Maternal allo-recognition of the fetus

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Immunological adjustments are needed to accommodate the close contact between two genetically different individuals, the mother and her baby, during mammalian pregnancy. Contact occurs between fetal somatic or placental cells that enter the maternal systemic circulation or between uterine immune cells and the invading extravillous trophoblast. Here we discuss two main types of maternal allo-recognition of the fetus. One depends on avoidance of maternal T cells recognizing and responding to paternally-derived non-self human leukocyte antigens class I and class I allotypes. The other is natural killer allo-recognition where maternally-inherited variable killer immunoglobulin-like receptors expressed by uterine natural killer cells bind to polymorphic fetal human leukocyte antigens-C molecules displayed by extravillous trophoblast. Genetic studies indicate that natural killer cell allo-recognition regulates placentation and the allocation of resources to the fetus. (Fertil Steril® 2017;107:1269–72. ©2017 by American Society for Reproductive Medicine.)
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Since the original paper by Peter Medawar in 1953 (1), the question that has dominated the field of reproductive immunology is, "Why is the fetus not rejected?" This question arose because Medawar (who had begun working on transplantation of skin grafts during World War II to treat pilots with burn injuries) showed that graft rejection is an immunological phenomenon (1, 2). His essay raised the question of why, in pregnancy, it is possible for two genetically different individuals to coexist without rejection of the fetus. We describe here the immunological basis of allo-recognition and how this relates to human pregnancy.

ANATOMY OF MATERNAL/FETAL INTERACTION

The implanting blastocyst is surrounded by trophectoderm that will develop into both the definitive villous placenta as well as the invading extravillous trophoblast cells (EVT) that invade into the uterus to tap into the maternal blood supply. Villous trophoblast is in contact with maternal blood circulating through the intervillous space. Syncytial knots are also shed from the villous placenta directly into the systemic circulation and become entrapped in the lung capillaries. Extravillous trophoblast comes into direct contact with tissue immune cells in the decidua and myometrium of the uterus. Thus, fetal somatic cells are normally completely separated from the maternal immune system by the placental trophoblast barrier (3).

Fetal cells can, however, cross over into the maternal circulation. This usually occurs during the trauma of delivery (although they can also cross during spontaneous or therapeutic abortions) and these cells are capable of initiating immune responses. In the early days of transplantation it was noted that multiparous women had antibodies to allogeneic leukocytes (allo-antibodies), now known to be specific for paternal human leukocyte antigens (HLA) (4). The presence of these allo-antibodies has no influence on the outcome of pregnancy but will affect the mother's chances of finding a compatible organ donor. The presence of anti-D antibodies in women who are negative for this blood group antigen also reveals pregnant women can generate antibodies to fetal allo-antigens, and therefore, are not immunosuppressed (5). For these reasons maternal immune responses in pregnancy should be considered separately as: systemic responses to fetal cells or soluble fetal antigens, systemic responses to villous syncytiotrophoblast, or uterine immune responses to EVT.

T CELL ALLO-RECOGNITION

The important cells capable of allo-recognition are lymphocytes: T cells, natural killer (NK) cells, and B cells that produce antibodies with T cell help (6).

T cells have a clonally-distributed receptor (TCR) that is generated during fetal development by somatic gene rearrangement. Any T cells that have a TCR specific for a self HLA molecule presenting a self-peptide are eliminated during T cell development to avoid self-reactivity (central tolerance). Allo-reactive T cells will be present amongst the huge diversity of an individual's T cells at a frequency of

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up to 10%. These T cells will be able to respond and attack organ grafts unless there is HLA matching of donor and recipient.

Rejection of solid organ grafts results from stimulation of the recipient's immune system by two pathways: direct and indirect allo-recognition (6). In direct allo-recognition, donor dendritic cells, antigen presenting cells (APC) that express donor HLA molecules, migrate from the graft to the draining lymph node. HLA class I and class II molecules bind directly to recipient's CD8+ and CD4+ T cells respectively in the lymph node. Effector T cells move into the graft with CD8+ T cells killing the graft and CD4+ T cells activating macrophages to initiate inflammation and provide help to B cells to produce antibodies. Indirect allo-recognition results from uptake of HLA and other allo-antigens from donor's cells by recipient APC that migrate to the regional lymph node. Peptides derived from the donor's HLA molecules are then presented to recipient's T cells initiating a CD4+ allo-reaction.

Why do maternal allo-reactive T cells not attack the fetal trophoblast? Several mechanisms have been described in both humans and mice. The villous syncytiotrophoblast in humans never expresses any HLA class I or class II molecules so it is not possible for any T cells to bind to the main placental barrier, clearly a highly effective mechanism to protect the placenta from being killed (7). The syncytial nature of the placental barrier is also likely to be important as small defects in the membrane can heal rapidly. In contrast, the EVT does express HLA class I but never class II molecules so it cannot act as an APC initiating direct allo-recognition to maternal CD4+ T cells. Furthermore, the set of HLA class I molecules expressed is unusual: HLA-C, HLA-G and HLA-E. Of these only HLA-C is polymorphic and so the paternal allele donated to the fetus will differ from the mother's. HLA-G is monomorphic and is unique amongst HLA class I molecules as it forms a homodimer that can bind with high avidity to LILRB1, an inhibitory receptor expressed by all decidual APC. This interaction probably deviates immune responses towards a tolerogenic rather than an immunogenic response (8). This has the added benefit of only occurring when there is direct physical contact between HLA-G+ EVT and uterine APC allowing maternal APC elsewhere in her body to function normally.

Regulatory T cells (Tregs) can suppress allo-reactive CD4+ and CD8+ T cells and are generated in the decidua in pregnancy in both humans and mice probably because of the unique microenvironment rich in factors such as TGFβ (9). However, it is still not clear whether the TCRs of these decidual Tregs have any specificity for trophoblast HLA-C class I molecules although one study analysing T cells in the decidua at term has shown there are increased percentages of functional Tregs in HLA-C mismatched pregnancies (10). Other mechanisms described in murine models include reduced migration of APC to draining lymph nodes, failure of effector T cell accumulation in the decidua by silencing of stromal cell-derived chemokines and global effects of progesterone on immune cells (11). Mouse models may not be as helpful in studying reproductive failure as they have been for analyzing the immunological basis of other human diseases. Pregnancy in the mouse only last 19 days, there is no menstrual cycle, and the anatomy of placentation is different with little trophoblast invasion and formation of decidua only triggered by implantation and not in the secretory phase of the pre-pregnant endometrium.

Although women in pregnancy are not immuno-suppressed as seen by responses to paternal HLA and other allo-antigens, they do respond differently to infectious agents and auto-antigens. For example, they are particularly susceptible to influenza, chicken pox and other viruses and the severity of auto-immune disorders such as rheumatoid arthritis and multiple sclerosis varies during pregnancy (12, 13). This may be due to a deviation towards making better Th1 type responses (cytotoxic and effective for viruses) than antibody-generating Th2 type responses in pregnancy although robust evidence for this in humans is still lacking. These alterations in the shape of immune responses are likely to result from changes in hormones and other pregnancy signals. Although these systemic differences in the type of immune responses seen in pregnancy mean, for example, that women need vaccination for influenza virus, it is important to state that there is still no evidence they have any impact on reproductive success. They are probably an epiphenomenon secondary to the high levels of progesterone and other hormones and placental products.

The important unanswered question is whether in humans T cells ever do bind and attack the trophoblast cells resulting in pregnancy failure? Placental mammals evolved ~150 million years ago and there will have been strong selective pressures to avoid T cell rejection of the fetus. Because there are multiple mechanisms already described to avoid effector T cell responses that might damage trophoblast cells it does seems most unlikely that will ever all fail together. Indeed, there are no convincing reports in humans that this does happen and that maternal T cells with specificity for trophoblast have caused killing of the placental cells. Perhaps it is time to move away from Medawar's famous question of 1953 and view the co-existence of the mother and her baby not as a dichotomy between rejection and acceptance but as a compromise.

NATURAL KILLER (NK) CELLS

Although NK cells were only discovered in the 1970s, in evolutionary terms they are much older than T cells (14). Equivalent cytotoxic cells are present in invertebrates whereas T cells only appeared in teleost fishes. NK cells resemble CD8+ T cells in many phenotypic, functional and morphological respects but crucially they lack a TCR generated by somatic gene rearrangement and rely on germ cell encoded receptors for target cell recognition. NK cells are particularly important in the early stages of viral infection and cancer. They were originally thought to be able to kill cells independently of HLA class I molecules but it then became clear that they are inhibited by binding to self-HLA and will therefore kill cells that lack self HLA class I molecules—known as the missing self-response (15). Thus, CD8+ T cells kill cells expressing 'non-self' HLA whilst NK cells kill cells 'lacking self' HLA class I molecules; either