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Dilemma of Epigenetic Changes Causing or Reducing Metabolic Disorders in Offsprings of Obese Mothers

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ABSTRACT

Maternal obesity is associated with fetal complications predisposing later to the development of metabolic syndrome during childhood and adult stages. High-fat diet seems to influence individuals and their subsequent generations in mediating weight gain, insulin resistance, obesity, high cholesterol, diabetes, and cardiovascular disorder. Research evidence strongly suggests that epigenetic alteration is the major contributor to the development of metabolic syndrome through DNA methylation, histone modifications, and microRNA expression. In this review, we have discussed the outcome of recent studies on the adverse and beneficial effects of nutrients and vitamins through epigenetics during pregnancy. We have further discussed about the miRNAs altered during maternal obesity. Identification of new epigenetic modifiers such as mesenchymal stem cells condition media (MSCs-CM)/exosomes for accelerating the reversal of epigenetic abnormalities for the development of new treatments is yet another aspect of the present review.

Introduction

According to the World Health Organization (WHO), heart disease, stroke, diabetes, cancer, and chronic lung disease that fall under the non-communicable diseases (NCDs) category collectively account for 74 % of all death throughout the world (WHO 2022). It also states that 86 % of people suffering from NCDs die prematurely or before reaching 70 years of age in low-income or middle-income countries [1]. The major factors that predispose the organism towards NCD include alcohol, tobacco, physical inactivity, and unhealthy diet [1]. Metabolic syndromes (MetS) are associated with various risk factors such as elevated blood pressure, elevated fasting plasma glucose (FPG), atherogenic dyslipidemia, and obesity which prone individuals to the development of NCDs including type 2 diabetes (T2D) and cardiovascular disease [2]. Metabolic disease research is more focused on the Developmental Origins of Health and Disease (DOHaD) hypothesis formulated by Barker and colleagues in the 1980s [3, 4]. DOHaD hypothesis explains that the late onset of diseases in offspring may stem from the conditions associated with pregnancy [3, 4]. Studies in both animal models and humans have shown that lifestyle factor during intrauterine or postnatal life has a prolonged influence on the offspring's health across generations [5]. Various reports have stated that offspring health is related to the epigenetic environment during embryonic/fetal development [6]. It is now well known that nutrition, micronutrients, macronutrients, micro minerals or trace elements, and phytochemicals can influence the epigenetic pattern either by remodelling chromatin structure or by influencing the availability of methyl groups [7]. In this review, we have discussed the epigenetic

influence of diet, vitamins, and lifestyle factors during pregnancy and its outcome on the development and/or prevention of MetS in offspring. Further, we have also shed light on the miRNAs modulated during maternal obesity as well as reported the findings to screen the maternal obesity biomarkers using stem cells as a model system. Lastly, we have also discussed MSCs paracrine secretion as epigenetic modifiers for combating the disorders associated with maternal obesity.

Implication of high fat diet and maternal obesity on epigenetics and metabolic syndrome

High-fat diet and maternal obesity cause short-term as well as long-term complications in offspring, including weight gain, and metabolic change, predisposing them to obesity, diabetes, dyslipidemia, hypertension, psychiatric disorders, and cardiovascular diseases [8]. Recent studies have provided cues about epigenetic mechanisms as the plausible candidate linking dietary intake and MetS [9–12]. Zhang et al. reported that maternal high-fat diet (MHFD) displayed glucose intolerance and insulin resistance in offspring. They further observed hypermethylation in the insulin receptor substrate 2 (Irs2) gene and hypomethylation of mitogen-activated protein kinase kinase 4 (Map2k4) gene and subsequently their decreased and increased expression, respectively, in the liver of offspring, which is associated with the development of diabetes in later life [9]. A study demonstrated a decrease in the expression of genes such as Acaa2, Acsl1, and Cox7a1 implicated in the thermogenesis and fatty acid oxidation due to hypermethylation in the brown adipose tissue (BAT) of the 16-week offspring born to dams fed on HF diet before and during pregnancy and lactation indicating the long term disorder of excessive energy intake [10]. Peng et al. revealed that offspring born from female mice fed on an HF diet before pregnancy followed by pregnancy and lactation exhibited glucose intolerance and hepatic steatosis. These offspring showed altered lipid homeostasis, methionine cycle, and abnormal one-carbon metabolism, which was associated with DNA hypermethylation and l-carnitine depletion and deactivated AMPK signalling and downregulation of PPAR-α and fatty acid oxidation genes [11]. Further, the same group observed that MHFD displayed exacerbated non-alcoholic fatty liver disease (NAFLD) phenotype in the offspring, which was induced by post-weaning HF diet and prevented by maternal one carbon supplement. They identified a differentially methylated region on Prkca, Plcb1, Dgkh, and Dgki, which was recovered by one carbon supplement [12]. Another group found that MHFD aggravated obesity in HF-fed female offspring with the increase in their weight, accumulation of more fat, and elevated leptin levels in the serum of adults, which was associated with the dysregulated gene expression and thousands of DNA methylation changes in hearts and livers, which was shown to affect the genes related to mitochondria, immune response and RNA processing. Further, they observed that between one-quarter and one-third of differentially expressed genes exhibited differentially methylated regions linked with maternal diet [13]. Recently, Penn et al. showed that MHFD resulted in a decrease in the 5hmC DNA methylation and an increase in 5-formyl cytosine (5fC) in two cell-stage embryos. They observed that 1.4 mM α-ketoglutarate resulted in a decrease in 5mC level in two cell embryos while 14.0 mM α-ketoglutarate led to an increased 5hmC:5mC ratio suggesting a link between metabolic intermediate and MHFD as well as indicating that MHFD might be influencing offspring metabolic state during early development [14].

Studies performed on primates have shown that a MHFD, which comprises 32–35 % fat as compared to control (13–14 % fat) increases fetal liver triglycerides and correlates with non-alcoholic fatty liver disease (NAFLD), which often leads to T2D and obesity. These changes were accompanied by the hyperacetylation of H3K14, H3K9, and H3K18 along with the depletion of fetal histone deacetylase 1 (HDAC1) and upregulation of key genes such as GPT2, DNAJA2, and Rdh12 and downregulation of Npas2 in the offspring born from mother fed on high fat diet [9, 10, 15, 16]. A recent study using a rat model has revealed that MHFD results in reduced H3K27me3, H2Ak119ub1, and DNA methylation levels with the concomitant decrease in the expression of enhancer of zeste homolog2 (EZH2) and DNMT3B enzymes. These alterations were associated with the upregulation of the genes involved in cardiac pathogenesis such as six homeobox 1 (Six1), isllimhomeobox 1 (Isl1), and mads box transcription enhancer factor 2, polypeptide C (Mef2c) [11, 17]. Research on non-human primates has shown that in utero MHFD-induced NAFLD in fetuses is associated with increased H3K14ac and decreased SIRT1 expression with diminished histone deacetylase activity. Furthermore, MHFD resulted in the deregulated expression of various genes such as PPARA, PPARG, SREBF1, CYP7A1, FASN, and SCD regulated by SIRT1 and implicated in NAFLD. These epigenetic changes were abrogated by diet reversal (14 % fat) during breeding and gestation suggesting diet as an epigenetic modifier [12, 18]. Moody et al., demonstrated that offspring born to HF dams were able to remodel hepatic epigenome when subjected to a postweaning control diet [19]. It has been reported that a paternal high-fat diet (PHFD) and MHFD comprising 62 % fat resulted in the downregulation of adiponectin and upregulation of leptin gene in offspring along with weight gain, increased blood pressure, glucose, insulin, total triglyceride level thus predisposing the offspring towards the development of metabolic syndrome including T2D [13, 14, 20, 21]. The differential expression of adiponectin and leptin was associated with the decreased level of acetyl H3K9 and increased expression of dimethyl H3K9 in the promoter region of the adiponectin gene and increased monomethyl H4K20 levels in the promoter region of the leptin gene suggesting HFD influence epigenetic markers. However, they found that control diet (CD) (12 % fat) consumption for two to three generation was able to abolish the epigenetic effect caused by PHFD and MHFD indicating epigenetic reversal using a control diet is a slow process [13, 14, 20, 21]. A study revealed that 5hmC modification on hypothalamic anorexigenic neuropeptide proopiomelanocortin (POMC) negatively correlates while 5mC modification positively correlates with the body weight of offspring born from HFD and control-fed dams. POMC expression in obese offspring was mediated by two-step epigenetic inhibitory mechanism where CpG methylation was associated with histone post-translational modification. Increased CpG methylation at the POMC promoter caused methyl-binding domain 1 (MBD1) to bind 5mC which then interacted with SET domain bifurcated 1 methyltransferase and resulted in the bimethylation of H3K9 residue thereby reducing POMC expression, which may alter offspring feeding regulation [22]. Further it was shown that offspring of HFD dams showed

hypermethylation in POMC promoter, which was associated with weight gain and the standard chow diet from weaning was unable to reprogram hypermethylation suggesting that diet is not able to reverse all epigenetic alteration and require a dire need for the screening additional epigenetic modifiers for using as combinational therapy to prevent the disease state [23].

Maternal obesity also influences epigenetic processes associated with disease conditions in later life. Maternal obesity and diabetes influence chromatin marks including DNA methylation, histone modification, and miRNAs in sperm and oocytes [24]. Gestational diabetes induces epigenetic alterations that can predispose offspring to various disease conditions including cardiovascular disorders, metabolic disorders, and obesity in later life [25, 26]. A study found that gestational diabetes is associated with the low level of DNA methylation at CpG1 and CpG2 in the melanocortin 4 receptor (MC4R*)* gene on the fetal side of the placenta indicating it might have implications in fetal growth and metabolism [27]. Another group observed that maternal obesity resulted in epigenetic changes in adiponectin and leptin genes and subsequently their downregulation in the human third-trimester placenta [28]. It is already known that adiponectin and leptin gene expression is controlled by histone modifications and thus suggesting its implication on fetal metabolism and development [20, 21]. Alba-Linares et al. found that maternal obesity and maternal obesity with gestational diabetes led to abundant DNA methylation alteration during the first six months of child development into the genes including CPT1B, FN3K, SLC35F3, and SLC38A4 involved in the metabolism of fatty acids, mitochondrial bioenergetics, and postnatal development processes [29].

Influence of caloric restriction on epigenetics and metabolic syndrome

Caloric restriction is one of the possible interventions to reduce obesity and diabetes. Caloric restriction without malnutrition was shown to prevent the impaired lipid metabolism and insulin resistance in gestational diabetes offspring [30]. Various studies showed that caloric restriction (CR) without malnutrition influences DNA methylation pattern, gene expression, and chromatin structure [31–33]. Hernandez-Saavedra et al. demonstrated that CR without malnutrition alters the epigenetic pattern by modulating the expression of genes involved in immune-metabolic processes and exerts beneficial effects by delaying the onset of chronic diseases [31]. It was observed that maternal low protein and post-weaning high-fat diet is associated with chromatin remodelling of hepatic genes and obesity in offspring suggesting a need for early intervention for the prevention of MetS [34]. However, it is yet to evaluate the pathways regulated by CR without malnutrition through the epigenetic mechanism in combating metabolic diseases. Moreover, most key biological processes including inflammation, metabolism, fatty acid oxidation, and oxidation stress are driven by the epigenetic modifications for early life programming and thus require the identification of epigenetic modifiers that can reverse the epigenetic abnormalities associated with maternal obesity. Caloric restriction with malnutrition has a detrimental effect on the offspring, leading to insulin resistance and the development of T2D [35]. It also indicates that a low-caloric diet with malnutrition and a high-fat diet both predispose the offspring towards metabolic disorders and it would be imperative to check if they share a common mechanism or what epigenetic window defines the propensity of offspring towards metabolic disorders. Persico et al. showed a decrease in the expression of the H3K4me3 mark in the liver tissue of mice fed on a low-calorie diet as compared to a high-fat diet indicating distinct mechanisms controlled by caloric restriction and high-fat diet [36].

Impact of maternal dyslipidemia on future cardiometabolic health in the offspring

It is also important to note that maternal lipidomic profile contribute to the development of offspring DNA methylation and suggesting the importance of lipid fraction in assessing the methylation pattern in offspring [37]. Comparison of lipidomic profile between the first-trimester maternal plasma (M1) and delivery maternal plasma (M3) showed that M3 saturated lysophosphatidylcholine is associated with differential methylation at 45 loci and M3 saturated lysophosphatidylethanolamine with 18 differential methylation loci [37]. A negative correlation between the maternal lipid profile including four phospholipids, four lysolipids, and a fatty acid was observed with newborn methylation [38]. A study exemplified that high total cholesterol, low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, and triglycerides were linked with 11 significant differential methylated CpGs in the placenta, which play a role in lipid metabolism and were related to dyslipidemia pathways and cardiometabolic disease [39]. High triglycerides were found to be related with decrease methylation of cg02785814 (ALX4) and its downregulation in the placenta [39]. Guay et al. illustrated that maternal total cholesterol changes were associated with the DNA methylation variation in the LDLR and LRP1 loci in the placenta, which were correlated with newborn cord blood leptin and triglycerides levels [40]. These studies indicate that maternal dyslipidemia can lead to cardiometabolic disease in offspring through epigenetic alteration in the placenta and offspring and placental lipid transfer. It was observed that arachidonic acid supplementation before mating and during the entire pregnancy corresponded with a decrease in the liver Scd1 promoter methylation of offspring, which was negatively correlated with the weight [41]. Rudolph et al. observed that a low ratio of omega-6 to omega-3 (n-6/n-3) polyunsaturated fatty acid (PUFA) in the maternal diet was associated with smaller adipocytes in pups, hypermethylation of Pparγ2 and its decreased expression along with the downregulation of Fabp4, and Plin1, several lipid metabolism mRNAs and upregulated adiponectin level which led adults resistant to diet-induced obesity with the improved metabolic condition [42]. These research findings demonstrate that the ratio of PUFA in the maternal diet regulate adipose tissue development and metabolic programming and may have a consequence for the development of metabolic disease in later life through epigenetic modifications.

Implications of folate, vitamin B12 intake on epigenetics and MetS during pregnancy

Folate also called vitamin B9 is an important methyl carrier and is needed for the generation of nucleotides and methionine [43]. Humans are unable to synthesise folate and Vitamin B12 and thus need to obtain them from the diet [44]. Previous findings have sug-

gested that offspring born from vitamin B12 deficient mothers showed higher triglycerides, total cholesterol, insulin resistance, TNF-α and IL-6, and lower leptin and adiponectin levels predisposing them towards the development of metabolic syndrome [45, 46]. It was shown using a mice model that vitamin B12 and folate deficiency resulted in decreased global DNA methylation in maternal tissue of F1 generation, and increased global DNA methylation in fetal tissue of F2 generation. In addition, folate deficiency led to increased global DNA methylation in the placenta of the F1 generation [47]. Moreover, vitamin B12 deficiency is also found to be associated with increased miR-221 levels in both F1 and F2 generation [47].

It was found that folate and vitamin B12 deficiency results in decreased expression of IGF2R in the placenta of the F1 generation, and fetal liver of the F2 generation of mice due to a reduced histone modification and increased DNA methylation [48]. Sinclair et al. (2007) revealed using a sheep model that less intake of methionine, folate, and vitamin B12 resulted in an altered DNA methylation pattern of 4 % of 1400 CpG islands in the offspring, which was associated with weight gain increased BP, immune response and insulin resistance in later life [49]. A study demonstrated that deficiency of folate, vitamin B12, and methionine in pregnancy caused alteration in the methylation pattern in the promoter region of 1032 genes involved in glucose and lipid metabolism, mitochondrial metabolism, ER stress, and the nervous system indicating it may affect the development of offspring [50]. Cho et al. revealed that methyl vitamins and folate alter hypothalamic gene expression and DNA methylation along with leptin and insulin receptor signalling dysfunction in the offspring of dams fed on high methyl vitamins [51]. It was found that folate and vitamin B12 deficiency during pregnancy leads to decrease body weight and an increase in central body mass, plasma-free fatty acids and myocardial hypertrophy in offspring through regulating the expression of SIRT1 and PRMT1 as well as due to the hypomethylation of PGC-1a [52]. Park et al. observed that obesity and maternal folate deficiency is associated with neural tube defect (NTD) due to hypomethylation of genes at CpG sites [53]. In the human cohort study, vitamin B12 supplementation was shown to regulate the expression of T2D-associated genes including FTO, SIRT1, TCF7L2, and CREBBP/CBP through miR-21 methylation [54]. Cho et al., found that high folate diet alters POMC methylation in rats along with weight gain and lower glucose response to insulin [55]. These studies suggest that folate and vitamins levels are associated with T2D and neurological disorders through altering epigenetic mechanism. However, it is yet to validate whether vitamin B12 and folate alteration during pregnancy is associated with these defects in offspring or not in order to understand the DoHaD hypothesis and for the development of early intervention therapies.

Influence of physical activity on epigenetics and maternal obesity

A study stated that vigorous physical activity has a beneficial effect on the risk of MetS while sedentary physical activity increases the risk of the development of MetS [56]. A survey of 24 178 Korean individuals was conducted to determine the influence of physical activity on metabolic syndrome and found that physical activity reduces the occurrence of metabolic syndrome [52, 57]. Recently, several studies have stated the beneficial effect of exercise through the epigenetic mechanism on the prevention and treatment of MetS and T2D [58–60]. It was shown using a mice model that physical exercise was able to restore altered glucose metabolism in offspring induced by a maternal high-fat diet through increasing H3K4me3 levels at the promoter region of glucose metabolic genes [61]. It was found that DNA methylation altered at 379 sites annotated to 370 genes in cord blood of offspring following physical activity of mothers with maternal obesity with or without a Mediterranean-like diet suggesting exercise has wide control on the methylation pattern of genes [62]. Among these, 17 methylation sites were found to be associated with body weight and 22 methylation patterns were related to offspring BMI z scores and early growth during the first 3 years of life [62]. Claycombe-Larson et al. observed that exercise reduced the risk for the development of T2D and obesity in offspring induced by postnatal HF by increasing H3K9 demethylases (KDM4C) and reducing H3K9me2 [63]. HF dams that were exercised during pregnancy were able to restore the dysregulated glucose metabolism in offspring caused by HFD through restoring H3K4me3 methyltransferase level and WD repeat-containing 82 (WDR82) carbonylation level and by suppressing reactive oxygen species [64]. The maternal exercise was also able to reduce the metabolic impairment of offspring induced by MHFD by eliminating the Pgc-1α promoter hypermethylation at CpG-260 [65, 66]. Axsom and Libonati presented a systematic review of the impact of parental exercise on the epigenetic modifications in offspring where they observed from different studies that maternal exercise was able to reverse HFD-associated methylation patterns in offspring. These differentially methylated genes were related to oxidative metabolism and glucose transport [67]. Maternal exercise was shown to increase Prdm16 promoter DNA demethylation and ameliorated BAT development and prevent the development of obesity in offspring upon induction by a high-energy diet [68]. These investigations show that exercise during pregnancy exerts beneficial effect on the metabolic status of offspring through epigenetic reprogramming.

Influence of air pollution on epigenetics and maternal obesity

Air pollution is a complex mixture of gases and particulate matter generated by industries, commercial and traffic [69–71]. The air pollution produced by traffic includes particulate matter [a mixture of black carbon, absorbed metals and polyaromatic hydrocarbons (PAHs), nitrogen oxides, and sulfur dioxide] that contribute significantly to the urban environment [71–73]. It has been stated by various reports that air pollution potentiates the risk for the development of cardiovascular disease, T2D, and metabolic abnormalities [74–77]. A study found that prenatal exposure to fine particulate matter (PM2.5) and ozone (O_3) is associated with differentiated methylated regions in cord blood implicated in pathways associated with immune function, inflammation, neurologic disorders, and cardiometabolic diseases [78]. Another study demonstrated that pregnant women living close to the major roadway (related to traffic pollution) delivered offspring with lower birth weight associated with hypomethylation of placental LINE1 [79]. Higher PM leads to the hypermethylation of hydroxysteroid 11-β-dehydrogenase 2 (HSD11B2), which is associated with elevated fetal

cortisol and reduced growth [80, 81]. These reports indicate that air pollution mediates its action in promoting MetS through epigenetics mechanisms.

MiRNAs modulated during maternal obesity

MiRNAs primarily exhibit 22 nucleotide lengths and are known as small non-coding RNAs that participate in gene regulation mechanisms [82]. They interact with the 3′UTR region of mRNAs in most cases and participates in gene suppression and translation repression [82]. Several reports have also demonstrated their binding to the 5′UTR region and promoter region and upregulating gene expression in certain cases [82]. The placenta microenvironment is crucial for the development of the fetus and abnormal placental function is associated with intrauterine growth restriction and adverse health outcomes for offspring [83]. Kennedy et al., identified the set of miRNAs including miR-876, miR-155, let-7c, miR- 216a, and miR-629 that regulate the placental cellular dynamics such as proliferation and differentiation through regulating various signalling pathways including TGF/β, calmodulin signalling, notch signalling, EGF/R, FGF/R, and IGF/R implicated in the formation and maintenance of placenta suggesting their role in the programming of fetal health [83]. These miRNAs may have a role in modulating the obese microenvironment of the placenta during maternal obesity. Several circulatory miRNAs are associated with gestational diabetes (GDM) include miR-29a-3p, miR-29b-3p, miR-16–5p, miR-330–3p, miR-17–5p, miR-19a/b-3p, miR-223–3p, miR-155–5p, miR-125-a/b-5p, miR-210–3p, and miR-132. Among these, miR-29a-3p and miR-29b-3p were upregulated before the development of GDM while miR-16–5p and miR-330–3p were elevated during late gestation [84]. Tryggestad et al. found a set of seven miRNAs including miR-30c-5p, miR-126–3p, miR-130b-3p, miR148a-3p, miR-452–5p, miR-let-7a-5p, and miR-let-7g-5p, which were upregulated in human umbilical vein endothelial cells (HUVECs) of infants of women with GDM. Among these, miR130b and miR140a were shown to downregulate the expression of AMPKα1, which was associated with a decrease in fat oxidation that may predispose the offspring to metabolic disease in future [85]. Diabetes exposure during pregnancy was associated with the downregulation of miR-148a-3p and miR-29a-3p by 40 % and 26 %, respectively, in the HUVECs of infants. Diabetes mellitus (DM) exhibited a differential effect on the expression of miR-126–3p in the placenta by birth weight where the expression of miR-126–3p was decreased with lower birth weight while DM exerting no influence on miR-126–3p at higher birth weight [86]. A study recognised a set of 20 miRNAs differentially expressed in the saliva of obese pregnant women as compared to normal-weight pregnant women. Among these, hsa-miR-505 and hsa-miR-616 were downregulated while hsa-miR-618, hsa-miR-206, hsa-miR-376a, hsa-miR-517c, hsa-miR-133a, hsa-miR-1285, hsa-miR-635, hsa-miR-551b, hsa-miR-548b-5p, hsa-miR-1256, hsa-miR-302c, hsa-miR-184, and hsa-miR-548c-5p were upregulated in obese pregnant women. These miRNAs were found to be associated with the TGF-β signalling pathway, fatty acids biosynthesis/metabolism, lysine degradation, and ECM-receptor interaction pathways through miRNA pathway enrichment analysis indicating the susceptibility of offspring towards metabolic disorder [87]. Zhao et al. observed 23 circulatory miRNAs including miR-15b, MiR-31, miR-122, miR-125b, miR-142, miR-130b, and miR-519d that were associated with obesity and weight gain [88]. Simino et al. found that micro RNA let-7a was upregulated in offspring born from the obese dam and associated with hepatic metabolic disturbances [89]. Recently, the same group identified that expression of miR-122, miR-370, and let-7a was altered in the liver of offspring born from an obese dam and partial hepatectomy normalised the expression of altered genes as well as miRNA levels post-surgery suggesting the possible reversal of epigenetic alteration through regenerative therapy [90]. Huang et al., observed increased expression of miR-122 in the adipose tissue-derived exosomes and regulating adipogenesis through VDR, SREBF1, peroxisome proliferator-activated receptor gamma, lipoprotein lipase, and adiponectin. They further found that miR-122 could alleviate obesity in obese males by controlling VDR/SREBF1 axis [91]. A study showed that miR-506–3p increases glucose uptake and regulate genes including PI3K, AKT, IRS1, and GLUT4, which are the key component of the PI3K/AKT insulin signalling pathway and thus play role in modulating insulin resistance [92]. It was found that 12-month-old offspring of obese dams had increased body weight and fat mass and exhibited an elevated level of hepatic miR-582–3p and miR-582-5p [93]. Zhou et al. characterised the exosomes from the adipose tissue of an obese sow and found they regulate endothelial cell migration and angiogenesis through miR-221 implicated in placental dysplasia during gestation [94]. A study analysed peroxisome proliferator-activated receptor (PPAR)-γ expression in cells of offspring from obese and overweight mothers and uncovered its relation with miRNAs [95]. They found miR-378 and triglyceride enhance the expression of (PPAR)-γ while high glucose decreases its expression. They further observed that offspring born from overweight mothers exhibited downregulated miR-155 and miR-221 and upregulated miR-146a while offspring born from obese mothers showed downregulated miR-155, miR-221, and miR-1301. They also revealed miR-146a, miR-155, and miR-378a upregulated in overweight mothers and miR-378a upregulated in obese mothers suggesting epigenetic marks for obesity may be established during intrauterine development [95]. A study identified a set of three miRNAs including miR-16-5p, -29a-3p, and -134-5p that were upregulated in normal glucose tolerance women who later developed gestational diabetes suggesting the predictive biomarkers of gestational diabetes [96]. Using an ovine model of maternal obesity, reduced expression of miRNA let-7g was shown to be linked with increased intramuscular adipogenesis and inflammation during fetal development [97]. Using *C. Elegans* as a model system, Garcia-Segura et al. identified 13 upregulated miRNAs including miR-34-3p, the family of miR-35-3p to miR-41-3p, miR-39-5p, miR-41-5p, miR-240-5p, miR-246-3p and miR-4813-5p and two downregulated miRNAs including let-7-3p and miR-85-5p during starvation, and most of them involved in the development and metabolic process indicating they might act as predictive markers for obesity [32]. Furthermore, it was observed in pregnant women with pregestational overweight/obesity or gestational obesity that reduced expression of microRNAs such as miR-100, miR-1285, miR-296, and miR-487 is associated with metabolic parameters and predictor for prenatal and postnatal growth [98]. A recent study has demonstrated a sex-specific alteration in microRNA and gene expression in offspring exposed to gestational diabetes and maternal obesity *in utero*[99]. A study stated that the downregulation of

miR-133 in maternal and fetal is associated with type 2 diabetes [47]. Another study reported that the knockdown of miR-133 is associated with cardiac hypertrophy [100]. Lino et al. found that miR-22 was upregulated in middle-aged mice fed on HFD and its deletion attenuated weight gain and glucose imbalance and prevented white adipose tissue senescence [101]. Numerous miRNAs including miR-15 and let 7 family members are required for neonatal heart development and dysregulated expression of miR-195 (a miR-15 family member) is associated with heart abnormalities and arrest of the cell cycle at premature stage [102, 103]. These studies suggest that several miRNAs including miR-133 and let-7 family members are associated with several pathologies with metabolic disorders and thus can be used as biomarkers to screen metabolic diseased conditions. These findings indicate that miRNAs can be used as early predictive biomarkers for the identification of metabolic disorders however further studies are needed to explore all miRNAs associated with disease conditions to design a miRNA screen tape for the identification of particular metabolic disorders. These studies also implicate the importance of miRNAs in maintaining the healthy status of an organism. However, whether these miRNAs can be substituted through stem cell therapy to prevent or ameliorate the metabolic disease condition would be another area of research.

Stem cells as an in vitro model to study MetS in offspring

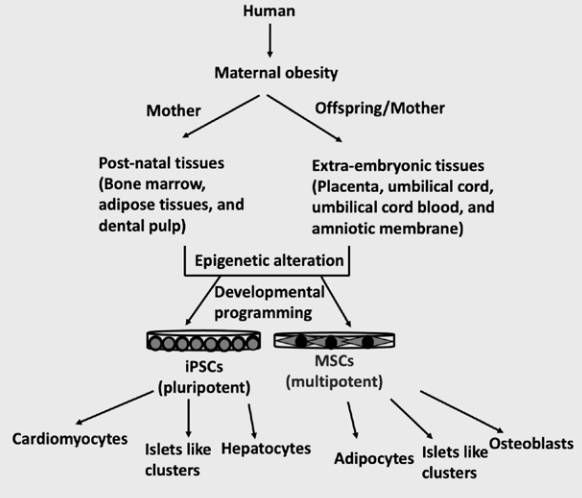
So far most of the studies on metabolic obesity have been conducted mainly using rodent model systems, which implicate a dire need to check whether these findings recapitulate in humans. Various biological phenomenon including metabolism, neurological network, physiological processes, drug metabolism as well as human genetic and epigenetic diversity is widely different in humans from animal models thus posing a dire need for the establishment of a human-based model system [104]. In recent years, research has also been focussed on the stem cells isolated from extra-embryonic tissues in demarcating the mechanism involved in pediatric obesity. Baker et al. (2017) observed a difference in the energy metabolism and gene expression profile in myocytes and adipocytes generated from umbilical cord-derived mesenchymal stem cells (UC-MSCs) from offspring born to normal and obese mothers. They observed maternal obesity led to the downregulation of various insulin-dependent energy-sensing pathways, including PI3K and AMPK in UC-MSCs. Further, they also noted the correlation between maternal obesity and upregulation of the mitochondrial respiratory chain and downregulation of mitochondrial biogenesis in UC-MSCs indicating a change in metabolic and gene expression profile in offspring [105]. Using rhesus macaques as a model system, it was found that a maternal high-fat diet is associated with reduced B cell differentiation and induction of the pro-inflammatory process in fetal bone marrow [106]. Hu et al. found using rats that a maternal high-fat diet led to increased body weight and neuronal network alteration in offspring through reduced neural stem cell proliferation and premature neuronal differentiation during postnatal hippocampal development [107]. It would be worthwhile to explore the differentiation propensity of human MSCs/iPSCs derived from the umbilical cord of offspring born from obese mothers to various cell types/progenitors to explore epigenetic biomarkers and screen the bioactive compounds/epigenetic modifiers to restore regenerative capacity/repair of tissue/organ during early development to prevent the later development of metabolic disorders. Boyle et al. 2016 demonstrated an increased propensity of UC-MSCs derived from fetal born to obese mothers to form adipocytes correlated with decreased beta-catenin suggesting altered signalling in infant MSCs implicated in lineage commitment [108]. The same group in another study revealed reduced fatty acid oxidation (FAO) and dysregulated AMPK activity in MSCs isolated from infants born to obese mother (ob-MSCs). These changes corresponded to increased adiposity and hypermethylation of genes PRKAG2, ACC2, CPT1A, and SDHC involved in FAO regulation in neonatal [109]. Laffaldano et al. observed lower glycolytic capacity, basal glycolysis, mitochondrial respiration rate, ATP-linked respiration and maximal respiration in MSCs isolated from the umbilical cord and amniotic membrane of the placenta of obese females after delivery suggesting altered metabolism in offspring and its predisposal towards metabolic disorders due to maternal obesity [110]. It was found that maternal free fatty acid level, triglyceride content and leptin positively correlate with increased mTOR and insulin signalling in hUC-MSCs [111]. The above studies clearly show that maternal obesity influences the MSCs population of the umbilical cord and dysregulation of the mitochondrial pathway. Various studies have reported a cross-talk between epigenetics and mitochondrial metabolism [112, 113]. Mitochondrial functions are controlled by nuclear DNA and mitochondrial DNA and both are susceptible to epigenetic modification. It is thus important to determine the epigenetic signature that controls mitochondrial function and drives metabolic disorders. These epigenome signatures can further be used to screen the susceptibility of offspring for metabolic disorders using stem cells as a model system. This also raises a possibility that dysfunction of MSCs under obese conditions might be associated with MetS in offspring in later life probably due to their decreased regenerative and repair capacity. A study found that HFD-induced maternal obesity led to the increased expression of senescence-related genes and PPARγ in embryonic mouse osteogenic calvarial cells through H3K27 acetylation and suppressed bone development in offspring. These results were recapitulated in hUC-MSCs isolated from the umbilical cord of offspring of obese and lean mothers after delivery highlighting the importance of mesenchymal stem cells as a candidate to diagnose/screen the defects/dysregulation associated with maternal obesity [114]. A study reported that sirt1 regulates sphingolipid homeostasis and neural differentiation through c-myc-SMPDL3B [115]. Comparative study between rat embryonic rat osteogenic calvarial cells (EOCCs) and human MSCs isolated from the umbilical cord of obese mother showed decreased glucose metabolism and insulin resistance and increased senescence signalling suggesting UC-MSCs recapitulated the finding of rat model system [116]. Several studies have suggested using animal models that various pathways including metabolism, inflammation, insulin resistance, and oxidative stress are driven by an epigenetic mechanism. It would be worthwhile to check if stem cells recapitulate the same phenomenon and to what extent epigenetic modifiers can reverse or prevent the development of metabolic syndromes. Furthermore, these studies suggest

that stem cells can be used as an in vitro model system for modelling the consequence of maternal obesity in offspring reducing the animal dependency on the same.

Moreover, the breakthrough in the discovery of human induced pluripotent stem cells (hiPSCs) has paved the way to model disease in a culture dish with a bulk supply of cells and generation of organs in a dish in a 3D microenvironment to mimic in vivo organ development and disease conditions as well as drug screening [104]. hiPSCs are sequentially directed to external cues to mimic the stages of internal organ development with the formation of organ buds and later organoids containing multiple cell types, ECM and interaction among them [104]. These organoids can be generated from the diseased patient cell types and biopsies and resemble more closely to the organs and conditions found inside the human body thus holding profound interest to study the disease condition [104]. A study showed that histone demethylase JMJD2A is associated with the expression of genes related to hypertrophy in cardiomyocytes derived from induced pluripotent stem cells [117]. hiPSCs can be derived from bone marrow blood and umbilical cord blood where the former is of the mother's origin while the latter signifies fetal origin. They can be used as an in-vitro model system to screen the pathophysiology of maternal obesity in mother and offspring by differentiating into various cell types or tissues or organoids such as cardiomyocytes, islets-like clusters, hepatocytes, etc. (▶ **Fig. 1**).

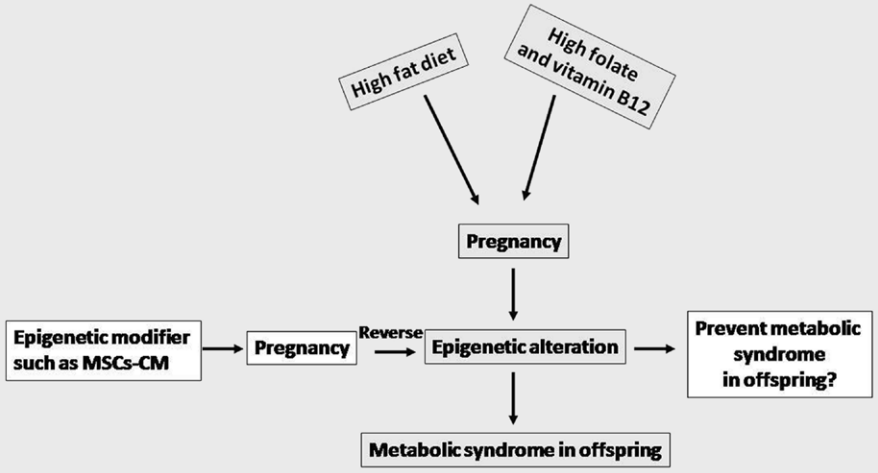
Can MSCs paracrine secretion act as epigenetic modifiers to reverse epigenetic alteration of metabolic disorders?

MSCs are known to mediate their action by paracrine secretion; therefore it is essential to study the secretome profile of MSCs under obese conditions and their influence on fetus growth. It is already known that maternal obesity is associated with altered levels of nutrients, hormones, and growth factors including insulin, adiponectin, leptin, proinflammatory cytokines, IGF-1, and lipids. These changes modulate placental function that alters the nutritional supply to the fetus and predisposes the offspring for the development of MetS in later life [118, 119]. The placenta is also a rich source of MSCs [120], it would be important to study the influence of above mentioned maternal obesity factors on the secretory properties of placental MSCs and their role in fetal development due to the therapeutic potential of paracrine secretion and their regulation by the epigenetic mechanism for the reversal of disease conditions. Recently, Kotikalapudi et al. showed that human placental MSCs were able to restore insulin level, glucose level, Glut4 expression, and dysregulated cytokines through the PI3K-Akt pathway in WNIN/GR-Obese rats suggesting the clinical importance of placental MSCs and its secretome [120]. A study suggests that repeated administration of human MSCs and MSCs lysate improved obesity-related MetS such as glucose intolerance, inflammation, NAFD, and nonalcoholic steatohepatitis in obese mice indicating the therapeutic potential of MSCs [121]. However, Meng et al. found increased expression of senescent markers in MSCs isolated from adipose tissue of pigs fed with an obese diet and their regulation by micro RNAs including miR27b through the MAPK pathway suggesting that obesity influences the morphological changes in MSCs and raises the question for their efficacy in treating metabolic disorders [122]. However, MSCs mediate their action through paracrine secretion, it is, therefore, worthwhile to check whether MSCs condition media obtained by preconditioning of MSCs in vitro can be used for ameliorating maternal obesity-related disorders.



▶ **Fig. 1** Stem cells as an in-vitro model system for maternal obesity.

MSCs secrete various paracrine factors such as vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF-1), fibroblast growth factor-2 (FGF-2), hepatocyte growth factor (HGF), transforming growth factor b (TGF-b), keratinocyte growth factor (KGF), brain-derived neurotrophic factor (BDNF), nerve growth factors, interleukins (IL-1b, IL-6, and IL-8), and C-C ligands (CCL-2, CCL-5, and CCL-23), etc. [123]. A study showed that hepatocyte growth factor-mediated global DNA methylation changes by upregulating the expression of DNA methyltransferase 1 (DNMT1) in HGF-treated normal liver cells (HL-7702 cells) and correlated with hepatocellular carcinoma (HCC) [124]. Fu et al. showed that FGF2 is important for Dnmt3b expression using blastocyst and embryonic stem cells (ESCs) as a model system [125]. A group showed that interleukin-1b induces the DNA methylation pattern that is associated with inflammation and the development of gastric diseases. Furthermore, the pro-inflammatory cytokine IL-6 was shown to regulate the expression of DNMT3B and DNMT1 enzymes [126]. Interestingly, the above-mentioned factors are the important component of MSCs paracrine secretion suggesting the suitability of MSCs condition media as an epigenetic modifier. In addition to various growth factors and cytokines, MSCs also secrete extracellular vesicles (EVs) as secretomes that actively participate in the repair and regeneration process [127, 128]. The content of EVs includes miRNA, long non-coding RNA (lncRNA), tRNA, growth factors, proteins, and lipids [129]. MSCs-derived EVs are known to exhibit various miRNAs including miR-125a, and miR-494 with angiogenic potential suggesting that these might also be important for maintaining placental function and development of offspring [130, 131]. Besides this, it is possible to modify the MSCs paracrine secretion through genomic modification and test its efficacy as the epigenetic modifier. It would be interesting to check to what extent MSCs secretome/EVs can act as epigenetic modifiers for preventing the complications and disorders associated with maternal obesity due to epigenetic alterations in offspring.



▶ **Fig. 2** MSCs secretome can act as epigenetic modifier.

Conclusion and future direction

Maternal obesity increases the risk for the development of various MetS including cardiovascular diseases and T2D in offspring. Lifestyle factors such as diet can modify the methylation pattern of DNA and alter gene expression which can cause or reduce metabolic disorders. However, epigenetic reversal using control diet is a slow process. Therefore, further studies are required to identify the epigenetic modifiers that can accelerate the reversal of epigenetic alteration and prevent the development of MetS in offspring. MSCs exosomes harbour growth factors, lipids, proteins and miRNA which have impact on regulating the metabolic, inflammatory, respiratory processes implicated in the development of MetS. It would be interesting to check whether MSCs can be used to produce exosomes with desired factors important to modulate the dysregulated signalling pathway and ameliorate maternal obesity related disorders in offspring. Further research would be needed for the development of method of injection or supplementation of these exosomes to pregnant mother or obese individual. Recently, we hypothesised whether mesenchymal stem cells (MSCs) can act as epigenetic modifiers upon systemic or local transplantation [132]. Therefore, it would be worthwhile to check whether MSCs-condition media (MSCs-CM) or exosomes can act as epigenetic modifiers to reverse the pathophysiology of maternal obesity by altering epigenetic marks (▶ **Fig. 2**). It would be also interesting to screen the bioactive compounds, which can preserve the molecular and secretory properties of MSCs to enhance their therapeutic value. Furthermore, iPSCs can also serve as an in-vitro model system to screen epigenetic modifiers such as MSCs-CM/exosomes for an epigenetic reversal for metabolic genes implicated in MetS formation. This will help to define health recommendations and the development of new therapeutic targets for the treatment of MetS in offspring and adulthood.

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SS and RB contributed to the concept, data collection and analysis of the manuscript. SS wrote the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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