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REVIEW ARTICLE

Epigenetic Programming of Adipose Tissue in the Progeny of Obese Dams

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Abstract: According to the Developmental Origin of Health and Disease (DOHaD) concept, maternal obesity and the resulting accelerated growth in neonates predispose offspring to obesity and associated metabolic diseases that may persist across generations. In this context, the adipose tissue has emerged as an important player due to its involvement in metabolic health, and its high potential for plasticity and adaptation to environmental cues. Recent years have seen a growing interest in how maternal obesity induces long-lasting adipose tissue remodeling in offspring and how these modifications could be transmitted to subsequent generations in an inter- or transgenerational manner. In particular, epigenetic mechanisms are thought to be key players in the developmental programming of adipose tissue, which may partially mediate parts of the transgenerational inheritance of obesity. This review presents data supporting the role of maternal obesity in the developmental programming of adipose tissue through epigenetic mechanisms. Inter- and transgenerational effects on adipose tissue expansion are also discussed in this review.

Keywords: Perinatal period, maternal obesity, developmental origin of health and disease, epigenome, gene expression, fat expansion.

1. INTRODUCTION

Obesity and associated metabolic diseases have become a global epidemic over the past decades. Obesity is defined as an increased body weight due to excessive accumulation of white adipose tissue (WAT) [1]. It is associated with the development of type 2 diabetes mellitus, nonalcoholic fatty liver disease, cardiometabolic diseases, some types of cancers, asthma and neurodegenerative diseases [1]. The worldwide prevalence of obesity has nearly tripled since 1975, with 13% of the world's adults being obese [2]. Environmental factors such as overnutrition, sedentary lifestyle and chemical exposure are the major contributors to the rapidly increasing prevalence [1]. Indeed, genetic variation only accounts for a modest proportion (<10%) of the risk of developing obesity at the population level [3]. This modest effect has heightened interest in identifying the "missing heritability" on the risk of developing obesity [4]. Interestingly, studies on both humans and animal models suggest that susceptibility to obesity is influenced by the perinatal environment, which initiates a vicious cycle of elevated disease risk across generations. This implies an epigenetic basis for obesity transmission [5].

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1.1. Heritability of Obesity

The concept of developmental origins of health and disease (DOHaD) proposes that adverse events, such as malnutrition, during the perinatal period can play a key role in the development of obesity later in life. This concept states that a poor nutrition environment *in utero* or during infancy can program gene expression and the metabolic profile of offspring to anticipate similar exposure to be experienced postnatally [6]. Unfortunately, this phenotype might become maladaptive, especially if the environment in later life differs from perinatal exposure. The importance of perinatal growth period was first highlighted by David Barker, who demonstrated that intrauterine growth retardation and low birth weight were associated with increased risk of obesity and cardiometabolic disorders during adulthood [6]. For instance, studies of the Dutch Hunger Winter, a severe famine that took place in the German-occupied Netherlands towards the end of World War II (1944-1945), has been very informative [7]. Offspring of mothers exposed to the famine had lower birth weights, though paradoxically a higher incidence of obesity, hypertension, glucose intolerance during adult life than the general population. In particular, low birth weight infants with rapid catch-up growth in the first years of life had the highest risk of obesity and metabolic syndrome in adulthood [7]. Subsequent studies reported similar findings in subjects exposed to maternal overnutrition and/or obesity during pregnancy and lactation [8]. Thus, the relationship between birth weight and later body mass index, waist-to-hip

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ratio and percent body fat exhibits a U-shaped curve such that those born small or large have an increased risk of obesity later in life [8]. It is currently well accepted that environmental stress during the first 1,000 days after fertilization strongly influences metabolic health not only in the current generation but over several generations.

The association between maternal obesity and its inheritance in offspring is of particular concern because 15%-40% of pregnant women are obese [9]. In humans, maternal obesity is mostly associated with macrosomia [10, 11] and an increased risk of obesity and cardiometabolic dysfunction in the progeny both in childhood [12, 13] and in adulthood [14, 15]. Guenard *et al.* showed that the siblings born after the mother had lost weight are less obese and exhibit improved cardiometabolic risk profiles carried into adulthood as compared to their siblings born when the mother was obese [16]. Maternal obesity may have immediate effects such as impaired organ growth during development whereas effects such as metabolic programming may be latent and may occur later in life in response to further stimuli [17]. This raises the question as to how the memory of early events is stored and later expressed, despite continuous cellular turnover. Among different underlying mechanisms, epigenetic modifications provide a potential molecular basis for the missing heritability in obesity.

1.2. Mechanisms of Epigenetic Regulation

The term "epigenetics," which literally means "on top of genetics", defines a variety of regulatory processes that can impact on phenotypes and be inherited in later generations without changing the genetic code itself [18]. These processes introduce mitotically and meiotically heritable marks on the chromatin, such as DNA (hydroxy)methylation, histone post-translational modifications (PTMs) and small and long non-coding RNA-associated gene silencing [19]. DNA methylation, which results from the transfer of a methyl group, by DNA methyltransferase (DNMT), to the cytosine residue within CpG dinucleotides to form 5-methylcytosine (5mC), promotes gene silencing. 5-hydroxymethylcytosine (5hmC) is another important cytosine modification catalyzed by the enzymes of the ten-eleven translocation methylcytosine dioxygenase (TET) family that serves as an intermediate for demethylation. It can also promote chromatin opening at transcriptional regulatory regions. Chromatin structure and accessibility, which are crucial for the regulation of gene expression, are also controlled by PTMs on histones. For example, acetylation of histone H3 lysine residues (H3Kac) and methylation of H3K4 (H3K4me3) are associated with active transcription while methylation of H3K9 (H3K9me3) generally indicates silenced chromatin. In particular, elevated H3K4me1/H3K27ac and lower H3K9me3 marks are linked to promoter and enhancer activation during adipocyte differentiation [20]. These histone PTMs are catalyzed by various enzymes, including histone acetyltransferase (HAT) as well as histone deacetylase (HDAC) whose activities are sensitive to cellular energy status [21, 22].

The complete repertoire of all these epigenetic marks in an individual is known as the epigenome. Exposures to the environmental impact on our epigenome and determine what and who we are. For instance, epigenomic differences between monozygotic twins, who share the same genome, may be an important contributing factor to phenotypic discordance. In humans, the critical period of the first 1000 days after fertilization mentioned above arises from the highly plastic and adaptive nature of the epigenome during this timeframe [23]. Previous studies have shown that maternal overnutrition and obesity during this crucial period alter the epigenome of the progeny [24], thereby potentially causing differential individual susceptibility to obesity and obesity-associated metabolic diseases. This review presents data on how maternal overnutrition (*i.e.*, high-fat (HF) diet) and obesity influence the offspring's predisposition to obesity and how this is developmentally programmed, by focusing on the changes in WAT phenotype through epigenetic mechanisms.

2. DEVELOPMENTAL ORIGIN OF ADIPOSITY

2.1. Adipose Tissue Organogenesis

The deleterious effects of maternal obesity seem to operate during periods of development where epigenetic mechanisms are particularly dynamic and sensitive to environmental cues. The most sensitive window for WAT epigenome programming is during adipogenesis, which is the terminal differentiation of adipocyte precursors into mature adipocytes [5, 25, 26]. However, the timing of this window differs between species.

WAT resides as depots at distinct locations throughout the body. The main WAT depots are positioned subcutaneously and viscerally, *i.e.*, within the abdominal cavity. In rodents, the development of subcutaneous adipose tissue (SAT) occurs during late gestation, between the 14^{th} and 18^{th} day, and its development continues during lactation until weaning. In contrast, visceral adipose tissue (VAT) formation is mainly initiated after birth [27]. In adult mice, the adipocyte reservoir remains fairly stable with a renewal of 10-20% of adipocytes per month [27]. In humans, WAT begins to develop during the second trimester of pregnancy between the 14^{th} and the 24^{th} week of gestation [28, 29]. During lactation, total fat mass increases rapidly due to the increase in fat cell size and number. The second peak of accelerated fat expansion occurs during puberty [30]. After puberty, adipocyte number and size become relatively stable in lean individuals with an annual turnover of 8% [31]. Although new adipocytes can be generated throughout life, such ability diminishes with age due to the reduction in the adipogenic progenitors population [32]. In adulthood, SAT depots have higher adipocyte turnover rates and new adipocyte formation in comparison with VAT [33, 34]. The femoral SAT of normal-weight young individuals expand through hyperplasia during overfeeding [35]. However, this adipogenic ability decline with age and obesity [36].

Thus, an anabolic nutritional and hormonal milieu during the perinatal period is believed to strongly influence adipocyte stem cells that are highly plastic and very sensitive to maternal factors.

2.2. Differentiation of White Adipocyte

WAT is a highly heterogeneous organ that exhibits depot specificity in many features, including the developmental origin of adipocytes. Mouse study suggests that adipocytes

in SAT and VAT depots originate from distinct cell lineages [37]. Lineage tracing in mice indicates that VAT depots originate from Wilms tumor 1 (WT1)-expressing precursors during development, a marker restricted to the intermediate and lateral plate mesoderm [38]. However, the precise origin of VAT seems to vary from depot to depot [27]. For example, in mice, adipocytes in the head and neck are generated from the neuroectoderm cells expressing a marker of neural crest (Sox10) [39]. Adipocytes in SAT descend from the cells marked by the homeobox gene Paired related homeobox 1 (Prx1) [40]. Overall, lineage tracing demonstrated that individual adipose depots are composed of adipocytes that are derived from distinct precursor populations and may contain progenitors through distinct lineages [41]. Together, these findings suggest a highly complex regulatory system that instructs the spatiotemporal development of different WAT depots. Thus, perturbation of the developmental programme could have huge impact on the whole body adiposity in the future.

During WAT development, progenitors become mature adipocytes through a two-phase differentiation process [42]. It is difficult to characterize distinct intermediate cellular stages between progenitors and mature adipocytes. For practical purposes, two main phases of adipocytes formation are described. The first phase, also termed "commitment", results in the conversion of the multipotent progenitors to preadipocytes. This phase is then followed by "terminal differentiation", during which specified preadipocytes acquire the characteristics of the mature adipocytes. They develop the ability to store lipids in a large monolocular lipid droplet and display endocrine properties as they secrete a repertoire of proteins termed adipocytokines that mediate a range of metabolic and inflammatory processes, including adipocyte-specific factors such as adiponectin and leptin [43].

The predominant source of our knowledge regarding adipogenesis has been established from several clonal preadipocyte cell lines, mostly murine 3T3-L1. Adipogenesis involves a complex and highly orchestrated gene expression program. The transcription factors CCAAT-enhancer-binding proteins (C/EBP) α, β and δ and peroxisome proliferator-activated receptor (PPAR) γ are the principal regulators of adipogenesis. In 3T3-L1 cells, C/EBPβ and C/EBPδ are quickly expressed within 4 hours after the induction of differentiation, which trigger the expression of C/EBPα and PPARγ. Subsequently, C/EBPα and PPARγ activate genes that define mature adipocyte phenotypes (*AdipoQ*, *Leptin*, *Glut4*, *Plin1*, *Lpl*…) [44-46]. Key players coordinating the differentiation of human adipocytes have also been identified in transcriptomic profiling of mature adipocytes derived from human mesenchymal stem cells [47, 48].

2.3. Chromatin Features in Adipocytes

In order to express adipocyte-specific genes, changes in chromatin conformation at specific developmental stages are necessary. This process is regulated through the remodelling of cell-specific histone marks and DNA (hydroxy)methylation orchestrated by specific transcription factors. Prior to terminal differentiation, the global state of chromatin in preadipocytes remains highly dynamic, which allows active expression of a wide range of genes [49]. These dynamics in chromatin architecture may be attributed to the function of transcription factors called « *pioneer factor* », which can directly bind condensed chromatin and initiate chromatin opening for transcription. In undifferentiated adipocyte, the adipocyte-specific genes (*Pparγ*, *Cebpα*, *Zfp423* gene loci) are considered to be in a poised state owing to the bivalent presence of the active H3K4me3 and repressive H3K9me3 marks in their promoters [50].

During the early phase of adipocyte differentiation, the "bivalent domains" are resolved to "open domains" containing monovalent H3K4me3 mark. This dynamic modulation of the chromatin landscape during the first hours of adipocyte differentiation is associated with the recruitment of multiple early transcription factors (including C/EBPβ/δ, glucocorticoid receptor, signal transducer and activator of transcription 5A, retinoid X receptor and mediator complexes) to chromatin regions to induce a reorganization of the chromatin structure. These events coincide with the removal of repressive histone marks, such as the H3K9me3 and the enrichment of active chromatin marks, including H3K27ac, and H3K4me3, as well as DNA hydroxymethylation, in the promoters of adipocyte-specific genes and many of the PPARγ-binding sites [46]. Interestingly, some early transcription factors (such as C/EBPβ) are found to bind PPARγ binding sites before the binding of PPARγ, suggesting that complexes containing C/EBPβ assist subsequent binding of PPARγ at these sites in late adipogenesis [49]. Thus, early chromatin remodeling primes genomic regions to allow the expression of CEBPα and PPARγ and their specific binding on the chromatin [46]. Altogether, a wave of chromatin-mediated through multiple mechanisms prepares the preadipocyte for the adipogenic actions of PPARγ and C/EBPα during terminal differentiation.

Genome-wide profiling of PPARγ by chromatin immunoprecipitation coupled with sequencing demonstrated that PPARγ binding sites are specifically enriched in the vicinity (mostly in intergenic and intronic regions) of most adipocyte specific-genes that are induced throughout adipogenesis [20, 51]. PPARγ itself is also a mediator of the chromatin remodeling that constitutes a key step for the induction of genes that define mature adipocyte phenotype, including *Glut4*, *Leptin*, *AdipoQ* and *Fatty acid synthase* [46]. Mechanistically, ectopic expression of PPARγ in preadipocytes increases the acetylation level of histone 3 lysine 9 (H3K9ac) at some PPARγ binding sites, which enhances binding efficiency [52]. PPARγ is also able to open up chromatin for transcription by the upregulation and recruitment of histone methyltransferases such as Setd8 and MLL3/4 [53, 54].

The epigenetic remodeling machinery in adipocyte precursors responds to environmental cues, including hormones, nutrients and metabolites derived from energy metabolism [55]. For example, histone acetylation is mediated by histone acetyltransferases (HATs), which utilize acetyl-CoA as a substrate. On the other hand, deacetylation of histone is mediated by enzymes called histone deacetylases (HDACs), including the sirtuins, that use nicotinamide adenine dinucleotideamine (NAD+) as a co-factor. Acetyl-CoA, the level of which is known to indicate glucose availability, is usually elevated in the fed state, whereas NAD+ accumulates

in the fasted state [22]. Thus, cellular metabolism and energy state are closely coupled with epigenetic remodelling, which orchestrates the developmental program of WAT.

Hence, in the context of the DOHaD, alterations of the maternal environment could affect adipogenesis through disturbance to the epigenome resulting in WAT dysfunction. In addition to immediate effects on the prenatal and neonatal development of WAT in offspring, the perturbed epigenome may persist throughout life, thereby increasing the risk for obesity in later life. Moreover, these epigenetic marks can act as a "memory" for the environment experienced and be passed on to yet later generations.

3. MATERNAL OBESITY ALTERS ADIPOSE TISSUE FUNCTION IN OFFSPRING THROUGH EPIGENETIC MECHANISMS

3.1. Adipose Tissue Expansion Programming

Although definitive proof supporting a direct link between maternal obesity and obesity in offspring is lacking, animal studies have shed light on the possible mechanisms through which this linkage can be established (Fig. **1**).

In obesity, WAT expands either by hyperplasia (increase in adipocyte number) or hypertrophy (increase in adipocyte size), where the latter is associated with insulin resistance and inflammation, as well as increased risk of metabolic diseases including type 2 diabetes [56, 57]. Previous studies have shown that maternal obesity impacts adipogenesis from the perinatal period [58-60] to adulthood [60, 61], resulting in an imbalance between adipocyte hyperplasia and hypertrophy and predisposition to obesity and associated metabolic diseases. The expression of adipogenic transcription factors such as ZFP423, CEBPβ, and PPARγ, during the development in offspring, is altered by maternal obesity, which results in metabolic dysfunction in WAT [59-63]. Of note, zinc finger protein (ZFP) 423 was identified as an important determinant of adipogenesis by promoting PPARγ expression [64] through the BMP/SMAD signaling pathway [65]. Dysregulation in its activity thus directly impacts the development of WAT and hence whole-body metabolism. Indeed, Yang *et al.* reported that male offspring of obese mother mice showed higher weight gain and adiposity correlated with persistently elevated ZFP423 activity in WAT [59]. The authors showed that the persistent increased in ZFP423 expression arises from the epigenomic remodeling of the *Zfp423* promoter, which occurs early during WAT development. As a key developmental gene, the *Zfp423* promoter exhibits a high density of CpG sites and is characterized by a "bivalent" region with the enrichment of both inactive (H3K27me3) and active (H3K4me3) histone marks [66]. Consistent with increased adipogenic potential, the repressive epigenetic marks H3K27me3 and DNA methylation were lower in the *Zfp423* promoter, whereas the enrichment of H3K4me3 was higher in fetal WAT (embryonic day 14.5) from obese mother mice [59]. At weaning, elevated ZFP423 activity results in increased and accelerated adipocyte differentiation, and hence higher adiposity through hyperplasia [59-61]. Persistent DNA hypomethylation in the *Zfp423* promoter and increased gene expression were associated with attenuated adipose expansion by hyperplasia in adulthood when challenged with a HF diet [60]. The authors conclude that accelerated adipogenesis early in life, due to maternal obesity, leads to premature exhaustion of the stock of resident adipocyte progenitors in WAT for more healthy expansion. Consequently, WAT undergoes adipocyte hypertrophy, a cause of hypoxia, inflammation and metabolic dysfunction [56].

We have previously demonstrated another mechanism by which maternal obesity leads to impaired WAT expansion and metabolic dysfunction in offspring. In rats, WAT of offspring from obese dams had persistently lower PPARγ2 mRNA and protein expression [63]. This persistent reduction in PPARγ2 expressions may occur, at least in part, through epigenomic remodeling in the *Pparγ2* promoter, taking place early during AT development. The exact underlying molecular mechanisms for this observation remain unclear. However, it is well established that DNA methylation and histone modifications regulate the PPARγ expression in WAT [67, 68]. During adipogenesis, the PPARγ expression is positively regulated through DNA demethylation [67] as well as the enrichment of active marks H3Kac, H4Kac [69] and H3K4me3 [20] at its promoter region. In weanling rats from obese dams, reduced PPARγ2 mRNA levels were observed together with DNA hypermethylation and lower enrichment of H3ac and H3K4me3 active marks in *Pparγ2* promoter region. Moreover, higher DNMT activity parallels the increase in global DNA methylation and CpGs methylation in the *Pparγ2* promoter. In adulthood, DNA hypermethylation in the *Pparγ2* promoter and the reduction of Pparγ2 mRNA expression levels were still observable [63, 70].

Several studies have reported that lower PPARγ2 expression is associated with WAT dysfunction and alteration of the ability of WAT expansion [71]. Given that, PPARγ2 promotes adipogenesis and lipid deposition and storage within adipocytes, it may seem paradoxical that maternal obesity reduces the PPARγ2 expression in WAT of offspring. It might be seen as an adaptative mechanism to prevent further fat accumulation and detrimental WAT expansion [72]. The purpose of this inter-generational effect on WAT development warrants further research.

Increasing evidence support an important role in the nutritional status of lactating mothers in the development of obesity in their offspring as they enter adulthood. Given that, lactation coincides with the developmental window of WAT in rodents, the quality of milk intake could have a long-lasting effect on WAT programming. Butruille *et al.* analysed milk composition and found that maternal HF feeding only during lactation induced qualitative changes in breast milk fatty acid (FA) composition (higher n-6/n-3 polyunsaturated FA ratio and lower medium-chain FA content) [73]. Pups feeding on this breast milk were predisposed to increased weight gain throughout life, showing hyperplasia in VAT with increased expression of stearoyl-CoA desaturase-1 (SCD1), a key enzyme of FA metabolism [73]. In adulthood, the overexpression of SCD1 was associated with reduced DNA methylation in *Scd1* promoter surrounding a PPARγ-binding region suggesting a functional link between PPARγ and DNA methylation at this site. Thus, it is tempting to speculate that low methylation levels facilitate more PPARγ binding to induce SCD1 expression or conversely the binding of PPARγ itself promotes DNA demethylation through interaction with TET enzymes [74]. Interestingly,

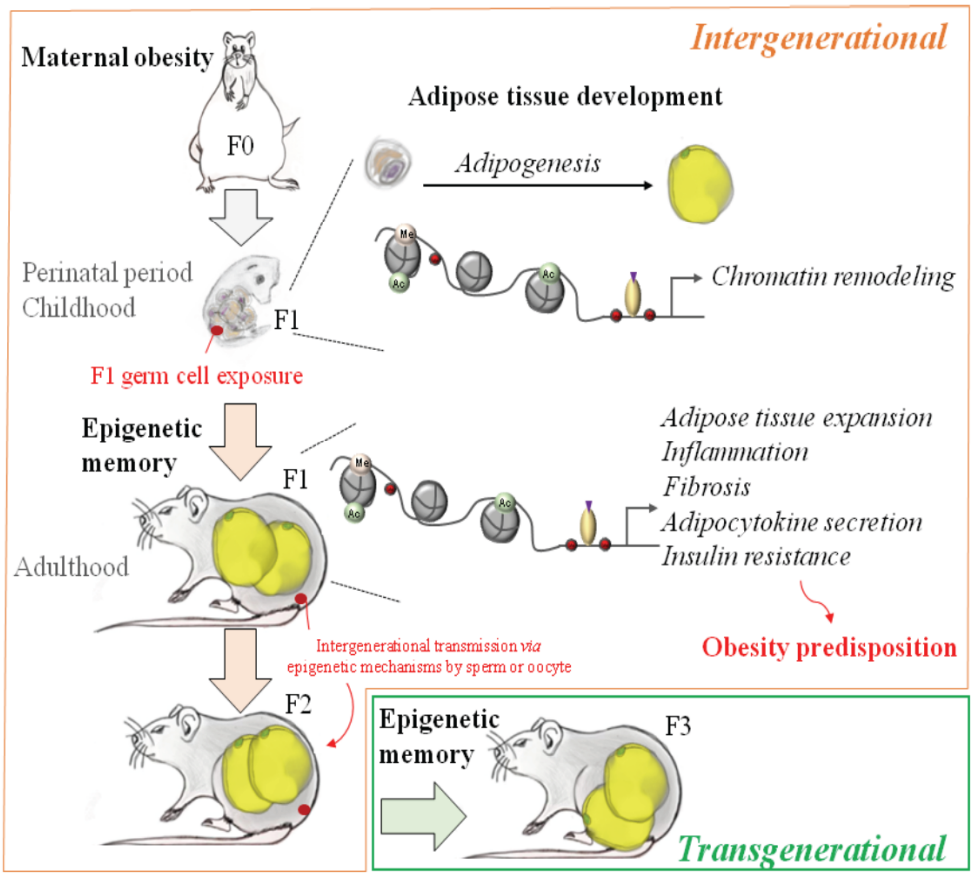

Fig. (1). Inter- and transgenerational inheritance of adipose tissue dysfunction in offspring from obese mothers. Maternal obesity implies that three generations are exposed to the nutritional environment: the pregnant mother (F0), the fetus (F1) and the germline of the fetus (the future F2). Altered nutritional and hormonal microenvironment induced by maternal obesity (F0) may alter chromatin remodeling during adipose tissue development in the prenatal or postnatal period (F1), as can the germline of the fetus (the future F2). These epigenetic remodeling leads to the deregulation of many genes essential for the adipocyte function. Once the epigenomic changes are established during the perinatal period, they might persist into adulthood as an epigenetic memory, resulting in obesity predisposition in adulthood. These are considered to be parental effects, leading to intergenerational epigenetic inheritance. A transgenerational effect refers to that found only in the F3 generation, which is not exposed to direct malnutrition as experienced by F0-F2 generations. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

hypomethylation of one of the CpGs in this region was already detected in pups during lactation. Thus, it is plausible that breast milk with altered FA composition leads to increased PPARγ expression through epigenetic remodeling during suckling, in turn, adjusts key FA-related genes (*i.e.*, *Scd1*) for long-term adaptation in WAT [73].

3.2. Adipocytokine Expression Programming

The WAT metabolic dysfunction plays an important role in the development of a chronic low-grade proinflammatory state associated with insulin resistance [57].

Leptin, first described as a satiety hormone [75], is the best known proinflammatory adipocytokine that increases in proportion to WAT mass. WAT of offspring from obese dams exhibits higher leptin mRNA expression levels, which are associated with hyperleptinemia, adipocyte hypertrophy and metabolic disorders [25, 26]. Leptin is a critical regulator of many physiological functions, ranging from satiety to immunity [75, 76]. However, the mechanisms underlying leptin gene expression remain unclear. Using a rat model, it has been confirmed that offspring from HF diet-fed dams prior to and during gestation and lactation displayed persistently higher whole-body adiposity, hyperleptinemia and elevated leptin gene expression in VAT [70, 77]. During the lactation period, the up-regulation of the leptin gene expression correlated with higher DNA hydroxymethylation and active histone modifications H3K4me1/H3K27ac especially in an upstream enhancer [77]. These histone marks were still retained marks that were visible in VAT of adult rats from obese dams that showed a persistent "expandable" (*i.e.*, persistent hypertrophy and hyperplasia) phenotype. In line with these findings, maternal HF diet feeding during pregnancy and/or lactation in mice leads to persistent hypermethylation of H4K20 in the promoter region of the leptin gene in offspring that may persist across multiple generations [78-80].

Interestingly, WAT inflammation and macrophage infiltration can be transmitted across generations through epigenetic mechanisms. In addition to leptin, elevated proinflammatory markers in WAT, possibly originating from immune cell infiltration, have been detected in the fetus of obese mice fed an HF diet before mating and throughout gestation [81]. One-month-old rat offspring from HF diet-fed

dams during gestation and lactation also displayed higher pro-inflammatory cytokine mRNA expression levels in WAT [82]. Thus, Ding *et al.* showed that multigenerational HF diet feeding in female mice results in gradually increased WAT weight, pro-inflammatory markers and immune cell infiltration associated with a gradual decrease in DNA methylation of inflammation-associated genes (*i.e.*, Toll-like receptors) in WAT across generations (up to F2) [83]. However, the effects of maternal HF diet *versus* maternal obesity on offspring's WAT inflammation remain unclear. Indeed, *in utero* exposure to a maternal HF diet results in increased pro-inflammatory markers in WAT of adult offspring in mice, independently of maternal obesity [84]. It also remains to be determined whether inflammation is a cause or consequence of transmitted WAT dysfunction [85-87].

Taken together, these findings demonstrate that maternal obesity results in the changing of early-life epigenetic marks in WAT during its development in offspring early in life, which could explain the long-term effects on WAT function. To what extent such developmental epigenetic mechanisms influence WAT development at a genome-wide level remains a challenging question.

4. INTER- AND TRANSGENERATIONAL INHERITANCE OF ADIPOSE TISSUE EXPANSION

It is well established from animal studies that maternal obesity predisposes the progeny to increased adiposity and associated metabolic disorders across multiple generations. However, care should be taken when talking about inter- and transgenerational inheritance. When a mother is obese, three generations are effectively exposed simultaneously to this "insult": the mother (F0), the fetus (F1) and the germline of the fetus (the future F2). These are considered to be direct parental effects on the somatic cells of the developing F1 embryo/fetus and also on the developing embryonic germ cells (which will become F1 adult gametes) and, in turn, directly affect F2 offspring. Thus, maternal obesity can have intergenerational effects in F1 and F2 generations [5]. A transgenerational effect, therefore, refers to that only found in F3 generation in the absence of the initial nutritional stimulus [88, 89].

The majority of studies so far concentrated on the intergenerational effects of maternal obesity (*i.e.*, altered metabolic phenotypes up to the F2). As illustrated above [59-61, 63, 73, 77, 83], among the mechanisms of epigenetic transmission, histone and DNA methylation modifications are considered to be of key importance. Maternal obesity may result in the modifications of nutritional and hormonal milieu of somatic cells (adipocyte-derived stem cells, preadipocytes and adipocytes) of the fetus (F1) as well as the germline of the fetus (the future F2). During the perinatal period, changes in energy and hormonal status may lead to aberrant activity of the epigenetic machinery that may, in turn, alter chromatin remodeling and DNA methylation during the adipogenesis in offspring. Histone-modifying enzyme activity and all methyl transferases (histone and DNA) are dependent on intermediary metabolites as substrates and hormonal responses [5, 90], therefore acting as a mediator for the crosstalk between the epigenome and the environment. Once established during the perinatal period, the epigenomic changes might persist into adulthood memory, resulting in obesity predisposition in adulthood (Fig. **1**).

There are very few studies investigating the effects of transgenerational effects of maternal obesity. Human epidemiological studies suggest that grandparental overnutrition increases the rates of diabetes and cardiovascular disease risk in F2 [91]. Increased risk for obesity was observed in children whose parents were of normal weight but whose grandparents were obese [92]. Using rodent models [93, 94], it has been shown that maternal obesity results in increased body weight and adiposity in mice that are transmitted up to the F3 generation in the absence of any further nutritional stimulus. Although the implication of epigenetic mechanisms in intergenerational effects is well accepted, the underlying mechanisms and the role of epigenetic marks in these effects are less well established. Indeed, true transgenerational epigenetic inheritance in mammals requires that epigenetic traits are transmitted through germline and are stably passed on for more than three generations maternally. Global epigenetic resetting during germline development and following fertilization represents a very efficient system to remove pre-existing epigenetic modifications, which limits the transmission of epigenetic signatures. Despite this limitation, it has been shown that maternal obesity programs F3 female body size through the paternal lineage [93]. These findings are consistent with animal studies showing evidence of paternal transmission, where sperms carry the epigenetic modifications to be passed on through the male progeny [95-101].

To date, studies on transgenerational effects of maternal obesity demonstrated that the male germline is a major player in transferring phenotypic traits in a transgenerational manner. However, the sperm methylome might not constitute the major carrier for the transmission [94]. Although the implication of histone modifications can not be totally excluded [95], small noncoding RNAs present in the male germline have emerged as an alternative mode of transgenerational epigenetic inheritance [94], regulating chromatin remodeling, DNA methylation, histone modifications and are important for germ cell development [102, 103].

CONCLUSION AND FUTURE PERSPECTIVES

To deal with the pandemic of obesity with a preventive approach, understanding of the molecular mechanisms involved in epigenetic regulation of WAT programming becomes essential. Thus, further investigation is needed to understand how the fate of adipocyte progenitors is controlled through DNA methylation and histone modification, and how environmental conditions (*i.e.*, maternal obesity) may subsequently affect gene expression during WAT development. In addition to DNA methylation, elucidating the dynamics of the recruitment of enzymes that govern PTMs of histones and the transcriptional consequences of specific modifications will be highly valuable to establish an understanding of how an obesogenic environment may affect WAT development. Developing techniques in epigenomics (*i.e.*, high-throughput DNA sequencing) to provide larger scale genome-wide profiling of global methylation and chromatin landscapes will be valuable. Methods using a high-throughput CRISPR-Cas9 screening system for epigenome editing could allow efficient characterization of crucial epigenetic marks that can be used for future therapeutic use [104].

Overall, understanding how environmental conditions (*i.e.*, maternal obesity) can be relayed through epigenetics to

the transcriptional machinery, and regulate the developmental program of WAT could lead to the discovery of novel therapeutic targets. Indeed, epigenetic effectors may represent attractive targets of WAT programming to counteract the deleterious effects of maternal obesity at an early stage. Two series of experiments have already validated this innovative approach. On the one hand, dietary supplementation of methyl donors in mothers was found to alleviate the adverse consequences of perinatal malnutrition [105, 106]. On the other hand, pharmacological modulation of the epigenome through drugs has already been recognized as a promising new treatment strategy targeting various diseases [107].

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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