

Immune cells at the maternal-fetal interphase: Role in implantation and establishment of tolerance

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ABSTRACT

Reproduction is essential to the survival of all species; hence, elaborate mechanisms ensure the persistence of pregnancy and the establishment of the fetus. For the establishment of fetus which is a semi allogeneic graft, immunological mechanisms which favor tolerance are preferred. A successful pregnancy is an outcome of interactions between the hormones produced by the placenta and the immune cells present in the decidua. The maternal-fetal interface (MFI) shows a predominance of cells involved in providing innate immunity, with uterine NK cells representing 70% of all immune cells. Human leucocyte antigen G (HLA-G), a non-classical major histocompatibility complex, is expressed by the trophoblast cells. The interaction between HLA-G present on the trophoblast and the receptors on NK cells is important for maintenance of immune tolerance. Macrophages, another important innate immune cells represent about 20%, while the adaptive T-cells account for <20% of all immune cells at the MFI. Different subpopulations of T-cells have also been identified at MFI. There is a growing evidence for the presence of unconventional $\gamma\delta$ T lymphocytes at the MFI. The T helper cells can be divided into Th1 and Th2. Macrophages can be grouped into subtypes M1 and M2. This subdivision is according to their activation status and the type of cytokines secreted by them. Th1 lymphocytes and M1 macrophages are pro-inflammatory while Th2 lymphocytes and M2 macrophages are anti-inflammatory. As fetus grows an equilibrium between pro- and anti-inflammatory immune mechanisms is maintained and that results in establishment of sustained pregnancy. Here, I have reviewed the characteristic features and the role of all these cells in implantation of the fetus and establishment of tolerance. Understanding the functions of immune cells and interactions among these cells can give a better insight of pregnancy-related complications.

1. INTRODUCTION

Humans and rodents show invasive and hemochorial type of implantation which is characterized by the presence of two surface of contact. First, a close contact is established between maternal immune cells at the decidua and the extravillous trophoblast (EVT), which allows the adherence of placenta to the uterus. EVT remodels spiral arteries in uterus and the invasive EVT activity decreases after first 3 months. Second is the contact established to connect the chorionic villi and maternal blood, whereby the circulatory immune cells of the mother come in close proximity with the syncytiotrophoblast (formed by fusion of cytotrophoblasts), which covers placental villi [1]. Remodeling of spiral arteries and invasion of the trophoblast is essential to implantation. In the first phase of spiral remodeling, there is formation of endothelial cell layer which is slowly replaced by the trophoblast cells during the next phase of spiral remodeling. During

pregnancy, degradation of trophoblast extracellular matrix (ECM) is required for the implantation of the fetus. Matrix metalloproteases (MMPs) are important proteases which function to degrade ECM during pregnancy, while tissue inhibitor of matrix metalloproteases (TIMP) is required to regulate this process. Cytokines, such as interleukin (IL)-1, IL-6, and IL-15, are seen to regulate the production of MMPs, while IL-11 secretion regulates the expression of TIMPs [2,3]. Implantation thus is dependent on a coordinated production of these molecules. Immune cells are responsible for the secretion of some of these mediators.

The decidua-associated lymphoid tissue (DALT) tries to provide an environment which allows for the tolerance of embryo. During the initial stage of pregnancy, more than 40% of the decidual cells are leukocytes. The migration of leukocytes to the endometrium is influenced by cytokines and chemokines, namely, CXCL-10, CXCL-16, IL-8, IL-15, and IL-6 [4,5]. The decidua is infiltrated with macrophages, uterine NK cells (uNK), dendritic cells (DCs), and various subsets of T cells. The uNK cells comprise about 70% of the total immune cells present and, hence, play a crucial role in establishment of pregnancy. The decidual macrophages represent 20%, and the various subsets of T-cells together account for about 20% of the total lymphocyte cell population present at MFI. About 2% of

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the cell population is represented by DCs, while B-cells are virtually undetectable [6].

The antigens present on the trophoblast induce an immune response; however, the response produced is a tolerogenic one. The establishment of tolerance is influenced by the mediators released by the immune cells (cytokines and chemokines) and the presence of non-classical major histocompatibility complex (MHC) on trophoblast. A fine balance in the number of M1/M2 cells, the Th1/Th2 and Treg/T17 cells, and the cytokines secreted by them is maintained throughout pregnancy [7]. Here, I would like to review the characteristic features, the mediators released and the function of the various immune cells in trophoblast invasion, spiral remodeling and establishment of tolerance at MFI.

2. IMMUNE CELLS AT MATERNAL FOETAL INTERFACE

2.1. Uterine Natural Killer Cells (uNK)

Natural Killer (NK) cells are large, granular lymphocytes, and exhibit non-specific cytotoxicity. NK cells are constitutively cytotoxic, do not exhibit MHC restriction, and have activation and inhibition receptors on their cell surface. NK cells perform their cytotoxic function through a fine tuning established between the signals produced and the mediators released by the engagement of these receptors. NK cells have killer immunoglobulin such as receptor (KIR) and immunoglobulin like inhibitory receptors (ILT) which can interact with classical and non-classical MHC. NK cells present at MFI are referred to as uNK and are different from the NK cells present in the periphery (pNK), both in phenotype characteristics and function. The uNK cells are CD56^{bright} 16^{dim} while peripheral NK (pNK) cells are CD56^{dim} 16^{bright} [8]. The cytotoxic potential of uNK cells is much less as compared to pNK cells despite the presence of more granules in these cells. This is primarily due to the interaction between the receptors present on uNK cells and non-classical HLA-G expressed by the EVT.

At the onset of menstrual cycle, the uNK cells are present in the uterus as tiny cells which lack the granules. As the cycle progresses, the uNK cells grow bigger and the granules containing various mediators increase in size; however, apoptosis of these cells starts 2 days before menstruation. The uNK cells comprise nearly 70% of the total lymphocytes present at the MFI. Before implantation, their concentration in the deciduas is only 25–40%. The cells increase in number as pregnancy proceeds with highest numbers being present at mid gestation and thereafter the numbers decline and are marked by complete absence at birth. To understand, the origin and presence of NK cells in the decidua a number of experiments have been done and conflicting results are observed. Research studies indicate that they could either mature from hematopoietic cells present in the decidua under the influence of stromal factors [9,10] or from the endometrial cells under the influence of IL-15 and progesterone [11]. Further, evidence also indicates that pNK cells could transform into uNK cells under the influence of chemoattractants, such as interferon γ -induced protein (IP-10) and monocyte chemoattractant protein-1, which are secreted by the trophoblast cells and the decidual cells [12,13].

The expression of CXCL10 and CXCL11 (inflammatory chemokines) by the decidual cells serve as chemo attractant for uNK cells, thereby influencing the recruitment of uNK cells in the immediate vicinity of the spiral arteries [4,5]. The receptors for CXCL10 and CXCL11 are upregulated on pNK and uNK cells during pregnancy. The expression of these chemokines can be influenced by progesterone and estrogen. uNK cells do not have receptors for progesterone; hence, progesterone shows an indirect effect on uNK cells by stimulating the secretion of

IL-15 by endometrial cells. IL-15 can promote differentiation and proliferation of uNK cells.

2.1.1. Subsets of NK cells

Three main subsets of NK cells, namely, NK1, NK2, and NK3 have been identified in humans and they all express CD49a marker. The expression of killer (KIR) genes, KIR2DS1, KIR2DS4, KIR2DL1, KIR2DL2, and KIR2DL3 which interact with HLA-G, is much higher on NK1 as compared to NK2 and NK3, while leukocyte immunoglobulin-like receptor B1 (ILT2) is exclusively present on dNK1-cell subset [14]. The X-C motif chemokine ligand (XCL1) is expressed at high levels on NK2 subtype and interacts with its receptor, XCR1 present on EVTs and DCs, thus helping in the recruitment of DCs and EVT at MFI [15]. dNK 3 subtype is present in very low amounts but play a role in EVT invasion which happens through the interaction of CCL5 and CCR1 present on EVT [16].

2.1.2. Role in trophoblast invasion

The expression of HLA-G, HLA E, and HLA-C on EVTs of fetal origin and their association with KIR on NK1 cells is important both for generation of tolerance at the MFI and vascular remodeling and trophoblast invasion [17,18]. The interaction of uNK cells with HLA C changes them into a senescent type which release pro-angiogenic and pro-inflammatory factors which are required for the invasion of trophoblast [19]. uNK cells secrete prokineticin 1, which further regulates the expression of leukemia inhibitory factor, IL-11 and prostaglandins, which assist in implantation. During the first half of pregnancy, the uNK cells produce significant amount of vascular endothelial growth factor (VEGF), placenta growth factor (PIGF), and angiopoietin 1 (ang 1) and angiopoietin 2 (ang 2), thereby promoting angiogenesis [20]. uNK cells can influence spiral remodeling by eliminating senescent decidual cells. uNK cells release MMP and various cytokines (IL8, IFN- γ IP-10) and growth factors (MCSF, GCSF) that stimulate EVT invasion [20]. The release of cytokines IFN- γ , TNF- α , and TGF- β by uNK cells helps to regulate excessive invasion of the trophoblast which can be detrimental to the fetus [21].

2.1.3. Cytotoxicity of NK cells

The cytotoxicity exhibited by uNK cells is much less in comparison to pNK cells, which is a consequence of interaction with non-classical MHC present on EVT. The non-classical HLA C and HLA E interact with KIR CD 94/NKG2A while HLA G interacts with KIR2DL1, KIR2DL2/L3 and ILT2 to weaken the killing potential of NK cells [22]. Indoleamine-2,3-Dioxygenase (IDO) is produced at MFI and it can down regulate the expression of NKp46 and NKG2D, thereby reducing the cytotoxicity of uNK cells. However, uNK cells can become active, start attacking the fetal tissue, and lead to abortion. uNK cells secrete IFN- γ which significantly lowers the Th17 cells (pro-inflammatory). IFN- γ production by NK cells can be inhibited by progesterone, thereby modulating the immune response toward tolerance. The inhibition of IFN- γ production by progesterone is mediated by the binding of this hormone on the nuclear glucocorticoid receptors (nGR) as uNK cells do not express receptors for progesterone. uNK cells have high number of cytotoxic granules as compared to pNK cells, which can be helpful in controlling infections in a pregnant female [23,24]. IFN- γ activates differentiation of Th1 cells which are crucial in providing immunity against microbes in pregnant females. Further studies are required to understand the process associated with the variability in function of NK cells from promoting tolerance in the mother at one hand to fighting infections at the other end of the spectrum.

2.2. Macrophages

Macrophages are mononuclear phagocytic cells that are dispersed throughout the body. They can be found circulating in the blood and lymph or become fixed in different tissues. Macrophages are present in the endometrium lining in non-pregnant women and in the decidua in pregnant females. In each menstrual cycle, macrophages help in the repair and regeneration of the endometrium lining. The macrophages present in the decidua represent 20% of the total immune cells present at the MFI and are present throughout the gestation period of 9 months. The endometrial macrophages can either differentiate from the hematopoietic precursors which are recruited to the endometrium or from the macrophages that have extravasated from the blood vessels by binding to the receptors present on the endothelial lining [25,26]. Chemokines and cytokines help in recruitment of macrophages at MFI [27].

2.2.1. Classification of Macrophages

Macrophages can be classified into two types M1 and M2, depending on their cytokine release pattern. M1 macrophages secrete cytokines which are antimicrobial and inflammatory in nature, while M2 macrophages secrete cytokines which control inflammation [28]. Cytokines IFN- γ and TNF- α have been seen to induce a shift to M1 type macrophage production while cytokines IL-4, IL-10, IL-33, IL-13, and TGF- β induce generation of M2 macrophages [29]. Further, signal transducer of active transcription (STAT 2) pathway and STAT 6 pathway is associated with the polarization of M1 and M2 subsets, respectively [30]. The M2 macrophages show enhanced expression of scavenger receptors and mannose receptors. Some researchers classify decidual macrophages as CD 11c^{HI} and CD 11c^{LO}, on the basis of differential expression of surface protein complement Cd11c. The genes for lipid metabolism and inflammation are expressed by CD 11c^{HI}, while the CD 11c^{LO} cells express genes whose products are required for extracellular matrix formation and tissue growth [31]. The amount of CD 11c is high in first trimester. Other researchers have classified decidual macrophages as CD 209 high and CD 209 low depending on the relative expression of C-type lectin CD 209 which interacts with intracellular cell adhesion molecule 3 (ICAM 3) [32]. The subsets of macrophages differ in the surface markers they present, the cytokines they secrete and their biological functions. The two subsets of macrophages display plasticity and can convert from one subtype to other depending on the cytokine milieu that they are surrounded with and the interaction with other immune cells present in close vicinity. The cytokines released by these two subpopulations of macrophages help in generation of tolerance at the MFI.

2.2.2. Role in trophoblast invasion

Decidual macrophages secrete numerous growth factors, proteases, cytokines, chemotactic molecules, and matrix components, suggesting that they can function in blastocyst implantation, trophoblast invasion, and spiral remodeling [33]. Activated macrophages secrete IL-1 β which in turn can increase the activity of MMP-2 and MMP-9 which are responsible for matrix degradation and subsequent trophoblast invasion [3]. Decidual macrophages secrete growth factors such as VEGF, placental growth factor (PlGF), and their receptor fms like tyrosine kinase (flt-1) which help in angiogenesis and implantation [34,35]. The inhibitory receptors ILT 2 and ILT 4 expressed on decidual macrophages interact with HLA-G expressed on EVT [36,37] and thereby impede the NK cell-mediated lysis of trophoblast cells. *In vivo* studies carried out in mice show that M2 subtype has greater angiogenic potential than M1 [38].

Decidual macrophages induce apoptosis and engulf dying trophoblast cells and thereby modulate trophoblast invasion [39]. Phagocytosis

of trophoblast cells ensures that these cells do not release cytokines responsible for inflammation in the surroundings [40,41]. T-cell immunoglobulin and mucin domain receptor (Tim-3) are always expressed by macrophages and have an important role in phagocytosing apoptotic cells [42]. Inflammatory cytokines TNF- α and IFN- γ can upregulate the expression of XAF1, a pro-apoptotic factor on the trophoblast cells [43]. TNF- α can also initiate apoptosis in activated macrophages and thereby inhibit trophoblast invasion [44].

2.2.3. Macrophages and inflammation

At the MFI, the comparative numbers of M1/M2 macrophage vary; however, a balance between the cytokines secreted by them is maintained as pregnancy proceeds. In early phase of implantation, M1 macrophages are attracted at the MFI. The M1 subsets are responsible for producing an inflammatory and cytotoxic response. The M1 cells can recognize the infectious organisms and help in providing protection against them. Once the placenta development is complete, a shift toward M2 macrophages is observed [45]. This shift helps in establishment of tolerance at the MFI. Under the influence of cytokines, IL-4, IL-10, and IL-13, the M-2 macrophages develop which are responsible for tissue remodeling and maintaining an anti-inflammatory environment which is conducive for pregnancy [46,47]. There is a reduction of IL-12 secretion by M-2 macrophages, a cytokine responsible for inflammation. The decidual macrophages secrete PGE 2, IL-10, TGF- β , and IDO, thereby providing a state of tolerance at the MFI [33]. Hence, we see that the M-2 polarization of macrophages induces an immunosuppressive state during pregnancy, which is essential for maintenance of pregnancy.

2.3. T cells

2.3.1. Th and Tc cells

The lymphocytes that mature in the thymus are referred to as T lymphocytes. In the first trimester of pregnancy, T lymphocytes represent about 10–20% of all immune cells present at MFI. They can be T helper (Th) cells or T cytotoxic (Tc) cells. The Th 1 cells are responsible for many cell-mediated functions and promotion of excessive inflammation, while the Th2 cells are primarily associated with humoral immune response and promote anti-inflammatory conditions. Th cell can further be divided into different subpopulations, namely, Th1, Th2, Th17, and Treg, which can be distinguished by the cytokines that they secrete. The differentiation of Th cells into these subpopulations is determined by the properties of antigen, the processing pathway of the antigen and the cytokine profile; they are exposed to at the time of differentiation. The initial implantation of the fetus is favored by an inflammatory response, wherein a high amount of cytokines released by subtype Th1 (IFN- γ , TNF- α , IL-1, and IL-12) are required and as pregnancy proceeds the Th2 cytokines (IL-4, 5, 6, 10, and 13) predominate to favor an anti-inflammatory response which favors the establishment of pregnancy [48,49]. Progesterone stimulates Th2 cells, which reduces secretion of inflammatory cytokines and allogeneic immune response. TNF- α and IL-1, under the influence of leukemia inhibitory factor secreted by stromal and epithelial cells, present at MFI provide signals to embryonic tissue and uterine epithelium facilitating implantation [50]. The down regulation of NF κ B and T-bet transcription factors at an appropriate time helps in down regulation of Th1 response and thus regulating the process of implantation [51].

2.3.2. Regulatory T lymphocytes (Treg) and Th17 cells

In normal human pregnancy, a large proportion of Treg cells circulate in the periphery and reside at the MFI [52]. The Treg cells are present

throughout pregnancy with numbers decreasing after child birth. Treg cells account for about 14% of the total CD4 T-cells present at MFI and play a crucial role in maintenance of pregnancy. Treg cells participate in spiral remodeling, modulate cytotoxic function of CD8+ cells as well as uNK cells and, also provide defense against uterine infections. The Treg cells control the release of IL-15 from DCs. The importance of these cells was first seen in mice, where removal of Treg cells led to abortion [53]. The Treg cells express CTLA4, which can augment expression of IDO by EVT, decidual and peripheral DCs and monocytes, which, in turn, can restrain utilization of tryptophan by T-cells at the MFI and their subsequent proliferation. IDO can further inhibit the switching of Treg cells to Th 17 cells, thereby facilitating tolerance. The Treg cells can change to Th17 cells when exposed to inflammatory cytokines [54]. The suppressive activity of Treg cells on Th-17 was decreased in women with recurrent abortions [55]. The Th17 cells secrete IL-17 and IL 22 which can have a positive or negative effect on pregnancy. This paradigm can be understood keeping in mind the fact that cytokines exhibit the properties of synergism, antagonism, and pleiotropism. IL-17 is an inflammatory cytokine which can recruit immune cells and has a synergistic effect in association with other pro inflammatory cytokines, namely, TNF, IL-1- β , IFN- γ , GM-CSF, and IL-22 [56]. A number of experiments have shown the association of IL-17 in pregnancy and its concentration is seen to rise in recurrent spontaneous miscarriage (RSM). The Th 17 cells can further differentiate into either Th 17/Th1 or Th17/Th2 subtypes. Majority of Th17/Th2 cells at the decidua secrete IL 17, along with IL 4 and show a synergistic action toward successful implantation. IL-17 secretion by Th2 cells favors trophoblast invasion by inhibiting apoptosis of trophoblast cells, thereby facilitating implantation. IL-22 in association with IL-4 also shows a positive effect on implantation [57]. Placenta-derived immune regulatory factors have been seen to control simultaneous release of IFN- γ and IL 17 by activated T-cells and regulate the differentiation of Th17/Th1 [58]. IL 22 is another pro-inflammatory cytokine secreted by Th 17 cells and shows a synergistic effect in association with IL 17 [59] and its serum concentration increases in RSM [60,61]. However, in successful pregnancies, the synergistic action of IL-22 and IL-4 has been observed at MFI [62]. IL-22 has a crucial role in epithelial regeneration and wound repair and so could be involved in the repair of damaged trophoblast cells. Interaction of IL-22 with its receptor results in a direct effect on proliferation of trophoblast and their decreased rate of apoptosis. Thus, we see that relative levels of the Th cells and the cytokines secreted by them are important for implantation, trophoblast invasion, and existence of tolerance at MFI.

2.3.3. $\gamma\delta$ T-cells

The unconventional $\gamma\delta$ T-cells which function in a manner characteristic of innate immunity are present at the MFI. The $\gamma\delta$ T-cells are either randomly dispersed among the stromal cells or are present as dense filtrates near the basalis lamina of the decidual glands [63]. They exhibit huge diversity in their receptor structure and do not recognize antigen in association with MHC. The $\gamma\delta$ T cells generally are Th1 type; however, some recent studies report them to have features with antigen presenting cells, Th2, Th17, and Treg lymphocytes [64]. The receptors present on their surface show similarities with activating and inhibitory killer receptors present on NK cells. The interaction between inhibitory receptor present on $\gamma\delta$ T-cells and HLA G and HLA E on trophoblasts helps in successful implantation. The $\gamma\delta$ T-cells show an upregulation of CCR5, tissue homing pro-inflammatory receptor during early pregnancy [65], and hence, CCR5 could have a role in accumulation of these cells at MFI. The $\gamma\delta$ T-cells found in the deciduas are pro-inflammatory during early pregnancy and have been seen to

down regulate immunological reactions against the fetus. Cytokines IL-10 and TGF- β are secreted at this time [66,67]. However, substantial amount of research needs to be conducted to understand the process involved and the pathways up regulated on activation of these cells

3. CONCLUSION

There have been exciting developments in the study of immune cells present at the maternal-fetus interface and the immune mechanisms prevalent in establishing tolerance at the MFI. However, there is a long way to go before we can define the relative role of uNK cells, macrophages and different subsets of T lymphocytes present at the maternal fetal interphase. The plasticity exhibited by macrophages and different types of T lymphocytes at the MFI, helps in proper implantation of the fetus, and can also help in raising appropriate immune response in the event of infection. The pregnancy-related complications are often associated with aberrant activation and function of decidual immune cells. Understanding the phenotype of these cells, the mediators released by them and interactions between them can help us to appreciate pregnancy-associated complications in a much better way. In future, we need to study the signaling mechanisms which allow different immune cells present at the MFI to cross talk with each other. The decidual immune cells have receptors for hormones secreted by the placenta. Hence, it will be interesting to see how the various hormones secreted by the placenta modulate the function of immune cells. All these research findings can ultimately be translated into therapeutic interventions which can be used to tackle pregnancy-related complications or failures encountered during *in vitro* fertilization.

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5. AUTHOR'S CONTRIBUTIONS

The review article was conceptualized by the author. Relevant research papers were analyzed and recent updates on the topic were collected. Thereafter, the article was drafted and critically reviewed before submission for publication. I am accountable for the review writing.

6. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

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8. CONFLICTS OF INTEREST

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9. DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

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