# Essay on immune tolerance in pregnancy

Family, Parents

# 1. 0 Background of Immune Tolerance

The immune system is the natural defense that combats disease causing agents in the body[ CITATION Gre02 l 1033 ] through an intricate and coordinated interactions of many classes of proteins and cells[ CITATION Len00 l 1033 ]. The immune system has a potential to destroy the body cells but in all vertebrates the system is capable of distinguishing “ self” from “ non-self” molecules. That way the immune system eliminates pathogens and molecules that are a threat to the integrity of the organism without “ self-destructing”[ CITATION Len00 l 1033 ]. The human body has several mechanisms of either suppressing or eliminating autoreactive immune cells. Some of these mechanisms have been implicated for the protection of the conceptus from the maternal immune system hence sustains pregnancy. It is therefore imperative to understand these mechanisms in general before an in-depth review of how they specifically work in pregnancy.

Central Tolerance is the process that eliminates immature autoreactive T and B cells by apoptosis. Central tolerance occurs in the thymus and bone marrow destroying lymphocytes capable of recognizing self antigens before they fully develop into immunocompetent cells. The process only occurs after the cells interactions with self antigens that are endogenously expressed in the thymus and bone marrow, that get to these sites via general circulation and that are in the thymus through a transcription factor called autoimmune regulator (AIRE). Peripheral tolerance deals with elimination of mature lymphocytes[ CITATION Ken04 l 1033 ]. Five mechanisms have been suggested to explain peripheral tolerance. The first

mechanism involves negative selection of autoreactive circulating lymphocytes through transcription factor (AIRE). Activation of T-cells requires their binding to the Major Histocompatibility Class molecule and a second signal (costimulation-mainly by B7) on the antigen presenting cell (APC). Cells presenting self antigens either fail to provide the second signal, in which case the T-cells encountering them self destruct, or provide an undefined signal that turns the T-cells into Tr (regulatory). Another peripheral tolerance mechanism involves anatomical barriers that create " immune privileged sites" such as the brain, testes and interior of the eye hence this sites are unreachable to T-cells. Also some cells, especially within the mentioned sites, have the Fas Ligand (FasL) onto which the Fas receptor on activated immune cells bind leading to the apoptosis of the activated immune cells. The last proposed mechanism of peripheral tolerance involves Tr cells that suppress other T-cells. The third categor of immune tolerance is the acquired form in which the immune system becomes uncreative to exogenous antigens as occurs in pregnancy. As will be shown in the next section some of these mechanisms are involved in gestational immune tolerance. It is also worth noting that these are just the major classifications of immune tolerance mechanisms the specific mechanisms identified in pregnancy are described in the next section [ CITATION Ken04 l 1033 ].

## 2. 0 Immune tolerance in pregnancy

From an immunological perspective pregnancy doesn't make sense because a fetus carries half the father's genome hence it is foreign to the mother. The suppression of the maternal immune system during pregnancy to accommodate the antigenically distinct fetus and placenta in the uterus was

first proposed by Medawar in 1953[ CITATION WDB03 l 1033 ]. Years down the line several mechanisms, collectively referred to as maternal/gestational immune tolerance, that prevent the maternal immune system from harming the fetus hence sustain pregnancy have been described. It is worth noting that these mechanisms are varied and tend to change from one gestational stage to another. Failure of these tolerance mechanisms has been attributed to spontaneous abortion. The gestational immune tolerance mechanisms act both systemically on the maternal immune system and locally at the placenta[ CITATION San04 l 1033 ]. Most of these mechanisms are mediated by the placenta which creates an immunologically safe zone by acting as an immunological barrier between the fetus and the mother[ CITATION Cal10 l 1033 ]. Most of the mechanisms involved in mediating maternal immune tolerance are not fully understood.

In the 1980s the heterogeneity of T helper (Th) cells was discovered and for several years this was the only premise of the gestational immune tolerance. Two distinct subsets of this T cells population were described: Th1 and Th2 alongside corresponding cytokines. While Th1 cells and cytokines were found to cause spontaneous abortion the Th2 cells and their cytokines were found to inhibit the action of the Th1 cells and cytokines. There is evidence suggesting that during the course of pregnancy the Th1 cells and cytokines decreases while the Th2 cells and cytokines increase. As earlier stated this was the only theory explaining the maternal immune tolerance but with time it has become clear that there are other mechanisms involving both the adaptive and innate immune responses[ CITATION Lei09 l 1033 ].

The first means by which the placenta creates immune tolerance is by creating a physical barrier. Unlike the epithelium the placenta forms a physical barrier (syncytium) by fusion of cells such that there are no extracellular spaces between cells. This cell fusion seems to be mediated by viral fusion proteins produced by endosymbiotic endogenous retrovirus. This immune-evasive mechanism is postulated to have initially been the means by which the virus spreads from one cell to another but has evolved to be a means by which the placenta protects the fetus by limiting the exchange of migratory immunological cells. However the placenta is permeable to IgG antibodies which cross to the fetus and protect it against infection but these antibodies don’t target the fetal cells unless the fetal cells cross the placenta and contact the B-lymphocytes stimulating them to produce antibodies targeting fetal targets[ CITATION Ger10 l 1033 ].

The placenta releases Neurokinin B molecules that contain phosphocholine and prevent the detection of the fetus by the maternal immune system in much the same way nematode parasites evade the immune system of the host. Researchers have also found lymphocytic suppressor cells in the placenta and in the fetus. This cells act by preventing the action of the maternal cytotoxic T lymphocytes by inhibiting their response to cytokines.

Chief among the placenta associated gestational tolerance mechanisms is the fact that the trophoblast cells do not express MHC Class I isotopes Human Leukocyte Antigens A and B (HLA-A and HLA-B) produced by other cells in the body. The genetic mechanism underlying this system involves the down regulation of the highly polymorphic HLA-A and HLA-B class I genes

in the trophoblast cells and increased expression genes of the nonpolymorphic HLA-G and HLA-E class Ib molecules by trophoblast cells, amnion cells and fetal cells. By this mechanism the trophoblast resists destruction by cytotoxic T cells and Natural killer (NK) cells[ CITATION JSz02 l 1033 ]. It is has been demonstrated that lack of the classical MHC class I isotopes (HLA-A and HLA-B), which are recognized by cytotoxic T-lymphocytes (CTL), prevents the destruction of the trophoblast by the maternal CTL. Cells that do not express the typical MHC class I isotopes are destroyed by the NK-cells thus by expressing atypical MHC class I (HLA-E and HLA-G) the placenta and fetal cells evade NK-cells. This component of the maternal immune tolerance is also known to dampen the action of interferons[ CITATION JSH05 l 1033 ].

Another placenta mediated immune tolerance mechanism involves the trophoblasts inducing the death of TC-ells as part of peripheral clonal deletion leaving T-cells that are unresponsive to antigenic activation. As such T-cells specific to fetal antigens have been found to reduce in an antigen-specific manner during pregnancy as a result of interaction with fetal cells expressing the MHC mentioned earlier[ CITATION Shi98 l 1033 ]. The study by Jiang and Vacchio (1998) also demonstrated that T cells that remain become progressively unresponsive to activation by fetal antigen. As part of the immune tolerance the maternal T-cells also reduce the production of their surface receptor molecule (CD) which interacts with antigenic cells; NK-cells are immobilized and the mononuclear phagocytes go into suppressed mode characterized by increased production of anti-inflamatory cytokines[ CITATION JSH05 l 1033 ]. In addition the maternal immune

response has been found to shift from the cellular immunity, which could target and destroy the fetal cells, to the antibody mediated immunity. Recent studies by Kahn and Baltimore (2010) found that the gestational immune tolerance is not just a passive process but the female body actively increaeses the production of Regulatory T cells (Tr). This Studies demonstrated the involvement of T-regulatory cell in gestational immune tolerance occurs in an antigen specific manner (their function requires the presence of fetal antigens) [ CITATION Cal10 l 1033 ].

Regulatory T cells, also referred to as suppressor T cells, are involved in modulating the immune system so that self cells are spared from destruction. These cells (Tr) come in different forms depending on the surface receptor (CD) expressed but they are all involved in suppressing the immune system after the pathogen has been eliminated. Once the fetal antigens get into contact with the maternal circulation the maternal immune system is activated to increase production of suppressor cells[ CITATION Cal10 l 1033 ]. Earlier studies by Guerin, Prins and Sarah Robertson (2009) found that the Tr cells population expanded in the course of pregnancy. This study established that from early in the first trimester the number of Tr cells increase in the mother’s deciduas and blood and that an insufficient number or a dysfunction of these cells are linked to miscarriage, pre-eclampsia and infertility.

Another mechanism of maternal immune tolerance involves the Fas Ligand (FasL), a soluble or membrane bond peptide that plays a vital role in suppressing immune response. FasL has been identified in several

immunoprivileged sites such as the testis and the anterior chamber of the eye where it plays a role in immunoregulation. Immunosuppression by FasL is achieved by interacting with its receptor (Fas) on the membrane of activated immune cells resulting in the death of these cells (apoptosis). The FasL receptors are only expressed on activated immune cells such as activated macrophages, T cells, B cells and NK cells. For decades it was not clear whether these peptides (FasL) played any role in maternal immune tolerance until recently when research revealed the expression of FasL by trophoblas cells, choriocarcinoma cells and placenta villi[ CITATION Bam97 l 1033 ]. Recent research concluded that FasL affords a local mechanism for gestational immune tolerance to the growing fetus. However the absolute necessity of FasL in providing maternal immune tolerance is yet to be demonstrated especially because mice with a mutation on FasL gene can reproduce[ CITATION Sco99 l 1033 ].

Research has demonstrated that Indoleamine 2, 3-dioxygenase (IDO), an enzyme that catabolyzes tryptophan, plays a crucial role in induction of immune tolerance during transplantation, infection, neoplasia and pregnancy. Expression of IDO has been demonstrated in various body tissues, including the placenta, induced by inflammatory cytokines such as IFN. IDO acts by suppressing T-cells response to antigens and two theories have been advanced to explain the mechanism involved. The tryptophan depletion theory postulates that IDO eliminates T-cells and inhibits their activation by starving them of tryptophan. Deprivation of tryptophan appears to reduce proliferation and increase apoptosis of the T-lymphocytes. The tryptophan utilization theory associates the catabolic products of tryptophan

such as oxygen radicals and kynurenine derivatives with the increased apoptosis and reduced proliferation of T-cells. An active form of IDO, which enhances proliferation of regulatory T-cells, has been recently identified[ CITATION Ant09 l 1033 ].

In addition to these placenta associated immune tolerance mechanisms there are other mechanisms that continue to be discovered. One such mechanism is the Eutherian fetoembroyonic defense system which has been postulates to induce tolerance during very early stages of pregnancy. This mechanism was first described as the human fetoembryonic defense system by Clark et al (1994). This system is postulated to comprise of soluble and surface bound glycoproteins that are found in the reproductive system and on gametes thus inhibit immune responses from harming the fetus. This system is inactivated as pregnancy progresses probably because the immunosuppressive effect of the glycoproteins is so effective that persistent leakage of the glycoprotein in into maternal circulation may compromise maternal immunity.

Therefore as pregnancy progresses other more targeted immunosuppressive mechanisms are activated. The glycoproteins associated with this system in humans include α-fetoproteins, glycodelin-A (placenta protein 14-pp14). Clark (2008) proposed that the failure of this system could be responsible for the loss of pregnancy that occurs even before the mother or the doctor detects. Some studies focusing on NK-cells indicate that uterine NK-cells, a specialized subset of the NK-cells, may play a role in gestational immune

tolerance but neither their specific role nor their origin have been identified[ CITATION Hak07 l 1033 ].

Finally systemically maternal immune tolerance is mainly mediated by immunoactive hormones such as progesterone and the human gonadotropin hormone (Hcg). The hormones appear to play a communication role between the conceptus and the maternal immune system. There is increasing evidence that the Th1-cytokines have a negative effect on mammalian pregnancy while Th2-cyokines have positive effect and that the Th1/Th2 ratio which decreases with advancing pregnancy is vital in the maternal immune tolerance. An immunomodulatory protein called progesterone-induced blocking factor (PIBF) appears to play a role in the shift of Th1 to Th2 cytokines as well as the suppression of the activity of NK cells during pregnancy. PIBF is produced by a subset of T-cells after interaction of progesterone with receptors on these cells. Hcg enhances maternal immune tolerance in several ways. Hcg increases proliferation of uterine NK cells and attracts regulatory T cells at the placenta. It also increases apoptosis of cytotoxic T-cells, decreases Th1/Th2 ratio and acts on C3 and CA/B (complements)[ CITATION Mar10 l 1033 ]. The study by Tsampalas et al. concluded that Hcg is the major mediator through which the embryo communicates its presence to the mothers system. This conclusion was based on the involvement of this hormone in almost all the mechanisms mediating maternal immune tolerance.

Failure of the gestational immune tolerance or insufficient tolerance has been associated with spontaneous abortion, infertility and diseases such as

Rh-disease and pre-eclampsia. Conversely the modification of the immune system during pregnancy has been known to contribute to maternal susceptibility to infection and severity of infectious disease.

In conclusion the immune system eliminates invading pathogen in an intricate and coordinated set of interaction involving many classes of proteins, molecules and cells that shows a high level of specificity. The immune system is potentially destructive to the organism’s cells but has specific mechanisms by which it identifies and tolerates “ self” while. The said mechanisms, immune tolerance, are vital in sustaining pregnancy by tolerating the fetus which is genetically foreign to the mother. Failure or insufficiency of the so called gestational immune response may lead to spontaneous abortion, infertility, pre-eclampsia and Rh-disease. Gestational modification of the immune system may predispose the mother to infection.

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