REPRODUCTION
REVIEW

Progress in the understanding of the etiology and predictability of fetal growth restriction

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Abstract

Fetal growth restriction (FGR) is defined as the failure of fetus to reach its growth potential for various reasons, leading to multiple perinatal complications and adult diseases of fetal origins. Shallow extravillous trophoblast (EVT) invasion-induced placental insufficiency and placental dysfunction are considered the main reasons for idiopathic FGR. In this review, first we discuss the major characteristics of anti-angiogenic state and the pro-inflammatory bias in FGR. We then elaborate major abnormalities in placental insufficiency at molecular levels, including the interaction between decidual leukocytes and EVT, alteration of miRNA expression and imprinted gene expression pattern in FGR. Finally, we review current animal models used in FGR, an experimental intervention based on animal models and the progress of predictive biomarker studies in FGR.

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Reproduction (2017) **153** R227–R240

Introduction

Fetal growth restriction (FGR) is a common pregnancy complication, which occurs in 5–10% of all pregnancies. It is the primary cause of perinatal mortality and morbidity. FGR is diagnosed by combining biometric measurement of fetal size with certain functional parameters to distinguish it from small for gestational age (SGA). Biometric measurement of fetal size signifying abdominal circumference or estimated fetal weight below the 3rd or 10th percentile indicates FGR. Functional parameters include either a solitary parameter, namely, absent end-diastolic flow (AEDF) in the umbilical artery or contributory parameters such as pulsatility index (PI) of the umbilical or uterine artery >p95, or cerebroplacental ratio (CPR) <p5 (Bamberg & Kalache 2004, Nardozza *et al.* 2012, Seravalli & Baschat 2015, Gordijn *et al.* 2016). Gestation is a critical period for developmental programming. Children surviving FGR are at a greater risk of developing neurodevelopmental dysfunction in childhood (Miller *et al.* 2016) and cardiovascular (Zohdi *et al.* 2015) and/or metabolic diseases in later life (Bale 2015). FGR also affects hormonal regulation and is associated with permanent changes in hormone levels. Additionally, individuals with FGR have a higher tendency to develop obesity (Ornoy 2011). Increased risk of cardiovascular disease results from increased workload of the fetal heart associated with postsystolic shortening and fetal exposure to higher levels of maternal cortisol (Jansson & Powell 2007, Crispi *et al.* 2014). FGR is a heterogeneous disease with varied clinicopathological subgroups. FGR preterm infants are more prone to postnatal infection with a disproportionately small thymus and low leukocyte, lymphocyte and macrophage counts (Longo *et al.* 2014). Late-onset FGR, which occurs after 32 weeks of gestation, is more complicated with less characteristic histological changes and its underlying mechanism still remains unknown (Mifsud & Sebire 2014). To date, timely and accurate prenatal detection of FGR is still a challenge. Preterm delivery is a major strategy to resolve this problem but may result in a nonviable fetus (Monier *et al.* 2015).

Emerging evidence indicates frequent association of placental insufficiency with the development of idiopathic FGR, signifying the absence of genetic or structural defects in the fetus. Placental insufficiency accounts for 70% of all FGR cases. It is caused by the failure of conversion of uteroplacental arteries, which is characterized by hypercoagulable state and placental thrombosis (Murthi *et al.* 2010, Higashijima *et al.* 2013). A new mouse model of FGR using selective ligation of one of the two uterine arteries mimicked multiple characteristics of placental vascular insufficiency in humans. Phenotype of this mouse model indicated

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ISSN 1470–1626 (paper) 1741–7899 (online)
DOI: 10.1530/REP-16-0287
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decreased birth weight of fetus. In addition, significant reduction was seen in placental labyrinth depth, volume and expression of placental growth factor (PGF), insulin-like growth factors-1 (IGF-1), and IGF-2 in placenta (Habli *et al.* 2013).

Placental dysfunction refers to the inefficient functioning of the placenta, which still meets the homeostatic requirements, resulting in babies born alive but small. Compared with placental dysfunction, placental failure is a more severe phenotype. Placental function is a critical regulator of fetal growth and development, and a mediator of fetal programming (Jansson & Powell 2007). During the early stage of pregnancy, the placenta is derived from the trophectoderm, the outer layer of blastocyst and functions as the fetal renal, respiratory, hepatic, gastrointestinal, endocrine and immune systems (Guttmacher *et al.* 2014, Lanner 2014). Comparative analysis of *Igf2* placental-specific P0 (*Igf2*-P0) knockout (KO) mice and *Igf2*-total KO mice indicate the specific role of placental dysfunction in determining the phenotypes of FGR. Since *Igf2*-P0 transcript is predominantly expressed in the fetal labyrinthine trophoblast, the key exchange barrier for nutrients, *Igf2*-P0 KO mice created by deletion of the U2 exon in the P0 promoter region show placental dysfunction and FGR because of an imbalance between fetal demand and placental supply. However, as the transcription of *Igf2* is unaffected in the fetus, *Igf2*-P0 KO mice eventually reach an equivalent size to wild type (WT) adults. Alternatively, in *Igf2*-total KO mice the expression of four main *Igf2* transcripts is inhibited in both the fetus and placenta. As a result, they develop FGR but remain small for life because of balanced but reduced fetal demand and placental supply (Mikaelsson *et al.* 2013).

Shallow extravillous trophoblast (EVT) invasion is associated with the development of FGR, resulting in abnormal placental formation and poor remodeling of the spiral artery. Defective remodeling of the spiral artery retains the contractile properties. This causes the hypoperfusion–reperfusion phenomenon that damages the villous architecture, eventually impairing the maternal–fetal exchange (Burton *et al.* 2009). Consequently, understanding the underlying mechanism of this pathological alteration is of great importance (Kadyrov *et al.* 2006). Invasion of EVT is a spatially- and temporally-dependent process controlled by a series of precise regulations (Zhu *et al.* 2014). This process is associated with interstitial trophoblast invasion, synthesis of nitric oxide and endothelial adhesion molecules in extravillous trophoblast, and the expression of selectins in maternal uterine endothelial cells. It is negatively regulated by macrophage-induced apoptosis of the trophoblast (Kaufmann *et al.* 2003). A fine balance between the production/activation of proteolytic pro-enzymes also characterizes it. Increased levels of matrix metalloproteinases (MMPs) with proteolytic functions, namely, collagenases, MMP-8, stromelysin-3 (MMP-11) and gelatinases (MMP-2 and -9) are reported to be related to FGR. Reduced levels of tissue inhibitors of metalloproteinases-1 (TIMP-1) and -3 are found in the placenta of FGR. They inhibit the MMPs by binding to their active sites (Zhu *et al.* 2014). In the present review, the pathological alterations associated with FGR, including dysregulated angiogenesis, microRNAs, imprinted gene, immune response in the placenta, and the interaction between EVT and decidual leukocytes are discussed. In addition, animal models, experimental intervention and potential predictive biomarkers of FGR are reviewed.

Pathological factors associated with FGR

Hypoxic stress and reduced placental angiogenesis in FGR

Angiogenesis is a major mechanism involved in the process of placentation. It is a complex biological process wherein new blood vessels are formed from pre-existing ones in response to hypoxia (Biyashev & Qin 2011). Normal pregnancy is associated with a balanced angiogenic state, while pregnancies complicated by FGR are often characterized by an anti-angiogenic bias. Accordingly, enhanced levels of anti-angiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt1), and decreased levels of proangiogenic factors, such as neuropilin-1 and placental growth factor (PGF) are seen in maternal circulation and the placenta (Girardi *et al.* 2006, Herraiz *et al.* 2015, Maulik *et al.* 2016).

The vascular endothelial growth factor (VEGF) family of growth factors and receptors comprise an important signaling pathway in angiogenesis. By binding to the respective receptors, these growth factors stimulate endothelial cell proliferation, migration and new vessel formation. Enhanced VEGF-A (commonly referred to as VEGF) gene activity in human placenta is associated with early-onset FGR. Rather than a key parameter in the etiology of FGR, increased placental VEGF-A gene activity is considered as a secondary response to hypoxic condition in the uterus (Szentpeteri *et al.* 2013). Hypoxic stress is common in placental insufficiency. Analyses of existing mice and rat models of antenatal maternal hypoxia-induced FGR, by Jang and coworkers concluded that 14% or lower level of oxygen for 3 days or more is sufficient to produce FGR in rodents. The duration of hypoxic exposure rather than the degree of hypoxia is significantly more effective in determining the development of FGR (Jang *et al.* 2015) (Fig. 1). During the first trimester of pregnancy, hypoxic intervillous space (IVS) resulting from plugs within maternal arteries formed by proliferative cytotrophoblast (CT) is pivotal for both placental and embryonic development. Abnormal maintenance of IVS hypoxia results in

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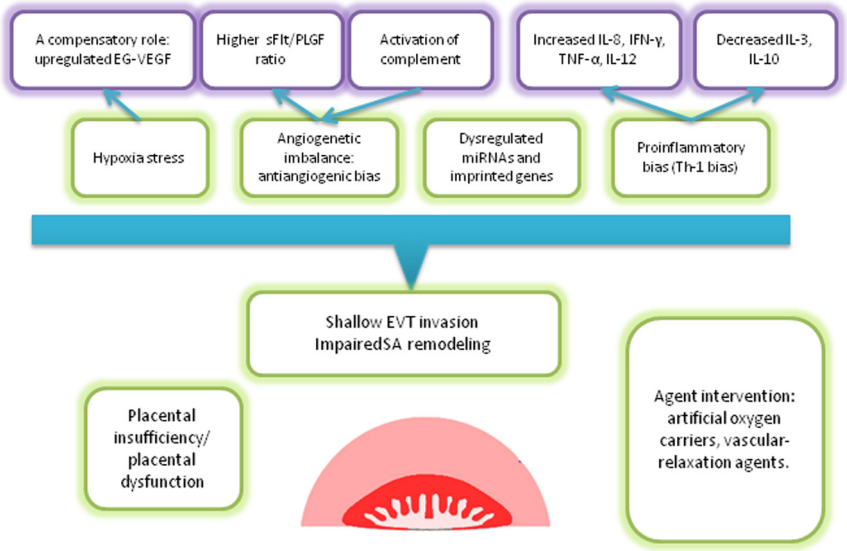

Figure 1 Schematic diagram showing that multiple pathologic states in the placenta of FGR, resulting in placental insufficiency or placental dysfunction. Some interventional strategies targeting to different pathological alterations are also shown.

shallow EVT invasion and is a major factor leading to FGR (Genbacev *et al.* 1997, James *et al.* 2006). In first trimester villous explants, hypoxia induces the expression of an E3 ubiquitin ligase, Mcl-1 ubiquitin ligase E3 (MULE), through hypoxia-inducible factor 1-alpha (HIF-1α) and promotes the development of FGR. HIF-1α levels are elevated in the placenta of FGR and further increase MULE expression, promoting trophoblast apoptosis by targeting the pro-survival Bcl-2 family member, Mcl-1 (Rolfo *et al.* 2012). Compared to normoxic chick embryos, the heart of hypoxic chick embryos showed left ventricular (LV) dilatation, loss of ventricular wall mass and increased number of apoptotic cardiomyocytes. Cardiomyopathy caused by embryonic hypoxia was found to be persistent in adult animals as well (Tintu *et al.* 2009).

Soluble fms-like tyrosine kinase-1 (sFlt-1), a soluble truncated variant of the type 1 VEGF receptor (Flt-1) is produced and secreted from the placenta to the maternal circulation. sFlt-1 binds to pro-angiogenic factors VEGF and PLGF and reduces their bioavailability. Thus, the most seriously dysfunctional placentas produce extremely high amounts of sFlt-1 from the earliest stages of pregnancy. Serum of early-onset preeclampsia patients have significantly higher sFlt-1/PGF ratio as compared with controls (Herraiz *et al.* 2015) (Fig. 1). Adenosine deaminase (ADA) irreversibly degrades adenosine, a regulator of cellular response to hypoxia, energy depletion and tissue damage. Iriyama and coworkers generated ADA-deficient mice with placenta that lacked ADA and showed that elevated placental adenosine was associated with significantly decreased fetal and placental weights, and impaired vasculature in the labyrinth zone. This was partly because of the elevated *Flt* mRNA in the placenta and sFlt-1 in maternal circulating. These results indicate an adverse impact of elevated placental adenosine on the fetus because of its ability to impair placental vasculature (Iriyama *et al.* 2015).

In FGR, during third trimester, endocrine gland-derived vascular endothelial growth factor (EG-VEGF), a novel growth factor secreted by placenta, is significantly upregulated in the placenta and circulating maternal serum. EG-VEGF interacts with prokineticin receptor (PROKR1), stimulates proliferation of CT and increases placental vascularization (Brouillet *et al.* 2013, Murthi *et al.* 2015). During the first trimester, placental expression of EG-VEGF is of vital importance as it creates a physiological hypoxic environment because of the production of functional trophoblast shells and plugs. However, by the end of the first trimester of pregnancy, elevated placental expression of EG-VEGF is deleterious as it inhibits the switch to normoxia in the placenta. Thus, elevated expression of EG-VEGF is considered a cause of FGR. In addition, EG-VEGF is induced by other predisposing factors causing FGR, such as hypoxia. Consequently, the role of EG-VEGF in FGR is still controversial and further studies are required to determine whether EG-VEGF/PROKR deregulation is a cause or consequence of FGR. In conclusion, angiogenesis is considered a necessary process for placentation, which is regulated by the balanced action of pro- and anti-angiogenic factors. In FGR, normal angiogenesis is disrupted because of impaired spiral artery (SA) remodeling in the placenta resulting in insufficient blood flow to the fetus and an aberrant maintenance of homeostasis under hypoxic conditions.

Modulation of fetal growth in FGR by aberrant inflammation and interaction between decidual natural killer (dNK) cells and EVT

FGR is characterized by altered maternal inflammation mediated by specific cytokines. A study group

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stimulated peripheral blood mononuclear cells (PBMC) with trophoblast (JEG cells) antigens and compared the cytokine profile of maternal lymphocytes between normal pregnancy and FGR group, and FGR group with and without placental insufficiency. Compared to the normal group, FGR group with placental insufficiency showed a stronger pro-inflammatory bias that was characterized by enhanced levels of pro-inflammatory cytokines interleukin-8 (IL-8), interferon gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), and decreased levels of anti-inflammatory cytokines IL-13 and IL-10. FGR group with placental insufficiency indicated a possible pro-inflammatory Th1-bias as seen from the elevated levels of IL-12, a Th1-inducing cytokine, than the FGR group without placental insufficiency (Raghupathy *et al.* 2012). A murine FGR model induced by multiple injections of antiphospholipid antibodies (aPLs) and mediated by Fc γ-receptor, revealed augmented levels of TNF-α in maternal plasma, deficient interstitial EVT invasion, impaired spiral artery remodeling and elevated placental nitrosative stress. In addition, deficient trophoblast invasion was associated with enhanced infiltration of macrophages around the spiral arteries with a subsequent increase in TNF-α, resulting in the regulation of trophoblast motility and migration (Kawaguchi *et al.* 2012, Cotechini *et al.* 2014*a*,*b*). FGR associated with antibody-dependent acquired immune response is frequently caused by diverse prenatal congenital infections. Some of these infections are caused by *Toxoplasma gondii*, rubella, cytomegalovirus (CMV), herpes simplex virus (HSV), *Varicella-zoster* virus (VZV) and *Treponema* (Longo *et al.* 2014). Among these, FGR caused by *Porphyromonas gingivalis* is well studied. *P. gingivalis* infects the periodontal tissue causing periodontitis. The infection activates the maternal immune and inflammatory responses, characterized by elevated levels of Th1-type cytokines, namely, TNF-α, IFN-γ and IL-2, and reduced levels of Th2-type cytokine IL-10 in the maternal serum, indicating a shift from placental anti-inflammatory Th2- to pro-inflammatory Th1-type of immune response (Lin *et al.* 2003*a*,*b*).

Normal pregnancy is considered a controlled systemic inflammatory state, as pregnant women have to maintain maternal-fetal immune tolerance (tolerance to non-self-antigens of the fetus). Pregnancy complications are often associated with complement activation, a component of the innate immune system. Frequent deposition of complement component 4d (C4d) in syncytiotrophoblast was detected in preeclampsia-FGR patients consistent with maternal vascular underperfusion (MVU) (Kim *et al.* 2015). Complement activation causes dysregulation of angiogenic factors required for normal vascularization leading to vascular underperfusion. *In vitro*, complement activation triggers the release of sFlt1 in human monocytes (Girardi *et al.* 2006). BPH/5, a mouse model with mild hypertension, revealed abnormal placentation, FGR, excessive C3 deposition and neutrophil infiltration in the ectoplacental cone at E6.5 and E8.5 respectively, consistent with reduced levels of VEGF in the placenta and enhanced levels of TNF-α released by neutrophils (Gelber *et al.* 2015). In addition, activation of mouse maternal innate immune system by intravenous administration of polyinosinic–polycytidylic acid (poly(I:C)), a nonpathogenic antigen, caused cerebellar neuropathology and behavioral abnormalities in the offspring, which were mediated by an increased IL-6 signaling in the placenta (Wu *et al.* 2017).

The decidua basalis is the main tissue site where cells from two individuals intermingle. It is differentiated from the endometrium and is characterized by the presence of EVT and a diverse population of leucocytes, such as dNK cells, decidual macrophages (dMϕ) and decidual T cells (dT) (Vesce *et al.* 2014). The decidua basalis is involved in implantation and placental development. This process is partly mediated by the close interaction between dNK cells and decidual EVT which is brought about by the action of natural killer cell receptors (NKR) and major histocompatibility complex (MHC) on their respective cell surfaces (Colucci *et al.* 2011). EVT migrating through deciduas can interact with decidual leukocytes and are specialized cells expressing human leukocyte antigen-G+ (HLA-G+). An *in vitro* co-culture model demonstrated that human EVT could transform CD4+ T cells to CD4+CD25^{HI}FOXP3+CD45RA+ resting regulatory T cells (Treg), thereby protecting the foreign fetal tissues from the maternal immune system (Tilburgs *et al.* 2015). Significantly reduced proportion of dNK cells were found in the human placentas obtained from pregnancies complicated by FGR, compared to control cases (Eide *et al.* 2006, Williams *et al.* 2009). Compared to peripheral blood NK cells, dNK cells exhibit distinct phenotypes characterized by the presence of predominant CD56 marker and enhanced expression of certain cell surface receptors including leukocyte immunoglobulin-like receptor B1 (LILRB1), killer-cell immunoglobulin-like receptors (KIRs), NKp46, NKG2D and NKp30, and sphingosine-1-phosphate receptor-5 (S1PR5) (El Costa *et al.* 2009). The behavior and function of dNK cells are regulated by the above-mentioned cell surface receptors in human (Fig. 2). Inhibition of S1P-S1PR5 pathway significantly decreases the expression of VEGF and prevents trophoblast migration induced by dNK cells (Zhang *et al.* 2013). The expression of the receptors is affected by the decidual microenvironment, namely, a steep decrease in the oxygen gradient from arteries to the intervillous space. In addition, such relative hypoxic environment regulates the EVT invasion-promoting capacity of dNK cells. Increased trophoblast invasion and network formation was associated with higher expression of the activating receptor NKG2D and secretion of invasion-promoting factors by dNK cells

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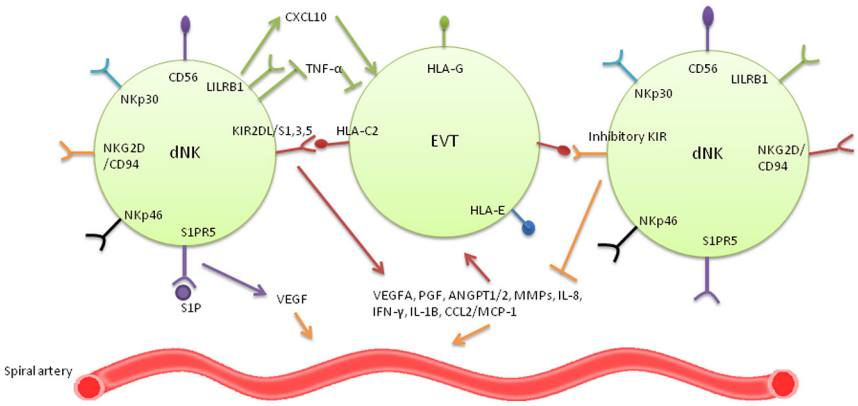

Figure 2 A close interaction between dNK cells and decidual EVT through NKR and MHC. EVT express human leukocyte antigen class I ligands (HLA-E, HLA-G, and HLA-C), recognized by receptors on dNK, such as CD94/NKG2, LILR, and KIR. Activating of S1P-S1PR5 pathway increases the expression of VEGF by dNK cells. Increased LILRB1 binding capacity are related to reduced expression of TNF-α and high expression of CXCL10. Binding frequency of inhibitory or activating KIR to HLA-C2 leads to decreased or increased secretion of cytokines, regulating angiogenesis and invasion of EVT.

cultured in 10% oxygen, rather than those cultured in 3 and 20% oxygen (Wallace *et al.* 2014). These results signify the role of oxygen concentration in the regulation of interaction between EVT and dNK cells.

The interaction between dNK cells and EVT regulates EVT invasion and spiral artery remodeling (Ain *et al.* 2003, 2004, Wallace *et al.* 2013). EVT express human leukocyte antigen class I ligands (HLA-E, HLA-G, and HLA-C) that are recognized by dNK cell surface receptors, such as CD94/NKG2, LILR and KIRs. Of these ligands and receptors, KIR and HLA-C genes encoding the KIR/HLA-C system are highly polymorphic. Thus, particular combinations of maternal KIR and fetal HLA-C, which could lead to birth weight difference, characterize each pregnancy. Accordingly, binding of the strongly inhibitory KIR to HLA-C2 inherited from the father leads to reduced secretion of cytokines from dNK cells, such as VEGF-A, PGF, angiopoietin-1 (ANGPT1), ANGPT2, MMPs, IL-8, IFN-γ, IL-1β and chemokine ligand 2 (CCL2/MCP-1), further causing low birth weight (Lima *et al.* 2014). Alternatively, activating KIR2DS1 together with fetal HLA-C2 is associated with increased birth weight (Fig. 2). Thus, maintenance of normal birth weight is dependent on the frequency of combination between activating or inhibitory KIR and HLA-C2 (Lash *et al.* 2011, Robson *et al.* 2012, Xiong *et al.* 2013, Moffett *et al.* 2015). First trimester of pregnancy with high uterine artery Doppler resistance index (RI), a high risk parameter for FGR, is associated with reduced number of dNK cells expressing activating KIR2DL/S1,3,5 and LILRB1 receptors, and reduced expression of HLA-C and HLA-G receptors on EVT in decidual tissue. dNK cells with decreased LILRB1 binding capacity showed higher expression of TNF-α and lower expression of CXCL10 (Moffett & Colucci 2015, Wallace *et al.* 2015). Together, these results suggest a pro-inflammatory nature of FGR placenta that causes placental damage and dysregulation of angiogenic factors manifested by complement deposition and placental underperfusion. Specifically, cytokines secreted by decidual immune cells, namely, dNK cells, modulate the behavior of EVT through antigen–antibody interaction. This is influenced by the decidual oxide environment, which eventually influences the birth weight.

Dysregulated microRNAs in FGR

microRNAs (miRNAs) are small (contains approximately 22 nucleotides), non-coding, single-stranded RNAs that function in gene silencing by targeting mRNAs at the post-transcriptional level. In a canonical way, miRNAs are first transcribed by RNA polymerase II. Two enzymes, DROSHA and DICER, process pri-miRNA to pre-miRNA and pre-miRNA to mature miRNA in the nucleus and cytoplasm respectively. Mature miRNAs are then transferred to an argonaute containing RNA inducing silencing complex (RISC) to silence targeted genes (Connerty *et al.* 2015).

Small non-coding RNAs are expressed in a tissue-specific manner and have emerged as major regulators of cellular processes involved in developmental biology, physiology, and pathology of the placenta, with potential clinical applications. The orchestrated regulation of miRNAs expressed in the placenta is important for placental morphology, structure and function. miRNA-21 enhances cellular proliferation, migration and invasion in HTR-8/SVneo immortalized trophoblast cells by altering the downstream targets, namely, by decreasing the expression of phosphatase and tensin homolog (PTEN), resulting in reduced levels of phosphorylated AKT (Chaiwangyen *et al.* 2015).

Most miRNAs specifically those expressed in human placenta are derived from two miRNA clusters, the chromosome 14-miRNA cluster (C14MC) and the chromosome 19-miRNA cluster (C19MC). Although C14MC produces many groups of miRNAs in the placenta, most of them are considered nonfunctional and the function of others remain unknown (Mouillet *et al.* 2015). Paternally inherited C19MC miRNAs are primate-specific and are the most abundant miRNAs in the human placenta and in the sera of pregnant women.

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Interestingly, higher expression of C19MC miRNAs is seen in villous trophoblasts than in invasive EVT. This is consistent with an *in vitro* observation, wherein, forced expression of C19MC miRNAs attenuated the migration of human EVT. The effects were mediated by C19MC miRNAs through their target genes associated with invasion, such as CXCL6, NR4A2 and FOXL2 (Xie *et al.* 2014). In addition, up-regulation of circulating C19MC microRNAs in the first trimester could predict the subsequent onset of gestational hypertension (Hromadnikova *et al.* 2014). However, Masuzaki and coworkers demonstrated that there was a significant decrease in certain placental-specific miRNAs located on C19MC in pregnancies complicated by FGR indicating that FGR may be associated with this downregulation. Nevertheless, no significant changes in the expression level of these placental-specific miRNAs were observed between the maternal plasma in FGR and normal pregnancies and the reason behind it still remains unknown (Higashijima *et al.* 2013).

The pathogenesis of FGR is related to dysregulation of miRNAs. The expression of miRNA-141 is elevated in the placenta of FGR pregnancies and is of high diagnostic value. miRNA-141 contributes to FGR by downregulating its target genes, *E2F3* and *PLAG1*. miRNA-141 decrease the mRNA level of *E2F3* and the mRNA and protein levels of PLAG1 (Tang *et al.* 2013). Li and coworkers reported enhanced expression of miRNA-424, a hypoxia-regulated miRNA, in the placenta of women with FGR. Compared to controls, the mRNA and protein levels of two of its target genes, mitogen-activated protein kinase 1 (MEK1) and fibroblast growth factor receptor 1 (FGFR1) in the placenta of women with FGR were significantly reduced. Since FGFR1 mediates the functions of VEGF, it is possible that increased miRNA-424 contributes to FGR by affecting the normal vascularity in the placenta (Huang *et al.* 2013). Significantly enhanced levels of a group of hypoxia-induced miRNAs are seen in the maternal blood of women diagnosed with FGR, suggesting increased expression and secretion of these miRNAs under hypoxic conditions in the placenta during FGR pathogenesis (Whitehead *et al.* 2013).

Several miRNAs have been demonstrated to regulate trophoblast invasion and migration through diverse downstream signaling pathways. miRNA-135b mediates low oxygen-induced reduction of extravillous trophoblast-derived HTR-8/SVneo cell invasion by inhibiting its target gene CXCL12, an invasion-promoting factor (Tamaru *et al.* 2015). MicroRNA-155 inhibits migration of human HTR-8/SVneo cell by downregulating cyclin D1 (Dai *et al.* 2012). miRNA-204 suppresses the invasion of BeWo cells by reducing the expression of its target gene MMP9 (Yu *et al.* 2015). miR-125b-1-3p inhibits trophoblast cell invasion by targeting S1PR1 in HTR8/SVneo cells (Li *et al.* 2014*a*). miR-210 inhibits trophoblast invasion in primary EVT cells partly through extracellular signal regulated kinase (ERK) signaling (Anton *et al.* 2013). miRNA-144 inhibits human trophoblast cell invasion by inhibiting titin and by subsequently reducing the expression of ERK1/2 and the activity of MMP2/9 (Liang *et al.* 2014). miR-29b inhibits the invasion and angiogenesis of trophoblast cells by inhibiting its target genes, myeloid cell leukemia sequence 1 (*MCL1*), *MMP2*, *VEGF-A* and *ITGB1* (integrin β1) genes (Li *et al.* 2013). miRNA-15b inhibits the invasion of HTR8/SVneo cells and the proliferation and tube formation of HUVECs by targeting the protein-encoding sequence of AGO2 mRNA, the effect of which on trophoblast cell invasion is determined by siRNA specific to AGO2. In an aberrant inflammatory condition mimicked by adding LPS to HTR8 cells, an increase of miR-15b expression mediated by LPS receptor TLR4 was seen which was consistent with the measured increased secretion of sFlt (Yang *et al.* 2016) (Fig. 3). This study indicates that the negative feedback loops between miRNA and AGO2 might play an important role in regulating the placentation process during the pathogenesis of FGR.

In contrast to the above-mentioned functions of miRNAs, miR-376c promotes migration and invasion of human HTR-8/SVneo cells by targeting Nodal and transforming growth factor-β (TGF-β) signaling. miR-376c targets activin receptor-like kinases *ALK5* and *ALK7*, encoding type I receptor for TGF-β and Nodal

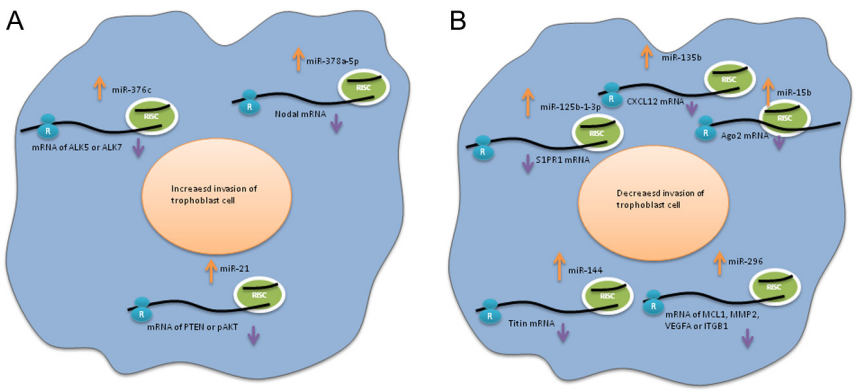

Figure 3 miRNAs linked to invasion of trophoblast cells. (A) Showing that three miRNAs are found to be able to promote invasion of trophoblast cells by degrading respective mRNAs; (B) showing that five miRNAs are found to decrease invasion of trophoblast cells by degrading respective mRNAs.

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respectively, thereby decreasing their expression (Fu *et al.* 2013). miR-378a-5p promotes trophoblast cell migration and invasion partly by targeting Nodal (Luo *et al.* 2012) (Fig. 3). Although the association of the above-mentioned miRNAs with FGR has not been investigated, there is a great possibility that these miRNAs are dysregulated in the placenta or plasma of pregnancies complicated by FGR, as impaired trophoblast invasion and/or migration is a primary cause of FGR. The validity of these altered miRNAs in maternal blood from pregnancies complicated by FGR, as a predictor of FGR, warrants further investigation.

Imprinted genes and epigenetic changes are involved in the control of birth weight and FGR pathogenesis

In mammals, mounting evidence indicate the role of imprinted genes in growth-related functions. Genomic imprinting is an epigenetically driven phenomenon that results in the preferential silencing of a copy of an autosomal gene while the other copy is expressed (Hutter *et al.* 2010). Imprinted genes that are exclusively expressed in the placenta play a role in the distribution of maternal resources to the fetus (Lambertini *et al.* 2011). According to the genetic conflict theory of imprinting, maternally imprinted genes that are paternally expressed, such as *Igf2*, *Peg1/Mest* and *Peg3*, promote fetal growth, while paternally imprinted genes that are maternally expressed, such as *H19*, *Igf2r*, *Cdkn1c*, *Phlda2* and *Grb10*, act as growth suppressors (Miguel Constância *et al.* 2002, Constancia *et al.* 2005, Tunster *et al.* 2011, Janssen *et al.* 2016) (Fig. 4). The disruption of paternally silenced gene *Grb10* in mice leads to overgrowth of both, the embryo and the fetus, because of modulation of placental size and efficiency in an *Igf2*-independent way (Charalambous *et al.* 2003, 2010). A mouse model overexpressing *Phlda2* exhibits late-onset and asymmetric restricted placental and fetal growth. In humans, placental PHLDA2 expression was significantly higher in pregnancies diagnosed with reduced fetal movements (RFM) resulting in the delivery of a growth restricted infant compared with a normal birth weight infant (Janssen *et al.* 2016).

To analyze the impact of imprinted genes on birth weight, a study group investigated the association between the expression of 108 established and putative imprinted genes expressed in human placenta and birth weight. Nine imprinted genes were positively associated with large for gestational age (LGA) status, including *MEST*, *BLCAP*, *H19*, *NDN*, *PLAGL1*, *DLK1*, *IGF2*, *MEG3* and *NNAT*, in an order of decreased odds ratio. *MEST* expression was negatively associated with a risk of SGA status, suggesting it as a novel biomarker for analyzing postnatal health outcomes (Kappil *et al.* 2015). Another study group found four downregulated genes (*CDKAL1*, *DHCR24*, *PLAGL1* and *ZNF331*) and five upregulated genes (*CCDC86*, *ILK*, *NNAT*, *PEG10* and *PHLDA2*) in the FGR placentas of human. Among them, *PLAGL1* and *ZNF331* were both paternally expressed genes and are in agreement with the 'parental conflict' theory. Two other genes (*NNAT* and *PEG10*) elevated in FGR placenta were paternally expressed, indicating that not all imprinted genes fit the 'parental conflict' theory (Diplas *et al.* 2009). Among these separate imprinted genes, paternally expressed *PLAGL1* seems to mediate a gene network for growth. As a transcription activator, PLAGL1 binds to the *H19* 39ems to mediate a ge *IGF2* and *H19*, and has a positive correlation with several growth-related genes, including *IGF2*, *H19*, *SLC2A4* and *PPARR1*. Interestingly, expression of PLAGL1 shows gender differences in FGR placenta. Total PLAGL1 expression was significantly lower in the placenta of FGR girls than those of boys. This difference was considered to be linked to the hormonal differences between the two sexes (Iglesias-Platas *et al.* 2014). Imprinted genes are involved in the regulation of placental development due to their effect on the trophoblast cell function. By silencing *PEG10* in trophoblast cells, Meng and coworkers demonstrated that PEG10 could enhance human trophoblast proliferation, differentiation and invasion, the latter

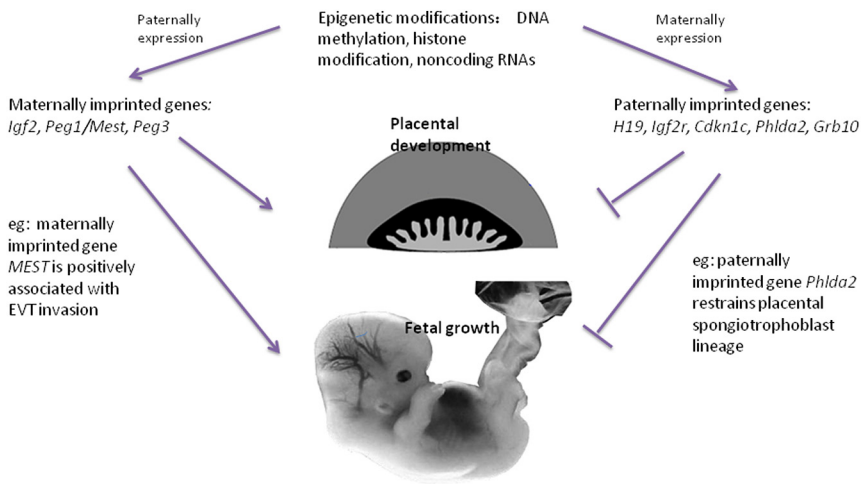

Figure 4 A diagram showing a genetic conflict theory of imprinting in mice. Imprinted genes regulated by epigenetic modifications play important roles in placental development and fetal growth. Maternally imprinted genes which are paternally expressed could promote placental development and fetal growth, while paternally imprinted genes which are maternally expressed play a contradictory role.

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was mediated by the up-regulation of MMP-2, MMP-9 and TIMP-1 (Chen *et al.* 2015). Significantly decreased invasive ability and migration were observed in EVT by knocking down the maternally imprinted gene *MEST* in HTR8/SVneo cells. This was partly because of the downregulation of the proteins N-cadherin and Vimentin (Peng *et al.* 2016). Paternally imprinted gene *Phlda2* restrained the placental spongiotrophoblast lineage and inhibited the corresponding hormone production in mice (Tunster *et al.* 2016).

Changes in epigenetic modifications contribute to stable alterations in gene expression. Imprinted genes are associated with multiple layers of epigenetic regulation, including DNA methylation at differentially methylated regions (DMRs) and histone modifications, resulting in monoallelic expression (Weaver & Bartolomei 2014). *IGF2* is one of the well-studied maternally imprinted genes expressed in maternal, fetal and placental tissues during early pregnancy contributing to fetal growth. Significantly decreased IGF2 mRNA levels were observed in the human placentas from pregnancies complicated by FGR. This was attributed to altered DNA methylation and relaxation of imprinting (Koukoura *et al.* 2011*a*). In a FGR mouse model manipulated by caloric restriction, the expression of glucose transporter, Glut3, a predominant isoform of trans-placental glucose transporter, was decreased in the placentas compared to the controls. This was partly due to the increased methylation of CpG island in the promoter of *glut3* gene and a series of epigenetic modulation, including enhanced MeCP2 binding to the CpG island, enhanced recruitment of histone deacetylase 2, and decreased Sp1 binding to the CpG island (Ganguly *et al.* 2014).

A recent study illustrated the relationship between epigenetic modifications and birth weight in human placenta. 5-Methylcytosine (5mC) enrichment at *IGF2* DMR0 and KvDMR, a CpG island located on *CDKN1C* gene, was independently and positively related to birth weight. 5-hydroxymethylcytosine (5hmC) enrichment within the *H19* gene body was also positively related to birth weight, although no significant relationship was found at any of the regions between the mRNA levels of *IGF2* and *CDKN1C* and 5mC or 5hmC (Piyasena *et al.* 2015). The *H19* imprinted gene clustered with the *IGF2* gene on human chromosome 11p15.5, is co-controlled with *IGF2* by differential methylation at an imprinting control region ICR1, located between *IGF2* and *H19*. DNA methylation at ICR1 on the paternal allele is permissive for *IGF2* gene expression. In contrast, the unmethylated maternal ICR1 activates *H19* expression. The placenta from women diagnosed with FGR showed significantly enhanced expression of H19 and decreased methylation in its promoter, which is consistent with a notion that *H19* produces an untranslated RNA that suppresses growth (Koukoura *et al.* 2011*b*, Piyasena *et al.* 2015). Although DNA methylation at ICR1 is proven to affect IGF2 expression, the methylation level at ICR1 is not significantly reduced in FGR placentas (Guo *et al.* 2008, Bourque *et al.* 2010). Together, these results indicate the important role played by imprinted genes that are highly expressed in the placenta and their epigenetic modifications in FGR pathogenesis.

Animal models and experimental intervention in FGR

In FGR, early delivery is the only intervention to reduce the risk of severe maternal complications and/or stillbirth of the baby. However, early delivery itself is associated with increased risk of neonatal mortality and morbidity. Therefore, there is a pressing need to develop new and effective treatments that can prevent or treat pregnancy complications like FGR (Cottrell & Sibley 2015). Developing new therapies for FGR requires the use of animal models to test the efficacy and safety of the therapy, and the characteristics of pregnancy in the particular animal model should be taken into consideration (Swanson & David 2015). Different types of animal models are used to study different types of human FGR. Asymmetrical FGR is studied in an animal model manipulated by knocking out the *NOS* gene. These animals show a phenomenon of 'brain sparing', a compensatory process wherein the fetus redistributes its cardiac output to maximize oxygen and nutrient supply to the brain at the expense of other structures such as the liver, abdomen and long bones (Cohen *et al.* 2015, Swanson & David 2015). Guinea pig shares several characteristics with humans. Pregnant guinea pigs exposed to hypoxia are considered an ideal model for placental vascular insufficiency. This animal model of placental hypoxia manifests certain abnormal placental developmental phenotypes, including increased trophoblast proliferation, and decreased migration and invasion of trophoblast into the spiral arteries (Thompson *et al.* 2016). In addition, the pregnant DBA/2J male mice-mated CBA/J or its sub-strain CBA/CaH female mice spontaneously develops FGR with placental histopathology, such as significantly decreased proportion of labyrinth, higher proportion of spongiotrophoblast and decreased placental efficiency measured as a ratio of placental weight to fetal weight. Importantly, this FGR animal model is ideal for the assessment and development of new therapeutics, since animal models created by genetic, surgical and pharmacological manipulation inadvertently introduce confounding factors when utilized for the same. Overall, an ideal animal model for studying the pathology of human placental insufficiency should recapitulate the changes in the placental morphology, alterations in genomic expression profile, cytokine milieu and transporter function (Habli *et al.* 2013).

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Numerous agents ameliorate FGR by targeting different pathological alteration, including decreased oxygen supply to fetus and impaired remodeling of spiral arteries. The application of artificial oxygen carriers, a kind of hemoglobin vesicles, which are nano-scale sized and blood-type antigens free, in a rat preeclampsia model induced by continuous administration of the NO synthetase inhibitor was demonstrated to reduce the hypoxic status of the placenta and fetus by supplying oxygen through the pathological narrow spiral arteries (Li *et al.* 2015). A set of vascular-relaxation agents, including antioxidant 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl (Tempol) (Stanley *et al.* 2012), Ligustrazine (Li *et al.* 2014*b*), Resveratrol (Poudel *et al.* 2013), and Sildenafil citrate (Dilworth *et al.* 2013), ameliorated blood rheological status and increased fetal weight in different FGR animal models (Fig. 1). However, considering the uncertainty regarding the safety and side effects of these agents in pregnant women, they do not find application in the clinic until further studies testify their efficacy and safety for pregnant women.

Prediction of FGR

In many cases, effective treatment strategy depends on timely diagnosis. Therefore, it is of great importance to develop a predictor for FGR with high specificity and sensitivity. Diverse pathological alterations play a predominant role in different gestations and hence, different predictive biomarkers are used to predict FGR in different gestations. Since placenta has an essential role in determining the outcome of pregnancy, detection of placental-derived factors in maternal blood has been suggested as a means to predict the fetal outcome of pregnancy. In the first trimester of pregnancy, increased maternal circulating IGFBP-4 is considered as a promising biomarker of FGR. It reflects an abnormally high IGFBP-4 protein content in the placental bed, consistent with the reduction of IGF-2 bioavailability. Importantly, it has a higher predictive value than many other biomarkers alone, including circulating human chorionic gonadotropin (b-hCG), α-fetoprotein (AFP), ADAM-12 (a disintegrin and metalloprotease-12), placental protein 13 (PP-13), soluble endoglin and s-Flt1 (Qiu *et al.* 2012). Pregnancy-associated plasma protein A (PAPP-A), a pregnancy related protein mediating IGFBP-4 degradation, measured in maternal serum in the first trimester, is reported to have a predictive value for FGR among Chinese population, especially severe FGR (Lo *et al.* 2015, 2016, Hansen *et al.* 2016). A prospective survey among low risk Asian population in the first trimester showed increased uterine artery pulsatility index (UPI) measured by uterine artery Doppler as the most important marker for FGR, compared with other biomarkers in maternal serum, such as PAPP-A and free β-hCG (Kumar *et al.* 2016). In clinically high-risk pregnancies, prediction of adverse perinatal outcomes using placental function testing is more effective in the second compared to the first trimester (Costa *et al.* 2008).

In the second trimester, sFlt1 can strongly predict severe adverse pregnancy outcome (APO) during 12–15 weeks of gestation among pregnant women with systemic lupus erythematosus (SLE) and/or antiphospholipid antibodies (APL) syndrome. Nevertheless, the combination of sFlt1 and PGF is the best predictive biomarker of APO during 16–19 weeks of gestation with low PGF and high sFlt1 among the same subjects (Kim *et al.* 2016). Increased expression of activating transcription factor-3 (ATF3) messenger RNA, a negative regulator of inflammation, was detected in

Table 1 Predictive biomarkers for FGR in different studies.

Biomarker	Function	Site of detection	Time of detection	Method of detection	Application	Reference
IGFBP-4	Reducing the bioavailability of IGF-2	Maternal blood	The first trimester	ELISA	Predicting FGR	Qiu *et al.* (2012)
PAPP-A	Mediating degradation of IGFBP-4	Maternal blood	The first trimester	ELISA	Predicting FGR	Lo *et al.* (2015, 2016), Hansen *et al.* (2016)
UPI	Reflecting utero-placental blood supply	uterine	The first trimester	Uterine artery Doppler	Predicting FGR	Kumar *et al.* (2016)
The ratio of sFlt-1 and PGF	Reflecting placental vascular function	Maternal blood	The second trimester	ELISA	Predicting severe APO	Kim *et al.* (2016)
ATF3 mRNA	A negative regulator of inflammation	Maternal blood	The second trimester	RT-PCR	Predicting FGR	Lim *et al.* (2016), Whitehead *et al.* (2016)
Pentraxin 3	Reflecting endothelial dysfunction in placenta	Maternal blood	The third trimester	ELISA	Differentiating physiological SGA from pathological FGR	Cozzi *et al.* (2012), Ibrahim *et al.* (2015)
Complement C3	C3 deposition in the placenta is associated with placental insufficiency	Placenta	All trimesters	MRI	Predicting placenta insufficiency	Girardi *et al.* (2015)

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maternal blood by RT-PCR at 26–30 weeks' gestation. It was found to be the most promising single biomarker for predicting late-onset FGR, compared to other significantly dysregulated mRNAs encoded by highly expressed genes of the placenta in the maternal blood (Lim *et al.* 2016, Whitehead *et al.* 2016).

In the third trimester, pentraxin 3 (PTX3), a C-reactive protein family member expressed in response to inflammatory stimuli is helpful in differentiating growth restricted babies into physiological SGA and pathological FGR. Pregnancies complicated by FGR have higher PTX3 concentrations in the maternal blood than controls. This increase was related to the severity of FGR, since increased PTX3 reflects endothelial dysfunction in the placenta (Cozzi *et al.* 2012, Ibrahim *et al.* 2015). A new, non-invasive approach involving binding to the C3 deposited tissue is proposed to predict placental insufficiency and abnormal fetal brain development in a mouse model representing antiphospholipid syndrome (APS). After intravenous injection of anti-complement C3-targeted ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles, which do not affect pregnancy outcome and liver function in the mother and the offspring, they bind to the C3 deposited tissue. This binding is observed as T2 and T2* relaxation time in magnetic resonance imaging (MRI). C3 deposition in the placenta is associated with placental insufficiency. C3 deposition in the brain is associated with cortical fetal brain abnormalities accompanied by increased anxiety-related behavior after birth. Thus, it is important to investigate whether there is excessive C3 deposition in the placenta and to determine the impaired degree of placentas during all trimesters (Girardi *et al.* 2015). The biomarkers mentioned above have been summarized in Table 1. Although several biomarkers are used as predictors for placental function and subsequent pregnancy outcome, the definitive predictive value of a biomarker has to be evaluated for exploring the possibility of using it in the clinic. Furthermore, a deeper understanding of the specific pathological alterations is needed. Convenience and feasibility has to be taken into account when translating basic research into clinical application.

Conclusion

FGR is a complex pathological status that predisposes the baby to a high risk of perinatal morbidity and mortality with long-term effects on neurological behavior and cardiovascular system of the fetus. Although the precise mechanism is still unknown, the adversity in the uterine during fetal development has a profound effect on the fetus. Maternal stress during pregnancy predisposes offspring to sex-biased neurodevelopmental disorder, which mostly occurs in boys (Bronson & Bale 2016). Placenta is of great importance during the process for it is located at the interface between the fetus and the mother, and plays a role in the exchange of oxygen and nutrients, buffering from deleterious maternal factors. In general, FGR is associated with abnormal placentation and an anti-angiogenic and pro-inflammatory bias. Furthermore, multiple layers of regulation are involved in the pathogenesis of FGR, including interaction between EVT and decidual leukocytes, altered expression of miRNA in placenta and maternal circulation, imprinted genes and their epigenetic modifications, among others. Although it is still unclear how these factors interact with each other to play a causal role in FGR, identifying these factors has helped us have a better knowledge of the physiology of fetal growth and the pathology of FGR. Furthermore, it is imperative to analyze valuable biomarkers and promising agents in a large cohort to examine whether they have a diagnostic/predictive or curative value, making it possible to recognize and treat FGR as early as possible, and to save the baby from an adverse pregnancy outcome.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work was supported by the National Basic Research Program of China (2012CB944903); the Ministry of Education Program for New Century Excellent Talents in University (NCET-12-0382).

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Received 19 June 2016
First decision 24 August 2016
Revised manuscript received 21 February 2017
Accepted 14 March 2017

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