Placenta 79 (2019) 53–61

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

The role of maternal T cell and macrophage activation in preterm birth: Cause or consequence?

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ARTICLE INFO

Keywords:
Macrophage
T lymphocyte
Maternal physiology
Parturition
Preterm birth

ABSTRACT

The role of the immune system in term (TL) and preterm labor (PTL) is unknown. Despite the fact that globally, PTL remains the most important cause of childhood mortality. Infection, typically of the fetal membranes, termed chorioamnionitis, is the best-understood driver of PTL, but the mechanisms underpinning other causes, including idiopathic and stretch-induced PTL, are unclear, but may well involve activation of the maternal immune system. The final common pathway of placental dysfunction, fetal membrane rupture, cervical dilation and uterine contractions are highly complex processes. At term, choriodecidual rather than myometrial inflammation is thought to drive the onset of labor and similar findings are present in different types of PTL including idiopathic PTL. Although accumulated data has confirmed an association between the immune response and preterm birth, there is yet a need to understand if this response is an initiator or a consequence of tissue-level dysregulation. This review focuses on the potential role of macrophages and T cells in innate and adaptive immunity relevant to preterm birth in humans and animal models.

1. Introduction

Preterm birth (PTB) stems from two distinct processes. One is placental dysfunction and medically indicated delivery, which includes the clinical conditions of preeclampsia and fetal growth restriction. The other preterm labor (PTL), which may be preceded by fetal membrane rupture, due to senescence, apoptosis, or necrosis [1,2], cervical dilatation, due to loss of cervical matrix organization; or the onset of myometrial contractions alone, which is due to myometrial dysregulation [3]. For decades, inflammation has been associated with these processes, prompting the commonly held view that a maternal anti-fetal immune response is a critical factor in many of these causes of PTB. The existence, in PTB, of histopathological lesions, including villitis of unknown etiology [4,5], chronic deciduitis [6] and chronic chorioamnionitis [7,8], with associated activated CD8 T cells [9] and macrophages [5,9,10] and occurring without infectious etiology [5], adds to the argument. However, conflicting data suggests that myometrial inflammation is a consequence, not an initiator, of labor at term [11]. Data suggesting increased inflammatory response in macaques after uterine over distention could be interpreted as supporting this assertion [12] Moreover, the theoretical construct of abnormal pregnancy as ensuing primarily from a failure of maternal tolerance has also been questioned [13]. We herein focus on the key cellular players in these lesions, macrophages and T cells, to reexamine the question of whether maternal immune system activation is initiator/cause versus responder/consequence in PTB.

2. Macrophages: between innate and adaptive immunity

Bone marrow monocytes enter the peripheral blood and circulate until, in response to chemotactic stimuli, they migrate into tissues. There, local environmental factors, including cytokines, growth factors and microbial products induce their differentiation into macrophages that are involved in host defense and angiogenesis. Macrophages also exist independently of monocytes as self-renewing residents in tissues, and are involved in tissue remodeling and phagocytosis of dead cells and foreign antigens. Macrophages can both drive inflammation, causing tissue damage, and repress inflammation, promoting tissue repair. In current thinking, macrophages are “polarized” into pro-inflammatory M1 (classically activated by INFγ and TNFα) or anti-inflammatory, wound healing M2 (alternatively activated by IL-4, IL-10, IL-13 and TGFβ) subpopulations. However, macrophage polarization is likely more complex than the simplistic M1/M2 categorization, with M2 particularly having multiple subtypes with subtle differences in the factors that induce their differentiation and the cytokines that they release. Macrophages exhibit functional plasticity, such that M1 or M2

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https://doi.org/10.1016/j.placenta.2019.03.003
Received 14 February 2019; Accepted 6 March 2019

macrophages will respond to M2 and M1 signals respectively to reprogram their function, and their predominant phenotype will determine the overall "macrophage" effect in a given situation. CCL2 importantly regulates monocyte migration and activation (see review [14]). In concert with other chemokines and adhesion molecules, CCL2 triggers monocyte margination, adhesion to the vascular endothelium and transmigration into target tissues. After phagocytosis, macrophages present foreign antigens to effector lymphocytes, providing the interface between the innate and acquired immune systems. Activated macrophages express high levels of co-stimulatory molecules, including CD40, 80 and 86. Activated M1 macrophages also produce pro-inflammatory cytokines, nitric oxide, and reactive oxygen species and promote Th1 and Th17 migration and differentiation, all working towards more effective pathogen killing. M2 macrophages demonstrate up-regulation of the mannose receptor (CD206) and arginase-1, and they release anti-inflammatory cytokines, promoting Th2 and regulatory T cell, migration and differentiation [15,16]. Arginase 1 also reduces the availability of arginine and represses T cell proliferation [17]. An integral part of macrophage function involves apoptosis; the subsequent uptake of apoptotic vesicles by other antigen-presenting cells completes another link between macrophages and adaptive immunity.

3. Macrophages in pregnancy, labor

Macrophages make up 20%–30% of decidual leukocytes [18], are usually, but not exclusively, M2 in nature and express an immunosuppressive phenotype [19–21], They are induced by local M-CSF and IL-10 [22] and produce IL-4, IL-10, and angiogenesis-related factors including VEGF and proteases (MMPs) [23]. They are likely to play a key role in vascular remodeling, acting with other cell types, including extravillous trophoblasts and uterine NK cells to facilitate the development of the utero-placental circulation. A $CD68^{+}$, $CD14^{-}$population of macrophages is present at the feto-maternal interface and based on studies in other tissue locations, these cells are not likely to express innate immune receptors or pro-inflammatory cytokines, while preserving phagocytic and bactericidal capacity [24]. They have been reported to be in close proximity to actively remodeling spiral arteries and shown to be MMP7 and 9 positive [25] others have shown that macrophages isolated from decidual space, break down extracellular matrix and engulf apoptotic smooth muscle cells, but have no impact on EVT invasion [23]. However, activated macrophages may actually inhibit extravillous trophoblast invasion [26], although this effect is reversed by IL-10 [27]. Overall, it seems likely that macrophages at least facilitate spiral artery modification, but in an inflammatory environment, they may actually inhibit the process of implantation [24].

An intense myometrial leukocyte infiltration predominantly made of neutrophils and macrophages and increased cytokine expression has been associated with human term labor. Histological studies as well as several myometrial gene-array studies of laboring myometrium confirm this association [11]. Collectively, these data placed myometrial inflammation in a central role in the onset of term labor. Further, inflammatory cells can enhance myometrial contractility though increased ROCK activity and prostaglandin synthesis [28,29] and repressed progesterone action [30–33]. However, an early description of myometrial inflammation showed that myometritis and chorioamnionitis was only present in 10% of asymptomatic intrapartum Caesarean sections [34]. Similarly, myometrial inflammation rarely occurred prior to the onset of labor in women undergoing caesarean section for a variety of indications [35]. Recently investigators in the Johnson laboratory have reexamined this issue using a combination of flow cytometry and immunohistochemistry and found no increase in myometrial inflammatory cell numbers, neutrophils or macrophages with the onset of term labor and that cytokine levels only increased in established labor and not before [11]. This suggested that there is no *myometrial* inflammatory signal for term labor.

Several studies have examined changes in the decidua [36] from women before the onset of labor at term, in early term labor, and after vaginal delivery, with variable results. A confounder of these findings is the study of women who had had a vaginal delivery where it is not possible to distinguish between choriodecidual changes which occur as part of the labor process itself, or had a role in the onset of labor is unclear. Johnson Laboratory examination of matched reproductive tissues, including myometrium, placenta, amnion and choriodecidua from women at term found that the choriodecidua exhibited an inflammatory signature in early labor (Singh et al., unpublished observation). This is consistent with other work from human pregnancy showing that the choriodecidua is inflamed as assessed by gene array [37] and rtPCR [38], increased cytokine and chemokine levels together with a relatively greater chemotactic activity [39,40]. The inflammatory changes seen in this tissue are still under assessment, as one source reported a 4-fold increase in macrophages, but no change in neutrophil, T-cell or NK cell numbers [41], while another reported increased memory-like T cells, but with a decline in granulocytes and no change in monocytes [40].

Although idiopathic PTL may be distinct from PTL in association with infection, or medical indication, some mechanisms, especially relating to tissue-level dysregulation, may be linked and therefore shared examination may be informative. Choridecidual inflammation precedes PTB in human and animal infection during pregnancy [42]. In studies of PTL associated with chorioamnionitis, decidual macrophages and neutrophil numbers were increased while in idiopathic PTL, T and NK cells were instead more abundant [41] Although there are observed changes in cell number, their functional impact were not directly examined. In these studies, cytokine mRNA levels were [43] increased, but the samples were obtained at varying stages of labour, leaving open the possibility that changes in abundance may be a consequence of the labour process rather than cause. Inappropriate differentiation into the M1 phenotype has been associated with hypertensive pregnancy [44,45]. However, a study of infectious and idiopathic causes of preterm labor, reported increased total macrophages and NK cells in idiopathic preterm labor, while only increased neutrophils in infective preterm labor [41]. Rather counter intuitively, studies report *reduced* M2 macrophage numbers in preterm pregnancies compared with term pregnancies irrespective of labor. However, in preterm labor, decidual macrophages express high levels of TNFα and IL-12 [46,47]. In addition, the macrophages in the decidua from women with recurrent miscarriages expressed higher levels of CD80 and CD86 and lower levels of IL-10 [44] and macrophages of the M1 phenotype damage the pregnancy via nitric oxide and TNF-α production [48]. Although these studies suggest an increase in decidual M1 macrophages in PTB, these studies are also limited by the inclusion of samples after a vaginal delivery, making it difficult to define whether the observed changes have any role in the onset of the preterm labor process or are merely a consequence of labor. To address this the Johnson laboratory has examined tissue from women having a preterm emergency caesarean section before active labor for a defined cause. The samples analyzed using rtPCR, multiplex and immunohistochemistry of myometrial samples (Singh et al., unpublished observation) showed that in chorioamnionitis, inflammation was present throughout all reproductive tissues and myometrial neutrophils and macrophages were increased. In idiopathic preterm labor, inflammatory changes were present only in the choriodecidua and not the myometrium.

Macrophages and rodent models of pregnancy: Macrophages are present in the placental bed of mice and rats, but do not appear to be related to spiral artery remodeling [49]. Towards the end of mouse pregnancy macrophages are the largest population of immune cells in the mesometrial triangle, the part of the uterus directly beneath the placenta [50]. At a similar stage in the rat limited numbers of M2 macrophages are present and overall numbers of macrophages increase prior to labor [41,51]. In the placenta and decidua of normal mouse pregnancy, the presence of macrophages does not change, while in the

myometrium, monocytes and macrophages peak on day 18, the day before the onset of parturition and declines with parturition. In these tissues, markers of macrophage activation (e.g., COX-2, CD86) do not increase over gestation, and cytokine products of activated macrophages only increase after the birth of the first pup [52]. Manipulation of the presence and action of progesterone with RU486 or exogenous administration of progesterone is associated with increased myometrial CCL2 expression and macrophage numbers or decreased CCL2 and macrophages, respectively [52]. Overall, these data suggest regulation of myometrium monocyte and macrophage numbers by progesterone, but suggest that inflammatory cells have a limited role in the onset of term parturition in the mouse. In terms of the intra-uterine LPS-model of preterm labor, the data show that LPS induces parturition through a direct effect on the myometrium and independent of myometrial inflammatory cell infiltration. Similarly, in terms of the fetal demise, this seemed to occur without evidence of fetal inflammation [53], implying that maternal inflammation affected placental perfusion. Indeed, repression of maternal inflammation with rosiglitazone delayed preterm labor and improved fetal outcomes in an LPS-induced PTB model in the mouse [47]. Overall, these data suggest that macrophages specifically and inflammatory cells in general have a limited role to play in rodent parturition, whether at term or preterm when induced with LPS or RU486.

4. Maternal T cells in theoretical context

Classical theory states that the fetus as “non-self” drives maternal T cells to respond and that successful pregnancy critically relies on mechanisms limiting responsiveness. These mechanisms act through limitation of fetal antigenicity [54], maternal-fetal cellular trafficking [55], and suppression or deviation. From this theoretical framework and in light of existing data it is possible to view early pregnancy loss, premature rupture of membranes, PTB, and other pregnancy complications, as manifestations of the breakdown of maternal immune tolerance [56,57]. This approach however, has not led to direct proof of the role of maternal T cells in PTB, nor has it yet led to viable diagnostic or therapeutic options for pregnancies at risk. Alternative theories of immunity do exist. An example is the ‘Danger’ model [58] that has provided a logical framework to understand normal [59] and abnormal pregnancies [13] and is influencing current thinking about spontaneous PTB [60]. In contrast to classical theory based on self-non-self-discrimination, this model focuses on the molecular generation and detection of damage, dysregulation, and dysfunction (for example, danger, associated molecular patterns, DAMPs [61,62]) as the driver of immune activation. Relevant molecules are upregulated or generated in the fetal-placental unit by oxidative or other metabolic stress [3] and directly drive preterm delivery in animal models [63]. These molecules moreover represent a larger family of endogenous signals that may share downstream pathways with signals generated by infection [64]. According to the model, danger signals and not fetal allo-genicity are the primary activators of maternal T cell activation and expansion. Further, the fetal-placental unit regulates the class of the immune response once activation occurs, and may sustain or limit the immune response given the level of dysregulation or damage that is occurring in the uterus. In the context of abnormal pregnancy, although classical theory and alternatives share experimental elements, the resulting data is interpreted differently, depending on theoretical context. For example, lack of fetal antigenicity and maternal-fetal cellular trafficking can be a structural or functional rule of the fetal-placental unit that breaks by fetal cell damage or dis-regulation. For another, regulation of class of the immune response or the persistence or limitation of the immune response based on the level of DAMP generation is, effectively, suppression. What then, is the sequence of events: T cell recognition of the fetus as non-self, followed by breakdown of tolerance, followed by immune activation, followed by damage to the fetal-placental unit or: damage and dis-regulation in the fetal-placental unit, followed by immune activation and T cell recognition of the fetus? The true answer may be a matter of quantum, probability, strength of signal, and antigen specificity. Although other immune-hormonal mechanisms may more efficiently [65] lead to membrane rupture, contractions, and fetal expulsion, it is useful to consider specifically how T cells may be involved.

The immune-anatomy of Maternal T cells pregnancy and labor: Before pregnancy begins, paternal cells and parts of cells are in contact with maternal vaginal epithelium, uterus, and peritoneum [66] and this exposure may determine pregnancy outcome [67]. Further, the maternal-fetal interface comprises several levels of potential contact between maternal and fetal cells. Multiple examinations have shown the existence of fetal cells [68–70], cell-free fetal genetic material [71,72] and macrovesicles that are likely of fetal origin [73] in maternal blood and tissues. As pregnancy progresses, so does direct contact between maternal and fetal tissues Fetal extravillous trophoblast contacts maternal decidua basalis and supersedes the endothelium of maternal vessels spilling blood into the intervillous space. In this space, fetal trophoblast interacts directly with maternal peripheral blood cells. In addition, fetal chorion interacts directly with maternal decidua “parietals”. In addition, maternal cells are present in fetal blood [74] and other tissues [75].

There is productive contact between maternal T cells and fetal antigens during pregnancy [69,76] or the post-partum period. Evidence in animals suggests [54,77] that this likely occurs via presentation of processed fetal antigens by maternal dendritic cells, as direct presentation of fetal antigens by fetal dendritic cells is limited. Moreover, under normal circumstances, processing and presenting of fetal antigens by dendritic cells of the uterus is also limited [78]. It is not clear if this changes with the inflammatory signals generated by fetal stress [1,2,79,80]. The wide phenotypic variability of dendritic cells in the uterus, draining nodes and spleen [81,82] suggest a flexibility in function that could contribute to a local immune activation, if needed. Evidence in animals also suggests that trafficking of maternal T cells to the decidua is regulated [55,83,84] via expression of chemokines important in T cell trafficking [55] and other related molecules. For example, T cells that traffic to the placenta may die due Fas/Fas-ligand interactions [85]. However, trafficking to the decidua can be upregulated by viral infection [86], moreover other studies in animals have documented the isolation of maternal T cells in decidual tissues [for example [87]). Evidence in humans suggests that maternal T cells may traffic to/in the decidua [88] and may ‘see’ fetal antigen in the context of HLA-C [89]. Human trophoblast expresses a mixture of maternal and paternal HLA-C, with varying degrees of immunogenicity. Women with recurrent miscarriage develop more antibodies to HLA-C, suggesting a potential role for productive interaction between maternal T cells, and this molecule in the context of abnormal pregnancy [90]. There exists evidence in humans that the process of labor itself may not lead to increased decidual trafficking of T cells, as Rinaldi et al. found that T cells, NK cells, B cells and invariant natural killer (iNKT) cell numbers were not changed by labor [43]. However, in idiopathic PTL, T and NK cells were increased [41]. This is consistent with the idea that tissue abnormality leads to increased T cell trafficking.

Naïve T cells that “see” antigen without the appropriate costimulatory signals die or become unresponsive [91]. Thus, expression of trophoblast major histocompatibility molecules is likely to lead to this altered state depending on local expression of co-stimulatory molecules [92,93]. Likewise, over expression of co-inhibitory molecules might limit activation of naïve T cells that traffic to the decidua or placenta [94].

Another mechanism that may regulate the function of maternal T cells in the decidua is that of exhaustion, resulting from fetal antigen-driven proliferation. In normal human pregnancy, early-decidual CD8 T cells have a unique phenotype. This suggests both activation and dysfunction, with expression of markers such as CD69 and HLA-DR (e.g. activation), co-inhibition (e.g. CTLA-4) and exhaustion (e.g. PD1, IL-7R,

FASL) as well as differentiation and effector function (e.g. CD 103, CD27, γ-interferon [95,96]) as well as enhanced expression of granzyme, but not perforin. This is consistent with a phenotype of enhanced proliferation in response to antigen [97,98]. Over time, at term, the cells express increased expression of metallothioneins indicating possible further dysfunction driven by altered metabolism. That this process is likely antigen load-dependent allows for decreased responsiveness to fetal antigens with retained functional capacity against viral and bacterial infection [96]. Evidence for this process supports a quantitative model of maternal tolerance [59]. The process can be broken with strong activation in vitro, raising the hypothesis that this may occur with tissue dysregulation in vivo. CD8 T cells, which make up a large proportion of decidual lymphocytes, predominate in villitis of unknown etiology. While it is likely that these cells represent cytotoxic T cells with a distinct molecular signature [99], studies to date have not completely elucidated their exact functional repertoire, including, production of cytokines, granzyme, or perforin [99,100]. In mouse models, the increased presence of maternal T cells that are PD1 [101] high, and have upregulated the IL7R and Fas ligand [102], and in the decidua, express high levels of granzyme [86] also suggests that this process may be active during mouse pregnancy [97].

Systemic activation may enhance molecules important for T cell trafficking to the uterus [103]. Appropriate interaction between CD4 T cells and antigen may lead to collaboration with other cells in the spleen, uterine draining lymph nodes, or in the decidua, fetal membranes, or placenta. Such collaboration could lead to systemic (e.g. in the blood) or local (e.g., decidua, membranes) secretion of harmful cytokines (e.g. TNF), or CD8 T cells that express cell-killing molecules such as perforin, or B cells that produce cytotoxic antibody. Such responses could stop at damage to the placenta or cross into the amniotic fluid (e.g. cytokines) or the fetus to cause damage to internal organs, including the brain [104,105] possibly leading to the processes that force medically indicated PTB or increasing morbidity in prematurely born infants. This later issue and the fetal defense against this is beyond the scope of this review and an extensive literature is elsewhere (e.g. Refs. [74,106]). Animal models have shown that injection of cytokines and other molecules can lead to expulsion of the feto-placental unit [107], thus activation of maternal T cells by fetal antigen could cause tissue disruption, even if this occurs at sites distant from the decidua or placenta. Direct intrauterine interaction between maternal effector T cells and fetal tissues may not be critical to T cell-mediated PTB.

"Innate" T cells and PTB: Maternal immune cells comprise not only members of the adaptive immune response, but also those T lineage populations that bridge innate and adaptive immunity. Activation of these cells is relatively rapid, and associated with high levels of cytokine expression.

One example are the invariant NKT-cells. These cells express the T cell alpha chain encoded by Vα14/Jα18 in mice and Va24/Ja18 in humans. On activation, they quickly secrete cytokines such as IL-4 [108,109] and γIFN [110]. These cells respond to molecules such as alpha galactosyl ceramide, a-Gal-Cer and related molecules [111] presented by CD1 [112]. At least two pathways of activation of these cells might mediate pregnancy loss or PTL, at least in animal models. Direct activation by a-Gal-Cer in early gestation mice may lead to expression of perforin in these cells and to increased resorption of the fetal-placental unit [113]. Later in gestation, activation of these cells with a-Gal-Cer leads to systemic increase in TNF and γIFN and subsequently to expulsion of the fetus [113]. Recently, studies using LPS in vivo in animals revealed a link between toll-like receptor signaling, iNKT function and PTB. These experiments suggest a model whereby activation of dendritic cells, and possibly activated macrophages [114] leads to an increase in the expression of CD1-glycolipid complexes that then can activate iNKT cells via their T cell receptor. This leads to elaboration of TNF, γIFN, and IL-4 and other signals causing activation of Th17 cells. Together cytokine signals from these cell types then participate in the cascade leading to PTL [115–118]. In humans, increased expression of CD1 in the decidua of pregnancies leading to PTL is among the developing evidence that activation of iNKT cells may promote PTB [43].

Another set of T-lineage cells [119] includes those whose receptor is composed of a gamma and a delta chain, as opposed to an alpha and a beta chain. These cells appear earlier in ontogeny than αβ T cells, as they are present as early as the first trimester in humans [120] and on or about embryonic day 15 in mice [121]. These cells have a restricted usage of T cell receptor genes, and it appears that waves of cells with one or the other of two TCR types migrate to different anatomical sites. For example, the Vδ2Vγ type comprises the majority of cells in the peripheral blood of humans. Within the uterus, the cells are predominantly vδ1vγ. There is also a potential functional bimodality, as cells generated in the thymus tend to become producers of γIFN or IL-17, depending on local signals, transcription factor expression, responses to antigen-presenting cell or macrophage cytokines (e.g. IL12 versus IL-23) and ability to respond to the growth promoting cytokines IL-7 or IL-15. As γIFN is important in vascular remodeling in the decidua [122], it is enticing to place γδcells into a supportive or antagonistic role with regard to pregnancy. However, the majority of uterine γδcells are IL-17 producers [123] and increased proportions of such cells is not in and of itself associated with spontaneous abortion [124]. The ligand for γδcells is far from clear. Activation of γδcells can occur via a mechanism involving CD1 molecules and endogenous lipids [125]. Another potential source of ligands may be the CD277 family of molecules. Activation of γδ cells also occurs in the context of the expression of phosphorylated molecules, such as isopentyl pyrophosphate and dimethylallyl diphosphate that are expressed by microorganisms or by dysregulation of certain metabolic pathways [119].

5. Fetal antigen specificity

To understand the role of adaptive immunity in PTB requires consideration of antigen specificity. At least in some animal models, polyclonal T cell activation, like activation of innate-like T cells, causes PTB (for example [126]). This suggests that activation of T cells specific for fetal antigen may not be necessary to produce fetal loss. In addition, "super" activation of fetal antigen-specific T cells in vitro with interleukin-2 and injection into pregnant mice leads to loss of both specific antigen expressing and non-expressing fetuses [127]. Such polyclonal activation could cause a systemic explosion of harmful cytokines, leading to loss of fetal-placenta tissues. Moreover, such a cytokine explosion could be associated with maternal to placental T cell trafficking [128]. Placental pathology occurs more frequently in the context of maternal autoimmune disease [129], suggesting shared maternal-fetal antigen target(s). The nature of these is still under investigation. However, polyclonal activation could also explain autoimmune disease related pathology. Moreover, antigens common to trophoblast and leucocytes may drive autoimmunity [130].

The male antigen, H−Y. Maternal T cells respond to paternal or fetal antigens during normal pregnancy. One example is the male antigen H−Y [131]. This antigen comprises a family of epitopes generated by proteins expressed in male cells [132]. H−Y drives transplant rejection, but also drives expansion of regulatory T cells after exposure to seminal fluid [67]. After the birth of one male infant, 32% of mothers have circulating HY-specific $CD8^+$ T cells, rising to 50% after two male pregnancies. These cells are also seen in the decidua where they may interact with trophoblast [95] In pregnancy, H−Y drives the expansion of CD8 T cells in both animals [69] and humans [133]. Despite this expansion, human pregnancy is associated with the prolonged presence of male cells [68]. Enhancing the population of male-specific CD8 T cells during pregnancy alone however, does not lead to loss of male pups in mice e.g. Refs. [134,135]. However, manipulation to decrease regulatory T cells is associated with a lower proportion of male pups [136]. Indeed, H−Y responses require CD4 T cell help [137], and so lack of help, either due to lack of CD4 T cell presence or functional

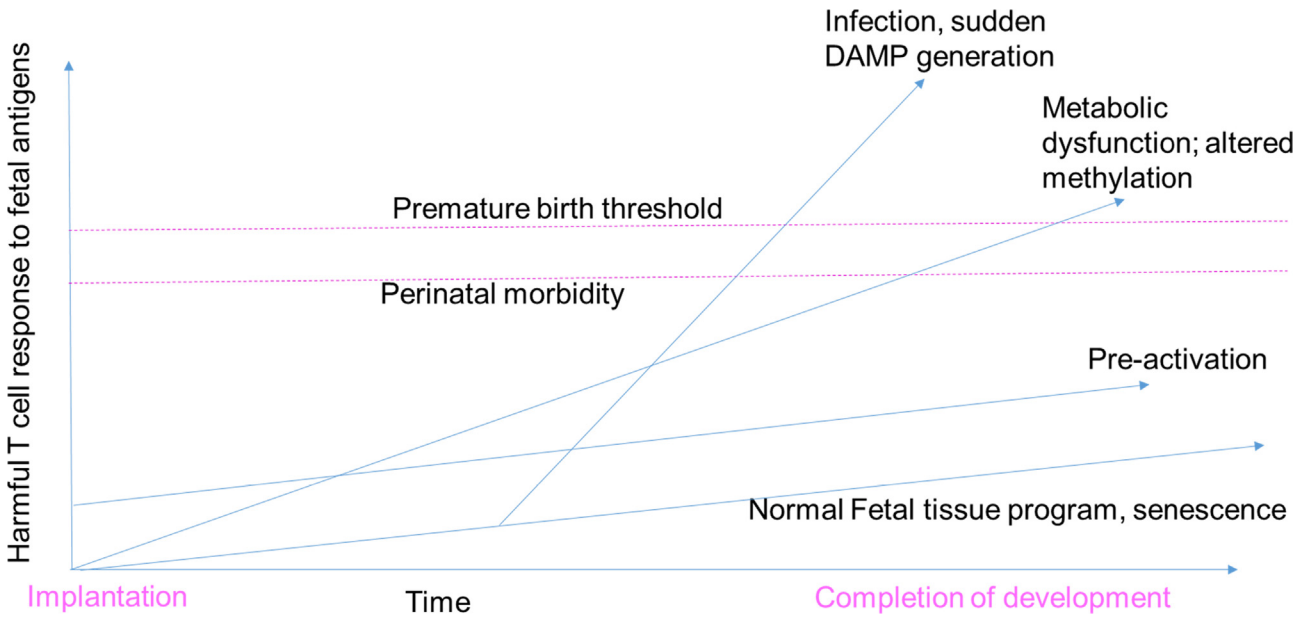

Fig. 1. A model for role of anti fetal T cells in PTB.Y axis, harmful anti fetal T-cell responces; X axis, time during pregnancy.

inhibition by regulatory T cells may explain why H−Y specific T cells, potentially in close proximity to this fetal antigen, do not normally cause loss of male infants. As for abnormal conditions in humans, groups have observed an association between PTB and a male infant [138] while the role of previous pregnancies with male infants in subsequent pregnancy outcome continues to be under investigation [139]. However, other pregnancy abnormalities may be associated with a female infant. The expression of other minor antigens in trophoblast raise the possibility of generation of other anti-fetal responses that might play a role in abnormal pregnancy [140]. In humans, minor antigens related to abnormal pregnancy may be presented in the context of HLA-C [90].

6. The growing family of regulatory maternal immune cells

Interest in cells with a suppressor phenotype has been long lived [141]. Many cell types, including macrophages, dendritic cells, NKT cells, γδcells, and B cells possess subsets with regulatory activity. While M2 macrophages support immune suppression or tolerance [142,143] and are increased in normal [144] but not abnormal pregnancy [145] and M1 type macrophages support immune activation [146] or autoimmunity [147] and are associated with abnormal pregnancy [148], the M1/M2 paradigm is under revision. Examination of the phenotype of macrophages in pathologic lesions is incomplete [149].

The nomenclature of regulatory T cells divided them into naturally occurring, thymus-derived cells and adaptive or “inducible Tregs” that occur out in the periphery [150]. Exposure to retinoic acid supports the generation of inducible Tregs [151]. However, agents such as Vitamin D3 and/or dexamethasone encourage the generation of a phenotypically different set of inducible Treg [152]. Subsets of the inducible Treg population can also convert, based on local tissue signals into cells that express IL-17 [153]. In addition to elaboration of cytokines, these subsets can differ from one another by expression of transcription factors, receptors for growth factors, or chemokines that regulate their presence in uterine tissues [103]. These cells may have a tissue-specific signature [154], raising the possibility of much more diversity than expected by current paradigm. With regard to pregnancy, a subset of regulatory T cells expand in syngeneic as well as allogeneic pregnancies [155,156]. Another subset is likely male antigen specific [136], while others are related to HLA-C expression [89]. However, H−Y− specific regulatory T cells may be more common in some groups of nulliparous women and women with female offspring, suggesting in utero exposure to male cells [157]. Relatively lower levels of CD4 T cells with the commonly held definition of regulatory CD4 T cells in association with a short cervix has been associated with PTL [158]. However, increased presence of regulatory T cells, defined with increased expression of either CD25 or FoxP3 in areas of CD4 and CD3 positive cells can occur in PTB-related villitis [159]. Classic theory suggests that these cells must be functionally defective in order to explain their increased presence in placenta of a compromised pregnancy. Testing of this hypothesis is ongoing [160]. Moreover, the role of other regulatory T cell subsets that may modify PTB in response to inflammatory stimuli [64] needs further investigation. The heterogeneity with regard to phenotype [161] and antigen specificity raises multiple possibilities for T cells with regulatory function including suppression of fetal-specific T cells; bystanders to immune responses against fetal and other antigens; and tissue-specific programmers controlling the class of immune response.

7. A model for the role of the maternal immune system in PTB

How does one incorporate T cell biology and theories of maternal tolerance [59] to explain the association between PTB and increased macrophages and CD8 T cells comprising pathological entities chronic villitis? Chronic villitis has been implicated in both fetal growth restriction and PTD and may represent a maternal “immune” recognition of fetal tissue, but since it can be seen in pregnancies with a normal outcome, caution has to be exercised in its interpretation [5]. Biological complexity argues against an all or nothing model, but one of interacting quanta of signals. Such a model does not start from assuming that allo-recognition of the fetus requires immune suppression for successful pregnancy, nor does it presume that dysregulation of fetal growth and metabolism is enough to generate the immune response required to expel the fetus [Fig. 1]. This model also does not necessarily require direct interaction between fetal and maternal cells, as fetal antigen can be processed away from the fetal-placental unit, and systemic presence of substances toxic to the fetus (e.g. cytokines) are associated with fetal-placental loss. The model assumes that both time and quantitative responsiveness to fetal antigens interact to produce an effect that may reach thresholds of either perinatal morbidity or prematurity. Between implantation and the fetus' completion of its developmental program, normal fetal growth and development might generate low frequencies of anti-fetal T cells. However, the overall response is below threshold

for pathology. In contrast, infection, Danger Associated Molecular Pattern (DAMP) generation, altered metabolism [162], depending on the strength of the sum of signals generated, may over short or longer time frames generate more or less responsiveness in maternal-anti fetal responsiveness that prematurely reaches threshold. In other words, 'Danger' related to tissue dysregulation, damage, and dysfunction could later antigen presentation and T cell activation [13,59]. A previous abnormal pregnancy may result in an altered set point of potential T cell responsiveness (e.g. memory T cells) but if the fetus in the index pregnancy does not undergo metabolic derangement, responsiveness does not go above threshold. Thus, the metabolic and developmental status of the fetus drives the presence of anti-fetal responsiveness, which over time accumulates and participates but may not be a critical driver in the outcome.

8. Future directions and animal models

In humans, choriodecidual macrophages likely occupy an important role in both promoting feto-placental tolerance *and in responding* to the signals associated with the onset of term labor. Although they are predominantly in an M2 polarity during pregnancy, the functional status of the increased number of cells seen after the onset of labor could shift, as spontaneous PTL is associated with increased choriodecidual inflammation and increased M1 macrophages and NK cells. The role of choriodecidual macrophages and other innate immune cells both in normal and complicated pregnancy needs further clarification. The role of macrophages in normal parturition in rodent models seems to be very different from the human and therefore these models may be of limited use in understanding normal human parturition. However, in pathological pregnancies, rodent models reproduce many of the innate immunological features seen in complicated human pregnancy and consequently, may prove to be useful.

Many opportunities exist to enhance our understanding of the role of T cells in PTB. Although we have an idea of the potential role of some fetal antigen specific T cells, careful delineation, monitoring and examination of epitope specific T cells in a clinical trial or research setting has not occurred. By design, many clinical trials have identified patients who were not responsive to intervention (e.g. progesterone), and a careful comparison of the T cell response in responders and non-responders would be informative. Finally, studies in animal models have generated data based on maternal T cell responses to several fetally expressed model antigens, and these could be utilized to test the potential mechanisms put for by clinical trials. Studies linking mechanisms of tissue of tissue dysregulation (e.g. senescence [1]) to T cell activation, expansion, and PTB could also be helpful. A careful examination of early pregnancy loss in humans [163] and animal models [2] in the context of quantum, probability, and strength of signal to T cells might also refine the model presented here.

9. Conclusions

The PTB syndrome includes placental dysfunction, premature uterine contractions, rupture of the fetal membranes and dilation of the cervix. Maternal macrophages and fetal-antigen-specific T cells may activate, expand and participate in the process locally or systemically. However, complexities of biology, theoretical context, and experimental data may challenge the idea that these cells are initiators or even primary drivers of this adverse outcome. Examination of their presence, phenotype and epitope specificity in diseased placentas may reveal novel PTB related developmental, nutritional, and metabolic disorders and the related underlying mechanisms.

Acknowledgements

The authors have been supported in part by the March of Dimes Prematurity Research Initiative Grant program (EB) and The Borne Charity(MJ) The authors would like to acknowledge colleagues whose work may not have been cited due to space considerations, and the help and support of our collaborators in the Preterm Birth International Collaborative.

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