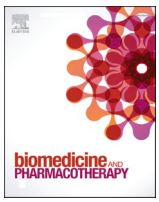
Biomedicine & Pharmacotherapy 151 (2022) 113103

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



Review

Influence of maternal obesity on the multi-omics profiles of the maternal body, gestational tissue, and offspring

Duan Zhao [1], Yusi Liu [1], Shanshan Jia, Yiwen He, Xiaowei Wei, Dan Liu, Wei Ma, Wenting Luo, Hui Gu [*], Zhengwei Yuan [*]

Key Laboratory of Health Ministry for Congenital Malformation, Shengjing Hospital, China Medical University, Shenyang 110004, China

ARTICLE INFO

Keywords:
Maternal obesity
Offspring
Epigenetics
Transcriptomics
Proteomics
Metabolomics

ABSTRACT

Epidemiological studies show that obesity during pregnancy affects more than half of the pregnancies in the developed countries and is associated with obstetric problems and poor outcomes. Obesity tends to increase the incidence of complications. Furthermore, the resulting offspring are also adversely affected. However, the molecular mechanisms of obesity leading to poor pregnancy outcomes remain unclear. Omics methods are used for genetic diagnosis and marker discovery. The aim of this review was to summarize the maternal and fetal pathophysiological alterations induced by gestational obesity,identified using multi-omics detection techniques, and to generalize the biological functions and potential mechanisms of the differentially expressed molecules.

1. Introduction

Excess weight is a serious threat to human health worldwide today [1,2]. In fact, currently more than 1.9 billion adults are overweight, of which more than 650 million are considered obese. The prevalence of overweight and obese individuals in the world's adult population is 39% and 13%, respectively, which represents more than half of the global adult population [3]. According to the body mass index (BMI) [calculated by dividing weight (kg) by height $(m)^2$] standard proposed by the World Health Organization (WHO), body weight is classified into the categories of underweight (BMI $<$ 18.5), normal (18.5 $\leq$ BMI $<$ 24.9), overweight (25.0 $\leq$ BMI $<$ 29.9), and obese (30.0 $\leq$ BMI) [4,5]. Owing to differences in the average body composition of different ethnic groups, the WHO considered the use of different standards for obesity classification [6]. Although BMI is not suitable for pregnant women, pre-pregnancy BMI and gestational weight gain (GWG) can reflect the nutritional status of pregnant women. Consequently, these metrics are considered to be important predictors of the perinatal period and the long-term outcomes of the mothers and children [7,8]. Epidemiological investigations show that a higher BMI before pregnancy is associated with an increased risk of pre-eclampsia [9], gestational diabetes mellitus (GDM) [10,11], miscarriage in the first trimester [12,13], cesarean section [14], postpartum hemorrhage [15,16], and macrosomia [17]. Changes in biomarkers observed in the maternal body (e.g., oocytes and uterus) and fetal developmental environment (placenta and amniotic fluid) are closely related to insulin resistance and a tendency to obesity in the offspring. When the fetus is exposed to a high-fat and high-sugar intrauterine environment, its developmental trajectory may be significantly affected during the blastocyst stage [18]. These changes can be the result of epigenetic mechanisms. In animal experiments, long-term changes in the molecular markers of multiple organs have been observed in the offspring [19,20]. This suggests that the impact of

Abbreviations: BMI, Body mass index; GWG, Gestational weight gain; GDM, Gestational diabetes mellitus; HFD, High-fat diet; CD, Control diet; DMR, Differentially methylated region; COBRA, Combined bisulfite restriction analysis; BS, Bisulfite sequencing; BSAS, Bisulfite amplicon sequencing; EWAS, Epigenome-wide association study; RRBS, Reduced representation bisulfite sequencing; PAA, Placental epigenetic age acceleration; WAT, White adipose tissue; PACE, Pregnancy and Childhood Epigenetics; SAGE, Serial analysis of gene expression; PBMCs, Peripheral blood mononuclear cells; PPAR, Peroxisome proliferator-activated receptor; NAFLD, Non-alcoholic fatty liver disease; GSEA, Gene set enrichment analysis; hA-MSCs, Human amniotic mesenchymal stem cells; ROS, Reactive oxygen species; MBD, Methyl CpG binding domain; TIGAR, TP53-induced glycolysis and apoptosis regulator.

* Corresponding authors.

E-mail addresses: zd1447320672@163.com (D. Zhao), albeyuyu@163.com (Y. Liu), jsscmu@163.com (S. Jia), yiwen041201@163.com (Y. He), weiweina20000513@163.com (X. Wei), liudancmu@126.com (D. Liu), cmu92294183@126.com (W. Ma), lvirginia@163.com (W. Luo), huier.99@hotmail.com (H. Gu), yuanzw@hotmail.com (Z. Yuan).

[1] These authors have contributed equally to this work and share first authorship.

https://doi.org/10.1016/j.biopha.2022.113103
Received 28 March 2022; Received in revised form 25 April 2022; Accepted 10 May 2022
Available online 20 May 2022

maternal obesity may accompany the offspring throughout life. Application of various omics methods, including epigenetics, transcriptomics, proteomics, and metabolomics, can help obtain information at the molecular level of DNA, RNA, proteins, and metabolites [21]. Furthermore, normalization and correlation analyses can accurately screen for relevant biomarkers.

The results of these studies can help us understand the overall impact of maternal obesity on the mother, the fetal developmental environment, and the fetus itself. These results have greatly contributed to our understanding of the role of molecular mechanisms in adverse pregnancy outcomes. Moreover, it creates the opportunity to screen for early warning molecular markers. We collated the available literature available on PubMed, Web of Science, and ClinicalTrials.gov on the effects of excess weight during pregnancy using the search terms obesity, overweight, pregnancy, fertility, genomics, epigenetics, transcriptomics, proteomics, and metabolomics (an exhaustive list of all keywords searched can be found in the supplementary material). Our aims were to comprehensively collate studies investigating obesity during pregnancy using the above types of omics technologies; to summarize the evidence of biological changes in pregnancy caused by simple obesity; to identify the differential genes or molecules observed in the results of high-throughput omics analyses; and to discuss the function and potential mechanisms of these genes or molecules.

2. Epigenomic studies

Many factors influence the occurrence and development of obesity, including the environment, and dietary structure as well as heredity which plays an important role [22]. Family studies have shown that obesity phenotypes are highly heritable [23–25].

Maternal obesity not only transmits obesity-susceptibility genes to offspring but also affects fetal programming through epigenetic mechanisms [26]. “Fetal adult diseases,” such as offspring metabolic syndrome, can be traced to intrauterine exposure to excess nutrition [27].

Epigenetics refers to the study of the heritable changes incurred in gene expression without the occurrence of the corresponding changes in DNA sequence. Epigenetic modifications include DNA methylations, histone modifications, and non-coding RNA (ncRNA) expression. The regulation of gene expression can affect the expression of genes in cells and the entire organism [28]. DNA methylation is established during gametogenesis and early embryonic development [29] and is important for normal embryonic development.

2.1. Maternal body

Ge et al. [30] investigated the effects of obesity during pregnancy on DNA methylation in maternal oocytes using an obese mouse model fed with a high-fat diet (HFD). Combined bisulfite restriction analysis (COBRA) and bisulfite sequencing (BS) showed that methylation levels in HFD mice were significantly higher than those in the control diet (CD) mice ($P < 0.01$). Obesity did not significantly affect DNA methylation in the differentially methylated region (DMR) of imprinted genes in oocytes, but methylation levels were significantly increased in the LEP promoters. Furthermore, the mean methylation levels of peroxisome proliferator-activated receptor (PPAR) -α promoters decreased. PPARα is a key gene that regulates adipocyte differentiation, inflammation, energy homeostasis, and lipoprotein and glucose metabolism [31]. Consequently, it is suggested that differential methylation plays a key role in development of overweight and/or obesity in the offspring.

In 2020, Del Vecchio et al. [32] examined cell-free DNA (cfDNA) methylation in maternal plasma using whole-genome BS. The results showed that maternal obesity was associated with reduced levels of placenta-derived DNA in maternal circulation. This result is consistent with the observations of previous studies [33] which revealed reduced apoptosis of placental cells and reduced cell renewal in individuals showing maternal obesity. Reduced placental cfDNA release has also been observed in obese mice [34]. Moreover, obese subjects also experienced total CG hypermethylation compared with normal-weight pregnant women.

Methyl CpG binding domain (MBD)-based genome-wide methylation sequencing showed that adpN DNA methylation in adipose tissue was significantly higher in obese women than in lean women ($P < 0.001$) [35]. Increased adpN DNA methylation is associated with lower mRNA and hypoadiponectin levels. Furthermore, maternal hypoadiponectin may downregulate the biological signaling of adpN receptors in various tissues, including those of the placenta.

2.2. Gestational tissue

In 2020, Narapareddy et al. reported genome-wide DNA methylation in a full-term marmoset placenta using BS [36]. Methylation of 74 genes was found to be associated with maternal weight during pregnancy. These genes are primarily involved in energy metabolism and homeostasis, including the pathways that regulate glycolysis and lipid metabolism.

Analysis of overall methylation levels in placental tissue showed that women with GDM and preeclampsia had lower overall methylation levels, while obese women had the highest levels of overall methylation in the placenta [37].

Nogues et al. [38] extracted the placental DNA set of obese pregnant women in the third trimester and performed bisulfite conversion and pyrosequencing. The LEP and ADIPOQ promoters were moderately methylated (<70%) in placental samples from the study group. The mean DNA methylation level of LEP in fetal placental samples from the obese group was significantly higher (1.2-fold), and this epigenetic modification was observed in the promoter regions close to the transcription factor binding sites (e.g., SP1, C/EBP, and TATA-box), all of which regulate leptin expression. ADIPOQ methylation was lower in the obese group (0.8-fold), and the methylation level of the ADIPOR1 promoter in the maternal placenta in the obese group was higher than that observed in the fetal placenta (1.5-fold). The methylation level of ADIPOR2 in the maternal placenta of the obese group was significantly higher than that of the control group (2.4-fold), and these expression differences may have functional consequences via the downregulation of the biological signals transmitted by ADIPORs in the placenta of obese women.

Human DNA methylation array tests of the placental villi of full-term pregnant women showed genome-wide differences in the methylated and hydroxymethylated regions [39], with a 21% increase in methylation and a 31% decrease in hydroxymethylation in the obese group compared to that in the lean group. Increased methylation and hydroxymethylation were evident around the transcription start sites of multiple genes in the GH/CSH and PSG gene clusters on chromosomes 17 and 19. Biological pathway analysis revealed that 262 genes that showed reciprocal differential methylation/hydroxymethylation were enriched in pregnancy-, immune response-, and cell adhesion-linked processes.

Shrestha et al. measured genome-wide placental DNA methylation in women of different body weights and identified new CpG sites for differential methylation [40]. Pre-pregnancy BMI was associated with DNA methylation at CG14568196 [EGFL7], CG15339142 [VETZ], and CG02301019 [AC092377.1]. Although weight gain in the first and second trimesters was associated with DNA methylation at CG17918270 [MYT1L], CG20735365 [DLX5], and CG17451688 [SLC35F3]. Furthermore, reduced EGFL7 expression has been reported to be associated with trophoblastic insufficiency [41] and early onset preeclampsia [42], but its role in placental development needs to be clarified in future studies.

Ouidir conducted a placental epigenome-wide association study (EWAS) of early pregnancy maternal dyslipidemia and found 11 differentially methylated CpG sites [43]. The top differentially methylated genes were enriched in pathways related to dyslipidemia, energy

homeostasis, and embryonic tissue morphology. High maternal triglyceride levels were associated with decreased methylation of CG02785814 annotated to ALX4 and decreased expression of the same gene in the placenta. Other loci, including *MOGAT2, ECI2, DHRS12, FAAH, SRM, BRD1*, and *RPTOR*, are relevant in the vascular and structural development of the placenta. In 2020, Thakali et al. assessed genome-scale DNA methylation in 150 full-term placentas from normal-weight (n = 72) and overweight/obese mothers (n = 78) using reduced representation bisulfite sequencing (RRBS) [44]. Maternal BMI category (normal weight or overweight/obese) and BMI (kg/m^2) were associated with methylation in 185 and 103 CpG sites, respectively ($P < 0.0001$). Gene ontology (GO) analysis of the 56 CpGs associated with both maternal BMI category and BMI showed that biological processes related to sterol regulatory element-binding protein (SREBP) signaling, phospholipid transport, granulocyte differentiation, and RNA pol II transcription were affected.

Disruption of the physiological aging of the placenta can lead to pregnancy complications and increase the risk of cardiovascular and metabolic diseases in childhood and adulthood. Placental epigenetic age acceleration (PAA) is defined as the difference between placental DNA methylation age and gestational age at birth, and it is associated with the early onset of preeclampsia. Moreover, 62 CpG sites have previously been found to predict placental epigenetic age with high accuracy [45]. An increase of 1 kg/week in GWG was associated with a 1.71-week (95% CI:−3.11, −0.32) reduction in PAA. Among mothers with male offspring, obesity before pregnancy was associated with a lower PAA of 1.24 weeks (95% CI:−2.24, 0.25) [46].

2.3. Offspring

The mother's diet and body composition have a profound effect on the offspring's risk of obesity and metabolic sequelae. These effects include systemic insulin resistance, liver steatosis, increased lipid biosynthesis, skeletal muscle mass loss, and glucose homeostasis disruption. Furthermore, adipose tissue plays a central role in coordinating and regulating the energy balance. In 2013, Borengasser et al. [47] assessed changes in genomic DNA methylation in the white adipose tissue (WAT) of the offspring of overfed obese female mice using BS. Only a small fraction of CpGs exhibited differential methylation, which may affect the expression of only a few genes in a given developmental environment. However, DNA methylation changes occur in the CGI (CpG islands) shore of development-related genes. These results suggest that obesity during pregnancy may induce epigenetic changes in WAT during early development.

In addition to being regulated within the cell, metabolic processes are regulated by communication between tissues and organs. The liver is the main organ for lipid synthesis, transformation, and secretion. Moreover, adipose tissue is responsible for lipid storage and oxidation, and the interaction between the liver and adipose tissue is extensive. In 2008, Aagaard-Tillery et al. [48] identified changes in site-specific histone H3 acetylation characteristics associated with transcriptional activation. Furthermore, the "reprogrammed" fetal genes in the liver, that is, Npas2 and Rdh12, were identified by ChIP -Seq. These results suggest that maternal obesity causes epigenetic changes in fetal chromatin structure through the covalent modification of histones, providing a molecular basis for the fetal origin of adult diseases.

Other effects on the liver of the offspring of overweight or obese individuals have also been observed. For instance, in 2013, Li et al. [49] analyzed differences in the CpG island methylation in the liver of the offspring of obese maternal mice. Subsequent GO analysis of genes with differential methylation ($P < 0.01$) between groups revealed a significant enrichment of development-related ontologies. Another effect on the liver was observed in the offspring of HFD maternal mice (OHFD) by Ge et al. [30], where increased LEP methylation and decreased PPARα methylation were detected by combining COBRA restriction analysis and BS analysis, consistent with the findings in maternal oocytes. In OHFD oocytes, the DNA methylation levels of the PPARα promoter were increased. These changes partly explain the adverse health effects of maternal obesity on the offspring.

In 2014, Suter et al. [50] analyzed genome-wide epigenetic changes in the fetal liver of obese Glut4 heterozygous knockout mice. Pathway analysis of ChIP data revealed differential enrichment of H3K14ac and H3K9me3 in pathways that regulate lipid metabolism, particularly in the promoter regions of *Pparg, Ppara, Rxra*, and *Rora*, which persisted up to 5 weeks of age. Changes in DNA methylation in the livers of offspring associated with maternal HFD were assessed using RRBS [51]. Maternal HFD did not alter the distribution of methylation in the CGIs or CGI promoters. The analysis identified 82 differentially methylated regions associated with maternal HFD. Moreover, the offspring of HFD dams had altered methylation patterns in the DMRs of genes that play important roles in hepatic fibrosis and lipid accumulation, including *Ppargc1β, Fgf21, Ephb2*, and *VWF*. These findings suggest that a maternal HFD is associated with epigenetic changes in pathways related to hepatic function and fibrosis.

The expression of imprinted genes is controlled by DMRs; DMR methylation is cleared in the primordial germ cell, re-established during gametogenesis, and passed on to the next generation. Moreover, the imprinting methylation of male germ cells occurs earlier than that of female germ cells and is more susceptible to interference from harmful uterine environments. In 2014, Ge et al. [52] investigated the changes in DNA methylation in the sperm of the offspring of obese mothers. Combined with the COBRA and BS results, DNA methylation of the maternal imprint gene *Peg3* was deduced to be significantly increased.

Global DNA methylation and bisulfite amplicon sequencing (BSAS) results showed that maternal obesity and excessive GWG were weakly correlated with umbilical cord DNA methylation patterns [53]. In 2013, Soubry et al. [54] used bisulfite pyrosequencing to examine the DNA methylation of leukocytes in the umbilical cord blood of newborns whose parents were obese before pregnancy. Paternal obesity was significantly associated with lower methylation levels in the DMRs *MEST*, *PEG3*, and *NNAT*. Maternal obesity was associated with increased *PLAGL1* methylation and decreased *MEG3* methylation. In 2013, Liu et al. [55] analyzed the epigenomic map of umbilical cord blood from 308 pairs of black mothers and infants. The methylation levels of 20 CpG sites were correlated with maternal BMI. These genes are involved in a wide range of chronic diseases, including cancer, cardiovascular diseases, and inflammation-mediated diseases, and this effect may vary with the sex of the offspring.

In 2014, Nomura investigated whether maternal GDM, preeclampsia, and obesity affect the overall methylation levels of placental tissue and umbilical cord blood [37]. However, the blood analysis found no significant differences in methylation levels among women with any of these maternal risk conditions compared with women without additional risk conditions. In a 2015 study involving 1018 mother-child pairs, Sharp et al. [56] found that there were 28 CpG sites of differential methylation in the DNA from the umbilical cord blood of offspring of obese mothers. Maternal obesity was more strongly associated with offspring methylation than paternal obesity, suggesting that maternal obesity may influence the neonatal epigenome via intrauterine mechanisms.

In 2019, Martin et al. [57] determined the umbilical cord blood DNA methylation of individuals who displayed pre-pregnancy obesity. Subsequently, they analyzed the sex-specific correlation of these factors with offspring BMI and blood pressure (BP) using epigenomic techniques. In this study, 74 CpG loci linked to maternal obesity (57 CpG in females and 17 CpG in males) were associated with the *TAPBP* gene. Differential methylation levels at some loci were related to cardiac function indicators such as systolic BP percentile and diastolic BP percentile of the offspring. Other genes corresponding to differentially methylated sites play important roles in cell proliferation, apoptosis, differentiation, immune response, and activation of inflammation. While small-scale studies have reported a strong association between

prenatal exposure and epigenetics, a study by the Pregnancy and Childhood Epigenetics (PACE) consortium found the opposite [58]. They performed a meta-analysis of the association between maternal BMI before pregnancy and methylation at more than 450,000 sites in neonatal blood DNA in 19 cohorts (9340 mother-newborn pairs). At 9044 sites throughout the genome, maternal BMI was associated with small methylation variations. After adjusting for cell proportions, the number of significant CpGs was significantly reduced, with 86 differential methylation sites spread throughout the genome without significant aggregation in chromosomal regions.

Furthermore, drastic interventions such as bariatric surgery can change the epigenetic effects on the offspring of obese individuals. In 2013, Guenard et al. [59] investigated the effect of maternal bariatric surgery on the methylation levels of genes related to cardiometabolic pathways in the offspring. Subsequently, 5698 differentially methylated genes were identified in the peripheral blood of the two groups of offspring, most of which are involved in carbohydrate regulation, inflammation, and vascular disease. Gene methylation levels, including of those associated with cardiometabolic pathways and diabetes, were significantly linked to insulin resistance in the offspring. Compared with offspring born before their mothers underwent bariatric gastrointestinal bypass surgery, children born after maternal surgery had lower levels of obesity and an improved cardiometabolic risk profile in adulthood.

2.4. Brief summary of the epigenomic studies

Studies have shown similar results at two distinct developmental stages: in oocytes and in the placenta in the third trimester [30,38]. In both stages, LEP methylation levels are generally higher in obese mothers. It is speculated that methylation changes in oocytes may be the developmental origin of obesity in the offspring. Furthermore, given that leptin and adiponectin are actively involved in the establishing the nutritive, secretory, and anchoring form and function of the placenta, it can be assumed that gestational obesity alters placental function.

DNA methylation changes in CGIs of development-related genes were found in the white fat and liver tissues of the offspring. Reprogramming of *Npas2* and *Rdh12* suggests that maternal obesity alters the structure of fetal chromatin through the covalent modification of histones. Increased *LEP* methylation and decreased *PPARα* methylation was observed in the liver of offspring, consistent with findings in maternal oocytes. This confirms mother-to-child epigenetic transmission of traits and provides a molecular basis for the presence of obesity and metabolic abnormalities in the offspring. Methylation of imprinted genes occurs in multiple organs of the offspring, including the oocyte, sperm, and liver. A large meta-analysis suggested that the association between maternal BMI and methylation variation is weak [58]. Therefore, further research is needed to explore the link between maternal obesity and offspring epigenetics.

3. Transcriptomic studies

The concept of a "transcriptome" was first established in the 1990s [60] to describe the study total gene transcription and regulation at cellular level [61]. This is the necessary link between the genetic information of the genome and the biological function of the proteome. The transcriptional stage is the most important stage of regulation in organisms and is currently the most studied regulatory stage. Understanding the genome-wide transcriptome and analyzing all coding and non-coding RNAs can reveal cell states in a specific environment. In recent times, serial analysis of gene expression (SAGE), which was first used in transcriptomics, has largely been replaced by microarray chips and high-throughput sequencing technology [62]. Transcriptomic technology has been widely applied to identify markers and explore the mechanisms of various pregnancy complications or adverse pregnancy outcomes, such as GDM [63,64], preeclampsia [65,66], intrauterine growth restriction [67,68], neural tube defects [69], cleft lip and palate [70]. Based on systematic reviews and meta-analyses, maternal obesity is a risk factor for these problems [11,71,72]. To date, transcriptomic studies have investigated the effects of obese pregnancy on the maternal reproductive system or fetal developmental environment in animal models and in humans.

3.1. Maternal body

In 2009, Farley et al. [73] isolated peripheral blood mononuclear cells (PBMCs) from full-term baboons and compared the transcriptomic differences between the obese and control groups. A total of 77 pathways were affected, and the most significant changes involved ubiquitin-mediated proteolysis, leukocyte transendothelial migration, and insulin signaling. This is consistent with observations in humans with obesity [74]. In 2020, Del Vecchio et al. examined plasma cfRNA using RNA-seq analysis during all trimesters of pregnancy [32]. Similar to the cfDNA signatures, obese subjects had lower placenta-derived cfRNA levels than normal-weight pregnant women, especially in the first trimester.

The effect of maternal obesity before pregnancy on the uterine transcriptome during the peri-implantation period was investigated by Shankar et al. [75] using microarrays. Differential expression of 403 transcripts ($\pm$ 1.3-fold, $P \leq 0.05$) was identified in overfed female mice; these transcripts are involved in the enhancement of biological functions, such as immune response, inflammation, and cytokine/chemokine signal transduction. Lipid staining revealed abnormal accumulation of lipid droplets in the uterine tissue during embryo implantation in the obese group, which verified the changes observed in the lipid metabolism-related genes in pathway analysis. Consequently, it is suggested that a high-fat uterine environment is likely to have an adverse effect on offspring development in early pregnancy, especially during implantation.

Furthermore, it has been shown that obesity adversely affects the ovarian environment and disrupts oocyte maturation and embryonic development. In the bioinformatics analysis of a microarray, a total of 284 differentially expressed genes between ovaries from lean and obese dams ($\pm$ 1.3 fold, $P < 0.05$) showed that overfeeding resulted in negative outcomes. These include induced proinflammatory responses, decreased gene expression of the ovarian glucose transporter, decreased phosphorylation status of the insulin-activated second messenger system, and altered expression of functional genes in the ovary. In 2017, Ruebel et al. [76] collected oocytes in different stages (GV, MI, and MII) from normal-weight and overweight/obese subjects undergoing fertility treatment and investigated oocyte mRNA profiles using a single-cell transcriptomic approach. These results indicated that obesity led to differential oocyte gene expression at all maturation stages, with specific upregulation of CXCL2 and DUSP1 and downregulation of TWIST1, ID3, GAS7, and TXNIP. These changes are associated with neuronal development and key metabolic pathways such as lipid metabolism and insulin signaling. In addition, these pathways may be influenced by post-transcriptional mechanisms. Combined with the discovery of the upregulation of pro-inflammatory and oxidative stress-related genes in oocytes, these results suggest that obesity impairs not only oocyte integrity and capacity, but also metabolism.

3.2. Gestational tissue

The placenta and amniotic fluid are the source of nutrition and shelter for the fetus, regulating the internal environment in which it is located. Consequently, the placenta is an important hub for the maternal supply of fetal nutrients and mother-fetal communication during pregnancy. It can secrete a variety of hormones that are important for maintaining normal fetal growth. The placenta has long been considered asexual, and most studies aggregate data from the placentas of male and female fetuses into one group [77]. In 2012, Gabory et al. [78] statistically analyzed the female and male placentas of rats fed CD or HFD

using the LIMMA linear model. Microarray results indicated that maternal obesity has a sexually dimorphic effect on placental gene expression. A total of 168 genes in females, and 190 genes in male placentas were affected by a maternal HFD. Only 16 genes were differentially expressed between the sexes, indicating sexual dimorphism. Dysregulated genes in the female placenta are mainly involved in cell death, white blood cell stimulation and binding, amino acid metabolism, and organ development and morphology. The differentially expressed genes in the male placenta are mainly related to the development and function of the cardiovascular system, fatty acid metabolism, glucose metabolism, elongation, and development of the nervous system.

Trophectoderm (TE) cells and ectoplacental cones (EPCs) are essential for placental development and support embryonic development. In 2018, Stuart et al. [79] explored the early placental transcriptional changes of maternal obesity in the window period between implantation of E4.5 and EPC formation of E6.5 by microarray hybridization and RNA-Seq. The results showed that inflammation and vascular development-related pathways represented by endothelin-1 (ET-1) signaling and p38 mitogen-activated protein kinase (p38 MAPK) signaling were upregulated in the TE of HFD mice. Only downregulated Fgfr2 has been shown to be associated with developmental failure of the labyrinthine layer and death after implantation in Fgfr2 mutant mice [80]. Transcriptome analysis of EPCs at E6.5 showed that Sphingosine-1-phosphate (S1P), p21 activated kinases (PAK), integrin-linked kinases (ILK), and peroxisome proliferator-activated receptor (PPAR) signaling pathways were disrupted in the HFD group. In addition, HFD-induced changes in TE at E4.5, and EPC at E6.5, overlap greatly, including the persistent upregulation of multiple antiangiogenic genes. VDR/RXR activation, ET-1 signaling, axonal guidance signaling, p38 MAPK signaling, and PPARα/RXRα activation in TE at E4.5, and EPC at E6.5, suggest that these pathways are important in the development of abnormal placental function in obese pregnancies.

In 2018, McCoski performed RNA sequencing to assess the effects of maternal obesity exposure on gene transcription in preimplantation sheep embryos [81]. Four of the 21 differentially expressed genes have known roles in placental development and function (ALCAM, BRCA1 GP2, GSTA4), and five are associated with obesity and insulin resistance (MPHOSPH9, BRCA1, ASP, ALCAM, GP2). In addition, the effect of maternal obesity on fetal sex differed, indicating that preimplantation sheep genome responses to maternal obesity are sex-dependent.

In 2021, Wang et al. [82] performed Next Generation Sequencing analysis of rat placenta to determine transcriptome expression after an HFD. 26 up-regulated genes and 27 downregulated genes were observed in the HFD group. Functional annotation clustering revealed that the ribosome was the most important Kyoto encyclopedia of genes and genomes (KEGG) pathway. Other altered KEGG pathways included oxidative phosphorylation, arginine and proline metabolism, and non-alcoholic fatty liver disease (NAFLD).

In 2013, Nardelli et al. [83] used TaqMan Array to evaluate the expression profiles of 365 miRNAs in the amniotic membranes of 10 obese (pre-pregnancy BMI>30, n = 10) and control (pre-pregnancy BMI<25, n = 5) women. Significant down-regulation of trophic factors, mammalian target of rapamycin, insulin, adipocytokines, actin cytoskeleton, and mitogen-activated protein kinase signaling pathways, which may affect placental growth and function, was observed. These factors increase the risk of neonates suffering from metabolic diseases in future.

RNA-seq showed that 288 genes were significantly different (± 1.4-fold, $P < 0.05$) in the placentas of obese women compared to those of control women [84] and were involved in biological processes such as development, stress response, immune response, differentiation, chromatin modification, and reproduction. Gene set enrichment analysis (GSEA) also revealed that the expression of genes involved in angiogenesis and lipid metabolism was significantly decreased, and maternal obesity was significantly associated with increased mRNA levels of lipid drop-associated protein CIDEA ($P < 0.001$). Overall, maternal obesity, in the absence of GDM and other comorbidities, affects the placental genome-wide transcriptome, and these changes correspond to increased placental lipid content oxidative stress, and inflammation. This provides evidence of Jun N-terminal kinase (JNK) signaling-mediated maternal obesity-induced placental lipid toxicity [85]. The lipotoxic placental environment may influence placental development and function, as demonstrated by the reduced levels of angiogenic factors and umbilical cord blood nutrients, leading to metabolic reprogramming in the offspring.

In 2015, Lassance et al. [86] collected placental tissue and blood samples from women who voluntarily terminated their pregnancies during the first trimester. Gene expression in placental trophoblast cells was analyzed using a genome-wide microarray. A total of 1342 differentially expressed genes related to carbohydrate synthesis, cell transport, lipid and energy production, cell metabolism, cell function, and cell structure were observed in obese and lean women. Several genes encoding mitochondrial pathways, including mitochondrial cytochrome and other genes, were downregulated in obese individuals. This result is consistent with those obtained in other studies [87,88], indicating that maternal obesity has a negative impact on the mitochondrial function of the placenta in early pregnancy, and obesity shapes the structure and function of the placenta during early development. In 2016, Bari et al. [89] conducted transcriptome analysis of trophoblasts isolated from the placenta of obese and normal weight pregnant women. The microarray results showed that 23 genes were differentially expressed between the two groups. The enriched GO terms included protein metabolic processes, RNA processing, gene expression, and translational processes. KEGG pathways, including the oxidative phosphorylation (Kegg:00190) and ribosome (Kegg:03010) pathways, were significantly enriched.

The placenta is an endocrine organ that produces hormones and growth factors critical for embryonic development and has a unique miRNA expression pattern [90]. Changes in placental miRNA expression are associated with adverse pregnancy outcomes [91,92]. In 2017, Carreras-Badosa et al. [93] studied the placental miRNA profile of pregnant women who were overweight/obese before pregnancy (preOB, n = 20) or obese during pregnancy (gestOB, n = 25), and 18 miRNAs were up- or downregulated by at least two-fold in placentas from preOB and gestOB women compared to those from control subjects. The expression of miR-100, miR-185, and miR-487 was decreased in the gestOB group and that of miR-1269, miR-1285, miR-181, miR-214, and miR-296 was decreased in the preOB and gestOB groups ($P < 0.03$). Differential miRNA expression was significantly associated with maternal metabolic (parturient BMI, HMW adiponectin, HDL cholesterol, HOMA-IR, and C-peptide) and growth parameters (placental weight, standard deviation score of birth weight, birth length, and weight gain) at birth and after follow-up. These miRNAs may be involved in regulating the growth-promoting effects of maternal obesity on offspring and may serve as early markers of prenatal development and postnatal growth.

Human amniotic mesenchymal stem cells (hA-MSCs) can differentiate into adipocytes and are, therefore, suitable models for studying adipocyte function in obesity. In 2016, Nardelli et al. used high-resolution small RNA sequencing to characterize miRNA profiles of hA-MSCs in 13 obese and 7 control pregnant women at delivery [94]. Twelve miRNAs were differentially expressed between the two groups. Important pathways malregulated by miR-138–5p and/or miR-222–3p/target interactions include adipocyte differentiation and deposition, lipid/carbohydrate homeostasis, response to stress, metabolic syndrome, heart disease, and ischemia. Overexpression of miR-138–5p/miR-222–3p and transcriptomic data suggest that differentially expressed miRNAs may disrupt metabolic pathways previously found in obese adults or obesity-related disease tissues.

In 2018, Sureshchandra et al. [95] used RNA sequencing to analyze transcriptomic changes in the placentas obtained from 11 lean and 14 obese women during full-term delivery. Placental genes whose

expression changed most significantly play a role in oxygen transport, which is consistent with the reported changes in the blood oxidative balance in obese pregnant women [96]. These changes in gene expression may signal an adaptation to inflammation and oxidative stress. The upregulated expression of tRNA encoding genes in the mitochondria also reflects oxidative stress. Vitamin A metabolism is an important process in embryonic development and immune system maturation [97], and the expression of genes involved in this process is downregulated. The list of differentially expressed genes overlaps with previous studies [98], such as downregulated expression of immune-related genes (IL1R2, IL2RB, TNFSF10, and FN1) as well as of those associated with pregnancy complications such as intrauterine growth restriction, placental insufficiency, advanced gestational age, miscarriage, and preeclampsia (*IGFBP1, IGFBP2, PRL, TAC3, RBP4, DKK1, TIMP3, FSTL3,* and *IGFBP1*) [99–101].

Amniotic fluid protects the fetus and maintains the balance of fetal body fluids. It has been widely analyzed to assess the maturity and health status of the fetus. In 2014, Edlow et al. [33] isolated fetal cfRNA from the amniotic fluid of obese (BMI≥30, n = 8) and non-obese (BMI<25, n = 8) pregnant women undergoing amniocentesis during the second trimester of pregnancy, and used it for genome-wide expression array analysis. The results showed that expression levels of 114 genes were significantly upregulated, where those of 91 genes were significantly downregulated. *ApoD* with highly specific expression in the central nervous system (CNS) showed the most upregulated expression (9-fold); in contrast, the expression of apoptosis-related genes in the CNS decreased, suggesting that maternal obesity may lead to poor neurodevelopmental outcomes in offspring through these two potential mechanisms occurring during the second trimester.

3.3. Offspring

Maternal obesity exerts pro-inflammatory effects on the fetus as early as the blastocyst stage. In 2011, Shankar et al. [75] performed transcriptomic analysis of blastocysts isolated from obese Sprague Dawley (SD) rats. Expression of 359 transcripts was affected by maternal obesity. Increase in the expression of NF-κb-regulated pro-inflammatory genes (*CCL4* and *CCL5*) and the decrease in the expression of antioxidant genes (*GPx3*) and mitochondrial genes (*TFAM* and *NRF1*) may be a potential mechanism for the increased susceptibility to obesity in offspring.

Umbilical cord blood can reflect fetal health status. In 2009, Farley et al. [73] investigated the transcriptomic regulatory effects of maternal obesity on PBMCs in the umbilical cord blood of offspring using baboons. The most significant pathways (total affected pathways=29) affecting fetal PBMCs were related to cell adhesion molecules, phosphatidylinositol, m-TOR, and VEGF. The significant upregulation of the VEGF signaling pathway may be related to increased capillarization and function of fetal organs. In 2015, Ghaffari et al. [102] conducted miRNA transcriptomic analysis of fetal umbilical cord blood obtained during the delivery of obese and normal-weight pregnant women. There were no significant differences in miRNA expression between the obese and normal groups as well as when the samples were regrouped by maternal weight gain, BMI at first pregnancy, BMI at last pregnancy, mode of delivery, fetal sex, and race.

The umbilical cord, as a readily accessible fetal tissue, contains cell types (endothelial, smooth muscle, and mesenchymal stem cells) associated with development. In 2014, Thakali et al. [103] identified 232 differentially expressed genes in the umbilical cord of offspring born to overweight/obese pregnant women using microarray analysis. These differentially expressed genes were associated with insulin receptor signaling, response to insulin stimulation, negative regulation of glucose input and transport, and cellular response to fatty acids. The mRNA expression levels of EGR1, periostin, and FOSB were upregulated in the overweight/obese group. In contrast, the expression levels of endothelin receptor B, KFL10, PEG3, and EGLN3 were reduced.

Maternal obesity caused by a high-energy diet increases the risk of obesity in the offspring. In 2013, Borengasser [47] performed a global transcriptome analysis of WAT in the offspring of obese mice. It was reported that maternal obesity alters the part of the genome involved in in lipid and carbohydrate metabolism, metabolic processes, transport, and cytoskeleton development. Furthermore, exposure to maternal obesity significantly alters lipid metabolism in fetal adipose tissue and facilitates lipid biosynthesis.

Skeletal muscle is one of the major sites of glucose and fatty acid utilization, and impaired myogenesis and increased adipogenesis have been reported in the muscles of fetuses in obese sheep. In 2012, Yan et al. [104] analyzed the longissimus dorsi of offspring of high-fat diet-fed ewes using miRNA microarray. Hsa-miR-381, hsa-let-7 g, and bta-miR-376D were differentially expressed between the obesogenic and control diet groups. miRNA let-7 g plays an important role in inhibiting stem cell proliferation, inflammatory cytokine expression, and adipogenic differentiation, and may be an important mediator linking inflammation and adipogenic tissue development.

In the early stages of development, insulin and leptin act as nutrient factors that are essential for neuronal development. Fetal exposure to high insulin and leptin may affect the development of fetal brain circuits, including the hypothalamus, which controls feeding behavior and other brain areas regulating various behavioral functions.

In 2013, Stachowiak et al. [105] performed total RNA microarray analysis of the brain tissue of progeny of high-carbohydrate (HC)-fed female rats. The results showed that in addition to the metabolism-related gene disorder caused by maternal obesity, the encoding genes involved in myelin synthesis were upregulated, indicating biological changes in oligodendrocytes and myelin formation. Dysregulation of gene expression associated with ion channels, synaptic proteins, and neurotransmitters may affect the normal development and activity of axons and synapses. This may be the basis of neurological diseases in future generations. In 2016, Bae-Gartz et al. [106] divided diet-induced obese mouse dams into obese (HFD) and obese intervention (HFD–running intervention) groups, which performed voluntary wheel running throughout gestation. Male offspring were compared to the offspring of the lean control group on postnatal day 21. The results of hypothalamus microarray analyses showed that obesity during pregnancy not only significantly affected inflammatory signals in the hypothalamus of offspring, but also affected related genes regulating neurogenesis. Exercise intervention during pregnancy could improve the changes in gene expression patterns involved in neurogenesis. Thus, exercise in obese pregnant mice may be a critical component for promoting and programming metabolic health in the offspring. In 2017, using RNA-seq, Barrand et al. [107] explored the effect of maternal HFD on hypothalamus gene expression in rat offspring on day 10 after birth. HFD caused differential expression of 86 genes in female offspring, including genes coding for proteins of the extracellular matrix, particularly Col1a1, Col1a2, Col3a1, and the imprinted Igf2 gene. Male offspring fed a HFD showed significant changes in Col1a1 and Col3a1 and significant upregulation of two genes involved in the regulation of dopamine availability in the brain, tyrosine hydroxylase (Th) and dopamine reuptake transporter Slc6a3 (also known as Dat1). These transcriptional changes could alter neuronal projection formation during early development, leading to abnormalities in the neuronal circuitry controlling appetite in later life, hence priming offspring for the development of obesity.

In 2002, Napoli et al. [108] observed early atherosclerosis in the offspring using a mouse model of hypercholesterolemia during pregnancy. Microarray analysis of the descendant's' aortas showed that 135 genes and expressed sequence tags (EST) showed significant differences between the groups. This implies an acute effect of oxidative stress or a result secondary to the formation of aortic fatty streaks. Epidemiological evidence indicates that offspring of obese mothers have an increased risk of myocardial dysfunction, including ventricular hypertrophy and myocardial fibrosis. In 2013, Maloyan et al. [109] examined the

expression of miRNAs in the heart of baboon fetuses exposed to maternal overnutrition. Twenty-two of the 80 differentially expressed genes were mapped to humans, and 14 miRNAs, including miR-17–92 and miR-181A, have been reported to be dysregulated in cardiovascular diseases. This suggests an increased risk of congenital heart defects in the offspring of obese women. In 2016, Wing-Lun et al. [110] investigated changes in cardiac miRNAs in obese mouse models. Compared to the control group, the abundance of eight cardiac miRNAs in the offspring of obese female mice changed significantly. The upregulation of miR-148–3p was the most significant, and it was overexpressed in multiple KEGG pathways, including pathways that are highly related to heart function or heart disease.

In 2009, Zhang et al. [111] analyzed the expression profile of miRNA in the liver to determine the changes in miRNA in the offspring of maternal rats fed an HF diet before and during pregnancy, as well as during lactation. Of the 579 miRNAs measured, 10 showed increased expression and 23 showed decreased expression, among which miR-483 * showed the greatest decrease. Let-7c, which regulates development time, and miR-122, which regulates fat oxidation, are also on the reduced list. This may have long-term effects on the health of the offspring. Another high-fat feeding mouse model study in 2009 by Kimberley et al. [112] verified that maternal fat intake contributes to the development of NAFLD in adult offspring. Total RNA microarray analysis showed that the levels of oxidative stress-related genes (Nos3, Nos2, Gstm6, and Lcn2) in the livers of HF maternal offspring increased, and similar expression patterns were observed for genes related to inflammation, Crp, Mmd2, Tnfsf1, and Il-12b. Furthermore, in 2010, Shankar et al. [113] used microarrays to clarify the overall transcriptome changes in the offspring of overweight female mice at weaning to identify the programming loci. The increase in the expression of many genes that regulate lipid biosynthesis appears to be coordinated by the lipid conversion transcription factor SREBP-1. The decrease in downstream PPAR-α signaling targets, including FGF21, is consistent with the increase in liver steatosis and susceptibility to obesity. Transcriptome analysis of offspring livers based on a gene chip showed that the expression of 45 transcripts (42 genes) was significantly altered by maternal obesity [49]. The most upregulated genes, major urinary proteins (MUPs), are involved in the regulation of energy expenditure. The two genes with the most downregulated expression (ATPASE6 and CYTB) belong to the mitochondrial genome. Changes in gene expression caused by maternal obesity point to a broad set of biological functions that are not limited to energy metabolism. In fact, in 2013, Mischke et al. [114] observed sex-specific molecular changes in the liver of male and female offspring in a maternal western-style high-fat/high-cholesterol diet mouse model. A total of 686 and 604 genes were differentially expressed in the livers of male and female offspring, respectively ($P \leq 0.01$). Only 10% overlap was observed between the sexes. Changes in gene expression associated with developmental functions and processes, such as Wnt/β-catenin signaling, were observed in male mice. Genes involved in lipid metabolism (including those involved in cholesterol synthesis) were altered in females.

Offspring from control or HFD-fed dams were given access to control or HFD, which led to four groups of offspring: offspring born to control diet-fed dams weaned onto Con (CC) or HFD (CH), and offspring born to HFD-dams weaned onto Con (HC) or HFD (HH) [51]. RNA-seq analysis confirmed the changes in the liver transcription profile in each group. The HFD alone altered the expression of 20 transcripts, and the combination of maternal and progeny HFD resulted in 243 differentially expressed transcripts, with genes involved in inflammatory pathways such as innate immune responses, immune system processes, and lipid metabolism upregulation. Genes involved in fibrosis (Cidea and Mmp12) and inflammation (Ly6d) were significantly upregulated in the liver of the HH group compared to the CH group. Overall, maternal HFD exposure significantly affected liver gene expression in the inflammatory and fibrotic pathways.

In 2018, Lomas-Soria et al. [115] used RNA-seq to determine the sex-dependent effects of female rat obesity on the liver transcriptome of offspring. Compared to the control group, 1365 genes were significantly altered in the livers of male offspring whose mothers were obese. GO and KEGG analysis showed the following altered pathways: insulin signaling, phospholipase D signaling, NAFLD and glycolysis/gluconeogenesis. In contrast, only 70 genes were significantly altered in female offspring. Human epidemiological data also showed an increased prevalence of NAFLD in men than in women [116]. Therefore, it is reasonable to speculate that maternal obesity programs sex-dependent changes in insulin, glucose, and lipid signaling pathways, leading to liver dysfunction and insulin resistance in offspring.

3.4. Brief summary of transcriptomic studies

Maternal obesity results in transcriptome changes in gestational tissues, which may be responsible for increased insulin resistance or obesity risk in offspring. This may lead to adverse developmental outcomes and long-term metabolic syndrome in offspring. The pro-inflammatory environment may alter the course of fetal development, increasing the risk of metabolic diseases, immune disorders, cognitive impairment, and cardiovascular disease in offspring. As early as the blastocyst stage, maternal obesity promotes inflammation and oxidative stress in offspring. This adverse effect was observed in the heart and liver of the offspring after birth. Therefore, maternal obesity has a long-term impact on the offspring. Multiple studies have collectively observed the differential expression of genes related to insulin receptor signaling and lipid and carbohydrate metabolism, indicating that maternal obesity changes the insulin sensitivity and promotes fat synthesis in offspring. miRNA let-7 g and miRNA let-7c were differentially expressed in the muscle and liver of offspring, respectively. The change in let-7 g may be related to the increase in adipogenesis in muscle tissue, whereas let-7c regulates developmental time. In addition, gene disorders related to myelin synthesis, synaptic proteins, and neurotransmitters were found in the brain tissues of the offspring of obese mothers, which may have adverse effects on the development of the nervous system.

4. Proteomic studies

Proteins are important organic molecules in cells and are the main builders of tissues, hormones, enzymes, and immune cells. Quantitative analysis of proteins is helpful in revealing the dynamic changes and molecular functions of proteins under physiological or pathological conditions. Proteomics, which uses mass spectrometry for high-throughput quantitative and qualitative analyses of proteins, has become an important analytical method for studying protein functions.

4.1. Maternal body

Evidence from oocyte donation and embryo transfer experiments suggests that obese individuals have poorer oocyte quality. In 2018, Wang et al. [117] explored the potential mechanism by which maternal obesity damage affects oocyte quality using Liquid Chromatography with tandem mass spectrometry (LC-MS/MS). The levels of TP53-induced glycolysis and apoptosis regulator (TIGAR) molecules in HFD oocytes were significantly decreased. Knockdown and overexpression showed that TIGAR could improve the oxidative stress of HFD oocytes; that is, TIGAR was involved in scavenging reactive oxygen species (ROS) during the development of normal oocytes. Loss of TIGAR expression is responsible for ROS stress in oocytes of obese animals.

4.2. Gestational tissue

Several studies have examined the effects of maternal obesity on placental protein profiles. In 2018, Liang et al. [118] used iTRAQ to perform proteomic analysis of placental tissues of sows with normal and high backfat thickness. A total of 413 proteins, related to lipid

metabolism and inflammatory responses, were significantly differentially expressed. The upregulation of lipid gene expression is associated with a decrease in AMPK and an increase in Wnt signal activation, leading to the lipid toxic environment of porcine full-term placenta and potentially causing placental dysfunction and fetal growth impairment.

Isobaric tags for relative and absolute quantitation (iTRAQ) proteomics have been used to analyze the placental tissues of obese sows during vaginal delivery [119]. Of the 4652 proteins identified, 343 were differentially expressed between the groups and were associated with abnormal carbohydrate and lipid metabolism, mitochondrial dysfunction, reduced steroid biosynthesis, and increased oxidative stress and inflammation in the placenta. In 2019, Fornes et al. [120] performed proteomic analysis of placentas of obese female rats fed a HFD or high-sugar diet using liquid chromatography/mass spectrometry. Pathway analysis revealed the differential expression of proteins related to metabolism, inflammation, angiogenesis, and cytoskeletal remodeling. Decreased phosphorylation of ATP-citrate synthase (ACLYS457), an enzyme that links glucose metabolism to fatty acid metabolism, has been shown to be associated with mitochondrial oxygen consumption and cellular ATP levels. In 2020, Kretschmer et al. [121] observed that basal membrane structure destruction, excessive lipid deposition in the maze area, and placental barrier function were impaired in HFD mice. Proteomic analysis revealed that proteins related to cell and focal adhesion, cell junction, laminin, and the main basal membrane were significantly downregulated in the maternal placenta of HFD mice. Decreased expression of E-cadherin and other proteins may lead to a decrease in the placental barrier in the maze area, thus affecting the placental transport of nutrients and oxygen.

In 2012, Oliva et al. [122] lysed placental tissues obtained by cesarean section of normal-weight and obese pregnant women and analyzed specific protein spots using two-dimensional gel electrophoresis and MALDI-TOF mass spectrometry. A1AT and GRP75 were upregulated in obese pregnant women, whereas ANXA5, ATPB, BASP1, FTL, HNRPC, and VIME were downregulated. A1AT enhances the LPS-induced production of specific cytokines/chemokines through NF-κB and plays an important role in amplifying the acute inflammatory response. ANXA5 has anti-inflammatory, anti-thrombotic, and anti-apoptotic properties, and the differential expression of these two proteins suggests increased placental inflammation. Low FTL and ATPB levels can induce oxidative stress injury, and the increase in GRP75 may be an adaptive response to stress. HNRPCs, BASP1, and VIME are involved in cell proliferation, cell integrity, and cytoskeleton stability, respectively, and their downregulation may have adverse effects on fetal development. Hoch performed a cell cycle protein array in the first-trimester placental tissue of lean and obese pregnant women [123]. A network of cell cycle regulators, in which breast cancer 1 (BRCA1) is a central player, is upregulated by maternal obesity. Thus, BRCA1 may play a role in trophoblastic biology during early pregnancy. Therefore, its upregulation due to maternal obesity may alter placental development, adversely affecting maternal and fetal health.

HA-MSCs are pluripotent and can be extracted from placental amniotic membranes. These cells are effective models for the study of metabolic changes. In 2016, Capobianco et al. [124] analyzed the proteome of hA-MSCs in obese women and identified 62 differentially expressed proteins, focusing on three groups of proteins involved in stress response, cytoskeleton, and metabolism. The role of these changes in increasing the susceptibility of pregnant women to obesity or obesity-related diseases requires further investigation.

4.3. Offspring

The impact of maternal obesity on offspring is manifold. Epidemiological studies have shown an association between maternal obesity and poor neurodevelopmental outcomes in the offspring. In 2015, Manousopoulou et al. [125] compared the overall proteomic characteristics of the cerebral cortex of offspring of female mice fed a high-fat or control diet. The results of two-dimensional liquid chromatography-mass spectrometry showed a correlation between maternal HFD and endophenotypic changes in the cerebral cortex of adult offspring. The offspring's responses to hypoxia/oxidative stress and apoptosis/endoplasmic reticulum (ER) stress were significantly activated. In 2015, Lee et al. [126] found that when rats were exposed to 50% food restriction during pregnancy, the offspring showed catch-up growth, obesity, and higher HDL, LDL, and leptin levels; six proteins showed differential expression in the brains of the offspring at 3 weeks, among which UCHL1 and SCRN1 were identified as obesity markers related to fetal programming.

Furthermore, in 2018, Morzel [127] proposed that maternal high-fat/high-sugar diets may have an impact on salivary gland function. Two-dimensional electrophoresis and LC-MS/MS detection results showed that heat shock proteins, proteasome subunits, and tubulin were overexpressed in the offspring of SD rats fed a Western diet, which may translate into strong metabolic activity. At the same time, it is accompanied by the enhancement of the functions of proteins that control oxidative stress (such as glutathione peroxidase and peroxidin) and active antioxidant molecules.

In 2019, Fornes [120] found that in addition to placental function, maternal obesity has a negative impact on fetal liver function. A higher expression of catechol-o-methyltransferase (COMT) phosphorylation was observed in the liver of the offspring of mice fed a high-sugar/high-fat diet. These results indicate a common regulatory mechanism for catecholamine metabolism in the placenta and fetal liver.

Offspring of obese mothers show increased susceptibility to obesity and decreased insulin sensitivity in adulthood. It is also important to note that the duodenum is the primary site for the uptake and absorption of triglycerides. In 2019, Suarez-Trujillo et al. [128] determined the effects of a maternal HFD during pregnancy and lactation on neonatal duodenal histomorphology and proteome. Activation of pathways involving antigen recognition, phagocytosis, and internal lysosomal processing, as well as potential activation of adaptive immune responses. Intestinal dysbiosis caused by an HFD may be a trigger for such activation.

The development of fetal kidneys largely depends on the adequate supply of macronutrients and micronutrients. In 2019, Nüsken [129] found that consumption of an HFD during pregnancy in mice significantly affected the expression of 56 proteins in the kidneys of full-term fetuses. The transcription and translation of several possible interacting proteins (RPL23, NCBP2, SRS11, GTF2F2, and PAF1) was upregulated. The upregulation of CHMP1B and CHMP2B, which are involved in the sorting of endosomes in transport complex III (ESCRT-III), implies an increase in the process of membrane remodeling.

In 2021, Breuer [130] performed proteome analysis of mouse offspring epigonadal WAT at P21. Proteins that showed differential expression according to maternal diet were involved in metabolic processes, such as fatty acid oxidation and CYP2E1 reactions, as well as fatty acid metabolism, specifically the synthesis of prostaglandins and thromboxanes.

4.4. Brief summary of proteomic studies

Dysregulation of proteins related to the cytoskeleton, oxidative stress, inflammatory response, and lipid metabolism was observed in the placenta, and the increased inflammatory response and oxidative stress status were similar to changes in non-gestational obesity. The decreased expression of E-cadherin was closely related to damage to basement membrane structure and barrier function. Downregulated expression of proteins involved in cytoskeleton regulation and remodeling may have adverse effects on fetal development. The effect of maternal obesity on the proteome of the offspring has been observed in the central nervous, digestive, and urinary systems. Enhanced oxidative and ER stress may be important factors for poor neurodevelopment. Activation of antigen recognition, phagocytosis, and adaptive immune response implies

intestinal dysbiosis caused by maternal obesity. Membrane remodeling and increased mitochondrial damage may impair kidney function.

5. Metabonomic studies

According to the central dogma, metabolites produced in living organisms are the final products of the entirety of the biological processes occurring at the genomic, transcriptomic, and proteomic levels. However, the types and levels of metabolites are directly influenced by changes in diet, environmental factors, and the gastrointestinal microbiome. Metabolomic techniques facilitate the comprehensive characterization of small-molecule metabolites, such as sugars, lipids, nucleic acids, and amino acids, as well as help elucidate metabolic pathway changes in specific biological systems.

5.1. Maternal body

In 2016, Dawn et al. [131] used gas chromatography and liquid chromatography-mass spectrometry (GC- and LC-MS) to detect metabolites in the serum and follicular fluid of diet-induced obese mares and used MALDI-TOF-MS to detect lipid differences in oocytes. Increased levels of linoleic acid, stearic acid, and insulin in the follicular fluid of the obese group may lead to ER stress in the granulosa cells, resulting in decreased progesterone production and changes in cell function. Whether reduced phospholipid content and increased triglyceride content in obese oocytes lead to changes in membrane fluidity or ER stress in oocytes or embryos remains to be clarified. In 2018, Dawn et al. [132] continued to explore the influence of maternal obesity before pregnancy on the uterine environment and lipid spectrum of pre-implantation embryos. In contrast to previous oocyte studies, elevated triglycerides were not observed in obese mare embryos, and it is possible that most triglycerides are used as an energy source during development [133], counteracting the differences in triglycerides in embryos. The reduction in the levels of multiple lipids observed in the obese group is critical for maintaining cell membrane integrity or second messenger signaling, which is consistent with the findings in oocytes.

Peripheral blood flows through all important organs, participating in metabolism, regulating, and maintaining the balance of functional activities, as well as the internal and external environments. Changes in the metabolites were reflected in the information obtained from the blood. In 2010, Cox et al. [134] analyzed the serum metabolic profiles of macaque mothers exposed to an HFD using GC-MS. Two major components of the vitamin E complex (α-tocopherol and γ-tocopherol) were elevated in the HFD group. These fat-soluble compounds act as antioxidants and react with lipid free radicals or trigger intracellular signaling cascades to protect cell membranes. In 2011, Grant et al. [135] constructed a model of maternal overnutrition in macaques and analyzed fatty acid differences in maternal plasma and breast milk between the experimental and control groups using GC-MS. The results showed that the plasma levels of DHA, EPA and total N-3 fatty acids were significantly decreased in HFD-fed mothers. Reductions in EPA and DHA levels have also been observed in breast milk. The lack of long-chain polyunsaturated fatty acids, particularly DHA, which is essential for infant growth and neurodevelopment, may have profound effects on the fatty acid composition of the brain, visual system, and retinal function in fetuses and infants. In 2018, Stuart et al. [79] analyzed the plasma metabolomics of HFD-fed maternal mice using GC-MS and LC-MS. The levels of multiple phospholipids, including 1-stearoyl-2-arachidonoyl-GPC, were elevated in obese maternal plasma at E6.5. This key phospholipid is an important regulator of p38 MAPK activity under conditions of cellular stress and lipotoxicity [136]. Several lysine metabolites were found to be differentially expressed in the HFD group. Another key change that may affect placental and fetal development is the significant reduction in inositol and chiro-inositol levels. These two stereoisomers play key roles in the insulin pathway, acting synergistically as insulin sensitizers by enhancing the peripheral tissue uptake of glucose and glycogen synthesis, and low levels of these important metabolites may contribute to insulin resistance associated with maternal obesity. In 2016 Sandler et al. [137] examined the association between BMI and maternal serum metabolomics using targeted and untargeted metabolomics. Individual metabolite, network, pathway, and random forest analyses showed a broad association between acylcarnitine, lipids and related metabolites, carbohydrates, organic acids, and maternal BMI. Furthermore, 3-hydroxybutyric acid level was positively correlated with maternal BMI, while the levels of medium-and long-chain fatty acids showed a mixture of negative and positive correlations. By-products of lipid metabolism produced by mothers with a high BMI may influence fetal growth and obesity. In 2021, Shearer et al. [138] used nuclear magnetic resonance spectroscopy to detect serum metabolites in normal-weight, overweight, and obese women and tested the correlation between metabolite levels and pre-pregnancy BMI, GWG, offspring health, and the levels of hormones related to intestinal metabolism. The metabolomic data of the three groups showed different characteristics, and a group of metabolites consisting of glutamic acid, lysine, pyruvate, and valine predicted a high GWG.

As the fetal gut is primarily colonized by microbiota from the mother's vaginal and fecal microbiota during delivery, the transfer of maternal gut microbiota may play a key role in offspring metabolism. In 2021, Wang et al. [82] explored obesity-induced alterations in the maternal gut microbiome using 16 S rRNA sequencing. Compared to the control group, HFD-fed dams showed a greater abundance of the genera *Romboutsia* and *Akkermansia*, whereas the control group showed a greater abundance of Lachospiraceae. The predicted functions of different gut microbiomes indicated a relationship with amino acid, glucose, and lipid metabolism. In 2021, Ruebel et al. [139] conducted a microbiome analysis using 16 S rRNA amplicon sequencing of samples collected from fetuses of pregnant women in the overweight/obese group (n = 80) in the first (T1), second (T2), and third (T3) trimester. The results suggested that maternal weight status and dietary fat, fatty acid, and protein types have a significant impact on the abundance of bacteria associated with intestinal inflammation and metabolic function. Consequently, dietary interventions during pregnancy can exert beneficial effects by regulating maternal gut microbiota and can thereby affect the health of offspring.

5.2. Gestational tissue

Autophagosome formation and activation of autophagosome-lysosomal fusion in male placentas in overweight and obese women were compared to those in normal-weight women [140]. The induction of autophagy has been shown to be associated with increased ceramide levels. Targeted metabolomic measurements showed that as maternal obesity increased, levels of C16 and C18 dihydroceramide in the male placenta increased. However, of the ceramides, only C20 was slightly elevated, suggesting that dihydroceramides themselves may be involved in autophagy and placental physiological activation, rather than merely being inactive precursors of ceramides.

Metabolomics revealed that placental levels of acylcarnitine C16:0, C18:2, and C20:4 were lower in obese women, indicating reduced β-oxidation [141]. The levels of glutamine, glutamate, α-ketoglutaric acid (αKG), and 2-hydroxyglutaric acid (2-Hg) were increased in the placenta of obese mothers, while the ratio of glutamine to glutamate was decreased ($P < 0.05$), suggesting that the induction of conversion of glutamate to αKG could maintain normal metabolic flux. Furthermore, placental tissues from 20 normal-weight and 18 obese women were collected during elective C-sections and analyzed by GC-MS metabolomics [142]. Metabolites involved in antioxidant defense, nucleotide production, lipid synthesis, and energy production differed in the obese group, suggesting higher placental metabolism. The placenta of the obese group also showed a fatty acid profile with decreased levels of LC-PUFA derivatives. The metabolic characteristics of the placentas of obese individuals may reflect changes in the intrauterine metabolic

environment, which may influence the development of adult diseases. In 2020, a lipidomic study indicated that two polyunsaturated lipids comprising two fatty acid residues (PC(36:4) and PE(38:6)) are less abundant in the placentas of lean individuals [143]. Lyso-PC(20:4), a possible degradation product of PC(36:4) and a marker of a variety of metabolic changes, is also abundant in the placentas of obese individuals. The higher abundance of fluidizing PC(36:4) suggests that membranes in the placentas of obese individuals may be more fluid than those in the placentas of lean individuals. Full-term placental DHA synthesis is increased by the programming effects of higher maternal BMI and higher blood glucose, which may in turn lead to increased birth weight [144].

In 2018, using 16 S rRNA gene amplicon sequencing, Sureshchandra et al. [95] revealed changes in microbial abundance and diversity in the placentas of obese mothers. A small increase in the relative abundance of Proteobacteria was accompanied by a decrease in the abundances of Firmicutes and Bacteroidetes. However, only the relative abundance of Bacteroidetes was significantly higher in the placentas of the obese mothers. It has previously been reported that microbial counts of obese mothers increased from the first to third trimester [145]. In addition, the number of Bacteroides in the offspring of obese mothers was higher than that in the offspring of lean mothers, suggesting a vertical transfer of these bacterial communities [146].

5.3. Offspring

To date, animal studies exploring the effects of maternal obesity on offspring metabolism have involved primate models. Compared to other mammals with different phylogenetic times, primate models have advantages in simulating the developmental origin of human diseases. Cox [134] classified female macaques as high-fat diet-sensitive (HFD-S) or-resistant (HFD-R), according to their sensitivity to high-fat feeding. Compared to the control group, six metabolites (cholesterol, α-tocopherol, hypoxanthine, inositol, un(698_103), and un(2298_144)) in the serum of HFD-S progeny showed significant changes. Significant changes in the levels of only α-tocopherol were observed in the serum of the HFD-R progeny. A comparison of HFD-S and HFD-R revealed that the levels of three fetal metabolites were significantly increased: hypoxanthine, inositol, and un(2298_144). Moreover, in 2011, Grant [135] fed female macaques three diets: HFD before and during pregnancy, CD, and diet reversal (conversion of high-fat diet to control diet during pregnancy). Lipid analysis by GC-MS showed that the fetal plasma in HFD fed macaques contained elevated levels of inflammatory cytokines as well as elevated levels of triglycerides and glycerols, which were highly correlated with maternal levels. Plasma levels of DHA and total N-3 fatty acids were also significantly reduced in HFD fetal circulation. Maternal dietary intervention can restore maternal and fetal plasma N-3 fatty acids to CD levels.

A study of 16 S metagenomics characterizing the intestinal microbiome of offspring revealed that after exposure to HFD during pregnancy, lactation, or after weaning, offspring exhibited significantly reduced *Epsilonproteobacteria Campylobacter*, and constant changes of *Epsilonproteobacteria Campylobacter* may promote anxious behaviors in offspring [147]. This indicates that diet during pregnancy can continuously alter the microbiota of the offspring and affect metabolic processes. In 2018, Pace et al. [148] collected serum from HFD macaques before and after probiotic supplementation. Lipid analysis showed that the triglyceride, cholesterol, and low-density lipoprotein levels were significantly reduced after supplementation ($p < 0.05$). 16 S metagenomic analysis showed that probiotic supplements caused little change to the gut microbiome, including a transient increase in the abundance of *Lactobacillus* species and a decrease in the abundance of a few bacterial genera, including in feces and in that of anaerobic *Vibrio*. In 2017, Wankhade et al. [51] examined changes in the microbial ecology of offspring from control and HFD-fed dams using 16 S rRNA amplicon sequencing. The results showed that maternal HFD significantly lowered the α-diversity of gut microbiota and led to reduced operational taxonomic unit numbers. In addition, the abundances of the *Tenericutes* and *Verrucomicrobia* phyla increased.

The monitoring of metabolic parameters in primates is limited in studies, and human studies exploring the effects of maternal obesity on fetal metabolism have been reported. Eighteen newborns who had been delivered vaginally and 56 who had been delivered by elective cesarean section were grouped according to their mothers' pre-pregnancy BMI [146]. 16 S rRNA sequencing was used to detect the association between neonatal gut microbes and the delivery mode and maternal obesity. Compared to neonates delivered vaginally from normal-weight mothers, neonates born from overweight or obese mothers had a distinct gut microbiota community structure, enriched in *Bacteroides* and depleted in *Enterococcus*, *Acinetobacter*, *Pseudomonas*, and *Hydrogenophilus*. These microbial signatures are predicted to result in functional differences in metabolic signaling and energy regulation. In contrast, among elective cesarean deliveries, maternal BMI was not associated with the neonatal gut microbiota community structure. These findings indicate that excess maternal pre-pregnancy weight is associated with differences in the neonatal acquisition of microbiota during vaginal delivery but not cesarean delivery. In 2020, Schlueter et al. [149] suggested that maternal obesity is the most important factor leading to differences in cord blood metabolomics. The elastic network regularization model identified 29 metabolites as potential early biomarkers of the intrauterine effects of maternal obesity, among which galactoacic acid, L-arabitol, indoxyl sulfate, 2-hydroxy-3-methylbutyric acid, and citric acid have not been previously reported to be associated with obesity or maternal obesity. In contrast, Shearer et al. [138] reached an opposite conclusion. The metabolomic data of 37 singleton full-term fetuses showed that there was no significant correlation between cord blood metabolites and the corresponding maternal serum metabolites, suggesting that the umbilical cord vein serum components may be determined by placental metabolism rather than the metabolic state of mothers. Variable analysis showed that there was no significant correlation between the cord blood metabolome and pre-pregnancy BMI or GWG; the overall cord blood metabolome was not affected by maternal obesity. Therefore, further research is needed to clarify the effect of maternal obesity on the metabolism of cord blood.

5.4. Brief summary of metabonomics studies

To date, changes in lipid levels caused by maternal obesity have been observed in follicular fluid and oocytes. Increased levels of linoleic acid, stearic acid, and triglycerides indicate increased ER stress. The levels of several lipids related to membrane integrity or fluidity in oocytes and preimplantation embryos are affected by obesity. In addition to the increase in cholesterol, the contents of DHA, EPA, and total n-3 fatty acids in the mother's peripheral blood were significantly reduced, which may have an abyssal effect on the development of the CNS and retinal function of the fetus. Regardless of whether the macaques were sensitive to HFD, the content of α-tocopherol in the serum of their offspring showed significant changes. As an antioxidant, α-tocopherol is closely related to the maintenance and promotion of reproductive functions and lipid metabolism. Elevated levels of inflammatory cytokines and triglycerides in the peripheral blood of the offspring are highly correlated with maternal levels. Plasma levels of DHA and total N-3 fatty acids were significantly reduced, while maternal dietary interventions corrected the peripheral blood levels of total N-3 fatty acids, demonstrating the influence of maternal nutritional levels. Supplementation with probiotics can effectively reduce triglyceride, cholesterol, and low-density lipoprotein contents in the peripheral blood of the offspring but has a smaller effect on the intestinal microbiome of the offspring. New metabolic markers for the intrauterine effects of maternal obesity have also been identified in human umbilical cord blood. However, current research results are contradictory and lacking, and further studies are needed to clarify the relationship between maternal obesity and the

umbilical cord blood metabolome and to explore the mode of action of differential metabolites.

6. Conclusions

Epigenomics, transcriptomics, proteomics, and metabolomics can integrate DNA, RNA, protein, or metabolite information at the molecular level. Obesity is a global health problem affecting the reproductive health of women of childbearing age. Obesity is the result of interactions between genetic and environmental factors. Several studies have been carried out in obese individuals, and obesity susceptibility genes have been identified. Pregnancy is undoubtedly a process of mother-to-child transmission of obesity-related genes. Obesity-related epigenetic changes were found in the oocytes of obese mothers, and similar evidence of gene methylation was also observed in placental tissues in the third trimester, suggesting that both the gamete and fetal development environment, which are determinants of embryo quality, are affected by maternal obesity, and the observed changes may persist. Transcriptomic studies have shown that obese mothers possess a proinflammatory and lipotoxic environment. Although high inflammatory responses have been observed in non-gestational obesity, gestational obesity exacerbates this effect, which increases the risk of metabolic diseases, immune disorders, cognitive impairment, and cardiovascular disease in the offspring.

Proteomic research has revealed the impact of maternal obesity on fetal development from two aspects: prenatal nutrition and postnatal nutrition. The placenta is an important organ for the mother to provide nutrients and oxygen to the fetus before childbirth. Decreased expression of adhesion proteins is related to the destruction of the placental basement membrane structure and impaired barrier function in obese mothers.

DNA methylation changes in CGIs of development-related genes were identified in the fat and liver tissues of the offspring of obese mothers. Differential methylation of genes has been associated with the development of cancer, cardiovascular diseases, and inflammation-mediated diseases. Significant changes at the transcriptome level were observed in both the blastocyst and postnatal progeny, suggesting that maternal obesity also has long-lasting effects on the offspring. Differentially expressed genes involved in carbohydrate metabolism and lipid synthesis could explain why the children of obese mothers have a higher chance of developing diabetes and obesity. In addition, the dysregulation of genes related to myelin synthesis, synaptic proteins, and neurotransmitters may adversely affect the development of the nervous system of the offspring. The CNS, digestive system, and urinary system of the offspring are all affected by maternal obesity. Bioinformatic analysis of differential proteins suggested enhanced oxidative stress and ER stress in the CNS. Antigen recognition, phagocytosis, and adaptive immune responses are activated in the digestive system. Membrane remodeling and increased mitochondrial damage may lead to impaired renal function. The metabolic profile of the peripheral blood of offspring was highly correlated with the maternal metabolic profile, while the intestinal microbiome was less affected by the maternal metabolic profile.

Integrated analysis of different omics is the development trend of omics research in the future. Changes in a variety of pathways caused by maternal obesity have been found in the maternal body, gestational tissue, and offspring. Fig. 1 illustrates the main pathways affected by maternal obesity. Due to the hypermethylation status of obese women,

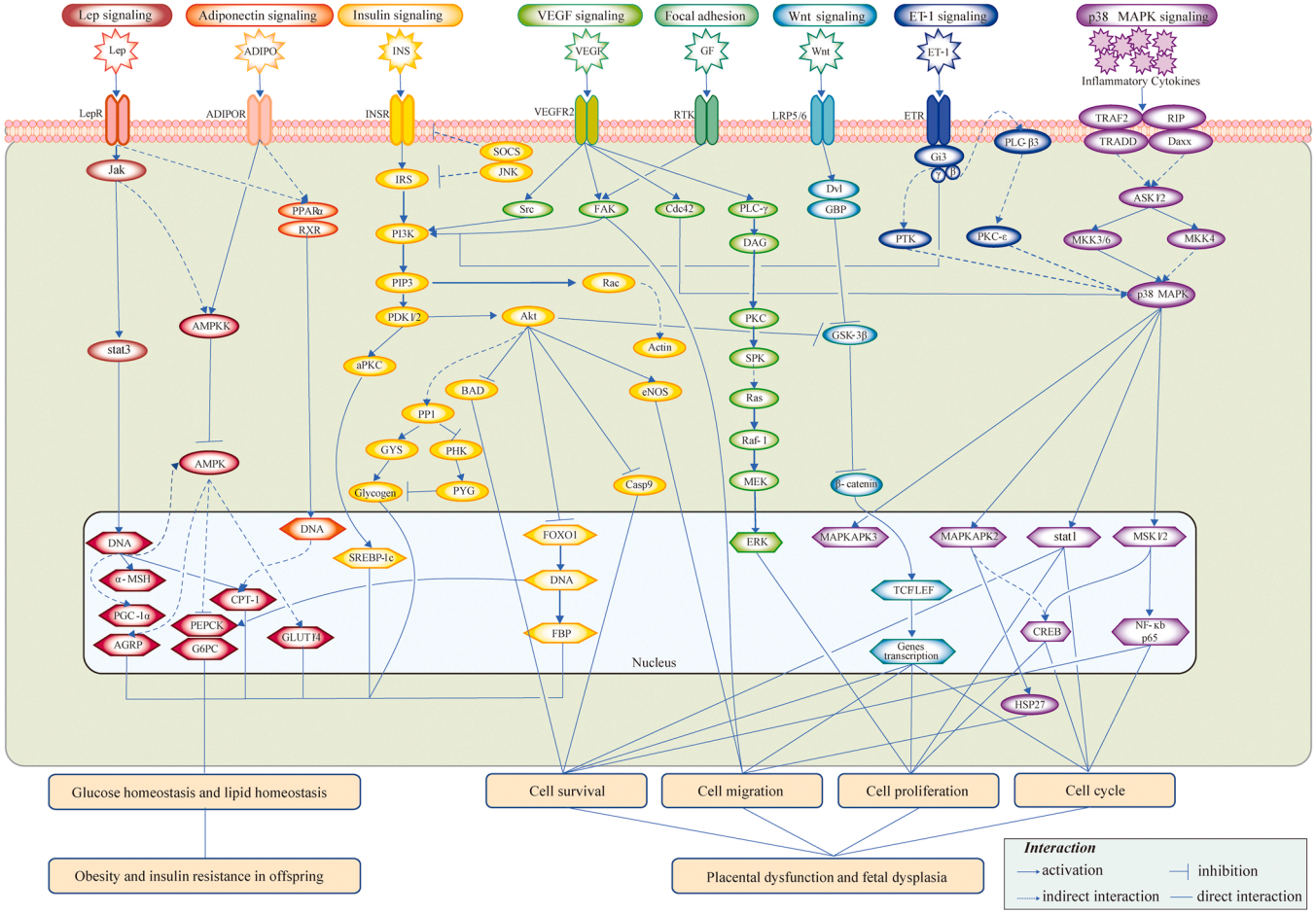


Fig. 1. Summary of main pathways affected by maternal obesity.

placenta-derived DNA in maternal circulation is reduced, and placenta-derived RNA levels are also lower than those in normal weight women. In the oocytes of obese mothers, LEP methylation increased and Ppar-α methylation decreased, and the differentially expressed mRNA was associated with lipid metabolism, accompanied by upregulation of pro-inflammatory and oxidative stress-related genes. The decreased expression of TIGAR in the protein profile also suggested the enhancement of oxidative stress. In addition, the obese group had increased levels of linoleic acid, stearic acid, and insulin in follicular fluid and enhanced ER stress in granulosa cells, resulting in decreased progesterone production, thus affecting oocyte maturation. In the placenta of obese mothers, increased ADIPOR methylation results in decreased ADIPOR signal transduction and abnormal expression of differentially expressed RNA and lipid metabolite-related proteins, suggesting a lipid-toxic environment in the placenta. Previous studies have reported abnormal methylation of placental development-related genes, downregulation of cytoskeletal pathways in the amniotic membrane, and downregulation of cytoskeletal remodeling-related proteins and cyclins (e.g., BRCA1) in the placenta using epigenetic, transcriptomic, and proteomic methods, respectively. These findings suggested that maternal obesity significantly affects placental development. Epigenetic studies of offspring livers revealed that lipid metabolism and liver fibrosis pathways were affected, development-related genes were differentially methylated, and miRNAs that regulate developmental timing and fat oxidation were downregulated. Transcriptomic results have also implicated the upregulation of liver fibrosis genes and enhanced inflammation and oxidative stress. Methylation levels of inflammation-related genes and inflammatory cytokines in the peripheral blood of offspring were also found to be significantly affected by maternal obesity.

Changes in LEP and PPARα methylation have been observed in epigenetic studies of obese mothers and their offspring. Combined with the differential expression of insulin receptor signal transduction-related genes in several offspring transcriptome studies, it can be concluded that maternal obesity can change the insulin sensitivity of the offspring. Differential expression of genes related to lipid and carbohydrate metabolism was observed at both the RNA and protein levels. In addition, proteomic analysis of the placenta of obese pregnant women has clarified the imbalance of proteins related to oxidative stress and inflammatory responses. Similar results were observed in the transcriptome data of the heart and liver of blastocyst fetuses and postnatal offspring. Disorders of myelin synthesis, synaptic proteins, neurotransmitter-related genes, and ER stress-related proteins may lead to nervous system dysplasia in offspring. The activation of antigen recognition, phagocytosis, and adaptive immune responses, as observed in proteomic studies, suggested an intestinal imbalance caused by maternal obesity, and observations of the intestinal microbiome of obese mothers and offspring verified the changes in intestinal flora. Maternal obesity causes changes in the transcriptional spectrum of skeletal muscles in offspring. Changes in the digestive and urinary systems were only backed by proteomics data. These single omics changes require further investigation.

In conclusion, the application of omics technology has helped us better explore the impact of maternal obesity during pregnancy on the maternal and fetal development environment as well as the offspring. However, further studies are still required to clarify certain aspects, such as the effect of maternal obesity on gene methylation in the peripheral blood of the offspring, and the effect of maternal obesity on the umbilical cord blood metabolome of the offspring, for which the conclusions reported are controversial. Experimental animals can be used as vehicles for further research to explore the link between maternal nutrition levels and multiomics changes in multiple organs of the mother and fetus. Given the obvious differences between regions, races, and individuals, human studies need to use larger cohorts and investigate multiple variables to eliminate as many confounders as possible to reach consistent and reliable conclusions. The maternal obesity-related gene loci and molecular markers discovered so far not only reveal the potential impact mechanism of maternal obesity but also provide a theoretical basis and potential intervention targets for clinically reducing the long-term complications of pregnancy and offspring.

Supplementary materials

All keywords of the searched literature:

Obesity, overweight, overnutrition, gestational weight gain, pregnancy, gestational, maternal, maternity, expectant, parturient, genomics, SNP, CNV, aCGH, NGS, sequencing, DNA methylation, histone modification, non-coding RNAs, ncRNA, transcriptomics, transcriptome, RNA-seq, transcriptome sequencing, RNA-seq sequencing, proteomics, proteome, metabonomics, metabolome, and metabolomics.

Funding

This work was supported by the National Key Research and Development Program (2021YFC2701003, 2021YFC2701104), the National Natural Science Foundation of China (Grant numbers: 82171649, 81871219, 81771595), the LiaoNing Revitalization Talents Program (XLYC1902099), and the 345 Talent Project of Shengjing Hospital.

CRediT authorship contribution statement

Duan Zhao: Conceptualization, Writing – original draft, Investigation. **Yusi Liu:** Writing – review & editing, Visualization. **Shanshan Jia:** Investigation. **Yiwen He:** Investigation. **Xiaowei Wei:** Investigation. **Dan Liu:** Writing – review & editing. **Wei Ma:** Writing – review & editing. **Wenting Luo:** Writing – review & editing. **Hui Gu:** Writing – review & editing, Project administration. **Zhengwei Yuan:** Conceptualization, Supervision, Funding acquisition.

Conflict of interest statement

The authors have no conflict of interests to disclose.

Acknowledgments

We would like to express our gratitude to all participants of this review.

References

[1] W.P. James, WHO recognition of the global obesity epidemic, Int. J. Obes. (2005) 32 Suppl 7 (2008) S120–S126, https://doi.org/10.1038/ijo.2008.247.
[2] *School of Public Health (Harvard T.H. Chan) Obesity causes.*, <⟨https://www.hsph.harvard.edu/obesity-prevention-source/obesity-causes/⟩>.
[3] Obesity and overweight, https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (2021).
[4] All About Adult BMI, <⟨https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html⟩> (2020).
[5] Body mass index - BMI, <⟨https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi⟩> (2020).
[6] V. Choo, WHO reassesses appropriate body-mass index for Asian populations, Lancet 360 (2002) 235, https://doi.org/10.1016/S0140-6736(02)09512-0.
[7] D. Aune, O.D. Saugstad, T. Henriksen, S. Tonstad, Maternal body mass index and the risk of fetal death, stillbirth, and infant death: a systematic review and meta-analysis, JAMA 311 (2014) 1536–1546, https://doi.org/10.1001/jama.2014.2269.
[8] Z. Yu, et al., Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis, PloS One 8 (2013), e61627, https://doi.org/10.1371/journal.pone.0061627.
[9] Z. Wang, et al., Maternal adiposity as an independent risk factor for pre-eclampsia: a meta-analysis of prospective cohort studies, Obes. Rev.: Off. J. Int. Assoc. Study Obes. 14 (2013) 508–521, https://doi.org/10.1111/obr.12025.
[10] S.Y. Kim, et al., Percentage of gestational diabetes mellitus attributable to overweight and obesity, Am. J. Public Health 100 (2010) 1047–1052, https://doi.org/10.2105/AJPH.2009.172890.
[11] S.Y. Chu, et al., Maternal obesity and risk of gestational diabetes mellitus, Diabetes Care 30 (2007) 2070–2076, https://doi.org/10.2337/dc06-2559a.

[12] C. Boots, M.D. Stephenson, Does obesity increase the risk of miscarriage in spontaneous conception: a systematic review, Semin Reprod. Med 29 (2011) 507–513, https://doi.org/10.1055/s-0031-1293204.
[13] M. Sugiura-Ogasawara, Recurrent pregnancy loss and obesity, Best. Pract. Res. Clin. Obstet. Gynaecol. 29 (2015) 489–497, https://doi.org/10.1016/j.bpobgyn.2014.12.001.
[14] V. O'Dwyer, et al., International variation in caesarean section rates and maternal obesity, J. Obstet. Gynaecol. 33 (2013) 466–470, https://doi.org/10.3109/01443615.2013.772128.
[15] A. Polic, T.L. Curry, J.M. Louis, The impact of obesity on the management and outcomes of postpartum hemorrhage, Am. J. Perinatol. (2020), https://doi.org/10.1055/s-0040-1718574.
[16] M. Blomberg, Maternal obesity and risk of postpartum hemorrhage, Obstet. Gynecol. 118 (2011) 561–568, https://doi.org/10.1097/AOG.0b013e31822a6c59.
[17] M. Lewandowska, Maternal obesity and risk of low birth weight, fetal growth restriction, and macrosomia: multiple analyses, Nutrients 13 (2021), https://doi.org/10.3390/nu13041213.
[18] E. Andreas, M. Reid, W. Zhang, K.H. Moley, The effect of maternal high-fat/high-sugar diet on offspring oocytes and early embryo development, Mol. Hum. Reprod. 25 (2019) 717–728, https://doi.org/10.1093/molehr/gaz049.
[19] M. Ueno, S. Liu, T. Kiyoi, M. Mogi, T. Sugiyama, Long-term impact of maternal dietary intervention on metabolic homeostasis in male offspring in mice, J. Nutr. Biochem. 108971 (2022), https://doi.org/10.1016/j.jnutbio.2022.108971.
[20] U.D. Wankhade, K.M. Thakali, K. Shankar, Persistent influence of maternal obesity on offspring health: Mechanisms from animal models and clinical studies, Mol. Cell Endocrinol. 435 (2016) 7–19, https://doi.org/10.1016/j.mce.2016.07.001.
[21] Y. Hasin, M. Seldin, A. Lusis, Multi-omics approaches to disease, Genome Biol. 18 (2017) 83, https://doi.org/10.1186/s13059-017-1215-1.
[22] H.H. Maes, M.C. Neale, L.J. Eaves, Genetic and environmental factors in relative body weight and human adiposity, Behav. Genet 27 (1997) 325–351, https://doi.org/10.1023/a:1025635913927.
[23] R.C. Whitaker, J.A. Wright, M.S. Pepe, K.D. Seidel, W.H. Dietz, Predicting obesity in young adulthood from childhood and parental obesity, N. Engl. J. Med. 337 (1997) 869–873, https://doi.org/10.1056/NEJM199709253371301.
[24] Y. Wang, J. Min, J. Khuri, M. Li, A systematic examination of the association between parental and child obesity across countries, Adv. Nutr. 8 (2017) 436–448, https://doi.org/10.3945/an.116.013235.
[25] A.J. Stunkard, T.T. Foch, Z. Hrubec, A twin study of human obesity, JAMA 256 (1986) 51–54.
[26] P.D. Gluckman, M.A. Hanson, T. Buklijas, F.M. Low, A.S. Beedle, Epigenetic mechanisms that underpin metabolic and cardiovascular diseases, Nat. Rev. Endocrinol. 5 (2009) 401–408, https://doi.org/10.1038/nrendo.2009.102.
[27] C.C. Wong, et al., A longitudinal study of epigenetic variation in twins, Epigenetics 5 (2010) 516–526, https://doi.org/10.4161/epi.5.6.12226.
[28] Z. Hochberg, et al., Child health, developmental plasticity, and epigenetic programming, Endocr. Rev. 32 (2011) 159–224, https://doi.org/10.1210/er.2009-0039.
[29] D. Lucifero, C. Mertineit, H.J. Clarke, T.H. Bestor, J.M. Trasler, Methylation dynamics of imprinted genes in mouse germ cells, Genomics 79 (2002) 530–538, https://doi.org/10.1006/geno.2002.6732.
[30] Z.J. Ge, et al., DNA methylation in oocytes and liver of female mice and their offspring: effects of high-fat-diet-induced obesity, Environ. Health Perspect. 122 (2014) 159–164, https://doi.org/10.1289/ehp.1307047.
[31] S.J. Bensinger, P. Tontonoz, Integration of metabolism and inflammation by lipid-activated nuclear receptors, Nature 454 (2008) 470–477, https://doi.org/10.1038/nature07202.
[32] G. Del Vecchio, et al., Cell-free DNA methylation and transcriptomic signature prediction of pregnancies with adverse outcomes, Epigenetics 16 (2021) 642–661, https://doi.org/10.1080/15592294.2020.1816774.
[33] A.G. Edlow, et al., Maternal obesity affects fetal neurodevelopmental and metabolic gene expression: a pilot study, PloS One 9 (2014), e88661, https://doi.org/10.1371/journal.pone.0088661.
[34] M. Mhatre, et al., The effect of maternal obesity on placental cell-free DNA release in a mouse model, Reprod. Sci. 26 (2019) 1218–1224, https://doi.org/10.1177/1933719118811647.
[35] M. Haghiac, et al., Patterns of adiponectin expression in term pregnancy: impact of obesity, J. Clin. Endocrinol. Metab. 99 (2014) 3427–3434, https://doi.org/10.1210/jc.2013-4074.
[36] L. Narapareddy, et al., Maternal weight affects placental DNA methylation of genes involved in metabolic pathways in the common marmoset monkey (Callithrix jacchus), Am. J. Prima 82 (2020), e23101, https://doi.org/10.1002/ajp.23101.
[37] Y. Nomura, et al., Global methylation in the placenta and umbilical cord blood from pregnancies with maternal gestational diabetes, preeclampsia, and obesity, Reprod. Sci. 21 (2014) 131–137, https://doi.org/10.1177/1933719113492206.
[38] P. Nogues, et al., Maternal obesity influences expression and DNA methylation of the adiponectin and leptin systems in human third-trimester placenta, Clin. Epigenetics 11 (2019) 20, https://doi.org/10.1186/s13148-019-0612-6.
[39] K. Mitsuya, et al., Alterations in the placental methylome with maternal obesity and evidence for metabolic regulation, PloS One 12 (2017), e0186115, https://doi.org/10.1371/journal.pone.0186115.
[40] D. Shrestha, M. Ouidir, T. Workalemahu, X. Zeng, F. Tekola-Ayele, Placental DNA methylation changes associated with maternal prepregnancy BMI and gestational weight gain, Int. J. Obes. (2005) 44 (2020) 1406–1416, https://doi.org/10.1038/s41366-020-0546-2.
[41] M. Massimiani, et al., Epidermal growth factor-like domain 7 promotes migration and invasion of human trophoblast cells through activation of MAPK, PI3K and NOTCH signaling pathways, Mol. Hum. Reprod. 21 (2015) 435–451, https://doi.org/10.1093/molehr/gav006.
[42] C.L. Whitehead, et al., EGFL7 gene expression is regulated by hypoxia in trophoblast and altered in the plasma of patients with early preeclampsia, Pregnancy Hypertens. 14 (2018) 115–120, https://doi.org/10.1016/j.preghy.2018.09.001.
[43] M. Ouidir, et al., Early pregnancy dyslipidemia is associated with placental DNA methylation at loci relevant for cardiometabolic diseases, Epigenomics 12 (2020) 921–934, https://doi.org/10.2217/epi-2019-0293.
[44] K.M. Thakali, Y. Zhong, M. Cleves, A. Andres, K. Shankar, Associations between maternal body mass index and diet composition with placental DNA methylation at term, Placenta 93 (2020) 74–82, https://doi.org/10.1016/j.placenta.2020.02.018.
[45] B.T. Mayne, et al., Accelerated placental aging in early onset preeclampsia pregnancies identified by DNA methylation, Epigenomics 9 (2017) 279–289, https://doi.org/10.2217/epi-2016-0103.
[46] T. Workalemahu, D. Shrestha, S.M. Tajuddin, F. Tekola-Ayele, Maternal cardiometabolic factors and genetic ancestry influence epigenetic aging of the placenta, J. Dev. Orig. Health Dis. 12 (2021) 34–41, https://doi.org/10.1017/S2040174419000801.
[47] S.J. Borengasser, et al., Maternal obesity enhances white adipose tissue differentiation and alters genome-scale DNA methylation in male rat offspring, Endocrinology 154 (2013) 4113–4125, https://doi.org/10.1210/en.2012-2255.
[48] K.M. Aagaard-Tillery, et al., Developmental origins of disease and determinants of chromatin structure: maternal diet modifies the primate fetal epigenome, J. Mol. Endocrinol. 41 (2008) 91–102, https://doi.org/10.1677/JME-08-0025.
[49] C.C. Li, et al., Maternal obesity and diabetes induces latent metabolic defects and widespread epigenetic changes in isogenic mice, Epigenetics 8 (2013) 602–611, https://doi.org/10.4161/epi.24656.
[50] M.A. Suter, et al., In utero exposure to a maternal high-fat diet alters the epigenetic histone code in a murine model, 463 e461-463 e411, Am. J. Obstet. Gynecol. 210 (2014), https://doi.org/10.1016/j.ajog.2014.01.045.
[51] U.D. Wankhade, et al., Enhanced offspring predisposition to steatohepatitis with maternal high-fat diet is associated with epigenetic and microbiome alterations, PloS One 12 (2017), e0175675, https://doi.org/10.1371/journal.pone.0175675.
[52] Z.J. Ge, et al., Maternal obesity and diabetes may cause DNA methylation alteration in the spermatozoa of offspring in mice, Reprod. Biol. Endocrinol.: RBE 12 (2014) 29, https://doi.org/10.1186/1477-7827-12-29.
[53] K.M. Thakali, et al., Maternal obesity and gestational weight gain are modestly associated with umbilical cord DNA methylation, Placenta 57 (2017) 194–203, https://doi.org/10.1016/j.placenta.2017.07.009.
[54] A. Soubry, et al., Newborns of obese parents have altered DNA methylation patterns at imprinted genes, Int. J. Obes. (2005) 39 (2015) 650–657, https://doi.org/10.1038/ijo.2013.193.
[55] X. Liu, et al., Maternal preconception body mass index and offspring cord blood DNA methylation: exploration of early life origins of disease, Environ. Mol. Mutagen 55 (2014) 223–230, https://doi.org/10.1002/em.21827.
[56] G.C. Sharp, et al., Maternal pre-pregnancy BMI and gestational weight gain, offspring DNA methylation and later offspring adiposity: findings from the Avon Longitudinal Study of Parents and Children, Int J. Epidemiol. 44 (2015) 1288–1304, https://doi.org/10.1093/ije/dyv042.
[57] C.L. Martin, et al., Maternal pre-pregnancy obesity, offspring cord blood DNA methylation, and offspring cardiometabolic health in early childhood: an epigenome-wide association study, Epigenetics 14 (2019) 325–340, https://doi.org/10.1080/15592294.2019.1581594.
[58] G.C. Sharp, et al., Maternal BMI at the start of pregnancy and offspring epigenome-wide DNA methylation: findings from the pregnancy and childhood epigenetics (PACE) consortium, Hum. Mol. Genet. 26 (2017) 4067–4085, https://doi.org/10.1093/hmg/ddx290.
[59] F. Guenard, et al., Differential methylation in glucoregulatory genes of offspring born before vs. after maternal gastrointestinal bypass surgery, Proc. Natl. Acad. Sci. USA 110 (2013) 11439–11444, https://doi.org/10.1073/pnas.1216959110.
[60] V.E. Velculescu, et al., Characterization of the yeast transcriptome, Cell 88 (1997) 243–251, https://doi.org/10.1016/s0092-8674(00)81845-0.
[61] R. Lowe, N. Shirley, M. Bleackley, S. Dolan, T. Shafee, Transcriptomics technologies, PLoS Comput. Biol. 13 (2017), e1005457, https://doi.org/10.1371/journal.pcbi.1005457.
[62] Z. Wang, M. Gerstein, M. Snyder, RNA-Seq: a revolutionary tool for transcriptomics, Nat. Rev. Genet 10 (2009) 57–63, https://doi.org/10.1038/nrg2484.
[63] L. Tang, P. Li, L. Li, Whole transcriptome expression profiles in placenta samples from women with gestational diabetes mellitus, J. Diabetes Investig. 11 (2020) 1307–1317, https://doi.org/10.1111/jdi.13250.
[64] M. Cao, et al., Differential mRNA and long noncoding rna expression profiles in umbilical cord blood exosomes from gestational diabetes mellitus patients, DNA Cell Biol. 39 (2020) 2005–2016, https://doi.org/10.1089/dna.2020.5783.
[65] A.P. Yadama, et al., Early-pregnancy transcriptome signatures of preeclampsia: from peripheral blood to placenta, Sci. Rep. 10 (2020) 17029, https://doi.org/10.1038/s41598-020-74100-1.
[66] S. Jiang, et al., Preeclampsia-associated lncRNA INHBA-AS1 regulates the proliferation, invasion, and migration of placental trophoblast cells, Mol. Ther. Nucleic Acids 22 (2020) 684–695, https://doi.org/10.1016/j.omtn.2020.09.033.

[67] M. Majewska, et al., Placenta transcriptome profiling in intrauterine growth restriction (IUGR), Int. J. Mol. Sci. 20 (2019), https://doi.org/10.3390/ijms20061510.
[68] G. Wang, et al., Whole-transcriptome sequencing uncovers core regulatory modules and gene signatures of human fetal growth restriction, Clin. Transl. Med 9 (2020) 9, https://doi.org/10.1186/s40169-020-0259-0.
[69] J. Yu, et al., Transcriptomic profile analysis of mouse neural tube development by RNA-Seq, IUBMB Life 69 (2017) 706–719, https://doi.org/10.1002/iub.1653.
[70] E. Soares, et al., Single-cell RNA-seq identifies a reversible mesodermal activation in abnormally specified epithelia of p63 EEC syndrome, Proc. Natl. Acad. Sci. USA 116 (2019) 17361–17370, https://doi.org/10.1073/pnas.1908180116.
[71] K.J. Stothard, P.W. Tennant, R. Bell, J. Rankin, Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis, JAMA 301 (2009) 636–650, https://doi.org/10.1001/jama.2009.113.
[72] S. Sohlberg, O. Stephansson, S. Cnattingius, A.K. Wikstrom, Maternal body mass index, height, and risks of preeclampsia, Am. J. Hypertens. 25 (2012) 120–125, https://doi.org/10.1038/ajh.2011.175.
[73] D. Farley, et al., Feto-placental adaptations to maternal obesity in the baboon, Placenta 30 (2009) 752–760, https://doi.org/10.1016/j.placenta.2009.06.007.
[74] U.N. Das, A.A. Rao, Gene expression profile in obesity and type 2 diabetes mellitus, Lipids Health Dis. 6 (2007) 35, https://doi.org/10.1186/1476-511X-6-35.
[75] K. Shankar, et al., Maternal obesity promotes a proinflammatory signature in rat uterus and blastocyst, Endocrinology 152 (2011) 4158–4170, https://doi.org/10.1210/en.2010-1078.
[76] M.L. Ruebel, et al., Obesity modulates inflammation and lipid metabolism oocyte gene expression: a single-cell transcriptome perspective, J. Clin. Endocrinol. Metab. 102 (2017) 2029–2038, https://doi.org/10.1210/jc.2016-3524.
[77] V.L. Clifton, Review: Sex and the human placenta: mediating differential strategies of fetal growth and survival, Placenta 31 Suppl (2010) S33–S39, https://doi.org/10.1016/j.placenta.2009.11.010.
[78] A. Gabory, et al., Maternal diets trigger sex-specific divergent trajectories of gene expression and epigenetic systems in mouse placenta, PloS One 7 (2012), e47986, https://doi.org/10.1371/journal.pone.0047986.
[79] T.J. Stuart, et al., Diet-induced obesity alters the maternal metabolome and early placenta transcriptome and decreases placenta vascularity in the mouse, Biol. Reprod. 98 (2018) 795–809, https://doi.org/10.1093/biolre/ioy010.
[80] T. Kunath, et al., Developmental differences in the expression of FGF receptors between human and mouse embryos, Placenta 35 (2014) 1079–1088, https://doi.org/10.1016/j.placenta.2014.09.008.
[81] S.R. McCoski, M.T. Vailes, C.E. Owens, R.R. Cockrum, A.D. Ealy, Exposure to maternal obesity alters gene expression in the preimplantation ovine conceptus, BMC Genom. 19 (2018) 737, https://doi.org/10.1186/s12864-018-5120-0.
[82] Y.W. Wang, et al., Maternal obesity related to high fat diet induces placenta remodeling and gut microbiome shaping that are responsible for fetal liver lipid dysmetabolism, Front Nutr. 8 (2021), 736944, https://doi.org/10.3389/fnut.2021.736944.
[83] C. Nardelli, et al., Characterization and predicted role of the microRNA expression profile in amnion from obese pregnant women, Int. J. Obes. (2005) 38 (2014) 466–469, https://doi.org/10.1038/ijo.2013.121.
[84] J. Saben, et al., Maternal obesity is associated with a lipotoxic placental environment, Placenta 35 (2014) 171–177, https://doi.org/10.1016/j.placenta.2014.01.003.
[85] J. Saben, et al., Early growth response protein-1 mediates lipotoxicity-associated placental inflammation: role in maternal obesity, Am. J. Physiol. Endocrinol. Metab. 305 (2013) E1–E14, https://doi.org/10.1152/ajpendo.00076.2013.
[86] L. Lassance, et al., Identification of early transcriptome signatures in placenta exposed to insulin and obesity, e641-611, Am. J. Obstet. Gynecol. 212 (2015) 647, https://doi.org/10.1016/j.ajog.2015.02.026.
[87] L. Lassance, M. Haghiac, J. Minium, P. Catalano, S. Hauguel-de Mouzon, Obesity-induced down-regulation of the mitochondrial translocator protein (TSPO) impairs placental steroid production, J. Clin. Endocrinol. Metab. 100 (2015) E11–E18, https://doi.org/10.1210/jc.2014-2792.
[88] J. Mele, S. Muralimanoharan, A. Maloyan, L. Myatt, Impaired mitochondrial function in human placenta with increased maternal adiposity, Am. J. Physiol. Endocrinol. Metab. 307 (2014) E419–E425, https://doi.org/10.1152/ajpendo.00025.2014.
[89] M.F. Bari, S. Ngo, C.C. Bastie, A.M. Sheppard, M. Vatish, Gestational diabetic transcriptomic profiling of microdissected human trophoblast, J. Endocrinol. 229 (2016) 47–59, https://doi.org/10.1530/JOE-15-0424.
[90] J.D. Aplin, Developmental cell biology of human villous trophoblast: current research problems, Int J. Dev. Biol. 54 (2010) 323–329, https://doi.org/10.1387/ijdb.082759ja.
[91] J.F. Mouillet, et al., The levels of hypoxia-regulated microRNAs in plasma of pregnant women with fetal growth restriction, Placenta 31 (2010) 781–784, https://doi.org/10.1016/j.placenta.2010.07.001.
[92] E.S. Vashukova, et al., Placental microRNA expression in pregnancies complicated by superimposed preeclampsia on chronic hypertension, Mol. Med Rep. 14 (2016) 22–32, https://doi.org/10.3892/mmr.2016.5268.
[93] G. Carreras-Badosa, et al., Dysregulation of placental miRNA in maternal obesity is associated with pre- and postnatal growth, J. Clin. Endocrinol. Metab. 102 (2017) 2584–2594, https://doi.org/10.1210/jc.2017-00089.
[94] C. Nardelli, et al., miR-138/miR-222 overexpression characterizes the miRNome of amniotic mesenchymal stem cells in obesity, Stem Cells Dev. 26 (2017) 4–14, https://doi.org/10.1089/scd.2016.0127.
[95] S. Sureshchandra, et al., Inflammatory determinants of pregravid obesity in placenta and peripheral blood, Front. Physiol. 9 (2018) 1089, https://doi.org/10.3389/fphys.2018.01089.
[96] S. Sen, C. Iyer, S.N. Meydani, Obesity during pregnancy alters maternal oxidant balance and micronutrient status, J. Perinatol. 34 (2014) 105–111, https://doi.org/10.1038/jp.2013.153.
[97] V. Azais-Braesco, G. Pascal, Vitamin A in pregnancy: requirements and safety limits, Am. J. Clin. Nutr. 71 (2000) 1325S–1333S, https://doi.org/10.1093/ajcn/71.5.1325s.
[98] S. Altmae, et al., Maternal pre-pregnancy obesity is associated with altered placental transcriptome, PloS One 12 (2017), e0169223, https://doi.org/10.1371/journal.pone.0169223.
[99] A. Okamoto, et al., IGFBP1 and Follistatin-like 3 genes are significantly up-regulated in expression profiles of the IUGR placenta, Placenta 27 (2006) 317–321, https://doi.org/10.1016/j.placenta.2004.12.007.
[100] Z. Zhang, H. Li, L. Zhang, L. Jia, P. Wang, Differential expression of beta-catenin and Dickkopf-1 in the third trimester placentas from normal and preeclamptic pregnancies: a comparative study, Reprod. Biol. Endocrinol.: RBE 11 (2013) 17, https://doi.org/10.1186/1477-7827-11-17.
[101] S. Sober, et al., Extensive shift in placental transcriptome profile in preeclampsia and placental origin of adverse pregnancy outcomes, Sci. Rep. 5 (2015) 13336, https://doi.org/10.1038/srep13336.
[102] N. Ghaffari, S. Parry, M.A. Elovitz, C.P. Durnwald, The effect of an obesogenic maternal environment on expression of fetal umbilical cord blood miRNA, Reprod. Sci. 22 (2015) 860–864, https://doi.org/10.1177/1933719114565032.
[103] K.M. Thakali, et al., Maternal pregravid obesity changes gene expression profiles toward greater inflammation and reduced insulin sensitivity in umbilical cord, Pedia Res 76 (2014) 202–210, https://doi.org/10.1038/pr.2014.72.
[104] X. Yan, et al., Maternal obesity downregulates microRNA let-7g expression, a possible mechanism for enhanced adipogenesis during ovine fetal skeletal muscle development, Int. J. Obes. (2005) 37 (2013) 568–575, https://doi.org/10.1038/ijo.2012.69.
[105] E.K. Stachowiak, et al., Maternal obesity affects gene expression and cellular development in fetal brains, Nutr. Neurosci. 16 (2013) 96–103, https://doi.org/10.1179/1476830512Y.0000000035.
[106] I. Bae-Gartz, et al., Running exercise in obese pregnancies prevents IL-6 trans-signaling in male offspring, Med Sci. Sports Exerc 48 (2016) 829–838, https://doi.org/10.1249/MSS.0000000000000835.
[107] S. Barrand, T.M. Crowley, R.J. Wood-Bradley, K.A. De Jong, J.A. Armitage, Impact of maternal high fat diet on hypothalamic transcriptome in neonatal Sprague Dawley rats, PloS One 12 (2017), e0189492, https://doi.org/10.1371/journal.pone.0189492.
[108] C. Napoli, et al., Maternal hypercholesterolemia during pregnancy promotes early atherogenesis in LDL receptor-deficient mice and alters aortic gene expression determined by microarray, Circulation 105 (2002) 1360–1367, https://doi.org/10.1161/hc1102.106792.
[109] A. Maloyan, et al., Identification and comparative analyses of myocardial miRNAs involved in the fetal response to maternal obesity, Physiol. Genom. 45 (2013) 889–900, https://doi.org/10.1152/physiolgenomics.00050.2013.
[110] E. Wing-Lun, et al., Nutrition has a pervasive impact on cardiac microRNA expression in isogenic mice, Epigenetics 11 (2016) 475–481, https://doi.org/10.1080/15592294.2016.1190895.
[111] J. Zhang, et al., 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 Genom. 10 (2009) 478, https://doi.org/10.1186/1471-2164-10-478.
[112] K.D. Bruce, et al., Maternal high-fat feeding primes steatohepatitis in adult mice offspring, involving mitochondrial dysfunction and altered lipogenesis gene expression, Hepatol. (Baltim., Md.) 50 (2009) 1796–1808, https://doi.org/10.1002/hep.23205.
[113] K. Shankar, et al., Maternal overweight programs insulin and adiponectin signaling in the offspring, Endocrinology 151 (2010) 2577–2589, https://doi.org/10.1210/en.2010-0017.
[114] M. Mischke, et al., Maternal Western-style high fat diet induces sex-specific physiological and molecular changes in two-week-old mouse offspring, PloS One 8 (2013), e78623, https://doi.org/10.1371/journal.pone.0078623.
[115] C. Lomas-Soria, et al., Maternal obesity has sex-dependent effects on insulin, glucose and lipid metabolism and the liver transcriptome in young adult rat offspring, J. Physiol. 596 (2018) 4611–4628, https://doi.org/10.1113/JP276372.
[116] J.L. Temple, P. Cordero, J. Li, V. Nguyen, J.A. Oben, A guide to non-alcoholic fatty liver disease in childhood and adolescence, Int. J. Mol. Sci. 17 (2016), https://doi.org/10.3390/ijms17060947.
[117] H. Wang, et al., Loss of TIGAR induces oxidative stress and meiotic defects in oocytes from obese mice, Mol. Cell. Proteom.: MCP 17 (2018) 1354–1364, https://doi.org/10.1074/mcp.RA118.000620.
[118] T. Liang, X. Jinglong, D. Shusheng, W. Aiyou, Maternal obesity stimulates lipotoxicity and up-regulates inflammatory signaling pathways in the full-term swine placenta, Anim. Sci. J. 89 (2018) 1310–1322, https://doi.org/10.1111/asj.13064.
[119] J.W. Li, J. Hu, M. Wei, Y.Y. Guo, P.S. Yan, The effects of maternal obesity on porcine placental efficiency and proteome, Anim.: Open Access J. MDPI 9 (2019), https://doi.org/10.3390/ani9080546.
[120] R. Fornes, et al., Mice exposed to maternal androgen excess and diet-induced obesity have altered phosphorylation of catechol-O-methyltransferase in the placenta and fetal liver, Int. J. Obes. (2005) 43 (2019) 2176–2188, https://doi.org/10.1038/s41366-018-0314-8.

[121] T. Kretschmer, et al., Maternal high fat diet-induced obesity affects trophoblast differentiation and placental function in micedagger, Biol. Reprod. 103 (2020) 1260–1274, https://doi.org/10.1093/biolre/ioaa166.
[122] K. Oliva, et al., The effect of pre-existing maternal obesity on the placental proteome: two-dimensional difference gel electrophoresis coupled with mass spectrometry, J. Mol. Endocrinol. 48 (2012) 139–149, https://doi.org/10.1530/jme-11-0123.
[123] D. Hoch, et al., Maternal obesity alters placental cell cycle regulators in the first trimester of human pregnancy: new insights for BRCA1, Int. J. Mol. Sci. 21 (2020), https://doi.org/10.3390/ijms21020468.
[124] V. Capobianco, et al., Proteome analysis of human amniotic mesenchymal stem cells (hA-MSCs) reveals impaired antioxidant ability, cytoskeleton and metabolic functionality in maternal obesity, Sci. Rep. 6 (2016) 25270, https://doi.org/10.1038/srep25270.
[125] A. Manousopoulou, et al., Are you also what your mother eats? Distinct proteomic portrait as a result of maternal high-fat diet in the cerebral cortex of the adult mouse, Int. J. Obes. (2005) 39 (2015) 1325–1328, https://doi.org/10.1038/ijo.2015.35.
[126] J.H. Lee, et al., Proteomic analysis of fetal programming-related obesity markers, Proteomics 15 (2015) 2669–2677, https://doi.org/10.1002/pmic.201400359.
[127] M. Morzel, et al., Protein expression in submandibular glands of young rats is modified by a high-fat/high-sugar maternal diet, Arch. Oral. Biol. 96 (2018) 87–95, https://doi.org/10.1016/j.archoralbio.2018.08.021.
[128] A. Suarez-Trujillo, et al., Maternal high-fat diet exposure during gestation, lactation, or gestation and lactation differentially affects intestinal morphology and proteome of neonatal mice, Nutr. Res. (N. Y., N. Y.) 66 (2019) 48–60, https://doi.org/10.1016/j.nutres.2019.03.014.
[129] E. Nusken, et al., Maternal high fat diet and in-utero metformin exposure significantly impact upon the fetal renal proteome of male mice, J. Clin. Med. 8 (2019), https://doi.org/10.3390/jcm8050663.
[130] S. Breuer, et al., Brain-restricted inhibition of IL-6 trans-signaling mildly affects metabolic consequences of maternal obesity in male offspring, Nutrients 13 (2021), https://doi.org/10.3390/nu13113735.
[131] D.R. Sessions-Bresnahan, K.L. Schauer, A.L. Heuberger, E.M. Carnevale, Effect of Obesity on the Preovulatory Follicle and Lipid Fingerprint of Equine Oocytes, Biol. Reprod. 94 (2016) 15, https://doi.org/10.1095/biolreprod.115.130187.
[132] D.R. Sessions-Bresnahan, A.L. Heuberger, E.M. Carnevale, Obesity in mares promotes uterine inflammation and alters embryo lipid fingerprints and homeostasis, Biol. Reprod. 99 (2018) 761–772, https://doi.org/10.1093/biolre/ioy107.
[133] E.G. Prates, J.T. Nunes, R.M. Pereira, A role of lipid metabolism during cumulus-oocyte complex maturation: impact of lipid modulators to improve embryo production, Mediat. Inflamm. 2014 (2014), 692067, https://doi.org/10.1155/2014/692067.
[134] J. Cox, S. Williams, K. Grove, R.H. Lane, K.M. Aagaard-Tillery, A maternal high-fat diet is accompanied by alterations in the fetal primate metabolome, Am. J. Obstet. Gynecol. 201 (281) (2009) e281–e289, https://doi.org/10.1016/j.ajog.2009.06.041.
[135] W.F. Grant, et al., Maternal high fat diet is associated with decreased plasma n-3 fatty acids and fetal hepatic apoptosis in nonhuman primates, PloS One 6 (2011), e17261, https://doi.org/10.1371/journal.pone.0017261.
[136] A. Koeberle, et al., Role of p38 mitogen-activated protein kinase in linking stearoyl-CoA desaturase-1 activity with endoplasmic reticulum homeostasis, FASEB J.: Off. Publ. Fed. Am. Soc. Exp. Biol. 29 (2015) 2439–2449, https://doi.org/10.1096/fj.14-268474.
[137] V. Sandler, et al., Associations of maternal BMI and insulin resistance with the maternal metabolome and newborn outcomes, Diabetologia 60 (2017) 518–530, https://doi.org/10.1007/s00125-016-4182-2.
[138] J. Shearer, et al., Maternal and cord blood metabolite associations with gestational weight gain and pregnancy health outcomes, J. Proteome Res. 20 (2021) 1630–1638, https://doi.org/10.1021/acs.jproteome.0c00854.
[139] M.L. Ruebel, et al., Associations between Maternal Diet, Body Composition and Gut Microbial Ecology in Pregnancy, Nutrients 13 (2021), https://doi.org/10.3390/nu13093295.
[140] S. Muralimanoharan, X. Gao, S. Weintraub, L. Myatt, A. Maloyan, Sexual dimorphism in activation of placental autophagy in obese women with evidence for fetal programming from a placenta-specific mouse model, Autophagy 12 (2016) 752–769, https://doi.org/10.1080/15548627.2016.1156822.
[141] M. Bucher, et al., Dyslipidemia, insulin resistance, and impairment of placental metabolism in the offspring of obese mothers, J. Dev. Orig. Health Dis. 12 (2021) 738–747, https://doi.org/10.1017/S2040174420001026.
[142] C. Fattuoni, et al., Preliminary metabolomics analysis of placenta in maternal obesity, Placenta 61 (2018) 89–95, https://doi.org/10.1016/j.placenta.2017.11.014.
[143] S. Furse, et al., A high-throughput platform for detailed lipidomic analysis of a range of mouse and human tissues, Anal. Bioanal. Chem. 412 (2020) 2851–2862, https://doi.org/10.1007/s00216-020-02511-0.
[144] O.C. Watkins, et al., Placental (13)C-DHA metabolism and relationship with maternal BMI, glycemia and birthweight, Mol. Med 27 (2021) 84, https://doi.org/10.1186/s10020-021-00344-w.
[145] M.C. Collado, E. Isolauri, K. Laitinen, S. Salminen, Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women, Am. J. Clin. Nutr. 88 (2008) 894–899, https://doi.org/10.1093/ajcn/88.4.894.
[146] N.T. Mueller, et al., Birth mode-dependent association between pre-pregnancy maternal weight status and the neonatal intestinal microbiome, Sci. Rep. 6 (2016) 23133, https://doi.org/10.1038/srep23133.
[147] J. Ma, et al., High-fat maternal diet during pregnancy persistently alters the offspring microbiome in a primate model, Nat. Commun. 5 (2014) 3889, https://doi.org/10.1038/ncomms4889.
[148] R.M. Pace, et al., Modulations in the offspring gut microbiome are refractory to postnatal synbiotic supplementation among juvenile primates, BMC Microbiol 18 (2018) 28, https://doi.org/10.1186/s12866-018-1169-9.
[149] R.J. Schlueter, et al., Prepregnant obesity of mothers in a multiethnic cohort is associated with cord blood metabolomic changes in offspring, J. Proteome Res. 19 (2020) 1361–1374, https://doi.org/10.1021/acs.jproteome.9b00319.