Inflammation Research (2025) 74:44
https://doi.org/10.1007/s00011-025-02015-6

Inflammation Research

REVIEW

The landscape of decidual immune cells at the maternal–fetal interface in parturition and preterm birth

Mu Lv[1] · Yuanhui Jia[1] · Jiaqi Dong[1] · Shengyu Wu[1] · Hao Ying[1]

Received: 2 November 2024 / Revised: 13 February 2025 / Accepted: 19 February 2025

Abstract

Background Parturition is similar to an inflammatory response in which resident and infiltrating immune cells release cytokines and chemokines into the maternal–fetal interface, promoting expulsion of the fetus from the mother. The untimely activation of these inflammatory pathways can result in preterm labor. The maternal–fetal interface is composed mainly of decidual tissue and placental villous space.

Objective The objective of this review is to examine the role and mechanisms of decidual immune cells during parturition and preterm birth. A deeper understanding of decidual immune cells at the maternal–fetal interface could provide significant insight into parturition and preterm birth pathogenesis.

Methods We searched major databases (including PubMed, Web of Science, and Google Scholar etc.) for literature encompassing decidual immune cells, parturition and preterm birth up to July 2024 and combined with studies found in the reference lists of the included studies.

Results Decidual neutrophils release inflammatory mediators that facilitate parturition. The M1/M2 ratio of decidual macrophages increases among preterm birth population. Mast cells may cause uterine contractions. In parturition and preterm birth, there is an increase in $CD56^{dim}CD16^{+}$ natural killer cells and immature dendritic cells. The increase of Th1/Th2 and Th17/Treg cells leads to preterm birth. Women with preterm birth had a higher proportion of decidual B cells. ILC2 can help protect the steady-state environment at the maternal–fetal interface. The activation of invariant NKT cells plays an important role in inflammation-induced preterm birth. These decidual immune cells communicate with each other. The development of sequencing technology enables a more in-depth study of decidual immune cells.

Conclusion The dynamic balance of the maternal–fetal immune microenvironment plays a crucial role in maintaining human pregnancy and in the initiation of delivery. A deep understanding of the mechanism of decidual immune dysfunction is crucial for understanding the pathogenesis of preterm birth.

Keywords Decidual immune cells · Maternal–fetal interface · Parturition · Preterm birth

Abbreviations

PTB	Preterm birth
sPTB	Spontaneous PTB
PPROM	Preterm premature rupture of membranes
MMPs	Matrix metalloproteinases
NK	Natural killer
iNKT	Invariant NK T
ILCs	Innate lymphoid cells
DCs	Dendritic cells
dNK	Decidual NK
IL-10	Interleukin-10
GM-CSF	Granulocyte-macrophage colony stimulating factor
IDO	Indoleamine 2,3-dioxygenase

Mu Lv and Yuanhui Jia contributed equally to this work.

Communicated by John Di Battista.

✉ Hao Ying
stephenying_2011@163.com

[1] Department of Obstetrics, Shanghai First Maternity and Infant Hospital, School of Medicine, Tongji University; Shanghai Key Laboratory of Maternal Fetal Medicine, Shanghai Institute of Maternal-Fetal Medicine and Gynecologic Oncology, Shanghai 200092, China

Published online: 04 March 2025

TGF-β	Transforming growth factor-β
SRC	Steroid receptor coactivators
PAF	Platelet activating factor
MCs	Mast cells
MCAS	Mast cell activation syndrome
pNK	Peripheral natural killer
trNK	Tissue-resident NK
SVD	Spontaneous vaginal delivery
CS	Cesarean section
TNL	Term not in labor
TL	Term in labor
IFN-γ	Interferon-γ
IL-1RA	Interleukin-1 receptor antagonist
Th cells	T helper cells
Th17 cell	T helper cell 17
uDCs	Uterine DCs
PB-n/aCAM	Preterm birth without acute chorioamnionitis
PB- w/aCAM	Preterm birth with acute chorioamnionitis
dCD8$^+$T	Decidual CD8$^+$T
TIM-3	T cell immunoglobulin domain and mucin domain protein-3
PD-1	Programmed cell death protein-1
Tregs	Regulatory T cells
Foxp3	Fork-helix transcription factor 3
HO-1	Heme oxygenase 1
hCG	Human chorionic gonadotropin
PIBF1	Progesterone-induced blocking factor 1
ILC1s	Type 1 ILCs
ILC2s	Type 2 ILCs
ILC3s	Type 3 ILCs
GATA3	GATA-binding protein 3
RORα	Retinoic acid receptor-related orphan receptor-α
LTi	Lymphoid tissue inducer
PNL	Preterm not in labor
PL	Preterm in labor
scRNA-seq	Single-cell RNA sequencing
BCR	B cell receptor
TCR	T cell receptor
EVTs	Extravillous trophoblasts
ICIs	Immune checkpoint inhibitors

Introduction

During parturition, complex changes in hormones, physiological functions, morphological characteristics, and immune functions occur. The maintenance of pregnancy and the initiation of labor are continuous and dynamic processes in which the mother and fetus interact in real-time. The fetal chromosomes are half-paternal and is therefore an allogeneic graft. An important feature of the interaction between the mother and fetus during pregnancy is the process of mutual balance and continuous transformation of maternal immune rejection/immune tolerance against the fetus, accompanied by a large number of inflammatory factors and the generation and differentiation of immune cells [1]. If the maternal–fetal immune balance is disrupted and the inflammatory response is advanced, preterm labor will occur.

Preterm birth (PTB), defined as birth before 37 weeks of gestation, is the primary cause of infant morbidity and mortality globally [2]. PTB is a widespread issue that is becoming more prevalent in developed countries, yet the great majority of cases occur in developing countries [3]. According to clinical categorization schemes, PTB can be broadly categorized into one of two clinical pathways: iatrogenic PTB and spontaneous PTB (sPTB) [4]. sPTB can be caused by either spontaneous preterm labor (defined as regular contractions with cervical changes at less than 37 weeks gestation) or preterm premature rupture of membranes (PPROM), which is defined as spontaneous rupture of the membranes at least one hour prior to the onset of labor and at less than 37 weeks [5]. sPTB can be caused by a variety of pathological conditions, such as infection or inflammation, uterine ischemia, uterine distension, aberrant allograft reactions, allergies, insufficient cervical tissue, and hormonal imbalances [6]. Among these, infection and inflammation are well-known etiologies of PTB [7]. Both maternal systemic infection and intrauterine infection are clear risk factors for sPTB [8].

The ultimate physiological processes of sPTB and term birth are comparable; however, these pathways are activated at an earlier point in sPTB [9]. An active parturition pathway includes contraction of the myometrium, activation of the decidual tissue, degradation of the extracellular matrix in the membranes, weakening and rupture of the membranes, and cervical ripening resulting in labor and delivery [5, 9]. The decidua, as an integral part of the maternal–fetal interface, plays a crucial physiological role. The commencement of parturition, both term and preterm, is accompanied by broad gene expression alterations in the decidua, many of which are linked to inflammatory signaling. The decidual immune system comprises many subsets of maternal immune cells, including natural killer (NK) cells, macrophages, T cells, B cells, and dendritic cells (DCs) [10]. A delicate balance must be struck by the maternal immune system during pregnancy: maintaining tolerance to fetal allografts while preserving innate and adaptive immunity against microbial challenges [11, 12]. Therefore, studying the frequencies, phenotypes, and functions of decidual immune cells is crucial to understanding the onset of delivery and the occurrence of sPTB.

Although decidual immune cells present during the first trimester have been described in great detail, the immunological landscape of the decidua is still poorly understood. Studies on the effects of immune cells at the maternal–fetal interface have been particularly useful not only for revealing the local cellular mechanisms that control maternal immune tolerance to semi-allogeneic fetuses, but also for increasing the number of possible interventions for pregnancy disorders caused by imbalances in the maternal–fetal interface [11–14]. The aim of our study was to investigate how decidual immune cell populations change both at term and preterm in connection with the onset of labor. We searched major databases (including PubMed, Web of Science, and Google Scholar) for research on decidual immune cells, parturition, and preterm birth up to July 2024, combining it with research discovered in the reference lists of the included articles. Enhancing our understanding of the molecular mechanisms that occur in the decidua during labor, both at term and preterm, is crucial for developing novel therapeutics to minimize the incidence of sPTB.

The function of decidua in the maternal–fetal interface

The maternal–fetal interface refers to the local locations of contact between maternal and fetal cells, which include the decidual tissues and the placental intervillous region [15]. The decidua can be divided into the decidua basalis and the decidua parietalis based on the site of contact with the fetal tissues. The decidua parietalis represents the decidual tissue in contact with the fetal membranes, specifically the chorion layer, whereas the decidua basalis represents the decidual tissue surrounding the placenta and invasive interstitial trophoblasts [16]. The decidua is a modified endometrial mucosal lining made up of newly formed maternal vascular cells, maternal immune cells, and terminally differentiated endometrial stromal cells [17]. Owing to elevated progesterone levels, decidualization occurs during the secretory phase of the menstrual cycle following ovulation. Decidualization triggers an influx of decidual leukocytes, which regulate the differentiation of endometrial stromal cells and spiral artery remodeling and aid in immunosuppression to prevent fetal rejection [15]. The decidua provides a distinct immunological landscape that promotes trophoblast invasion, maternal tolerance, debris clearing, and antimicrobial defense [15].

As early as the 1980s, “decidual activation” was proposed to be critical to labor to understand the role of the decidua in parturition [18]. The progression of labor has been shown to be aided by increased prostaglandin output and the decidua’s production of pro-inflammatory mediators such as cytokines and matrix metalloproteinases (MMPs), which in turn cause myometrial contractions and extracellular matrix remodeling in the fetal membranes and cervix [19]. In addition to stromal cells, the decidua contains a remarkable number of maternal lymphocytes (40%). These maternal leukocytes are attracted by chemokine gradients generated by trophoblasts and decidual stromal cells [20]. Their phenotypes and functions are generally different from those of their peripherally circulating counterparts. Numerous innate subsets, primarily neutrophils [21], mast cells [22], DCs [23], NK cells [24, 25], and macrophages [26, 27], as well as adaptive immune cells, such as T cells [28] and a proportion of B cells [29], make up the cellular immune repertoire of the maternal–fetal interface. These cellular subsets change throughout gestation (Fig. 1). At the maternal–fetal interface, cell types that mediate innate and adaptive immune responses have also been identified. These include innate lymphoid cells (ILCs) [30, 31] and invariant natural killer T (iNKT) cells [32] (Fig. 1). Throughout pregnancy, each of these subsets performs distinct functions, including promoting placental growth, preserving maternal–fetal tolerance, and playing a role in the inflammatory processes that coincide with labor [33]. As a result, disturbance of these various immune cell subsets is frequently linked to unfavorable pregnancy outcomes [34–36]. Therefore, a deeper comprehension of the functions of maternal immune cells at the maternal–fetal interface in late gestation and in the physiological and pathological aspects of labor is necessary.

Innate immune cells

When foreign antigens are encountered for the first time, the innate immune system is the first arm of the immune system to respond. Cytokines are secreted, antigens are presented, and additional immune cells are recruited to trigger the particular immune response. In addition to acting as the first line of defense against pathogens, decidual innate immune cells play important roles in the initiation and maintenance of pregnancy and labor induction (Fig. 2). Innate immune cell dysfunction can result in preterm labor.

Decidual neutrophils

Neutrophils are the most common immune cells in peripheral blood, and they play an important role in acute inflammation. Neutrophils are a major source of inflammatory mediators during birth. Pregnant women have more neutrophils in their peripheral blood and myometrium than non-pregnant women do [46]. Neutrophils accumulate in the decidua and myometrium during lipopolysaccharide (LPS)-induced preterm labor and during term labor, but

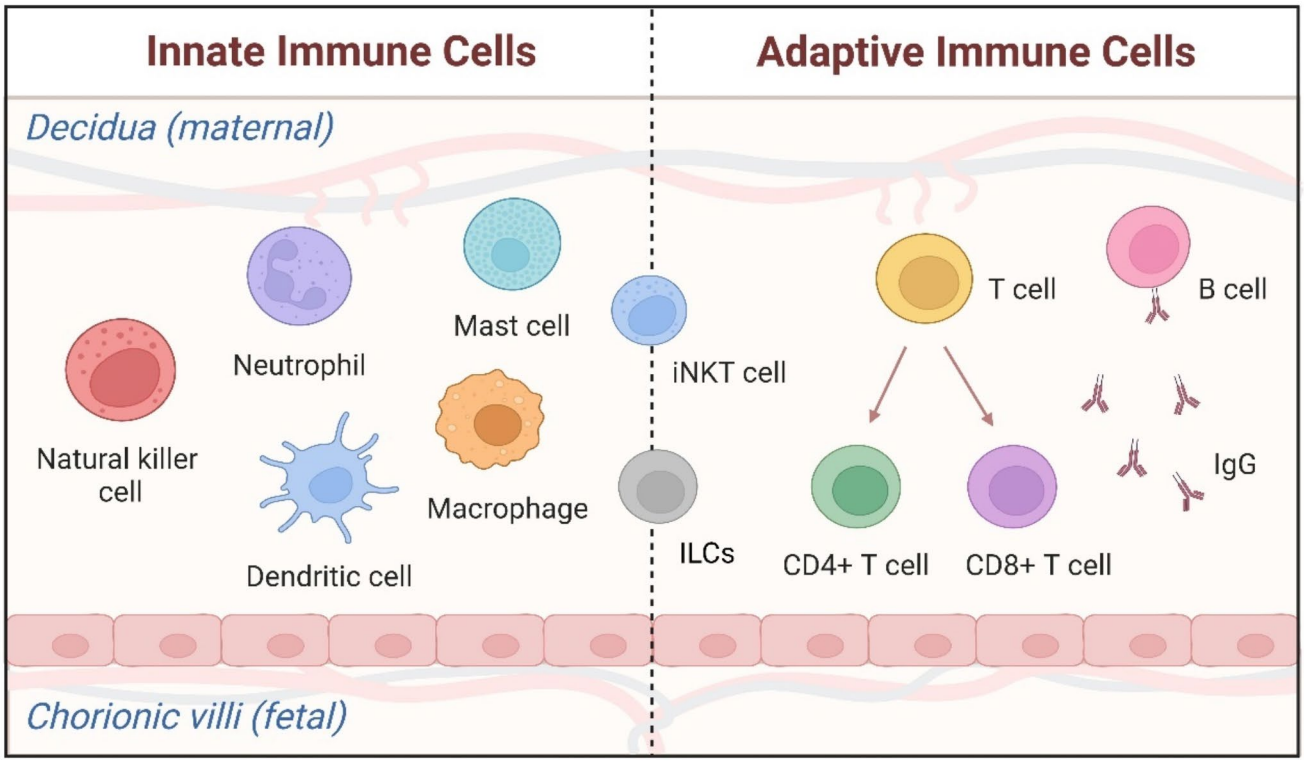

Fig. 1 Decidual immune cells at the maternal–fetal interface in parturition and sPTB. Innate immune cells include neutrophils, mast cells, DCs, NK cells and macrophages. Adaptive immune cells include T cells and B cells. Cell types that link the innate and adaptive immune systems, mainly including ILCs and iNKT cells

not in mifepristone-induced preterm labor (a non-infectious model) [47, 48]. LPS injection also causes a 7-fold increase in the number of neutrophils in the uteri of preterm rats [49]. Furthermore, TLR2 and TLR4 expression increased on the surfaces of neutrophils in pregnant women with sPTB, possibly as a result of the induction of inflammation [21] (Fig. 2a). This finding is also consistent with the observation that maternal blood monocytes from women with sPTB exhibit high expression levels of TLR4 [50]. Notably, LPS-induced preterm delivery is not prevented by neutrophil number reduction in animal models, indicating that neutrophils are not the cause of infectious preterm labor [36, 49, 51]. Nevertheless, depleting neutrophils before administering LPS still decreases the pro-inflammatory reactions shown by IL-1β expression in the uteroplacental tissues of mice [49], which is noteworthy because systemic injection of IL-1β alone can cause premature delivery in animal models [52]. These findings might point to the importance of neutrophils within the ultimate pathway of infectious and inflammatory preterm delivery, even if they are not necessary.

Acute chorioamnionitis is a major cause of preterm labor in humans [53]. In acute chorioamnionitis, neutrophils are the most common leukocytes invading the decidua [54]. Compared with women with term gestations (with or without labor) and women with sPTB without chorioamnionitis, women with preterm labor associated with chorioamnionitis had higher neutrophil counts in decidual tissues [55]. Fluorescence in situ hybridization was used to determine the maternal origin of decidual leukocytes (e.g., neutrophils) in preterm labor/birth associated with acute chorioamnionitis [37]. As part of a clinically relevant model of acute sterile chorioamnionitis in rhesus macaques, neutrophils rapidly and robustly invade the decidua, activate, and express pro-inflammatory cytokines/chemokines (e.g., TNF-α and IL-8) and the regulatory enzyme indoleamine (IDO) [56]. In both term and preterm labor, human decidual neutrophils secrete a variety of inflammatory mediators and MMPs that degrade the fetal membranes' extracellular matrix and thereby aid in birth [37, 38] (Fig. 2a). Taken together, these findings point to a role for decidual neutrophils in pathological PPROM and physiological membrane rupture during both term and preterm labor.

Neutrophils are additionally essential for cervical ripening. Compared with women in the early stages of pregnancy, those who have recently undergone spontaneous vaginal delivery have many more neutrophils in their cervix [46, 57]. During term labor without infection, mouse decidua have low neutrophil counts, which is consistent with findings from human decidual tissues [55]. This is also in line

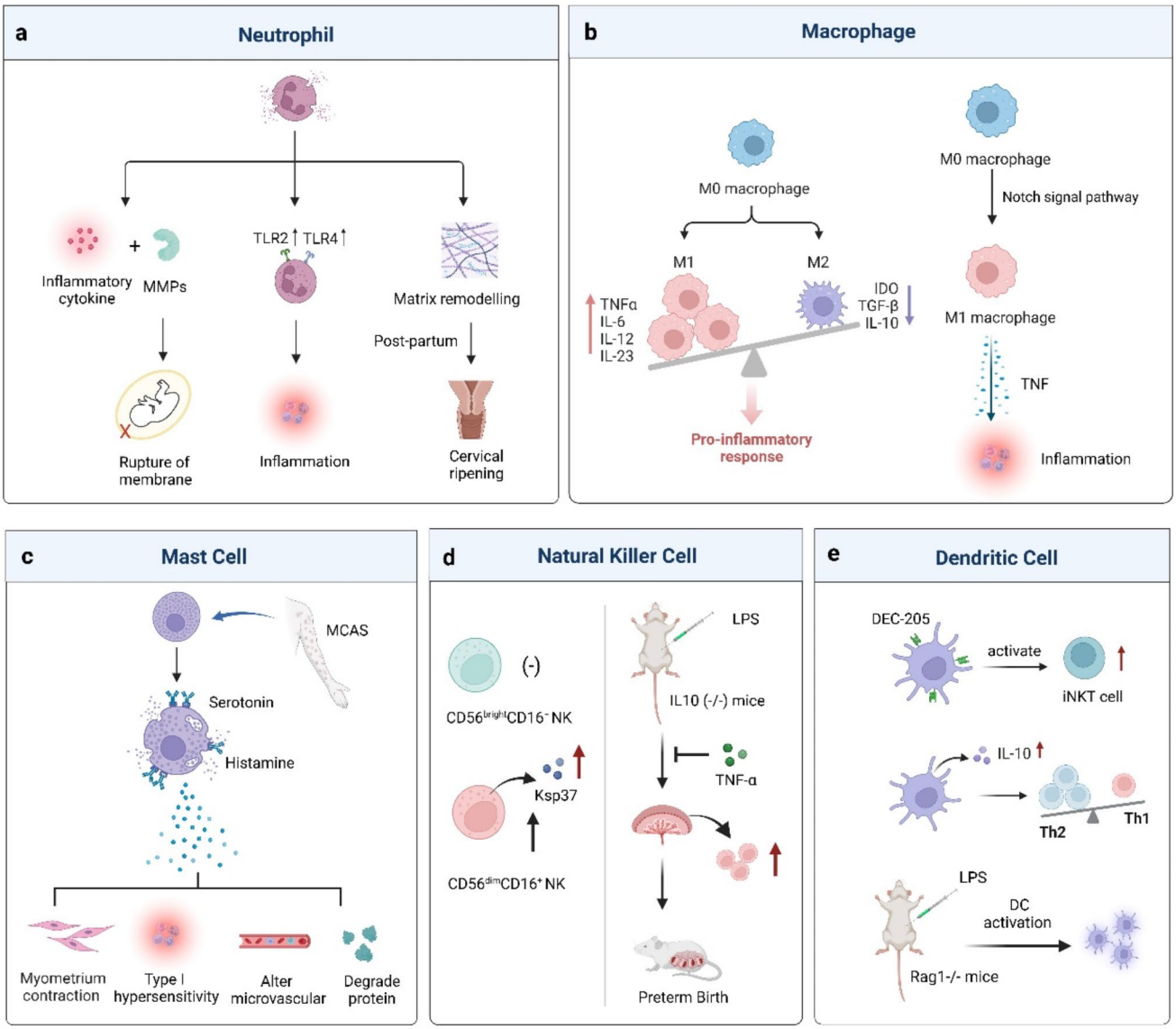

Fig. 2 Schematic diagram of the roles of five types of decidual innate immune cells in the regulation of labor initiation and PTB. **a** Decidual neutrophils release inflammatory mediators and MMPs that degrade the extracellular matrices of the fetal membrane, thereby promoting fetal delivery [37, 38]. Higher TLR-2 and TLR-4 expression on the surface of maternal neutrophils is associated with sPTB through triggering an inflammatory response [21]. In addition, neutrophils play a central role in cervical maturation [39]. **b** Compared with the TL group, the PTL group presented a reduced number of M2 macrophages and increased TNF-α expression in proinflammatory M1 macrophages in the decidua [40]. In a mouse model of sPTB, decidual macrophages were found to be polarized to the M1 subtype through activation of the Notch signaling pathway [41]. **c** In the third trimester of pregnancy, mast cells can secrete histamine and serotonin through degranulation to regulate myometrium contraction, alter microvasculature, triggers type I hypersensitivity reactions and degrade proteins [42]. MCAS is a chronic multisystem disease that mediates abnormal accumulation of mast cells and abnormal secretion of mediators [43]. **d** In human, the abundance of $CD56^{dim}CD16^{+}$ dNK cells increased during the third trimester, whereas the abundance of $CD56^{bright}CD16^{-}$ dNK cells did not change significantly [44]. In mouse models, the TNFα-IL-10 axis of uterine NK cells plays an important role in the occurrence of sPTB [45]. **e** $DEC\text{-}205^{+}$ DCs can activate iNKT cells. DCs regulate the Th1/Th2 balance to maintain Th2 polarization, with an increase in the production of IL10. Uterine DC activation was found in T and B cell-deficient (*Rag1*$^{-/-}$) mice given LPS injections to trigger PTB. MCAS, mast cell activation syndrome

with other findings that have demonstrated that neutrophil counts in the mouse myometrium [48] do not increase until after delivery and with related cervical research in mice [58]. These findings suggest that neutrophils play a role in postnatal tissue healing and postpartum uterine remodeling [39]. Neutrophils help remodel the matrix during post-partum decidual breakdown and myometrial involution, which is a vital step in the reproductive cycle (Fig. 2a). Sufficient and effective postpartum remodeling is needed to safeguard

the entire reproductive system against infections and enable future conception [59].

Decidual macrophages

Decidual macrophages are the primary antigen-presenting cells, accounting for approximately 20–25% of immune cells at the maternal–fetal interface [60]. Their important functions as immune effector cells and pathogen sensors imply a key role for these cells in inflammatory responses to decidual infection. Macrophages are often classified into two phenotypes: M1 and M2. M1 macrophages are pro-inflammatory cells that contribute to bactericidal and inflammatory responses, produce IL-12, IL-23, and reactive nitrogen oxides, have a potent antigen-presenting capacity, and stimulate Th1-type immune response. M2 macrophages have a potent immunosuppressive capacity because they generate anti-inflammatory molecules including IL-10, TGF-β, IDO, and so on. This helps the Th2-type immune response to play an immunomodulatory role [10]. In humans, substantial macrophage concentrations are present in uterine tissues from the beginning of pregnancy until the commencement of labor at term. Furthermore, their densities rise significantly during labor [61].

Pique-Regi et al. reported that the decidua's most differentially expressed genes were detected in macrophages throughout both term and preterm labor [62]. Compared with term birth without labor (e.g., elective cesarean section), term labor and idiopathic (i.e., noninfectious) preterm labor can also cause the selective accumulation of decidual macrophages [55]. The proportion of decidual macrophages in mice increases prior to birth (18 days post conception (dpc)) compared with mid/late gestation (15 dpc) [47]. High infiltration of macrophages into the myometrium and decidua at term has been observed in rats [55, 63]. Compared with that in the myometrium, there is a 3.8-fold increase in decidual macrophage infiltration in rats immediately before labor [55]. These results emphasize the significance of decidual macrophages during sPTB and imply that they may play a role before labor begins.

M2 macrophages constitute the predominant phenotype in decidua tissues during late gestation. At term and preterm labor, the number of M1 macrophages increases significantly in decidua tissues. During labor, there is a considerable increase in the production of IL-6 and NLRP3, indicating that macrophages display proinflammatory characteristics [64]. The polarization states of uterine decidual macrophages significantly differs at the maternal–fetal interface in women who have sPTB compared to that in pregnant women at term. This is primarily evident based on an increase in the M1/M2 ratio and a reduction in the quantity of M2 macrophages [65] (Fig. 2b). In the decidua basalis and parietalis, preterm women with spontaneous labor presented higher TNF-α expression in proinflammatory M1 macrophages and fewer M2 macrophages than did women at term in labor [40]. M1 bias and the accompanying increase in proinflammatory cytokine production may be significant aspects of term labor, and they are more pronounced during preterm labor. Moreover, rosiglitazone administration can stimulate the PPARγ signaling pathway, which could lead to a novel avenue for the treatment of preterm labor by reducing inflammatory responses mediated by M1-type macrophages and preventing preterm labor from occurring [27]. It was discovered that the Notch signaling pathway causes decidual macrophages to polarize to the M1 subtype in a mouse model of inflammation-induced sPTB [41] (Fig. 2b).

Decidual mast cells

Mast cells (MCs) play a key role in innate immunity during late gestation and labor due to their ability to manufacture and secrete or release multiple mediators within a short period in response to immunogenic and nonimmunogenic stimuli in many organs, including the uterus [66]. There are two types of short-term mediators [42]. Among the mediators that are preformed and stored in cytoplasmic granules are histamine, serotonin, heparin, proteoglycans, and certain proteases. Another type of mediator is the products of cyclooxygenase or lipoxygenase pathways that include arachidonic acid metabolism, such as prostaglandins and leukotrienes, but are not retained by MCs. MCs have the capacity to generate a variety of multifunctional cytokines, including IL-1β, IL-3, and IL-6, over an extended period. MCs are located adjacent to blood vessels in the myometrium and myometrial glands. MCs can trigger acute hypersensitivity responses and allergic disorders, thereby preventing pathogen infections. Degranulation of MCs triggers type I hypersensitivity reactions when they are exposed to allergens, so the connection between MCs and allergens may be one of the causes of premature birth [67]. In guinea pigs, allergic reactions resulted in a decrease in the premature birth rate when histamine receptor antagonists were used prior to birth [43]. Nevertheless, studies have demonstrated that there are considerably more MCs in the decidua of term pregnancies than in those of preterm births [22]. The presence of histopathological chorioamnionitis does not impact MC numbers [22].

There is an increasing amount of evidence that MCs may contribute to uterine contractions [36, 42]. During late pregnancy, MCs release serotonin and histamine to control contractions of the uterine muscle [36] (Fig. 2c). Mast cell degranulation causes a significant increase in rat uterine contractility in both the nonpregnant and pregnant stages [42].

This phenomenon was demonstrated in vitro via the use of compound 48/80 (a connective tissue mast cell-degrading agent) on uterine strips from both sensitized and unsensitized animals. Given that MCs are known to be a source of inducible nitric oxide synthase, there may be a relationship between nitric oxide and MCs [42]. It is possible that nitric oxide controls uterine contractility. The degranulation of MCs may also be affected. In addition to 5-hydroxytryptamine and histamine, MCs are known to produce prostaglandins, leukotrienes, platelet-activating factor, and cytokines, all of which can cause uterine contractions. Additionally, MCs release mediators that affect leukocyte and fibroblast responses, alter microvascular tissue, and degrade proteins (Fig. 2c). Thus, MCs have enormous potential functions in the uterine wall. MC stabilizers may be beneficial in delaying the activation of the processes that contribute to labor and delivery.

Furthermore, abnormal constitutive and reactive MC mediator release is a chronic multisystem disease known as mast cell activation syndrome (MCAS), which often results in allergies, dystrophic, and inflammatory reactions [68]. MCAS is characterized by the abnormal release of varied subsets of mast cell mediators and/or the buildup of pathogenic mast cells in possibly any or all organs and tissues [69]. MCAS shows a significant bias toward women. The increased number of MCs releases mediators such as histamine, prostaglandins, and leukotrienes, which promote uterine muscle contraction, alter microvascular tissue, and thus promote the occurrence of PTB (Fig. 2c). In addition, MC tryptase can increase the generation and release of matrix metalloproteinases from endometrial stromal cells [70]. As a result, MCAS has an unavoidable influence on the parturition and the occurrence of PTB. Clinicians should pay attention to the possibility of PTB in MCAS patients throughout pregnancy. Treatment for symptoms that aims to lessen the impact of mediators works well when antihistamines and mast cell stabilizers such as cromolyn sodium are used [71].

Decidual natural killer cells

NK cells are cytotoxic innate lymphoid cells that were initially acknowledged for their capacity to kill tumor cells. They were later revealed to kill pathogen-infected cells [72]. In humans, typical NK cells are found in peripheral blood (pNK cells) and are spread throughout the body. Cluster of differentiation $CD3^{-}CD56^{dim}CD16^{+}$ cells and $CD3^{-}CD56^{bright}CD16^{-}$ cells are the two main types of pNK cells. It has been discovered that 90–95% of pNK cells, which are $CD56^{dim}$ NK cells, are cytotoxic and display high expression levels of CD16. $CD56^{bright}$ NK cells are recognized for generating a variety of cytokines with poor cytolytic activity [73]. NK cells are also found in peripheral tissues, such as the liver, lungs, skin, and uterus, and are called "tissue-resident NK" (trNK) cells [74]. The majority of trNK cells are $CD56^{bright}$ NK cells. The latter have distinct signatures associated with their native tissue and demonstrate elevated expression of trNK cell-specific markers such as CD69, CD103, and CD49a [75]. Decidual NK (dNK) cells are a specific subset of trNK cells located in endometrial decidual tissues. Compared with pNK cells and trNK cells, dNK cells exhibit a variety of distinct phenotypic and functional traits [76]. The majority of dNK cells have $CD56^{bright}CD16^{-}$ phenotypes, which are characterized by poor cytotoxicity and strong secretory activity [77]. It is hypothesized that uterine hematopoietic stem cells and/or the development of thymic or peripheral NK cells are the progenitors of dNK cells [78–80]. The final differentiation into mature dNK cells is thought to be influenced, at least in part, by uterine IL-15 production [81].

Several studies have shown that dNK cells are crucial during parturition in humans and mice. As pregnancy progresses, dNK cells lose cytoplasmic granules, indicating a required functional change during late gestation for parturition [82]. The decidua of the term placenta has a greater percentage of $CD3^{-}CD16^{+}$ NK cells than does the peripheral blood [44]. The abundance of $CD3^{-}CD16^{+}CD56^{dim}$ NK cells at the maternal–fetal interface and the concomitant increase in Ksp37 expression, which is highly expressed in $CD16^{+}$ NK cells, during late pregnancy imply the likely participation of the cytolytic armamentarium during parturition [44] (Fig. 2d). Dynamic variations in decidual NK cell distribution are linked to labor. Tissues from women who had undergone elective cesarean section (CS) and spontaneous vaginal delivery (SVD) did not differ in the percentages of $CD56^{bright}CD16^{-}$ dNK cells between the decidua basalis and decidua parietalis, according to the flow cytometry data [83]. Compared to those from women who had undergone CS, the decidua basalis and parietalis from women who had undergone SVD had a noticeably greater quantity of $CD56^{dim}CD16^{+}$ NK cells [83]. Additionally, the quantity of uterine NK cells that are positive for CD94/NKG2A expression is highest following an elective CS and modest following a vaginal full-term birth [84]. These results suggest that NK cells that are positive for CD94/NKG2A expression may be associated with the continuation of pregnancy. Furthermore, immune cells in the decidua parietalis were extracted from term not in labor (TNL) or term in labor (TL) samples, and the results revealed that CD4 expression on $CD8^{-}$NK cells was lower in term labor samples than in non-labor samples, implying that NK cells may migrate to other regions during labor [85].

Gomaa et al. reported that $CD16^{+}$ $CD56^{dim}$ uterine NK cells were detected in just one out of 30 term delivery placentae (3.3%); however, they were observed in 21 out of 30

(70%) preterm placental samples [86]. $CD16^{+}CD56^{dim}$ cells are present in both the decidua and the villi of individuals who experience idiopathic preterm labor, indicating a link between uterine NK cell dysregulation and idiopathic human preterm labor. These findings imply an association between human preterm labor and the dysregulation of decidual NK cells. In addition, a correlation between abnormal uterine NK cell expression and idiopathic sPTB in mice was first demonstrated by Murphy et al. in 2008 [45]. The group discovered that in a mouse model, infection or inflammation-induced preterm labor/delivery is initiated mostly via the uNK cell-TNFα-IL10 axis [45] (Fig. 2d).

Decidual dendritic cells

Decidual DCs play an important role in the formation of the maternal–fetal immune microenvironment. In humans, mature myeloid DCs, known as $CD83^{+}$ cells, are found in first-trimester decidua at a density of approximately 1–5 cells/mm^2. Fewer mature DCs, known as $CD205^{+}$ cells, are found at a density of approximately 2 cells/mm^2 [87]. $CD83^{+}$ DCs are found in the cycling endometrium, with densities ranging from ~3 cells/mm^2 during the proliferation phase to ~9 cells/mm^2 during the late secretory phase [88]. These data suggest that full decidualization is associated with a decrease in $CD83^{+}$ DC density after pregnancy begins. This constraint would be favorable in terms of decreasing immunogenic, migratory DC-mediated T cell responses to fetal/placental antigens [89].

In mice, the number of uDCs decreases through late pregnancy. Later in pregnancy (17.5 days after coitum), the primary DC subset in the uterus is $CD11c^{+}CD8\alpha^{-}MHCII^{-}$ (immature phenotype) [90]. Immature DCs may be involved in the genesis of preterm labor because they express IL-10, an anti-inflammatory cytokine that may be used as an early indicator of premature delivery [90]. Furthermore, uterine DC activation was detected in T and B cell-deficient ($Rag1^{-/-}$) mice given LPS injections to cause preterm delivery, indicating that DCs are involved in the induction of labor [91] (Fig. 2e). In the human decidua, DCs are mostly myeloid DCs, and they appear to modulate the Th1/Th2 balance to sustain Th2 polarization, with an increase in the production of IL10 [92] (Fig. 2e). Thus, this anti-inflammatory cytokine may serve as a possible early sPTB biomarker [36]. However, no particular studies that conclusively demonstrate DC function have been described.

It has been proposed that decidual $CD209^{+}$ ($CD14^{+}$) macrophages might be a source of DC progenitors because when $CD14^{+}$ decidual macrophages (which are composed of 50–70% $CD209^{+}$ cells) are treated with IL-1β, TNF-α, IL-6, and PGE2, they produce cells that express CD83 at a higher level and have the capacity to stimulate T cell proliferation in a mixed leukocyte reaction with a potency comparable to that of cytokine-simulated, peripheral blood monocyte–derived DCs [93]. Previous research has indicated that decidual macrophages develop into DC-like cells at term, promoting T cell activation, proliferation, and differentiation into IFN-γ-producing T cells, which are likely implicated in labor activation [94] (Fig. 3). Basal decidual macrophages may serve as a cellular reserve during term pregnancy, supplying the functionally developed DCs required for immune response activation to fetal antigens and thereby preparing the uterine milieu for labor.

In addition, cellular communication has been observed between DEC-205^{+}DCs and iNKT cells (Fig. 3). Moreover, DEC-205^{+}DCs can stimulate iNKT cells and increase the prevalence of preterm delivery [95]. Research has revealed that PTB in women without acute chorioamnionitis (PB-n/aCAM) is associated with a greater number of iNKT cells than PTB in women with acute chorioamnionitis (PB-w/aCAM). DEC-205^{+} DCs from women with PB-n/aCAM preferentially stimulate iNKT cell proliferation [96]. Arora et al. demonstrated that DEC-205^{+} DCs selectively collect glycolipid antigens, and that DC-iNKT cell communication contributes to the immune response [97]. These results imply that the control of immunological balance at the maternal–fetal interface during pregnancy may be mediated by cellular contact between DCs and iNKT cells.

Adaptive immune cells

The adaptive immune system identifies and responds to antigens, and memory cells persist after the antigen has been eliminated to prepare for a quick immune response to the next antigen exposure. During pregnancy, the maternal and fetal immune systems are tolerant of one other; however, if the equilibrium is broken early, sPTB can occur.

Decidual T cells

In the human decidua during the first trimester of pregnancy, total leukocytes are composed of 10–20% $CD3^{+}$ $TCR\alpha\beta^{+}$ T cells, approximately 30–45% of which are $CD4^{+}$ T cells, and 45–75% of which are $CD8^{+}$ T cells [98]. The percentage of $CD4^{+}$T cells increases and the percentage of $CD8^{+}$T cells decreases in late pregnancy [99]. According to a study using comparative immunohistochemistry, the proportion of $CD45^{+}CD3^{+}$ cells in the human term decidua is significantly greater than that in the first trimester. This increase is accompanied by an increased number of T cells expressing CD4, CD8, TCRαβ, or TCRγδ, indicating that there is a general increase in the number of decidual T cells in late pregnancy [100]. The frequencies of $TCR\gamma\delta^{+}$ and $CD8^{+}$ T

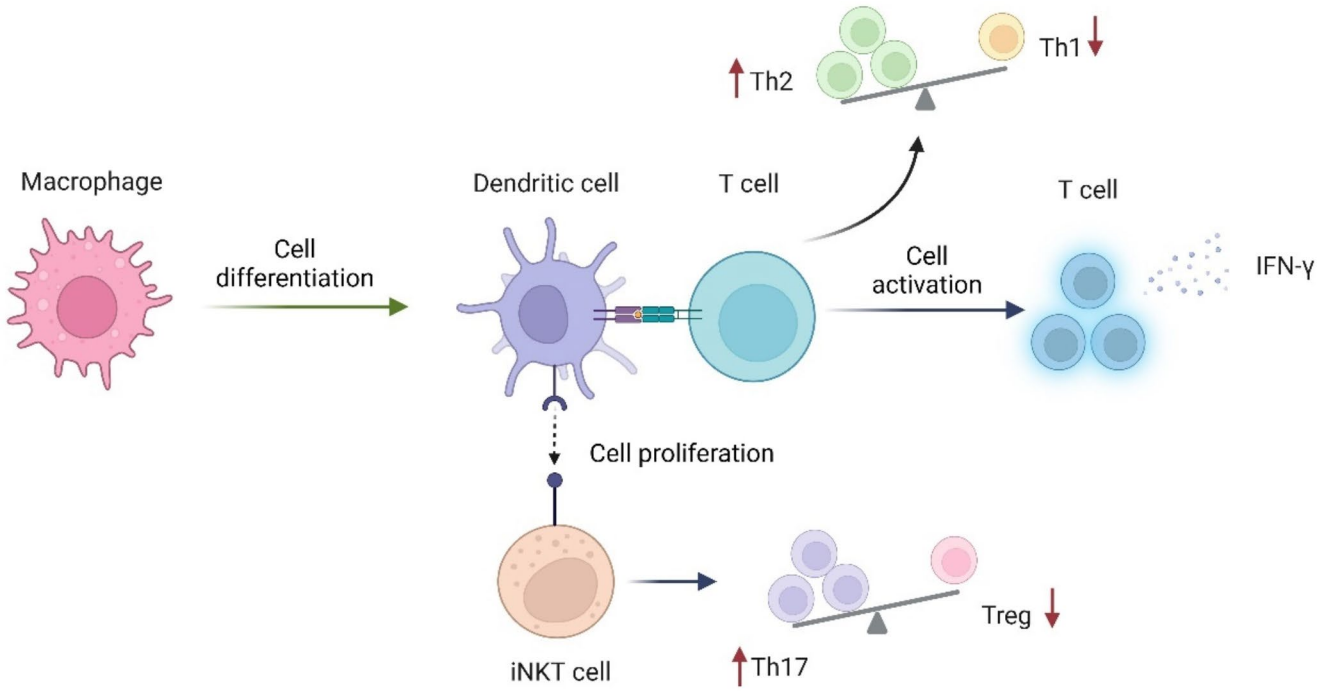

Fig. 3 Interaction of immune cells on decidua related to parturition and sPTB. Decidual macrophages can differentiate into DC-like cells, which further stimulate T cell activation, proliferation and differentiation. Decidual DCs maintain Th2 polarization by regulating the Th1/Th2 balance. DCs induce iNKT cell proliferation in women with PTB. iNKT cell expansion at the maternal–fetal interface was accompanied by an increase in the number of Th17 cells and a decrease in the number of Treg cells

cells are greater in the decidua parietalis than in the decidua basalis, whereas the opposite is true for $CD4^+$ T cells, according to a study of specific T-cell subsets across the two primary locations of the maternal–fetal interface at term [101]. In addition to the aforementioned findings, numerous investigations have also indirectly verified the existence of conventional T cells at the maternal–fetal interface by identifying $CD4^+$ and $CD8^+$ T cells in the murine placenta during late pregnancy via immunofluorescence microscopy [102] or immunophenotyping [103]. These findings show that T cells reside at the maternal–fetal interface during full pregnancy, even prior to the commencement of labor, which is why it is important to time them precisely (Fig. 4).

$CD8^+$ T cells

As the predominant T cell subset at the maternal–fetal interface in the early stages of pregnancy, $CD8^+$ T cells mostly have a memory-type T cell phenotype. Decidual $CD8^+$ T ($dCD8^+$ T) cells express granzyme B and perforin at lower levels than peripheral $CD8^+$ T cells do. $dCD8^+$ T cells have been shown to produce perforin and granzyme B at high levels in vitro, but Tregs may be responsible for their low levels of expression in vivo, in which they show distinct differentiation traits [104]. Furthermore, $dCD8^+$ T cells produce programmed cell death protein-1 (PD-1), T cell immunoglobulin domain and mucin domain protein-3 (TIM-3), and programmed cell death protein-1 (PD-1), which inhibits the fetal antigen-stimulated growth of $CD8^+$ T cells. Additionally, this study demonstrated that the decidua had a substantially greater concentration of $CD8^+IL\text{-}10^+$ Treg cell subsets than did the peripheral blood, indicating a strong capacity for cytokine release and proliferative activity. To control infection, $CD8^+$ T lymphocytes are activated during intrauterine infection and produce IFN-γ [105].

The fraction of $CD8^+CD45RA^+CCR7^+$ T cells is greatly increased in preterm birth patients, indicating that initial T cells may play a key role in the premature birth process [106]. Initial investigations revealed that the infiltration of cytotoxic T lymphocytes into decidual tissues, a type of placental lesion categorized as chronic histological chorioamnionitis, can occur in a fraction of term births, but is more commonly detected in situations of preterm labor and birth, PPROM, and fetal loss [107, 108].

$CD4^+$ T cells

During pregnancy, $CD4^+$ T cells play a more important role than $CD8^+$ T cells. The two primary subgroups of $CD4^+$ T cells are Tregs and Th2 cells, which have regulatory and immunosuppressive functions, and Th17 and Th1 cells, which have immunological effects. Interactions between the

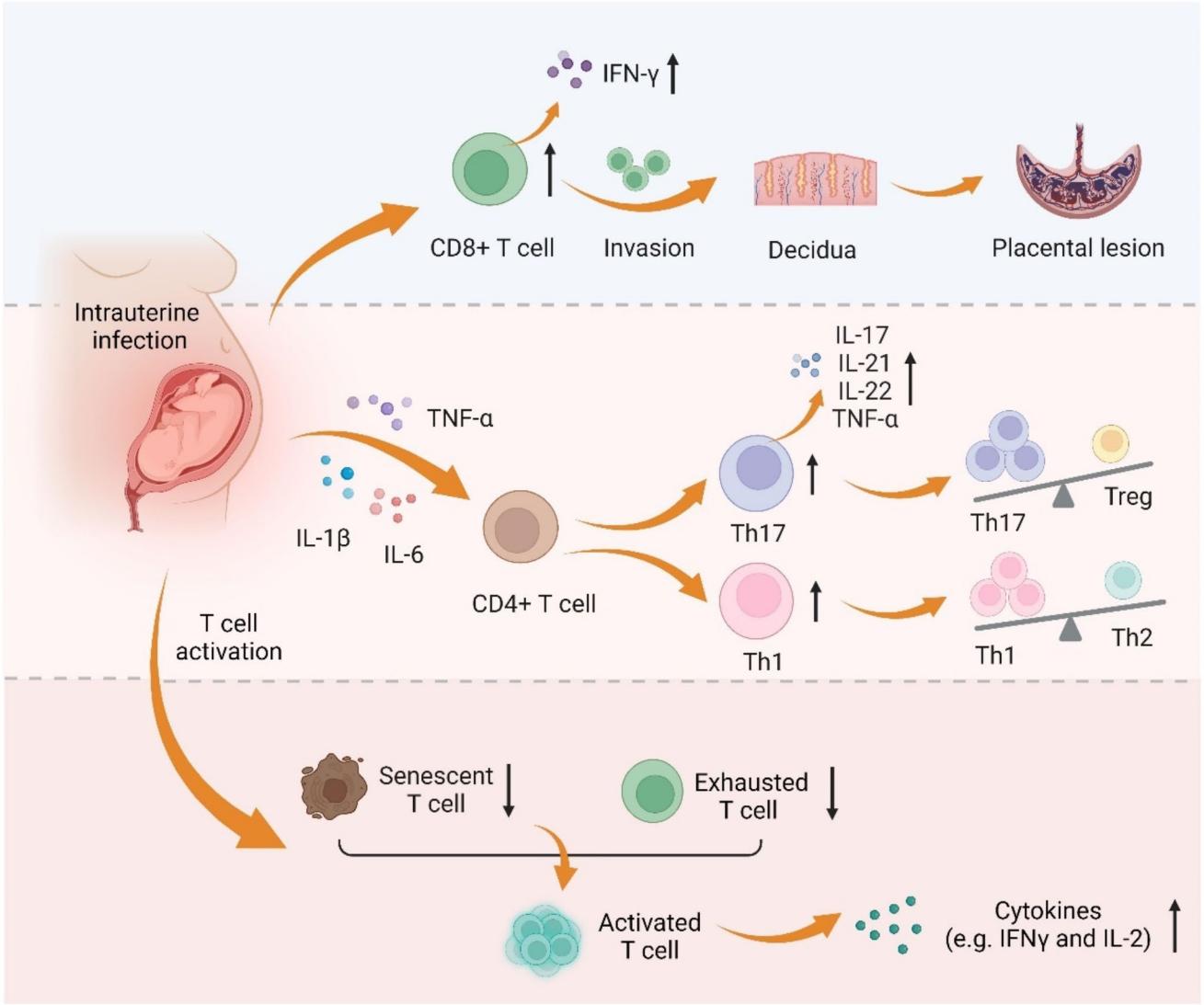

Fig. 4 Mechanisms of decidual T cells in regulating labor initiation and sPTB. When an intrauterine infection occurs, $CD8^+$T cells are activated and release IFN-γ to regulate the infection. $CD8^+$T cells invade decidual tissue and cause placental lesions, which occur in full-term births but are more common in preterm births. After exposure to a local microenvironment containing inflammatory cytokines such as IL-6, IL-1β, and TNF-α, $CD4^+$ T cells differentiate into Th17 cells. Th17 cells secrete inflammatory factors such as IL-17, IL-21, IL-22, and TNF-α, and participate in inflammatory processes. Decidual Th1 and Th17 cell numbers were increased in women with PTB. In addition, the inflammatory response that accompanies sPTB may reactivate senescent and exhausted T cells at the maternal–fetal interface, leading to abnormal effect T cell responses that trigger parturition and sPTB

two groups help maintain somewhat balanced secretion of cytokines. An increase in the ratio of Th1/Th2 to Th17/Treg cells, or a weakening of the inhibitory impact, might result in problems such as premature labor and miscarriage.

T helper cells T helper (Th) cells release cytokines, which interact with one another to maintain the immunological tolerance of the microenvironment. Research has shown that the Th1/Th2 cell balance is one of the mechanisms regulating maternal–fetal tolerance. Th2 cells mediate the humoral immune response, promote antibody formation, suppress inflammation, and reduce excessive damage, which is beneficial for embryo implantation and development. In contrast, Th1 cells induce a strong delayed immune response in macrophages, causing inflammation and tissue damage, inhibiting embryo implantation, and suppressing trophoblast production. All of these effects are detrimental to the maintenance of pregnancy. In utero, Th2 dominance and temporary inactivation of Th1 cells determine fetal survival by altering the Th1/Th2 cytokine ratio [109].

When exposed to inflammatory cytokines including IL-6, IL-1β, and TNF-α, $CD4^+$ T cells develop into Th17 cells. Th17 cells are responsible for the secretion of inflammatory

cytokines that are involved in numerous inflammatory processes, including IL-17 A, IL-17 F, IL-21, IL-22, and TNF-α [110]. Th17 cells, crucial pro-inflammatory immune cells involved in the inflammatory process, are more prevalent at the maternal–fetal interface in preterm births to women with chorioamnionitis than in normal deliveries. Thus, elevated numbers of Th17 cells might be the cause of premature labor [111]. Although Th17 cells are detrimental to the maintenance of maternal–fetal tolerance, their ability to scavenge invading microbes plays an important protective role in the uterus [112]. Higher levels of IL-17 were detected in amniotic fluid and at the maternal–fetal interface in tissues from women with chronic inflammation of the placenta who had undergone preterm labor than in women who had undergone preterm labor without this lesion. This lesion may be caused by Th17 cells invading the chorioamniotic membrane [113]. Furthermore, a recent transcriptomic analysis revealed that women who had undergone preterm labor and PPROM had downregulated expression of fork-helix transcription factor 3 (Foxp3) at the maternal–fetal interface and elevated expression of genes linked to Th1 and Th17 cells [114]. Taken together, these data suggest a potential connection between dysregulated Th17 responses and premature labor.

Regulatory T cells Regulatory T cells (Tregs) express Foxp3 and downregulate immunological responses via cell–cell interactions or by secreting cytokines that suppress the activity of other immune cells [109]. When Treg cells come into contact with effector T cells, they release granzymes and perforins, and transmit inhibitory signals to regulate their levels [112]. The primary cytokines secreted include IL-10, TGF-β, IDO, and HO-1. Treg cells are vital to the success of pregnancy [115].

Upon the observation that the proportions of $CD3^+CD4^+CD25^+$ T cells in the decidua basalis and decidua parietalis were lower in women who had spontaneous term labor than in those who had term cesarean sections, a function for decidual Tregs late in term gestation was originally proposed [83]. The authors suggested that this fraction may comprise decidual Tregs that "disappeared" before the commencement of labor [83]. Subsequent research examined the $CD4^+CD25^{dim}$ and $CD4^+CD25^{bright}$ populations in decidual tissues from term births (vaginal and cesarean sections) in the second trimester and revealed that these populations remained constant throughout gestation [116]. The $CD4^+CD25^{bright}$ decidual population was composed primarily of Tregs with high proportions of Foxp3, CTLA-4, and HLA-DR expression, whereas the $CD4^+CD25^{dim}$ population exhibited an activated phenotype with high percentages of $CD69^+$ cells. These findings were obtained after the same $CD4^+CD25^+$ population was further characterized by the expression of Foxp3 and other cellular markers associated with Tregs [117]. Taken together, these findings provide a basic summary of Tregs at the maternal–fetal interface in term births, stimulating further research. According to one study, the decidua contains three different Treg subsets that are identified by high expression of TIGIT, PD-1, or CD25 [28]. Although the proportions of the $CD25^+$ and $TIGIT^+$ Treg subsets tended to be greater in the decidua parietalis, the authors' comparison of the Treg populations in the decidua basalis and decidua parietalis revealed no discernible variations in the Treg populations between these tissues [28].

Furthermore, compared with first trimester decidual tissues, the ability of decidual Tregs to inhibit $CD4^+$ effector T-cell proliferation is much lower at term, indicating that the functional capabilities of decidual Tregs decrease but do not fully decrease at the end of gestation [28]. Several studies in mice have consistently revealed a Treg population in decidual tissues prior to term delivery [118, 119]. Studies on humans and animals have concurred that Tregs are present and operate at the maternal–fetal interface during term gestation. A groundbreaking study revealed that PTB was not caused by decrease in the number of $CD25^+$ cells during late pregnancy [120]. However, because CD25 is a less precise marker for Tregs than Foxp3 [121], it remains unclear whether changes in the quantity or function of decidual Tregs contribute to the beginning of preterm labor.

Exhausted and senescent T cells

T-cell exhaustion often occurs in the setting of persistent antigen exposure/stimulation, resulting in a gradual loss of function and increased expression of several inhibitory receptors such as TIM-3, PD-1, CTLA-4, and LAG-3 [122]. According to recent findings, this process may also occur during pregnancy [123, 124]. In the third trimester, decidual cytotoxic T lymphocytes present a transcriptome signature indicating a mix of malfunction and activation that may be reversed by in vitro stimulation [123]. An immunophenotypic investigation indicated that a high number of $CD4^+$ and $CD8^+$ effective memory T cells displayed an exhausted-like $PD\text{-}1^+TIM\text{-}3^+$ phenotype at the maternal–fetal interface [125]. Notably, as gestational age increases, the percentage of exhausted $CD4^+$ T cells in the decidua parietalis also increases. This finding suggests that increased regulation of these cells is necessary to prevent aberrant T-cell activation due to the prolonged exposure to antigens (fetal, microbial, or even self) that occurs during pregnancy [125].

Exhausted T cells in the decidua basalis and decidua parietalis are differently affected by the physiological labor process; in the decidua basalis of women who have undergone term parturition, there is a significant decrease in the

proportions of exhausted $CD4^+$ and $CD8^+$ T cells compared to with those of nonlabor controls [125]. These results demonstrate that T-cell exhaustion occurs physiologically at the maternal–fetal interface throughout late gestation; however, more research is needed to determine the clinical ramifications of aggravated T-cell depletion during term gestation, including dystocia, prolonged labor, and delayed parturition.

Women who have experienced preterm labor and delivery and had acute inflammatory lesions on the placenta have lower percentages of exhausted T cells in the decidua basalis [125]. These findings imply that, while T-cell exhaustion is a normal process in late gestation, unfavorable events such as pathological inflammation might reactivate these cells. In vitro activation of exhausted decidual T lymphocytes restores effector capabilities, supporting this hypothesis [123, 125]. After immune cells were isolated from TNL or TL samples from the decidua parietalis, Mosebarger et al. reported a reduction in CD38 expression on $CD8^+$ $CD57^+$ T cells throughout labor, which is suggestive of cytotoxic T cell senescence [85]. Given that decidual senescence has been hypothesized to be a novel mechanism of pathogenesis for preterm labor and delivery, research on senescent T lymphocytes is pertinent to pregnancy complications [126]. In concert with this idea, a considerably lower percentage of senescent T cells in the decidua basalis has been linked to the occurrence of acute placental inflammation in women with preterm gestations, but not in those of women at term [125]. Since T-cell senescence has been shown to be reversible in vitro [127, 128], it is possible that the pathological inflammation associated with particular groups of women who undergo preterm labor would induce senescent T cell reversal in decidual tissues, hence exacerbating inflammation.

All of these findings point to the possibility that the inflammatory reactions that coincide with preterm labor might revive exhausted and senescent T cells at the maternal–fetal interface, resulting in an abnormal effector T-cell response that could cause preterm labor and delivery. However, more research into how the multiple causes of preterm labor impact fatigued and/or senescent T lymphocytes at the maternal–fetal interface is needed to develop innovative methods to prevent the poor neonatal outcomes associated with this disease.

Decidual B cells

B cells, as key components of specific immunity, play various roles, such as those of antibody production, antigen presentation, and the release of immunomodulatory substances. There are two types of B lymphocytes: B-1 and B-2 B cells [129]. During pregnancy, B cells modulate immunological tolerance and suppress effector immune responses by secreting IL-10, which decreases TNF-α release by $CD4^+$ Th cells. Furthermore, fetal antigens can cause apoptosis in B cells in response to human chorionic gonadotropin (hCG) [130].

B cells are involved in the processes of maternal–fetal tolerance in the early stages of pregnancy [131, 132]. The number of decidual B cells increases slightly between weeks 27 and 33 of pregnancy and then slightly decreases at term [133]. Multiple investigations have revealed that B lymphocytes are present at the decidua basalis and decidua parietalis in the absence of labor at term [25, 134]. Furthermore, B cells appear to be present in increased numbers in the decidua basalis, but not in the decidua parietalis, throughout the physiological phase of labor at term [25].

According to a recent study, a connection may exist between B cells and the pathophysiology of preterm labor. The percentage of B cells in the decidua parietalis was greater in women who experienced sPTB than in those who went into labor at term [135]. A high concentration of $CD20^+CD70^-$type B lymphocytes in the decidua of pregnant women who have preterm births, leading to a decrease in the production of progesterone-induced blocking factor 1 (PIBF1) and a decrease in the release of IL-33, may be the cause of preterm labor [135]. Leng et al. discovered that in the absence of acute or chronic chorioamnionitis, total B lymphocytes are more plentiful in the decidua parietalis of women who delivered preterm than those who delivered at term, independent of the course of labor [29]. However, women who experienced term or preterm delivery with chronic chorioamnionitis had a greater proportion of B1 B cells and plasmablasts than those who did not have this placental lesion. Decidual B cells can produce pro- and anti-inflammatory cytokines. In summary, the B-cell compartment at the maternal–fetal interface changes in women who experience chronic chorioamnionitis and labor at term or preterm, indicating that these adaptive immune cells are involved in the labor process linked to persistent placental inflammation.

Bridge between the innate and adaptive immune systems

Decidual innate lymphoid cells

It has been demonstrated that innate and adaptive immune cells are crucial for the maintenance and outcome of pregnancy [136]. The discovery of innate lymphoid cells (ILCs), which link the innate and adaptive immune systems, has opened a new avenue of research with the potential to shed light on the complicated immunological state of pregnancy. The following traits characterize ILCs: (1) lack of

antigen-specific receptors; (2) lack of expression of recognized markers of immune cell lineages; and (3) lymphoid cellular morphology [136, 137]. ILCs are classified into three main classes according to their functions and phenotypes [137]. Type 1 ILCs (ILC1s) are characterized by the expression of the transcription factor T-bet and include both classic NK cells and noncytotoxic IFNγ-producing ILC1s [137, 138]. Type 2 cytokines, such as IL-5 and IL-13, are released by type 2 ILCs (ILC2s) to perform their functions [139]. ILC2 cells are hypothesized to rely mostly on GATA-binding protein 3 (GATA3) and retinoic acid receptor-related orphan receptor-α (RORα) expression during differentiation [137, 140]. Type 3 ILCs (ILC3s) are classified into two primary groups: lymphoid tissue inducer (LTi) cells and non-LTi ILC3s (referred to hereafter as ILC3s) [137]. LTi cells play crucial roles in the development of isolated lymphoid tissues, such as Peyer's patches, and secondary lymphoid organs throughout fetal development [141]. In adults, such cells are known as LTi-like cells since they do not produce new lymphoid tissue [142]. LTi cells and ILC3s can produce IL-17 A and/or IL-22 and depend on RORγt expression for their development [141].

ILC1s constitute the rarest ILC subset in the human decidua at the end of pregnancy. They do not change when spontaneous labor occurs, indicating that because of their distinct cytokine profile, these cells may play a relatively small role in late gestation, a role that may be shared by other decidual ILC subsets [143]. On the other hand, in the third trimester, as the most prevalent decidual ILC subgroup, ILC2s could help preserve the homeostatic environment at the maternal–fetal interface [143]. ILC2s are thought to have a homeostatic nature [144], making them unnecessary in early pregnancy when the inflammatory processes of implantation and tissue remodeling occur inside the endometrium. Women who undergo preterm labor have a greater proportion of total ILCs in their decidua parietalis; ILC1s constitute a modest subgroup of decidual ILCs throughout both preterm and term gestations [143]. Interestingly, ILC2s have been shown to be more common in the decidua basalis of women who undergo spontaneous preterm labor than in those who deliver preterm without labor [143], indicating that this ILC subgroup may be involved in the chronic inflammatory process that occurs during pathological pregnancy.

Furthermore, ILC2s from third-trimester human decidual tissues seem to share the production of cytokines such as IL-13 and IL-22 with ILC3s, indicating that decidual ILC subsets may have shared functions near the end of pregnancy [143]. ILC3s are the most investigated of the known ILC subgroups in the human decidua [30, 145]. Interestingly, women who experience spontaneous preterm labor present increased numbers of ILC3s in the decidua parietalis [143], indicating that these patients may experience a local dysregulation of these cells. It is unclear whether decidual ILC3s directly contribute to the inflammation associated with sPTB or are produced as a result of such a process. These results provide evidence that ILCs function at the maternal–fetal interface during the pathological phase of preterm labor.

Invariant NKT cells

NKT cells are a distinct lymphocyte subset that expresses markers and properties of both the adaptive and innate immune systems. NKT cells identify lipid antigens presented by nonpolymorphic CD1D molecules, which are produced by trophoblast cells, placenta, and choriocarcinoma cells [146]. NKT cells are classified into two types: I and II [147]. Type I NKT cells, also known as invariant NKT (iNKT) cells, can be observed at the maternal–fetal interface in early and late gestation [148, 149]. The concentration of iNKT cells in the decidua parietalis with parturition signals (labor and/or rupture of the membrane) is greater than that without parturition indicators [32]. Studies have shown that activating iNKT cells causes premature labor by increased cytotoxicity. The peripheral blood levels of CD69, perforin, and IFN-γ are higher in preterm labor patients than in women who give birth normally. Additionally, there is an increased percentage of activated iNKT cells in the decidua basalis. These factors can lead to preterm labor by disrupting the delicate balance between maternal and fetal immune tolerance [150]. St Louis et al. reported that activated NK T-like cells were more prevalent in the decidua basalis of women who underwent preterm labor, and that in vivo NK T-cell activation caused preterm labor by triggering a maternal systemic proinflammatory response [150].

A transcriptomic investigation of decidual lymphocytes in humans revealed that preterm labor and birth were associated with higher expression of CD1D, an established iNKT-cell receptor, than labor at term [25]. Human decidual tissues from a preterm birth with labor had higher concentrations of activated iNKT-like cells than decidua from a preterm birth without labor, suggesting that sterile inflammation caused by these cells may cause preterm labor, birth, or both [150]. Furthermore, compared with wild-type controls, iNKT-knockout mice intraperitoneally administered LPS at 15 days of gestation exhibited a substantial reduction in preterm labor rates, indicating that iNKT cells regulate inflammatory preterm labor caused by bacterial products [151]. The activation of decidual iNKT cells is a key factor in inflammation-induced preterm delivery. Pregnant mice deficient in iNKT cells are less vulnerable to endotoxin-induced PTB, suggesting that iNKT-cell activation may be deleterious to pregnancy outcomes [152, 153].

Pathological inflammation is linked to sPTB. Activating iNKT cells with α-galactosylceramide leads to PTB by stimulating innate immune responses systemically and locally (i.e., in the decidua and myometrium) [154]. This systemic activation of iNKT cells results in their proliferation at the maternal–fetal interface as well as corresponding decreases in the local populations of total T cells and Tregs, indicating an inverse link between Tregs and iNKT cells in this compartment [154] (Fig. 3). Furthermore, this proliferation of iNKT cells at the maternal–fetal interface is accompanied by an increase in the number of Th17 cells [154]. As a result, iNKT-cell activation affects both the systemic and local T-cell subsets prior to PTB. PTB caused by iNKT-cell activation is partially prevented by rosiglitazone treatment [154]. PPARγ gene targets were downregulated by α-galactosylceramide; however, these effects were recovered by rosiglitazone therapy, which activated the PPARγ pathway and prevented PTB. The number of T cells in the spleen was largely recovered when rosiglitazone was administered to mice that had received injections of α-galactosylceramide [154]. The fact that rosiglitazone inhibits iNKT-cell multiplication might help to explain it. However, rosiglitazone treatment did not increase the number of T lymphocytes at the maternal–fetal interface in mice injected with α-galactosylceramide. This result may explain why rosiglitazone may not completely prevent PTB.

Multi-omics testing of decidual immune cells in parturition and sPTB

Recently, single cell transcriptome sequencing has extended the "transcriptomics" area as new methods have been developed. The use of these methodical techniques might aid in the identification of certain biomarkers for sPTB diagnosis and treatment (Table 1). Recent cutting-edge molecular surveys using next-generation sequencing technologies have provided a deep characterization of the many immune cell

Table 1 Multi-omics testing of decidual immune cells in parturition and sPTB

Omics type	Year	Ethnic groups	Center	Tissue	Patients	Group
Transcriptomics [25]	2017	European	University of Edinburgh	Decidua parietalis immune cells	36 (TNL, $n=8$; TL, $n=7$; PNL, $n=5$; PL, $n=5$).	TNL, TL, PNL, PL,
Transcriptomics [156]	2017	American	University of Texas at Austin	Maternal blood, chorion, amnion, placenta, decidua, fetal blood, and myometrium	35 (PL, $n=8$; PNL, $n=10$; TL, $n=7$; TNL, $n=10$)	TNL, TL, PNL, PL
Transcriptomics [157]	2022	American	Columbia University Irving Medical Center	Placenta samples	18 (T1, $n=8$; T2, $n=4$; T3, $n=6$)	first trimester (T1); second trimester (T2); third trimester (T3)
scRNA-seq [61]	2019	American	Wayne State University	Placental samples [the villi, basal plate (including the decidua basalis) and chorioamniotic membranes (including the decidua parietalis)]	9 women (25 placental samples)	TNL, TL, PL
scRNA-seq [162, 163]	2021	Asian	Xiangya Hospital Central South University	Decidual samples	6 (3 Vaginal delivery; 3 Caesarean section)	Labor onset, Non-labor
scRNA-seq [166]	2022	C57BL/6mice	Stanford University	Placenta with intact decidua	47 mice	47 mice over the course of 9 gestational days (embryonic days 10.5–18.5)
scRNA-seq [167]	2022	Holtzman Sprague–Dawley rats	Boston Children's Hospital	Uterine–placental interface tissues	gd 15.5 ($n=3$ pregnancies/gd) and 19.5 ($n=4$ pregnancies/gd)	Uterine–placental interface tissues from gd 15.5 and 19.5 were dissected
scRNA-seq [164]	2023	Black	University of Chicago	Decidual samples	55 (TNL, $n=12$; TL, $n=16$; PNL, $n=14$; PL, $n=13$).	TL vs. PL; TL vs. TNL; PL vs. PNL; TNL vs. PNL
scRNA-seq [161]	2023	American	University of California	Decidua basalis immune cells	102 women who had cesarean deliveries	first-trimester, at term
scRNA-seq [160]	2024	American	Eunice Kennedy Shriver national institute of child health and human development	Placental and decidua tissues	42 (TL, $n=24$; TNL, $n=18$)	TL, TNL

subsets present in decidual tissues as well as their interaction networks, allowing researchers to delve more deeply into the cellular immune repertoire of the maternal–fetal interface.

Transcriptomics

The whole complement of mRNA present in a cell or tissue at any time is known as the transcriptome [155]. Transcriptomics has been used to characterize the global mRNA expression of a specific tissue, revealing transcriptional changes between two or more states. Parturition can be broadly divided into four complimentary phenotypes on the basis of the time and presence of labor: TNL; TL; preterm not in labor (PNL); and preterm in labor (PL), according to fetal or maternal indications [156]. Decidual lymphocytes were extracted from fresh decidual tissue, and transcriptomic sequencing revealed that CD1D, a nonclassic MHC-protein, is overexpressed in PTL decidual samples, indicating that decidual iNKT cells may be activated more frequently. Both term and PTL were linked to extensive gene expression alterations, notably those related to inflammatory signaling [25]. Bukowski et al. thoroughly examined the mRNA transcriptome that defines preterm and term labor in decidual tissues using properly phenotyped samples [156]. The gene expression profiles revealed a reduction in chemokine expression in TNL samples, removal of this repression in TL samples, activation of numerous inflammatory pathways in PL samples, and an immunological rejection profile in PNL samples [156]. These findings show that chemokine level downregulation at the maternal–fetal interface helps to preserve pregnancy. Withdrawal of this downregulation causes term birth, which is overridden by the activation of various immune system pathways in sPTB.

To construct a reference gene expression map of the first (T1), second (T2), and third trimester human placenta, and examine changes in the transcriptome in maternal vs. fetal side tissue sections of the full-term placenta, Suryawanshi et al. discovered that the number of monocytes and NK cells increased in T3 compared with T1 and T2, but the fraction of Hofbauer cells increased considerably in T2 and subsequently decreased in T3 [157]. For the most part, at least at the resolution of the biopsy samples, gene expression patterns change temporally throughout the trimesters but not geographically across the placenta.

Single cell transcriptome sequencing

With the rapid development of single-cell RNA sequencing (scRNA-seq) technology, numerous research groups have started looking at the cellular makeup of the maternal–fetal interface and/or decidua at various stages of pregnancy. The decidua facilitates communication between two semiallogenic persons, the mother and the fetus, and it is the epitome of intercellular communication [158]. Therefore, improved knowledge of intercellular communication in the decidua might improve our understanding of the fundamental foundation of pregnancy and aid in the discovery of pathogenic processes in pregnancy-related illnesses. Intercellular communication network research utilizing scRNA-seq of the human term placenta demonstrated that the decidua is the core of intercellular signal transduction and suggested the major involvement of growth factors and immunological signals in intercellular crosstalk [159].

The establishment of a single-cell atlas of the human placenta reveals variations in transcriptomic activity in both fetal and maternal cell types during labor [160]. Fetal stromal and maternal decidual cells in the chorioamniotic membranes, as well as maternal and fetal myeloid cells in the placenta, are the cell types most affected by labor. Using scRNA-seq, Sureshchandra et al. reported that decidual immune cells show signs of heightened activation state at term in comparison with the first trimester [161]. Moreover, there is a simultaneous decrease in the frequencies of macrophages and NK cells at term with an increase in the relative abundance of T cells. Compared with their blood counterparts, decidual T cells exhibit greater regulatory and Th17 responses, but Th1 responses are reduced, which is consistent with immunological tolerance [161].

Huang et al. discovered that after delivery, there are varying degrees of activation of T-cell subtypes, decidual stromal cells, and extravillous trophoblasts [162]. T cell intercellular communication analysis revealed substantial maternal–fetal immune-tolerance-related communication, such as TNFSF14-TNFRSF14/LTBR and FASLG-FAS signaling. They investigated the properties of the B cell receptor (BCR) and T cell receptor (TCR) repertoires via single-cell BCR/TCR sequencing. There were no significant variations in the clonal proliferation of B/T cells between the decidua before and after delivery, indicating that adaptive immunity at the maternal–fetal interface did not change significantly during delivery [163]. Pique-Regi et al. employed scRNA-seq to characterize the placental villous trees, basal plates, and chorioamniotic membranes of women who did or did not undergo term labor, as well as preterm labor. Maternal macrophages from the chorioamniotic membranes presented the greatest alterations in gene expression (e.g., NFKB1) in both phases of labor; nevertheless, specific gene expression modifications were also found during preterm labor [62]. Liu et al. found that at the maternal–fetal interface, 31 cell groups, comprising 25 immune cell types and 6 nonimmune cell types, exist. Among immune cells, term laboring women had lower levels of maternal $PD1^{+}$ $CD8^{+}$ T cell subsets among immune cells than term nonlaboring

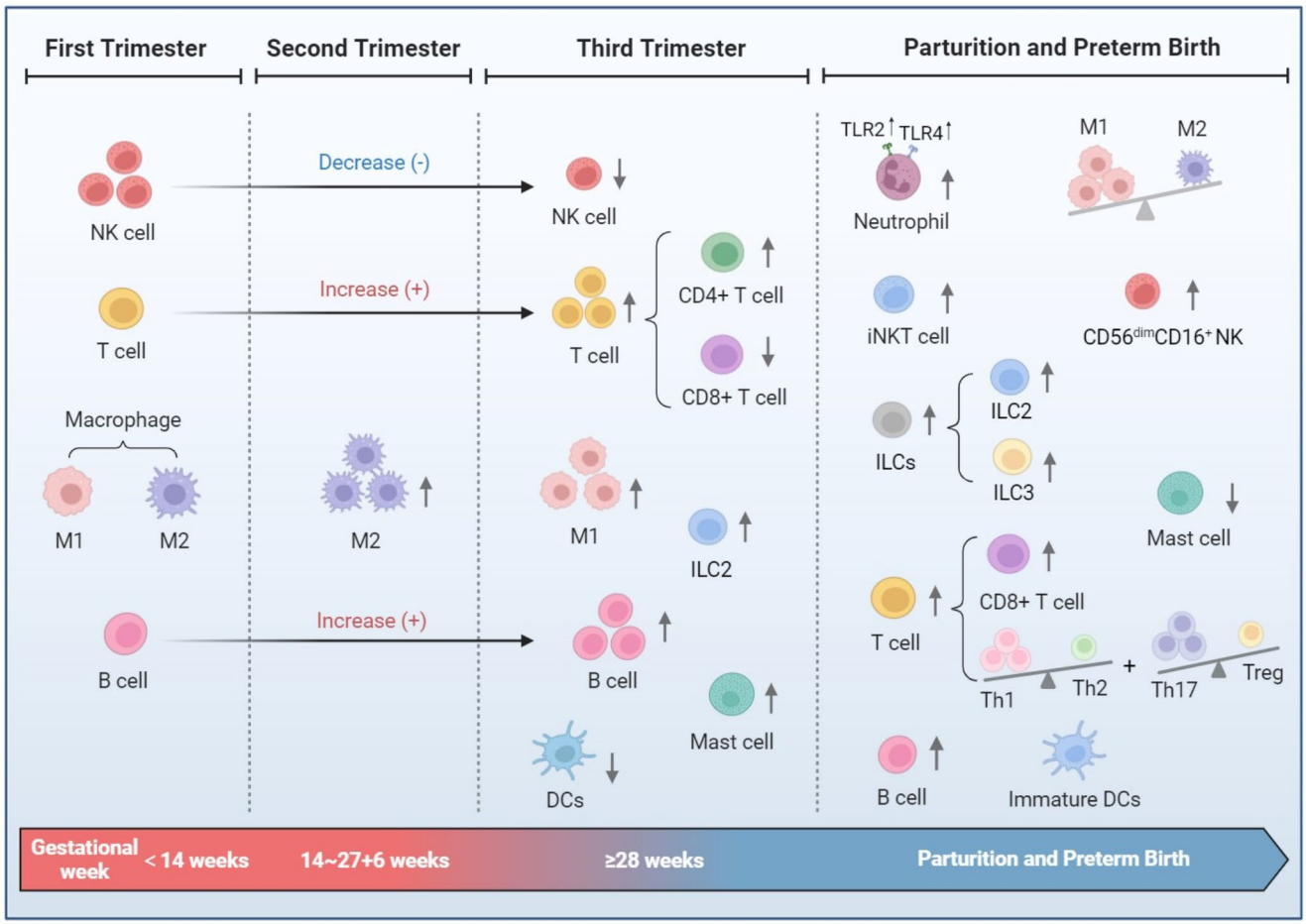

Fig. 5 Dynamic changes of decidual immune cells during normal pregnancy and preterm birth. As pregnancy progresses, the number of decidual NK cells decreases. The abundance of $CD56^{dim}$ $CD16^{+}$ NK cells increases in the decidua of the term and PTB. The percentage of $CD4^{+}$T cells increases and the percentage of $CD8^{+}$T cells decreases in late pregnancy. The fraction of $CD8^{+}$ T cells is greatly increased in preterm birth patients. An increase in the ratio of Th1/Th2 to Th17/Treg cells result in PTB. M2 macrophages constitute the predominant phenotype in decidua tissues during late gestation. At term and preterm labor, the number of M1 macrophages increases significantly. The number of decidual B cells increases slightly in the third trimester and was greater in women who experienced PTB than in those who went into labor at term. In the third trimester, ILC2 could help preserve the homeostatic environment at the maternal–fetal interface. ILC2 and ILC3 have been shown to be more common in the decidua basalis of women who undergo sPTB than in those who deliver preterm without labor. MCs play a key role in innate immunity during late gestation. There are considerably more MCs in the decidua of term pregnancies than in those of preterm births. The number of DCs decreases through late pregnancy and immature DCs may be involved in the genesis of PTB. The concentration of iNKT cells in the decidua parietalis with parturition signals is greater than that without parturition indicators. In both term and preterm labor, human decidual neutrophils secrete inflammatory mediators and thereby aid in birth. Furthermore, TLR2 and TLR4 expression increased on the surfaces of neutrophils in pregnant women with sPTB

women did [164]. These findings imply that immunological tolerance and rejection may be out of balance, and that the PD-1/PD-L1 pathway at the maternal–fetal interface may be responsible for the onset of sPTB.

Both mice and humans have hemochorial placentas and comparable decidual immune compositions [165]. During the second half of mouse gestation, Moore et al. mapped maternal immune cells at the maternal–fetal interface via single-cell mass cytometry [166]. They discovered a critical function for the innate immune system, in which phagocytes and neutrophils influence the temporal architecture of the placenta via impressively varied populations, including $PD\text{-}L1^{+}$ subsets with compartmental and early gestational bias. The transcriptomes of invasive trophoblast cell lineages and other cell populations within the rat uterine–placental interface were characterized by Scott et al. via single-cell RNA sequencing during the early (gestation day [gd] 15.5) and late (gd 19.5) stages of intrauterine trophoblast cell invasion [167]. This study revealed discrepancies in the spatial interactions between invasive trophoblast cells and immune cells [167]. Within the uterine-placental interface, macrophage populations (Lyz2 positive) are scattered among invasive trophoblast cells. In contrast, NK cells (Prf1 positive) and invasive trophoblast cells (Prl7b1 positive)

displayed a reciprocal relationship and little overlap in their spatial distribution.

Conclusion and perspectives

The maternal–fetal interface, which is formed of cells of both maternal and fetal origin, is a crucial heterogeneous organ that links the maternal and fetal systems during pregnancy and plays important functions in delivery [168]. The decidua, an essential tissue situated inside the maternal–fetal interface, is the location of intercellular crosstalk, which plays critical roles in integrating the maternal and fetal systems, maintaining pregnancy, and transitioning to labor [169]. In this article, we review the landscape of decidual immune cells during parturition and preterm birth (Fig. 5). The decidual immune cells are classified into three groups: innate immune cells, adaptive immune cells, and cell types that mediate innate and adaptive immunological responses. Each of these subgroups has a particular function, such as preserving maternal fetal tolerance and increasing inflammatory processes associated with the birth process. As a result, the disruption of these various immune cell subpopulations is frequently connected with parturition and preterm birth. Furthermore, these immune cells interact with one another, maintaining immunological balance at the maternal–fetal interface and promoting appropriate pregnancy development.

Currently, many "-omics" publications regarding sPTB have analyzed specific types of "-omics" data, such as genomes, transcriptomics, or proteomics in isolation. Researchers can now better understand the cellular immune repertoire of the maternal–fetal interface via recent state-of-the-art molecular surveys that employ next-generation sequencing technologies to provide a deep characterization of the various immune cell subsets present in decidual tissues as well as their interaction networks. Many of these "-omics" articles have failed to be replicated, and their practical relevance has been limited, with little translation into clinical practice. The limited performance of single techniques highlights the importance of integrated approaches for investigating complex phenotypes spanning "-omics" categories. The use of these methodical techniques might aid in the identification of certain biomarkers for sPTB diagnosis and treatment.

In addition, there are still many areas that need to be explored; For example, there is limited research on the metabolic characteristics of decidual immune cells associated with parturition and preterm birth, and the mechanisms are largely unclear. In addition, with the development of single-cell sequencing and multi-omics sequencing, there has been a deeper exploration of subpopulations of decidual immune cells. How to detect and study specific subgroups of decidual immune cells in normal and abnormal pregnancies may be worth future research. Even with the aid of technological advancements, we still do not fully comprehend the decidua's highly interwoven and dynamic nature or how it functions throughout pregnancy and delivery. Determining how molecular networks that control immune cells at the maternal–fetal interface are altered in sPTB patients once they are identified is difficult. Most importantly, large-scale clinical studies are still needed to evaluate decidual immune cell markers associated with preterm birth.

Acknowledgements Not applicable.
Not applicable.

Author contributions LM and JYH conceived the idea and wrote the manuscript. WSY and DJQ collected the literature together. YH modified the manuscript critically for important intellectual content and final approval of the version to be published. All authors reviewed and approved the final manuscript.

Funding This study was supported in part by the National Key Research and Development Program (2022YFC2704602 and 2022YFC2704600), the National Natural Science Foundation of China (Nos. 82271719 and 82071678), the Shanghai Municipal Science and Technology Commission Research Fund (No. 21140903800), the Program of Shanghai Academic/Technology Research Leader(23XD1402700), and the Key Research Project of Pudong New Area Population and Family Planning Commission (No. PW2020E-1).

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interests The authors declare no competing interests.

Ethics approval and consent to participate Not applicable.

Consent for publication All authors have reviewed the final version of the manuscript and approved it for publication.

Institutional review board statement Not applicable.

Informed consent Not applicable.

References

1. Tafuri A, Alferink J, Möller P, Hämmerling GJ, Arnold B. T cell awareness of paternal alloantigens during pregnancy. Science. 1995;270:630–3.
2. Vogel JP, Chawanpaiboon S, Moller AB, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth, best practice and research. Clin Obstet Gynaecol. 2018;52:3–12.
3. Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, Rubens C, Menon R, Van Look PF. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ. 2010;88:31–8.
4. Gracie S, Pennell C, Ekman-Ordeberg G, Lye S, McManaman J, Williams S, Palmer L, Kelley M, Menon R, Gravett M. An integrated systems biology approach to the study of preterm birth using -omic technology–a guideline for research. BMC Pregnancy Childbirth. 2011;11:71.
5. Menon R. Spontaneous preterm birth, a clinical dilemma: etiologic, pathophysiologic and genetic heterogeneities and Racial disparity. Acta Obstet Gynecol Scand. 2008;87:590–600.
6. Kennedy C, O'Dwyer V. Predicting spontaneous preterm birth. Ir Med J. 2019;112:964.
7. Chan RL. Biochemical markers of spontaneous preterm birth in asymptomatic women. Biomed Res Int. 2014;2014:164081.
8. Romero R, Gómez R, Chaiworapongsa T, Conoscenti G, Kim JC, Kim YM. The role of infection in preterm labour and delivery. Paediatr Perinat Epidemiol. 2001;15(Suppl 2):41–56.
9. Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, Chaiworapongsa T, Mazor M. The preterm parturition syndrome. BJOG: Int J Obstet Gynecol 113 Suppl 3 (2006) 17–42.
10. Faas MM, de Vos P. Uterine NK cells and macrophages in pregnancy. Placenta. 2017;56:44–52.
11. Erlebacher A. Immunology of the maternal–fetal interface. Annu Rev Immunol. 2013;31:387–411.
12. PrabhuDas M, Bonney E, Caron K, Dey S, Erlebacher A, Fazleabas A, Fisher S, Golos T, Matzuk M, McCune JM, Mor G, Schulz L, Soares M, Spencer T, Strominger J, Way SS, Yoshinaga K. Immune mechanisms at the maternal–fetal interface: perspectives and challenges. Nat Immunol. 2015;16:328–34.
13. Arck PC, Hecher K. Fetomaternal immune cross-talk and its consequences for maternal and offspring's health. Nat Med. 2013;19:548–56.
14. Mor G, Cardenas I, Abrahams V, Guller S. Inflammation and pregnancy: the role of the immune system at the implantation site. Ann New York Acad Scis; 2011; 1221:80–7.
15. Ander SE, Diamond MS, Coyne CB. Immune responses at the maternal–fetal interface. Sci Immunol. 2019;4:eaat6114.
16. Vondra S, Höbler AL, Lackner AI, Raffetseder J, Mihalic ZN, Vogel A, Saleh L, Kunihs V, Haslinger P, Wahrmann M, Husslein H, Oberle R, Kargl J, Haider S, Latos P, Schabbauer G, Knöfler M, Ernerudh J, Pollheimer J. The human placenta shapes the phenotype of decidual macrophages. Cell Rep. 2023;42:111977.
17. Mori M, Bogdan A, Balassa T, Csabai T, Szekeres-Bartho J. The decidua-the maternal bed embracing the embryo-maintains the pregnancy. Semin Immunopathol. 2016;38:635–49.
18. Casey ML, MacDonald PC. Biomolecular processes in the initiation of parturition: decidual activation. Clin Obstet Gynecol. 1988;31:533–52.
19. Snegovskikh VV, Bhandari V, Wright JR, Tadesse S, Morgan T, Macneill C, Foyouzi N, Park JS, Wang Y, Norwitz ER. Surfactant protein-A (SP-A) selectively inhibits prostaglandin F2alpha (PGF2alpha) production in term decidua: implications for the onset of labor. J Clin Endocrinol Metab. 2011;96:E624–632.
20. Huang Y, Zhu XY, Du MR, Li DJ. Human trophoblasts recruited T lymphocytes and monocytes into decidua by secretion of chemokine CXCL16 and interaction with CXCR6 in the first-trimester pregnancy. J Immunol 2008;180:2367–2375.
21. Prearo N, Moço RA, Camargo Batista L, Fernandes Martin LG, de Oliveira CM, Garcia de Lima Parada L, Alarcão Dias-Melicio M, de Assis Golim M. Guimarães Da Silva, Toll-Like Receptor-2 and–4 expression by maternal neutrophils in preterm labor, gynecologic and obstetric investigation. Gynecol Obstet Invest 2018;83:1–8.
22. Needham K, Fadia M, Dahlstrom JE, Harrington K, Shadbolt B, Robson SJ. Significance of mast cell distribution in placental tissue and membranes in spontaneous preterm birth. J Inflamm Res. 2016;9:141–5.
23. Hsu P, Nanan RK. Innate and adaptive immune interactions at the fetal-maternal interface in healthy human pregnancy and preeclampsia. Front Immunol. 2014;5:125.
24. Takahashi H, Yamamoto T, Yamazaki M, Murase T, Matsuno T, Chishima F. Natural cytotoxicity receptors in decidua natural killer cells of term normal pregnancy. J Pregnancy. 2018;2018:4382084.
25. Rinaldi SF, Makieva S, Saunders PT, Rossi AG, Norman JE. Immune cell and transcriptomic analysis of the human decidua in term and preterm parturition. Mol Hum Reprod. 2017;23:708–24.
26. Jiang X, Du MR, Li M, Wang H. Three macrophage subsets are identified in the uterus during early human pregnancy. Cell Mol Immunol. 2018;15:1027–37.
27. Xu Y, Romero R, Miller D, Kadam L, Mial TN, Plazyo O, Garcia-Flores V, Hassan SS, Xu Z, Tarca AL, Drewlo S, Gomez-Lopez N. An M1-like macrophage polarization in decidual tissue during spontaneous preterm labor that is attenuated by rosiglitazone treatment. J immunol. 2016;196:2476–2491.
28. Salvany-Celades M, van der Zwan A, Benner M, Setrajcic-Dragos V, Bougleux Gomes HA, Iyer V, Norwitz ER, Strominger JL, Tilburgs T. Three types of functional regulatory T cells control T cell responses at the human Maternal-Fetal interface. Cell Rep. 2019;27:2537–e25472535.
29. Leng Y, Romero R, Xu Y, Galaz J, Slutsky R, Arenas-Hernandez M, Garcia-Flores V, Motomura K, Hassan SS, Reboldi A, Gomez-Lopez N. Are B cells altered in the decidua of women with preterm or term labor? Am J Reprod Immunol 2019;81:e13102.
30. Vacca P, Montaldo E, Croxatto D, Loiacono F, Canegallo F, Venturini PL, Moretta L, Mingari MC. Identification of diverse innate lymphoid cells in human decidua. Mucosal Immunol. 2015;8:254–64.
31. Doisne JM, Balmas E, Boulenouar S, Gaynor LM, Kieckbusch J, Gardner L, Hawkes DA, Barbara CF, Sharkey AM, Brady HJ, Brosens JJ, Moffett A, Colucci F. Composition, development, and function of uterine innate lymphoid cells. J Immunol. 2015;195:3937–45.
32. Kato M, Negishi Y, Shima Y, Kuwabara Y, Morita R, Takeshita T. Inappropriate activation of invariant natural killer T cells and antigen-presenting cells with the elevation of HMGB1 in preterm births without acute chorioamnionitis. Am J Reprod Immunol 2021;85:e13330.
33. Miller D, Gershater M, Slutsky R, Romero R, Gomez-Lopez N. Maternal and fetal T cells in term pregnancy and preterm labor. Cell Mol Immunol. 2020;17:693–704.
34. Yang F, Zheng Q, Jin L. Dynamic function and composition changes of immune cells during normal and pathological pregnancy at the maternal–fetal interface. Front Immunol. 2019;10:2317.
35. Arenas-Hernandez M, Romero R, St Louis D, Hassan SS, Kaye EB, Gomez-Lopez N. An imbalance between innate and adaptive

immune cells at the maternal–fetal interface occurs prior to endotoxin-induced preterm birth. Cell Mol Immunol. 2016;13:462–73.
36. Gomez-Lopez N, StLouis D, Lehr MA, Sanchez-Rodriguez EN. Arenas-Hernandez, immune cells in term and preterm labor. Cell Mol Immunol. 2014;11:571–81.
37. Steel JH, O'Donoghue K, Kennea NL, Sullivan MH, Edwards AD. Maternal origin of inflammatory leukocytes in preterm fetal membranes, shown by fluorescence in situ hybridisation. Placenta. 2005;26:672–7.
38. Helmig B.R., Romero R, Espinoza J, Chaiworapongsa T, Bujold E, Gomez R, Ohlsson K, Uldbjerg N. Neutrophil elastase and secretory leukocyte protease inhibitor in prelabor rupture of membranes, parturition and intra-amniotic infection. J Maternal-Fetal Neonatal Med Off J Eur Assoc Perinat Med Federation Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2002;12:237–46.
39. Timmons B, Akins M, Mahendroo M. Cervical remodeling during pregnancy and parturition, trends in endocrinology and metabolism. Trends Endocrinol Metab 2010;21:353–61.
40. Gomez-Lopez N, Garcia-Flores V, Chin PY, Groome HM, Bijland MT, Diener KR, Romero R, Robertson SA. Macrophages exert homeostatic actions in pregnancy to protect against preterm birth and fetal inflammatory injury. JCI Insight 2021;6.
41. Agrawal V, Jaiswal MK, Pamarthy S, Katara GK, Kulshrestha A, Gilman-Sachs A, Hirsch E, Beaman KD. Role of Notch signaling during lipopolysaccharide-induced preterm labor. J Leukoc Biol. 2016;100:261–74.
42. Garfield RE, Bytautiene E, Vedernikov YP, Marshall JS, Romero R. Modulation of rat uterine contractility by mast cells and their mediators. Am J Obstet Gynecol. 2000;183:118–25.
43. Bytautiene E, Romero R, Vedernikov YP, El-Zeky F, Saade GR, Garfield RE. Induction of premature labor and delivery by allergic reaction and prevention by Histamine H1 receptor antagonist. Am J Obstet Gynecol. 2004;191:1356–61.
44. Hayano C, Koi H, Ogawa K, Nagata K, Matsumoto Y, Nakamura M, Aso T. Accumulation of CD16+cells with secretion of Ksp37 in decidua at the end of pregnancy. Am J Reprod Immunol 2002;48:57–62.
45. Murphy SP, Hanna NN, Fast LD, Shaw SK, Berg G, Padbury JF, Romero R, Sharma S. Evidence for participation of uterine natural killer cells in the mechanisms responsible for spontaneous preterm labor and delivery. Am J Obstet Gynecol. 2009;200:e308301–309.
46. Zhang J, Shynlova O, Sabra S, Bang A, Briollais L, Lye SJ. Immunophenotyping and activation status of maternal peripheral blood leukocytes during pregnancy and labour, both term and preterm. J Cell Mol Med. 2017;21:2386–402.
47. Shynlova O, Nedd-Roderique T, Li Y, Dorogin A, Nguyen T, Lye SJ. Infiltration of myeloid cells into decidua is a critical early event in the labour cascade and post-partum uterine remodelling. J Cell Mol Med. 2013;17:311–24.
48. Shynlova O, Nedd-Roderique T, Li Y, Dorogin A, Lye SJ. Myometrial immune cells contribute to term parturition, preterm labour and post-partum Involution in mice. J Cell Mol Med. 2013;17:90–102.
49. Rinaldi S.F., Catalano R.D., Wade J., Rossi A.G., Norman J.E. Decidual neutrophil infiltration is not required for preterm birth in a mouse model of infection-induced preterm labor. J Immunol. 2014;192:2315–25.
50. Pawelczyk E, Nowicki BJ, Izban MG, Pratap S, Sashti NA, Sanderson M, Nowicki S. Spontaneous preterm labor is associated with an increase in the Proinflammatory signal transducer TLR4 receptor on maternal blood monocytes. BMC Pregnancy Childbirth. 2010;10:66.
51. Timmons BC, Mahendroo MS. Timing of neutrophil activation and expression of Proinflammatory markers do not support a role for neutrophils in cervical ripening in the mouse. Biol Reprod. 2006;74:236–45.
52. Romero R, Mazor M, Tartakovsky B. Systemic administration of interleukin-1 induces preterm parturition in mice. Am J Obstet Gynecol. 1991;165:969–71.
53. Gravett MG, Rubens CE, Nunes TM. Global report on preterm birth and stillbirth (2 of 7): discovery science. BMC Pregnancy Childbirth. 2010;10(Suppl 1):S2.
54. Redline R.W. Inflammatory response in acute chorioamnionitis. Semin Fetal Neonatal Med. 2012;17:20–5.
55. Hamilton S, Oomomian Y, Stephen G, Shynlova O, Tower CL, Garrod A, Lye SJ, Jones RL. Macrophages infiltrate the human and rat decidua during term and preterm labor: evidence that decidual inflammation precedes labor. Biol Reprod. 2012;86:39.
56. Presicce P, Senthamaraikannan P, Alvarez M, Rueda CM, Cappelletti M, Miller LA, Jobe AH, Chougnet CA, Kallapur SG. Neutrophil recruitment and activation in decidua with intra-amniotic IL-1beta in the preterm rhesus macaque. Biol Reprod. 2015;92:56.
57. Karenberg K, Hudalla H, Frommhold D. Leukocyte recruitment in preterm and term infants, molecular and cellular pediatrics, 3 (2016) 35.
58. Timmons BC, Fairhurst AM, Mahendroo MS Temporal changes in myeloid cells in the cervix during pregnancy and parturition. J Immunol. 2009;182:2700–7.
59. Holt R, Timmons BC, Akgul Y, Akins ML, Mahendroo M. The molecular mechanisms of cervical ripening differ between term and preterm birth. Endocrinology. 2011;152:1036–46.
60. Zhang YH, He M, Wang Y, Liao AH. Modulators of the balance between M1 and M2 macrophages during pregnancy. Front Immunol. 2017;8:120.
61. Thomson AJ, Telfer JF, Young A, Campbell S, Stewart CJ, Cameron IT, Greer IA, Norman JE. Leukocytes infiltrate the myometrium during human parturition: further evidence that labour is an inflammatory process. Hum Reprod (Oxford England). 1999;14:229–36.
62. Pique-Regi R, Romero R, Tarca AL, Sendler ED, Xu Y, Garcia-Flores V, Leng Y, Luca F, Hassan SS. N. Gomez-Lopez, single cell transcriptional signatures of the human placenta in term and preterm parturition. eLife; 2019. p. 8.
63. Shynlova O, Tsui P, Dorogin A, Lye S.J. Monocyte chemoattractant protein-1 (CCL-2) integrates mechanical and endocrine signals that mediate term and preterm labor. J Immunol. 2008;181:1470–9.
64. Shan Y, Shen S, Long J, Tang Z, Wu C, Ni X. Term and preterm birth initiation is associated with the macrophages shifting to M1 polarization in gestational tissues in mice. Biology 2022;11.
65. Zha Y, Liu H, Lin X, Yu L, Gao P, Li Y, Wu M, Gong X, Bian X, Kang Q, Zhi P, Dang X, Wang J, Feng L, Qiao F, Huang Y, Zeng W. Immune deviation in the decidua during term and preterm labor. Front Immunol. 2022;13:877314.
66. Menzies FM, Shepherd MC, Nibbs RJ, Nelson SM. The role of mast cells and their mediators in reproduction, pregnancy and labour. Hum Reprod Update. 2011;17:383–96.
67. Bytautiene E, Vedernikov YP, Saade GR, Romero R, Garfield RE. IgE-independent mast cell activation augments contractility of nonpregnant and pregnant guinea pig myometrium. Int Arch Allergy Immunol. 2008;147:140–6.
68. Dorff SR, Afrin LB. Mast cell activation syndrome in pregnancy, delivery, postpartum and lactation: a narrative review. J Obstet Gynaecology: J Inst Obstet Gynecol. 2020;40:889–901.
69. Valap S, Millns P, Bulchandani S. Management of a parturient with mast cell activation syndrome. Int J Obstet Anesth. 2013;22:83–4.
70. Zhang J, Nie G, Jian W, Woolley DE, Salamonsen LA. Mast cell regulation of human endometrial matrix metalloproteinases:

a mechanism underlying menstruation. Biol Reprod. 1998;59:693–703.
71. Arora N, Akin C, Kovalszki A. Mastocytosis in pregnancy. Immunol Allergy Clin North Am. 2023;43:159–68.
72. Koch J, Steinle A, Watzl C, Mandelboim O. Activating natural cytotoxicity receptors of natural killer cells in cancer and infection. Trends Immunol. 2013;34:182–91.
73. Cooper MA, Fehniger TA, Turner SC, Chen KS, Ghaheri BA, Ghayur T, Carson WE, Caligiuri MA. Human natural killer cells: a unique innate immunoregulatory role for the CD56(bright) subset. Blood. 2001;97:3146–51.
74. Zhang X, Wei H. Role of decidual natural killer cells in human pregnancy and related pregnancy complications. Front Immunol. 2021;12:728291.
75. Björkström NK, Ljunggren HG, Michaëlsson J. Emerging insights into natural killer cells in human peripheral tissues. Nat Rev Immunol. 2016;16:310–20.
76. Jabrane-Ferrat N. Features of human decidual NK cells in healthy pregnancy and during viral infection. Front Immunol. 2019;10:1397.
77. Yougbaré I, Tai WS, Zdravic D, Oswald BE, Lang S, Zhu G, Leong-Poi H, Qu D, Yu L, Dunk C, Zhang J, Sled JG, Lye SJ, Brkić J, Peng C, Höglund P, Croy BA, Adamson SL, Wen XY, Stewart DJ, Freedman J, Ni H. Activated NK cells cause placental dysfunction and miscarriages in fetal alloimmune thrombocytopenia. Nat Commun. 2017;8:224.
78. Vosshenrich CA, García-Ojeda ME, Samson-Villéger SI, Pasqualetto V, Enault L, Richard-Le Goff O, Corcuff E, Guy-Grand D, Rocha B, Cumano A, Rogge L, Ezine S, Di Santo JP. A thymic pathway of mouse natural killer cell development characterized by expression of GATA-3 and CD127. Nat Immunol. 2006;7:1217–24.
79. Freud AG, Becknell B, Roychowdhury S, Mao HC, Ferketich AK, Nuovo GJ, Hughes TL, Marburger TB, Sung J, Baiocchi RA, Guimond M, Caligiuri MA. A human CD34(+) subset resides in lymph nodes and differentiates into CD56bright natural killer cells. Immunity. 2005;22:295–304.
80. van den Heuvel M, Peralta C, Bashar S, Taylor S, Horrocks J, Croy BA. Trafficking of peripheral blood CD56(bright) cells to the decidualizing uterus–new tricks for old dogmas? J Reprod Immunol. 2005;67:21–34.
81. Ye W, Zheng LM, Young JD, Liu CC. The involvement of Interleukin (IL)-15 in regulating the differentiation of granulated metrial gland cells in mouse pregnant uterus. J Exp Med. 1996;184:2405–10.
82. Williams PJ, Searle RF, Robson SC, Innes BA, Bulmer JN. Decidual leucocyte populations in early to late gestation normal human pregnancy. J Reprod Immunol. 2009;82:24–31.
83. Sindram-Trujillo AP, Scherjon SA, van Hulst-van Miert PP, Kanhai HH, Roelen DL, Claas FH. Comparison of decidual leukocytes following spontaneous vaginal delivery and elective Cesarean section in uncomplicated human term pregnancy. J Reprod Immunol. 2004;62:125–37.
84. Mazi E, Altunkaynak Z, Aydin I, Kocak I, Guven D, Turkmen AP, Yildiran A. Is parturition-timing machinery related to the number of inhibitor CD94/NKG2A positive uterine natural killer cells? Arch Gynecol Obstet. 2016;294:261–5.
85. Mosebarger A, Vidal MS Jr., Bento GFC, Lintao RCV, Severino MEL, Kumar Kammala A, Menon R. Immune cells at the feto-maternal interface: comprehensive characterization and insights into term labor. J Reprod Immunol. 2024;163:104239.
86. Gomaa MF, Serag Eldeen IF, Farid LA, El-Saeed MME, Abas AM, Aawd NM. Uterine natural killer cells dysregulation in idiopathic human preterm birth: a pilot study, the journal of maternal–fetal & neonatal medicine: the official journal of the European association of perinatal medicine, the federation of Asia and Oceania perinatal societies. Int Soc Perinatal Obstet, 30 (2017) 1782–6.
87. Kemp B, Schmitz S, Krusche CA, Rath W. Von Rango, dendritic cells are equally distributed in intrauterine and tubal ectopic pregnancies. Fertil Steril. 2011;95:28–32.
88. Rieger L, Honig A, Sütterlin M, Kapp M, Dietl J, Ruck P, Kämmerer U. Antigen-presenting cells in human endometrium during the menstrual cycle compared to early pregnancy. J Soc Gynecol Investig. 2004;11:488–93.
89. Tagliani E, Erlebacher A. Dendritic cell function at the maternal–fetal interface. Expert Rev Clin Immunol. 2011;7:593–602.
90. Blois SM, Alba Soto CD, Tometten M, Klapp BF, Margni RA, Arck PC. Lineage, maturity, and phenotype of uterine murine dendritic cells throughout gestation indicate a protective role in maintaining pregnancy. Biol Reprod. 2004;70:1018–23.
91. Bizargity P, Del Rio R, Phillippe M, Teuscher C, Bonney EA. Resistance to lipopolysaccharide-induced preterm delivery mediated by regulatory T cell function in mice. Biol Reprod. 2009;80:874–81.
92. Cappelletti M, Della Bella S, Ferrazzi E, Mavilio D, Divanovic S. Inflammation and preterm birth. J Leukoc Biol. 2016;99:67–78.
93. Kämmerer U, Eggert AO, Kapp M, McLellan AD, Geijtenbeek TB, Dietl J, van Kooyk Y, Kämpgen E. Unique appearance of proliferating antigen-presenting cells expressing DC-SIGN (CD209) in the decidua of early human pregnancy. Am J Pathol. 2003;162:887–96.
94. Wang H, He M, Hou Y, Chen S, Zhang X, Zhang M, Ji X. Role of decidual CD14(+) macrophages in the homeostasis of maternal–fetal interface and the differentiation capacity of the cells during pregnancy and parturition. Placenta 2016;38:76–83.
95. Negishi Y, Ichikawa T, Takeshita T, Takahashi H. Miscarriage induced by adoptive transfer of dendritic cells and invariant natural killer T cells into mice. Eur J Immunol. 2018;48:937–49.
96. Negishi Y, Shima Y, Takeshita T, Takahashi H. Distribution of invariant natural killer T cells and dendritic cells in late pre-term birth without acute chorioamnionitis. Am J Reprod Immunol 2017;77.
97. Arora P, Baena A, Yu KO, Saini NK, Kharkwal SS, Goldberg MF, Kunnath-Velayudhan S, Carreño LJ, Venkataswamy MM, Kim J, Lazar-Molnar E, Lauvau G, Chang YT, Liu Z, Bittman R, Al-Shamkhani A, Cox LR, Jervis PJ, Veerapen N, Besra GS, Porcelli SA. A single subset of dendritic cells controls the cytokine bias of natural killer T cell responses to diverse glycolipid antigens. Immunity. 2014;40:105–16.
98. Tilburgs T, Claas FH, Scherjon SA. Elsevier trophoblast research award lecture: unique properties of decidual T cells and their role in immune regulation during human pregnancy. Placenta. 2010;31:S82–86.
99. Liu S, Diao L, Huang C, Li Y, Zeng Y, Kwak-Kim JYH. The role of decidual immune cells on human pregnancy. J Reprod Immunol. 2017;124:44–53.
100. Vargas ML, Sántos JL, Ruiz C, Montes MJ, Alemán P, García-Tortosa C. E. García-Olivares, Comparison of the proportions of leukocytes in early and term human decidua. Am J Reprod Immunol 1993;29:135–140.
101. Sindram-Trujillo A, Scherjon S, Kanhai H, Roelen D, Claas F. Increased T-cell activation in decidua parietalis compared to decidua basalis in uncomplicated human term pregnancy. Am J Reprod Immunol 2003;49:261–268.
102. Constantin CM, Masopust D, Gourley T, Grayson J, Strickland OL, Ahmed R, Bonney EA. Normal establishment of virus-specific memory CD8 T cell pool following primary infection during pregnancy. J Immunol 2007;179: 4383–4389.
103. Norton MT, Fortner KA, Oppenheimer KH, Bonney EA. Evidence that CD8 T-cell homeostasis and function remain intact during murine pregnancy. Immunology. 2010;131:426–37.

104. Crespo Â C, van der Zwan A, Ramalho-Santos J, Strominger JL, Tilburgs T. Cytotoxic potential of decidual NK cells and CD8+T cells awakened by infections. J Reprod Immunol. 2017;119:85–90.
105. Costa ML, Robinette ML, Bugatti M, Longtine MS, Colvin BN, Lantelme E, Vermi W, Colonna M, Nelson DM, Cella M. Two distinct myeloid subsets at the term human fetal-maternal interface. Front Immunol. 2017;8:1357..
106. Arenas-Hernandez M, Romero R, Xu Y, Panaitescu B, Garcia-Flores V, Miller D, Ahn H, Done B, Hassan SS, Hsu CD, Tarca AL, Sanchez-Torres C. N. Gomez-Lopez, Effector and activated T cells induce preterm labor and birth that is prevented by treatment with progesterone. J Immunol. 2019;202:2585–2608.
107. Kim CJ, Romero R, Chaemsaithong P, Kim JS. Chronic inflammation of the placenta: definition, classification, pathogenesis, and clinical significance. Am J Obstet Gynecol. 2015;213:S53–69.
108. Lee J, Kim JS, Park JW, Park CW, Park JS, Jun JK, Yoon BH. Chronic chorioamnionitis is the most common placental lesion in late preterm birth. Placenta. 2013;34:681–9.
109. Alijotas-Reig J, Llurba E, Gris JM. Potentiating maternal immune tolerance in pregnancy: a new challenging role for regulatory T cells. Placenta. 2014;35:241–8.
110. Peck A, Mellins ED. Plasticity of T-cell phenotype and function: the T helper type 17 example. Immunology. 2010;129:147–53.
111. Nakashima A, Ito M, Shima T, Bac ND, Hidaka T, Saito S. Accumulation of IL-17-positive cells in decidua of inevitable abortion cases. Am J Reprod Immunol 2010;64:4–11.
112. La Rocca C, Carbone F, Longobardi S, Matarese G. The immunology of pregnancy: regulatory T cells control maternal immune tolerance toward the fetus. Immunol Lett. 2014;162:41–8.
113. Ito M, Nakashima A, Hidaka T, Okabe M, Bac ND, Ina S, Yoneda S, Shiozaki A, Sumi S, Tsuneyama K, Nikaido T, Saito S. A role for IL-17 in induction of an inflammation at the fetomaternal interface in preterm labour. J Reprod Immunol. 2010;84:75–85.
114. Lyubomirskaya ES, Kamyshnyi AM, Krut YY, Smiianov VA, Fedoniuk LY, Romanyuk LB, Kravets NY, Mochulska OM. SNPs and transcriptional activity of genes of innate and adaptive immunity at the maternal–fetal interface in woman with preterm labour, associated with preterm premature rupture of membranes. Wiadomosci Lekarskie 2020;73:25–30.
115. Teles A, Schumacher A, Kühnle MC, Linzke N, Thuere C, Reichardt P, Tadokoro CE, Hämmerling GJ, Zenclussen AC. Control of uterine microenvironment by foxp3(+) cells facilitates embryo implantation. Front Immunol. 2013;4:158.
116. Tilburgs T, Roelen DL, van der Mast BJ, van Schip JJ, Kleijburg C, de Groot-Swings GM, Kanhai HH, Claas FH, Scherjon SA. Differential distribution of CD4(+)CD25(bright) and CD8(+)CD28(-) T-cells in decidua and maternal blood during human pregnancy. Placenta 2006;27 suppl A:S47–53.
117. Tilburgs T, Roelen DL, van der Mast BJ, de Groot-Swings GM, Kleijburg C, Scherjon SA, Claas FH. Evidence for a selective migration of fetus-specific CD4+CD25bright regulatory T cells from the peripheral blood to the decidua in human pregnancy. J Immunol. 2008;180:5737–5745.
118. Gomez-Lopez N, Olson DM, Robertson SA. Interleukin-6 controls uterine Th9 cells and CD8(+) T regulatory cells to accelerate parturition in mice. Immunol Cell Biol. 2016;94:79–89.
119. Furcron AE, Romero R, Mial TN, Balancio A, Panaitescu B, Hassan SS, Sahi A, Nord C, Gomez-Lopez N. Human chorionic gonadotropin has anti-inflammatory effects at the maternal–fetal interface and prevents Endotoxin-Induced preterm birth, but causes dystocia and fetal compromise in mice. Biol Reprod. 2016;94:136.
120. Shima T, Sasaki Y, Itoh M, Nakashima A, Ishii N, Sugamura K, Saito S. Regulatory T cells are necessary for implantation and maintenance of early pregnancy but not late pregnancy in allogeneic mice. J Reprod Immunol. 2010;85:121–9.
121. Fan MY, Low JS, Tanimine N, Finn KK, Priyadharshini B, Germana SK, Kaech SM, Turka LA. Differential roles of IL-2 signaling in developing versus mature Tregs. Cell Rep. 2018;25:1204–e12131204.
122. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol. 2015;15:486–99.
123. van der Zwan A, Bi K, Norwitz ER, Crespo C, Claas ÂFHJ, Strominger JL, Tilburgs T. Mixed signature of activation and dysfunction allows human decidual CD8(+) T cells to provide both tolerance and immunity. Proc Natl Acad Sci USA. 2018;115:385–90.
124. Wang SC, Li YH, Piao HL, Hong XW, Zhang D, Xu YY, Tao Y, Wang Y, Yuan MM, Li DJ, Du MR. PD-1 and Tim-3 pathways are associated with regulatory CD8+T-cell function in decidua and maintenance of normal pregnancy. Cell Death Dis 2015;6:e1738.
125. Slutsky R, Romero R, Xu Y, Galaz J, Miller D, Done B, Tarca AL, Gregor S, Hassan SS, Leng Y. N. Gomez-Lopez, Exhausted and senescent T cells at the maternal–fetal interface in preterm and term labor. J Immunol Res, 2019 (2019) 3128010.
126. Sultana Z, Maiti K, Dedman L, Smith R. Is there a role for placental senescence in the genesis of obstetric complications and fetal growth restriction? Am J Obstet Gynecol. 2018;218:S762–73.
127. Di Mitri D, Azevedo RI, Henson SM, Libri V, Riddell NE, Macaulay R, Kipling D, Soares MV, Battistini L, Akbar AN. Reversible senescence in human CD4+CD45RA+CD27- memory T cells. J Immunol 2011;187:2093–2100.
128. Lanna A, Henson SM, Escors D, Akbar AN. The kinase p38 activated by the metabolic regulator AMPK and scaffold table 1 drives the senescence of human T cells. Nat Immunol. 2014;15:965–72.
129. Montecino-Rodriguez E, Dorshkind K. B-1 B cell development in the fetus and adult. Immunity. 2012;36:13–21.
130. Fettke F, Schumacher A, Canellada A, Toledo N, Bekeredjian-Ding I, Bondt A, Wuhrer M, Costa SD, Zenclussen AC. Maternal and fetal mechanisms of B cell regulation during pregnancy: human chorionic gonadotropin stimulates B cells to produce IL-10 while Alpha-Fetoprotein drives them into apoptosis. Front Immunol. 2016;7:495.
131. Schumacher A, Ehrentraut S, Scharm M, Wang H, Hartig R, Morse HC 3rd, Zenclussen AC. Plasma cell alloantigen 1 and IL-10 secretion define two distinct peritoneal B1a B cell subsets with opposite functions, PC1(high) cells being protective and PC1(low) cells harmful for the growing fetus. Front Immunol. 2018;9:1045.
132. Ziegler KB, Muzzio DO, Matzner F, Bommer I, Ventimiglia MS, Malinowsky K, Ehrhardt J, Zygmunt M, Jensen F. Human pregnancy is accompanied by modifications in B cell development and Immunoglobulin profile. J Reprod Immunol. 2018;129:40–7.
133. Bartmann C, Segerer SE, Rieger L, Kapp M, Sütterlin M, Kämmerer U. Quantification of the predominant immune cell populations in decidua throughout human pregnancy. Am J Reprod Immunol 2014;71:109–119.
134. Solders M, Gorchs L, Gidlöf S, Tiblad E, Lundell AC, Kaipe H. Maternal adaptive immune cells in decidua parietalis display a more activated and coinhibitory phenotype compared to decidua basalis. Stem Cells Int. 2017;2017:8010961.
135. Huang B, Faucette AN, Pawlitz MD, Pei B, Goyert JW, Zhou JZ, El-Hage NG, Deng J, Lin J, Yao F, Dewar RS 3rd, Jassal JS, Sandberg ML, Dai J, Cols M, Shen C, Polin LA, Nichols RA, Jones TB, Bluth MH, Puder KS, Gonik B, Nayak NR, Puscheck E, Wei WZ, Cerutti A, Colonna M, Chen K. Interleukin-33-induced expression of PIBF1 by decidual B cells protects against preterm labor. Nat Med. 2017;23:128–35.
136. Bonney EA. Alternative theories: pregnancy and immune tolerance. J Reprod Immunol. 2017;123:65–71.

137. Spits H, Artis D, Colonna M, Diefenbach A, Di Santo JP, Eberl G, Koyasu S, Locksley RM, McKenzie AN, Mebius RE, Powrie F, Vivier E. Innate lymphoid cells–a proposal for uniform nomenclature. Nat Rev Immunol. 2013;13:145–9.
138. Bernink JH, Peters CP, Munneke M, te Velde AA, Meijer SL, Weijer K, Hreggvidsdottir HS, Heinsbroek SE, Legrand N, Buskens CJ, Bemelman WA, Mjösberg JM, Spits H. Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. Nat Immunol. 2013;14:221–9.
139. Price AE, Liang HE, Sullivan BM, Reinhardt RL, Eisley CJ, Erle DJ, Locksley RM. Systemically dispersed innate IL-13-expressing cells in type 2 immunity. Proc Natl Acad Sci USA. 2010;107:11489–94.
140. Wong SH, Walker JA, Jolin HE, Drynan LF, Hams E, Camelo A, Barlow JL, Neill DR, Panova V, Koch U, Radtke F, Hardman CS, Hwang YY, Fallon PG, McKenzie AN. Transcription factor RORα is critical for nuocyte development. Nat Immunol. 2012;13:229–36.
141. Eberl G, Marmon S, Sunshine MJ, Rennert PD, Choi Y, Littman DR. An essential function for the nuclear receptor RORgamma(t) in the generation of fetal lymphoid tissue inducer cells. Nat Immunol. 2004;5:64–73.
142. Zhong C, Zheng M, Zhu J. Lymphoid tissue inducer-A divergent member of the ILC family. Cytokine Growth Factor Rev. 2018;42:5–12.
143. Xu Y, Romero R, Miller D, Silva P, Panaitescu B, Theis KR, Arif A, Hassan SS, Gomez-Lopez N. Innate lymphoid cells at the human maternal–fetal interface in spontaneous preterm labor. Am J Reprod Immunol 2018;79:e12820.
144. Molofsky AB, Nussbaum JC, Liang HE, Van Dyken SJ, Cheng LE, Mohapatra A, Chawla A, Locksley RM. Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. J Exp Med. 2013;210:535–49.
145. Croxatto D, Micheletti A, Montaldo E, Orecchia P, Loiacono F, Canegallo F, Calzetti F, Fulcheri E, Munari E, Zamò A, Venturini PL, Moretta L, Cassatella MA, Mingari MC, Vacca P. Group 3 innate lymphoid cells regulate neutrophil migration and function in human decidua. Mucosal Immunol. 2016;9:1372–83.
146. Jenkinson HJ, Wainwright SD, Simpson KL, Perry AC, Fotiadou P, Holmes CH. Expression of CD1D mRNA transcripts in human choriocarcinoma cell lines and placentally derived trophoblast cells. Immunology. 1999;96:649–55.
147. Kumar V, Delovitch TL. Different subsets of natural killer T cells May vary in their roles in health and disease. Immunology. 2014;142:321–36.
148. Wang S, Li C, Kawamura H, Watanabe H, Abo T. Unique sensitivity to alpha-galactosylceramide of NKT cells in the uterus. Cell Immunol. 2002;215:98–105.
149. Boyson JE, Rybalov B, Koopman LA, Exley M, Balk SP, Racke FK, Schatz F, Masch R, Wilson SB, Strominger JL. CD1d and invariant NKT cells at the human maternal–fetal interface. Proc Natl Acad Sci USA. 2002;99:13741–6.
150. St Louis D, Romero R, Plazyo O, Arenas-Hernandez M, Panaitescu B, Xu Y, Milovic T, Xu Z, Bhatti G, Mi QS, Drewlo S, Tarca AL, Hassan SS. N. Gomez-Lopez, Invariant NKT cell activation induces late preterm birth that is attenuated by rosiglitazone. J Immunol. 2016;196:1044–1059.
151. Li L, Shi L, Yang X, Ren L, Yang J, Lin Y. Role of invariant natural killer T cells in lipopolysaccharide-induced pregnancy loss. Cell Immunol. 2013;286:1–10.
152. Li L, Yang J, Jiang Y, Tu J, Schust DJ. Activation of decidual invariant natural killer T cells promotes lipopolysaccharide-induced preterm birth. Mol Hum Reprod. 2015;21:369–81.
153. Li LP, Fang YC, Dong GF, Lin Y, Saito S. Depletion of invariant NKT cells reduces inflammation-induced preterm delivery in mice. J Immunol. 2012;188:4681–4689.
154. Gomez-Lopez N, Romero R, Arenas-Hernandez M, Schwenkel G, St Louis D, Hassan SS, Mial TN. In vivo activation of invariant natural killer T cells induces systemic and local alterations in T-cell subsets prior to preterm birth. Clin Exp Immunol. 2017;189:211–25.
155. Hegde PS, White IR, Debouck C. Interplay of transcriptomics and proteomics. Curr Opin Biotechnol. 2003;14:647–51.
156. Bukowski R, Sadovsky Y, Goodarzi H, Zhang H, Biggio JR, Varner M, Parry S, Xiao F, Esplin SM, Andrews W, Saade GR, Ilekis JV, Reddy UM, Baldwin DA. Onset of human preterm and term birth is related to unique inflammatory transcriptome profiles at the maternal fetal interface. PeerJ. 2017;5:e3685..
157. Suryawanshi H, Max K, Bogardus KA, Sopeyin A, Chang MS, Morozov P, Castano PM, Tuschl T, Williams Z. Dynamic genome-wide gene expression and immune cell composition in the developing human placenta. J Reprod Immunol. 2022;151:103624.
158. Pavličev M, Wagner GP, Chavan AR, Owens K, Maziarz J, Dunn-Fletcher C, Kallapur SG, Muglia L, Jones H. Single-cell transcriptomics of the human placenta: inferring the cell communication network of the maternal–fetal interface. Genome Res. 2017;27:349–61.
159. Tsang JCH, Vong JSL, Ji L, Poon LCY, Jiang P, Lui KO, Ni YB, To KF, Cheng YKY, Chiu RWK, Lo YMD. Integrative single-cell and cell-free plasma RNA transcriptomics elucidates placental cellular dynamics. Proc Natl Acad Sci USA. 2017;114:E7786–95.
160. Garcia-Flores V, Romero R, Tarca AL, Peyvandipour A, Xu Y, Galaz J, Miller D, Chaiworapongsa T, Chaemsaithong P, Berry SM, Awonuga AO, Bryant DR, Pique-Regi R. Gomez-Lopez, Deciphering maternal–fetal cross-talk in the human placenta during parturition using single-cell RNA sequencing. Sci Transl Med. 2024;16:eadh8335.
161. Sureshchandra S, Doratt BM, True H, Mendoza N, Rincon M, Marshall NE, Messaoudi I. Multimodal profiling of term human decidua demonstrates immune adaptations with pregravid obesity. Cell Rep. 2023;42:112769.
162. Huang J, Li Q, Peng Q, Xie Y, Wang W, Pei C, Zhao Y, Liu R, Huang L, Li T, Xie L, Zhang J, Dai L, Chen J, Sun J, Zhang W. Single-cell RNA sequencing reveals heterogeneity and differential expression of decidual tissues during the peripartum period. Cell Prolif. 2021;54:e12967.
163. Huang J, Zhang W, Zhao Y, Li J, Xie M, Lu Y, Peng Q, Zhang J, Li P, Dai L. Deciphering the intercellular communication network of peripartum decidua that orchestrates delivery. Front Cell Dev Biol. 2021;9:770621.
164. Liu X, Aneas I, Sakabe N, Anderson RL, Billstrand C, Paz C, Kaur H, Furner B, Choi S, Prichina AY, Enninga EAL, Dong H, Murtha A, Crawford GE, Kessler JA, Grobman W, Nobrega MA, Rana S, Ober C. Single cell profiling at the maternal–fetal interface reveals a deficiency of PD-L1(+) non-immune cells in human spontaneous preterm labor. Sci Rep. 2023;13:7903.
165. Hemberger M, Hanna CW, Dean W. Mechanisms of early placental development in mouse and humans. Nat Rev Genet. 2020;21:27–43.
166. Moore AR, Vivanco Gonzalez N, Plummer KA, Mitchel OR, Kaur H, Rivera M, Collica B, Goldston M, Filiz F, Angelo M, Palmer TD, Bendall SC. Gestationally dependent immune organization at the maternal–fetal interface. Cell Rep. 2022;41:111651.
167. Scott RL, Vu HTH, Jain A, Iqbal K, Tuteja G, Soares MJ. Conservation at the uterine-placental interface. Proc Natl Acad Sci USA. 2022;119:e2210633119.
168. Maltepe E, Fisher SJ. Placenta: the forgotten organ. Annu Rev Cell Dev Biol. 2015;31:523–52.

169. Areia AL, Rodrigues P, Alarcão A, Ladeirinha A, Moura P, Carvalho L. Is preterm labor influenced by the Maternal–Fetal interface??. Fetal Pediatric Patholo 2017;36:89–105.