# Mechanisms allowing human milk to increase energy expenditure and protect from childhood obesity

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**Key words**
- adiposity
- breastfeeding
- childhood obesity
- metabolism
- obesity

**Abstract**

Childhood obesity is a crucial contributor to adult obesity, diabetes and cardiovascular disease and since its prevalence is rising sharply, it poses a serious public health challenge today. Recent findings suggest that breastfeeding reduces the likelihood of developing obesity in childhood, and some human milk components have been identified as important factors in shaping body composition and metabolism during early development. Human milk not only provides metabolic fuels, but also delivers unique signals that stimulate the differential utilization of nutrients and control energy expenditure. This Review provides an overview on our current understanding of the effects of human milk signals on energy expenditure, which may protect from adiposity in childhood.

**Kulcsszavak**
- adipozitás
- anyagcsere
- anyatej
- elhízás
- gyermekkori elhízás

## Az anyatej szerepe az újszülöttkori energiafelhasználás szabályozásában és az elhízás elleni védelemben

A gyermekkori elhízás jelentősen megnöveli a felnőttkorban kialakuló elhízás és az ezzel összefüggő cukorbetegség, valamint szív- és érrendszeri megbetegedések kockázatát. Mivel a gyermekkori elhízás előfordulási aránya rohamosan növekszik világszerte, napjaink egyik egészségügyi kihívásává vált a folyamat megfékezése és visszafordítása. Az utóbbi évek kutatásai az anyatejes táplálás jelentőségére hívják fel a figyelmet, mivel egyes megfigyelések szerint az anyatejjel táplált újszülöttek körében csökken a gyermekkori elhízás kialakulásának esélye. Az anyatej ugyanis

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nemcsak tápanyagokkal látja el az újszülöttet, hanem olyan molekulákat is tartalmaz, melyek jelátvivő szerepet töltenek be az anya és a gyermeke között, és meghatározzák a tápanyagok hasznosulását az újszülött szervezetében. Többek között az anyatej egyes molekulái serkentik a zsírszövet és az izomzat energiatermelő folyamatait, ezáltal csökkentik a depózsír kialakulását. Ebben az összefoglaló közleményben azokat a legújabban feltárt molekuláris mechanizmusokat tekintjük át, melyek nélkülözhetetlenek az egészséges testösszetétel kialakulásához és képesek lehetnek csökkenteni a gyermekkori elhízás kockázatát.

Childhood obesity rates have risen sharply in the last 30 years and efforts to understand its causes and curb its progression have had limited success.[1] Approximately one-third of children worldwide currently have some degree of overweight and nearly 11% of children aged 5–9 years and 7% of adolescents aged 10–19 years experienced obesity in 2022.[2] Moreover, ~50% of children with obesity and 80% of adolescents with severe obesity will carry their obesity through to adulthood.[1,3] Body mass index (BMI) and BMI trajectories that reflect the rate of growth during childhood, can predict BMI in adulthood.[1,3] The latest trends in childhood BMI trajectories indicate that nearly 57% of young individuals will become obese in adulthood.[1] Childhood obesity not only increases the likelihood of lifelong overweight or obesity, but also doubles the risk of diabetes, hypertension and cardiovascular disease.[1] Pediatric obesity is thus a crucial contributor to adult obesity and metabolic diseases and poses a serious public health challenge *(Figure 1, 2)*.

There are two critical periods during infancy and early childhood that determine body adiposity and impact BMI trajectories *(Figure 3)*: the first occurs during the first year of life, characterized by an infancy peak of BMI, and the second is the so-called adiposity rebound at ~5.5 years of age.[3] Rapid weight gain within the first year of life increases the likelihood of early adiposity rebound,

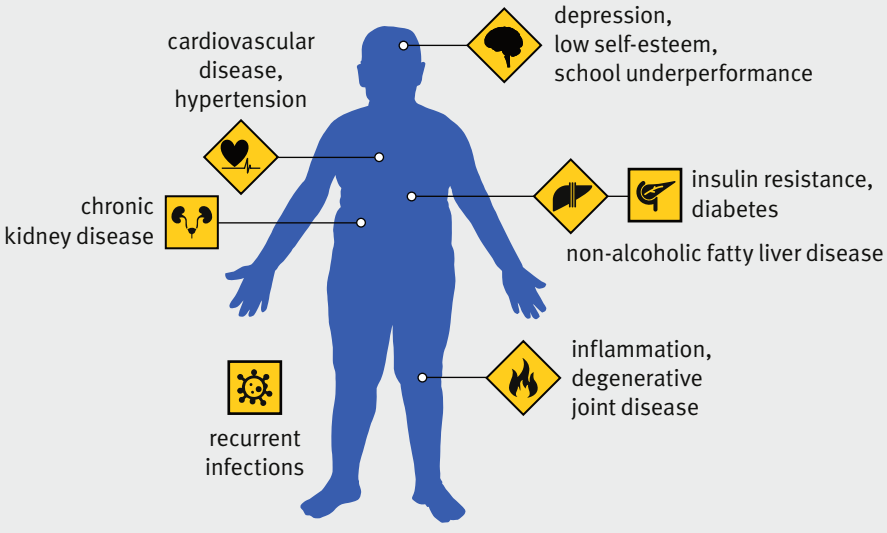


**Figure 1.** Health risks of pediatric obesity

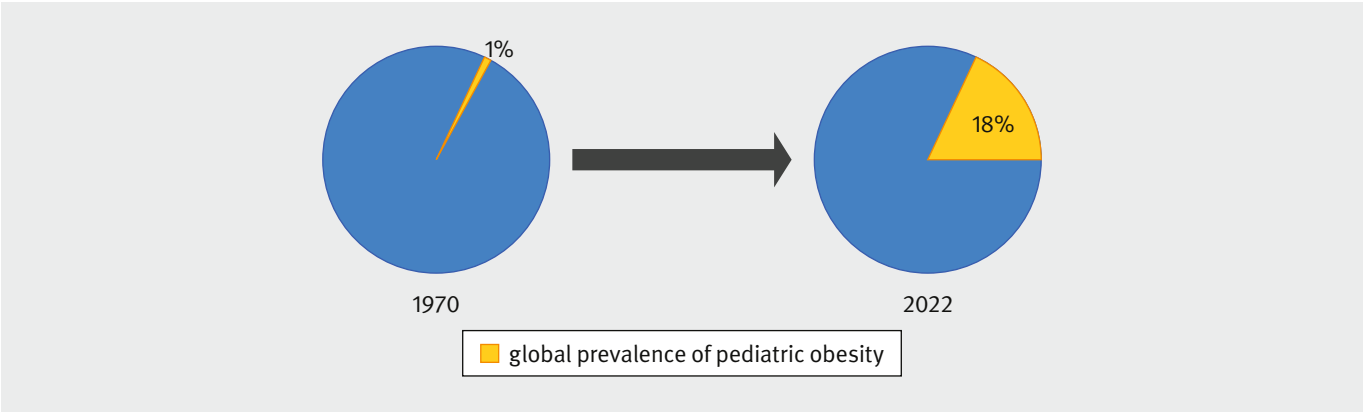


**Figure 2.** Clinical relevance of pediatric obesity – Rapid increase in the global prevalence of pediatric obesity from the 1970s to the 2020s

leading to overweight or obesity in adulthood.[4,5] It is estimated that developing obesity at 2 years of age is associated with a 74.9% probability of developing obesity at 35 years of age.[5] This contrasts with non-obese children for whom the risk of experiencing obesity in adulthood decreases with age.[5]

The World Health Organization recommends that infants should be exclusively breastfed for the first 6 months of their life, with continued human milk feeding up to 2 years, while also being introduced to complementary foods.[6] However, breastfeeding may be insufficient due to the failure of lactation on the part of the mother, or to shortening of the breastfeeding period. There is a potential link between inadequate human milk feeding and the progressive escalation of childhood obesity, leading to a higher prevalence of overweight and obesity in adulthood.[7,8,9,10] There is evidence that human milk feeding protects against overweight and obesity in early childhood.[11,12] Moreover, there is an increased diabetes risk in infants who never received human milk.[12,13]

Several molecules specific to human milk have been discovered recently that promote the differential use of

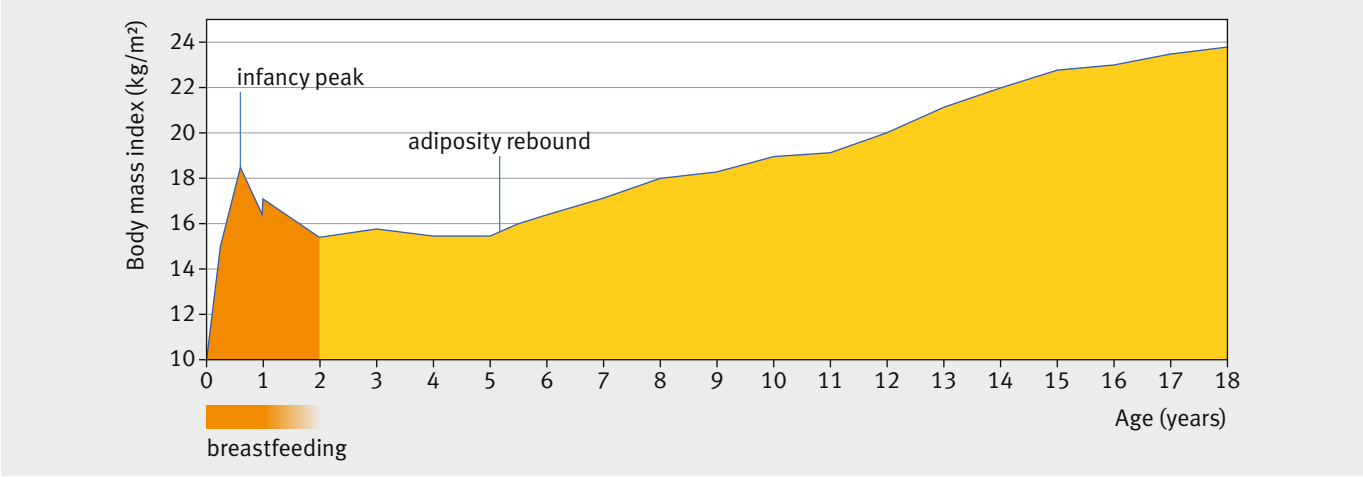


**Figure 3.** Body mass index trajectory of infants and children, indicating critical periods that determine adiposity


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metabolic fuels and protect from adiposity.[14,15] Many of these constituents are absent or present in low amounts in infant formula, which is mostly a highly processed derivative of cow's milk or soy milk. These findings have paved the way for the novel concept of a mother-to-child signaling axis that conveys maternal cues to regulate the metabolism of offspring through human milk components.[7,8,9,10]

From a clinical perspective, the metabolic effects of breastfeeding have implications for the life quality of children. This review updates our knowledge on the metabolic benefits of human milk, and the mechanisms linking breastfeeding to energy utilization.

## HUMAN MILK COMPONENTS INCREASE THERMOGENIC FAT DEVELOPMENT

Because the relative body surface of a newborn is orders of magnitude greater than that of an adult, and because extrauterine life begins with an adaptation to a hypothermic environment, it is vital that metabolic fuels are rapidly broken down in uncoupled mitochondrial respiration to generate heat.[16] Animal studies have demonstrated that suckling increases thermogenesis in the adipose tissue, ultimately increasing energy expenditure.[9,15,17]

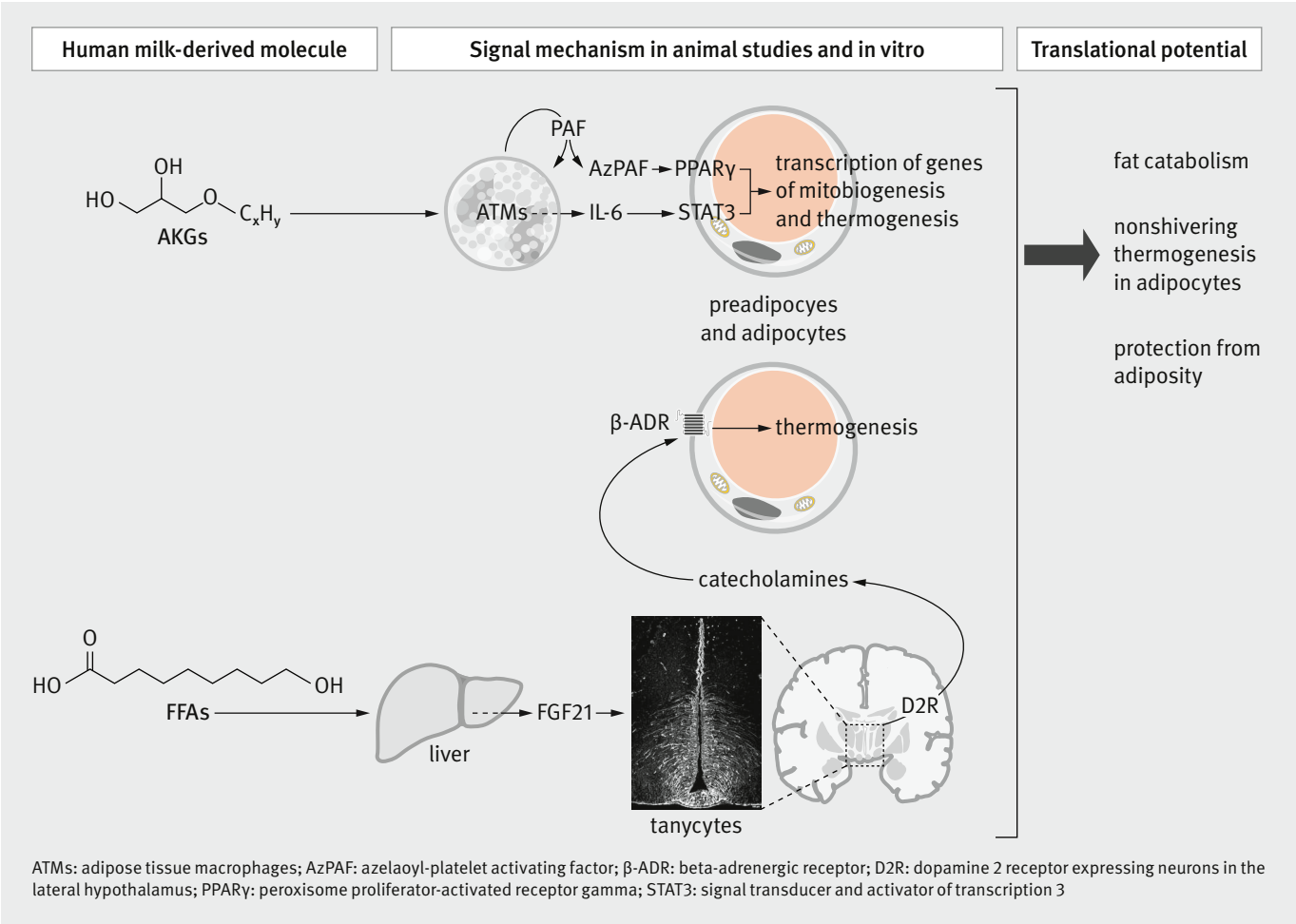
One of the best characterized mechanisms that accounts for this effect is the presence of alkylglycerols (AKGs) in human milk. AKGs belong to a unique ether lipid family, and promote macrophage-dependent thermogenic adipocyte development in mice[9] *(Figure 4)*. Early-life supplementation with AKGs in mice reduces fat mass by increasing mitochondrial thermogenesis and fat oxidation,[9] replicating the effects of prolonged breastfeeding observed in rats.[15] The level of milk AKGs is species-specific, and they are absent in cattle milk.[9,18] Accordingly, formula-fed infants do not experience the benefits of human milk AKGs.[9,18] Indeed, infants who are not adequately breastfed lose thermogenic fat prematurely, an effect phenocopied by AKG-free artificial rearing in mice.[9,19]

The effect of AKGs is dependent on adipose tissue macrophages (ATMs), which colonize adipose tissue early in life in both mice and humans.[9] ATMs metabolize AKGs into platelet-activating factor (PAF), which is used to produce nuclear receptor ligands and interleukin-6 (IL-6).[9] *(Figure 4)*. Adipose tissue in young mice exhibits elevated PAF-mediated signaling, and impaired PAF signaling in mice lacking the PAF receptor causes early-onset obesity.[9,20] Paracrine IL-6 signaling stimulates the expression of thermogenic genes and induces mitobiogenesis and the burning of fat as heat in mouse and human adipocytes.[9,21]

Another mechanism that explains the beneficial effect of breastfeeding on thermogenesis is the hepatic production of the hormone fibroblast growth factor 21 (FGF21) induced by prolonged suckling in rats.[15] Milk-derived fatty acids increase the production of FGF21, which is ultimately shuttled by specialized ependymal cells, so-called tanycytes, into the lateral hypothalamic area where they stimulate the expression of D2 dopaminergic receptors *(Figure 4)*. This results in increased sympathetic nerve stimulation,[22] which triggers mitochondrial uncoupling and thermogenesis in adipocytes.[15] FGF21 also activates fatty acid oxidation in liver, skeletal muscle, and heart, in addition to its effects on the regulation of food preference in mice.[15,23] At pharmacologic doses in mice, FGF21 triggers weight loss and improves glucose control.[24]

Other, less characterized human milk metabolites that stimulate adipocyte thermogenesis in animal studies include prostaglandin E2, succinate and β-aminoisobutyric.[25,26,27] Moreover, the beneficial effect of milk on the development of the intestinal microbiota in mice supports adipose tissue thermogenesis,[17] and germ-free mice have impaired thermogenic fat development.[28] The underlying mechanism however remains undefined.

Inducing the thermogenic potential of storage fat depots is considered as a therapeutic strategy to boost energy expenditure in obesity.[29] However, the impact of thermogenic fat is greater in rodents than in humans, and the development and anatomical distribution of thermogenic fat depots vary greatly among species.[29] The newborn mouse has thermogenic adipocytes in the interscapular brown fat depot and the inguinal subcutaneous fat, with the latter gradually disappearing after weaning to be replaced by storage fat.[9,17] Human infants and children have thermogenic adipocytes scattered throughout the subcutaneous fat depots.[9,30,31] The premature loss of thermogenic adipocytes is associated with obesity in young mice, rats, and humans, and both AKGs and FGF21 protect from obesity in the post-weaning periods in mice




ATMs: adipose tissue macrophages; AzPAF: azelaoyl-platelet activating factor; β-ADR: beta-adrenergic receptor; D2R: dopamine 2 receptor expressing neurons in the lateral hypothalamus; PPARγ: peroxisome proliferator-activated receptor gamma; STAT3: signal transducer and activator of transcription 3

**Figure 4.** Mechanisms allowing human milk signals to stimulate energy expenditure

Schematic illustration of human milk-derived molecules, their target cells, and the mechanisms known from animal studies and in vitro analysis of human cells. Histology images showing tanycytes surrounding the third ventricle (immunostaining against vimentin, courtesy of *Maria Dreher* and *prof. dr. Annika Herwig,* Ulm University, Germany).

and rats, respectively.[9,15,21,30] These findings suggest that the early life protection of thermogenic adipocytes by human milk-derived signals might prevent obesity later in early childhood.

## IMPACT OF HUMAN MILK COMPONENTS ON MITOCHONDRIAL FATTY ACID OXIDATION

Birth marks a rapid shift from a intrauterine metabolism based on carbohydrates to one based mainly on human milk lipids, accompanied by an increase in fat catabolism.[16] Animal studies show that milk-derived signals may support skeletal muscle, hepatic and cardiac β-oxidation of fatty acids[14,15,32] *(Figure 5)*, and newborn mice fed phospholipids of human milk fat globules are protected from diet-induced obesity in later life.[33,34] The underlying molecular mechanism is largely unknown but includes an increase in the hepatic carnitine pool and stimulation of β-oxidation, the Krebs cycle and mitochondrial antioxidative functions.[33,34] The lipid metabolite 12,13-dihydroxy-9Z-octadecenoic acid (2,13-diHOME) (also known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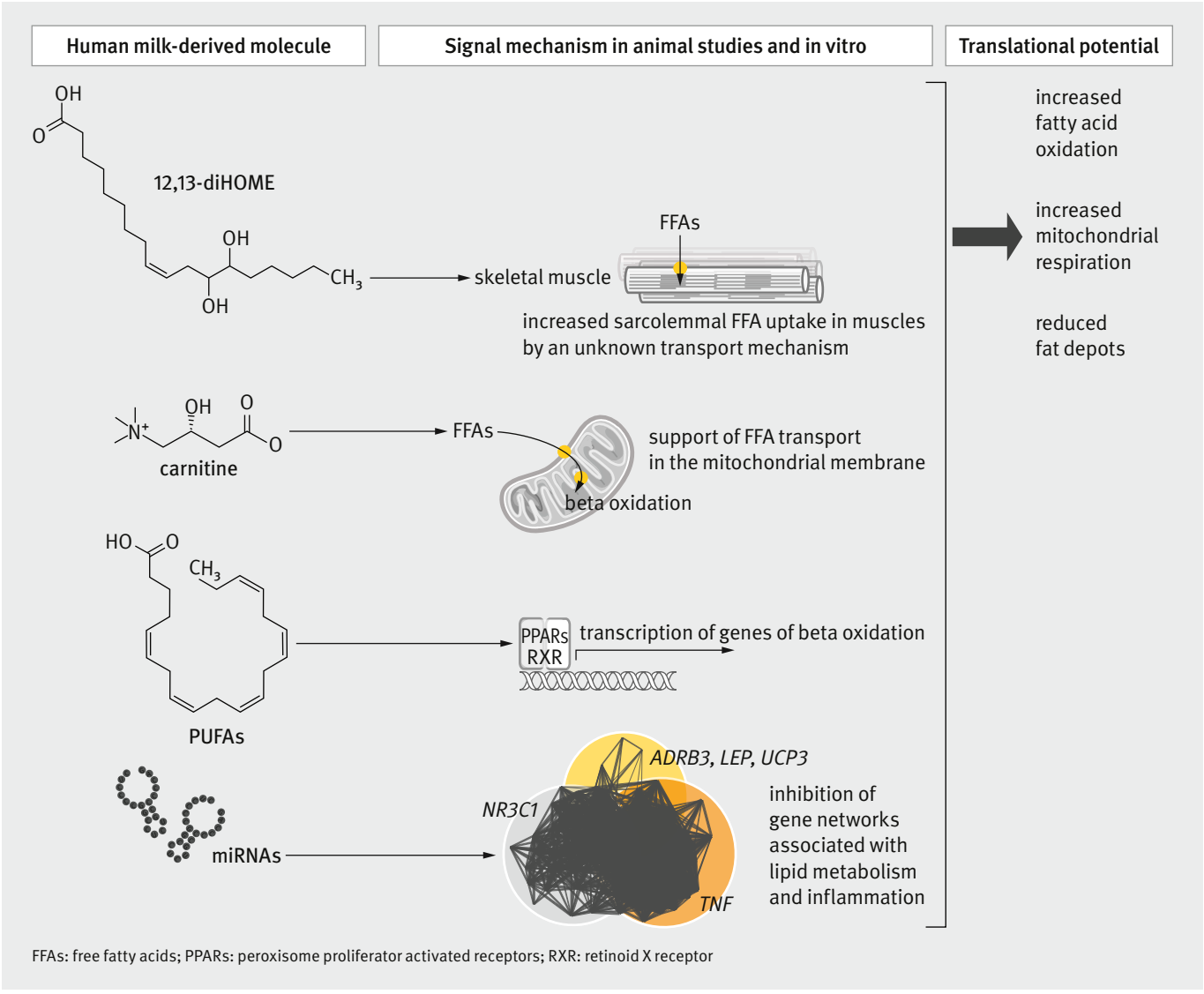


**Figure 5.** Human milk-derived signal mechanisms that stimulate fatty acid catabolism

Schematic illustrations of the mechanisms that mediate human milk effects on mitochondrial fatty acid oxidation and respiration. Transmission electron microscopy shows cellular targets of human milk-derived signals: cell membrane and mitochondria of muscles, and mitochondria of adipocytes.

as isoleukotoxin) is a circulating lipokine released by brown adipocytes in response to exercise and cold exposure in mice, and is also present in human milk.[14] It may increase fatty acid uptake by skeletal muscles, counteracting fat storage in adipocytes. A greater abundance of 12,13-diHOME in human milk at 1-month postpartum is associated with lower subcutaneous fat mass in infants and with a reduced gain in body mass in the first six months of infancy.[14] Thus, 12,13-diHOME and its related metabolites appear to protect against adiposity *(Figure 5)*.

Several other human milk metabolites are necessary for the transport of fatty acids into mitochondria for β-oxidation, including carnitine, sphingomyelins, palmitic-acid-9-hydroxy-stearic-acid (9-PAHSA) and

kynurenic.[33,35,36] Human milk is rich in polyunsaturated fatty acids (PUFAs), in particular ω-3 fatty acids and their metabolites, with a peak level in early lactation.[37] Several PUFAs and their metabolites increase the transcription of fatty acid catabolism-related genes in mice[38,39] *(Figure 5)*. A recent study suggests that cardiac fatty acid catabolism in mice is triggered by a milk-derived ω-6 PUFA;[32] however, ω-6 PUFAs appear to promote adiposity and fatty liver in human infants and children.[40] Indeed, the levels of ω-6 PUFAs in human milk are higher in mothers with overweight and obesity than in normal-weight mothers.[40] Overall, it is still unclear whether human milk-derived PUFAs increase fat catabolism in human newborns.

Finally, there is the possibility of early life programming of fat catabolism by human milk-derived micro RNAs (miRNAs). Because premature delivery is associated with a unique change in the miRNA profile of human milk,[41] and the greater intestinal permeability in preterm infants may allow for the improved absorption of miRNAs,[42] it has been postulated that human milk miRNAs may have a metabolically relevant role in preterm infants. Premature delivery reduces the human milk level of miRNAs that target uncoupling protein 3 (UCP3), leptin (LEP) and tumor necrosis factor alpha (TNF) and increases those miRNAs that target beta-adrenergic receptor 3 (ADRB3) and glucocorticoid receptor (NR3C1). As human fat depots – including thermogenic fat depots – develop in the last trimester of pregnancy,[43] premature infants have a reduced abundance of subcutaneous fat layers, making them vulnerable to hypothermia. It is believed that the unique miRNA signature in preterm human milk facilitates the development of fat depots in preterm infants, enabling them to attain the same growth trajectory as their full-term counterparts.[41] Conversely, human milk miRNAs may protect thermogenic fat depots and impede fat storage in full-term infants.[41]

## SUMMARY AND PERSPECTIVES

Human milk provides signals that shape metabolism in the infancy phase of human growth and reduces risk for obesity. At the cellular level, human milk-derived signals bolster lipid catabolism, thermogenesis and mitochondrial biogenesis in adipocytes and muscle cells, which increases energy expenditure.

However, some substantial knowledge gaps in our understanding of the underlying mechanisms remain, which will require further examination. For instance, the effects of human milk components on the liver, on adipocyte proliferation and apoptosis, and on skeletal muscle protein synthesis remain blind spots. Moreover, most studies have been undertaken in murine models, raising the question about their translation to humans. There are also practical obstacles and ethical implications to studying the long-term effects of human milk components on body composition and metabolic health in human populations.[44] The unique composition of human milk differs significantly between individuals and is dynamic over time and cannot be replicated by infant formula. Maternal health, diet, lifestyle, and drug use, can all potentially affect human milk composition, hence may influence the effectiveness of breastfeeding. Infant formula feeding may also lead to caloric excess and promote adipose tissue expansion, overshadowing a protective effect of partial breastfeeding.[45]

Human milk is a rich source and a complex biological matrix of metabolic regulators that interact and function collectively in the breastfed infant. A quote attributed to the philosopher and culinary writer Anthelme *Brillat-Savarin* (1755–1826), states that "the future of a society depends on its nutritional habits".[46] Indeed, early nutritional exposure through breastfeeding has a major and lasting impact on the health of our society.

## CONFLICT OF INTEREST STATEMENT

None.

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