Review

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Preterm Labor, a Syndrome Attributed to the Combination of External and Internal Factors

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Abstract

Preterm labor (before 37 weeks' gestation) is the leading cause of neonatal mortality and morbidity, which can be divided into iatrogenic preterm labor, infectious preterm labor, and spontaneous preterm labor (sPTL). Up to now, there continue to be great difficulties in prediction and prevention of sPTL, owing to multiple risk factors, pathogenesis, and pathologic processes contributing to the event, which have not been fully clarified. Pregnancy maintenance and parturition is a complicated process with continuous maternal-fetal dialogue, in which both maternal and fetal factors participate and affect the outcome of pregnancy, including sPTL. Besides, external factors can also participate in sPTL, individually or through the interaction with internal factors. In this article, we summarize recent studies regarding sPTL from our and other groups, and discuss the risk factors and pathogenesis of preterm birth from both external and internal (maternal and fetal) aspects, so as to provide theoretical evidences for the diagnosis, prevention, and treatment of sPTL in the future.

Keywords: Obstetric labor, premature; Maternal factor; Fetal factor; Maternal-fetal crosstalk; External factor

Introduction

The incidence of preterm labor is about 12% world-wide, and remains the leading cause of neonatal mortality and morbidity, bringing heavy emotional and financial burdens to both family and society.[1] According to a report by the World Health Organization in 2015, preterm birth is the top cause of all deaths among newborns and children under 5 years of age. Of the 2.76 million newborn deaths worldwide, 34.95% are attributed to complications caused by preterm birth. In China, preterm birth accounts for 17.4% of deaths among infants under 5 years of age,[2] in which 60% of infant deaths occur in the neonatal period.[3] Even if premature infants survive, the incidence of infectious diseases, hemorrhagic diseases, neurodevelopmental disorders, and respiratory and gastrointestinal complications during neonatal period, and even the incidence of diseases in adulthood, are significantly higher than those of full-term infants.[4]

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According to their pathogenesis, preterm labor was usually classified into three types: (1) infectious preterm labor caused by the intra-uterine or genital tract infection; (2) iatrogenic preterm labor due to maternal or fetal indications, such as preeclampsia (PE), intrauterine growth restriction, and others; (3) spontaneous preterm labor (sPTL).[5,6] While the infectious preterm labor and iatrogenic preterm labor have explicit causes and higher success rates of prevention and treatment, the etiology, risk factors, and pathogenesis of sPTL have not been fully clarified, which brings great limitations to the prediction, diagnosis, and intervention of these patients. This review aims to discuss the recent studies on the external and internal risk factors, pathogenesis, and the underlying mechanisms of sPTL, or so-called unexplained premature birth, which accounts for 70% of the incidence of preterm labor.[7,8]

External risk factors affecting preterm labor

Pregnant women obtain nutrients and micro elements essential for physiological functions from food, water, or even air. However, a number of studies showed that exposure to air pollution (PM2.5), ozone, and heat was associated with increased risk of preterm birth.[9] Heat and air pollution are independent risk factors of preterm birth.[10,11] Many chemical contaminants, such as nitrate, diisobutyl phthalate metabolites, bisphenol-S, and ethyl paraben have been found to be risk factors for sPTL,[12–14] while 2, 5-dichlorophenol is inversely correlated with overall PTL.[14]

Food and nutrition

High intake of fruits and proteins and less intake of added sugars, saturated fats and fast foods, which is similar to Mediterranean-style diet, is associated with a lower risk of preterm birth.[15–18] High-fat diet-potentiated sPTL is

mediated by increased inflammation, gut dysbiosis, and reduced antioxidant capacity in murine model, which can be partly reversed by the induction of immune tolerance via endotoxin priming.[19]

Micro elements obtained from food, such as copper (Cu), manganese (Mn), selenium (Se), zinc (Zn), and iron (Fe) are necessary for human body to play physiological functions as well as in pregnancy. However, their roles in preterm birth are controversial. Cohorts in Australia and in China confirmed that Cu level is positively associated with the risk of sPTL in first trimester,[20] and its potential mechanism may be increasing plasma total cholesterol and triglycerides.[21] In a Puerto Rico cohort, maternal blood Mn was associated with shorter gestational age and higher odds of PTL.[22] Women who underwent sPTL had higher level of Mn in serum[23] and lower Se in blood and urine.[24] The association between high serum Mn level and increased risk of sPTL can be modified by SNPs of antioxidant enzymes of superoxide dismutase 2(MnSOD), superoxide dismutase 3 (EcSOD)and catalase (CAT).[23] Se metabolism genes are also involved in gestational length, and maternal dietary Se intake is associated with low risk of preterm delivery.[25] The associations between Zn and PTL varied by infant sex. Blood Zn was negatively associated with gestational age only among female infants.[22] A Ma'anshan birth cohort study in China suggested that prenatal Hg levels are associated with the risk of preterm birth and that high maternal serum Zn levels alleviate the negative effects.[26] These studies suggested that reasonable diet and proper supplement of some micro elements, such as Se and Zn, may contribute to the reduction of sPTL incidence.

Heavy metals in pollutions

Although some micro elements are essential for normal pregnancy, with the development of industrial society, association between excess exposure of heavy metals in pollutions and PTL has been eliciting increasing concerns. It has been reported that heavy metals such as arsenic (As), cadmium (Cd), chromium (Cr), mercury (Hg), and lead (Pb) are related to sPTL.[22,26–31] Heavy metals and metalloids may promote the oxidative stress, epigenetic modification, and inflammation in the placenta,[31] as well as induce decidual cell death and inflammation[32] and endocrine disruptions,[31] which subsequently lead to sPTL.

However, different designs, sample size, and exposure levels to the toxic metals may result in controversial results across different studies.[27] Some studies showed no significant associations between the serum toxic metals (i.e., As, Cd, Cr, Hg, and Pb) and the sPTL risk.[24,27,29] A cohort in Shanxi Province, China, suggested Hg in serum and Hg in blood cells individually did not show association with sPTL, but higher concentration ratio of Hg in serum and Hg in blood cells in the first trimester was positively associated with an elevated risk of sPTL.[33] Further studies are needed to address the effects and underlying mechanisms of the toxic metals on the occurrence of sPTL.

Internal risk factors affecting preterm labor

Maternal risk factors

Maternal age (<18 years, or >40 years), ethnicity (Black race), body mass index (<19 kg/m^2), smoking, stress (depression, anxiety), heavy physical labor, education, poverty, and other social factors have all been reported to be associated with sPTL.[34,35] The intrinsic factors like maternal genetic variations, immune response, obstetric factors (such as prior preterm delivery, uterine curettage, cervical factors, multiple gestations, and adverse outcome of previous term pregnancy[33]) may also increase the risk of sPTL. Moreover, some diseases or disorders during pregnancy, such as kidney dysfunction,[36] renovascular disease,[37] cesarean section at term,[38] history of surgery for endometriosis[39] or cervical intraepithelial neoplasia,[40] were all associated with an increased risk of sPTL.

Maternal genetic variations

The incidence of preterm birth varies among human populations, which may be due to their different genetic mutations. Progesterone (P4) plays a central role in the process of reproduction in females. Progesterone receptor (PR) differentiation brings different risks of preterm birth among human populations. Remodeling PR expression specifically in the ovary determined a significant association of early sPTL with the variants.[41]

Multiple genome-wide association studies (GWAS) have been done in European or Caucasian ancestry, and variants at the early B-cell factor 1 (EBF1), eukaryotic elongation factor, selenocysteine tRNA-specific (EEFSEC), angiotensin II receptor, type 2 (AGTR2), RAB31, member RAS oncogene family (RAB31) and recombination signal binding protein for immunoglobulin kappa J region (RBPJ) loci were identified to be associated with PTL.[42,43] Multi omics (GWAS, whole exon sequencing, and transcriptome sequencing) also showed multiple correlations between hot shock protein, nuclear receptors, and preterm birth.[44] Genetic variations related with PTL have been revealed to involve in development, growth, EGFR and prolactin signaling, Notch 1 signaling, and inflammation- and immunity-related pathways.[43,45,46] However, in Asians, GWAS related with PTL is still absent.

Genetic variations may function via increased susceptibility to sPTL, or the so-called "two-hit" concept. The variations are the "first hit", and the epigenetic regulations are the "secondary hit". The "two hit" leads to the potential molecular mechanisms of sPTL.[47] For example, genetic variation of the sarcomere gene, titin (TTN), which encodes the protein Titin, and methylation of the uterine contraction-associated sarcomeric and desmosomal genes (actin (ACT), myosin (MYO), troponin (TNNT), cystain (CST)) could constitute of the "two hit".[47] However, most GWAS studies focused on revealing the association between genetic variations and preterm birth; the means by which the variations of these genes cause sPTL still need further mechanism analysis.

Cervical and myometrium modification and remodeling

Uterine quiescence, contractility, and the transition between the two states are important for a successful pregnancy. Onset of the term human parturition involves in myometrial gene expression changes to transform the uterus from a quiescent to a contractile phenotype. A series of genome-wide screening studies were conducted in

human uterus to dissect the differentially expressed genes between different phases in gestation.[48–50] However, these studies mainly focused on the inflammatory profile or contractility changes in uterus during pregnancy and labor.[51–53] For example, GPR91 expression was significantly higher in myometrium in term labor (TL) compared to term not in labor. In a mouse model, GPR91 was involved in interleukin 1β (IL1β) and tumor necrosis factor α (TNF-α) induced preterm birth by regulating the expression/secretion of proinflammatory cytokines (GM-CSF, IL1α, IL1β, and IL6), chemokines (CXCL8 and CCL2), myometrial contractility (prostaglandin F receptor (PTGFR), C-C motif chemokine ligand 2 (CCL2), prostaglandin F2α (PGF2α), and nuclear factor kappa B subunit 1 (NF-κB)).[54] Towards term, the adaptive mechanosensitive response may transit to increase the force producing capacity in preparation for the final initiation of laboring contractions; however, the molecular basis for uterine remodeling during late gestation was largely ignored. Our group found that src-homology phosphatase type-1 was significantly decreased in human myometrium in labor compared with that not in labor, which increased phosphorylation at Tyr397 and Tyr576/577 sites of focal adhesion kinase and enriched plasmalemmal dense plaques in myometrial cells. Timed-pregnant mice injected intraperitoneally with the specific src-homology phosphatase type-1 inhibitor, protein tyrosine phosphatase inhibitor I (PTPI-1), manifested significantly preterm labor.[55]

Besides proteins, gasotransmitters also have been found to participate in the regulation of uterine contraction. Nitric oxide causes uterine relaxation through both classical pathway and 3′,5′-cyclic guanosine monophosphate (cGMP)-independent pathway. The nitric oxide metabolites S-nitrosoglutathione (GSNO) and peroxynitrite (ONOO−) mediate S-nitrosation and cytotoxicity, respectively, to promote uterine relaxation and cervical remodeling.[56] Another gasotransmitter, hydrogen sulfide, inhibits the expression of contraction associated protein genes (Connexin 43 (CX-43), PTGFR, oxytocin receptor (OTR)) to suppress spontaneous contraction of the human uterus[57] and reverses the lipopolysaccharides (LPS)-induced PTL by its anti-inflammatory effects.[58]

Mammalian microRNAs (miRNA/miR) play especially powerful roles in smooth muscle cells and in female reproduction, wherein they have been implicated in hormone responsiveness.[59] The identification of miRNAs as hormonally regulated modulators of gene expression prompted researchers to uncover the differential expression of miRNA in myometrium between labor and term not in labor, as well as their interactive roles with sexual hormones in regulation of contraction-associated genes during pregnancy and labor. Renthal *et al.*[60] uncovered the miR-200 family and their targets, zinc finger E-box binding homeobox proteins (ZEB) 1 and ZEB2, as unique P4- and PR-regulated modulators of uterine quiescence and contractility via regulating contraction associated proteins genes during pregnancy and in term and preterm labor. Among them, miR-200a plays a key role in the induction of local P4 metabolism through its bona fide target StAT5b and subsequent 20α-HSD expression in the pregnant uterus.[61] In the opposite, miR-199a-3p/miR-214 cluster and miR181a family were significantly decreased in laboring myometrium of pregnant mice and humans, and they could regulate myometrial contractility through cyclooxygenase 2 (COX2) and TNF-α, respectively. Interestingly, estrogen (E2) suppressed whereas P4 enhanced uterine miR-199a-3p/214 expression mediated by ZEB1, which is induced by P4 and inhibited by E2. Similarly, E2 suppressed miR181a expression and this suppression was reciprocally reinforced by the upregulation of miR-181a target, ERα expression and its binding enrichment to the miR-181a/b-1 regulatory region.[62] Taken together, these findings identify specific miRNAs closely coordinated with E2 and P4 during labor to comprehensively regulate myometrium contractility, resulting in the decline in PR function, and eventually leading to labor or preterm labor.

Maternal blood

The metabolites, proteins, RNAs, and exosomes contained in maternal peripheral blood have undergone great changes during pregnancy week by week. Owing to their non-invasive, convenient, and quantifiable attributes, circulating molecules are naturally promising biomarkers for non-invasive PTL prediction.[14,63–68] An untargeted metabolomics profiling by Liang *et al.*[69] found the metabolic clock of pregnancy based on the highly dynamic metabolic changes, in which 460 annotated compounds and 34 human metabolic pathways were significantly changed during healthy pregnancy. Based on their dynamic and precise change during pregnancy, with just three metabolites (THDOC, Androstane-3,17-diol, and Estriol-16-glucuronide), the metabolome accurately predicted an upcoming delivery event within 2 weeks with area under the receiver operating characteristic curve close to 0.9.[69] Another plasma lipidomics study in women at 20 weeks of gestation identified an sPTL group having lower levels of 26 lipids, including 20 glycerophospholipids and six sphingolipids and higher level of diaglyceride compared to TL group.[64] Maternal metabolism may function in sPTL by affecting uterine contractility. Obese pregnant women typically have low circulating adiponectin level, which inhibits uterine contraction and is associated with increased risk for PTL.[70]

The circulating protein signals of sPTL can be detected as early as 11 weeks of gestation. Protein profile of maternal serum samples at $11–13^{+6}$ weeks' gestation identified 30 proteins significantly increased or decreased in the sPTL group, including nine phosphoproteins and 11 glycoproteins. The most significant change is complement activation (increase in complement factors C4-A, factor B, and H, but a decrease in complement C3), which could be potential early biomarkers for sPTL.[71] Another proteomic assessment in maternal serum identified insulin-like growth factor–binding protein 4 was up-regulated in sPTL cases, and sex hormone–binding globulin was down-regulated in sPTL cases. Ratio of insulin-like growth factor–binding protein 4/sex hormone–binding globulin levels combined with a body mass index interval of >22 kg/m^2 and ≤ 37 kg/m^2 could predict ~75% of women destined to sPTL at 19–20 weeks.[63]

Multiple studies have demonstrated the potential of circulating fetal RNA or mRNA in maternal blood for predicting preterm labor. Seven circulating fetal RNA

transcripts (chloride voltage-gated channel 3 (CLCN3), dual adaptor of phosphotyrosine 3-phosphoinositides 1 (DAPP1), pro-platelet basic protein (PPBP), MAP3K7 C-terminal like (MAP3K7CL), MOB kinase activator 1B (MOB1B), RAB27B and regulator of G protein signaling 18 (RGS18)) accurately classified women who delivered preterm up to 2 months in advance of labor.[65] In whole blood, an optimal random forest classifier model to predict sPTL was achieved using nine differentially expressed genes (zinc finger, DHHC-type containing 19 (ZDHHC19), hydroxyprostaglandin dehydrogenase 15-(NAD) (HPGD), G protein-coupled receptor 84 (GPR84), 5-oxoprolinase (ATP-hydrolysing) (OPLAH), methyltransferase like 18 (METTL18), tudor domain containing 9 (TDRD9), ATPase, class II, type 9A (ATP9A), UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 14 (GALNT14) and golgin A8 family, member A (GOLGA8A)) between women with threatened preterm labor who did or did not have a sPTL within 48 hours of hospital admission.[72] In addition, RNA sequencing in both whole blood and peripheral monocytes from women undergoing preterm labor (24–34 weeks of gestation) revealed that ADAM metallopeptidase with thrombospondin type 1 motif 2 (ADAMTS2) expression was significantly increased compared to healthy pregnant controls.[73] Comprehensive miRNA profiling of women undergoing sPTL in both whole blood and peripheral monocytes identifies a number of miRNAs (such as miR-495–3p and miR-381-3p in whole blood, miR-223 in plasma, and miR-1291-5p in monocytes) changes with sPTL, although they are limited to the small sample size to perform any predictive analyses.[68]

In preterm pregnant women, cell-free circulating microparticles are also different from those in women undergoing term labor, which can be detected even in early pregnancy. Cantonwine *et al.*[74] did proteomic analysis in circulating microparticles at 10–12 weeks gestation from term in labor and PTL women, and differentially expressed proteins were found in pathways related to coagulation, fibrinolysis, immune modulation, and the complement system. Maternal plasma exosome analysis identified 72 proteins enriched in inflammatory and metabolic signaling pathways, which are associated with term and preterm birth.[75] Proteins in circulating microparticles also have the potential to predict sPTL. A panel of circulating microparticles proteins (coagulation factor XIII A chain (F13A), fibulin-1 (FBLN1), inhibitor of C1 (IC1), inter-alpha-trypsin inhibitor heavy chain 2 (ITIH2) and lecithin-cholesterol acyltransferase (LCAT)) obtained in the late first trimester predicted sPTL $\leq$35 weeks, and showed an area under curve of 0.74.[66] Circulating exosomal miRNA profile manifested dramatic changes between TL and PTL as well, revealing a total of 173 differentially expressed miRNAs related to TGF-β signaling, p53, and glucocorticoid receptor signaling, according to Menon *et al.*[76]

The changes of molecules in maternal blood may be just the consequence of PTL, or involved in the occurrence of PTL. Current studies mainly focused on the association between the blood molecules and PTL. In-depth research focusing on the potential biological functions of these molecules in the occurrence of PTL is warranted. On the other hand, most biomarker discovery studies were conducted in European and American populations, and the amount of samples used in the verification stage is relatively small. Large-scale, multi-center clinical verification of the biomarker applicability in different ethnicity is urgently needed.

Fetal risk factors

Fetal genetic variations

Although the maternal factors draw most attention in preterm labor studies, signals from fetus play important roles in normal parturition and preterm labor, as well. A fetal genome-wide association meta-analysis in 84,689 infants showed a locus on chromosome 2q13 is associated with gestational duration, and the association is driven by fetal genotype. The lead SNP, rs7594852 and rs7594852-C allele may delay signaling from the fetus to the mother, thus prolonging gestation.[77] Fetal SLIT2 variants are also correlated with susceptibility to sPTL. The upregulated levels of SLIT2 and its receptor ROBO1 in sPTL placentas could regulate the expression of several pregnancy-specific beta-1-glycoprotein genes and inflammation related genes.[78] Fetal cord arterial blood exosomes proteomics analysis revealed the increase of C4BPA, which binds to CD40 of placental villous trophoblast to activate p100 processing to p52, and in turn, the upregulation of pro-labor genes.[79] Menon and Taylor[80] collected amniotic fluid, cord blood, and maternal plasma in four conditions (term not in labor, TL, PTL, and premature rupture of fetal membranes), and measured the expression of two damage-associated molecular pattern markers (high-mobility group box-1 and uric acid), and two acute phase response markers (IL-6 and C-reactive protein). Accumulation of high-mobility group box-1 and an overall increase in inflammation were observed in PTL group on the fetal side (amniotic fluid and cord blood), but not on the maternal side.[80]

Placenta

The specific fetal organ, placenta, is the interface between fetal and maternal circulations, and is closely related to pregnancy and delivery. Placental insufficiency and hypermaturity are both potential causes of preterm labor.[81,82] Tryptophan is crucial for proper placental function. Genes involved in tryptophan metabolism/transport were highly expressed in placentas associated with sPTL.[83] Placenta RNA-seq and metabolomics studies suggest that placenta mitochondrial function and energy metabolism are altered, and the imbalanced glycolysis and unconventional lactate oxidation may be associated with sPTL.[84,85] The placenta-derived extracellular vesicles proteins proteome revealed that nonspecific inflammation coagulation was upregulated while complement activation-related proteins were downregulated in cargo from first trimester in sPTL.[86]

These differentially expressed molecules in placenta exerted different roles in the occurrence of sPTL. Higher levels of SLIT2 and its receptor ROBO1 upregulate pregnancy-specific beta-1-glycoprotein genes and inflammation-related genes in trophoblast-derived cells.[78] Placental serum amyloid A1 increases during syncytialization and may participate in the onset of labor in the presence or absence of infection by increasing the production of

proinflammatory cytokines and PGF2α in the placenta.[87] Our previous studies suggested a human placenta specific hormone, corticotropin-releasing hormone, could increase estradiol production and inhibit P production, which cause the increase in the proportion of intrauterine local E2/P4 ratio and facilitate parturition.[88] Ferroptotic cell death is a newly discovered pathway in placental trophoblast, characterized by excessive accumulation of hydroperoxy-arachidonoyl (C20:4)- or adrenoyl (C22:4)- phosphatidylethanolamine (Hp-PE), which is apparent in sPTL placenta caused by GPX4 inhibition and can be mitigated by the phospholipase PLA2G6, known to metabolize Hp-PE to lyso-PE and oxidized fatty acid.[89]

Fetal membrane

Besides placenta, fetal membrane is also a source of labor initiating signals. A proteomic study of fetal membrane between preterm and full-TL revealed 62 proteins differentially expressed, which were involved in inflammation, T cell/macrophage activation, metabolism and synthesis, cell adhesion, proteolysis, and extracellular matrix pathways.[84] As an important barrier between fetus and mother, cortisol degradation and regeneration in the fetal membranes is a requisite event in parturition.[90] Cortisol involves in the rupture of fetal membranes through decreasing collagen I, III, IV, or inducing serum amyloid A1 to remodel extracellular matrix.[90,91] Cortisol can also upregulate prostaglandin E2 and PGF2α, which play key roles in cervical ripening, membrane rupture, uterus contraction, and gestational tissues' inflammation in parturition.[92] 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), COX-2, and CCAAT enhancer binding protein δ (C/EBPδ) are increased in late gestation in human and mouse fetal membranes. Transcription factor C/EBPδ induces the expression of COX-2 and 11β-HSD1, which are the key enzymes in production of amnion-derived prostaglandin E2 and cortisol. Inhibition of the C/EBPδ in mouse may delay labor onset in preterm birth.[93]

Fetal lung

Maturation of the fetal lung and increased production of pulmonary surfactant components have been proposed to provide signals for the initiation of parturition.[94–96] Surfactant synthesis by alveolar type II cells is initiated in the fetal lung after ~80% of gestation is complete and is secreted into amniotic fluid. After birth, surfactant functions to reduce alveolar surface tension and is essential for air breathing. The first evidence that fetal lung surfactant could promote an inflammatory response within fetal membranes came from studies of López Bernal *et al.*[97] who found that surfactant from human amniotic fluid stimulated prostaglandin synthesis in human amnion discs. Surfactant protein (SP), SP-A, a C-type lectin (collectin) that acts postnatally within the lung alveolus to enhance macrophage function to engulf microorganisms,[98] is developmentally upregulated in fetal lung with surfactant phospholipid synthesis. Pregnant mice injected with SP-A at 15.5 dpc delivered prematurely at 16.5–17.5 dpc from the injected horn only, while intra amniotic injection of an SP-A antibody resulted in a 24 hours delay in labor.[94]

In Mendelson and Gao's recent work,[96] they generated a line of mice model in which steroid receptor coactivator (SRC), a known coactivator that recruit thyroid transcription factor-1 (TTF-1, also known as Nkx2.1) and NF-κB bound to the surfactant protein (SP)-A promoter, was knocked-out. SRC-1/SRC-2 doubly heterozygous females manifested a pronounced delay in parturition timing. Intriguingly, wild-type females bred with SRC-1/SRC-2 doubly deficient males showed an equivalent delay in parturition timing, suggesting the SRC-1/2 deficiency of the fetuses delays the timing of birth. In light of the prior work, it was found that SRC-1/-2–dependent production of SP-A, and another potent proinflammatory phospholipid known to promote myometrial contractility, platelet-activating factor, are crucial for this process.[96] In the subsequent studies, we observed impaired fetal lung development in SRC-1/-2$^{d/d}$ fetuses, and did the genome wide analysis in the SRC-1/-2$^{d/d}$ fetal lungs. The mRNA expression of 11β-HSD1, C/EBPα, and C/EBPβ was significantly decreased in SRC-1/-2$^{d/d}$ fetal lungs compared with wild type fetal lungs.[99] As mentioned above, 11β-HSD1 catalyzes conversion of inactive 11-dehydrocorticosterone to the active form, corticosterone, and it can be upregulated by glucocorticoids in various cell types via induction of C/EBP.[94] Taken together, the impaired lung development and surfactant synthesis in SRC-1/-2$^{d/d}$ fetuses may be partly caused by break in the glucocorticoid-induced positive feedforward loop mediated by 11β-HSD.[99]

Maternal-fetal interaction

The maintenance of pregnancy and the initiation of parturition is a continuous and dynamic process during which real-time interactive dialogues sustain between mother and fetus. Fetal blood and maternal blood exchange nutrients, waste, and gas through the placenta. As an allogeneic transplant, the fetus carries half of the paternal genes. The maternal-fetal interface, i.e., decidua, constitutes an immune tolerant microenvironment between mother and fetus during most of pregnancy to prevent premature initiation of labor. Therefore, the important feature of the mother-fetal dialogue during pregnancy is the balance and transformation between the immune rejection and immune tolerance.[100] The lack or abnormality of maternal-fetal immune tolerance in the middle and late stages of pregnancy may be closely related to the occurrence of preterm birth.

On the fetal side, the extravillous trophoblast cells of the placenta express non-classical human leucocyte antigen class I molecules, such as human leukemia antigen (HLA)-G, HLA-C, and HLA-E, but do not express the classic HLA-A, HLA-B, and HLA-II molecules. This unique combination only exists in extravillous trophoblast cells, but not in any other somatic or extraembryonic cells.[101] At the same time, fetal trophoblasts also express multiple complement proteins such as CD55, CD46, CD59, complement receptor 1 related protein (Crry), etc.[102,103] Recent studies have also found that the functional dendritic cells (DCs) exist in the fetus as early as the 13th week of gestation. However, unlike adult DCs in response to allogeneic antigens, fetal DCs promote the induction of regulatory T cells through arginase 2 and

inhibit the production of TNF-α, thereby helping the fetus maintain immune tolerance to maternal cells.[104]

On the maternal side, there are also multiple mechanisms for the mother to maintain the immune tolerance to the fetus. In early pregnancy, the maternal-fetal immune tolerance starts when the paternal antigen carried by the sperm contacts the mother, and is presented to the immune cells at the decidua via DCs to promote the proliferation and differentiation of antigen-specific Treg cells, and these work together with a variety of immune cells to create a tolerant microenvironment for embryo implantation.[105] Meanwhile, immune cells also promote the generation and remodeling of uterine blood vessels to provide nutrition supply for embryo implantation.[106] If the immune tolerance environment is disordered or the blood supply is not established properly, it will cause implantation failure and miscarriage. The physical barrier of decidua can also restrict T cells and B cells from entering the fetal circulation to protect it from the immune attack.[107,108] In the third trimester of pregnancy, the white blood cells (WBC) in the circulating blood were attracted to the reproductive tissues (uterine muscle and cervix) to activate the uterus through the secretion of inflammatory cytokines leading to the parturition.[109]

WBCs were found to be significantly upregulated in laboring women compared to pregnant women not-in-labor,[110] whereas different types of WBC play different roles in preterm labor. The current research on the relationship between maternal-fetal immune tolerance and preterm birth mainly focuses on comparing the numbers and proportions of neutrophils, macrophages, natural killer (NK) cells, T cells, and B cells in the maternal-fetal interface and circulation, whereas the conclusions are contradictory. Decidual neutrophils contribute to the physiological rupture of membranes and premature rupture of fetal membranes during term and preterm labor.[111] In a mouse model with preterm labor induced by LPS, the number of decidual neutrophils increased, but the depletion of neutrophils did not delay LPS-induced preterm birth.[112] Macrophages contribute to multiple processes in parturition, including the uterine contraction, cervical ripening, and rupture of membranes through the production of proinflammatory cytokines and matrix metalloproteinase 9 (MMP-9).[113,114] Macrophages showed diverse functions in preterm labor due to both promoting and suppressing inflammation. The amniotic concentration of monocyte chemotactic protein-1, a monocyte/macrophage chemoattractant, is increased in women with sPTL.[115] Macrophage depletion during pregnancy can prevent cervical remodeling and PTL induced by LPS in mice model.[116] However, the different functions of M1/M2 phenotypes of macrophages during labor and preterm labor are not fully demonstrated. Further studies are required to elucidate the roles of different clusters of macrophages in the physiological process of labor and the pathological induction of sPTL.

Decidual NK cells are the major immune cells at the maternal-fetal interface during early pregnancy, which can regulate the maternal uterine spiral artery remodeling and trophoblast cell invasion to play important roles in implantation and miscarriage.[117,118] As the pregnancy progresses, NK cells in the decidua gradually decrease, accompanied by an increase in T cells. Invariant natural killer T (iNKT) cells activate premature delivery by increasing cytotoxicity. In patients with threatened premature delivery, the proportion of activated iNKT in the decidua is increased, and the levels of iNKT related effectors, CD69, perforin, and IFN-γ in peripheral blood are higher than those in normal delivery women.[109,119] Compared with the wild-type control group, the preterm birth rate was significantly reduced in iNKT cell knockout mice receiving intraperitoneal injection of LPS at 15 days of pregnancy, indicating that iNKT cells regulate the inflammatory preterm birth induced by bacterial products.[120] Peroxisome proliferator-activated receptor γ (PPARγ) pathway has potential as a target for prevention of sPTL induced by innate and adaptive immune response initiated by activated iNKT cell.[119]

It was shown that the proportion of lymphocytes at the maternal-fetal interface of preterm birth is significantly changed,[121] and the increased proportion of lymphocytes in mononuclear cells can be used as predictors for preterm birth.[122] The ratio of $CD45RA^+CCR7^+CD8^+$ T cell in preterm patients was significantly increased, suggesting that naïve T cells may play an important role in the process of preterm delivery.[123] For the two major subtypes of $CD4^+$ T cell, T helper type 17 cells and Treg cells share a common precursor cell (naïve $CD4^+$ T cell) but play an antagonistic role in maintaining immune tolerance at the maternal-fetal interface.[106,124] DCs are also involved in the regulation of T cell differentiation. Studies have found that in the second trimester (16–22 weeks), fetal DCs promote Treg cell differentiation through upregulating arginase 2, and at the same time reduce the production of pro-inflammatory cytokine TNF-α to enhance the fetal immune tolerance to allogeneic antigens. Near delivery, the content of placental $CD11c^+$ DCs and Treg cells decreased, and the cytokines IL-9 and IL-35 secreted by them also decreased accordingly.[125] Exhausted and senescent T cells can be reactivated at the maternal-fetal interface by inflammatory responses accompanying preterm labor, leading to an aberrant effector T-cell response that can trigger preterm labor.[126] As an important part of adaptive immunity, B cells also participate in the regulation of immune tolerance during pregnancy, by secreting IL-10 and reducing the TNF-α secretion of $CD4^+$ T cells.[127] A high proportion of $CD20^+CD70^-$ B cells was found in the decidua of sPTL women, leading to a decrease in the expression of progesterone-induced blocking factor 1 and a decrease in IL-33 secretion, which may be an incentive of premature delivery.[128]

The immune cells at the maternal-fetal interface have strong heterogeneity. Even in a certain type of known immune cells (such as Treg cells), there are subgroups with different functions.[129] Therefore, traditional "bulk" transcriptomic analysis will not be sufficient to reveal the specific pathways implicated in preterm labor. There is an urgent need to dissect the subtypes, distribution, and regulation of immune cells of the third trimester between TL and sPTL at single-cell transcriptomic level, to clarify the characteristics of mother-fetal dialogue in the immune microenvironment specific for preterm labor, and provide new theories for the ultimate solution to the mystery of labor initiation and preterm delivery.

Interactions between external and internal factors

The interactive effects of external and internal risk factors on preterm labor have also been gradually recognized. Psychosocial stress intensified the adverse associations between heavy metals and PTL.[130] Among women with "poor" psychosocial status, higher Ni was associated with lower odds of PTL, but higher blood Mn increased odds of PTL (overall and sPTL).[22,130] Maternal type 1 diabetes has been linked to preterm birth and other adverse pregnancy outcomes.[131] Exposure to higher levels of air pollution increased the risk of poor placental vascularization in women with type 1 diabetes and may result in PTL.[132]

Microbiota is another important external factor interacted with human internal factors contributing to PTL. Forty to fifty percent of preterm births are associated with microbial etiologies.[133] Population shifts from high proportions of lactobacilli to mixed species communities, as seen with bacterial vaginosis, have been linked to a twofold increased risk of sPTL.[134] Longitudinal analyses in a cohort of women predominantly of African ancestry with harbingers of preterm birth identifies women who delivered preterm exhibited significantly lower vaginal levels of *Lactobacillus crispatus* and higher levels of bacterial vaginosis associated bacterium 1, *Sneathia amnii*, TM7-H1 (a species of bacteria in the phylum *Candidatus Saccharibacteria*), a group of *Prevotella* species, and nine additional taxa, which were correlated with proinflammatory cytokines in vaginal fluid.[133] Another study in a cohort of African American women identified seven cervicovaginal bacterial taxa significantly associated with increased risk of sPTL.[135] Although most cervicovaginal bacterial taxa found in these two cohorts were different, lower level of *Lactobacillus crispatus* was found in both to be associated with sPTL. *Lactobacillus crispatus* is strongly linked to full-term pregnancies, act as a protective effect by suppressing inflammation through H_2O_2 signaling to control NF-κB activity, or has an indirect effect, whereby the inhibition of bacterial vaginosis-associated bacteria prevents the occurrence of proinflammatory response to the vaginosis.[134] *Lactobacillus*-depleted microbiota in cervicovaginal is significantly associated with short cervix, which is a risk factor for sPTL.[136,137]

Since the placenta is generally considered as a sterile organ, the question of whether microbiome exists in placenta during non-infectious pregnancy is still controversial. More and more evidences and rigorously designed studies support no existence of a microbiome in placenta from term deliveries or sPTL, and no significant relationship between placental infection with bacteria and the risk of preterm birth.[138,139] The previous microbiome reported in placenta seemed to be of more possibility of contamination from sampling or procedure of sample processing.[140,141] Besides the microbiome in genital tract, a decrease in α-diversity of microbiome,[142] and increased oral originated bacteria [92] in the gut were both correlated with sPTL.

Conclusion

Preterm labor is a syndrome attributed to external factors, maternal factors, fetal factors, and the maternal-fetal crosstalk as well as the interaction between external factors and internal factors. Along with the development of industrial society and the changes in human living style, the risk factors may vary as well from one generation to the next. However, the fundamental mechanisms controlling the length of gestation and the intrinsic triggers for initiation of labor remain constant. The innovation of this article is to comprehensively recognize both external and internal risk factors, as well as emphasizing their interaction in the occurrence of sPTL. However, due to the complexity of preterm birth, the discussion of the mechanisms underlying these risk factors contributing to sPTL are limited, and the further investigation will help us to elucidate perturbations in the maternal-fetal dialogue and provide new strategies for the prediction and treatment of sPTL.

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Conflicts of Interest

None.

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