Review

Maternal-Fetal Medicine®

OPEN

Basic Research Advances in China on Embryo Implantation, Placentation, and Parturition

Haili Bao[1], Haibin Wang[1,2,*]

Abstract

This review aimed to summarize the major progress in maternal-fetal medicine achieved by Chinese scientists in recent years. PubMed was systematically searched from January 2020 to November 2023. Publications that reported the progress in embryo implantation, placentation, and parturition made by Chinese scientists in the last 3 years were selected. The milestone events during gestation, embryo implantation, endometrial decidualization, placentation, and parturition are pivotal to a successful pregnancy. Embryo implantation requires intricate interactions between implantation-competent blastocysts and receptive endometrium. To adapt to pregnancy, endometrial stromal cells transform into specialized decidual cells, which occur spontaneously under the influence of ovarian hormones in humans but require the presence of embryos in mice. With embryonic development, the placenta forms to support fetal growth until parturition. The maternal-fetal interface is composed of diverse cell types, including endometrial decidual cells, placental trophoblast cells, endothelial cells, and various immune cells, a sophisticated interplay among which contributes to the maintenance of pregnancy. Near term, the uterus transitions from quiescence to contractility, in preparation for delivery. Disruptions to these events lead to pregnancy-related disorders such as repeated implantation failure, recurrent pregnancy loss, preeclampsia, fetal growth restriction, preterm birth, and infertility. In recent years, Chinese scientists have made prominent achievements in basic research on the aforementioned pregnancy events. Chinese scientists have made remarkable contributions to reproductive biology and maternal-fetal medicine research in recent years, highlighting future research directions in this field.

Keywords: Embryo implantation; Decidualization; Placentation; Maternal-fetal interface; Parturition

Introduction

In mammals, reproduction begins with fertilization. The zygote undergoes divisions and morphogenesis to form the blastocyst, which has two distinct cell lineages: the inner cell mass (ICM) and the trophectoderm.[1] The blastocyst interacts with the endometrium both physically and physiologically to initiate the process of embryo implantation. Acquisition of implantation competence by the blastocyst and establishment of uterine receptivity are prerequisites for successful implantation.[2,3] To accommodate embryo implantation, endometrial stromal cells undergo decidual transformation. In humans, decidualization is regulated by estrogen and progesterone during each menstrual cycle. In mice, however, the decidual reaction only occurs in the presence of embryos or artificial stimulus.[4,5] Peri-implantation pregnancy loss is relatively common in humans. The maximum chance of pregnancy in one menstrual cycle is limited to about 30%. Despite significant developments in assisted reproductive technologies, pregnancy success rates remain low, largely due to implantation failure and decidualization defects.[6]

Upon completion of implantation, the outer trophectoderm of the blastocyst begins to differentiate and eventually forms the placenta, a transient organ that exchanges gases, nutrients, and waste between the mother and fetus, and produces pregnancy-associated hormones and growth factors.[7,8] Serving an important role as the maternal-fetal interface, placental trophoblast cells interact with various other cell types, including decidual cells, immune cells, and endothelial cells, to facilitate vasculature remodeling and immune tolerance, contributing to pregnancy maintenance of until parturition.[9] Dysregulation of cell compositions and behaviors, such as insufficient trophoblast invasion, defective spiral arterial remodeling, and compromised immune modulation, give rise to the development of pregnancy-related diseases, including recurrent pregnancy loss (RPL), fetal growth restriction, and preeclampsia, a severe pregnancy-related disorder characterized by hypertension and proteinuria.[7]

Elucidating the molecular regulatory mechanism underlying embryo implantation, endometrial decidualization, placentation, and parturition is key to revealing the pathogenesis of pregnancy-related disorders. In this review, we summarize the recent contributions to maternal-fetal medicine by Chinese researchers, which may help advance our understanding of the pathogenesis of pregnancy-related complications.

[1]Fujian Provincial Key Laboratory of Reproductive Health Research, Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen 361102, China; [2]State Key Laboratory of Vaccines for Infectious Diseases, Xiang An Biomedicine Laboratory, School of Medicine, Xiamen University, Xiamen 361102, China.

* Corresponding author: Haibin Wang, Fujian Provincial Key Laboratory of Reproductive Health Research, Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xiamen University, Xiamen 361102; State Key Laboratory of Vaccines for Infectious Diseases, Xiang An Biomedicine Laboratory, School of Medicine, Xiamen University, Xiamen 361102, China. E-mail: haibin.wang@vip.163.com

Maternal-Fetal Medicine (2024) 6:1

Received: 23 October 2023 / Accepted: 14 November 2023

First online publication: 16 January 2024

http://dx.doi.org/10.1097/FM9.0000000000000210

Recent progress in embryo implantation research, in humans and mice

Embryo implantation requires synchronization between the acquisition of implantation competency by the blastocyst and the establishment of a receptive state by the endometrium. This takes place within a limited time period referred to as the implantation window. Embryo implantation involves intricate physical and physiological interactions between the embryo and maternal endometrium, which consists of three stages: apposition, adhesion/attachment, and penetration. Disturbances during the peri-implantation period adversely influence subsequent gestation events and, ultimately, pregnancy outcome.[2,3]

In humans

Ethical restrictions and the lack of an appropriate in vitro culture system challenge studies of embryo implantation in humans, and thus, our current understanding of peri-implantation embryonic development remains obscure. In recent years, Chinese scientists have made great contributions to the development and improvement of three-dimensional (3D) embryo culture, which mimics in vivo developmental landmarks and 3D structures, enabling in vitro study of human embryogenesis.[10] An embryo-like assembloid (E-assembloid) assembling naive embryonic stem cells and extraembryonic cells, developed by Ai *et al.*[11] offers a useful model for disentangling cellular behaviors and signaling interactions in pre-gastrulation human embryos. Another study by Gong *et al.*[12] described an embedded 3D culture system that allows the extended ex utero culture of cynomolgus monkey embryos. Ex utero cultured monkey embryos largely recapitulated key events of in vivo development, providing a robust and reproducible platform for studying primate embryogenesis ex utero. Meanwhile, with the rapid development of single-cell RNA sequencing and single-cell multiomics sequencing, peri-implantation embryos have been systematically analyzed, providing deeper insight into the complex molecular mechanisms underlying embryo implantation.[13,14]

In mice

Endometrial receptivity is under the precise control of ovarian steroid hormones, as well as a variety of transcription factors, growth factors, cytokines, and lipid signaling mediators. It is widely accepted that estrogen and progesterone play predominant roles in uterine receptivity. In mice, preovulatory ovarian estrogen stimulates the proliferation of uterine epithelial cells on day 1 of pregnancy (the day when the vaginal plug is seen). From day 3, the rising level of progesterone from the newly formed corpus luteum initiates stromal cell proliferation. On the morning of day 4, a small surge of estrogen, along with progesterone, is crucial for determining uterine receptivity. Meanwhile, uterine epithelial cells stop proliferation and gradually decrease their polarity. Embryo implantation takes place at the end of day 4 of pregnancy in mice.[2,3] The effects of estrogen and progesterone are mainly mediated by their respective nuclear receptors, estrogen receptor (ER) and progesterone receptor (PR). Evidence from knockout mice has shown the indispensable roles of ER and PR in embryo implantation and female fertility.[15–18] Expression levels and transcription activities of ER and PR can be modulated at multiple levels, including transcriptional, posttranscriptional, and posttranslational regulation. Recent studies have demonstrated the significance of N^6-methyladenosine (m^6A) in embryo implantation by affecting progesterone and estrogen signaling at the posttranscriptional level. m^6A, the most abundant form of mRNA modification in eukaryotes, controls gene expression by regulating mRNA splicing, translocation, stabilization, and translation. m^6A modification is catalyzed by a methyltransferase complex consisting of the methyltransferase like 3 (METTL3) and the methyltransferase like 4 (METTL4), along with other regulatory subunits.[19] The significance of m^6A modification in embryo implantation remains unclear. In recent studies, Zheng *et al.*[20] and Wan *et al.*[21] revealed the m^6A-mediated mechanisms for ensuring normal progesterone and estrogen signaling during embryo implantation. Uterine-specific deletion of the m^6A writer METTL3 culminates in implantation failure due to preimplantation embryo loss and compromised uterine receptivity. Further investigation showed that METTL3 directly targets the mRNAs of Pgr (the encoding gene of PR), and that m^6A modifications in the 5′ untranslated region of Pgr enhance its translation efficiency. Thus, METTL3 deficiency leads to decreased PR protein levels, ultimately interfering with progesterone signaling.[20] Meanwhile, another study revealed that METTL3-dependent m^6A also modulates the estrogen pathway to maintain the balance between progesterone and estrogen signaling. Loss of m^6A modifications causes estrogen dominance and progesterone resistance. Specifically, m^6A-seq analysis identified m^6A modifications in the 3′ untranslated region of several estrogen-responsive genes, mRNAs of which exhibited increased stability upon METTL3 depletion.[21] In addition to posttranscriptional regulation, steroid nuclear receptor activities are also regulated by posttranslational modifications, such as phosphorylation and ubiquitination.[22,23] Tang *et al.*[24] recently reported that uterine deficiency of p38α-impaired uterine receptivity ascribed to reduced PR protein levels and reduced progesterone responsiveness in the uterine stroma. Mechanistically, p38α phosphorylated ubiquitin protein ligase E3C, a HECT family E3 ubiquitin ligase, and restrained its polyubiquitination activity toward PR for proteasome-mediated degradation (Fig. 1). These findings by Chinese scientists are of high clinical relevance, because aberrant progesterone and estrogen signaling are often associated with uterine pathophysiology.

In addition to ovarian steroid hormones, embryo-derived signals, including growth factors, cytokines, and hormones, also facilitate the establishment of uterine receptivity.[25–27] Recently, Chinese scientists have identified crucial embryo-derived factors that affect uterine epithelial differentiation during the window of receptivity (Fig. 1). Combining single-cell RNA sequencing for pregnant or pseudopregnant uteri and bulk RNA sequencing for embryos, Wang *et al.*[28] found that estrogen-responsive uterine luminal epithelial cells functionally differentiated into adhesive epithelial cells and supporting epithelial cells under the regulation of progesterone; furthermore, embryonic Pdgfa and Efna3/4 signaling, together with maternal signals, activated adhesive epithelial cells and supporting epithelial cells, respectively, promoting embryo attachment to the endometrium. In another study, Wang *et al.*[29] delineated the global gene expression changes in the luminal epithelium of pregnant mice compared with that in pseudopregnant mice. Further exploration proved that blastocyst-derived Igf2 induced the activation of epithelial Stat3 and upregulated expression of lysosomal hydrolases, leading to a significant increase in both the number and acidification of lysosome, which

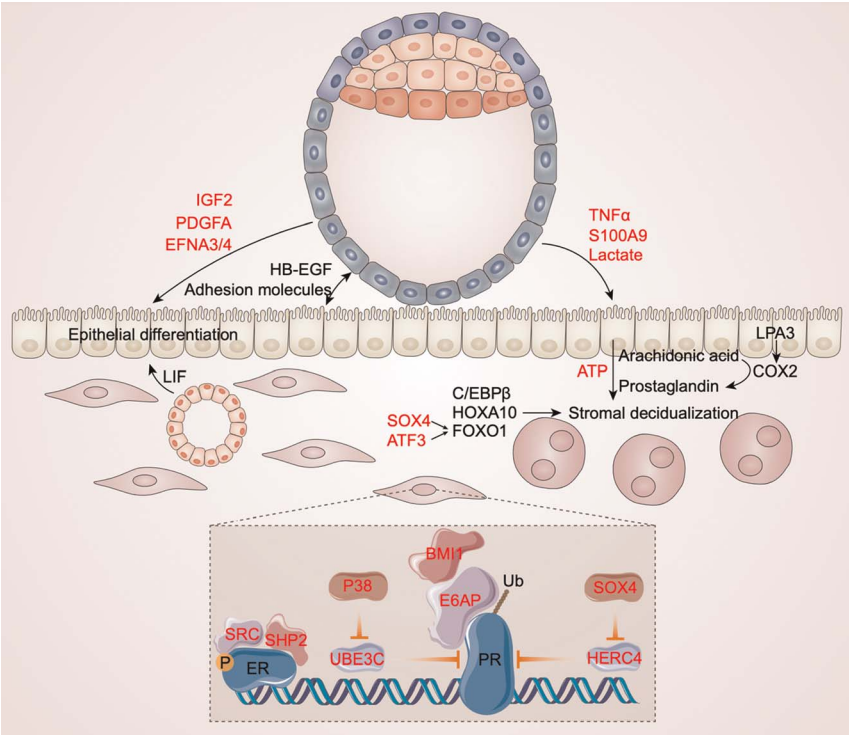

Figure 1. Signaling networks governing embryo implantation and decidualization. The dynamic process of embryo implantation and decidualization involves complex interactions among the embryo, uterine epithelium, and stroma. Critical signals regulating cell-cell interplay are portrayed here. Establishment of uterine receptivity and progression of decidualization are under the precise control of ER-mediated estrogen signaling and PR-mediated progesterone signaling. The transcriptional activity of ER and PR are modulated at the posttranslational level. Posttranslational regulation of ER and PR is illustrated here, with contributions by Chinese scientists highlighted in red. ATF3: activating transcription factor 3; ATP: adenosine triphosphate; C/EBPβ: CCAAT/enhancer-binding protein beta; ER: estrogen receptor; HB-EGF: heparin binding EGF Like Growth Factor; IGF2: insulin-like growth factor 2; LIF: leukemia inhibitory factor; PDGFA: platelet-derived growth factor subunit A; PR: progesterone receptor; SOX4: SRY-Box transcription factor 4; S100A9: S100 calcium-binding protein A9; TNFα: tumour necrosis factor alpha.

mediated the degradation of Cldn1 and Muc1, two well-known downregulated molecules for successful implantation.

Previous studies have revealed an important role of glucose metabolism during the peri-implantation period.[30] Given that the precursor of the O-linked β-D-*N*-acetylglucosamine (*O*-GlcNAc) modification, uridine diphosphate N-acetylglucosamine, connects the metabolic pathways of glucose, fatty acids, nucleic acids, and nitrogen, *O*-GlcNAcylation is engaged in diverse metabolic and physiological processes by rapidly and reversibly sensing a wide range of signals and affecting protein localization, interaction, activity, and degradation.[31] In their recent study, Zhang *et al.*[32] identified an unexpected role of *O*-GlcNAcylation in modulating endometrial cell functions and influencing embryo implantation. *O*-GlcNAcylation of Glut1 increased glucose uptake and Warburg-like glycolysis during the window of implantation, and *O*-GlcNAcylation modification of aquaporin 3 mediated the intracellular transport of glycerol to compensate for increased glycolysis. Furthermore, *O*-GlcNAcylation of the transcription factor SP1 enhanced its stability and promoted transcription of downstream aquaporin 3.

Various adhesion molecules, such as integrins, selectins, and cadherins, are thought to participate in blastocyst apposition and attachment during implantation, among which β3-integrin has been broadly investigated in both humans and mice. In the human endometrium, a high level of β3-integrin is observed in luminal and glandular epithelial cells during the mid-secretory phase, implying its potential role in endometrial receptivity. Indeed, aberrant expression of β3-integrin is associated with RPL and female infertility.[33] In mice, interfering with β3-integrin–mediated trophectoderm–luminal epithelial crosstalk compromises embryo implantation.[34] Recently, Cai *et al.*[35] showed that a signal axis of Mst1/Nur77/β3-integrin is potentially involved in embryonic-endometrial interactions. Specifically, Mst1 enhanced the transcription activity of Nur77 by phosphorylating Nur77 at threonine 366, and thus upregulated the expression of target gene β3-integrin. Reduced levels of Mst1 have been observed in women with recurrent implantation failure (RIF).

Current studies of uterine receptivity and embryo implantation mainly rely on traditional gene knockout strategies, such as PR-cre–mediated gene knockout. This method has limitations, because PR is expressed at early uterine development stages; thus, implantation failure might be attributed to developmental defects. Thus, the inducible knockout strategy is warranted toward solving this issue. Further development and improvement of an in vitro implantation model is also needed to study embryo implantation in humans.

Recent progress in endometrial-decidual transformation research, in humans and mice

Decidualization refers to the transformation of endometrial stromal cells into specialized secretory decidual cells in adaptation to gestation. Fully developed decidua can provide nutrition for the growing fetus, control trophoblast invasion,

and establish immune tolerance, which are essential for successful pregnancy.[4,5] PR-mediated progesterone signaling is essential for decidualization in both humans and mice. Moreover, PR chaperons, such as Fkbp52, downstream mediators of progesterone signaling including C/EBPβ, *Hoxa10*, Bmp2, and Wnt4, and other transcription factors (eg, Foxo1) and cytokines (eg, Il11) also serve as important determinants for decidualization.[4,5]

In humans

In humans, decidualization is regulated by estrogen and progesterone during the secretory phase of each menstrual cycle, in preparation for embryo implantation. Stromal-decidual transformation is first initiated around the spiral arteries. Although the initiation of decidualization in humans is considered independent of implantation, it is prolonged in the presence of embryos.[4,36] Gu *et al.*[37] showed that blastocyst-derived lactate induces release of non-lytic ATP, which promotes secretion of epithelial IL8 to facilitate the decidualization process.

PR and other transcription factors, including C/EBPβ, Hoxa10, and Foxo1, are essential for decidualization. Recently, Huang *et al.*[38] reported that SOX4 is a key regulator of human endometrial stromal decidualization by directly regulating FOXO1 expression and modulating PR stability, which it does by repressing E3 ubiquitin ligase HERC4-mediated degradation and derailed SOX4/HERC4/PR axis potentially, contributing to decidual defects in patients with RIF (Fig. 1). Ni *et al.*[39] discovered that overexpression of circSTK40, a circular RNA upregulated in RIF samples, inhibits the decidualization process in human endometrial stromal cells (hESCs), in part because of declined FOXO1 level. In another study, these authors revealed that knockdown of ATF3, which is significantly downregulated in the endometrium of patients with RIF, hampers hESC decidualization via impaired FOXO1 expression.[40] Cui *et al.*[41] found that decreased circadian gene Rev-erbα level causes defective decidualization, which is attributed to reduced expressions of PR and C/EBPβ. Although the coding genes of the HOX family have been defined as critical regulators in endometrial decidualization, Zhao *et al.*[42] found an unexpected role of the long noncoding RNAs in the HOX gene family in decidualization. In that study, the authors noticed that HOXA11-AS was the most reduced lncRNA in the HOX family during the window of implantation and was elevated in patients with RIF. Mechanistically, HOXA11-AS negatively regulated decidualization via competitive interaction with PTBP1, an RNA-binding protein, which limited PTBP1 availability to regulate PKM1/2 alternative splicing, and thus attenuated decidualization.

The process of endometrial-decidual transformation is accompanied by remarkable metabolic reprogramming.[43] Using liquid chromatography with mass spectrometry-based metabolite profiling, Tang *et al.*[44] found that accumulated α-ketoglutarate derived from activated glutaminolysis contributes to decidual transformation, whereas hESCs obtained from patients with recurrent spontaneous miscarriage exhibited glutaminolysis blockade and decidual defects. Further investigation revealed that enhanced α-ketoglutarate flux decreased histone methylation and supported ATP production during decidualization.

Although the initiation of a decidual reaction is thought to be an inflammatory response, hyperactivated inflammatory responses compromise decidual functions and pregnancy outcomes.[45] Gαq deficiency leads to an aberrantly activated inflammatory reaction during decidualization from enhanced NF-κB signaling, which defers blastocyst hatching and adhesion in vitro. Furthermore, Gαq expression in the decidua is significantly lower in women with RPL.[46]

In a recent report, aldosterone biosynthesized in endometrial glands during mid-secretory phase facilitated decidualization. Expression of the aldosterone receptor, mineralocorticoid receptor (MR), was elevated in the stroma during the mid-secretory phase. Glandular aldosterone activated stromal MR to promote decidualization via the MR/LKB1/p-AMPK/PDK4/p-CREB/FOXO1 signaling pathway.[47]

In mice

In mice, the decidual reaction is elicited by embryo implantation or artificial stimulus. In response to embryo attachment, stromal cells surrounding the blastocyst experience extensive proliferation and differentiation to form the primary decidual zone (PDZ). Stromal cells adjacent to the PDZ further proliferate and differentiate, establishing the secondary decidual zone and leaving a thin layer of undifferentiated stromal fibroblasts.[2,3,5] The process of decidualization shows regional differentiation in mice. However, we incompletely understand this regional decidualization process because we have lacked high-resolution spatial transcriptomics. Using scStereo-seq technology, Yang *et al.*[48] for the first time portrayed the context of functional decidual hubs as distinct decidual stromal, immune, endothelial, and trophoblast cells during early pregnancy in mice. Another study revealed the important role of Men1, a member of the H3K4 methyltransferase complex, in mediating decidual regionalization. Uterine-specific deletion of Men1 reduced Ptx3, which led to aberrant activation of Erk1/2 in the secondary decidual zone due to unrestrained Fgf2 signals from the undifferentiated stromal layer, therefore blunting Bmp2 induction and decidual differentiation.[49] That study highlighted, for the first time, the epigenetic machinery governing regional decidualization.

Previous studies have demonstrated the importance of epithelial-stromal crosstalk in the initiation of decidualization.[3,5] However, few embryo-derived factors that influence decidualization have been identified. Recently, Chinese scientists have characterized several embryonic-derived signals that contribute to stromal decidualization (Fig. 1). Li *et al.*[50] found that blastocyst-derived TNFα induces epithelial IHH, which stimulates expression of SHH in the stroma and thereby augments decidualization. Chen *et al.*[51] further discovered that TNFα produced by the embryo promotes release of arachidonic acid from the epithelium to ignite fibroblast activation and decidualization through PGI2 and PPARδ. In addition, lactate from blastocysts stimulates ATP release from epithelial cells and enhances stromal decidualization via the ATP receptor P2y2.[52]

Considering that the process of endometrial-decidual transformation is distinct between humans and mice, the use of nonhuman primate models will allow novel opportunities to explore and understand human decidualization. Furthermore, because the endometrium experiences dynamic remodeling, shedding, and regeneration during the menstrual cycle, the presence and characteristics of endometrial stem/progenitor cells merit further investigation.

Recent progress in trophoblast differentiation and placentation research, in humans and mice

The placenta, a transient organ formed during pregnancy to support fetal growth, participates in the exchange of gases, nutrients, and waste between the mother and fetus.

In humans

In humans, highly proliferative and undifferentiated cytotrophoblast (CTB) cells derived from the trophectoderm undergo differentiation through two pathways. In the villous pathway, mononucleated CTB cells fuse into multinucleated syncytiotrophoblast (STB) cells, covering the floating villi. STB is responsible for the production of pregnancy-related hormones and nutrient and waste exchanges between the mother and fetus. In the extravillous pathway, CTB cells proliferate to form anchoring villi and differentiate into either interstitial extravillous trophoblast (EVT) cells (which invade the deep layer of the maternal decidua and even the myometrium) or endovascular EVT cells (which penetrate the uterine spiral arteries and replace endothelial cells to remodel the maternal vasculature).[7,8,53] Jiang *et al.*[54] recently depicted the transcriptomic atlas of the cynomolgus macaque placenta at a single-cell resolution. Comparative analyses of human and macaque placentas have revealed the conserved features of placentation and the discrepancies of EVTs between the two species.

Cell-cell fusion, or syncytialization, is a crucial step of STB formation. The physiological advantages of forming such an extensive multinucleated cellular structure and the regulatory mechanisms underlying this process remain to be explored. Zhang *et al.*[55] demonstrated that Ca^{2+} influx through the Ca^{2+} permeable transient receptor potential vanilloid channel TRPV4 is critical for TMEM16F activation and subsequent trophoblast fusion. Meanwhile, Shao *et al.*[56] discovered that STB uniquely induces macropinocytosis by inhibiting mTOR signaling, serving as an adaptation to the cellular nutrient status, which helps support fetal survival under nutrient deprivation (Fig. 2).

Trophoblast invasion/migration is tightly regulated by a variety of transcription factors, growth factors, and other signaling molecules. Insufficient trophoblast invasion gives rise to RPL, fetal growth restriction, and preeclampsia. Transcription coactivator NCOA6 has been reported to be important for CTB invasion and migration, at least partly by activating NF-κB–mediated MMP9 transcription.[57] In addition to transcriptional regulation, posttranscriptional modifications are involved in regulating placentation and trophoblast invasion. Zheng *et al.*[58] revealed an unexpected role of N1-methyladenosine, one of the most prevalent posttranscriptional modifications in RNAs, in trophoblast migration and invasion. The N1-methyladenosine reader YTHDF3 promoted degradation of IGF1R mRNAs and thus inhibited the translation of IGF1R proteins, repressing the downstream MMP9 signaling, which consequently compromised the migration and invasion of trophoblast cells. Emerging evidence has also demonstrated indispensable roles of microRNAs, circular RNAs, and long noncoding RNAs in trophoblast invasion. Abnormally elevated miR21 dampens EVT mobility via the PP2A Bβ/Hippo axis.[59] miR-18a inhibits expression of SMAD2(FL), leading to enhanced trophoblast cell invasion, whereas a lack of miR-18a contributes to development of preeclampsia.[60] circ_0111277, a circular RNA upregulated in the placenta

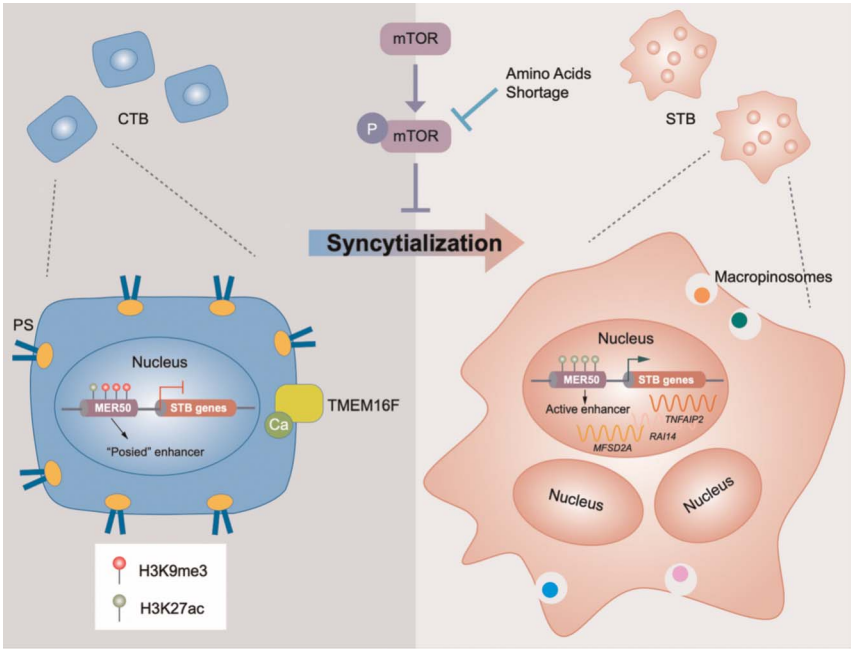

Figure 2. Regulatory mechanisms underlying syncytialization during STB formation. Mononucleated CTB cells fuse into multinucleated STB cells responsible for exchanging nutrients and waste between the mother and fetus. During syncytialization, TMEM16F activation facilitates cell fusion by translocating PS to the cell surface. Meanwhile, bivalent ERV-derived enhancer MER50 profoundly rewires the transcriptional program of syncytialization. STB can efficiently uptake large molecules by the macropinocytosis machinery, which is enhanced during reduced amino acid supply. CTB: cytotrophoblast; ERV: endogenous retrovirus; PS: phosphatidylserine; STB: syncytiotrophoblast.

with preeclampsia, attenuates trophoblast cell migration/invasion by modulating the miR-494-3p/HTRA1/NOTCH-1 axis.[61] Long noncoding RNAs INHBA-AS1 and SH3PXD2A-AS1 are considered potential causal factors in preeclampsia, owing to their ability to prohibit trophoblast invasion and migration during placentation.[62] Furthermore, recent studies have revealed the potential roles of aberrant WNT, SHH, BMP2, and GDF15 signaling in several pregnancy-related diseases, including preeclampsia and RPL.[63–66]

Posttranslational protein modifications are important to the differentiation and behaviors of trophoblast cells. Liu *et al.*[67] established a database of *O*-GlcNAcylated proteins in human placental trophoblasts, among which cystathionine γ-lyase CSE exhibits the most significant change. *O*-GlcNAcylation of CSE enhances its enzymatic activity to produce H2S, which in turn represses trophoblast differentiation by inhibiting androgen receptor dimerization. Consistent with this, remarkably elevated CSE *O*-GlcNAcylation and H2S production have been observed in the placenta during preeclampsia. Cui *et al.*[68] also showed that serum epiregulin and protein *O*-fucosyltransferase 1 (poFUT1), the key enzyme for the biosynthesis of *O*-fucosylation of specific glycoproteins, is higher in pregnant women compared with nonpregnant women and is significantly decreased in patients with spontaneous abortion. Further investigation found that epiregulin upregulated poFUT1 expression and increased *O*-fucosylation on uPA, which further activated the PI3K/Akt pathway, facilitating EMT behaviors of trophoblast cells.

Endogenous retroviruses (ERVs) have been proposed as a driving force for the development of the mammalian placenta.[69] However, ERV-derived regulatory elements and transcription factors that target these elements in human trophoblast stem cells (hTSCs) remain obscure. Yu *et al.*[70] recently delineated the dynamic landscape of bivalent ERV-derived enhancers with dual occupancy of H3K27ac and H3K9me3 in hTSCs, demonstrating that ERVs profoundly rewire the transcriptional program of trophoblast syncytialization. In particular, bivalent enhancers derived from the Simiiformes-specific MER50 transposons were linked to a cluster of genes important for STB formation (Fig. 2). Moreover, Du *et al.*[71] confirmed that transcription factors GATA2/3, MSX2, and related factors exhibit prevalent binding on many ERV families in hTSCs, implying their broad impacts on ERV-derived enhancers. Nevertheless, aberrant expression of ERVs in trophoblast cells might result in catastrophic consequences. The deficiency of Pr-set7, the sole enzyme catalyzing H4K20me1, leads to ERV derepression, double-stranded RNA stress, overwhelming viral mimicry responses, and trophoblast necroptosis.[72]

The placenta serves as an endocrine organ and produces various hormones, including human chorionic gonadotropin, prolactin, estrogen, and progesterone, to guarantee successful pregnancy maintenance.[7] A recent study showed an uncharacterized role of RGS2 in the production of estrogen by the placenta. Specifically, RGS2 promoted protein degradation of HAND1 and restored transcription of HAND1-inhibited aromatase, leading to increased estrogen levels.[73] In addition to the abovementioned hormones, Yu *et al.*[74] identified placensin, a peptide hormone derived from the placenta, which is capable of stimulating glucose secretion and trophoblast invasion. Serum placensin level rises in a stage-dependent manner during pregnancy and is significantly increased in patients with gestational diabetes mellitus during the third trimester.

In mice

In mice, the trophectoderm, at the outermost layer of the blastocyst, differentiates into different trophoblast lineages of the placenta. Trophectoderm cells covering the ICM proliferate and form the extraembryonic ectoderm and ectoplacental cone, whereas trophectoderm cells away from the ICM cease dividing but continue DNA replication, forming the primary polyploid trophoblast giant cells (TGCs). With embryonic development, the allantois (originating from the extraembryonic mesoderm) comes into contact with the chorionic epithelium (derived from the extraembryonic ectoderm), in a process termed *chorioallantoic fusion*. The chorionic epithelium starts to fold, and fetal blood vessels invaginate into these folds. Trophoblast cells and the connected fetal blood vessels branch extensively, eventually forming a dense structure known as the labyrinth, in which the exchange of nutrients and waste between the mother and fetus occurs. Meanwhile, cells in the ectoplacental cone develop to form a junctional zone, consisting of spongiotrophoblast cells, glycogen trophoblast cells, and TGCs. The outer region of the ectoplacental cone differentiates to form more TGCs that envelop the whole fetus.[75,76] To comprehensively decipher this complex developmental process in mice, Jiang *et al.*[77] performed single-cell RNA sequencing on trophoblast cells of extraembryonic tissues on embryonic days 7.5 and 8.5, and placental tissues from embryonic days 9.5 to 14.5. In that study, previously unreported progenitor cells and intermediate precursor cells were identified, and the lineage of differentiation trajectory was mapped during placentation in mice.

Wnt signaling is a critical determinant for the maintenance and differentiation of stem/progenitor cells, including trophoblast stem cells during placental development. Hyperactivation of Wnt signaling is associated with human trophoblast diseases. Bao *et al.*[78] used mouse models, with either double knockout of Sfrp1 and Sfrp5 or expressing an exon 3–deleted β-catenin, to reveal that hyperactivation of the canonical Wnt pathway disturbed trophoblast differentiation by repressing Ascl2 expression, resulting in an overabundance of TGCs at the expense of spongiotrophoblast cells.

Cell-cell fusion or syncytialization is a crucial step during placentation. Recently, Zhang *et al.*[79] revealed the essential role of TMEM16F, a Ca^{2+}-activated phospholipid scramblase, in placental trophoblast fusion by translocating phosphatidylserine to the cell surface independent of apoptosis. TMEM16F knockout mice exhibited defective trophoblast syncytialization, leading to perinatal lethality.

Under some circumstances, pregnancy-related disorders are attributed to dysregulated metabolism in trophoblast cells. With mouse models, Xu *et al.*[80] discovered that AMPK activation during placentation exacerbated preeclampsia but alleviated trophoblast cell death. Specifically, AMPK activation in trophoblasts contributed to GLUT3 translocation and subsequent glucose metabolism, which were redirected into gluconeogenesis, resulting in deposition of glycogen and accumulation of phosphoenolpyruvate; the latter enhanced viability but compromised trophoblast invasion. These findings revealed a novel homeostasis between trophoblast invasiveness and viability. Another study described the correlation between reduced succinate levels and recurrent spontaneous abortion (RSA). Methylation of the succinate dehydrogenase complex iron sulfur subunit (SDHB) promoter recruited MBD1 and excluded c-Fos, inactivating SDHB expression

and causing intracellular succinate accumulation, which mimicked hypoxia; however, low succinate levels reversed this effect and increased abortion risk in the mouse model.[81]

Numbers of pregnancies at advanced maternal age (AMA) are rapidly increasing and are associated with aberrant trophoblast cell function, poor placentation, and unfavorable pregnancy outcomes, presumably due to premature placental senescence.[82] However, the underlying causes of placental senescence remain largely unknown. Xiong *et al.*[83] discovered that the loss of SIRT1, the only downregulated sirtuin in the placenta of women with AMA, increased P53 acetylation and P21 expression and impaired trophoblast invasion/migration by modulating vimentin acetylation, leading to AMA-associated placental senescence.

An important endocrine organ during pregnancy, the placenta secretes hormones and other factors into the circulation to coordinate other maternal organs to maintain pregnancy. Further investigations are warranted to reveal the functions of placental-derived hormones and factors, as well as the adaptational changes of target organs.

Recent progress in cell-cell interplay research at the maternal-fetal interface, in humans and mice

The maternal-fetal interface involves a complex interplay between multiple cell types, including decidual cells, trophoblast cells, endothelial cells, and various immune cells.[9] In recent years, Chinese scientists have contributed much to characterizing cell heterogeneity at the maternal-fetal interface, helping to expand our understanding of this complex cell-cell crosstalk. Because most of the studies described in this section are based on findings from both humans and mice, they are not divided into subsections.

Applying single-cell RNA sequencing and spatial transcriptomic analysis, several studies have revealed the spatiotemporal landscape of the maternal-fetal interface at a single-cell resolution in both humans and mice. Du *et al.*[84] illustrated the heterogeneity of the maternal decidua in patients with RSA, finding that aberrant decidualization obviously obstructed communication between stromal cells and other cell types in samples of women with RSA. Guo *et al.*[85] systematically compared leukocyte subtypes isolated from patients with RPL and healthy controls, finding markedly different distributions of immune cell subsets and altered intercellular interactions between leukocytes and other cell types in the RPL group. In mice, Yang *et al.*[86] provided a global transcriptomic profile of uterine receptivity. These authors also predicted the signaling crosstalk between the blastocyst and the receptive uterus. Another study defined different functional hubs in the mouse decidua, discovering a dual-featured type of immune-featured decidual cells (iDSCs), which enable immune cell recruitment and suppression, govern vascularization, and promote cytolysis. Dysfunctional and spatially disordered iDSCs disrupt decidual hub specification and eventually lead to pregnancy complications.[48]

The abundant decidual natural killer (dNK) cells that accumulate at the maternal-fetal interface are believed to play vital roles in immune modulation. During the first trimester of pregnancy, dNK cells are the dominant lymphocyte in the decidua.[9] The reduction and dysfunction of dNK cells at the maternal-fetal interface contribute to pregnancy-related diseases.[87] Wang *et al.*[88] recently described a CD49a^{+} PBX1^{+} dNK subset capable of promoting fetal development in both humans and mice. They found that PBX1 drove expression of pleiotrophin and osteoglycin in dNK cells. Decreased PBX1 level or mutations were correlated with fetal growth restriction and unexplained RSA. Meanwhile, Tao *et al.*[89] identified another immunomodulatory dNK subset, CXCR4^{+} CD56^{bright} dNK cells, which display a less cytotoxic phenotype but show enhanced immunomodulatory potential in both humans and mice. These CXCR4^{+} CD56^{bright} dNK cells, recruited and reprogrammed by trophoblasts, could induce Th2 differentiation; a reduction of this dNK subset was observed in patients with recurrent miscarriage. Tissue-resident natural killer (trNK) cells are crucial components of local immunity. Han *et al.*[90] recently characterized uterine trNK cells longitudinally during pregnancy by single-cell RNA sequencing and found that an IL-21R-STAT3 axis was essential for initiating the trNK cell differentiation. The fully differentiated trNK cells exhibited enhanced functionality necessary for remodeling spiral arteries in the decidua. In addition, they identified an apoptotic program specific to the terminal differentiation stage, which might preclude tissue damage by these highly activated trNK cells. Several other studies have reported complex crosstalk between dNK cells and other cell types at the maternal-fetal interface. Extracellular vesicles derived from trophoblasts promote secretion of IFN-γ and VEGFα by dNK cells, which are necessary for angiogenesis, trophoblast growth, and inhibition of Th17 in patients with RSA and abortion-prone mouse models.[91] Furthermore, activated glutaminolysis in dNK cells contributes to trophoblast invasion and embryo growth via IGF-1 and GDF-15. Blocking dNK glutaminolysis leads to early embryo implantation failure, spontaneous abortion, and/or fetal growth restriction in pregnant mice.[92]

Macrophages, the second largest leukocyte type at the maternal-fetal interface, play an important role in the maintenance of pregnancy. Following environmental cues, macrophages can be polarized into two subpopulations: proinflammatory M1 macrophages and anti-inflammatory M2 macrophages.[93] M1 macrophages are elevated in the decidua of patients with RSA. A recent study revealed that M1 macrophages suppressed trophoblast invasion and migration by secreting extracellular vesicles, illuminating a novel mechanism by which M1 macrophage regulates trophoblast invasion in both humans and mice.[94] Several investigations have illustrated the correlation between macrophage polarization and RPL from the aspect of metabolic regulation. Using samples of women with RPL and mouse models, Gao *et al.*[95] discovered that lactic acid metabolism could trigger macrophage polarization via oxidative phosphorylation and glycolysis regulation, and that this plays a vital role in decidual macrophages-mediated RPL. Sheng *et al.*[96] reported positive feedback from IL-33/ST2-efferocytosis leading to pregnancy failure through metabolic reprogramming of decidual macrophages. The disruption of the IL-33/ST2 axis in patients with RPL increases cell apoptosis and macrophage efferocytosis. Decidual macrophages that engulf apoptotic cells secrete more sST2 and less TGF-β, promoting M1 polarization. Moreover, elevated sST2 further exacerbates disruption of the IL-33/ST2 pathway. In addition, IL-33 knockout mice demonstrate poor pregnancy outcomes, and exogenous supplementation with mouse IL-33 reduced embryo losses.

Liu *et al.*[97] recently showed a correlation between activation of neutrophils and the development of preeclampsia. They observed significantly increased IL-32β levels in the placentas of

patients with severe preeclampsia. IL-32β activated neutrophils, which were better able to adhere to endothelial cells and enhance the expressions of VCAM-1 and ICAM-1. That study provided evidence of the involvement of IL-32β in the pathogenesis of preeclampsia.

Regulatory T cells (Tregs) are important for maintaining systemic immune homeostasis and are required for establishing immune tolerance at the maternal-fetal interface during pregnancy.[98] Using the conditional knockout mouse model, Zhang *et al.*[99] found that deficiency of H3K36me2 methyltransferase Nsd2 leads to a significant decrease in Tregs at the maternal-fetal interface, disrupting immune tolerance and causing severe fetal loss. Mechanistically, Nsd2 upregulates CXCR4 expression via H3K36me2 modification to recruit Tregs into the decidua. Ma *et al.*[100] uncovered a unique immune-regulatory characteristic of placental endovascular EVTs to promote naive CD4+ T-cell differentiation into immunosuppressive FOXP3+ Tregs by secreting TGF-β1 in humans. Cao *et al.*[101] used mouse models to report that activation of invariant natural killer T cells, a minor immune cell population at the maternal-fetal interface, predisposes offspring to cardiac injury.

In addition to immune tolerance, uterine spiral artery remodeling is another critical event at the maternal-fetal interface that is essential for the maintenance of pregnancy. Atrial natriuretic peptide and corin have been reported to facilitate spiral artery remodeling. Deficiency of atrial natriuretic peptide or corin in mice leads to defective decidualization and reduced production of TRAIL by decidual cells, which induce apoptosis in uterine spiral arterial smooth muscle cells. Subsequently, cyclophilin B from apoptotic smooth muscle cells upregulated endothelial TRAIL receptors, causing apoptosis in endothelial cells.[102]

A successful pregnancy requires both sophisticated multicellular cooperation at the maternal-fetal interface in the uterus and adaptational changes of other maternal organs. Among these, the liver undergoes dramatic enlargement to meet increased metabolic demands during pregnancy. He *et al.*[103] recently used a proliferation recording system, the ProTracer, to examine the spatial-temporal proliferation of hepatocytes during pregnancy, which is under the influence of estrogen.

Considering the complex cell-cell interplay at the maternal-fetal interface, improvement and application of high-resolution spatial sequencing (eg, spatial transcriptomics, spatial ATAC-seq, spatial CUT&Tag) will provide a more comprehensive perspective for studying this system.

Recent progress in parturition research, in humans and mice

Labor onset involves the transition of the myometrium from a quiescent state to a contractile state under the influences of corticotrophin-releasing hormone, oxytocin, and prostaglandin, and a shift from progesterone to estrogen dominance.[104] Abnormalities in the initiation of parturition lead to preterm or postterm delivery. Preterm birth, defined as delivery occurring before 37 weeks' gestation, affects 11.1% of pregnancies worldwide and is the leading cause of neonatal mortality and morbidity. It is also associated with elevated blood pressure and increased risks of cancer, diabetes, and cardiometabolic disease later in life.[105]

In humans

Emerging evidence indicates that the maternal decidua plays a critical role in parturition initiation. Huang *et al.*[106] have revealed the transcriptomic profile of the peripartum decidua at the single-cell resolution, providing a new perspective for the study of parturition.

Parturition involves the infiltration of immune cells and secretions of cytokines. Single-cell RNA sequencing and spatiotemporal transcriptomic analyses have been performed on human myometrium at term labor and nonlabor, portraying a comprehensive landscape of immune cells, including transcriptional characteristics, distributions, functions, and intercellular communications during labor.[107] Inflammation is currently recognized as a major cause of premature delivery. Chen *et al.*[108] discovered that lipopolysaccharide reduces expression of IL-33, resulting in increased calcium concentration, endoplasmic reticulum stress, and phosphorylation of nuclear factor κB and p38 mitogen-activated protein kinase. These data suggest that IL-33 is involved in the initiation of labor by leading to endoplasmic reticulum stress via an influx of calcium ions in human uterine smooth muscle cells.

In mice

Preterm birth is attributed to a dramatic switch from quiescence to contractility in the myometrium. Chen *et al.*[109] recently found that mice injected intraperitoneally with PTPI-1, the specific inhibitor of phosphatase SHP-1, manifested preterm labor. Furthermore, SHP-1 is significantly decreased in the human myometrium during labor compared with not in labor. This study suggests a potential strategy for preventing preterm birth via modulation of SHP-1.

The cumulative evidence indicates that the maternal decidua and epithelium play critical roles in parturition initiation. Zhao *et al.*[110] provided insights into parturition initiation through single-cell RNA sequencing. They revealed that stromal cells prepare for parturition by regulating local retinol acid synthesis. Their study expanded knowledge about parturition that opened potential avenues for interventions to prevent preterm birth. Liu *et al.*[111] revealed a critical role of epithelial SHP2 in parturition initiation via COX1- and COX2-derived PGF2α. Epithelial-specific Shp2 knockout mice had delayed parturition initiation, dystocia, and fetal deaths. Thus, their study explained a previously unknown role of the epithelium in parturition preparation (Fig. 3).

Notwithstanding maternal contributions to parturition, emerging evidence shows that labor initiation also requires fetal-derived signals. Yu *et al.*[112] recently discovered that wild-type female mice carrying Src1/2 double-deficient fetuses exhibit postponed labor and impaired fetal lung development. Lungs from Src1/2 double-knockout fetuses showed decreased expression of Arg1 and increased Arg1 substrate L-arginine. Knockdown of Arg1 in fetal lungs also led to delayed labor onset. Moreover, L-arginine significantly inhibited spontaneous contractions in human myometrial smooth muscle cells. These authors' work highlighted the role of fetus-derived factors in the initiation of parturition. In another study, they demonstrated that amnion C/EBPδ transcriptionally induced expression of COX-2 and 11β-HSD1, ensuring the production of prostaglandin E2 and cortisol by amnion fibroblasts, which are essential for labor onset[113] (Fig. 3).

Parturition initiation involves a complex interplay among myometrial cells, decidual cells, immune cells, and fetal-derived tissues. Thus, the use of high-resolution spatial transcriptomics will facilitate future research. Moreover, nonhuman primates may serve as appropriate animal models for the study of parturition in humans.

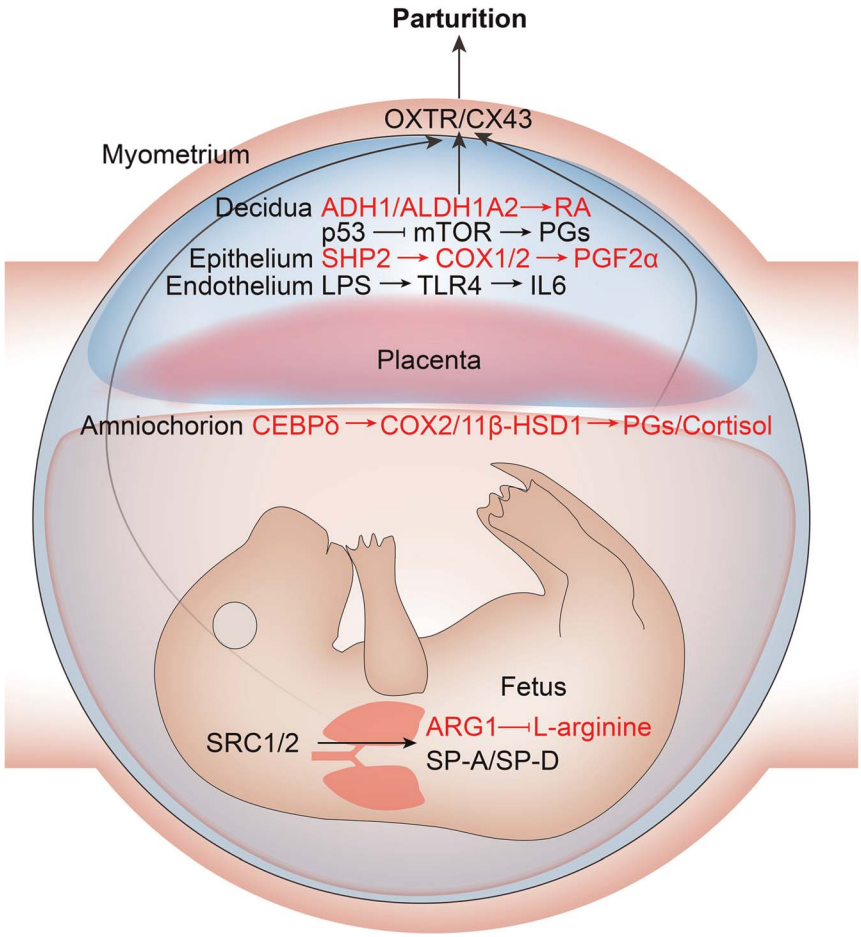

Figure 3. Signaling networks regulating parturition. Labor onset relies on signals derived from the maternal decidua, epithelium, and endothelium, and the fetus. This diagram summarizes the signaling networks governing parturition, with contributions by Chinese scientists highlighted in red.

Recent research progress in organoids and 3D embryo culture

In recent years, Chinese scientists have made many significant contributions to the development and improvement of organoid models, facilitating the study of embryo implantation, placentation, and pregnancy-related diseases.

The endometrium consists of various types of epithelial and stromal cells. Although models such as gland-like structures and endometrial assembloids have been successfully established,[114,115] the lack of intact luminal epithelium makes it difficult to recapitulate endometrial receptivity. Using an improved matrix and air-liquid interface culture method, Tian *et al.*[116] developed a novel ALI-EnAo model composed of endometrial epithelial cells and stromal cells. ALI-EnAos recapitulated endometrial anatomy, cell composition, gene expression profiles, and hormone-induced menstrual cycle changes in vitro. In addition to cell composition and hormone responsiveness, fundamental physical features like mechanical properties and microstructures need to be considered when building in vitro platforms that mimic the uterus for embryo implantation. Gu *et al.*[117] have constructed a uterus-inspired niche by grafting collagen gels onto polydimethylsiloxane, simulating the mechanics and microstructures of the mouse uterus. This novel system supported embryo invasion and development into the early organogenesis stage. Furthermore, Zhang *et al.*[118] evaluated the feasibility of using endometrial organoids to treat posttraumatic endometrial regeneration disorders in a mouse model of intrauterine adhesion. They found that transplanted organoids not only reconstructed the structural integrity of the endometrial epithelium but achieved its functional repair.

hTSC-based 3D organoid has been used as a transformative model for studying placental development.[119] Interactions among trophoblasts, stroma cells, and immune cells at the maternal-fetal interface are crucial for successful pregnancy outcomes. Thus, Huang *et al.*[120] developed a robust, reliable method for generating placenta villi organoids using air-liquid surface culture; they used this to accurately recapitulate the cellular components and genetic alterations of corresponding source tissue. In addition, placenta villi organoids derived from patients with preeclampsia exhibited specific pathological features such as inflammation, antiangiogenic imbalance, and decreased syncytin expression. Ruptured ectopic pregnancy, a pregnancy complication caused by aberrant implantation, deep invasion, and overgrowth of embryos in fallopian tubes, accounts for 4% to 10% of pregnancy-related deaths. The lack of ectopic pregnancy phenotypes in rodents limits our understanding of its pathological mechanisms. Recently, Zhao *et al.*[121] used an organoid co-culture model

to investigate the intricate communications between trophoblasts and endothelial/endothelial progenitor cells in the ruptured ectopic pregnancy context.

Conclusion

Over recent years, Chinese scientists have made marked contributions to research progress in maternal-fetal medicine, addressing problems that range from the molecular regulatory mechanisms underlying critical pregnancy events to the pathogenesis of pregnancy-related disorders. Despite the identification of various signaling pathways that govern the process of embryo implantation, endometrial decidualization, placentation, and parturition, a comprehensive landscape of the molecular network during gestation remains elusive. The ultimate goal of maternal-fetal medicine research is to improve the diagnosis and treatment of infertility and other pregnancy-related diseases. Thus, it is urgent to identify reliable biomarkers for the prevention and diagnosis of these diseases and to seek potential therapeutic targets.

To date, maternal-fetal medicine research has relied primarily on conditional knockout mouse models and traditional cell lines, which have certain limitations. Many genes that may participate in gestational events cannot be thoroughly investigated using currently available Cre mouse lines, as their knockout leads to embryonic lethality or developmental defects. Hence, inducible Cre systems need to be developed, to enable more precise assessments at different stages of pregnancy. Moreover, it is imperative to develop and improve novel in vitro culture models, such as organoids, to overcome the current limitations, uncover molecular regulatory mechanisms, and facilitate exploration of therapeutic targets for diseases.

Collectively, Chinese scientists have achieved remarkable reproductive biology and maternal-fetal medicine research in recent years. This work has been strongly supported by the government. Scientific collaboration within and outside China will further accelerate future developments in this field.

Acknowledgments

We are grateful to Ran H *et al.* (China Agricultural University), Xin Q *et al.* (China Agricultural University), Zhou C *et al.* (China Agricultural University), Wang P *et al.* (China Agricultural University), Tang Y *et al.* (Fujian Normal University), Chen S *et al.* (Guizhou University), Yu Y *et al.* (Naval Medical University), Lu J *et al.* (Ren Ji Hospital, Shanghai Jiao Tong University), Gu X *et al.* (South China Agricultural University), Wang H *et al.* (The Affiliated Drum Tower Hospital of Nanjing University Medical School), Wang Z *et al.* (The Affiliated Drum Tower Hospital of Nanjing University Medical School), Huang P *et al.* (The First Affiliated Hospital of Guangxi Medical University), He B *et al.* (Xiamen University), Zhao H et al. (Xiamen University), Liu M *et al.* (Xiamen University) for their contributions to the figures.

Funding

Work incorporated in this article was partially supported by the National Key R&D Program of China (2022YFC2702500 and 2021YFC2700302) and National Natural Science Foundation of China (82288102).

Conflicts of Interest

None.

Editor Note

Haibin Wang is one of the editorial board members of *Maternal-Fetal Medicine*. The article was subject to the journal's standard procedures, with peer review handled independently of this editor and the associated research groups.

References

[1] Cockburn K, Rossant J. Making the blastocyst: Lessons from the mouse. J Clin Invest 2010;120(4):995–1003. doi: 10.1172/JCI41229.
[2] Wang H, Dey SK. Roadmap to embryo implantation: clues from mouse models. Nat Rev Genet 2006;7(3):185–199. doi: 10.1038/nrg1808.
[3] Zhang S, Lin H, Kong S, et al. Physiological and molecular determinants of embryo implantation. Mol Aspects Med 2013;34(5):939–980. doi: 10.1016/j.mam.2012.12.011.
[4] Gellersen B, Brosens JJ. Cyclic decidualization of the human endometrium in reproductive health and failure. Endocr Rev 2014;35(6):851–905. doi: 10.1210/er.2014-1045.
[5] Ramathal CY, Bagchi IC, Taylor RN, et al. Endometrial decidualization: of mice and men. Semin Reprod Med 2010;28(1):17–26. doi: 10.1055/s-0029-1242989.
[6] Norwitz ER, Schust DJ, Fisher SJ. Implantation and the survival of early pregnancy. N Engl J Med 2001;345(19):1400–1408. doi: 10.1056/NEJMra000763.
[7] Ji L, Brkić J, Liu M, et al. Placental trophoblast cell differentiation: physiological regulation and pathological relevance to preeclampsia. Mol Aspects Med 2013;34(5):981–1023. doi: 10.1016/j.mam.2012.12.008.
[8] Red-Horse K, Zhou Y, Genbacev O, et al. Trophoblast differentiation during embryo implantation and formation of the maternal-fetal interface. J Clin Invest 2004;114(6):744–754. doi: 10.1172/JCI22991.
[9] Vento-Tormo R, Efremova M, Botting RA, et al. Single-cell reconstruction of the early maternal-fetal interface in humans. Nature 2018;563(7731):347–353. doi: 10.1038/s41586-018-0698-6.
[10] Xiang L, Yin Y, Zheng Y, et al. A developmental landscape of 3D-cultured human pre-gastrulation embryos. Nature 2020;577(7791):537–542. doi: 10.1038/s41586-019-1875-y.
[11] Ai Z, Niu B, Yin Y, et al. Dissecting peri-implantation development using cultured human embryos and embryo-like assembloids. Cell Res 2023;33(9):661–678. doi: 10.1038/s41422-023-00846-8.
[12] Gong Y, Bai B, Sun N, et al. Ex utero monkey embryogenesis from blastocyst to early organogenesis. Cell 2023;186(10):2092–2110.e23. doi: 10.1016/j.cell.2023.04.020.
[13] Liu D, Chen Y, Ren Y, et al. Primary specification of blastocyst trophectoderm by scRNA-seq: new insights into embryo implantation. Sci Adv 2022;8(32):eabj3725. doi: 10.1126/sciadv.abj3725.
[14] Zhou F, Wang R, Yuan P, et al. Reconstituting the transcriptome and DNA methylome landscapes of human implantation. Nature 2019;572(7771):660–664. doi: 10.1038/s41586-019-1500-0.
[15] Hewitt SC, Harrell JC, Korach KS. Lessons in estrogen biology from knockout and transgenic animals. Annu Rev Physiol 2005;67:285–308. doi: 10.1146/annurev.physiol.67.040403.115914.
[16] Lee H-R, Kim T-H, Choi K-C. Functions and physiological roles of two types of estrogen receptors, ERα and ERβ, identified by estrogen receptor knockout mouse. Lab Anim Res 2012;28(2):71–76. doi: 10.5625/lar.2012.28.2.71.
[17] Lubahn DB, Moyer JS, Golding TS, et al. Alteration of reproductive function but not prenatal sexual development after insertional disruption of the mouse estrogen receptor gene. Proc Natl Acad Sci U S A 1993;90(23):11162–11166. doi: 10.1073/pnas.90.23.11162.
[18] Lydon JP, DeMayo FJ, Funk CR, et al. Mice lacking progesterone receptor exhibit pleiotropic reproductive abnormalities. Genes Dev 1995;9(18):2266–2278. doi: 10.1101/gad.9.18.2266.
[19] Meyer KD, Jaffrey SR. The dynamic epitranscriptome: N^6-methyladenosine and gene expression control. Nat Rev Mol Cell Biol 2014;15(5):313–326. doi: 10.1038/nrm3785.
[20] Zheng ZH, Zhang GL, Jiang RF, et al. METTL3 is essential for normal progesterone signaling during embryo implantation via m^6A-mediated translation control of progesterone receptor. Proc Natl Acad Sci U S A 2023;120(5):e2214684120. doi: 10.1073/pnas.2214684120.
[21] Wan S, Sun Y, Zong J, et al. METTL3-dependent m(6)A methylation facilitates uterine receptivity and female fertility via balancing estrogen

and progesterone signaling. Cell Death Dis 2023;14(6):349. doi: 10.1038/s41419-023-05866-1.
[22] Ran H, Kong S, Zhang S, et al. Nuclear Shp2 directs normal embryo implantation via facilitating the ERα tyrosine phosphorylation by the Src kinase. Proc Natl Acad Sci U S A 2017;114(18):4816–4821. doi: 10.1073/pnas.1700978114.
[23] Xin Q, Kong S, Yan J, et al. Polycomb subunit BMI1 determines uterine progesterone responsiveness essential for normal embryo implantation. J Clin Invest 2018;128(1):175–189. doi: 10.1172/JCI92862.
[24] Tang Y, Qiu J, Tang Z, et al. P38α MAPK is a gatekeeper of uterine progesterone responsiveness at peri-implantation via Ube3c-mediated PGR degradation. Proc Natl Acad Sci U S A 2022;119(32):e2206000119. doi: 10.1073/pnas.2206000119.
[25] He B, Zhang H, Wang J, et al. Blastocyst activation engenders transcriptome reprogram affecting X-chromosome reactivation and inflammatory trigger of implantation. Proc Natl Acad Sci U S A 2019;116(33):16621–16630. doi: 10.1073/pnas.1900401116.
[26] Tu Z, Wang Q, Cui T, et al. Uterine RAC1 via Pak1-ERM signaling directs normal luminal epithelial integrity conducive to on-time embryo implantation in mice. Cell Death Differ 2016;23(1):169–181. doi: 10.1038/cdd.2015.98.
[27] Zhou C, Lv M, Wang P, et al. Sequential activation of uterine epithelial IGF1R by stromal IGF1 and embryonic IGF2 directs normal uterine preparation for embryo implantation. J Mol Cell Biol 2021;13(9):646–661. doi: 10.1093/jmcb/mjab034.
[28] Wang H-Q, Liu Y, Li D, et al. Maternal and embryonic signals cause functional differentiation of luminal epithelial cells and receptivity establishment. Dev Cell 2023;58(21):2376–2392.e6. doi: 10.1016/j.devcel.2023.08.004.
[29] Wang P, Du S, Guo C, et al. The presence of blastocyst within the uteri facilitates lumenal epithelium transformation for implantation via upregulating lysosome proteostasis activity. Autophagy 2023;1–18. doi: 10.1080/15548627.2023.2247747.
[30] Murdoch RN. Glycolysis in the mouse uterus during the early post-implantation stages of pregnancy and the effects of acute doses of ethanol. Teratology 1987;35(2):169–176. doi: 10.1002/tera.1420350202.
[31] Slawson C, Copeland RJ, Hart GW. O-GlcNAc signaling: a metabolic link between diabetes and cancer? Trends Biochem Sci 2010;35(10):547–555. doi: 10.1016/j.tibs.2010.04.005.
[32] Zhang H, Qi J, Pei J, et al. O-GlcNAc modification mediates aquaporin 3 to coordinate endometrial cell glycolysis and affects embryo implantation. J Adv Res 2021;37:119–131. doi: 10.1016/j.jare.2021.06.022.
[33] Lessey BA, Castelbaum AJ, Sawin SW, et al. Integrins as markers of uterine receptivity in women with primary unexplained infertility. Fertil Steril 1995;63(3):535–542.
[34] Illera MJ, Cullinan E, Gui Y, et al. Blockade of the alpha(v)beta(3) integrin adversely affects implantation in the mouse. Biol Reprod 2000;62(5):1285–1290. doi: 10.1095/biolreprod62.5.1285.
[35] Cai X, Jiang Y, Cao Z, et al. Mst1-mediated phosphorylation of Nur77 improves the endometrial receptivity in human and mice. EBioMedicine 2023;88:104433. doi: 10.1016/j.ebiom.2022.104433.
[36] Evans J, Salamonsen LA, Winship A, et al. Fertile ground: human endometrial programming and lessons in health and disease. Nat Rev Endocrinol 2016;12(11):654–667. doi: 10.1038/nrendo.2016.116.
[37] Gu X-W, Yang Y, Li T, et al. ATP mediates the interaction between human blastocyst and endometrium. Cell Prolif 2020;53(2):e12737. doi: 10.1111/cpr.12737.
[38] Huang P, Deng W, Bao H, et al. SOX4 facilitates PGR protein stability and FOXO1 expression conducive for human endometrial decidualization. Elife 2022;11:e72073. doi: 10.7554/eLife.72073.
[39] Ni T, Zhang Q, Li Y, et al. CircSTK40 contributes to recurrent implantation failure via modulating the HSP90/AKT/FOXO1 axis. Mol Ther Nucleic Acids 2021;26:208–221. doi: 10.1016/j.omtn.2021.06.021.
[40] Wang Z, Liu Y, Liu J, et al. ATF3 deficiency impairs the proliferative-secretory phase transition and decidualization in RIF patients. Cell Death Dis 2021;12(4):387. doi: 10.1038/s41419-021-03679-8.
[41] Cui L, Xu F, Xu C, et al. Circadian gene Rev-erbα influenced by sleep conduces to pregnancy by promoting endometrial decidualization via IL-6-PR-C/EBPβ axis. J Biomed Sci 2022;29(1):101. doi: 10.1186/s12929-022-00884-1.
[42] Zhao H, Hu S, Qi J, et al. Increased expression of HOXA11-AS attenuates endometrial decidualization in recurrent implantation failure patients. Mol Ther 2022;30(4):1706–1720. doi: 10.1016/j.ymthe.2022.01.036.
[43] Tamura I, Fujimura T, Doi-Tanaka Y, et al. The essential glucose transporter GLUT1 is epigenetically upregulated by C/EBPβ and WT1 during decidualization of the endometrium. J Biol Chem 2021;297(4):101150. doi: 10.1016/j.jbc.2021.101150.
[44] Tang L, Xu XH, Xu S, et al. Dysregulated Gln–Glu–α-ketoglutarate axis impairs maternal decidualization and increases the risk of recurrent spontaneous miscarriage. Cell Rep Med 2023;4(5):101026. doi: 10.1016/j.xcrm.2023.101026.
[45] Yockey LJ, Iwasaki A. Interferons and Proinflammatory cytokines in pregnancy and fetal development. Immunity 2018;49(3):397–412. doi: 10.1016/j.immuni.2018.07.017.
[46] Jiang Y, He Y, Liu S, et al. Gαq-PKD/PKCμ signal regulating the nuclear export of HDAC5 to induce the IκB expression and limit the NF-κB-mediated inflammatory response essential for early pregnancy. Elife 2023;12:e83083. doi: 10.7554/eLife.83083.
[47] Li S-Y, Song Z, Yan Y-P, et al. Aldosterone from endometrial glands is benefit for human decidualization. Cell Death Dis 2020;11(8):679. doi: 10.1038/s41419-020-02844-9.
[48] Yang M, Ong J, Meng F, et al. Spatiotemporal insight into early pregnancy governed by immune-featured stromal cells. Cell 2023;186(20):4271–4288.e24. doi: 10.1016/j.cell.2023.08.020.
[49] Liu M, Deng W, Tang L, et al. Menin directs regionalized decidual transformation through epigenetically setting PTX3 to balance FGF and BMP signaling. Nat Commun 2022;13(1):1006. doi: 10.1038/s41467-022-28657-2.
[50] Li B, Yan Y-P, He Y-Y, et al. IHH, SHH, and primary cilia mediate epithelial-stromal cross-talk during decidualization in mice. Sci Signal 2023;16(774):eadd0645. doi: 10.1126/scisignal.add0645.
[51] Chen S-T, Shi W-W, Lin Y-Q, et al. Embryo-derive TNF promotes decidualization via fibroblast activation. Elife 2023;12:e82970. doi: 10.7554/eLife.82970.
[52] Gu X-W, Chen Z-C, Yang Z-S, et al. Blastocyst-induced ATP release from luminal epithelial cells initiates decidualization through the P2Y2 receptor in mice. Sci Signal 2020;13(646):eaba3396. doi: 10.1126/scisignal.aba3396.
[53] Maltepe E, Bakardjiev AI, Fisher SJ. The placenta: transcriptional, epigenetic, and physiological integration during development. J Clin Invest 2010;120(4):1016–1025. doi: 10.1172/JCI41211.
[54] Jiang X, Zhai J, Xiao Z, et al. Identifying a dynamic transcriptomic landscape of the cynomolgus macaque placenta during pregnancy at single-cell resolution. Dev Cell 2023;58(9):806–821.e7. doi: 10.1016/j.devcel.2023.03.012.
[55] Zhang Y, Liang P, Yang L, et al. Functional coupling between TRPV4 channel and TMEM16F modulates human trophoblast fusion. Elife 2022;11:e78840. doi: 10.7554/eLife.78840.
[56] Shao X, Cao G, Chen D, et al. Placental trophoblast syncytialization potentiates macropinocytosis via mTOR signaling to adapt to reduced amino acid supply. Proc Natl Acad Sci U S A 2021;118(3):e2017092118. doi: 10.1073/pnas.2017092118.
[57] Wu L, Zhao KQ, Wang W, et al. Nuclear receptor coactivator 6 promotes HTR-8/SVneo cell invasion and migration by activating NF-κB–mediated MMP9 transcription. Cell Prolif 2020;53(9):e12876. doi: 10.1111/cpr.12876.
[58] Zheng Q, Gan H, Yang F, et al. Cytoplasmic m1A reader YTHDF3 inhibits trophoblast invasion by downregulation of m1A-methylated IGF1R. Cell Discov 2020;6:12. doi: 10.1038/s41421-020-0144-4.
[59] Hu M, Zheng Y, Liao J, et al. miR21 modulates the Hippo signaling pathway via interference with PP2A Bβ to inhibit trophoblast invasion and cause preeclampsia. Mol Ther Nucleic Acids 2022;30:143–161. doi: 10.1016/j.omtn.2022.09.006.
[60] Xu P, Li Z, Wang Y, et al. miR-18a contributes to preeclampsia by downregulating Smad2 (full length) and reducing TGF-β signaling. Mol Ther Nucleic Acids 2020;22:542–556. doi: 10.1016/j.omtn.2020.09.019.
[61] Ou Y, Zhu L, Wei X, et al. Circular RNA circ_0111277 attenuates human trophoblast cell invasion and migration by regulating miR-494/HTRA1/Notch-1 signal pathway in pre-eclampsia. Cell Death Dis 2020;11(6):479. doi: 10.1038/s41419-020-2679-6 .
[62] Jiang S, Chen Q, Liu H, et al. Preeclampsia-associated lncRNA INHBA-AS1 regulates the proliferation, invasion, and migration of placental trophoblast cells. Mol Ther Nucleic Acids 2020;22:684–695. doi: 10.1016/j.omtn.2020.09.033.
[63] Deng J, Zhao HJ, Zhong Y, et al. H3K27me3-modulated Hofbauer cell BMP2 signalling enhancement compensates for shallow trophoblast invasion in preeclampsia. EBioMedicine 2023;93:104664. doi: 10.1016/j.ebiom.2023.104664.
[64] Lyu C, Ni T, Guo Y, et al. Insufficient GDF15 expression predisposes women to unexplained recurrent pregnancy loss by impairing

extravillous trophoblast invasion. Cell Prolif 2023;e13514. doi: 10.1111/cpr.13514.
[65] Pan Y, Yan L, Chen Q, et al. Dysfunction of Shh signaling activates autophagy to inhibit trophoblast motility in recurrent miscarriage. Exp Mol Med 2021;53(1):52–66. doi: 10.1038/s12276-020-00530-6.
[66] Zhang L, Sang M, Li Y, et al. WNT3 hypomethylation counteracts low activity of the WNT signaling pathway in the placenta of preeclampsia. Cell Mol Life Sci 2021;78(21–22):6995–7008. doi: 10.1007/s00018-021-03941-4.
[67] Liu J, Shao X, Qin W, et al. Quantitative chemoproteomics reveals O-GlcNAcylation of cystathionine γ-lyase (CSE) represses trophoblast syncytialization. Cell Chem Biol 2021;28(6):788–801.e5. doi: 10.1016/j.chembiol.2021.01.024.
[68] Cui X, Wang H, Li Y, et al. Epiregulin promotes trophoblast epithelial-mesenchymal transition through poFUT1 and O-fucosylation by poFUT1 on uPA. Cell Prolif 2020;53(2):e12745. doi: 10.1111/cpr.12745.
[69] Dunlap KA, Palmarini M, Varela M, et al. Endogenous retroviruses regulate periimplantation placental growth and differentiation. Proc Natl Acad Sci U S A 2006;103(39):14390–14395. doi: 10.1073/pnas.0603836103.
[70] Yu M, Hu X, Pan Z, et al. Endogenous retrovirus-derived enhancers confer the transcriptional regulation of human trophoblast syncytialization. Nucleic Acids Res 2023;51(10):4745–4759. doi: 10.1093/nar/gkad109.
[71] Du C, Jiang J, Li Y, et al. Regulation of endogenous retrovirus-derived regulatory elements by GATA2/3 and MSX2 in human trophoblast stem cells. Genome Res 2023;33(2):197–207. doi: 10.1101/gr.277150.122.
[72] Zhou X, Xu Y, Ren S, et al. Trophoblast PR-SET7 dysfunction induces viral mimicry response and necroptosis associated with recurrent miscarriage. Proc Natl Acad Sci U S A 2023;120(25):e2216206120. doi: 10.1073/pnas.2216206120.
[73] Tang C, Ji M, Ma B, et al. RGS2 promotes estradiol biosynthesis by trophoblasts during human pregnancy. Exp Mol Med 2023;55(1):240–252. doi: 10.1038/s12276-023-00927-z.
[74] Yu Y, He J-H, Hu L-L, et al. Placensin is a glucogenic hormone secreted by human placenta. EMBO Rep 2020;21(6):e49530. doi: 10.15252/embr.201949530.
[75] Cross JC. How to make a placenta: mechanisms of trophoblast cell differentiation in mice—a review. Placenta 2005;26(Suppl A):S3–S9. doi: 10.1016/j.placenta.2005.01.015.
[76] Simmons DG, Cross JC. Determinants of trophoblast lineage and cell subtype specification in the mouse placenta. Dev Biol 2005;284(1):12–24. doi: 10.1016/j.ydbio.2005.05.010.
[77] Jiang X, Wang Y, Xiao Z, et al. A differentiation roadmap of murine placentation at single-cell resolution. Cell Discov 2023;9(1):30. doi: 10.1038/s41421-022-00513-z.
[78] Bao H, Liu D, Xu Y, et al. Hyperactivated Wnt–β-catenin signaling in the absence of sFRP1 and sFRP5 disrupts trophoblast differentiation through repression of Ascl2. BMC Biol 2020;18(1):151. doi: 10.1186/s12915-020-00883-4.
[79] Zhang Y, Le T, Grabau R, et al. TMEM16F phospholipid scramblase mediates trophoblast fusion and placental development. Sci Adv 2020;6(19):eaba0310. doi: 10.1126/sciadv.aba0310.
[80] Xu P, Zheng Y, Liao J, et al. AMPK regulates homeostasis of invasion and viability in trophoblasts by redirecting glucose metabolism: implications for pre-eclampsia. Cell Prolif 2023;56(2):e13358. doi: 10.1111/cpr.13358.
[81] Wang X-H, Xu S, Zhou X-Y, et al. Low chorionic villous succinate accumulation associates with recurrent spontaneous abortion risk. Nat Commun 2021;12(1):3428. doi: 10.1038/s41467-021-23827-0.
[82] du Fossé NA, van der Hoorn M-LP, van Lith JMM, et al. Advanced paternal age is associated with an increased risk of spontaneous miscarriage: a systematic review and meta-analysis. Hum Reprod Update 2020;26(5):650–669. doi: 10.1093/humupd/dmaa010.
[83] Xiong L, Ye X, Chen Z, et al. Advanced maternal age-associated SIRT1 deficiency compromises trophoblast epithelial-mesenchymal transition through an increase in vimentin acetylation. Aging Cell 2021;20(10):e13491. doi: 10.1111/acel.13491.
[84] Du L, Deng W, Zeng S, et al. Single-cell transcriptome analysis reveals defective decidua stromal niche attributes to recurrent spontaneous abortion. Cell Prolif 2021;54(11):e13125. doi: 10.1111/cpr.13125.
[85] Guo C, Cai P, Jin L, et al. Single-cell profiling of the human decidual immune microenvironment in patients with recurrent pregnancy loss. Cell Discov 2021;7(1):1. doi: 10.1038/s41421-020-00236-z.
[86] Yang Y, Zhu Q-Y, Liu J-L. Deciphering mouse uterine receptivity for embryo implantation at single-cell resolution. Cell Prolif 2021;54(11):e13128. doi: 10.1111/cpr.13128.
[87] Arck PC, Hecher K. Fetomaternal immune cross-talk and its consequences for maternal and offspring's health. Nat Med 2013;19(5):548–556. doi: 10.1038/nm.3160.
[88] Zhou Y, Fu B, Xu X, et al. PBX1 expression in uterine natural killer cells drives fetal growth. Sci Transl Med 2020;12(537):eaax1798. doi: 10.1126/scitranslmed.aax1798.
[89] Tao Y, Li YH, Zhang D, et al. Decidual CXCR4(+) CD56(bright) NK cells as a novel NK subset in maternal-foetal immune tolerance to alleviate early pregnancy failure. Clin Transl Med 2021;11(10):e540. doi: 10.1002/ctm2.540.
[90] Han M, Hu L, Wu D, et al. IL-21R-STAT3 signalling initiates a differentiation program in uterine tissue-resident NK cells to support pregnancy. Nat Commun 2023;14:7109. doi: 10.1038/s41467-023-42990-0.14:7356.
[91] Jiang L, Fei H, Jin X, et al. Extracellular vesicle-mediated secretion of HLA-E by trophoblasts maintains pregnancy by regulating the metabolism of decidual NK cells. Int J Biol Sci 2021;17(15):4377–4395. doi: 10.7150/ijbs.63390 .
[92] Yang SL, Tan HX, Lai ZZ, et al. An active glutamine/α-ketoglutarate/HIF-1α axis prevents pregnancy loss by triggering decidual $IGF1^{+}GDF15^{+}$NK cell differentiation. Cell Mol Life Sci 2022;79(12):611. doi: 10.1007/s00018-022-04639-x.
[93] Shapouri-Moghaddam A, Mohammadian S, Vazini H, et al. Macrophage plasticity, polarization, and function in health and disease. J Cell Physiol 2018;233(9):6425–6440. doi: 10.1002/jcp.26429.
[94] Ding J, Zhang Y, Cai X, et al. Extracellular vesicles derived from M1 macrophages deliver miR-146a-5p and miR-146b-5p to suppress trophoblast migration and invasion by targeting TRAF6 in recurrent spontaneous abortion. Theranostics 2021;11(12):5813–5830. doi: 10.7150/thno.58731.
[95] Gao L, Xu QH, Ma LN, et al. Trophoblast-derived lactic acid orchestrates decidual macrophage differentiation via SRC/LDHA signaling in early pregnancy. Int J Biol Sci 2022;18(2):599–616. doi: 10.7150/ijbs.67816.
[96] Sheng Y-R, Hu W-T, Shen H-H, et al. An imbalance of the IL-33/ST2-AXL-efferocytosis axis induces pregnancy loss through metabolic reprogramming of decidual macrophages. Cell Mol Life Sci 2022;79(3):173. doi: 10.1007/s00018-022-04197-2.
[97] Liu D, Li Q, Ding H, et al. Placenta-derived IL-32β activates neutrophils to promote preeclampsia development. Cell Mol Immunol 2021;18(4):979–991. doi: 10.1038/s41423-021-00636-5.
[98] Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. Nat Immunol 2004;5(3):266–271. doi: 10.1038/ni1037.
[99] Zhang L, Long X, Yin Y, et al. Histone methyltransferase Nsd2 ensures maternal-fetal immune tolerance by promoting regulatory T-cell recruitment. Cell Mol Immunol 2022;19(5):634–643. doi: 10.1038/s41423-022-00849-2.
[100] Ma Y, Yang Q, Fan M, et al. Placental endovascular extravillous trophoblasts (enEVTs) educate maternal T-cell differentiation along the maternal-placental circulation. Cell Prolif 2020;53(5):e12802. doi: 10.1111/cpr.12802.
[101] Cao D, Liu Y, Chen X, et al. Activation of iNKT cells at the maternal-fetal interface predisposes offspring to cardiac injury. Circulation 2022;145(13):1032–1035. doi: 10.1161/CIRCULATIONAHA.121.054239.
[102] Zhang W, Li S, Lou J, et al. Atrial natriuretic peptide promotes uterine decidualization and a TRAIL-dependent mechanism in spiral artery remodeling. J Clin Invest 2021;131(20):e151053. doi: 10.1172/JCI151053.
[103] He S, Guo Z, Zhou M, et al. Spatial-temporal proliferation of hepatocytes during pregnancy revealed by genetic lineage tracing. Cell Stem Cell 2023;30(11):1549–1558.e5. doi: 10.1016/j.stem.2023.09.002.
[104] Ilicic M, Zakar T, Paul JW. The regulation of uterine function during parturition: an update and recent advances. Reprod Sci 2020;27(1):3–28. doi: 10.1007/s43032-019-00001-y.
[105] Rubens CE, Sadovsky Y, Muglia L, et al. Prevention of preterm birth: harnessing science to address the global epidemic. Sci Transl Med 2014;6(262):262sr5. doi: 10.1126/scitranslmed.3009871.
[106] Huang J, Li Q, Peng Q, et al. Single-cell RNA sequencing reveals heterogeneity and differential expression of decidual tissues during the peripartum period. Cell Prolif 2021;54(2):e12967. doi: 10.1111/cpr.12967.
[107] Ji K, Chen L, Wang X, et al. Integrating single-cell RNA sequencing with spatial transcriptomics reveals an immune landscape of human

myometrium during labour. Clin Transl Med 2023;13(4):e1234. doi: 10.1002/ctm2.1234.
[108] Chen L, Song Z, Cao X, et al. Interleukin-33 regulates the endoplasmic reticulum stress of human myometrium via an influx of calcium during initiation of labor. Elife 2022;11:e75072. doi: 10.7554/eLife.75072.
[109] Chen HY, Gao LT, Yuan JQ, et al. Decrease in SHP-1 enhances myometrium remodeling via FAK activation leading to labor. Am J Physiol Endocrinol Metab 2020;318(6):E930–E942. doi: 10.1152/ajpendo.00068.2020.
[110] Zhao H, Wang Y, Xu H, et al. Stromal cells-specific retinoic acid determines parturition timing at single-cell and spatial-temporal resolution. iScience 2023;26(10):107796. doi: 10.1016/j.isci.2023.107796.
[111] Liu M, Ji M, Cheng J, et al. Deciphering a critical role of uterine epithelial SHP2 in parturition initiation at single cell resolution. Nat Commun 2023;14:7356. doi: 10.1038/s41467-023-43102-8.
[112] Yu Y, Liu Y, Sui X, et al. Arginase 1 and L-arginine coordinate fetal lung development and the initiation of labor in mice. EMBO Rep 2023;24(8):e56352. doi: 10.15252/embr.202256352.
[113] Lu JW, Wang WS, Zhou Q, et al. C/EBPδ drives key endocrine signals in the human amnion at parturition. Clin Transl Med 2021;11(6):e416. doi: 10.1002/ctm2.416.
[114] Rawlings TM, Makwana K, Taylor DM, et al. Modelling the impact of decidual senescence on embryo implantation in human endometrial assembloids. Elife 2021;10:e69603. doi: 10.7554/eLife.69603.
[115] Rawlings TM, Tryfonos M, Makwana K, et al. Endometrial assembloids to model human embryo implantation in vitro [published online July 5, 2023]. Methods Mol Biol. doi: 10.1007/7651_2023_495.
[116] Tian J, Yang J, Chen T, et al. Generation of human endometrial assembloids with a luminal epithelium using air-liquid interface culture methods. Adv Sci (Weinh) 2023;10(30):e2301868. doi: 10.1002/advs.202301868.
[117] Gu Z, Guo J, Zhai J, et al. A uterus-inspired niche drives blastocyst development to the early organogenesis. Adv Sci (Weinh) 2022;9(28):e2202282. doi: 10.1002/advs.202202282.
[118] Zhang H, Xu D, Li Y, et al. Organoid transplantation can improve reproductive prognosis by promoting endometrial repair in mice. Int J Biol Sci 2022;18(6):2627–2638. doi: 10.7150/ijbs.69410.
[119] Wu H, Wang Y, Wang H. Generation of human trophoblast stem cell-dependent placental in vitro models [published online December 15, 2022]. Methods Mol Biol. doi:10.1007/7651_2022_463.
[120] Huang L, Tu Z, Wei L, et al. Generating functional multicellular organoids from human placenta villi. Adv Sci (Weinh) 2023;10(26):e2301565. doi: 10.1002/advs.202301565.
[121] Zhao X, Zhang Z, Zhu Q, et al. Modeling human ectopic pregnancies with trophoblast and vascular organoids. Cell Rep 2023;42(6):112546. doi: 10.1016/j.celrep.2023.112546.

Edited By Yang Pan

How to cite this article: Bao H, Wang H. Basic Research Advances in China on Embryo Implantation, Placentation, and Parturition. Maternal Fetal Med 2024;6(1):37–49. doi: 10.1097/FM9.0000000000000210.