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D. Lissauer, M.D. Kilby, P. Moss

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Maternal effector T cells within decidua: the adaptive immune response to pregnancy?

Lissauer D[1], Kilby, MD[1]. and Moss, P[2, 3]

[1] Centre for Women's and Newborn's Health and Centre of Endocrinology, Diabetes and Metabolism [CEDAM], College of Medical and Dental Sciences, University of Birmingham and Birmingham Health Partners, UK

[2] Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham and Birmingham Health Partners, UK

[3] Corresponding Author. p.moss@bham.ac.uk

Abstract

In human pregnancy the maternal immune system plays a critical role in the regulation of many aspects of human reproduction including implantation, placentation and defence against infection. Interest has been focussed on the role of uterine natural killer cells (uNK) in the maternal decidua whereas effector CD4+ and CD8+ T cells have received much less attention despite the observation that they represent a major proportion of decidual leucocytes in the latter phase of pregnancy. A range of recent studies have demonstrated that human decidual T cells are highly differentiated, express a range of cytokines and cytotoxic markers, and demonstrate a unique transcriptional profile characterised by high level expression of genes involved in interferon-signalling. Moreover, subpopulations of effector T cells demonstrate specificity for fetal tissue and are regulated through expression of inhibitory checkpoint proteins and T regulatory cells. Nevertheless, many questions remain to be answered, such as the potential role of maternal effector T cells in either supporting successful pregnancy or potentially clearing fetal cells that have entered the maternal circulation. In addition, there is an increasing interest in the role of maternal effector T cells in the pathogenesis of disorders such as chronic villitis miscarriage, stillbirth, fetal growth restriction and pre-eclampsia. Current debates in relation to these questions will be discussed within this review.

Maternal effector T cells comprise the major population of leucocytes within decidua by the end of pregnancy

The maintenance of a semi-allogeneic fetus within the mother represents a considerable challenge to the maternal immune system during pregnancy [1]. A wide range of mechanisms have been postulated as being important and have evolved in order to limit maternal immune recognition of fetal tissue. One of the most straightforward approaches might have been to exclude effector CD4+ and CD8+ T cells from the decidual bed. However, effector T cells represent around 60% of the T cell pool in the later stages of pregnancy [2] and whilst NK cells are relatively more numerous in the early stages of pregnancy their numbers remain stable whilst those of T cells show a gradual increase with advancing gestation [2,3]. As such this temporal replacement of NK cells by T cells mirrors the kinetics of a peripheral adaptive immune response and the uterine environment may perhaps be seen to recapitulate short term lymphocyte dynamics over a 9 month period [4]. CD45RO+ effector T cells comprise around 60% of the decidual T cell repertoire at term whilst representing only 30% of T cells within blood. This relative increase in 'antigen-experienced' T cells could potentially indicate evidence of local activation although it may also reflect selective recruitment of effector cells into decidual tissue. In this regard it is important to compare the phenotypic and functional features of T cells in the two compartments and this is shown in Table 1. This reveals a number of differences between effector cells in decidua and blood, including the observation that decidual effector cells are more highly differentiated than peripheral cells, with over 40% of such cells demonstrating a CD27-CD28- phenotype compared to less than 20% in blood [5].

This pattern of local activation of decidual T cells might be taken to represent recognition of fetal tissue. Fetal trophoblast cells downregulate the expression of HLA-A and HLA-B, and observation that mismatch of polymorphic HLA-C alleles between mother and fetus was associated with increased levels of T cell activation provided some of the first support for this hypothesis [6].

The CXCL10-CXCR3 axis is important in attracting effector T cells to decidual tissue

Chemokines are important regulators of leukocyte migration and are therefore likely to play a major role in reproductive biology. CXCR3 is a receptor for inflammatory chemokines and studies within pregnant mice have shown that it undergoes epigenetic silencing on T cells within decidua [7], although this may be overcome in the setting of local inflammation [8]. In contrast our findings reveal CXCR3 to be expressed on 17% of human decidual CD4+ T cells, one of many differences found between the immunological environment between mice and humans [5]. CXCL10, an important ligand for CXCR3, is strongly expressed and identifies the CXCL10-CXCR3 axis as an important mediator of effector cell migration into decidual tissue.

Maternal effector T cells within decidua can recognize fetal tissue

It is now clear that an adaptive immune response against fetal tissue develops in most, if not all, human pregnancies. This is indicated most clearly in the development of alloreactive HLA-specific antibodies and the development of sensitive assays has revealed that these are found in most mothers following a single pregnancy [9]. Moreover, the presence of IgG isotypes reveals that antigen-specific T cell 'help' has also been established. The potential importance of these antibodies in relation to fetal health is uncertain and such responses may simply reflect an epiphenomenon that is of no consequence to pregnancy outcome. However some studies do reveal a weak clinical association and HLA-C specific antibodies have been shown to be more common in women with recurrent fetal loss (miscarriage) [10].

Given this observation, it is perhaps not surprising that maternal cellular adaptive immune responses against fetal tissue are also generated during human pregnancy. Culture and expansion of maternal T cells *in vitro* first identified cells that were able to recognise paternal cells [11] and these observations have been substantiated by techniques that directly visualise T cells with alloreactive potential. Indeed our own work [12, 13], and that of others [14-16], has identified HY-specific CD8+ T cells in the maternal circulation following male pregnancies. These CD8 T cells are present for many years following pregnancy and can be reactivated *in vitro* to generate highly cytotoxic T cells that lyze male cells. HY-specific CD8+ cells were detectable in 32% of women following a single male pregnancy and this proportion rose to 50% of those with 2 or more male pregnancies, indicating that alloreactive cellular immunity is boosted by recurrent episodes of fetal microchimerism. Until recently, it has not been possible to directly identify T cells with fetal specificity within decidual tissue but

we have also utilized HLA-peptide multimer technology to identify HY-specific CD8 T cells in decidual tissue [5]. Indeed, the frequency of such cells is greatly increased compared to peripheral blood and indicates that cytotoxic cells with specificity for fetal tissue are localised in direct anatomical contact.

Effector T cells within decidua display a novel profile of functional activity

Tilbergs et al studied CD8+ effector T cells within decidual tissue and demonstrated a unique Th1 pattern of high level IFNγ expression together with low levels of perforin and granzyme [17]. Our own studies of decidual CD4 and CD8+ T cells confirmed IFNγ expression in many cells but also revealed expression of IL-4 in a minority population. In particular whilst IFNγ expression was observed in 60% of CD8+ T cells, 1.2% of cells also expressed IL-4, a value which, whilst relatively modest, was higher than expression within 0.7% of CD8+ cells within maternal peripheral blood. Comparable values for CD4+ T cells were 25% and 5% respectively and Il-4 expression was markedly higher than on maternal T cells from peripheral blood [5]. Interestingly, Il-4 expression can be induced from peripheral T cells following incubation with progesterone and this 'T_{prog}' phenotype may therefore partially reflect the effect of the local hormonal microenvironment [18, 19].

We recently completed a comparative transcriptional analysis of effector CD4 and CD8+ T cells from decidua and maternal peripheral blood. A wide range of genes were differentially expressed in decidual T cells with a striking upregulation of those which encode proteins involved in the signalling response to interferon [5]. This profile is highly unusual within effector T cells and suggests that decidual tissue is characterized by high levels of local interferon production. This subject has been relatively poorly studied although immunohistochemical expression of type 1 interferon has been observed within cells of the monocytic lineage [20,21]. It is interesting to speculate on what may drive interferon production but it is well established that endogenous retroviruses play an important role in the generation of syncytiotrophoblast [22-26]. Notably, the *Syncytin-1* protein encoded from the *env* gene of *ERVW-1* has an essential role in formation of the syncytiotrophoblast and is released into the periphery via placental microvesicles which are themselves able to illicit a T cell response [27].

Effector T cells within decidua demonstrate specificity for pathogens

Pregnancy is associated with altered regulation of immune responses that can potentially increase susceptibility to some infectious diseases. The increased mortality rate of pregnant women following avian influenza infection is one such example. As such, it is not surprising that T cells within decidual tissue exhibit specificity for local pathogens [28]. T cells with specificity for cytomegalovirus and Epstein-Barr virus are preferentially recruited into decidua and mediate pathogen surveillance of maternal cells [29]. Importantly, these populations recognise peptides restricted by HLA-A and HLA-B alleles which are themselves not presented on fetal trophoblast. Recent investigations have also shown that effector cells can recognise peptides restricted through HLA-C alleles, potentially indicating efficacy in control of infected fetal tissue [30].

The function of effector T cells is modulated through intrinsic and extrinsic regulation

The finding of large numbers of functional effector T cells within decidual tissue raises the question of how such cells are regulated in order to limit potential immunopathology or fetal damage. In this regard extrinsic regulation mediated through T regulatory cells and cell-intrinsic expression of inhibitory checkpoint proteins are both emerging as important control mechanisms.

T regulatory cells are increased within decidual tissue at term pregnancy and can comprise over 20% of all CD4+ T cells [31-33]. Indeed, murine experiments have shown that depletion of T regulatory cells can trigger fetal rejection [34] and it has been suggested that the evolution of the FoxP3+ T regulatory cell was a key event in the development of eutherian reproduction [35]. In line with previous reports [33], we also find that decidual T cells proliferate in response to cord blood lymphocytes and that this is increased following depletion of T regulatory cells [5]. These observations indicate that such decidual populations do have specificity for maternal antigens and that this is at least partly regulated through the action of autologous T regulatory populations.

Checkpoint proteins such as PD-1 and TIM-3 are now considered to be amongst the most important molecules within clinical medicine [36, 37]. This is due to the dramatic efficacy of antibody-mediated blockade of PD-1 function in the treatment of solid tumours [38]. PD-1 expression on T cells is often taken to represent an

'exhausted' state and is believed to reflect cells that have undergone repeated stimulation within antigen. However, despite the considerable success of checkpoint blockade in cancer therapy there is less understanding as to the physiological role of checkpoint proteins in human T cell physiology. Interestingly, a high level of checkpoint protein expression is observed on T cells within decidua [39]. Wang et al reported large populations of Tim-3+PD-1+ CD8+ T cells within decidua during early human pregnancy and showed that incubation of CD8 T cells with trophoblast led to further checkpoint upregulation [40,41]. Interestingly, PD-L1 is expressed on syncytiotrophoblast, as well as intermediate trophoblastic cells located in the chorion laeve and implantation site [42], and some studies have indicated that PD-1 blockade in pregnant mice may result in fetal loss [43]. Of note, these observations provide further evidence that the study of reproductive immunology will be of huge importance in understanding tumour immunology and lend support to the concept of cancer as a 'somatic pregnancy' [44].

Fetal-specific maternal T cells may play a role in limiting fetal microchimerism

It is now generally accepted that pregnancy leads to a state of microchimerism within the mother in which significant amounts of fetal tissue and cells are released into the maternal circulation [45]. Moreover, these fetal cells have been shown to survive for long periods within the mother and have even been implicated in a range of clinical disorders such as thyroiditis. Whilst such fetal cells may provide potential benefit to the mother, such as potentially supporting repair of maternal tissue, it would seem reasonable that such chimerism would need to be controlled by the maternal immune system. In this regard, the humoral and cellular maternal response against fetal tissue may have an important role in the suppression of fetal chimerism. Indeed, some support for this hypothesis comes from the observation that the degree of chimerism has been reported to fall with repeated pregnancies, whilst the magnitude of fetal-specific immunity appears to increase [46]. These observations could provide important insights into the regulation of chimerism in disorders such as transplantation.

Maternal T cell responses against fetal tissue may be associated with obstetric complications

The observation that maternal T cells demonstrate antigenic specificity for fetal tissue raises the obvious question as to whether these may be implicated in the pathogenesis of pregnancy complications. Relatively little evidence exists to implicate maternal T cell responses in the development of pre-eclampsia and this may reflect the fact that the cardinal feature of impaired trophoblast invasion of maternal spiral arteries is determined early within pregnancy and at a time when natural killer cells dominate the cellular infiltrate. More recently, Leavey et al have suggested that T cell mediated pathology may indeed be related to a subset of mothers with preeclampsia who demonstrate a form of disorder characterized by poor fetal outcome and growth restriction but relatively less impact on maternal health [47].

Despite this, fetal-specific immunity is strongly implicated in the development of chronic villitis ('villitis of uncertain/unknown aetiology'; VUE) which is a relatively common cause of fetal growth restriction and pre-term delivery [48-51]. VUE is characterized by an inflammatory cell infiltrate of placental macrophages and T cells within the villi which develops in the absence of infection. A specific feature is non-uniform involvement of villi and ultimately this can lead to "obliterative fetal vasculopathy". Interestingly, this maternal infiltrate typically shows a CD8:CD4 ratio around 3:1 and T cells comprise almost half of the cellular infiltrate. It has been suggested that such villitis may represent relatively uncontrolled maternal immune recognition of fetal tissue and this is supported by the finding that antibodies against fetal tissue are commonly observed in this disorder and associate with the deposition of C4 complement components. However caution is needed in this interpretation as some degree of VUE can been observed in around 10% of pregnancies and as such this process might even be regarded as a 'normal variant'.

Maternal effector T cells represent a fascinating topic for future investigation

Within a relatively short period of time conventional wisdom has moved from the belief that the placenta represents an effective barrier between the mother and fetus to an understanding that cells traffic between circulations and immune cells play an important role in supporting pregnancy. Decidual NK cells have been shown to possess a range of unique functional properties that represent novel immunotherapeutic opportunities [52] (Figure 1). Investigation into the physiological and potential immunopathological role of maternal alloreactive T cells has followed

more slowly. Despite this, it is now clear that maternal effector CD45RO+ T cells represent the majority of T cells within decidual tissue in the latter stages of pregnancy and display a range of novel properties. It remains possible that the primary role of these cells lies in the control of local infection with no major significance in relation to reproductive outcome. Nevertheless, further investigation into the specificity and unique properties of these remarkable cells may uncover novel insights into the physiology of human placentation, the pathogenesis of reproductive disorders and offer clues towards a range of additional disorders such as cancer and transplantation biology.

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Figure 1. Representation of maternal effector T cells within decidua and their potential functions. These are likely to include (1) recognition of fetal antigen *or* virally-infected EVT through peptides on HLA-C alleles, (2) potential access to maternal blood vessels to limit systemic fetal chimerism and (3) potential to breach syncytiotrophoblast and damage fetal blood vessels

	Effector T cells within decidua	**Effector T cells within maternal peripheral blood**
Percentage of total T cell repertoire	~60%	~30%
Degree of differentiation	**more** differentiated (~40% CD27-CD28-)	**less** differentiated (~20% CD27-CD28-)
Pattern of cytokine production following stimulation with PMA/Ionomycin mitogen	**CD4+**: IFNγ, 25%; Il-4, 5% **CD8+** IFNγ, 60%; Il-4, 1.2%	**CD4+**: IFNγ, 17% ; Il-4, 2% **CD8+** IFNγ, 41% ; Il-4, 0.7%
Expression of checkpoint proteins	**CD4+** 43% PD-1+ **CD8+** 68% PD-1+	**CD4+** 20% PD-1+ **CD8+** 25% PD-1+
Frequency of fetal-specific T cells	Use of HLA-peptide multimers reveals **increased** numbers compared to blood	Rare – but potential role in **controlling fetal chimerism**
Differentially expressed genes	Increase in genes which mediate **interferon signaling response**	

Table 1. Comparison of the features of CD45RO+ effector T cells within decidua and maternal peripheral blood at term. Data from Powell et al, (Submitted).

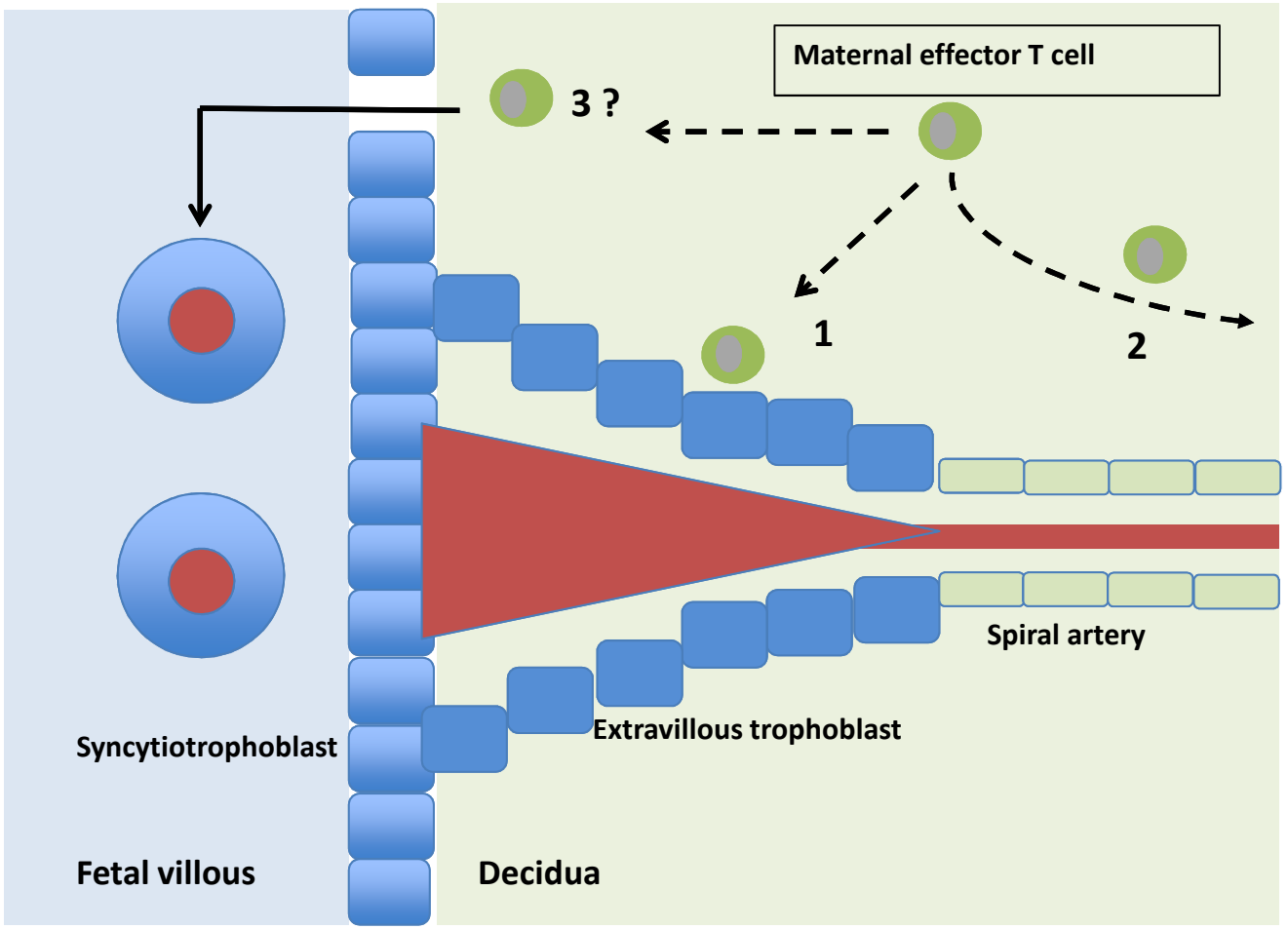

Figure 1. Representation of maternal effector T cells within decidua and their potential function. These are likely to include (1) recognition of fetal antigen *or* virally infected EVT through peptides on HLA-C alleles, (2) potential access to maternal blood vessels to limit systemic fetal chimerism and (3) potential to breach damaged syncytiotrophoblast and damage fetal blood vessels

Highlights

Maternal effector T cells within decidua: the adaptive immune response to pregnancy?

Lissauer D[1], Kilby, MD[1]. and Moss, P[2, 3]

Highlights

CD45RO+ effector T cells comprise the majority of CD4+ and CD8+ T cells in decidua and are more highly differentiated than T cells in blood

Human effector T cells express CXCR3 which may guide cells to decidua

These cells include populations that can produce IFNγ or Il-4

Microarray shows that decidual T cells demonstrate a transcriptional response to interferon signalling

T cells proliferate to cord blood indicating a response to fetal antigen and this is increased when T regulatory cells are removed.