HHS Public Access

Author manuscript

FEBS J. Author manuscript; available in PMC 2022 June 09.

Published in final edited form as:

FEBS J. 2022 June ; 289(11): 3058–3071. doi:10.1111/febs.16173.

Prenatal exercise in fetal development: a placental perspective

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Abstract

Maternal obesity (MO) and gestational diabetes mellitus (GDM) are common in western societies, which impair fetal development and predispose offspring to metabolic dysfunction. Placenta is the organ linking the mother to her fetus, and MO suppresses the development of vascular system and expression of nutrient transporters in placenta, thereby affecting fetal development. For maintaining its proper physiological function, placenta is energy demanding, which is met through extensive oxidative phosphorylation. However, the oxidative capacity of placenta is suppressed due to MO and GDM. Recently, several studies showed that physical activity during pregnancy enhances oxidative metabolism and improves placental function, which might be partially mediated by exerkines, referring to cytokines elicited by exercise. In addition, as an endocrine organ, placenta secretes cytokines, termed placentokines, including apelin, superoxide dismutase 3 (SOD3), irisin and adiponectin, which mediate fetal development and maternal metabolism. Possible molecular mechanisms linking ME and placentokines to placental and fetal development are further discussed. As an emerging field, up to now, available studies are limited, mostly conducted in rodents. Given the epidemics of obesity and metabolic disorders, as well as the prevalence of maternal sedentary lifestyle, the effects of exercise of pregnant women on placental function and placentokine secretion, as well as their impacts on fetal development, need to be further examined.

Graphical Abstract

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Author contributions

S.A.C. and J.S.S. were involved in writing of the manuscript. M.D. reviewed and edited the manuscript.

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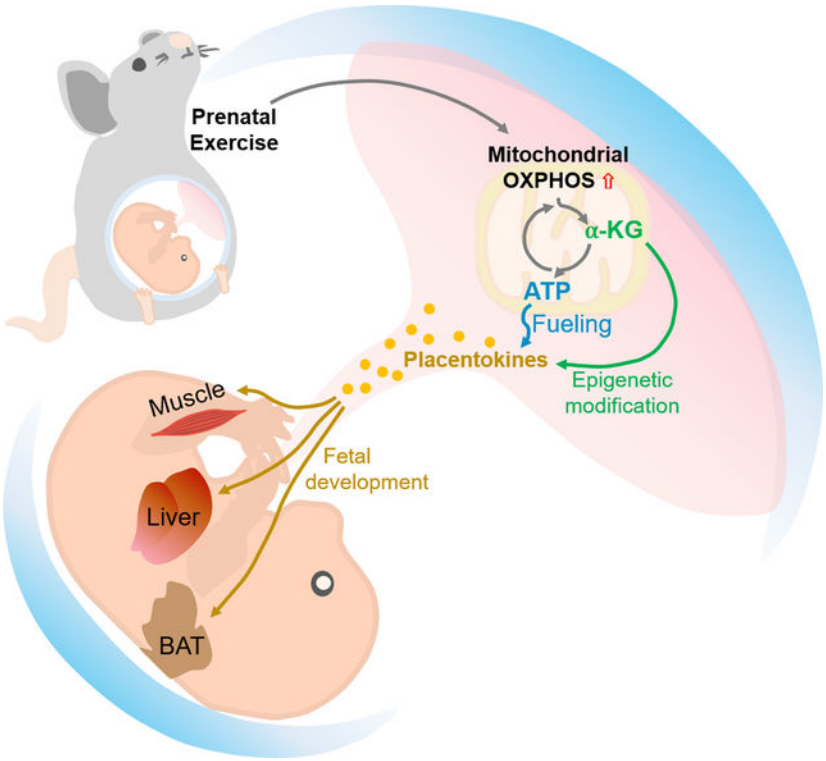
Conflict of interest

The authors declare no conflict of interest.



Placenta mediates the delivery of oxygen and nutrients from the mother to her fetuses, and also exerts endocrine functions. To maintain its physiological functions, placenta is energy demanding, which is mainly met by oxidative phosphorylation. Physical activity during pregnancy enhances placental oxidative metabolism and function, which is partially mediated by exercise-derived cytokines (exerkines). In addition, exercise stimulates the secretion of cytokines from placenta, termed as placentokines, which further mediate fetal development and may exert long-term effects on the metabolic health of offspring.

Keywords

Development; exerkine; maternal exercise; metabolism; placenta

1. Introduction

The population of women at reproductive age with overweight and obesity is rapidly increasing [1], accompanied with increased cases and rates of gestational hypertension (number of cases: 122,667 cases; incidence rate: 29.7%) and preeclampsia (number of cases: 132,800; incidence rate: 32.1%) in the United States in 2004 [2, 3]. Even worse, these deleterious maternal disorders affect fetal development, which predisposes children to metabolic diseases later in life [4, 5]. Furthermore, gestational diabetes mellitus and preeclampsia during pregnancy negatively affect birth size [6]. A number of previous reports have been reviewed, showing the association between birth size and impairment of glucose and insulin metabolism [7]. In particular, low birth weight predisposes offspring to increased insulin resistance and decreased insulin sensitivity, thereby leading to increasing incidence

of type 2 diabetes mellitus [8]. The accumulating evidence of developmental origins of adult diseases highlights the importance of gestational management.

Given placenta as a mediator between mother and fetus, a reasonable explanation of intergeneration effects is that the fetus absorbs more glucose and lipids delivered through the placenta, which promotes fetal white adipose tissue development and elicits chronic inflammation [9–11], while suppressing muscle and brown adipose tissue development [12, 13]. Another possibility is due to the decreased levels of cytokines released from placenta into the fetal circulation, affecting fetal development [14]. These placenta-oriented cytokines are named as placentokines (PLACENTa + cytOKINE) [15]. Several studies suggest the importance of placentokines in regulating placental and fetal development [16–18]. In addition to nutritional and hormonal changes, maternal obesity induces mitochondrial, dysfunction, which impairs the generation of adenosine triphosphate (ATP) by oxidative phosphorylation, a critical source of energy for placenta [19]. Inversely, these disorders can be effectively reversed by physical activity during pregnancy [20].

Exercise has been recognized as a medicine [21], which is partially mediated by exercise-induced cytokines, termed exerkines [22]. In addition, maternal exercise enhances the secretion of apelin, an exerkine, which improves placental and fetal development, partially through enhancing oxidative metabolism [16, 23]. Recent studies further suggest that mitochondrial oxidative metabolism has key roles in mediating placental function and placentokine secretion [24–26]. In this review, we focus on studies examining the importance of placental oxidative function in mediating fetal development. In addition, the endocrine roles of placenta, via placentokines, in mediating placental and fetal development are also discussed.

2. Placenta as a key regulator of fetal development and maternal/fetal interaction

2.1. Placental structure and vascular system

The placenta is a unique organ mediating maternal and fetal interaction. The chorionic villi which are made of two cellular layers: the outer syncytiotrophoblast layer and the inner cytotrophoblast layer, are the basic functional units of the placenta [27]. In the maternal side, the uterine and ovarian arteries deliver blood through the arcuate arteries, radial arteries and spiral arteries to the intervillous space [27, 28]. In the fetal side, a syncytiotrophoblast layer separates maternal blood from the fetal components, which contain additional cytotrophoblasts, connective tissue from extraembryonic mesoderm, and fetal capillary endothelium [27, 28]. Nutrients and oxygen in maternal blood crosses syncytiotrophoblasts into the fetal side, and then delivered to the fetus through the umbilical vein [27]. Insufficient oxygen delivery due to placental functional deficiency exposes fetuses to hypoxic stress and nutrient deficiency, restricting fetal development [29, 30]. The nutrient uptake by placenta is mediated by nutrient transporters, including glucose transporters (GLUTs), amino acid transporters and fatty acid transporters (FATPs) [31]. Glucose is a critical nutrient for fetal development [32], and fetal glucose uptake is mainly mediated by GLUT1 [33], which is highly expressed in placenta [34]. GLUT1 level is increased due to

insulin-dependent gestational diabetes mellitus (GDM) [35], whereas oxidative stress and SIRT1 activation down-regulate GLUT1 expression [36]. Hypoxic environment stimulates GLUT1 expression in placenta, which is mediated by hypoxia inducible factor-1a (HIF-1a) [37].

Successful pregnancy requires the proper development of placental vascular systems, which mediates gas and nutrient exchanges between the mother and her fetus [38]. The placental vascular system is developed through vasculogenesis and angiogenesis [39]. In the early stage of placental development, under the stimulus of vascular endothelial growth factor (VEGFA) primarily secreted by cytotrophoblasts, mesenchymal cells in the villous core are differentiated into hemangioblasts, which are then differentiated into endothelial cells (ECs) and hematopoietic cells (HSs). Then, these ECs organized into new vessels, referred as vasculogenesis [40]. Afterwards, the vascular system expands through angiogenesis [41, 42]. The major regulators of angiogenesis include placental growth factor and angiopoietins, in addition to oxygen tension as a key mediator [43].

2.2. Placenta as an endocrine organ

Beside nutrient and gas exchange, the placenta has a key endocrine function by producing various peptides and lipid hormones/cytokines [44]. Syncytiotrophoblasts secrete numerous placental hormones: human chorionic gonadotropin (hCG), progesterone, estrogen, placental lactogen and growth hormone, which are critical for maintaining pregnancy [45].

Human chorionic gonadotropin (hCG) is a heterodimeric protein with two linked subunits: α and β, which is an important hormone during early pregnancy, synthesized by syncytiotrophoblasts [46]. hCG binds to luteinizing hormone/choriogonadotropin receptor (LHCGR), a G protein-coupled receptor (GPCR), which activates G_s subunit and adenylyl cyclase (AC), concomitant with activation of protein kinase A (PKA) [47]. At the early stage of pregnancy, hCG promotes differentiation of cytotrophoblasts into syncytiotrophoblasts via stimulating PKA signaling [48]. hCG-induced endothelial cell migration promotes capillary formation in placenta [49] by stimulating placental VEGF signaling pathway [50] and microvascular endothelial cell proliferation to form the vascular system [51]; it also mediates maternal immunotolerance via stimulating the proliferation of uterine natural killer cells [52].

Leptin, a peptide hormone mainly secreted by adipose tissue, was introduced as a novel placenta-derived hormone, which regulates placental development and function through para/autocrine actions [53]. Placenta is one of the dominant organs secreting and releasing leptin into bloodstream [54]. Leptin has a pivotal role in mediating the feto-placental interface during the first trimester [55], which promotes trophoblast cell proliferation [56] and prevents apoptosis of trophoblast cells [57]. Moreover, leptin fundamentally acts as a modulator of immune system in the placenta [58], leading to enhancing innate and adaptive immunity in the placenta [59]. However, mechanisms stimulating leptin secretion in placenta remains to be defined.

Progesterone is a steroid hormone synthesized by oxidation of cholesterol inside mitochondria of syncytiotrophoblasts [60], and an endosome protein, metastatic lymph node

64 (MLN64), mediates cholesterol transferring into mitochondria [61]. In the mitochondrial inner membrane, the type 1 3beta-hydroxysteroid dehydrogenase (3β-HSD) isomerase, stimulated by p38 phosphorylation [62], converts pregnenolone into progesterone [63]. Progesterone is required for maintenance of pregnancy [64, 65].

Placental estrogens, made up of four steroid hormones: estrone (E_1), 17β-estradiol (E_2), estriol (E_3) and estetrol (E_4), are produced by corpus luteum during the first week of gestation [66], and these hormones are then secreted by the placenta [67]. The estrogens mediate several hormonal events during gestation via their nuclear estrogen receptors, ERα and β [45]; in addition, estrogens also activate a G-protein coupled receptor which mediate intracellular Ca^{2+} mobilization and PKA activation [68, 69]. ERα and β in the placenta are differentially activated: ERα is mainly expressed in the cytotrophoblasts, but ERβ in syncytiotrophoblasts [70]. As the most abundant estrogen, estradiol not only stimulates proliferation of mammary epithelial cells for preparation of breastfeeding [71], but also inhibits lipolysis and elevates fat storage [72]. In addition to estrogens, the placental lactogen (PL) and growth hormone (PGH) are placental polypeptide hormones, which are mainly synthesized within syncytiotrophoblasts [73, 74].

2.3. Importance of placental mitochondriogenesis in mediating its nutrient transportation and endocrine function

Placental functions, including substrate exchange and endocrine functions, as well as its development, require energy [75]. As multifunctional organelles, mitochondria produce ATP by oxidative phosphorylation [76]. Although ATP is produced during placental glycolysis, mitochondrial oxidative phosphorylation provides most ATP. As a result, pregnant women with mitochondrial dysfunction have high risks of pregnancy complications including pre-eclampsia, GDM and miscarriage [77]. Thus, maintaining mitochondrial homeostasis and oxidative function have profound impacts on placental function.

Mitochondrial adaptation in placenta occurs during pregnancy to support fetal development [78], which correlates with peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) activation in the labyrinth zone of placenta [79]. Consistently, markers of placental mitochondrial biogenesis, including the expression of PGC-1α and mitochondrial transcription factor A (TFAM), are up-regulated in response to maternal caloric restriction [80], suggesting maternal nutrient-dependent mitochondrial adaptation. In addition, a hypoxic environment leads to placental angiogenesis, which is partially mediated by mitochondrial oxidative stress and the production of mitochondrial reactive oxygen species [79, 81]. Placental angiogenesis improves the placental vascular system, which facilitates oxygen and nutrient delivery [82]. In short, the mitochondria-vascular system axis indirectly enhances the efficiency of nutrient delivery of placenta.

Besides nutrient transport efficiency, mitochondrial adaptation further regulates endocrine function of the placenta [45, 79]. Obesity and metabolic dysfunction during pregnancy increase risks of pregnancy complications such as pre-eclampsia and GDM [83], which might be associated with mitochondrial dysfunction of the placenta [84]. High fat diet-induced obesity during pregnancy decreases mitochondrial biogenesis [85, 86], which impairs placental function and fetal development [86]. Mitochondrial oxidative stress

negatively affects secretion of endocrine hormones by placental syncytiotrophoblasts [87]. In summary, placental mitochondrial oxidation is important for placental endocrine function, which is negatively affected by poor environmental conditions, including malnutrition, hypoxia and obesity during gestation [88].

3. Maternal exercise, cytokines and their impacts on placental development and function.

3.1. Maternal exercise, obesity and other physiological changes

The beneficial effects of exercise during pregnancy are affected by duration and types of physical activities [85, 89–93]. Depending on the duration and intensity, exercise can be systematically separated into aerobic and anaerobic. During aerobic exercise, ATP is generated through oxidative phosphorylation within mitochondria. Anaerobic exercise, on the other hand, utilizes glycolysis to provide energy. Furthermore, regular aerobic exercise enhances cardiovascular function and muscle endurance capacity [94], while anaerobic exercise stimulates muscle hypertrophy and strength, which is more beneficial to the secretion of myokines [22]. Aerobic exercise with 40 to 60% of maximal oxygen consumption rates (VO_2max) for 60 to 150 min/week is recommended for pregnant women [95, 96]. For anaerobic exercise, resistance exercise at moderate intensity is recommended for pregnant women [97–99]. In animal studies, voluntary wheel running (VWR) and forced treadmill exercise are commonly used for studying maternal exercise and fetal development [90–92], and the intensity of treadmill exercise during pregnancy is recommended at 40 to 65% VO_2max [14, 16, 85, 93]. In human studies, both aerobic and anaerobic exercise training with intensity ranging from light to high have been tested in pregnant women in previous studies [97, 100].

Generally, exercise is beneficial for individuals with metabolic diseases such as obesity, type 2 diabetes mellitus and cardiovascular disorders [101]. Consistently, the recent meta-analysis of clinical trials showed that both aerobic and anaerobic exercises during pregnancy reduce the risk of gestational obesity and diabetes [20]. Furthermore, maternal exercise (ME) reduces risk factors of macrosomia and fetal metabolic dysfunction [102]. Furthermore, maternal aerobic exercise improves infant physical capacity, rendering them to be physically more active and thereby reducing risk of obesity in the early life [103]. Offspring born to exercised mothers have lower body mass index (BMI) compared to sedentary mothers [104, 105].

Beside human studies, similar beneficial effects of ME were observed in animal studies [16, 106]. ME reduces body weight gain and improves glucose tolerance in both mothers and their offspring [91, 92]. These benefits might be due to enhanced energy expenditure, because ME has long-term effects in improving brown fat thermogenesis and skeletal muscle oxidative function of offspring [14, 85]. Consistently, accumulating data suggest that maternal exercise pre- and/or during gestation is beneficial for metabolic health of female and male offspring, improving glucose tolerance in tissues including liver, muscle and pancreas [20, 107].

Obesity and type 2 diabetes mellitus are recognized as risk factors for placental dysfunction [108], which predisposes metabolic dysfunctions in offspring, even when offspring has a healthy lifestyle [91, 92]. Indeed, mothers with pre-gestational obesity have higher risks for developing GDM and metabolic complications, which impairs placental exchange functions [109, 110]. Consistently, obese mothers show less efficient placental function and fetal macrosomia, likely due to excessive fatty acid supply [16, 111, 112]. Obesity severely impedes placental vascularization, which impairs oxygen and nutrient delivery into the fetus [16, 113]. Consistent with the previous studies reporting the beneficial effects of ME on placental development [114, 115], we found that gestational exercise enhanced placental vascularization and activated nutrient transportation, protecting against the adverse effect of maternal obesity on fetal development [16].

3.2. Definitions of exerkines

Organs and tissues secrete their unique cytokines which are termed as myokines (secreted by muscle), adipokines (by adipose tissue) and placentokines (by placenta) [22, 116]. Their secretion and biological functions can be stimulated by external factors such as physical activity [117]. Those cytokines secreted in response to exercise are named as exerkines (exercise + cytokines) [118]. Thus, myokines, adipokines and placentokines can also be exerkines when their secretion is stimulated by physical activities (Fig. 1). For example, irisin is not only a myokine, but also an adipokine [119]; its secretion is further elevated by exercise, functioning as an exerkine [120]. Thus, irisin is a myokine, an adipokine and an exerkine depending on the contexts.

3.3. Exerkines regulating placental development

Maternal exercise is beneficial to placental development. In clinical trials, maternal aerobic exercise enhances placental functional and reduces the risk factors of metabolic dysfunction in pregnant women [121, 122]. Consistently, maternal strenuous exercise positively associates with placental amino acid metabolism and transport activity in a clinical study [123]. Simultaneously, maternally derived exerkines optimize placental development and function [23]. Here we reviewed key exerkines regulating placental development and function.

Apelin is a peptide hormone, which binds Gαi protein-coupled receptor, APJ [85, 124], activating AMP-activated kinase (AMPK) [125]. Exercise-induced apelin activation stimulates fatty acid oxidation and improves metabolic homeostasis [126–128]. Furthermore, apelin-APJ activation improves placental function [129, 130]. Maternal exercise stimulates apelin secretion by placenta, which enhances vascularization and nutrient delivery efficiency of placenta [16, 131]. However, the direct role of apelin in mediating the effects of maternal exercise on placental function remains to be examined.

Irisin is a cleaved form of fibronectin type III domain-containing 5 (FNDC5), which is up-regulated by the activation of PGC-1α [120]. Exercise activates PGC-1α, which stimulates irisin secretion. As a novel hormone, irisin enhances energy expenditure of skeletal muscle and adipose tissue, improving glucose homeostasis [132–134]. Interestingly, irisin also promotes trophoblast differentiation and placental development [135], and its

level in circulation increases during gestation [135–137]. However, pregnancy complications such as preeclampsia and GDM are correlated with lower levels of circulatory irisin [136], suggesting that irisin may mediate placental function impaired due to obesity and GDM. Furthermore, irisin is highly secreted by ovary [138] and placenta themselves, suggesting its autocrine role for stimulating placental development [139].

Adiponectin, also known as AdipoQ, is an adipokine, with molecular weight at 30 kDa (ACRP30) [140]. Adiponectin is mainly secreted by white adipocytes [141]. Circulatory adiponectin level is negatively associated with obesity in both animals and humans [142, 143]. Exercise dramatically increases circulating adiponectin levels in patients with metabolic dysfunction, which might improve insulin sensitivity [144]. In addition, adiponectin is also secreted by placenta [145], which regulates cytotrophoblast differentiation [146] and potentially trophoblast invasion of the decidua [147]. Moreover, adiponectin administration during pregnancy reduces placental malfunction resulted from obesity [148] (Fig. 2).

3.4. Placentokines, fetal development and long-term effects on offspring

3.4.1. Maternal exercise-induced placentokines and fetal development—

Placentokines enhance fetal development and exert long-term effects on offspring metabolic health [129, 130, 136], consistent with a recent study showing that ME increased placental weight which negatively associated with the risk of preterm birth [149]. Here, we briefly review three placentokines with potentials as therapeutic targets, including apelin, superoxide dismutase 3 (SOD3) and adiponectin, which improve fetal development.

Exercise during pregnancy elevates apelin levels in fetal circulation and stimulates placentokine apelin expression [14], which enhances mitochondrial biogenesis and the expression of PGC-1α, facilitating functional development in offspring muscle [85]. At the same time, apelin activates fetal brown adipogenesis, which persists in the BAT of offspring, improving their metabolic health when challenged by HFD [14, 85].

Besides, it was recently discovered that maternal exercise elevates serum and placental SOD3 in both mice and women [150]. Secreted SOD3 releases into the fetal liver and activates AMPK/isocitrate dehydrogenase (IDH)/α-Ketoglutarate (α-KG)/ten-eleven translocation (TET) axis [151], which results in hypomethylation of promoter regions of glucose metabolic genes, thereby leading to improvement of offspring metabolic homeostasis [150].

Consistent with the role of SOD3 as a mediator, adiponectin administration during pregnancy regulates fetal growth and glucose homeostasis, and protects offspring against adverse effects due to maternal obesity [148]. Similarly, irisin is activated by exercise, which improves metabolic health of women [152], and also reduces fetal growth abnormalities [153]. Furthermore, FNDC5 genetic polymorphisms in mothers are related with preterm birth [154], which are associated with elevation of infant mortality and morbidity [155]. Consistently, small for gestational age infants have lower serum irisin levels compared to counterparts [156].

In summary, current knowledge about placentokines stimulated by maternal exercise remains very limited. Additional placentokines, together with mechanisms linking placentokines to placental and fetal development, need to be further explored.

3.4.2. Maternal exercise and long-term improvement of metabolic health in progeny.—ME is effective in preventing metabolic dysfunction of offspring born to obese mothers [91]. Notably, middle-aged offspring born to mothers fed HFD during pregnancy show impaired glucose tolerance [91, 92]. The expression of PGC-1α, a key regulator of mitochondrial biogenesis, was down-regulated in offspring muscle due to maternal HFD intake, which was prevented by ME [90]. In addition, ME further enhances mitochondrial biogenesis in offspring skeletal muscle by persistent activation of apelin-APJ axis, which is associated with hypomethylation in the promoter of *Ppargc1a* gene in offspring muscle [85]. Up to now, studies on the long-term effects of ME on offspring metabolic health remain very limited and most available studies were conducted in animals; clinical studies are needed (Fig. 3).

4. Placental oxidative metabolism in linking maternal exerkines, placentokines and placental function

Epigenetic modifications regulate gene expression [157]. DNA methylation and demethylation are key mechanisms regulating gene expression [158]. We recently found that ME activates AMPK and induces apelin secretion in placenta, which then releases into the fetal circulation to stimulate fetal brown fat and skeletal muscle development [14, 85]. Furthermore, we found that α-ketoglutarate (α-KG), a key mediator of the TCA cycle, mediates DNA demethylation the *Prdm16* promoter via facilitating ten-eleven translocation (TET)-mediated DNA demethylation, which enhances fetal brown fat development [14, 85, 151]. Thus, activation of mitochondrial oxidative capacity not only provides energy for maintaining placental function, but may also facilitate epigenetic modifications in genes needed for placental vasculogenesis and nutrient delivery [16]; in addition, placenta secretes placentokines to regulate fetal development [14, 159]. Supportively, another possible placentokine, irisin, regulates the differentiation of placental trophoblast cells primarily via activating AMPK [135], and cord irisin levels were decreased in newborns of small for gestational age [153]. Up to now, potential roles of placentokines linking ME to placental and fetal development remain poorly defined.

Besides, fuel consumption of the placenta is essential for placental development and maintenance of its physiological functions, which is supported by oxidative phosphorylation in placental mitochondria [160]. Dysfunction of placental respiratory capacity caused by preeclampsia and GDM, indeed, can severely impair placental structure and function [160]. Although exercise improves mitochondrial adaptation and oxidative phosphorylation in different tissues such as skeletal muscle and adipose tissue [161, 162], the evidence supporting exercise in improving placental oxidative metabolism and fetal development remains weak, and more studies, especially, human studies are needed (Fig. 4).

5. Conclusion and future perspectives

The importance of intrauterine condition on fetal development has been well established [163, 164]. Placenta, the only tissue linking the mother to her fetus, is critical for proper fetal development [28]. As potential mediators for placental development, ME stimulates the secretion of exerkines facilitating placental development. Placental oxidative metabolism is critical for maintaining placental function, and ME enhances placental mitochondrial biogenesis and vascularization, which is partially mediated by placentokines. Placentokines in response to exercise during pregnancy regulate placental development and function, as well as fetal development, which may generate long-term effects on offspring metabolic health. However, additional placentokines need to be further identified and the types of placental cells secreting placentokines need to be further examined. Understanding molecular mechanisms linking exercise-induced placentokines to placental function and fetal development, as well as long-term metabolic health of offspring will help to identify therapeutic targets for improving both maternal and offspring health.

Acknowledgements

This work was supported by the National Institutes of Health (NIH R01-HD067449).

Abbreviations

AC	Adenylyl cyclase
ACRP30	adipokine with molecular weight at 30 kDa
AMPK	AMP-activated kinase
3β-HSD	3beta-hydroxysteroid dehydrogenase
BMI	body mass index
E_1	estrone
E_2	17β-estradiol
E_3	estriol
E_4	estetrol
FNDC5	fibronectin type III domain-containing 5
GDM	gestational diabetes mellitus
GLUTs	glucose transporters
GPCR	G protein-coupled receptor
hCG	human chorionic gonadotropin
HIF-1a	hypoxia inducible factor-1a
LHCGR	luteinizing hormone/choriogonadotropin receptor

ME	maternal exercise
MO	maternal obesity
VO_2max	maximal oxygen consumption rates
MLN64	metastatic lymph node 64
SOD3	superoxide dismutase 3
TFAM	mitochondrial transcription factor A
PGC-1α	peroxisome proliferator-activated receptor γ coactivator-1α
PL	placental lactogen
PGH	placental growth hormone
PKA	protein kinase A
VEGFA	vascular endothelial growth factor
VWR	voluntary wheel running

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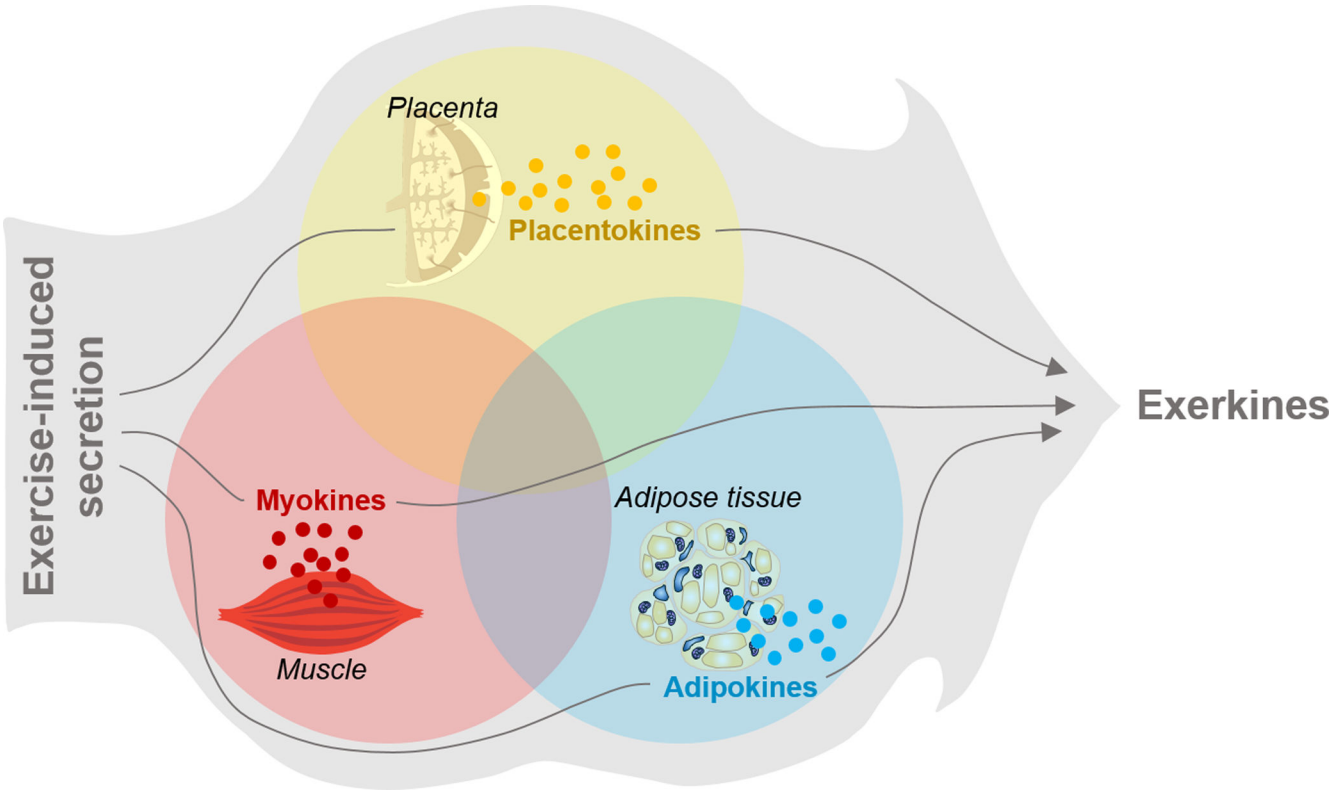

Figure 1.
Diagram showing the definition of exerkines and organ/tissue secreted cytokines.

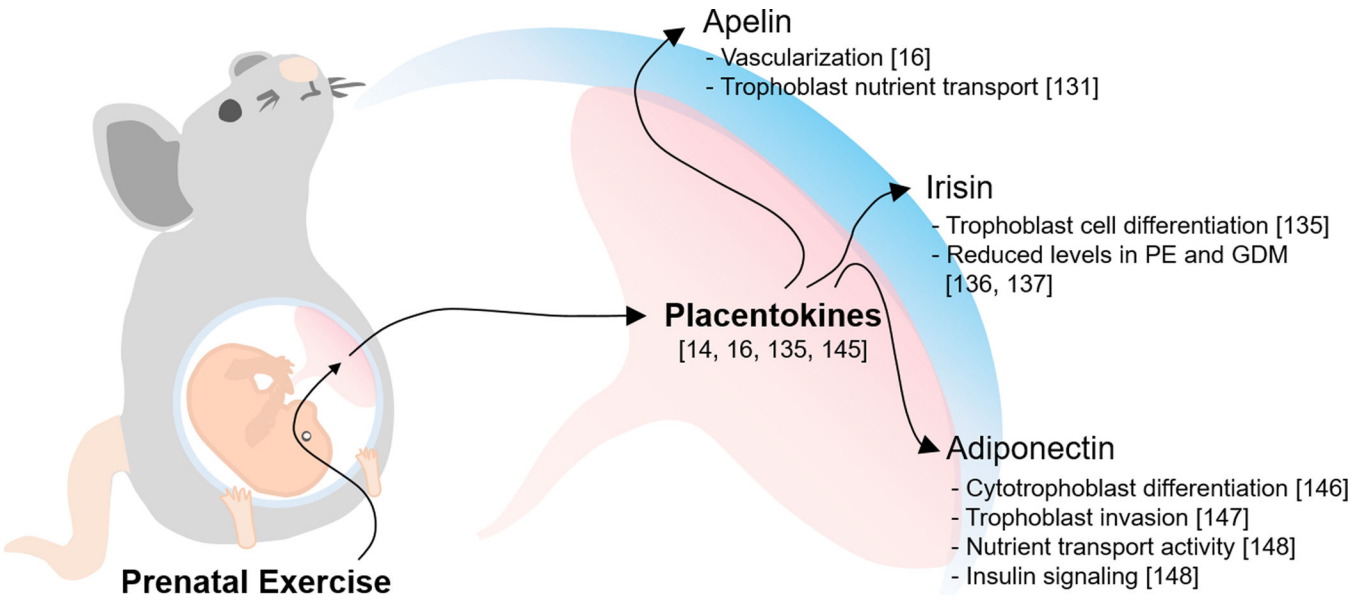

Figure 2.

Exercise-induced placentokines regulating placental development. Exercise adaptation during pregnancy positively stimulates the secretion of placentokines including apelin, irisin and adiponectin.

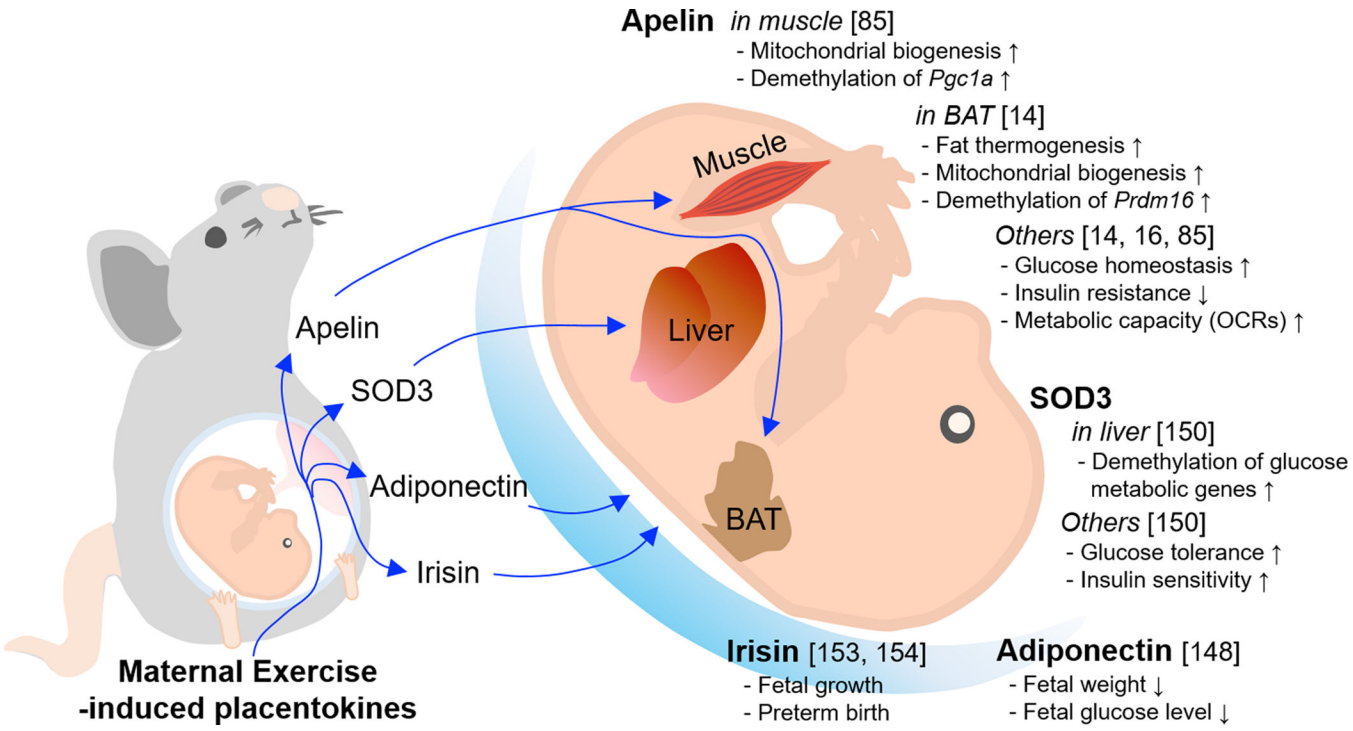

Figure 3.

The effects of maternal exercise-derived placentokines on fetal development and its long-term effects on the offspring.

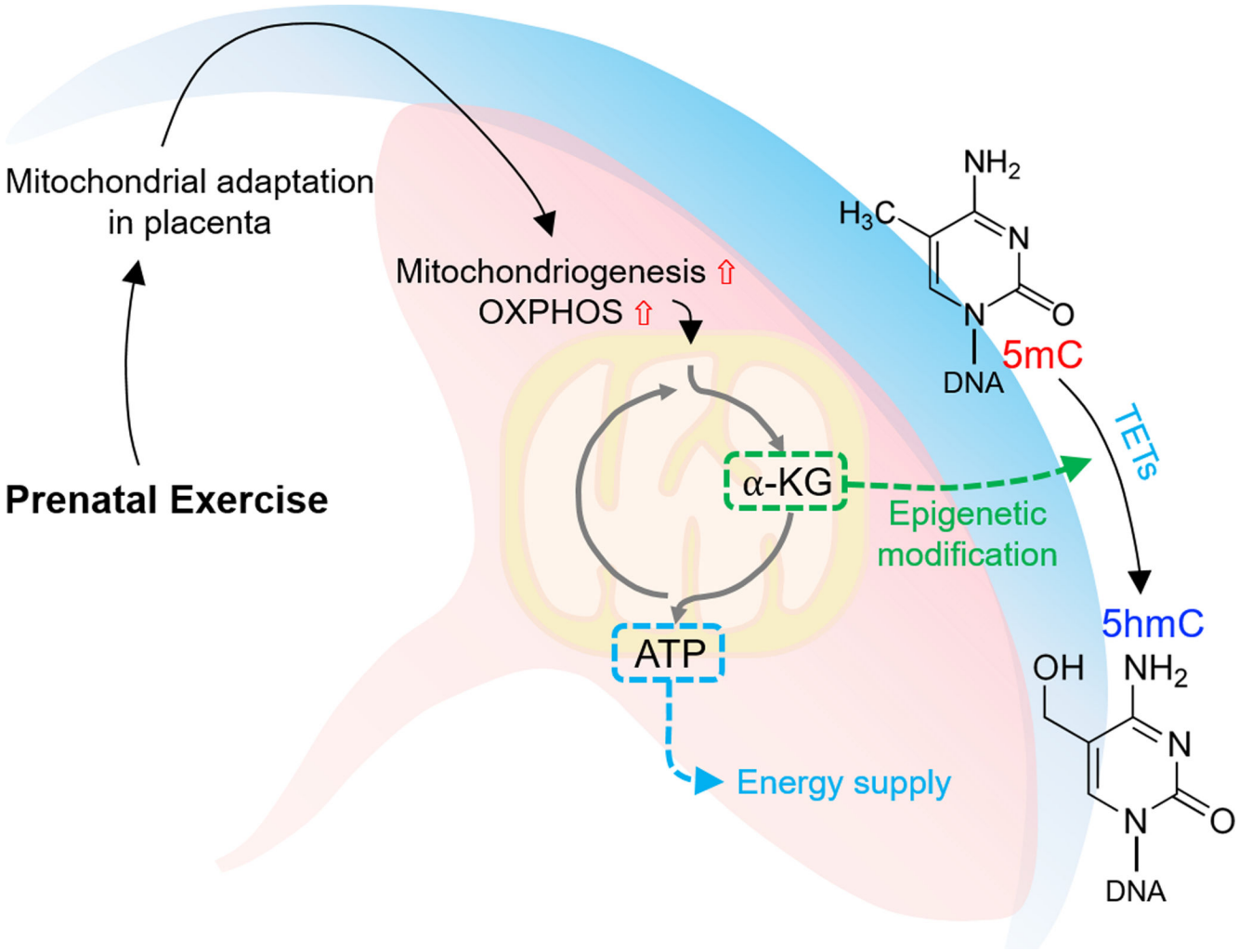

Figure 4.

Potential mechanisms regulating epigenetic modifications of developmental genes in placenta in response to exercise during pregnancy. Prenatal exercise-dependently induced placental mitochondrial adaptation via providing α-ketoglutarate (α-KG), which facilitates TETs-mediated DNA demethylation [conversion of 5-methylcytosine (5-mC) to 5-hydroxy-methylcytosine (5-hmC)]).