



REVIEW

Up-and-down immunity of pregnancy in humans [version 1; referees: 2 approved]

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Abstract

One part of the human placenta in early pregnancy is particularly important for local immunity: the *decidua basalis*, which is transformed endometrium located at the site of embryo implantation. This placental bed tissue contains both maternal uterine immune cells, including decidual natural killer (NK) cells, the dominant leukocyte population exhibiting a unique phenotype, and fetal extravillous trophoblast which comes into direct contact with maternal decidual cells. To establish a successful placental development and healthy pregnancy outcome, the maternal immune system must tolerate paternal antigens expressed by trophoblast cells yet remain efficient for clearing any local pathogen infection. This review deals mainly with decidual NK cells. A key element, among others, to achieve such dual functions is the direct interaction between activating and inhibitory receptors expressed by decidual NK cells and their specific ligands presented by trophoblast or other decidual cells. Depending whether maternal decidual cells and trophoblast are infected by viruses, the balance between activating and inhibitory receptor signals mediated by decidual NK cell–trophoblast cross-talk results in tolerance (healthy pregnancy) or specific killing (pathogen-infected cells).

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Introduction

The human placenta consists of two components—a fetal and a maternal one—that must interact successfully for a healthy pregnancy outcome¹. The maternal component is the endometrium, which undergoes modifications to form the *decidua basalis* from the very earliest stages of pregnancy. The only fetal component is the trophoblast in contact with maternal immune cells, constituting the junction between two immunologically distinct individuals (mother and fetus). A recent report has developed a thorough classification system based on specific markers to identify the different trophoblast subpopulations in the first trimester of pregnancy². Invasive extravillous cytotrophoblast (EVCT) is present in the *decidua basalis*^{3,4}. Differing from the *decidua basalis*, the *decidua parietalis* lines the uterine cavity and is in direct contact with HLA-G⁺ trophoblast in the chorion laeve with no invasion in spiral arteries⁴. EVCT is also present in the distal ends of spiral arteries in contact with maternal blood, contributing to the uterine vascular remodeling⁵⁻⁷. Such remodeling is critical to ensure optimal utero-placental blood flow during pregnancy. In early pregnancy decidua, EVCT comes into close contact with various maternal immune cells: prominent granulated decidual natural killer (dNK) cells, macrophages, CD4⁺ T cells, including T helper 17 (Th17) cells⁸, and CD8⁺ T cells⁴. Another maternal-fetal interface is constituted by the multinucleated syncytiotrophoblast, the outer part of chorionic villi, which is in contact with maternal immune cells present in the maternal blood of the intervillous blood space⁹. This review focuses mostly on the role of EVCT and dNK cells in pregnancy immunity.

During pregnancy, the maternal immune system responds to fetal trophoblast antigens. In particular, it produces maternal anti-paternal antibodies, but oddly these antibodies are not harmful for the fetus¹⁰⁻¹². Furthermore, in normal pregnancy, trophoblast is never destroyed by maternal decidual immune cells¹³, suggesting the occurrence of very efficient immunosuppressive mechanisms. Yet recent findings demonstrate that viral infection awakes maternal decidual immunity to rapidly clear pathogens and avoid further spreading to the fetus^{6,14,15}. These intriguing, contradictory observations raise the following question: how do the interactions between maternal immune cells and fetal trophoblast either lead to downregulation of maternal anti-paternal immunity or trigger efficient maternal immunity against decidual pathogen-infected cells? The aim of this review is to analyze some of the recent scientific advances that contribute to explain these intriguing, contradictory observations. One key element of such up-and-down local decidual immunity lies in the specific receptor-ligand interactions occurring at the cell surface of maternal decidual immune cells and fetal trophoblast. Among the different control mechanisms described to date, the crucial role exerted by dNK cells in both healthy and virus-infected pregnancies will be the focus of this review.

Healthy pregnancy: down-modulated adaptive and innate decidual immunity

Unique array of HLA class I molecules on trophoblast

In contrast to most somatic cells, infiltrating EVCT cells do not express the polymorphic T-cell ligands HLA-A and HLA-B class I¹⁶⁻¹⁸ nor do they express HLA class II molecules¹⁷. The absence

of polymorphic HLA-A and HLA-B expression thus limits fetal antigen presentation by non-infected EVCT to the maternal CD8⁺ cytotoxic T cells^{19,20}. Moreover, it has been shown that cytotoxic T cells in the decidua express less perforin and granzyme B than CD8⁺ T cells present in the peripheral blood (PB)^{21,22}. This is one of the various mechanisms used by the fetus for avoiding killing by CD8⁺ T cells of the invading EVCT which plays a crucial role in uterine vascular remodeling and placental development⁵. EVCT cells express the fetal polymorphic class I molecule, HLA-C, only in the β 2-microglobulin-associated form and at a high level²²⁻²⁴. HLA-C is the ligand of activating or inhibitory killer-cell immunoglobulin receptors (KIRs). Engagement of these inhibitory receptors by specific, and so-far-unknown, trophoblast ligands downregulates the cytotoxic function of dNK cells¹⁵. In addition, EVCT expresses the non-polymorphic HLA-E, HLA-G, and HLA-F^{7,25}. HLA-E is the ligand of CD94/NKG2A heterodimer inhibitory dNK cell receptor (see next section). HLA-G molecules are expressed at the cell surface of EVCT with a prolonged half-life⁶. HLA-G is the ligand of LILRB1 inhibitory receptor present on about 40% of dNK cells¹⁸. LILRB1 has a high affinity for the dimeric form of HLA-G on EVCT¹⁸. Such strong binding contributes to limit the cytotoxic function of dNK cells²⁶. This is an additional inhibitory mechanism. Syncytiotrophoblast, the outer part of chorionic villi, in contact with the maternal blood of the intervillous space, is devoid of classical and non-classical HLA class I surface expression¹⁷. Thus, it cannot present fetal antigens to the maternal CD8⁺ T cells present in the intervillous space. Though a matter of debate^{27,28}, some reports indicate that syncytiotrophoblast produces soluble HLA-G^{29,30}. Soluble HLA-G might exert an immunosuppressive protective role in pregnancy¹⁹ by triggering the killing of maternal activated CD8⁺ T cells present in the *decidua basalis* as well as in the maternal blood of the intervillous space³¹.

Decidual natural killer cells in healthy pregnancy: lack of cytotoxic function

dNK cells constitute the great majority of maternal immune cells present in early *decidua basalis* (about 70% of leukocytes present), where the EVCT infiltrates into maternal tissue. The dNK phenotype in healthy pregnancy is unique, differing from PB NK cells¹⁴. The major dNK subpopulation is characterized as CD56^{bright}/CD16⁻/CD160⁻ (non-cytotoxic phenotype), whereas about 90% of the PB NK cells are CD56^{dim}/CD16⁺/CD160⁺ (cytotoxic phenotype)³². Although their abundant intracellular lytic granules contain perforin, granzyme, and granzyme³³, dNK cells are poorly cytotoxic⁹. In contrast to circulating NK cells, dNK cells display a poor ability to kill various non-infected cell target lines, including human K562 and .221 as well as murine P815 cell lines³⁴. Other dNK cell functions—regulation of trophoblast invasion and subsequent spiral artery remodeling—are controlled by dNK cell receptors that interact with specific HLA class I or non-major histocompatibility complex (non-MHC) class I ligands present on EVCT³⁵. Similarly, in mice, MHC molecules were shown to educate uterine NK cells to trigger uterine arterial remodeling³⁶. Although dNK cells express several activating receptors, including NKp46, NKp30, NKG2D, and CD94/NKG2C, and some activating receptors of the KIR family, they are not cytotoxic against EVCT¹³. Several studies have characterized the

different mechanisms preventing the dNK cells from exerting cytotoxic function. First, this is due to specific interactions between dNK inhibitory receptors and specific ligands. We reported that the engagement of CD94/NKG2A inhibitory receptor with its specific ligand HLA-E expressed by EVCT is a dominant negative regulatory mechanism that prevents cytotoxicity toward trophoblast³⁷. Second, another inhibitory mechanism is provided by engagement of the LILRB1 inhibitory receptor by its specific HLA-G ligand expressed at the cell surface of EVCT³⁸. Third, a report demonstrated that VEGF-C secreted by dNK cells in the first trimester of pregnancy triggered upregulation of TAP-1 in EVCT, protecting them from a cytotoxic role³⁹. Thus, in normal pregnancy, there is an obvious resistance to dNK cell killing function, although dNK cells are potentially capable of cytolytic activity³⁷.

Pathogen-infected pregnancy: awakened decidual immunity

Contact with autologous decidual human cytomegalovirus-infected cells restores decidual natural killer cell killing potential

Human pregnancy is characterized by tolerance to the fetus through down-local decidual immunity but balanced with fetal decidual defense against pathogens. dNK cells are poorly cytotoxic in healthy pregnancy yet possess a likely functional lytic machinery¹⁴. Indeed, using a redirected cell lysis assay, a study reported that specific engagement of NKp46 and, to a lesser extent, NKp30 activating receptors on isolated dNK cells from early decidua induced P815 cell target lysis³⁷. Human cytomegalovirus (HCMV) infection modulates the dNK cell receptor repertoire. Co-culture of dNK cells with HCMV-infected autologous stromal cells increased the number of CD56^{dim} dNK cells associated with the appearance of CD16 and NKG2C activating receptors⁴⁰. Such a phenotype is consistent with the acquisition of a cytotoxic profile. Similarly, isolated dNK cells infected with *Toxoplasma gondii* were shown to express markers of cytotoxicity, including increased expression of CD16 and NKG2D receptors, and to acquire a CD56^{dim} phenotype⁴¹. These different observations indicated that dNK cells acquire cytotoxic potential in the pregnant uterus when the decidua is infected by pathogens. dNK cells become cytotoxic when in contact with HCMV-infected autologous decidual stromal cells⁴². dNK cells engage immune synapse with HCMV-infected autologous stromal cells and polarize their lytic machinery toward infected cells. In contrast, purified dNK cells in contact with uninfected autologous stromal cells do not exert their killing function⁴⁰. Furthermore, via immunohistochemistry, the presence of dNK cells was observed in the vicinity of HCMV-positive cells in placental tissue obtained after elective pregnancy termination⁴⁰. Another article indicated that isolated dNK cells expressing KIR2DS1 activating receptor acquired higher cytotoxic function than KIR2DS1^{negative} dNK cells when in contact with HCMV-infected decidual stromal cells¹³. Moreover, a recent study reported that a structural modulation of HLA-C is required for a potent KIR2DS1-mediated NK cell activation⁴³. Whether such HLA-C modulation could occur at the cell surface of HCMV-infected EVCT in pregnancy remains to be determined. Thus, dNK

cells were shown to clearly exert a cytotoxic function in the pregnant uterus when the decidua is infected by pathogens.

A controversial question can legitimately arise from the above results obtained from *in vitro* co-culture of isolated dNK cells and stromal cells from the same early pregnancy sample: is there a bias due to the limited type of decidual cells surrounding dNK cells in these *in vitro* experiments? The beginning of an answer has been provided by a recent article⁴⁴. The authors used a multi-cell-type solid placental tissue containing a variety of immune and non-immune cells, including fetal and maternal cells which more closely resemble infection *in vivo*. In the latter study, it was demonstrated that HCMV infection triggered a robust interferon-gamma (IFN- γ) and IFN- γ -inducible protein-10 (IP-10) release by dNK cells, thus differing from another study that used *in vitro* co-culture with only two cell components: autologous dNK and decidual stromal cells⁴⁰. In the latter case, no upregulation of IFN- γ but rather down-modulation of IP-10 by dNK cells was observed⁴⁰. These different results demonstrate the crucial influence of the cellular microenvironment.

Decidual CD8⁺ T cells present in early pregnancy are fully functional¹⁵. They can recognize fetal HLA-C expressed at high levels on the cell surface of EVCT^{6,20}. HLA-C expressed by EVCT thus exerts a dual role: it can present pathogen-derived peptides to decidual CD8⁺ T cells when EVCT is infected. HLA-C expressed by EVCT is also a specific ligand for various activating KIR dNK receptors²⁴. Such interactions result in the stimulation of dNK cell cytotoxic function¹⁵. Whether virus-specific and HLA-C restricted decidual CD8⁺ T cells are present in infected decidua and able to kill infected cells remains to be determined. Detection of virus-specific CD8⁺ T cells in decidual tissue⁴⁵ suggests that this might be the case. Moreover, a recent study demonstrated that activation of dNK cells through KIR2DS4 activating receptor (which also binds HLA-C) stimulates EVCT migration needed for subsequent placental development⁴⁶.

Concluding remarks

During pregnancy, there is a conflicting need for both reproductive success and protection against congenital transmission of viruses and other pathogens. To date, many mechanisms have been described that contribute to block potentially harmful maternal-anti-paternal immune response¹⁹. Until recently, little was known about the ways used by the maternal immune system to eradicate local decidual infection. dNK cells present in large numbers in *decidua basalis* play different roles at the beginning of pregnancy by interacting with specific EVCT-bound ligands, including HLA class I. On the one hand, dNK cells are poorly cytotoxic, thus preventing the killing of EVCT. On the other hand, dNK cells acquire cytotoxic potential when they interact with infected decidual cells. Besides, the immunity of pregnancy requires the involvement of other limbs of the immune system⁴⁷. Indeed, several studies have identified additional mechanisms that contribute to T-cell tolerance in the *decidua basalis*^{6,48}. Several other innate and adaptive immune interactions occur at the maternal-fetal interface⁴⁹. Important to

consider is the role of regulatory T cells^{50–52} as well as Th17 cells in the human decidua⁸. Whether the same dNK-mediated target recognition similarly blocks other viral congenital infections that may occur is yet to be elucidated. It would be important to study how local immunity in pregnancy may control infections of hepatitis C virus⁵³, human immunodeficiency virus⁵⁴, Zika virus⁵⁵, and *T. gondii* parasite⁴¹.

Competing interests

The authors declare that they have no competing interests.

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The referees who approved this article are:

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