AITC, cold temperature) and endogenous irritants and inflammatory substances (formalin, H_2O_2), as well as environmental pollutants (acrolein, nicotine, tear gases). It plays a role in both proinflammatory and protective responses such as tearing, airway resistance, and cough [122]. Recent studies suggest that since TRPA1 is activated by both reactive and nonreactive compounds, it acts as an important chemosensor being responsible for tissue homeostasis [123,124].

TRPA1 has been described to be overexpressed in some tumors; however, data are controversial on its role. TRPA1 activation in glioblastoma cells by excessive production of intracellular reactive oxygen species [125] or a synthetic agonist leads to apoptosis [126]. Furthermore, in glioma cells, TRPA1 activation resulted in decreased expressions of the DNA repair enzyme O6-methylguanine DNA-methyltransferase and several antioxidant enzymes. These led to mitochondrial

dysfunction and ultimate cell apoptosis, while receptor antagonism exerted the opposite effect [126]. In contrast, TRPA1 activation increases intracellular Ca^{2+} level and consequently antiapoptotic pathway activation leading to cell migration and presumably tumor cell invasion [90]. Elevated TRPA1 expression was detected in human small cell lung cancer (SCLC). In contrast to glioma cells, TRPA1 activation prevented apoptosis and thus promoted cell survival in this type of cancer cells [94] (Table 23.1).

In poorly differentiated pancreatic adenocarcinoma MIA-Paca-2 and Panc-1cell lines, TRPA1 expression has been reported, but only a modest proportion of cells responded to the TRPA1 agonist AITC during both Ca^{2+} microfluorimetry and patch-clamp experiments. These results were contradictory with immunofluorescence results showing high TRPA1 protein expression in 90% of pancreatic cells [88]. This suggests either nonspecific TRPA1 immunostaining or other factors regulating TRPA1 receptor translocation and functional expression in these tumor cells. In HepG2 human hepatocellular carcinoma cells, high dose ($\geq$20 μM) AITC induced significant DNA-damage and reduced the cell viability and migration [89]. The anticancer effects of AITC treatment were also demonstrated in bladder [92] and cervix cancer cells [93].

Moving toward head and neck located cancers, upregulated TRPA1-like immunopositivity was described in nasopharyngeal carcinoma with negative predictive value for disease-specific metastasis and local recurrence-free survival [6,127] (Table 23.1). Elevated *TRPA1* mRNA expression was observed in human oral squamous cell carcinoma (OSCC) samples compared with healthy oral mucosa using RT-qPCR and RNAScope in situ hybridization. The functionality of TRPA1 was also proved after AITC administration in PECA/PJ-41 oral squamous cell carcinoma cell line. Furthermore, incubation with AITC significantly reduced the viability of the OSCC cell line [128].

TRP channels in cancer pain

Chronic pain is a common symptom during cancer progression, which represents a unique and distinct mechanism. It is caused by the cancer proliferation and metastasis formation (e.g., bones) and/or the cancer treatment (chemotherapy, targeted treatments), which further complicates the prognosis and significantly decreases the quality of life [129]. Moderate and severe cancer pain is often treated with opioid-based pharmacotherapy, but these drugs have many side effects; therefore, it is a huge unmet need where novel drug targets and mechanisms are inevitable.

TRP channels are crucial in the transduction of nociceptive stimuli. Mediators released in the tumor microenvironment can modulate the activity of TRP channels through the regulation of intracellular signaling pathways. Their modulation is related to the peripheral sensitization observed in cancer patients, which results in mild noxious sensory stimuli being perceived as severe spontaneous pain, hyperalgesia, and allodynia. TRPV1 expression in cells involved in detecting cancer pain and their role in pain processing makes them potential targets for analgesics. Although their direct activation on primary sensory neurons plays a key role in the development of cancer pain [130], oxidizing agents produced by the cancer and other cells (e.g., immune, vascular, endothelial cells and fibroblasts) sensitize these channels [131,132]. TRPV1 sensitization is also mediated by protease-activated receptor 2 signaling in these fibers innervating the cancer microenvironment [133].

TRPV1 is upregulated on sensory neurons that innervate oral cancers by which it mediates pain [134,135].

Pharmacological modulation of TRPV1 represents a strategy for the treatment of chronic pain. The validation of TRPV1 as a therapeutic target for the control of pain and inflammatory conditions in a variety of diseases has prompted the development of several TRPV1 agonists and antagonists that have entered clinical trials. There are several distinct outcomes in preclinical pain models in the case of TRPV1 antagonists (AMG517, ABT-102, JTS653, AZD-1386, MK-2295) such as affecting core body temperature causing adverse effects (hyperthermia and impaired noxious heat sensation) in humans, leading to their withdrawal from clinical trials [136].

TRPV1 is unique among drug targets in that its initial excitation by agonists is followed by a lasting refractory state (traditionally referred to as desensitization) in which TRPV1-expressing neurons are not responsive to stimulation. Currently, there are several clinical trials with therapeutic formulation of capsaicin, as capsaicin patch (Qutenza, 8%) or gel (0.025%) for the treatment of neuropathic pain in various diseases [136,137].

The transdermal capsaicin patch was approved as effective adjuvant therapy, either alone or in combination with other analgesics and offers a low-risk choice for patients for pain control. Its systemic absorption has severe side effects on blood pressure and respiration, but several improvements of topical and injectable agents are tested [137]. In the future, there are alternative approaches, such as gene editing of the expression or posttranslational modification of TRPV1 [21]. Finally, in cancer and chemotherapy-induced pain, either pharmacological blockade or genetic manipulation of TRPV1 has proved to be effective experimentally [134,138].

Similar to TRPV1, TRPA1 is also highly expressed on nociceptors and involved in pain and inflammation [136]. TRPA1 has the greatest sensitivity to oxidative stress and can be activated by a diverse series of oxidative by-products such

as H_2O_2, nitrooleic acid, 4-hydroxy-trans-2-nonenal, 4-oxononenal, and acrolein [139] that are present at high amount in cancerous tissues [140]. Furthermore, irradiation and antineoplastic agents such as anthracyclines (e.g., doxorubicin, epirubicin, daunorubicin), alkylating agents, platinum containing complexes (e.g., cisplatin, carboplatin, oxaliplatin), epipodophyllotoxins (e.g., etoposide, teniposide), and camptothecins (e.g., topotecan, irinotecan) generate high levels of oxidative stress [141,142]. Moreover, in vivo studies also demonstrated that TRPA1 can directly be activated by the chemotherapeutic agent dacarbazine used in the treatment of Hodgkin lymphoma and melanoma [143], and aromatase inhibitors such as letrozole and anastrozole representing first-line chemotherapeutic agents in breast cancer [144]. Various preclinical models have shown the involvement of TRPA1 in cancer pain. Genetic deletion of TRPA1 attenuated both mechanical and cold allodynia and thigmotaxis behavior of mice injected with B16−F10 melanoma cells. TRPA1 mRNA expression was elevated in cultured trigeminal ganglion neurons of these animals [145]. In a mouse model of breast cancer, both the TRPA1 receptor antagonist HC-030,031 and the TRPA1 receptor antisense oligonucleotide exerted antiallodynic and antinociceptive effects. Moreover, the antioxidant lipoic acid (shown to act as a TRPA1 antagonist [146] reduced pain thresholds in this model [147]. TRPA1 deletion decreased pain behaviors in a mouse model of chemotherapy-induced peripheral neuropathy [139,148].

Summary

All these data demonstrate the expression and activity changes of a broad range of TRP channels in different types of cancers (Fig. 23.1) and suggest that these receptors may serve as valuable biomarkers to predict cancer prognosis or as potential therapeutic targets. Several mechanisms including mitochondrial dysfunction and caspase3 (Casp3) activation, focal adhesion kinase (FAK) activation, the MAPK/ERK, and PI3K/AKT through TRP-dependent Ca^{2+} signaling may affect apoptosis, proliferation, migration, and invasion ability of cancer cells altering progression and metastasis formation in both directions depending on cancer type and complex tumor−neuro−vascular−immune interactions in the microenvironment [7] (Fig. 23.2).

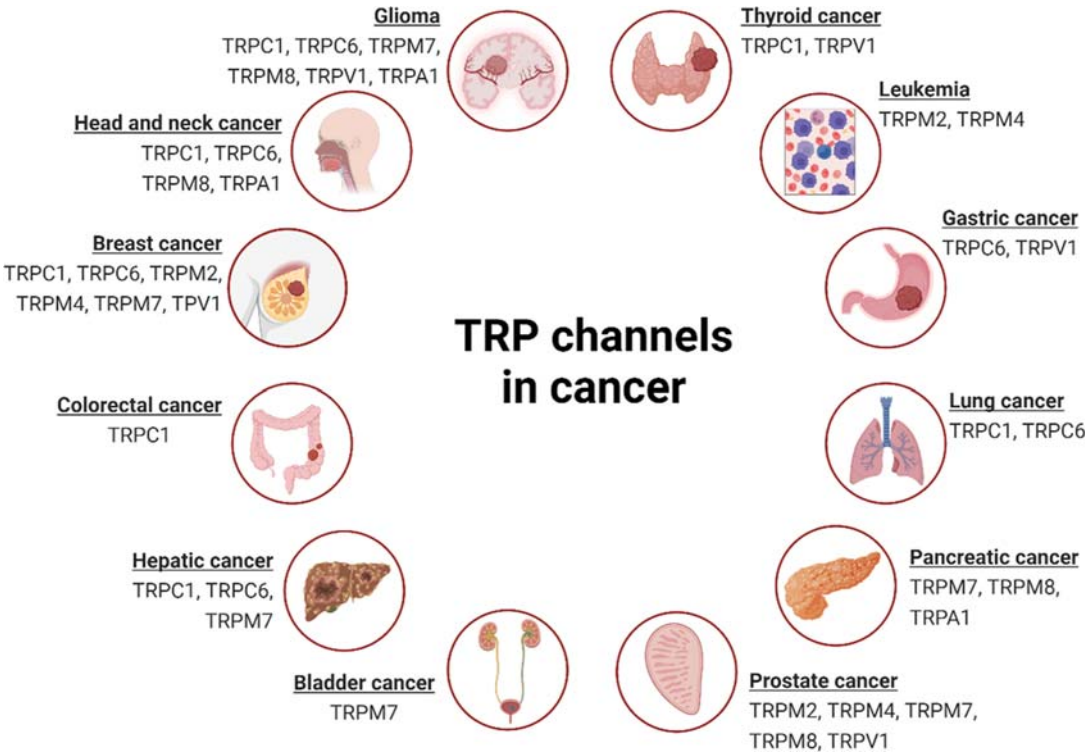

FIGURE 23.1 Overview of the expression and/or functional changes of several TRP channels in different types of cancers. Adapted from "increased risk of cancers with Obesity template", by BioRender.com (2023). *Retrieved from https://app.biorender.com/biorender-templates.*

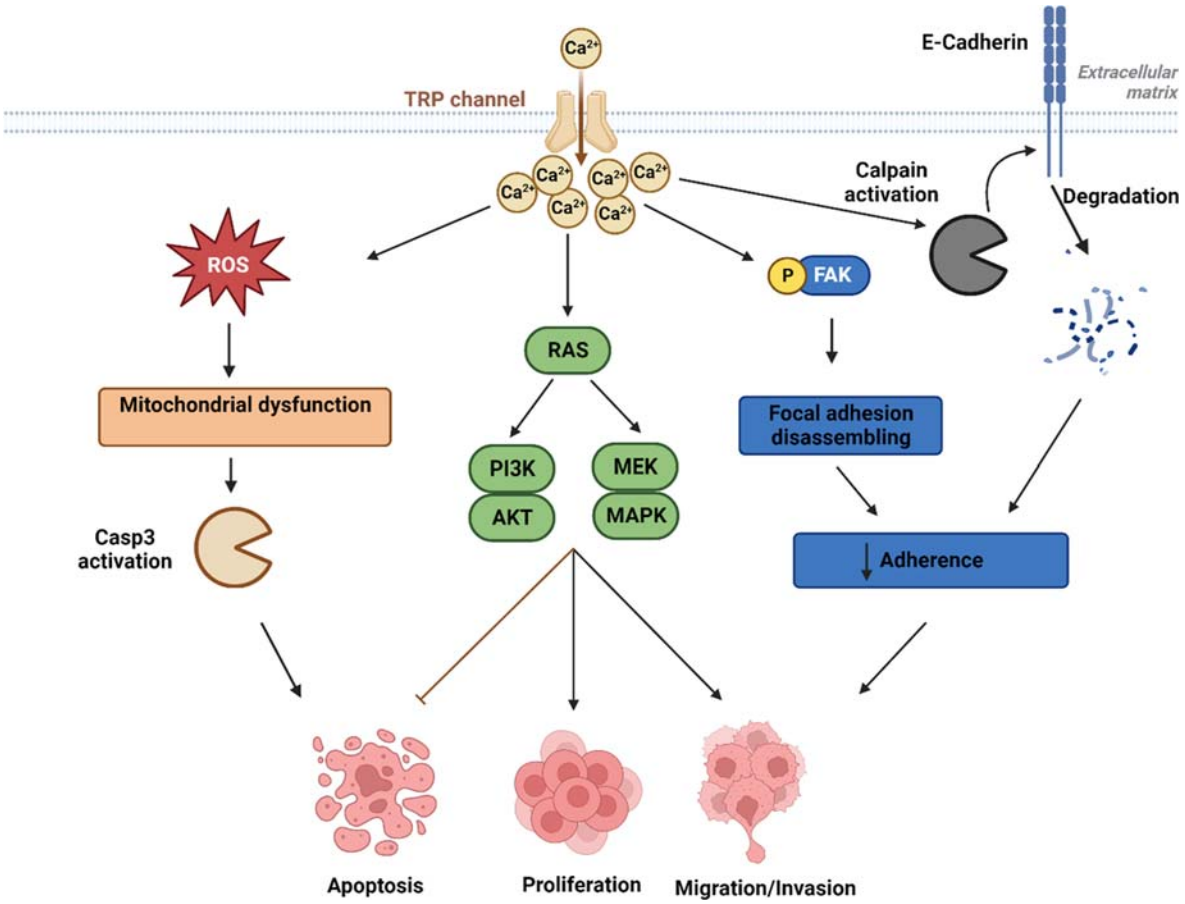

FIGURE 23.2 Representative image of the role of TRP channels-mediated Ca^{2+} signaling on cancer cellular processes. *Created with http://www.BioRender.com.*

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