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Review article

The role of decidual immune cells on human pregnancy

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ABSTRACT

The maternal-fetal interface undergoes dynamic changes to allow the fetus to grow and develop in the uterus, despite being recognized by the maternal immune cells. Within the innate immune system, decidual natural killer cells and antigen presenting cells (including macrophages and dendritic cells) that comprise a large proportion of the decidual leukocyte populations play an important role in modulating trophoblast invasion, angiogenesis and vascular remodeling. On the other hand, within the adaptive immune system, $CD8^+$ T cells, effector $CD4^+$ T cells, $Foxp3^+$ regulatory T cells and $CD4^+HLA\text{-}G^+$ suppressor T cells are identified as potential players in maintaining immune tolerance toward the semi-allogeneic fetus. This review discusses how these key immune cells contribute to pregnancy outcome and the complex interactions between the innate and adaptive immune system during human pregnancy.

1. Introduction

Pregnancy is a remarkable biological event that presents significant challenges to the maternal immune system. Apposition, adhesion and implantation of the embryo into the uterine lining are critical stages of human pregnancy. After the implantation, the maternal immune system must tolerate the semi-allogeneic fetus approximately 280 days of human pregnancy. Sir Peter Brian Medawar in the 1950s first proposed the concept of “fetal allograft” as an immunological myth. He proposed three factors that contribute to the remarkable nature of this phenomenon, and can be applicable to the modern era of research: the anatomical separation between the mother and the fetus; the decreased antigenic property of the fetus; and the immunological inertness of the maternal immune system. This proposal has influenced many subsequent researches on the mechanism of innate and adaptive immune responses regulating human pregnancy.

It is now well-known that the extravillous trophoblast (EVT) cells have poor antigenic properties owing to lack of classical major histocompatibility complex (MHC) class I molecules (except HLA-C) and MHC class II molecules (Apps et al., 2009). However, these cells still have the capability to induce maternal immune activation and produce anti-paternal HLA antibodies during pregnancy (Morin-Papunen et al., 1984; Lee et al., 2013). A maternal-fetal HLA-C mismatch could lead to an increased percentage of $CD4^+CD25^{dim}$ activated T cells in decidua tissue (Tilburgs et al., 2009a). Alternatively, it was also reported that anti-paternal HLA antibodies were produced via the presentation of fetal antigens by maternal antigen presenting cells (APCs) at the maternal-fetal interface (Erlebacher et al., 2007). Immunotropism and angiogenesis are the two main events at the maternal-fetal junction. A variety of immune cells are recruited to the placental bed to secure and promote the pregnancy. Therefore, the decidua is an important site where the maternal immune system must develop tolerance to fetal antigens. The abnormal frequencies and functions of these immune cells in human decidua have been reported in various obstetrical complications, such as recurrent pregnancy losses (RPL), preterm delivery and pre-eclampsia (Wilczynski 2006; Redman and Sargent, 2010; Lee et al., 2013). In this review, we aim to discuss the possible roles of decidual innate and adaptive immune cells in developing tolerance mechanisms at the maternal-fetal interface, particularly, highlighting the interactions among these cells.

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2. Natural killer cells

2.1. Phenotypic characteristics and origins of decidual NK cells

NK cells are mainly classified as $CD56^{dim}CD16^{+}$ and $CD56^{bright}CD16^{-}$ NK cells identified by their surface phenotype. $CD56^{dim}CD16^{+}$ NK cells are the main population in the peripheral blood, which account for 10%–15% of lymphocytes, whereas $CD56^{bright}CD16^{-}$ NK cells are mainly present in the endometrium, which account for 20% of lymphocytes in the proliferative phase, increase to 40%–50% in the secretory phase and reach a maximum (70%-80%) in human early pregnancy decidua (Moffett-King, 2002; Dosiou and Giudice, 2005). Although the origin of the uterine NK cells (uNK) remains unclear, there have been several studies documenting the origin of uNK cells: 1) recruitment of $CD56^{bright}CD16^{-}$ NK cells from peripheral blood into the uterus, 2) recruitment and differentiation of peripheral blood $CD56^{dim}CD16^{+}$ NK cells, 3) immature NK precursors in the uterus, and 4) maturation from the uterine hematopoietic $CD34^{+}$ precursors (Keskin et al., 2007; Male et al., 2010; Vacca et al., 2011b). It has been reported that CXCL12/CXCR4 axis contributes to the recruitment of decidual NK (dNK) cells at the maternal-fetal interface (Tao et al., 2015). Since the studies concerning the origin of uNK cells are not mutually exclusive, uNK cells may originate from multiple sources and participate in various processes to support a successful pregnancy (Vacca et al., 2011a).

2.2. Functional capabilities of dNK cells

The dNK cells are localized in close proximity to the invading trophoblasts in the decidua, suggesting that they have an important role in modulating the degree of trophoblast invasion (Lash et al., 2010). The dNK cells have been shown to express killer immunoglobulin receptor (KIR) (Boyington et al., 2001), CD94/NKG2A (King et al., 2000) and ILT2 (Long et al., 2001), which are receptors for HLA-C, HLA-E and HLA-G, respectively, on trophoblast cells (Fig. 1). KIRs are expressed by a greater proportion of dNK cells than peripheral NK (pNK) cells in pregnancy women, indicating that the NK cell receptor repertoire is skewed towards HLA-C-recognition in the uterus (Hiby et al., 1997; Verma et al., 1997). Since HLA-C is dimorphic and KIR is highly polymorphic, different combinations of paternally derived fetal HLA-C and maternal uNK-cell KIRs should occur during pregnancy (Verma et al., 1997). dNK cells express high levels of the inhibitory receptor CD94/NKG2A, which is the receptor for HLA-E (King et al., 2000). Since HLA-E is expressed on both maternal cells and trophoblast cells, the interaction between CD94/NKG2A and HLA-E might prevent the lysis of trophoblast and other maternal cells in the vicinity. It has been shown that the binding affinity of CD94/NKG2A for HLA-E is greater than that of the activating CD94/NKG2C receptor, which is also transcribed in uNK cells. Additionally, the affinity of HLA-E complexed with HLA-G leader-sequence peptide, which binds to CD94/NKG2C is great enough to trigger an NK-cell response, thus uNK cells could respond differently to trophoblast HLA-E and maternal $HLA\text{-}E^{+}HLA\text{-}G^{-}$ cells (Llano et al., 1998; Vales-Gomez et al., 1999). Hence, HLA-G expressed only on EVT could influence the maternal response indirectly through HLA-E. On the other hand, the interaction between HLA-G and ILT2 that is expressed on a small proportion of dNK cells (Long et al., 2001) has been shown to increase the secretion of inflammatory and pro-angiogenic factors, such as IL-1β, IL-6, IL-8 and TNF-α by dNK cells (Rajagopalan et al., 2006). Actually, since Saito and his colleagues firstly reported the cytokine production by decidual $CD56^{bright}CD16^{-}$ NK cells in 1993, the study on the role of these cytokines in pregnancy is increasing these years (Saito et al., 1993). A recent study demonstrated the dual role of dNK cells in both mounting cytolytic responses during viral infections and providing immune tolerance to the fetus and facilitating placental growth (Tilburgs et al., 2015). The low cytotoxicity of dNK cells is the result of an intrinsic block in the polarization of cytolytic granules to the immune synapse. The restoration of dNK cytolytic capacity by proinflammatory cytokines such as IL-15 is crucial for dNK cells to clear viral infections. Additionally, the inhibitory molecule T-cell immunoglobulin domain and mucin domain-containing molecule-3 (Tim-3) was reported to be expressed on over 60% of dNK cells (Li et al., 2016). The $Tim\text{-}3^{+}$ dNK cells serve as an immune-tolerant subset, which produced higher IL-4 and lower TNF-α and perforin. Moreover, the Tim-3 expression in dNK cells declines in human miscarriages, indicating the importance of $Tim\text{-}3^{+}$ dNK cells in the maintaining of normal pregnancies.

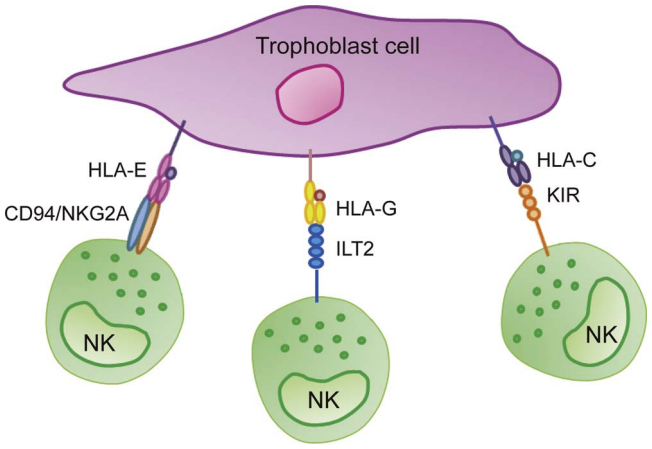

Fig. 1. Receptors on dNK cells that bind to trophoblast HLA class I molecules. The dNK cells have been shown to express CD94/NKG2A, ILT2 and KIR, which are receptors for HLA-C, HLA-E and HLA-G on trophoblast cells, respectively.

NK cells are also involved in decidual spiral artery remodeling during pregnancy, which is a critical process to increase blood flow to the placenta and developing fetus (Hanna and Mandelboim, 2007; Zhang et al., 2011a,b; Moffett and Colucci, 2014). dNK cells modify the decidual vasculature through both direct and indirect interactions. The direct interaction includes cellular interactions with vascular smooth muscle cells (VSMC), endothelial cells, pericytes and trophoblast cells, whereas, the indirect action is mediated by a series of factors secreted by dNK cells that contribute to vascular remodeling (Pijnenborg et al., 2006; Smith et al., 2009; Hazan et al., 2010). It has been reported that human dNK cells accumulate around spiral arteries and lead to the disruption of the vascular wall through secretion of matrix metalloproteinase (MMP) that breaks down the extracellular matrix (ECM) of VSMC (Smith et al., 2009; Hazan et al., 2010). There has been an evidence implicating that angiopoietin-1 (ANG1) and ANG2, vascular endothelial growth factor (VEGF)-C, IFNγ and MMPs secreted by human dNK cells contribute to modulating cell to cell and cell to ECM interaction in the early stage of spiral artery remodeling (Robson et al., 2012). Additionally, altered numbers of dNK cells are associated with defective vascular growth, reduced angiogenesis and reduced trophoblast invasion in human pregnancy pathogenesis (Fukui et al., 2011, 2012). In animal models, it has been shown that NK-deficient mice have reduced placental blood supply compared with those of normal control mice (Zhang et al., 2011a).

2.3. Crosstalk between dNK with innate and adaptive immune cells

There have been emerging evidences suggesting that dNK cells interact and modulate other maternal immune cells. The interaction between dNK and dendritic cell-specific ICAM-grabbing nonintegrin $(DC\text{-}SIGN)^{+}$ APCs occurs through intercellular adhesion molecule 3 (ICAM3, expressed on NK cells) and DC-SIGN (Kammerer et al., 2003). Interestingly, dNK cells could modulate decidual $CD14^{+}$ cells and promote the induction of regulatory T (Treg) cells characterized by $CD25^{bright}Foxp3^{+}$ phenotype *in vitro* (Vacca et al., 2010). The