Programming mediated by fatty acids affects uncoupling protein 1 (UCP-1) in brown adipose tissue

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Abstract

Brown adipose tissue (BAT) has recently been given more attention for the part it plays in obesity. BAT can generate great amounts of heat through thermogenesis by the activation of uncoupling protein 1 (UCP-1), which can be regulated by many environmental factors such as diet. Moreover, the build-up of BAT relates to maternal nutritional changes during pregnancy and lactation. However, at present, there is a limited number of studies looking at maternal nutrition and BAT development, and it seems that the research trend in this field has been considerably declining since the 1980s. There is much to discover yet about the role of different fatty acids on the development of BAT and the activation of UCP-1 during the fetal and the postnatal periods of life. A better understanding of the impact of nutritional intervention on the epigenetic regulation of BAT could lead to new preventive care for metabolic diseases such as obesity. It is important to know in which circumstances lipids could programme BAT during pregnancy and lactation. The modification of maternal dietary fatty acids, amount and composition, during pregnancy and lactation might be a promising strategy for the prevention of obesity in the offspring and future generations.

Key words: **Brown adipose tissue: Uncoupling protein 1: Fatty acids: Fetal programming: Obesity**

There is substantial evidence suggesting that the perinatal nutritional environment has profound implications for the development and long-term health outcomes in the off-spring[1–3]. This may be a consequence of 'fetal programming', a phenomenon that describes the adaptive responses of the offspring to the environmental cues during the initial phases of life[1,2].

Fetal metabolic programming occurs because of the modulation of gene expression mediated by epigenetic mechanisms that can permanently affect the structure and functions of tissues and organs, changing the number, distribution and differentiation of different cell types[3]. The higher plasticity rate and sensibility to the environmental changes generate a unique genetic opportunity, which can influence the phenotype[4]. Since the past decades, a plethora of epidemiological and experimental evidence supports the allegation that fetal and early postnatal timings, compared with other phases of life, are paramount to establish the susceptibility for non-communicable chronic diseases such as obesity[5,6].

Therefore, the early-onset and increased rates of obesity seen nowadays should not be attributed to genetic and/or environmental factors alone. It is well known that obesity has a multifactorial and complex aetiology, which derives from an energy imbalance – when energy intake is greater than energy expenditure. Obesity is defined by adipose tissue storage and white adipose tissue (WAT) expansion that occurs through adipocyte hypertrophy and hyperplasia[7]. WAT is recognised by its secretory capacity and role in the energy homoeostasis for storing TAG when energy exceeds or releasing free fatty acids (FFA) when there is an energy deficit[8]. On the other hand, brown adipose tissue (BAT) is recognised by its thermogenic function, but also plays a role in the energy homoeostasis and could contribute to obesity control[9].

Obesity, considered a pandemic disease, has more than doubled since 1980. It is one of the greatest challenges of public health care in the world[10]. The increased consumption of red meats, refined cereals, industrialised and fried foods, which are characteristics of a Western diet, low in fibre, high in fat and carbohydrates of poor quality, contributes to increasing these indices[11].

Diet, besides its impact on health and disease, can also influence the offspring's phenotype, depending on what the mother ate during gestation and lactation periods[1–3]. Experimental models showed that it is expected to find phenotypes of

body weight loss in the neonate and obesity and cardiometabolic risk in the offspring whose maternal diets were poor in proteins[12], rich in fats[13] and Western diet style[14], respectively. A similar process occurs between diet and BAT: diet can stimulate[15] and programme the development of this tissue, as it can act directly on the uncoupling protein 1 (UCP-1)[16]. The epigenetic mechanisms are possibly the main explanation for the potential evolutionary reasons that offspring BAT might be programmed by maternal diet[17]. Researchers revealed that foods typical of a Western diet – for instance, margarine – were related to impaired BAT function and UCP-1 activation in experimental models of fetal programming[18]; similar outcomes were found in adult animals[19].

In BAT, the mitochondrial inner membrane holds UCP-1, which is the main factor responsible for thermogenesis. The mechanism of action of UCP-1 is to uncouple oxidative phosphorylation from an ADP molecule, resulting in greater oxidation of substrates, and heat production[20]. During cellular respiration, the uncoupling of oxidative phosphorylation represents 20–50 % of all energy expended by the mitochondria of a normal functioning cell[21]. Under conditions of controlled cold exposure, estimates are that 60 g of BAT could contribute to up to 20 % of heat production in humans[22].

Seemingly, there exists a direct relation among balanced diet, UCP-1 metabolism and fetal BAT programming, as well as a potential connection between an inadequate diet and impaired BAT function, which may be correlated with the onset of obesity. Therefore, we question what might be the real action of the fatty acids on the BAT. Also, we wonder whether different fatty acids might modulate BAT and UCP-1 differently and how strong is the evidence that fatty acids from the maternal diet could programme BAT in experimental models. In addition, research investments on fetal programming concerning BAT may represent a relevant way to tackle obesity and its comorbidities. Therefore, this review brings to light the relation of fetal programming mediated by fatty acids on the offspring BAT.

Methods

We have selected published manuscripts from 1988 to 2018, in the English language, using a combination of the following index terms: brown adipose tissue, uncoupling protein 1, fetal programming and fatty acids. Five databases of published literature were used: PubMed, Cochrane Library, EMBASE, Medline and ScienceDirect.

Brown adipose tissue

It was once believed that BAT was only present in hibernating animals, rodents and newborns[23]. The interest in BAT grew after studies found it in adult humans, which inversely correlated with BMI[24]. Increased BAT and UCP-1 activity are also related to glucose and lipid metabolism improvement[9,25]. In newborns, BAT is responsible for non-shivering thermogenesis, assuring an efficient adaptation to the environment, preventing hypothermia and possibly neonatal death[23]. Consequently, the uncoupling oxidative phosphorylation process is paramount in
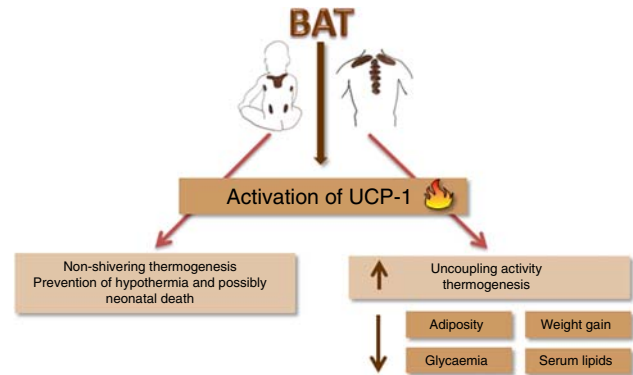

Fig. 1. Mechanism of action of uncoupling for the prevention of neonatal death and metabolic adult diseases. BAT, brown adipose tissue; UCP-1, uncoupling protein 1.

the regulation of energy balance in many developmental phases (Fig. 1).

Uncoupling protein-1 activation rate in BAT depots vary according to the fatty acid availability and flow into the cells[26]. For this reason, there is a potential for dietary fatty acids to act on the fetal BAT and UCP-1 activation. It is acknowledged that BAT depots and UCP-1 differ between species and with age[27,28]. There are differences in the main BAT depots at birth between different animal species. In rats, BAT is found mainly in the interscapular region and small quantities at birth, which reaches its capacity to produce heat only after birth[29]. In human babies, there are huge BAT depots, and these are located in the supraclavicular and neck, pericardium and perirenal regions. Moreover, they also have an axial BAT depot[30].

Distinct from WAT, BAT is characterised by multilocular lipid droplet phenotype, higher mitochondrial density and lower secretory activity. Regarding cell lineage, brown pre-adipocytes derive from cellular precursors that express encoding myogenic factor 5, a gene expressed in myogenic cell lineage[31]. Despite their differences in function and development, they have in common the primary adipogenesis regulators, which are transcriptional factors such as peroxisome proliferator-activated receptor (PPAR) and CCAAT-enhancer binding proteins (C/EBPp)[32].

Regulation of brown adipose tissue thermogenesis by dietary fatty acids

Brown adipose tissue is highly vascularised and innervated by the sympathetic nervous system, and its response varies depending on the nature of the external stimulus, such as age, sex, genetics and also diet[33]. One of the first works published in 1988 showed that 48 h of fasting reduced interscapular BAT depots and UCP-1 gene expression, and lowered the thermogenic capacity in adult mice. Moreover, a refeeding period of 10–15 d was enough to re-establish normal thermogenic capacity in the animals, highlighting a pivotal role of the diet in the functioning of this tissue and the activation of UCP-1[34].

Despite diet-induced thermogenesis being a controversial subject in the literature[35], there is not yet a consensus about which nutritional cue may activate UCP-1 in BAT. However, vitamin A[36–41], some amino acids such as L-arginine[42] and

L-ornithine[43], some bioactive compounds such as anthocyanins[44], resveratrol[45–47], isoflavones[48,49], catechins[50–52] and flavonoids[53] may stimulate UCP-1 in adult rats BAT. Because fatty acids sustain lipid oxidation and act as uncouplers of mitochondrial oxidative phosphorylation, thus increasing thermogenesis[54,55], a plethora of experimental model studies are now investigating how dietary fats activate UCP-1 in BAT.

Authors have shown positive regulation of UCP-1 mRNA and protein levels in the BAT of adult rats and young mice, after a high-fat diet intake[19,57,58]. However, higher UCP-1 gene expression not always means lower adiposity and weight gain[37,41,59]. A recent study showed that a high-fat diet during lactation causes increased weight gain, body fat depots and UCP-1 gene expression in offspring BAT after weaning[59]. In addition, the transcription of other genes involved in the thermogenesis, such as positive regulatory domain containing 16 (PRDM16), PPARγ coactivator 1α (PGC-1α), cell-death-inducing DNA fragmentation factor A-like effector A (CIDEA), cytochrome c oxidase subunit 7-α (COX7) and elongation of very-long-chain fatty acids like 3 (ELOVL3) was unaltered in BAT. Moreover, when these animals were exposed to cold, they showed reduced UCP-1 gene expression, suggesting a decline in the cold-induced adaptive thermogenesis. During adulthood, they showed reduced UCP-1 gene expression and the above-cited thermogenesis markers in BAT[59]. The authors concluded that a high-fat diet damaged the thermogenesis in BAT, and it has been associated with persistent adiposity and the development of metabolic syndrome in adulthood[59]. Therefore, evidence indicates that high lipid levels could propitiate a momentary increase of UCP-1 in the offspring, albeit it does not overcome the adiposity that this diet can cause[60].

Supplementation with 30 % of olive oil, rich in MUFA, for 28 d reduced body weight and weight gain, and increased UCP-1 gene expression in BAT of 7-month-old male Sprague–Dawley rats[61]. Other scientists fed adult male Wistar rats having an average body weight of 240 (SD 2) g with 40 % of total energy from olive oil for 4 weeks, and they have not found body weight alteration, but as already seen by other studies they found increased UCP-1 mRNA in the interscapular BAT[62]. Besides, oral supplementation with oleic and 2-hydroxyoleic acids and long-chain MUFA C18 (600 mg/kg), every 12 h for 7 d, did not change UCP-1 gene expression in BAT but caused weight loss in 16-week-old male Wistar Kyoto rats. The absence of changes in UCP-1 gene expression in BAT could be related to the short-term exposure to treatment[63]. Hence, despite the time of diet exposure being an important factor, these studies confirm that the type and amount of fatty acids prompt UCP-1 gene expression in BAT.

In the literature, PUFA, especially the n-3 family, could stimulate thermogenesis, lipid metabolism and lead to weight loss[64]. DHA (22 : 6n-3), a type of n-3 PUFA, is associated with weight loss in obese women[65]. A similar outcome was seen in overweight mice that consumed one daily portion of fish for 16 weeks[66]. A 3-month-old male C57BL/6 mice supplemented with 119 and 238 g/kg of fish oil containing EPA and DHADHA for 8 weeks improved metabolic profile and positively affected UCP-1 mRNA and protein expression in BAT. In the same study, increased thermogenesis positively correlated with lower

weight gain[67]. However, n-3 PUFA may lower the expression of lipogenic proteins such as acetyl-CoA carboxylase, fatty acid synthase and malonyl-CoA and raise protein expression of carnitine palmitoyltransferase 1. The latter is responsible for fatty acid translocation from the cytoplasm to the mitochondria, favouring β-oxidation, which in turn can contribute to thermogenesis[68]. Although the literature still requires more insights into the mechanisms of action of different fatty acids on BAT, UCP-1 and lipogenic proteins, considerable advances have been made in the identification of the transcriptional factors and co-regulatory proteins promoting embryological development and the acquisition of thermogenic profile in BAT. Among the transcriptional factors, highlight the PPAR, even though UCP-1 could be induced in their absence, PPAR are related to diet and fatty acids[69]. PPARα and PPARγ are regulated by PGC-1α[70,71]. PGC-1α is a transcriptional coactivator that has a critical role in the activation of cAMP-dependent protein kinase A, the protein responsible for lipolysis and thermogenesis in BAT, which responds to cold and diet triggers via β-adrenergic receptors under norepinephrine control[72]. Another gene highly expressed in BAT, and regulated by PPARα, is PRDM16. PPARα can induce gene transcription of PGC-1α in brown adipocytes (BA) through mechanisms involving PRDM16. Thus, PPARα regulates thermogenesis in brown fat by inducing gene expression of PGC-1α and PRDM16, which leads to higher UCP-1 expression and mitochondrial oxidative activity[70]. Other proteins such as CIDEA can control thermogenesis by inducing UCP-1 expression[73]. Also, a protein product of fibroblast growth factor 21 (FGF21) may act as a potential adipogenic adipokine, which influences thermogenesis by upregulating UCP-1 expression in progenitors isolated from human cervical fat differentiated into BA-like[74]. There are also the sirtuin 1 (SIRT1) and sirtuin 3 (SIRT3), protein family of seven histone deacetylases (class III), that function as redox sensors that respond to changes in NAD/NADH levels. The stimulation of SIRT1 and SIRT3 may lead to an increased UCP-1 expression in BAT[75]. SIRT3 is also positively regulated by PGC-1α[76], increasing UCP-1 and mitochondrial gene expression in this tissue[75,76]. Published research shows that these proteins could be regulated by fatty acids, in particular EPA[73,75,77]. Additionally, the presence of G-protein-coupled receptor 120 (GPR120, also known as FFA receptor 4 (FFAR4)), a cellular receptor for PUFA in the BA, may cooperate in the regulation of the transcriptional factors. Corroborating this view, a recent study found that the activation of GPR120 induces the release of FGF21 by BA[78]. Hence, EPA may activate some transcriptional factors, such as PPAR, in the BA nucleus. In turn, it causes an increased UCP-1 gene expression and boosts BA activity, thus leading to accretion in the energy expenditure.

Epigenetic mechanisms are involved with UCP-1 and thermogenesis[17,79]. These are responsible for the formation, maintenance and reversion of gene transcriptional patterns. The main epigenetic events include DNA methylation, histone post-translational modifications (acetylation, methylation, phosphorylation and others) and non-coding RNA[80]. Damped DNA methylation in the promoter region of the UCP-1 gene was inversely related to the expression of this protein[79]. Histone acetylation is involved in gene transcriptional control of

thermogenesis in BAT[81]. In this context, class 1 and class 3 of sirtuin deacetylases (SIRT1 and SIRT3) altered the thermogenic function by deacetylation of PGC-1α. In contrast with the thermogenic function activated by the inhibition of histone deacetylases, in this same study, the overexpression of SIRT1 in 2-month-old mice increased BAT activity, leading to a greater energy expenditure[82]. Demethylases were also found to be involved in the differentiation process of BA in mice BAT[83]. Recently, it has been shown that BA release exosomes, and the activation of BAT increases their release[80]. MicroRNA are a subclass of non-coding RNA that regulate protein expression[84]. The literature conveys that they may be implicated in the functioning of this tissue[85]. In adult humans, miR-92a exosome levels were inversely correlated with BAT activity, which was measured by positron emission tomography with F-18 fluorodeoxyglucose (18F-FDG PET/CT). In this study, microRNA was considered a potential human serum biomarker of BAT activity[17]. It has been revealed that EPA is related to increased gene expression of promoters of brown fat development, as well as UCP-1, through mechanisms that entail microRNA modulation in subcutaneous pre-adipocytes of women with a BMI range of 28.1–29.8 kg/m^2[86]. A study with palmitic acid, oleic acid and EPA found that the latter (100 mM) was associated with microRNA clusters at inducing the activation of the FFAR4, which is also known as GPR120, in primary brown cells. Later, this signalling axis (EPA/FFAR4/microRNAs) was confirmed in C57BL/6 adult male mice fed fish oil (15 %) for 12 weeks[87].

There is still a lot to discover about the epigenetic mechanisms in BAT and UCP-1 expression, and even more about their regulation mediated by different fatty acids in the diet. In spite of this, at the moment, the literature has shown that the mechanisms involving fatty acids, especially EPA, beta-oxidation enzymes, thermogenic transcriptional factors, specific receptors and other thermogenic proteins, seem to be interconnected to regulate and activate UCP-1 and thermogenesis in BAT. Therefore, they could be a plausible target to increase energy expenditure and aid in the treatment of obesity (Fig. 2).

Fetal programming of brown adipose tissue by maternal dietary fats

Clearly, UCP-1 gene expression and thermogenesis in BAT are sensible to dietetic changes. Such changes are also closely related to fetal programming[88,89]. It is now thoroughly known that not just the amount but also the quality of the maternal diet matters as a variable in the epigenetic regulation in the offspring[90]. For this reason, it is important to think about the beneficial effects of nutrition on fetal programming of BAT, setting up thermogenesis and preventing obesity.

Maternal dietary fat composition during gestation and lactation is the most important determinant of the quality of fatty acids that reach the fetus through the placenta, or the infant through breast-feeding[90,91]. Fetuses and newborns can synthesise SFA and MUFA, but they have limited capacity to synthesise long-chain PUFA (LCPUFA)[92]. After birth, LCPUFA are transferred to the infant through maternal milk, in which the
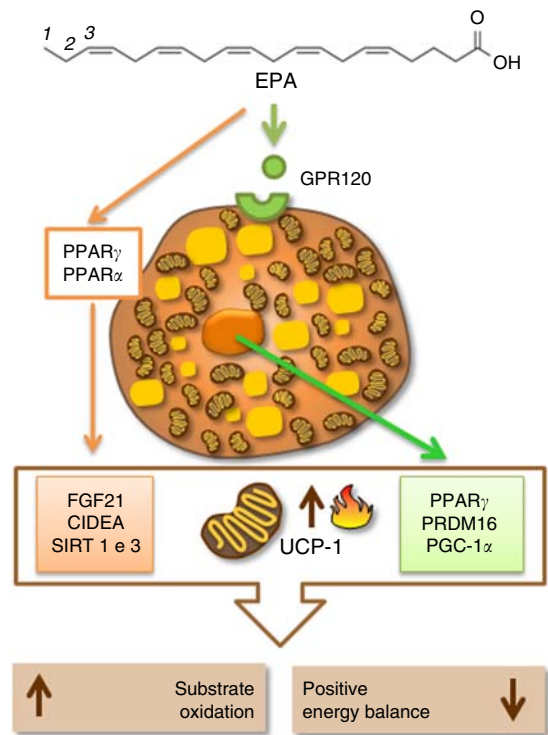

Fig. 2. Eicosapentaenoic acid regulating thermogenesis and uncoupling protein 1 (UCP-1) expression by activation of specific cellular receptors (G-protein-coupled receptor 120 (GPR120)) in the brown adipocyte or by activation of proteins related to fatty acid oxidation, mitochondrial biogenesis and thermogenesis in brown adipose tissue (BAT). CIDEA, cell-death-inducing DNA fragmentation factor A-like effector A; FGF21, fibroblast growth factor 21; PGC1α, PPARγ coactivator 1α; PRDM16, PR domain containing 16; SIRT1, sirutin 1.

content of arachidonic acid remains relatively constant, whereas the amount of EPA and DHA are dependent on the maternal dietary habits[92].

Despite the diversity of placental structure between mammal species, placental basic morphology, the main cellular type and function are conserved between many species. Trophoblastic cells make up the placenta and assure a bi-directional flux of appropriate nutrient residues required for the normal growth and maturation of the embryo[93]. Many maternal dietary cues, such as MUFA and *n*-3 PUFA[94], foods rich in bioactive compounds[95–98], prebiotics[99] and some probiotics[100], pass through the placenta and programme different fetal tissues by modulating proteins with the perspective of protecting the organism from many diseases throughout life. Studies on fetal programming and the impact of these nutritional compounds on the BAT are rare.

In humans, BAT development occurs mainly in the third gestational trimester and expands its mass in the early postnatal period, keeping a relatively stable size until adolescence, and gradually regressing with age[101]. A study in mice showed that ageing makes BAT morphology more similar to beige adipose tissue, with unilocular lipid droplets, bigger cellular size and higher TAG content[102]. Such morphologic alterations lead to reduced thermogenic and lipolytic capacity, which may increase the development of diseases[103].

In 1988, a study revealed that a low-energy diet during pregnancy caused lower birth weight in the rat offspring, and did not change UCP-1 thermogenic activity in BAT. However, when dams that had mild maternal undernutrition during lactation nursed these offspring, they kept lower neonatal body weight, and significantly repressed UCP-1 expression in BAT (assessed on the 4th and 13th day of life). In contrast, when dams were fed a normal energetic diet during lactation, neonatal body weight was restored, and BAT remained unaltered in the offspring. Therefore, it implied that slight maternal undernutrition during lactation could alter UCP-1 expression in offspring BAT[16].

In light of the above, a study using ewes subjected to 30 % energy restriction for 60 d before conception and during gestation caused increased UCP-1 mRNA in perirenal offspring BAT. However, restricted food intake by 50 % fewer energy content in late gestation lowered UCP-1 mRNA and fetal fat depot. Hence, this study showed that different phenotypes could be established depending on the degree of the maternal diet restriction, timing and length of duration[104].

Corroborating, another research finding on ewes treated during late gestation with energy restriction of 40 % of total energy requirements resulted in reduced UCP-1 gene expression, and reduced expression of other genes related to thermogenesis, such as the β3-adrenergic receptor and deiodinase type 2, in the pericardial BAT of newborn offspring. However, these alterations were absent in the 30-d-old offspring[105]. On the other hand, early to mid-pregnancy diet restriction followed by ad libitum diet intake increased UCP-1 expression and the expression of genes involved in the browning of adipose tissue, such as bone morphogenetic protein 7 and C/EBPp, in the near-term (140 d) fetus. These alterations were also associated with increased fetal pericardial adiposity and body weight. These results suggested that UCP-1 could re-establish normal levels upon offspring growth, and the rise of this protein associated with pericardial adiposity may be an important factor in neonatal viability[106].

A study on a high-fat diet (45 % energy from fat) during the postweaning, and preceded by maternal protein undernutrition (9 % of casein) during gestation, did not change the final body weight, energy expenditure and UCP-1 in the interscapular BAT, but increased the adiposity in male mice offspring aged 30 weeks. Though, offspring not exposed to maternal protein restriction (18 % of casein) during pregnancy, only postweaning high-fat diet, increased energy expenditure and UCP-1 mRNA in BAT. The authors concluded that a high-fat diet increases energy expenditure by diet-induced thermogenesis, and this is attenuated in mice when their mothers were fed a protein-restricted diet during gestation and lactation, probably resulting in obesity in adulthood[107].

As with total dietary fat quantity, UCP-1 seems to be sensitive to changes in the type of maternal dietary fatty acids in fetal programming. A maternal diet rich in olive oil, butter or margarine from the 14th day of gestation until the 20th day of lactation resulted in increased UCP-1 in the interscapular BAT of 21-d-old male rat offspring from dams fed olive oil, which is rich in oleic acid. In addition, oleic acid was found in the maternal milk and the offspring's serum, and it correlated positively with lessening weight gain in these animals during lactation[18].
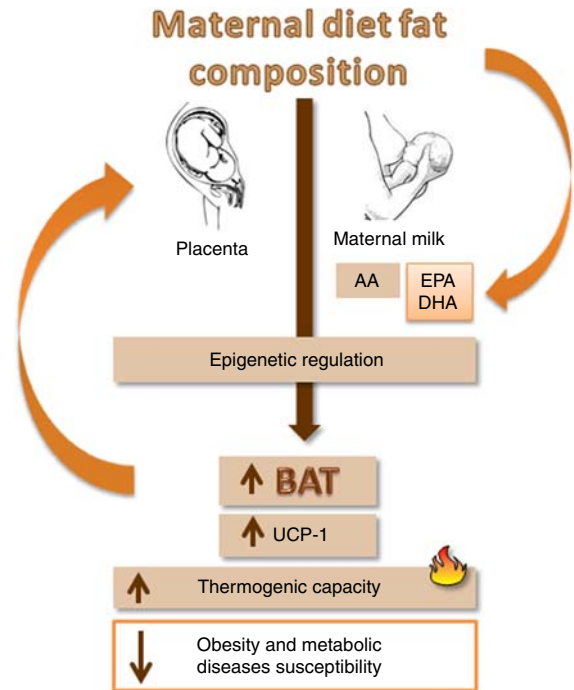

Fig. 3. A schematic diagram showing the impact of maternal nutrition, especially EPA and DHA ingestion, in fetal metabolic programming of brown adipose tissue (BAT) and uncoupling protein 1 (UCP-1) expression and consequently influence on the susceptibility to obesity. AA, arachidonic acid.

Previous studies showed that maternal supplementation with hydrogenated vegetable fats, rich in trans fatty acids, in a normolipidic diet model during pregnancy and lactation led to low-grade inflammation in the subscapular BAT of male Wistar rat offspring after weaning. Furthermore, maternal supplementation with the fruit of juçara palm, rich in MUFA and anthocyanins, studied by this same research group, was associated with repair of the BAT homoeostasis by increased UCP-1 protein expression and protected against stunting and reduced carcass fat deposits[108].

Despite the scarcity of studies on this subject, the discussed data suggest mechanisms that are integrating fetal programming in BAT and maternal dietary fatty acids, regulating UCP-1 expression and thermogenesis in the offspring (Fig. 3).

Future research directions

The maternal consumption of Western diet in early gestation and during lactation, even in the absence of pre-gestational maternal obesity, can entail increased adiposity, including higher body weight and adipocyte hypertrophy in the offspring after weaning[109,110]. During lactation, maternal diet is critical to the development of obesity and metabolic consequences in the offspring[109,111]. Increased offspring adiposity could be amplified if during lactation the maternal diet is high in fat[112], demonstrating that maternal nutrition is an important regulator of obesity in the offspring. In animal models, there is evidence that maternal dietary fat programme BAT is strong[16,104–108]. There is a limitation to human testing for ethical reasons, but the altered UCP-1 expression in offspring BAT from mothers whose diets were high in fat or had a low-quality fat source, for

instance hydrogenated vegetable fats, during gestation and lactation could be a possible cause for the increased trend in childhood obesity. Hereby, we remark the importance of more research on the impact of different fatty acids on fetal programming in BAT during different programming periods and in different species. More insights into the epigenetic mechanisms involved in the regulation of UCP-1 expression on fetal programming in future research may contribute to the explanation of various results found in the literature. BAT amount and activity are normally analysed by FDG-PET in combination with CT[24]. These techniques require cold condition and expose individuals to ionising radiation, which is not recommended during pregnancy, in newborns and infants until 6 months of age. It is still missing diagnostic tools that allow safe and easy assessment of BAT in humans, in particular during phases of development. With this in mind, future research directions should search for BAT biomarkers that could be easily screened by blood analysis, and that could reflect BAT activity.

Conclusion

The need to understand fetal programming as regards BAT is emphasised by the growing obesity prevalence. Diet is a regulatory factor in the activation of UCP-1 in BAT. A high-fat diet and different fatty acid profiles seem to regulate the UCP-1 expression in BAT positively. However, the molecular mechanisms that explain the activation of UCP-1 in this tissue still need to be more unearthed. There is a limited number of studies looking at the maternal nutrition and BAT development, and it seems that the research trend in this field has been considerably declining since the 1980s. Thus, a better understanding of the impact of a nutrition intervention with fatty acids on the activation of UCP-1 in BAT could lead to new preventive care for metabolic diseases such as obesity.

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