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Mitochondrial dysfunction and epigenetics underlying the link between early-life nutrition and non-alcoholic fatty liver disease

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Abstract

Early-life malnutrition plays a critical role in foetal development and predisposes to metabolic diseases later in life, according to the concept of 'developmental programming'. Different types of early nutritional imbalance, including undernutrition, overnutrition and micronutrient deficiency, have been related to long-term metabolic disorders. Accumulating evidence has demonstrated that disturbances in nutrition during the period of preconception, pregnancy and primary infancy can affect mitochondrial function and epigenetic mechanisms. Moreover, even though multiple mechanisms underlying non-alcoholic fatty liver disease (NAFLD) have been described, in the past years, special attention has been given to mitochondrial dysfunction and epigenetic alterations. Mitochondria play a key role in cellular metabolic functions. Dysfunctional mitochondria contribute to oxidative stress, insulin resistance and inflammation. Epigenetic mechanisms have been related to alterations in genes involved in lipid metabolism, fibrogenesis, inflammation and tumorigenesis. In accordance, studies have reported that mitochondrial dysfunction and epigenetics linked to early-life nutrition can be important contributing factors in the pathogenesis of NAFLD. In this review, we summarise the current understanding of the interplay between mitochondrial dysfunction, epigenetics and nutrition during early life, which is relevant to developmental programming of NAFLD.

Keywords: **Early-life nutrition: Epigenetics: Mitochondria: Developmental programming: NAFLD**

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Introduction

Non-alcoholic fatty liver disease (NAFLD) includes a spectrum of liver disorders, ranging from simple liver steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis, which can lead to the development of liver cancer[1]. The mechanisms underlying the development of this metabolic disease are complex, resulting from the interaction of genetic and environmental factors. Maternal diet during gestation and lactation is an important environmental condition that has direct effects on liver development[2]. In addition, early malnutrition can affect mitochondrial function and epigenetics[3,4]. In this sense, a growing body of evidence indicates that inadequate nutrition during preconception, pregnancy and early infancy can affect the metabolic phenotype of the progeny, thus contributing to the development of NAFLD in later life, according to the concept of 'developmental programming'[5].

The regulation of metabolism is strongly related to mitochondrial function. Mitochondria are subcellular organelles that play a significant role in energy homoeostasis by metabolising nutrients as well as in ATP synthesis. Additionally, these organelles are involved in a variety of processes, including regulation of apoptosis, calcium homoeostasis and generation of reactive oxygen species (ROS)[6]. In the past years, evidence has supported the notion that mitochondrial dysfunction has a central role in the pathophysiology of NAFLD. Alteration of mitochondrial function was related to fat liver deposition, lipid peroxidation, hepatic oxidative stress and accumulation of mitochondrial DNA (mtDNA) damage[3,7]. Moreover, it has been reported that mitochondrial dysfunction is linked to liver insulin resistance[8].

Epigenetic mechanisms involve changes in gene expression and phenotype not associated with modifications in primary DNA sequence. These alterations are heritable and induced by the exposure to different environmental factors[2,9]. Epigenetics has been related to alterations in genes involved in lipid metabolism, fibrogenesis, inflammation and tumorigenesis[10]. Studies have demonstrated that nutritional perturbances during early development can lead to epigenetic dysregulation, which may be later associated with NAFLD development[2].

The aim of the present review is to discuss the interplay between mitochondrial dysfunction and epigenetics and their relation to the development of NAFLD associated with early-life nutrition. We first outline the concept of developmental programming and its relation to early-life nutrition. Next, we present an overview of mitochondrial biology, including bioenergetics, biogenesis and biodynamics. Then, we discuss the involvement

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of mitochondrial dysfunction and epigenetics in the pathogenesis of NAFLD, related to disturbances in early-life nutrition. Finally, we conclude by establishing a link between NAFLD, nutrition, epigenetics and mitochondrial dysfunction, and describe future scopes of research in this field.

Developmental programming of NAFLD: Impact of early-life nutrition

The nutritional environment during preconception, pregnancy and early life plays a critical role in the development of the progeny and is related to the incidence of acute and chronic diseases later in life[11]. Early nutritional environment, including undernutrition, macronutrient excess or micronutrient deficiency, has been related to long-term metabolic disorders[12]. Certainly, human epidemiological evidence and animal studies have reported an association between maternal undernutrition and the appearance of metabolic diseases in adulthood, such as diabetes and NAFLD[13]. Maternal obesity has also been demonstrated to be an important risk factor for NAFLD[14]. These events are in accordance with the 'developmental origins of disease hypothesis', which posits that exposure to an adverse environment during sensitive periods of cellular plasticity confers an augmented risk of developing diseases later in life[15]. This process, known as 'developmental programming', is directly related to the 'thrifty phenotype' hypothesis. This argues that, when a foetus is exposed to undernutrition, it adapts to nutrient availability limitation, thus conferring the capacity of short-term survival under these adverse conditions. However, these metabolic adaptations increase susceptibility to long-term metabolic diseases when exposed to an adequate nutrient environment[16]. Similarly, maternal obesity and micronutrient deficiency lead to the programming of the foetus as in maternal undernutrition, since these nutritional environments represent a form of foetal malnutrition[12].

Several animal studies have reported an association between a maternal obesogenic environment and the development of NAFLD in the progeny. In this regard, it has been shown that exposure to a high-fat diet (HFD) during preconception, pregnancy and lactation leads to a NAFLD phenotype in rodents and non-human primates[17,18]. Moreover, the administration of a HFD after weaning exacerbated this phenotype, with the offspring developing NASH in early adulthood, while the ones exposed to a normal diet exhibited only simple steatosis[19,20]. Regarding the influence of high-calorie processed foods during early life, Sánchez Blanco *et al.* reported that 21-day-old pups from dams administered cafeteria diet during preconception, gestation and lactation present increased plasma triacylglycerol levels[21]. In another study the long-term influence of cafeteria diet during pregnancy and lactation was evaluated in 14-month-old male rats, showing an increase in triacylglycerol and fatty acid content in liver[22]. Furthermore, the effects of maternal junk food rich in energy, fat, sugar and salt were studied, demonstrating that offspring exposed to this diet during foetal life developed several exacerbated signs of NAFLD, such as liver steatosis, oxidative stress and hepatocyte ballooning at the end of adolescence, when compared with animals that had only received this diet from weaning[23]. Interestingly, liver steatosis and oxidative stress were also present in offspring from junk-food-fed mothers that had received a regular diet after weaning[23]. Maternal Western-style diet administration during prenatal and post-weaning periods also programmes susceptibility to liver disease into male offspring, as a result of alterations in inflammation and lipid metabolism[24]. Additionally, a considerable body of evidence from animal models has shown a link between *in utero* undernutrition and the development of NAFLD in the offspring. In this respect, it has been demonstrated that the administration of low-protein diets during pregnancy and lactation is conducive to liver steatosis in rats during adulthood[25,26]. With regard to early micronutrient deficiency, it has been shown that vitamin B12 restriction in maternal diets is conducive to increased body fat mass, diabetes mellitus type 2, augmented plasma cholesterol levels and dysregulation of fatty acid metabolism pathways[27–29]. Another study reported that vitamin B12 and folate deficiency during gestation and lactation induces rat liver steatosis at weaning and is related to impaired mitochondrial fatty acid oxidation and a significant reduction in birth weight in the offspring[30]. Sharma *et al.* demonstrated that maternal calcium and vitamin D deficiency is conducive to abnormal lipid metabolism and liver gene expression in female offspring rats, resulting in liver steatosis, even though control diet was administered after weaning[31]. Given that NAFLD has become one of the most prevalent liver metabolic diseases worldwide, much interest has been given to developmental programming, its association with the nutritional environment and the potential underlying mechanisms.

Mitochondria: Bioenergetics, biogenesis and biodynamics

Mitochondria are double-membrane organelles that contain their own DNA. The outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM) enclose distinct proteins and have different functions. The OMM is more permeable and characterised by the establishment of membrane contact sites with endoplasmic reticulum, lysosomes, peroxisomes, plasma membrane, endosomes and lipid droplets. The IMM includes the mitochondrial invaginations known as cristae, which contain electron transport chain (ETC) complexes and ATP synthase. A small intermembrane space is found between the outer and inner mitochondrial membranes. IMM delimits the mitochondrial matrix, which includes enzymes involved in glycolysis, tricarboxylic acid (TCA) cycle and fatty acid β-oxidation (FAO). In addition, the matrix encloses a circular mtDNA which is packaged in nucleoids. mtDNA encodes two ribosomal RNAs, twenty-two transfer RNAs, thirteen polypeptide subunits of ETC and some noncoding RNAs, while the rest of proteins are encoded by the nuclear genome.

Mitochondria are known as the 'powerhouses of the cell'[32]. They generate energy in the form of ATP through oxidative metabolism of nutrients[33]. Glucose, amino acids and fatty acids from nutrients are metabolised, and then enter the TCA cycle. As a result, electrons are released and stored in the carriers NADH and $FADH_2$. These reducing agents transfer electrons to the ETC in the IMM[34]. Mitochondrial ETC includes five

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enzyme complexes. Complex I (NADH ubiquinone reductase) collects electrons from NADH, while complex II (succinate dehydrogenase) obtains them from $FADH_2$. Then, electrons from these complexes are transferred to coenzyme Q, which donates them to complex III (ubiquinol–cytochrome c reductase). Complex IV (cytochrome c oxidase) oxidises cytochrome c and transfers electrons to oxygen, forming water. This flow of electrons along the ETC is employed to pump protons into the intermembrane space[35], which establishes the electrochemical gradient necessary for the generation of ATP through complex V (ATP synthase) in the process of oxidative phosphorylation[36].

As described above, the transfer of electrons along the ETC through oxygen is coupled to the generation of ATP. However, a fraction of electrons commonly leak from the ETC, reacting directly with oxygen and generating superoxide radicals[37]. These ROS may be converted to hydrogen peroxide (H_2O_2), and then to hydroxyl radicals through the Fenton reaction[32]. Even though there exist eight sites involved in the production of these ROS, mitochondrial complexes I, II and III are the main contributors to ROS generation[38]. Fortunately, mitochondria have antioxidant mechanisms to scavenge these extremely reactive ROS, thus protecting molecules from oxidative damage. These antioxidant defences comprise enzymatic and non-enzymatic mechanisms. The mitochondrial enzyme superoxide dismutase converts superoxide anion into H_2O_2, which is less reactive[39]. H_2O_2 can then be converted to water by different enzymes, including catalase, peroxiredoxins (PRX) and glutathione peroxidases (GPX)[40]. While PRXs are abundant in mitochondria, only isoform 4 of GPx is located in this compartment and catalase is found in peroxisomes[40]. Mitochondrial enzymes PRX3 and PRX5 are oxidised by H_2O_2, and then reduced by thioredoxin 2 and thioredoxin reductase 2[41]. In turn, GPX4 is oxidised by H_2O_2 and then reduced by the non-enzymatic antioxidant glutathione[40]. It has been proposed that PRXs are the principal mitochondrial antioxidant enzymes involved in the elimination of minimal levels of H_2O_2, as a result of their high abundance and their high rate constant. On the contrary, due to their lower abundance, GPXs are critical for scavenging higher levels of H_2O_2, when they can compete with PRXs for substrate[42]. Under physiological conditions, ROS have intracellular messenger actions and their production is controlled by mitochondrial antioxidant defences, to prevent cellular oxidative injury[43]. However, when these protective mechanisms are insufficient, the overproduction of ROS results in oxidative damage to lipids, mtDNA and proteins in mitochondria[44]. In addition, mitochondria have an important role in the defence against ROS from other subcellular compartments such as peroxisomes[45]. Other reactive species can be found in mitochondria. Although the presence of nitric oxide synthase in mitochondria has been controversial, either nitric oxide derived from ETC or that produced in a different compartment, after diffusing through the mitochondrial membranes, can react with superoxide, forming peroxynitrite inside the mitochondria [46]. Even though peroxynitrites can affect different proteins, they are efficiently detoxified by PRXs and GPXs[47]. Since mitochondria have a critical role in the production and maintenance of physiological levels of ROS, alterations in these organelles can lead to oxidative stress, which is considered to be an important factor in the generation of hepatocyte injury in the context of NAFLD[48]. In animal models of NAFLD, enhanced ROS formation has been reported as a result of impairment of mitochondrial ETC activity[49]. Similar observations were made in patients with NAFLD[50]. In addition, a diminished expression and activity of antioxidant enzymes has been described in *in vitro* and *in vivo* models of NAFLD[51]. Thus, excessive ROS production and decreased antioxidant capacity can contribute to NAFLD pathogenesis.

Mitochondrial biogenesis is defined as the process by which cells augment their mitochondrial mass via increasing their size and number[52]. The majority of mitochondrial constituents are synthesised in the nucleus[53]. These nuclear proteins have to be imported into mitochondria. Therefore, mitochondrial biogenesis requires the coordinated expression of nuclear and mitochondrial genes[54]. Different factors are involved in the regulation of this process. Peroxisome proliferator-activated receptor γ co-activator-1 α (PGC-1α) is a co-activator that promotes mitochondrial biogenesis through the activation of different nuclear receptors and nuclear transcription factors, including nuclear respiratory factors (NRF) 1 and 2[55]. NRF-1 and NRF-2 induce the transcription of almost every component of the ETC, and promote the expression of mitochondrial transcription factor A (Tfam), which leads to mtDNA synthesis[56]. Additionally, PGC-1α co-activates other factors such as thyroid hormone, glucocorticoid, oestrogen, peroxisome proliferator-activated receptors (PPAR) and oestrogen-related receptors (ERR) α and γ[57]. By acting as a co-activator of PPAR α and δ, PGC-1α induces the expression of mitochondrial FAO genes[58]. PGC-1α also affects mitochondrial biogenesis by interacting with ERRs, which are involved in fatty acid metabolism and oxidative phosphorylation[59]. In turn, PGC-1α is regulated by AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1). AMPK phosphorylates PGC-1α in response to acute energy deprivation[60]. The protein deacetylase SIRT1 activates PGC-1α in liver in response to fasting[61]. In contrast, the mitochondrial SIRT3 is a downstream target of PGC-1α. SIRT3 up-regulates several proteins such as FAO enzymes and ETC complexes I and II, thus affecting mitochondrial biogenesis[62]. PGC-1β is another co-activator that regulates this process through NRF-1[63]. Different studies have shown that alterations in mitochondrial biogenesis are related to obesity and type II diabetes[64,65], establishing an important link with NAFLD development.

Mitochondrial dynamics involves the balance between fusion and fission mechanisms to maintain normal mitochondrial function. Mitochondrial fusion refers to the union of two mitochondria resulting in one mitochondrion. This event is mediated by mitofusin 1 (MFN1) and mitofusin 2 (MFN2), which enable the fusion of OMMs, and optic atrophy 1 (OPA1), which allows the fusion of IMMs[66,67]. Mitochondrial fission involves the division of a mitochondrion into two mitochondria. It is mediated by different proteins such as dynamin-related protein 1 (DRP1), mitochondrial fission factor (MFF), mitochondrial dynamics proteins of 49 kDa (MID49) and 51 kDa (MID51), and mitochondrial fission 1 protein (FIS1)[68–71]. In this process, DRP-1 translocates from the cytosol to mitochondria, and then binds to MFF, MID49,

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MID51 and FIS1 in the OMM. This allows for DRP1 oligomerisation and posterior mitochondrial division[72]. The balance between fusion and fission events depends on the metabolic state and the nutrient availability of cells[73]. In response to an enriched nutrient environment, mitochondria undergo fragmentation, while starvation induces mitochondria elongation[74–76]. Thus, mitochondrial fragmentation leads to reduced ATP production and nutrient storage, in an attempt to prevent energy waste. On the contrary, mitochondrial elongation leads to maintenance of ATP generation, through an increase in mitochondrial bioenergetic efficiency[77]. Additionally, a shift toward fission is related to degradation of injured mitochondria through the process of mitophagy[78].

Mitochondrial dysfunction, NAFLD and early-life nutrition

Different mechanisms are involved in the development and progression of NAFLD. The 'two-hit hypothesis' was initially postulated to explain the occurrence of this metabolic disorder[79]. According to this theory, the 'first hit' is represented by liver accumulation of lipids as a consequence of sedentary lifestyle, hyperenergetic diets, insulin resistance and obesity. Afterwards, this fatty liver becomes more vulnerable to a 'second hit', which induces inflammation and fibrosis. However, accumulating research has shown that this theory is insufficient to explain the complex alterations observed in human NAFLD patients. Nowadays, the most accepted model is the 'multiple-hit hypothesis'. This theory posits that multiple factors act in conjunction in genetically susceptible individuals to lead to the development of NAFLD. These 'hits' include dietary factors, insulin resistance, adipose tissue dysfunction and changes in gut microbiome[80]. The high levels of NEFAs, free cholesterol and other lipid metabolites that are derived from the above-described insults induce lipotoxicity[81]. This environment in the liver leads to an impaired mitochondrial function that favours an excessive production of ROS and inflammation[82]. The 'multiple-hit hypothesis' considers mitochondrial dysfunction a critical player in the development of NAFLD[78]. In fact, evidence shows that hepatic mitochondrial dysfunction occurs before NAFLD development in rodents[83]. Accordingly, livers from NASH patients showed structural and functional mitochondrial alterations. Structural damage includes morphological changes, such as para-crystalline inclusions in megamitochondria and mtDNA depletion, which may be related to the liver injury developed in NAFLD patients[84,85]. Functional modifications include impaired mitochondrial protein synthesis which is related to uncoupling and decrease of ETC complex activities, alterations in mitochondrial biogenesis and biodynamics, and reduced concentrations of antioxidant enzymes[85]. Similar alterations have been observed in ob/ob mice, which showed modifications in ROS production and glutathione levels, lipid peroxidation and changes in mitophagy and mitochondrial biogenesis[78].

Mitochondrial structure and function are directly related to the cellular metabolic state. An enriched nutrient environment induces fragmentation of mitochondria, increase of mitochondrial ROS production and mtDNA damage, whereas undersupply of nutrients restricts mtDNA damage and induces fusion and elongation of mitochondria. A continuous metabolic imbalance induces alterations in mitochondrial morphology that could affect mitochondrial function and mtDNA quality that, in turn, can alter the susceptibility to long-term metabolic diseases[3,86,87]. Importantly, studies have demonstrated that even mitochondria in the fertilised oocyte are prone to damage by nutritional stressors. Oocytes exposed to a high-fat high-sucrose diet showed a diminishment in mitochondrial membrane potential and in the metabolites involved in ATP production, and absence of mitophagy, thus resulting in the transmission of dysfunctional mitochondria[88]. Moreover, the maintenance of this altered mitochondrial phenotype has been demonstrated across generations, and has been proven to favour the development of insulin resistance in the offspring[89]. In this regard, it is important to note that the transfer of these mitochondrial disturbances through three generations was observed between obese mothers and female offspring, supported by the fact that these organelles are maternally inherited[89].

Several studies have demonstrated a strong relationship between early-life malnutrition, NAFLD and mitochondrial disturbances (Table 1). In this regard, different alterations in mtDNA, mitochondrial bioenergetics, biogenesis and biodynamics have been related to metabolic disorders, including obesity, diabetes and NAFLD[48,90,91]. Alfaradhi *et al.* reported that young offspring (8 weeks of age) exposed to a high-fat, high-sugar diet during pregnancy and lactation, which reflects a Western obesogenic environment, presented augmented mitochondrial complex I and II activities and diminished mitochondrial cytochrome c and glutamate dehydrogenase levels, showing hepatic dysfunctional mitochondria[92]. These detrimental changes were associated with an increase in hepatic lipid content, oxidative damage, PPARγ expression and insulin levels, and a decrease in triacylglycerol lipase[92]. Another study showed that adult offspring exposed to a semisynthetic not obesogenic Western-style diet (rich in energy, moderate in fat and cholesterol) from prenatal to post-weaning developed microvesicular fat accumulation and diminished plasma β-hydroxybutyrate and mRNA levels of PPARα, showing an imbalance between mitochondrial FAO and augmented production of fatty acids, which is consistent with mitochondrial dysfunction[24]. Impairment of mitochondrial ETC complex activities (I, II, III and IV) and reduced serum concentrations of β-hydroxybutyrate were also demonstrated by others in offspring fed a HFD (42 % kcal from fat) that had been born to obese mothers, during gestation and post-weaning[18,93]. Burgueño *et al.* reported that exposure to a HFD (40 % fat added to standard diet) 2 weeks before breeding and during gestation and lactation resulted in adult offspring (18 weeks of age) with reduced hepatic mtDNA content and male-specific diminishment in hepatic transcriptional activity of PGC1α, which was further related to insulin resistance and abnormal liver fat accumulation[94]. Other studies have shown that post-weaning HFD-fed adult offspring (45 % kcal from fat) born to pre-pregnancy obese dams presented reduced levels of regulators of mitochondrial dynamics (PGC1α, PGC1β and ERRα) and mitofusins in liver[95]. In another set of experiments, de Velasco *et al.* demonstrated the effecs of

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Table 1 Studies associated with the interplay between early-life nutrition, NAFLD and mitochondrial disturbances

Early-life nutritional insult	Diet description	Species	Mitochondrial dysfunction	Effects on offspring related to NAFLD	Reference
Western-type (not obesogenic) diet during prenatal, lactation and post-weaning periods	Energy-rich- semisynthetic Western diet (45 % kcal fat, 20 % kcal protein, 35 % kcal carbohydrate; 4·73 kcal/g)	Mouse	↓plasma β-hydroxybutyrate imbalance between mitochondrial FAO and ↑production of fatty acids	↑microvesicular lipid accumulation ↑inflammation ↑liver injury	24
Obesogenic diet (high-fat, high-sugar) during pregnancy and lactation	Energy-rich highly palatable obesogenic diet (10 % simple sugars, 20 % animal lard, 28 % polysaccharide, 23 % protein (wt/wt), 28·43 kJ/g) supplemented with sweetened condensed milk (16 % fat, 33 % simple sugars, 15 % protein, 13·7 kJ/g)	Mouse	↑mitochondrial complex I and II activities ↓cytochrome c ↓glutamate dehydrogenase	↑hepatic lipid content ↑oxidative stress ↑PPARγ expression hyperinsulinemia ↓triacylglycerol lipase	92
High-fat obesogenic diet during prenatal, gestation, and post-weaning periods	Diet (42 % kcal fat, 42·7 % kcal carbohydrates, 15·2 % kcal protein; 4·5 kcal/g)	Mouse	↓mitochondrial ETC complex activities (I, II, III and IV) ↓plasma β-hydroxybutyrate	↓reduced sensitivity to insulin ↑serum leptin, insulin, triacylglycerol, glucose and NEFA levels	93
High-fat diet during 2 weeks before conception, gestation and lactation	Solid diet (40 % wt/wt bovine and porcine fat added to the standard chow)	Rat	↓liver mtDNA copy number	Fatty liver Insulin resistance and hyperleptinemia in male offspring	94
Maternal intra-uterine obesity and/or high-fat diet during post-weaning period	Obesogenic liquid diet (5 % kcal fat, 20 % kcal protein, 75 % kcal carbohydrate) at 220 kcal/kg per day (40 % excess of calories) and/or high-fat diet (45 % kcal from fat)	Rat	↓transcriptional regulators of mitochondrial dynamics (PGC1α, PGC1β and ERRα) ↓MFN1 and MFN2	↓energy expenditure Impaired fat utilisation	95
Normolipidic diets rich in Trans-unsaturated fatty acids or inter-esterified fat during pregnancy and lactation	Isoenergetic diets (17·2 kJ/g of dry diet) containing 6 % partially hydrogenated vegetable oil plus 1 % soyabean oil, or 5 % inter-esterified fat plus 2 % soyabean oil	Mouse	Respiration impairment ↑liver H_2O_2 production ↓mitochondrial Ca^{2+} retention capacity	Impaired glucose homoeostasis Alterations in serum and hepatic lipids profile	96

FAO, fatty acid β-oxidation; ETC, electron transport chain; mtDNA, mitochondrial DNA; PGC1, peroxisome proliferator-activated receptor-γ co-activator α; ERR, oestrogen-related receptor; MFN, mitofusin; PPAR, peroxisome proliferator-activated receptor.

maternal consumption of isoenergetic and normolipidic diets rich in trans-fatty acids, that is, hydrogenated fat, or its industrial substitute lipid source, interesterified fatty acids, during pregnancy and lactation[96]. These early-life insults predispose to hepatic mitochondrial dysfunction in adult offspring (postnatal day 110), related to changes in mitochondrial bioenergetics, which includes respiration impairment, augmentation of H_2O_2 production in the liver and compromised mitochondrial membrane permeability[96]. The current research provides convincing evidence for the critical role of these mitochondrial alterations in offspring programming related to malnutrition and NAFLD development.

Epigenetics, NAFLD and early-life nutrition

Although the exact mechanisms underlying NAFLD development have not been completely described, epigenetics arises as an important player contributing to NAFLD pathophysiology[91]. Furthermore, studies have established a link between environmental factors, epigenetics and developmental programming[97]. In this regard, it is important to mention that inadequate nutrition during preconception, pregnancy and early infancy has been related to epigenetic modifications in genes involved in lipid metabolism and inflammation, which may favour the development of metabolic alterations later in life[97,98]. The epigenetic mechanisms that regulate nuclear gene expression include non-coding RNAs, DNA methylation and post-translational modifications of histones. DNA methylation refers to methylation of cytosine nucleotides at CpG-rich promoters[10]. While hypermethylation blocks gene transcription, hypomethylation induces gene activation, which depends on the activity of DNA methyltransferases (DNMT)[2]. Post-translational modifications of histones include acetylation, methylation, ubiquitylation, phosphorylation and SUMOylation[2]. Histone acetylation is the most reported mechanism. While acetylation is related to promotion of gene transcription, deacetylation is associated with gene inactivation[2]. Among non-coding RNAs, microRNAs (miRNA) are the most studied. MiRNAs are non-coding single-stranded RNAs with nineteen to twenty-three nucleotides that modulate mRNA degradation or inhibition of translation[2].

In the past years, several studies have shown the interplay between adverse maternal nutrition, epigenetic modifications and developmental programming of this liver disease[97] (Table 2). Researchers found that a high-fat lard diet rich in unsaturated fatty acids (35 %) during preconception and pregnancy until gestation days 18–20 modulated the epigenome of foetal livers, evidenced by the promotion of DNA methylation and histone acetylation, leading to liver lipid accumulation[99]. Keleher *et al.* reported that a maternal HFD induced thousands of DNA methylation alterations in livers of post-weaning HFD-fed offspring mice (42 % kcal from fat), which were also evident in adulthood[93]. In addition, in HFD-fed daughters, these epigenetic alterations were associated with obesity and diabetes-related phenotypic changes[93]. Similarly, Seki *et al.* showed that exposure to a maternal high-fat lard diet during preconception, gestation and lactation results in global hepatic DNA hypermethylation in male offspring[100]. Persistent methylation of three genes involved in growth and metabolism (*Arhgef19*, *Zbtb17/Miz-1* and *Mmp9*) was observed in these offspring throughout life[100]. Exposure to a Western diet (rich in energy and moderate in fat and cholesterol) during preconception, pregnancy, lactation and post-weaning results in phenotypic alterations compatible with NAFLD in the offspring, which were further associated with significant methylation differences in *PPARα*, an important gene involved in lipid metabolism[24]. In accordance, Whankhade *et al.* showed that maternal overnutrition via *in utero* exposure to a HFD (45 % fat) induced alterations in DNA methylation of *PGC1α* and *Fgf21* in livers of post-weaning HFD offspring, which may be involved in NAFLD development[97]. A maternal HFD (22·6 % fat) during pregnancy and lactation has also been demonstrated to affect miRNA expression in adult offspring livers[101]. Furthermore, it was evidenced that an adverse intra-uterine environment induced by a high-sucrose (72 %), low-copper diet induces significant modifications in DNA methylation of 327 regions corresponding to 183 genes in offspring rat livers. The affected pathways were associated with metabolic disease, insulin resistance and carbohydrate metabolism[102]. A high-fat high-cholesterol Western-type diet before and during gestation and lactation given to apolipoprotein (Apo) E-deficient dams resulted in augmented hepatic methylation of CpG nucleotides on the promoter region of ApoB genes of male adult offspring[103]. The progeny also developed hyperinsulinemia, insulin resistance, glucose intolerance and hepatic steatosis[103]. Another study showed that perinatal exposure to an obesity-inducing diet rich in saturated fat, fructose and cholesterol, used to reproduce the Western fast-food diet, induced alterations compatible with NAFLD in the offspring (10 weeks of age), which were further related to differential expression and methylation of genes associated with fibrosis and cell death pathways[104]. Interestingly, these authors also demonstrated that this phenotype could be reversed if a healthy diet is administered after weaning to the offspring; otherwise, the progeny would develop a NASH phenotype following re-exposure to this Western fast-food diet in adulthood[104]. Du *et al.* reported that the male offspring born to mothers exposed to 50 % food restriction during gestation presented a dysregulated hepatic metabolism through alterations in taurine levels and hepatocyte nuclear factor 4 A (HNF4A) methylation that is associated with alterations in hepatic lipogenesis and gluconeogenesis[105]. In another study, which fed pregnant rats a low-protein (8 %) diet, maternal protein restriction during gestation led to histone acetylation of liver X receptor α (Lxrα) in male rat offspring[106]. This finding suggests that its promoter was epigenetically silenced, thus leading to glucose intolerance in adulthood[106]. Intra-uterine growth restriction as a result of maternal low-protein diet (8 %) during pregnancy and lactation induced repressive histone modifications at hepatic cholesterol 7α-hydroxylase promoter in adult rat offspring, leading to an increase in cholesterol levels[107]. In non-human primates, *in utero* exposure to a HFD (32 % calories from fat), but not maternal obesity *per se*, altered the foetal metabolome through augmented acetylation of histone H3 (H3K14ac) and decreased SIRT1 expression in foetal livers[108]. These modifications were related to altered expression of PPARα, PPARγ, SREBF1, Cyp7A1, Fasn and SCD, which are modulated by SIRT1 and known to be dysregulated in

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Table 2 Studies related to the link between early-life nutrition, NAFLD and epigenetics

Early-life nutritional insult	Diet description	Species	Epigenetic alterations	Effects on offspring related to NAFLD	Reference
Western-type diet during preconception, pregnancy and lactation	Energy-rich- semisynthetic Western diet (not obesogenic) (20 % kcal protein, 35 % kcal carbohydrate, 45 % kcal fat; 4·73 kcal/g)	Mouse	↑DNA methylation in *PPARα*, *Insig2*, and *Fasn* genes	↑hepatic lipid content ↑oxidative stress ↑PPARγ expression hyperinsulinemia ↓triacylglycerol lipase	24
High-fat obesogenic diet during prenatal, gestation and post-weaning periods	Diet (15·2 % kcal protein, 42·7 % kcal carbohydrates, 42 % kcal fat; 4·5 kcal/g)	Mouse	DNA methylation differences in thousands of hepatic genes	↓sensitivity to insulin ↑serum leptin, insulin, triacylglycerol, glucose and NEFA levels	93
High-fat lard diet dietary rich in unsaturated fatty acids during prenatal period and pregnancy until gestation days 18–20	Diet containing 35 g lard fat/100 g diet	Rat	Foetal livers: ↑global DNA methylation↑DNMT1 activity ↓acetylated H2A and H2B levels ↓HAT activity	↑adipogenesis in foetal livers	99
Obesogenic diet during preconception, pregnancy, lactation and post-weaning periods	Diet (14·7 % kcal protein, 40·7 % kcal carbohydrate, 44·6 % kcal total fat: 61 % SFA, 30 % MUFA, 9 % PUFA; 4·7 kcal/g)	Mouse	DNA methylation alterations in PGC1ß and Fgf21	Hepatic steatosis ↑inflammation ↑pro-fibrogenic gene expression	97
High-fat diet during 2 weeks before conception, pregnancy and lactation	Obesogenic diet containing 35·5 % fat as lard, 20 % protein, 36·3 % carbohydrate, (5·49 kcal/g)	Mouse	Persistent DNA methylation alterations in Arhgef19, Zbtb17/Miz-1 and Mmp9	↑adiposity impaired glucose tolerance and insulin sensitivity	100
High-fat diet prior to conception, during pregnancy and lactation	Diet (22·6 % fat, 23 % protein, 48·6 % carbohydrate, wt/wt)	Mouse	↓expression of miR-709, miR-122, miR-494, miR-192, miR-194, miR-26a, let-7a, let7b and let-7c, and miR-483	↑hepatic mRNA levels of genes involved in fat metabolism (PPARα, cpt-1a, IGF2)	101
Maternal high fat/high cholesterol Western-type diet before and during pregnancy and lactation	High-fat, high-cholesterol diet composed of 43 % kcal from fat, 16·5 % kcal from protein, 38·7 % kcal from carbohydrate and 0·2 % cholesterol	Mouse	Hypermethylation of hepatic ApoB gene	Hyperinsulinemia Insulin resistance Glucose intolerance Hepatic steatosis	103
Obesity-inducing diet rich in fat, fructose and cholesterol (Western fast-food diet) before conception and during gestation and lactation	Diet composed of 40 % energy as fat (12 % saturated fatty acid, 0·2 % cholesterol) with fructose (23·1 g/L final concentration) and glucose (18·9 g/L) in the drinking-water	Mouse	Differential methylation linked to profibrogenic and pro-inflammatory gene signature	Hepatocellular ballooning Lipoapoptosis ↑liver steatosis ↑liver injury ↑liver inflammation ↑liver fibrosis	104
Maternal food restriction during gestation	50 % food-restriction diet	Rat	Changes in HNF4A methylation	↑liver lipid accumulation ↑plasma glucose levels	105
Low-protein diet during gestation	Isoenergetic low-protein diet containing 8 % protein	Rat	↓acetylation of histone H3 (K9,14) surrounding transcriptional start site of hepatic Lxrα	Glucose intolerance	106
Low-protein diet during pregnancy and lactation	Isoenergetic low-protein diet containing 8 % protein	Rat	↓acetylation and ↑methylation of histone H3 (K9,14) surrounding promoter region of hepatic Cyp7a1	↑serum and hepatic cholesterol levels	107
Maternal intra-uterine exposure to high-fat diet	Diet composed of 32 % calories from fat, 18 % from protein and 45 % from carbohydrates	Macaque	↑acetylation of histone H3 (H3K14ac)	Alterations in expression of PPARα, PPARγ, SREBF1, Cyp7a1, Fasn and SCD in foetal livers	108

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Table 2 (*Continued*)

Early-life nutritional insult	Diet description	Species	Epigenetic alterations	Effects on offspring related to NAFLD	Reference
Maternal high-fat high-sucrose diet prior to conception and until gestation day 165	Diet (45 % energy from fat, 4·62 % from glucose, 5·64 % from fructose and 2·32 % from sucrose, regular protein content, 4·03 kcal/g) with free access to a sugar-containing drink	Baboon	Alterations in miR-130a-3p, miR-186-5p, miR-96, miR-130a-3p, miR-143-3p, miR-1285-3p, miR-199a-5p, miR-182-5p, miR-1285-3p, miR-185-5p, miR-194-3p, miR-145-3p, miR-183-5p	Dysregulated TCA cycle, proteasome, glycolysis, oxidative phosphorylation and Wnt/β-catenin pathways Excessive hepatic lipid accumulation	109
Periconceptional exposure to famine	* Individuals born alive 50–58 years ago during the Dutch Hunger Winter (November 1943 to February 1947) in the Wilhelmina Gasthuis, Amsterdam * Individuals born alive six decades ago during the Dutch Hunger Winter (winter of 1944–1945)	Human	↓methylation of IGF2 DMR	Glucose intolerance Obesity Atherogenic lipid profile	111,119

PPAR, peroxisome proliferator-activated receptor; Insig2, insulin-induced gene 2; Fasn, fatty acid synthase; DNMT1, DNA methyltransferase 1; HAT, histone acetyltransferase; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; PGC1β, peroxisome proliferator-activated receptor γ co-activator 1-β; Fgf21, fibroblast growth factor 21; Arhgef19, rho guanine nucleotide exchange factor 19; Zbtb17/Miz-1, Myc-interacting zinc finger protein 1; Mmp9, matrix metallopeptidase 9 ; Cpt-1a, carnitine palmitoyltransferase 1a; IGF2, insulin-like growth factor 2; ApoB, apolipoprotein B; HNF4A, hepatocyte nuclear factor 4 α; Lxrα, liver X receptor α; SREBF1, sterol regulatory element binding transcription factor 1; Cyp7a1, cholesterol 7α-hydroxylase; SCD, stearoyl-CoA desaturase; DMR, differentially methylated region.

NAFLD[108]. Maternal obesity induced by a high-fat high-fructose diet during preconception and pregnancy until gestation day 165 showed dysregulated TCA cycle, proteasome, glycolysis, oxidative phosphorylation and Wnt/β-catenin pathways along with excessive lipid accumulation in foetal baboon livers[109]. This was correlated with the identification of several miRNAs that were inversely expressed with key genes in these pathways that have been shown to be regulated by these miRNAs, suggesting that these foetal hepatic miRNA–gene interactions may affect these pathways, thus leading to regulation of cell proliferation, liver steatosis, hepatic fibrosis and lipid metabolism[109]. In conjunction, the available evidence strongly supports the notion that modulation of the nuclear epigenome mediated by early-life nutrition plays an important role in NAFLD pathophysiology. Thus, current epigenetic studies not only may explain the mechanisms underlying the development of NAFLD, but also provide evidence concerning the role of epigenetic modifications in the developmental programming of this liver disease.

Due to evident ethical restrictions, there exists limited evidence concerning a link between adverse maternal nutrition, metabolic disease and epigenetic alterations in human offspring. The famine suffered by pregnant human females during the Dutch Hunger Winter in 1944–1945 provides evidence about the consequences of long-term exposure to maternal undernutrition in humans[110,111]. In this regard, it was reported that human offspring who were exposed to famine during the first and second trimester *in utero* had lower birth weights than those not exposed[112]. Moreover, prevalence of obesity in young men was augmented in those individuals who had been exposed to famine undernutrition during the first half of pregnancy[113]. In addition, epidemiological studies from the Chinese Great Famine (1959–1961) have demonstrated a significant association between early-life undernutrition and augmented risk of later NAFLD development, where steatosis degree was determined by abdominal ultrasonography[114,115]. Early famine exposure has also been linked to obesity, type 2 diabetes and metabolic syndrome, which are closely related to NAFLD[116–118]. It is important to mention that, even though findings that link early famine exposure to NAFLD development have been reported, we cannot conclude that higher risks for NAFLD in early famine-exposed individuals are exclusively related to early-life malnutrition.

Even though human studies usually employ reduced birth weight to demonstrate the effects of an inadequate maternal nutrition, researchers showed that a lower birth weight was insufficient to probe epigenetics involvement[119]. Interestingly, while human offspring born alive (50–58 years ago) with a normal birth weight who were exposed to famine during the Dutch Hunger Winter at early gestation showed epigenetic alterations, those offspring with low birth weight exposed to this famine during late gestation did not present epigenetic modifications[119] (Table 2). In fact, other researchers reported lower DNA methylation of the insulin-like growth factor II gene in human offspring born alive exposed to this famine (winter of 1944–1945) during periconception, in comparison with their unexposed siblings of the same sex, six decades later[111]. These data support the notion that, in humans, adverse maternal nutrition leads to epigenetic alterations during the first stages of

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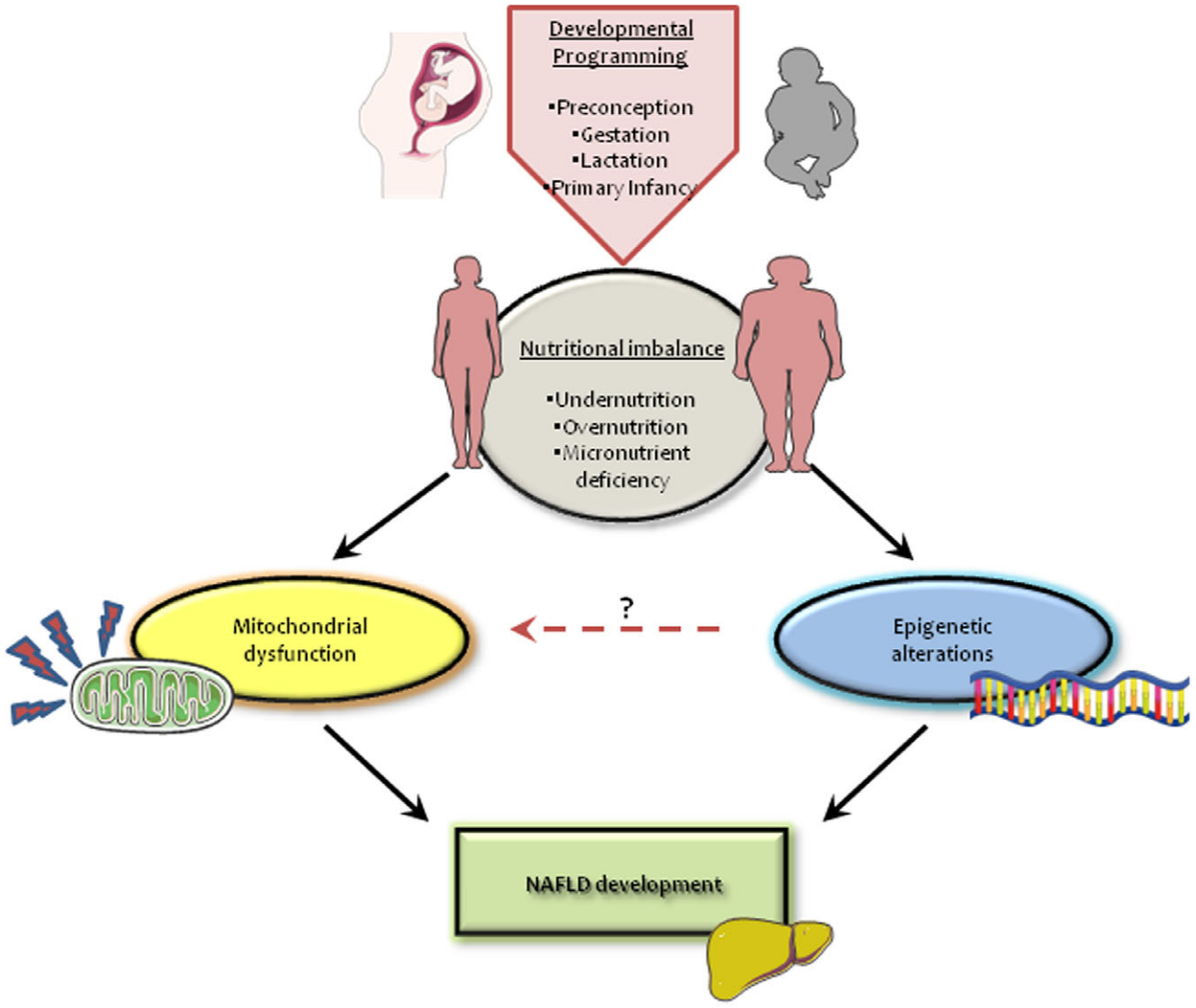

Fig. 1. Interplay between mitochondrial dysfunction, epigenetics and nutrition during early life, which is relevant to developmental programming of NAFLD. Different types of early nutritional imbalances, including undernutrition, overnutrition and micronutrient deficiency, have been related to long-term metabolic disorders. Accumulating evidence has demonstrated that disturbances in nutrition during the period of preconception, pregnancy and primary infancy can affect mitochondrial function and epigenetic mechanisms. In addition, in the past years, special attention has been given to mitochondrial dysfunction and epigenetic alterations as probable mechanisms underlying non-alcoholic fatty liver disease (NAFLD). Dysfunctional mitochondria contribute to oxidative stress, insulin resistance and inflammation. Epigenetic mechanisms have been related to alterations in genes involved in lipid metabolism, fibrogenesis, inflammation and tumorigenesis. Mitochondria are highly sensitive to environmental factors and could acquire epigenetic alterations that may disrupt mitochondrial function. Thus, mitochondrial dysfunction and epigenetics linked to early-life nutrition can be important contributing factors in the pathogenesis of NAFLD.

development that are maintained over time, which may be related to metabolic liver disease during adulthood.

Interestingly, while epigenetic regulation of nuclear DNA has been extensively reported, that of mtDNA has recently been demonstrated[120,121]. Moreover, in the past years, studies have reported the complex interaction between mitochondrial metabolism, epigenetics and environmental changes[122]. Mitochondria are highly sensitive to environmental factors and could acquire epigenetic alterations that may disrupt mitochondrial function[123]. Maternal nutrition is described as a relevant factor that may affect these epigenetic modifications[124]. In addition, since mitochondria depend on nuclear-encoded proteins to function, it is crucial to explain the link between nuclear and mitochondrial DNA and the subsequent epigenetic alterations to nuclear DNA that may affect mitochondrial metabolism. Mitochondrial epigenetic mechanisms include mtDNA methylation, post-translational modifications of nucleoid-associated proteins and non-coding RNAs (ncRNA)[122].

Over the last years, the epigenetic mechanism of mtDNA methylation has been extensively studied. However, it is far from being clearly understood. Studies have centred on mtDNA methylation at CpG sites, though adenine and non-CpG methylations have also been discovered[125,126]. Moreover, it has been hypothesised that mtDNA methylation on adenine is the principal alteration among them[122]. Given that environmental factors could affect mtDNA methylation, maternal diet arises as an important contributor to mtDNA regulation. In this

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regard, it has been reported that a maternal low-protein diet during pregnancy alters DNA methylation and hydroxymethylation of mtDNA-encoded oxidative phosphorylation gene promoters in a sex-specific manner, in livers of newborn piglets[127]. These modifications may be associated with long-term consequences in energy homoeostasis[122] that, in turn, could be involved in the development of liver metabolic disease.

Unlike nuclear DNA, mtDNA is not surrounded by histones. However, mtDNA is organised in nucleoids. Thus, this epigenetic mechanism is referred to as post-translational modification of nucleoid-associated proteins. The principal protein present in mitochondrial nucleoids is Tfam, which is a nuclear-encoded binding factor also required for mtDNA transcription[128]. Different post-translational modifications of Tfam have been reported, including acetylation, glycosylation, phosphorylation and ubiquitination[122,129–131]. For instance, phosphorylation and acetylation of Tfam reduce the binding affinity of Tfam to DNA, thus resulting in a decreased mtDNA compaction that ultimately leads to alterations in mtDNA transcription[122]. Although it can be hypothesised that all of those alterations may affect Tfam function, which, in turn, could lead to mitochondrial dysfunction that may later be involved in NAFLD development, until now there is no evidence supporting the notion that epigenetic modifications of Tfam are associated with NAFLD pathophysiology.

Recently, it was reported that the presence of ncRNAs inside mitochondria was associated with epigenetic regulation of mitochondrial gene expression[122,132]. These ncRNAs include nuclear-encoded and mitochondria-encoded ncRNAs (nuclear ncRNAs and mt-ncRNAs, respectively). While the former are involved in anterograde communication, the latter are associated with retrograde communication[133]. With regard to mt-ncRNAs, long non-coding RNAs (mt-lncRNA) and small non-coding RNAs (mt-sncRNA) are included. The discovery of these ncRNAs in mitochondria increases the level of complexity in mitochondrial gene expression. However, few studies have related mt-ncRNAs to the development of diseases, such as cancer and cardiovascular diseases[134,135]. Therefore, until now, data are insufficient to establish a link between mitochondrial epigenetics and NAFLD development. However, it can be envisioned that the association between mt-ncRNAs and human diseases in general, and NAFLD in particular, may be potent as they are relevant in mitochondrial homoeostasis and communication. In this sense, mt-ncRNAs may be employed as biomarkers of different diseases.

Conclusion and perspectives

In summary, the reviewed data support the relevance of mitochondrial dysfunction and epigenetic modifications as contributors to the dysregulated mechanisms underlying the developmental programming of NAFLD. Rodent and non-human primate studies have shown that early-life exposure, including preconception, pregnancy, lactation and early infancy, to an adverse nutritional environment is linked to long-term alterations in mitochondrial function and epigenetics in the offspring (Fig. 1). Due to evident ethical limitations, human studies concerning this association are scarce. Given that dysfunctional mitochondria are strongly related to NAFLD development, mitochondrial epigenetics could also be involved in the regulation of NAFLD pathogenesis, in the context of early-life malnutrition. However, the association of mitochondrial epigenetics and NAFLD in this adverse context has yet to be elucidated.

The increasing prevalence of NAFLD in the past years positions it as an emerging health concern. Therefore, clarification of the modulation of the epigenome and mitochondrial function related to nutritional disturbances during early life may contribute to the progress in this emerging field of research. Advances in the understanding of these dysregulated mechanisms in NAFLD are essential to design early interventions applied during the critical periods of human development intended to prevent this liver disease. More research in this field would aid the development of adequate treatment strategies, focused on mitochondrial function improvement and epigenome modulation, to prevent and/or treat NAFLD. Furthermore, this knowledge would be beneficial for the design of new diagnostic biomarkers..

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Conflict of interest

The authors have no conflicts of interest to declare.

Authorship

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References

1. Friedman SL, Neuschwander-Tetri BA, Rinella M, *et al.* (2018) Mechanisms of NAFLD development and therapeutic strategies. *Nat Med* **24**, 908–922.
2. Campisano S, La Colla A, Echarte SM, *et al.* (2019) Interplay between early-life malnutrition, epigenetic modulation of the immune function and liver diseases. *Nutr Res Rev* **32**, 128–145.
3. Picard M & Turnbull DM (2013) Linking the metabolic state and mitochondrial DNA in chronic disease, health, and aging. *Diabetes* **62**, 672–678.
4. Calcaterra V, Cena H, Verduci E, *et al.* (2020) Nutritional surveillance for the best start in life, promoting health for neonates, infants and children. *Nutrients* **12**, 3386.
5. Brumbaugh DE & Friedman JE (2014) Developmental origins of nonalcoholic fatty liver disease. *Pediatr Res* **75**, 140–147.
6. Kim J-A, Wei Y & Sowers JR (2008) Role of mitochondrial dysfunction in insulin resistance. *Circ Res* **102**, 401–414.

https://doi.org/10.1017/S0954422422000038 Published online by Cambridge University Press

7. Xu L, Nagata N & Ota T (2019) Impact of glucoraphanin-mediated activation of Nrf2 on non-alcoholic fatty liver disease with a focus on mitochondrial dysfunction. *Int J Mol Sci* **20**, 5920.
8. Wiederkehr A & Wollheim CB (2006) Minireview: implication of mitochondria in insulin secretion and action. *Endocrinology* **147**, 2643–2649.
9. Del Campo JA, Gallego-Durán R, Gallego P, *et al.* (2018) Genetic and epigenetic regulation in nonalcoholic fatty liver disease (NAFLD). *Int J Mol Sci* **19**, 911.
10. Xu F & Guo W (2020) The progress of epigenetics in the development and progression of non-alcoholic fatty liver disease. *Liver Res* **4**, 118–123.
11. Black RE, Victora CG, Walker SP, *et al.* (2013) Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* **382**, 427–451.
12. Li M, Reynolds CM, Segovia SA, *et al.* (2015) Developmental programming of nonalcoholic fatty liver disease: The effect of early life nutrition on susceptibility and disease severity in later life. *Biomed Res Int* **2015**, 437107.
13. Ross MG & Beall MH (2008) Adult sequelae of intrauterine growth restriction. *Semin Perinatol* **32**, 213–218.
14. Thompson MD (2020) Developmental programming of NAFLD by parental obesity. *Hepatol Commun* **4**, 1392–1403.
15. Barker DJP (2007) The origins of the developmental origins theory. *J Intern Med* **261**, 412–417.
16. Gluckman PD & Hanson MA (2004) The developmental origins of the metabolic syndrome. *Trends Endocrinol Metab* **15**, 183–187.
17. McCurdy CE, Bishop JM, Williams SM, *et al.* (2009) Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates. *J Clin Invest* **119**, 323–335.
18. Bruce KD, Cagampang FR, Argenton M, *et al.* (2009) Maternal high-fat feeding primes steatohepatitis in adult mice offspring, involving mitochondrial dysfunction and altered lipogenesis gene expression. *Hepatology* **50**, 1796–1808.
19. Gregorio BM, Souza-Mello V, Carvalho JJ, *et al.* (2010) Maternal high-fat intake predisposes nonalcoholic fatty liver disease in C57BL/6 offspring. *Am J Obstet Gynecol* **203**, 495.e1-8.
20. Souza-Mello V, Mandarim-de-Lacerda CA & Aguila MB (2007) Hepatic structural alteration in adult programmed offspring (severe maternal protein restriction) is aggravated by post-weaning high-fat diet. *Br J Nutr* **98**, 1159–1169.
21. Sanchez-Blanco C, Amusquivar E, Bispo K, *et al.* (2016) Influence of cafeteria diet and fish oil in pregnancy and lactation on pups' body weight and fatty acid profiles in rats. *Eur J Nutr* **55**, 1741–1753.
22. Sánchez-Blanco C, Amusquivar E, Bispo K, *et al.* (2019) Dietary fish oil supplementation during early pregnancy in rats on a cafeteria-diet prevents fatty liver in adult male offspring. *Food Chem Toxicol* **123**, 546–552.
23. Bayol SA, Simbi BH, Fowkes RC, *et al.* (2010) Maternal 'junk food' diet in pregnancy and lactation promotes nonalcoholic fatty liver disease in rat offspring. *Endocrinology* **151**, 1451–1461.
24. Pruis MGM, Lendvai A, Bloks VW, *et al.* (2014) Maternal western diet primes non-alcoholic fatty liver disease in adult mouse offspring. *Acta Physiol (Oxf)* **210**, 215–227.
25. Campisano SE, Echarte SM, Podaza E, *et al.* (2017) Protein malnutrition during fetal programming induces fatty liver in adult male offspring rats. *J Physiol Biochem* **73**, 275–285.
26. Erhuma A, Salter AM, Sculley DV, *et al.* (2007) Prenatal exposure to a low-protein diet programs disordered regulation of lipid metabolism in the aging rat. *Am J Physiol Endocrinol Metab* **292**, 1702–1714.
27. Deshmukh U, Katre P & Yajnik CS (2013) Influence of maternal vitamin B12 and folate on growth and insulin resistance in the offspring. *Nestle Nutr Inst Workshop Ser* **74**, 145–54.
28. Khaire A, Rathod R, Kale A, *et al.* (2015) Vitamin B and omega-3 fatty acids together regulate lipid metabolism in Wistar rats. *Prostaglandins Leukot Essent Fatty Acids* **99**, 7–17.
29. Ahmad S, Kumar KA, Basak T, *et al.* (2013) PPAR signaling pathway is a key modulator of liver proteome in pups born to vitamin B(12) deficient rats. *J Proteomics* **91**, 297–308.
30. Pooya S, Blaise S, Moreno Garcia M, *et al.* (2012) Methyl donor deficiency impairs fatty acid oxidation through PGC-1α hypomethylation and decreased ER-α, ERR-α, and HNF-4α in the rat liver. *J Hepatol* **57**, 344–351.
31. Sharma SS, Jangale NM, Harsulkar AM, *et al.* (2017) Chronic maternal calcium and 25-hydroxyvitamin D deficiency in Wistar rats programs abnormal hepatic gene expression leading to hepatic steatosis in female offspring. *J Nutr Biochem* **43**, 36–46.
32. Spinelli JB & Haigis MC (2018) The multifaceted contributions of mitochondria to cellular metabolism. *Nat Cell Biol* **20**, 745–754.
33. Walsh CT, Tu BP & Tang Y (2018) Eight kinetically stable but thermodynamically activated molecules that power cell metabolism. *Chem Rev* **118**, 1460–1494.
34. Zhao R-Z, Jiang S, Zhang L, *et al.* (2019) Mitochondrial electron transport chain, ROS generation and uncoupling (Review). *Int J Mol Med* **44**, 3–15.
35. Sazanov LA (2015) A giant molecular proton pump: structure and mechanism of respiratory complex I. *Nat Rev Mol Cell Biol* **16**, 375–388.
36. Watt IN, Montgomery MG, Runswick MJ, *et al.* (2010) Bioenergetic cost of making an adenosine triphosphate molecule in animal mitochondria. *Proc Natl Acad Sci U S A* **107**, 16823–16827.
37. Murphy MP (2009) How mitochondria produce reactive oxygen species. *Biochem J* **417**, 1–13.
38. Brand MD (2010) The sites and topology of mitochondrial superoxide production. *Exp Gerontol* **45**, 466–472.
39. Schieber M & Chandel NS (2014) ROS function in redox signaling and oxidative stress. *Curr Biol* **24**, 453–462.
40. Sena LA & Chandel NS (2012) Physiological roles of mitochondrial reactive oxygen species. *Mol Cell* **48**, 158–167.
41. Cox AG, Winterbourn CC & Hampton MB (2009) Mitochondrial peroxiredoxin involvement in antioxidant defence and redox signalling. *Biochem J* **425**, 313–325.
42. Winterbourn CC & Hampton MB (2008) Thiol chemistry and specificity in redox signaling. *Free Radic Biol Med* **45**, 549–561.
43. Ray PD, Huang B-W & Tsuji Y (2012) Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. *Cell Signal* **24**, 981–990.
44. Betteridge DJ (2000) What is oxidative stress? *Metabolism* **49**, Suppl. 1, S3–S8.
45. Wang B, Van Veldhoven PP, Brees C, *et al.* (2013) Mitochondria are targets for peroxisome-derived oxidative stress in cultured mammalian cells. *Free Radic Biol Med* **65**, 882–894.
46. Radi R, Cassina A, Hodara R, *et al.* (2002) Peroxynitrite reactions and formation in mitochondria. *Free Radic Biol Med* **33**, 1451–1464.
47. Trujillo M, Ferrer-Sueta G & Radi R (2008) Peroxynitrite detoxification and its biologic implications. *Antioxid Redox Signal* **10**, 1607–1620.
48. Simões ICM, Fontes A, Pinton P, *et al.* (2018) Mitochondria in non-alcoholic fatty liver disease. *Int J Biochem Cell Biol* **95**, 93–99.

https://doi.org/10.1017/S0954422422000038 Published online by Cambridge University Press

49. Petrosillo G, Portincasa P, Grattagliano I, *et al.* (2007) Mitochondrial dysfunction in rat with nonalcoholic fatty liver Involvement of complex I, reactive oxygen species and cardiolipin. *Biochim Biophys Acta* **1767**, 1260–1267.
50. Pérez-Carreras M, Del Hoyo P, Martín MA, *et al.* (2003) Defective hepatic mitochondrial respiratory chain in patients with nonalcoholic steatohepatitis. *Hepatology* **38**, 999–1007.
51. Besse-Patin A, Leveille M, Oropeza D, *et al.* (2017) Estrogen signals through peroxisome proliferator-activated receptor-γ coactivator 1α to reduce oxidative damage associated with diet-induced fatty liver disease. *Gastroenterology* **152**, 243–256
52. Onyango IG, Lu J, Rodova M, *et al.* (2010) Regulation of neuron mitochondrial biogenesis and relevance to brain health. *Biochim Biophys Acta* **1802**, 228–234.
53. Scarpulla RC, Vega RB & Kelly DP (2012) Transcriptional integration of mitochondrial biogenesis. *Trends Endocrinol Metab* **23**, 459–466.
54. Wallace DC (2018) Mitochondrial genetic medicine. *Nat Genet* **50**, 1642–1649.
55. Irrcher I, Adhihetty PJ, Sheehan T, *et al.* (2003) PPARγ coactivator-1α expression during thyroid hormone- and contractile activity-induced mitochondrial adaptations. *Am J Physiol Cell Physiol* **284**, 1669–1677.
56. Virbasius JV & Scarpulla RC (1994) Activation of the human mitochondrial transcription factor A gene by nuclear respiratory factors: a potential regulatory link between nuclear and mitochondrial gene expression in organelle biogenesis. *Proc Natl Acad Sci U S A* **91**, 1309–1313.
57. Jornayvaz FR & Shulman GI (2010) Regulation of mitochondrial biogenesis. *Essays Biochem* **47**, 69–84.
58. Vega RB, Huss JM & Kelly DP (2000) The coactivator PGC-1 cooperates with peroxisome proliferator-activated receptor α in transcriptional control of nuclear genes encoding mitochondrial fatty acid oxidation enzymes. *Mol Cell Biol* **20**, 1868–1876.
59. Giguère V (2008) Transcriptional control of energy homeostasis by the estrogen-related receptors. *Endocr Rev* **29**, 677–696.
60. Winder WW, Holmes BF, Rubink DS, *et al* (2000) Activation of AMP-activated protein kinase increases mitochondrial enzymes in skeletal muscle. *J Appl Physiol* **88**, 2219–2226.
61. Rodgers JT, Lerin C, Haas W, *et al.* (2005) Nutrient control of glucose homeostasis through a complex of PGC-1α and SIRT1. *Nature* **434**, 113–118.
62. Kong X, Wang R, Xue Y, *et al.* (2010) Sirtuin 3, a new target of PGC-1α, plays an important role in the suppression of ROS and mitochondrial biogenesis. *PLoS One* **5**, e11707.
63. Lin J, Handschin C & Spiegelman BM (2005) Metabolic control through the PGC-1 family of transcription coactivators. *Cell Metab* **1**, 361–370.
64. Ritov VB, Menshikova EV, He J, *et al.* (2005) Deficiency of subsarcolemmal mitochondria in obesity and type 2 diabetes. *Diabetes* **54**, 8–14.
65. Lowell BB & Shulman GI (2005) Mitochondrial dysfunction and type 2 diabetes. *Science* **307**, 384–387.
66. Delettre C, Lenaers G, Griffoin JM, *et al.* (2000) Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy. *Nat Genet* **26**, 207–210.
67. Cipolat S, Martins de Brito O, Dal Zilio B, *et al.* (2004) OPA1 requires mitofusin 1 to promote mitochondrial fusion. *Proc Natl Acad Sci U S A* **101**, 15927–15932.
68. Smirnova E, Griparic L, Shurland D-L, *et al.* (2001) Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells. *Mol Biol Cell* **12**, 2245–2256.
69. Otera H, Wang C, Cleland MM, *et al.* (2010) Mff is an essential factor for mitochondrial recruitment of Drp1 during mitochondrial fission in mammalian cells. *J Cell Biol* **191**, 1141–1158.
70. James DI, Parone PA, Mattenberger Y, *et al.* (2003) hFis1, a novel component of the mammalian mitochondrial fission machinery. *J Biol Chem* **278**, 36373–36379.
71. Palmer CS, Osellame LD, Laine D, *et al.* (2011) MiD49 and MiD51, new components of the mitochondrial fission machinery. *EMBO Rep* **12**, 565–573.
72. Losón OC, Song Z, Chen H, *et al.* (2013) Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission. *Mol Biol Cell* **24**, 659–667.
73. Nasrallah CM & Horvath TL (2014) Mitochondrial dynamics in the central regulation of metabolism. *Nat Rev Endocrinol* **10**, 650–658.
74. Molina AJA, Wikstrom JD, Stiles L, *et al.* (2009) Mitochondrial networking protects beta-cells from nutrient-induced apoptosis. *Diabetes* **58**, 2303–2315.
75. Gomes LC, Di Benedetto G & Scorrano L (2011) During autophagy mitochondria elongate, are spared from degradation and sustain cell viability. *Nat Cell Biol* **13**, 589–598.
76. Jheng H-F, Tsai P-J, Guo S-M, *et al.* (2012) Mitochondrial fission contributes to mitochondrial dysfunction and insulin resistance in skeletal muscle. *Mol Cell Biol* **32**, 309–319.
77. Schrepfer E & Scorrano L (2016) Mitofusins, from mitochondria to metabolism. *Mol Cell* **61**, 683–694.
78. Mansouri A, Gattolliat C-H & Asselah T (2018) Mitochondrial dysfunction and signaling in chronic liver diseases. *Gastroenterology* **55**, 629–647.
79. Peverill W, Powell LW & Skoien R (2014) Evolving concepts in the pathogenesis of NASH: beyond steatosis and inflammation. *Int J Mol Sci* **15**, 8591–8638.
80. Buzzetti E, Pinzani M & Tsochatzis EA (2016) The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism* **65**, 1038–1048.
81. Cusi K (2009) Role of insulin resistance and lipotoxicity in non-alcoholic steatohepatitis. *Clin Liver Dis* **13**, 545–563.
82. Satapati S, Kucejova B, Duarte JAG, *et al.* (2016) Mitochondrial metabolism mediates oxidative stress and inflammation in fatty liver. *J Clin Invest* **125**, 4447–4462.
83. Rector RS, Thyfault JP, Uptergrove GM, *et al.* (2010) Mitochondrial dysfunction precedes insulin resistance and hepatic steatosis and contributes to the natural history of non-alcoholic fatty liver disease in an obese rodent model. *J Hepatol* **52**, 727–736.
84. Sanyal AJ, Campbell-Sargent C, Mirshahi F, *et al.* (2001) Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. *Gastroenterology* **120**,1183–1192.
85. Koliaki C, Szendroedi J, Kaul K, *et al.* (2015) Adaptation of hepatic mitochondrial function in humans with non-alcoholic fatty liver is lost in steatohepatitis. *Cell Metab* **21**, 739–746.
86. Liesa M & Shirihai OS (2013) Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. *Cell Metab* **17**, 491–506.
87. Westermann B (2010) Mitochondrial fusion and fission in cell life and death. *Nat Rev Mol Cell Biol* **11**, 872–884.
88. Boudoures AL, Saben J, Drury A, *et al.* (2017) Obesity-exposed oocytes accumulate and transmit damaged mitochondria due to an inability to activate mitophagy. *Dev Biol* **426**, 126–138.
89. Saben JL, Boudoures AL, Asghar Z, *et al.* (2016) Maternal metabolic syndrome programs mitochondrial dysfunction via germline changes across three generations. *Cell Rep* **16**, 1–8.

https://doi.org/10.1017/S0954422422000038 Published online by Cambridge University Press

90. Cheng Z & Almeida FA (2014) Mitochondrial alteration in type 2 diabetes and obesity: an epigenetic link. *Cell Cycle* **13**, 890–897.
91. Lee J, Kim Y, Friso S, *et al.* (2017) Epigenetics in non-alcoholic fatty liver disease. *Mol Aspects Med* **54**, 78–88.
92. Alfaradhi MZ, Fernandez-Twinn DS, Martin-Gronert MS, *et al.* (2014) Oxidative stress and altered lipid homeostasis in the programming of offspring fatty liver by maternal obesity. *Am J Physiol Regul Integr Comp Physiol* **307**, R26–R34.
93. Keleher MR, Zaidi R, Shah S, *et al.* (2018) Maternal high-fat diet associated with altered gene expression, DNA methylation, and obesity risk in mouse offspring. *PLoS One* **13**, e0192606.
94. Burgueño AL, Cabrerizo R, Gonzales Mansilla N, *et al* (2013). Maternal high-fat intake during pregnancy programs metabolic-syndrome-related phenotypes through liver mitochondrial DNA copy number and transcriptional activity of liver PPARGC1A. *J Nutr Biochem* **24**, 6–13.
95. Borengasser SJ, Lau F, Kang P, *et al.* (2011) Maternal obesity during gestation impairs fatty acid oxidation and mitochondrial SIRT3 expression in rat offspring at weaning. *PLoS One* **6**, e24068.
96. De Velasco PC, Chicaybam G, Ramos-Filho DM, *et al.* (2017) Maternal intake of trans-unsaturated or interesterified fatty acids during pregnancy and lactation modifies mitochondrial bioenergetics in the liver of adult offspring in mice. *Br J Nutr* **118**, 41–52.
97. Wankhade UD, Zhong Y, Kang P, *et al.* (2017) Enhanced offspring predisposition to steatohepatitis with maternal high-fat diet is associated with epigenetic and microbiome alterations. *PLoS One.* **12**, e0175675.
98. Zheng J, Xiao X, Zhang Q, *et al.* (2014) DNA methylation: the pivotal interaction between early-life nutrition and glucose metabolism in later life. *Br J Nutr* **112**, 1850–1857.
99. Ramaiyan B & Talahalli RR (2018) Dietary unsaturated fatty acids modulate maternal dyslipidemia-induced DNA methylation and histone acetylation in placenta and fetal liver in rats. *Lipids* **53**, 581–588.
100. Seki Y, Suzuki M, Guo X, *et al.* (2017) In utero exposure to a high-fat diet programs hepatic hypermethylation and gene dysregulation and development of metabolic syndrome in male mice. *Endocrinology* **158**, 2860–2872.
101. Zhang J, Zhang F, Didelot X, *et al.* (2009) Maternal high fat diet during pregnancy and lactation alters hepatic expression of insulin like growth factor-2 and key microRNAs in the adult offspring. *BMC Genomics* **10**, 478.
102. Petropoulos S, Guillemin C, Ergaz Z, *et al.* (2015) Gestational diabetes alters offspring DNA methylation profiles in human and rat: Identification of key pathways involved in endocrine system disorders, insulin signaling, diabetes signaling, and ILK signaling. *Endocrinology* **156**, 2222e2238.
103. Chen HC, Chen YZ, Wang CH, *et al.* (2020) The nonalcoholic fatty liver disease-like phenotype and lowered serum VLDL are associated with decreased expression and DNA hypermethylation of hepatic ApoB in male offspring of ApoE deficient mothers fed a with Western diet. *J Nutr Biochem* **77**, 108319.
104. Gutierrez Sanchez LH, Tomita K, Guo Q, *et al.* (2018) Perinatal nutritional reprogramming of the epigenome promotes subsequent development of nonalcoholic steatohepatitis. *Hepatol Commun* **2**, 1493–1512.
105. Du JE, You YA, Kwon EJ, *et al.* (2020) Maternal malnutrition affects hepatic metabolism through decreased hepatic taurine levels and changes in HNF4A methylation. *Int J Mol Sci* **21**, 9060.
106. Vo TX, Revesz A, Sohi G, *et al.* (2013) Maternal protein restriction leads to enhanced hepatic gluconeogenic gene expression in adult male rat offspring due to impaired expression of the liver X receptor. *J Endocrinol* **218**, 85–97.
107. Sohi G, Marchand K, Revesz A, *et al.* (2011) Maternal protein restriction elevates cholesterol in adult rat offspring due to repressive changes in histone modifications at the cholesterol 7α-hydroxylase promoter. *Mol Endocrinol* **25**, 785–798.
108. Suter MA, Chen A, Burdine MS, *et al.* (2012) A maternal high-fat diet modulates fetal SIRT1 histone and protein deacetylase activity in nonhuman primates. *FASEB J* **26**, 5106–5114.
109. Puppala S, Li C, Glenn JP, *et al.* (2018) Primate fetal hepatic responses to maternal obesity: epigenetic signalling pathways and lipid accumulation. *J Physiol* **596**, 5823–5837.
110. Burger GCE, Drummond JC & Sandstead HR (1948) Malnutrition and Starvation in Western Netherlands, September 1944 July 1945 parts I and 11. 's-Gravenhage: Staatsuit to geverij.
111. Roseboom T, de Rooij S & Painter R (2006) The Dutch famine and its long-term consequences for adult health. *Early Hum Dev* **82**, 485–491.
112. Lumey LH (1992) Decreased birthweights in infants after maternal in utero exposure to the Dutch famine of 1944–1945. *Paediatr Perinat Epidemiol* **6**, 240–253.
113. Ravelli GP, Stein ZA & Susser MW (1976) Obesity in young men after famine exposure in utero and early infancy. *N Engl J Med* **295**, 349–353.
114. Wang N, Chen Y, Ning Z, *et al.* (2016) Exposure to famine in early life and non-alcoholic fatty liver disease in adulthood. *J Clin Endocrinol Metab* **101**, 2218–2225.
115. Qi H, Hu C, Wang S, *et al.* (2020) Early life famine exposure, adulthood obesity patterns and the risk of nonalcoholic fatty liver disease. *Liver Int* **40**, 2694–2705.
116. Wang B, Cheng J, Wan H, *et al.* (2021) Early-life exposure to the Chinese famine, genetic susceptibility and the risk of type 2 diabetes in adulthood. *Diabetologia* **64**, 1766–1774.
117. Liu D, Yu DM, Zhao LY, *et al.* (2019) Exposure to famine during early life and abdominal obesity in adulthood: Findings from the Great Chinese Famine During 1959–1961. *Nutrients* **11**, 903.
118. Li Y, Jaddoe VW, Qi L, *et al.* (2011) Exposure to the Chinese Famine in early life and the risk of metabolic syndrome in adulthood. *Diabetes Care* **34**, 1014–1018.
119. Heijmans BT, Tobi EW, Stein AD, *et al.* (2008) Persistent epigenetic differences associated with prenatal exposure to famine in humans. *Proc Natl Acad Sci U S A* **105**, 17046–17049.
120. Saini SK, Mangalhara KC, Prakasam G, *et al.* (2017) DNA Methyltransferase1 (DNMT1) Isoform3 methylates mitochondrial genome and modulates its biology. *Sci Rep* **7**, 1525.
121. Mposhi A, Van der Wijst MG, Faber KN, *et al.* (2017) Regulation of mitochondrial gene expression, the epigenetic enigma. *Front Biosci (Landmark Ed)* **22**, 1099–1113.
122. Sharma N, Pasala MS & Prakash A (2019) Mitochondrial DNA: epigenetics and environment. *Environ Mol Mutagen* **60**, 668–682.
123. Jang HS, Shin WJ, Lee JE, *et al.* (2017) CpG and non-CpG methylation in epigenetic gene regulation and brain function. *Genes (Basel)* **8**, 148.
124. Oestreich AK & Moley KH (2017) Developmental and transmittable origins of obesity-associated health disorders. *Trends Genet* **33**, 399–407.
125. Bellizzi D, D'Aquila P, Scafone T, *et al.* (2013) The control region of mitochondrial DNA shows an unusual CpG and non-CpG methylation pattern. *DNA Res* **20**, 537–547.
126. Koh CWQ, Goh YT, Toh JDW, *et al.* (2018) Single-nucleotide-resolution sequencing of human N6-methyldeoxyadenosine reveals strand-asymmetric clusters associated with

https://doi.org/10.1017/S0954422422000038 Published online by Cambridge University Press

SSBP1 on the mitochondrial genome. *Nucleic Acids Res* **46**, 11659–11670.
127. Jia Y, Li R, Cong R, *et al.* (2013) Maternal low-protein diet affects epigenetic regulation of hepatic mitochondrial DNA transcription in a sex-specific manner in newborn piglets associated with GR binding to its promoter. *PLoS One* **8**, e63855.
128. Nicholls TJ & Gustafsson CM (2018). Separating and segregating the human mitochondrial genome. *Trends Biochem Sci* **43**, 869–881.
129. King GA, Hashemi Shabestari M, Taris K-KH, *et al.* (2018) Acetylation and phosphorylation of human TFAM regulate TFAM–DNA interactions via contrasting mechanisms. *Nucleic Acids Res* **46**, 3633–3642.
130. Lu B, Lee J, Nie X, *et al.* (2013) Phosphorylation of human TFAM in mitochondria impairs DNA binding and promotes degradation by the AAA+ Lon protease. *Mol Cell* **49**, 121–132.
131. Dong Z, Pu L & Cui H. (2020) Mitoepigenetics and its emerging roles in cancer. *Front Cell Dev Biol* **8**, 4.
132. Mercer TR, Neph S, Dinger ME, *et al.* (2011) The human mitochondrial transcriptome. *Cell* **146**, 645–58.
133. Zhao Y, Sun L, Wang RR, *et al.* (2018) The effects of mitochondria-associated long noncoding RNAs in cancer mitochondria: new players in an old arena. *Crit Rev Oncol Hematol* **131**, 76–82.
134. Wang K, Gan T-Y, Li N, *et al.* (2017) Circular RNA mediates cardiomyocyte death via miRNA-dependent upregulation of MTP18 expression. *Cell Death Differ* **24**, 1111–1120.
135. Villota C, Campos A, Vidaurre S, *et al.* (2012) Expression of mitochondrial non-coding RNAs (ncRNAs) is modulated by high risk human papillomavirus (HPV) oncogenes. *J Biol Chem* **287**, 21303–21315.

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