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A Review of the Immunological Mechanisms That Promote Materno-Foetal Tolerance.

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Abstract : *The foetus is a semi- allograft. Why it is not rejected by the maternal immune system has been the focus of research for years. The earlier beliefs were that the foetus is not antigenically mature, there is a physical barrier between maternal and foetal tissues, and that the mother's immune system is inactive. These have however been proved wrong. This review discusses the placental and maternal factors which have been reported so far to promote tolerance. Some of the factors expressed by the placenta which promote maternal-foetal tolerance include the pattern of MHC expression (non-classical HLA-E, HLA-F and HLA-G); this induces tolerance in the maternal leukocytes. The B7 family molecules modulate the immune system. IDO suppresses T-cell levels and activity via tryptophan catabolism. Progesterone and human placenta growth hormone, LIF, Annexin II, HO-1, CD95/CD95R, CEACAMS and TRAIL are other factors expressed by the placenta that promote maternal tolerance of the foetus. From the maternal side, there is an increase in the number of T-regs which are immunosuppressive, the uterine NK cells are non-toxic and the dendritic cells are immature. The immune response is tilted towards the anti-inflammatory Th-2, and the anti-inflammatory cytokine TGF-β is increased in pregnancy.*

Keywords: *Foetus, Tolerance, Rejection, Maternal, Immune system, Pregnancy.*

I. Introduction

The foetus inherits half of its genes from the father and the other half from the mother. The genes from the father are foreign to the mother, and it is expected immunologically, that the mother's immune system should react to the foreign antigens by rejecting the foetus. This is however not the case as the mother seem to tolerate the foetus till term. How the mother is able to carry the foetus without rejecting it has been the focus of lots of research. However, Medawar in 1953 was the first to propose mechanisms by which a mother tolerates the foetal allograft without rejection. Medawar had proposed that the foetus is not mature antigenically. Secondly, that there is a physical barrier between maternal tissues and foetal tissues and thirdly, that the mother's immune system is inactive [1].

Works done after him had proved his hypothesis wrong. There is a physical contact between maternal tissues and the trophoblast, and the maternal immune system is actually active and can mount an immune reaction against the foetus. The point about the foetal tissue being immature antigenically however, may not be completely wrong based on recent findings. Several mechanisms have been put forward as reasons why the maternal immune system is tolerant of the foetal allograft, most of them are overlapping and a number of them are still controversial.

II. Tissue Graft Rejection

The immune system of a recipient mounts a response against alloantigen on a tissue transplant. This involves both cell mediated and humoral immune responses. There are two stages; the afferent and the effector stages. In the afferent stage, T- cells are activated or sensitized by two signals. The first is activation when self-antigen presenting cells (APCs) present these antigens via self- major histocompatibility (MHC) molecules to T-cells. T-cells can also be directly sensitized by the allo-APCs and allo-MHC molecules on the surface of the transplanted tissue[2].There is also a co-stimulatory signal involving interactions between CD28 on the T-cells with the surface ligands such as the B7-1(CD80) and B7-2(CD86) on APCs. There is however, an inhibitory signal if the co-stimulatory ligands bind with cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) [3]. The stimulatory signals activates the T-cells resulting in the effector stage with proliferation and differentiation into T-helper (Th) cells and cytotoxic T-cells, cytokine secretion, especially IL-2 and IFN-γ. These would cause cytolysis and apoptosis of the graft, either directly via cytotoxic granules such as granzymes or via the Fas ligand, with a resultant destruction of the allograft [4].Natural killer (NK) cells are also activated without the MHC molecule (missing self-hypothesis), to cause apoptosis by the release of cytokines, direct toxicity, FasL and TNF-related apoptosis inducing ligand (TRAIL) [5]. The humoral response can be of two types; preformed antibodies which are mostly of IgM type can directly attack a graft in the hyper acute rejection or B-cells stimulated by activated T cells would produce antibodies mostly of the IgG type in the acute rejection. In both

scenarios, these antibodies also activate the complement pathway which will result in cytolysis and destruction of the graft [6].These mechanisms for transplant rejection has been compared to the foetal allograft [7].

III. Immunobiology of Pregnancy.

During implantation, the trophoblast which is the outer wall of the blastocyst differentiates into the syncytiotrophoblast and the cytotrophoblast. The syncytiotrophoblast erodes the maternal tissues and comes in direct contact with the maternal tissues. Subsequently, cells of the cytotrophoblast form the extra villous trophoblast by penetrating through the syncytiotrophoblast to the maternal endometrium, eroding its glands and blood vessels. The extra villous trophoblast is thus in direct contact with the uterine tissues. The trophoblast cells and the uterus are central in the tolerance of the maternal immune system to the foetus, from pre-implantation and throughout the gestational period.

The uterus is usually prepared for implantation by hormones such as progesterone. These hormones regulate APCs and lymphocytes, influencing their activity and consequently the immune response which they would mount in pregnancy [8, 9]. The decidual macrophages secrete cytokines which regulates T cell and NK cell growth [10]. The trophoblast also secretes cytokines and other mediators which also influence the maternal immune responses. The place of the uterus and placenta (trophoblast), the molecules and mediators they secrete and express which help to modulate the maternal immune responses were reviewed by Hunt et al [11].

IV. Why The Foetus Is Not Rejected By The Maternal Immune System.

Several mechanisms have been proposed and hypothesized for the maternal tolerance to the foetus. Quite a number of them have been confirmed by several other workers but a few are still controversial as other workers may have found conflicting results. Basically these mechanisms seem to overlap and affect the cell-mediated immunity, humoral immunity and complement pathway. The basic mechanisms are down regulation of T cells and APCs, apoptosis of activated T cells and inhibition of complement activation. The trophoblast and uterine cells express a variety of molecules and receptors that cause this immune-modulation. These molecules do this by various mechanisms and would be discussed first; the other ways by which the foetus is protected against the maternal immune attack will be discussed after that.

4.1 MHC Expression

The foetal cells do not express MHC -II or the classical MHC-I molecules except HLA-C. Rather the syncytiotrophoblast which is in direct contact with the maternal tissues expresses the non-classical type 1 molecule- the HLA-E, HLA-F and HLA-G [11]. These antigens cause tolerance in the maternal leukocytes. The HLA-G genes are not as polymorphic as the classical MHC molecules, they have alternative splicing which makes them to produce two forms; membrane and soluble. Their main function is inhibition of maternal immune cells and dampening of their activating signals, not necessarily antigen presentation. They bind to inhibitory receptors of NK cells, decidual leukocytes, and T and B cells. These receptors include Ig-like transcript receptors (ILTR) for T, B and NK cells [12], and killer inhibitory receptor (KIR) of NK cells [13]. They suppress mononuclear cells by the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β [14]. They have been shown to inhibit the cytotoxic effect of CD8 T-cells which may be due to apoptosis of these CD8 T-cells that react against paternal antigens [15].

HLA-C is expressed by trophoblast cells but weakly, it may stimulate the maternal immune system against paternal allo- antigens but this usually is very mild and does not cause any problems for the foetus [16]. This pattern of MHC expression and the inhibitory receptors have also been reviewed [17].

4.2 B7 Family Molecules

These are trans-membrane proteins that modulate the immune system. They are secreted by the placenta. They include B7-1, B7-2, B7-H1, B7-DC, and ICOS.They belong to the immunoglobulin super family and have been found to be abundant in the placenta, increasing as the pregnancy advances [18]. They act as co-stimulators for T cell activation when they bind CD28 but causes inhibition when they bind CTLA-4 therefore inhibiting activation and proliferation of T cells [19], with subsequent apoptosis of the T cells [20]. They thus promote maternal tolerance of the foetus by negatively regulating T cells and other immune cells, and their production of cytokines [19].

Indoleamine 2, 3 - Dioxygenase (IDO)

IDO is an enzyme that is expressed by trophoblasts and EVT, It catabolises the amino acid, tryptophan. T cells are extremely sensitive to tryptophan levels, and reduced levels of tryptophan will normally suppress T cells and their activities [21, 22]. In humans, it's been discovered that tryptophan levels reduces as pregnancy advances [23]. Pregnant mice treated with IDO inhibitors or high tryptophan diet lost their foetuses with inflammation and complement activation found in the placentas [24]. However, pregnant mice that are deficient

for IDO still went on to have normal pregnancies [25]. IDO has also been found to inhibit complement activation via tryptophan catabolism [26].

Leukaemia Inhibitory Factors (LIF)

The LIF is a molecule secreted by maternal endometrium [27] and decidua [28]. Its receptors are expressed on the blastocyst [27] and syncytiotrophoblast, as well as Th2 cells [28]. It has been implicated as a requirement for successful implantation of the blastocyst, and in maternal tolerance of the foetus [27]. It is also said to affect the Th1-Th2 balance (discussed later), and has been shown to promote foetal losses when reduced in pregnancy [29].

Annexin II

Annexin II is a membrane glycoprotein molecule secreted by the placenta which has been shown to promote foetal tolerance by inhibition of the secretion of maternal antibodies, especially IgG and IgM [30, 31].

4.6 CD95 and its Ligand (Fas and FasL)

CD95 and CD95L also known as Fas and FasL belong to the TNF and TNF receptor family and is an apoptotic pathway used in various cellular processes in the immune system and other systems. Binding of CD95 to its ligand CD95L sends apoptotic signals. Activated immune cells bear CD95 while the EVT and syncytiotrophoblast express CD95L [32]. Thus the activated immune cells of the mother are disposed of by apoptosis sparing the foetus which is the target. It was shown experimentally that those mice that do not express FasL had lot of leukocytes in their decidua and this affected the outcome of the pregnancies negatively [33]. The expression and activity of Fas and FasL is a kind of immune privilege in the placenta.

CD 200 and CD200R

CD200 and the receptor CD200R function like the B7 family of co-stimulators. It is expressed by activated immune cells of the mother. Binding of the CD200 to its receptor CD200R inhibits these immune cells, and promotes tolerance of the foetus [34-36]. CD200 and CD200R binding also promotes maternal-foetal tolerance by up-regulating IDO secretion [37], increasing the production of T regulatory cells and favouring of the Th 2 cytokines production [34, 35]. Experimentally, reduced CD200R is associated with foetal wastages [38].

Complement Regulatory Proteins.

Complement pathways activation is very crucial in allograft rejection, and the foetal allograft is not exempt from this. However, the cytotrophoblast expresses molecules which help to prevent this in pregnancy. These are the decay accelerating factor (DAF), the membrane co-factor protein (MCP) and CD59 [38]. While DAF increases the rate of clearance of complement components, MCP inhibits complement activation by down-regulating the activation of C3 and C4 components [38]. CD59 inhibits the effects of complement activation by blocking the assembly of membrane attack complex [39]. In mice, the complement receptor-1 related gene/protein-y (Crry) carries out the function of inhibiting complement as the other factors are absent in mice [40].

Hormones

Pregnancy hormones such as progesterone and human placental growth hormone are secreted by the placenta. They take part in maternal-foetal tolerance by inhibiting the maternal immune responses. Progesterone is able to blunt maternal immune responses by enhancing the production of LIF (discussed above) and tilting the Th1/Th2 balance towards Th 2[41, 42]. Prostaglandins also play a role in promoting tolerance by stimulating the production of anti-inflammatory cytokines, IL-10 and TGF-β which also help with the enhancement of Th2 responses [10].

Carcinoembryonic Antigen-Related Cell Adhesion Molecules (CEACAMS)

CEACAMS are adhesion molecules of the foetal antigen- carcinoembryonic antigen(CEA).CEACAM-1 is expressed on EVT cells, and can bind to themselves or to CEA. Uterine lymphocytes were shown to express CEACAM-1 when cultured with IL-2 in vitro [43]. When the CEACAM on activated immune cells such as T and NK cells bind to that on target sites such as the EVT cells, it inhibits the growth and differentiation, as well as the effector functions of these cells [43]. Thus suppressing the immune responses and protecting the foetus.

TNF-Related Apoptosis Inducing Ligand (TRAIL)

TRAIL is a protein of the TNF family that is involved in apoptosis just like Fas. It's been shown to be expressed by cytotrophoblasts, EVT cells, and syncytiotrophoblast[44]. Its role is majorly in the apoptosis of

uterine tissues to allow for implantation, but it is also being postulated that it could be involved in maternal-foetal tolerance by the inhibition of IL-2 mediated T lymphocyte proliferation [45].

Heme Oxygenase 1 (HO-1)

This is an enzyme that catalyses heme. Heme can be toxic to foetal tissues, and HO-1 is expressed on trophoblast cells. A reduction in HO-1 has been associated with poor pregnancy outcome, and H0-1 is said to help in the protection of the foetus by stimulating anti-inflammatory cytokine production and enhancing regulatory T cells [46, 47]. The mechanisms discussed so far are illustrated in fig. 1.

TH1:TH2 balance and anti-inflammatory cytokines.

When T cells are activated, they can differentiate into Th1 subset or Th2 subset of cells. Th1 cells favour inflammatory responses with the production of pro-inflammatory cytokines such as IL-2, IL-6, IFN-γ, and TNF-α. If this occurs in pregnancy, it can be deleterious to the foetus, causing a rejection. Th2 cells are associated with cytokines which are anti-inflammatory: IL-4, IL-5, IL-10, IL-13, etc, with IL-10 and IL- 4[49] being the most important. These cytokines favour pregnancy and prevent foetal rejection. A tilt of the Th1: Th2 balance towards Th2 is said to play a role in protecting the foetus and preventing rejection of the foetus[9,29,49]. The regulation of this balance towards Th2 response is made possible by some of the molecules already discussed above. Th1 responses have been found to be increased in decidua of women with miscarriages [50]; however it was shown in mice that lack the Th2 cytokines, pregnancies were still successful. This has been explained to mean that Th2 cytokines may not be so essential for pregnancy and that the finding of increased Th1 cytokines may be secondary [51].

Another important cytokine in pregnancy is the TGF-β secreted by Th3 cells; it also has a suppressive role on the maternal immune responses [52]. However, IL-6 which is a Th1 cytokine plays a dual role; on one hand, it helps in the development of the trophoblast but it also has negative effects by down regulating maternal asymmetric antibodies[53] (discussed later) and so putting the foetus at risk of rejection.

The Role of Regulatory T Cells (Tregs)

This subset of T cells help to regulate the activities of other T cells and plays a role in the prevention of autoimmunity. Treg cells (CD4+CD25+) have been found to be increased in pregnancy alongside its transcriptional factor FOXP3, this is partly contributed by hormones such progesterone and prostanglandin[54,55]. They express a number of factors which have suppressive effects on the maternal immune cells; these are GITR, CTLA-4, TGF-β, and IL-10[54]. It can also cause tryptophan degradation by up-regulating IDO, and also increases the expression of LIF [56]. The combined effects of these are the inhibition of the activation, proliferation and effector functions of other T cells which would have attacked the foetus.

The Role of Uterine NK Cells, Macrophges and Dendritic Cells

NK cells in the innate immune system attack and remove its target by cytotoxicity. However, the uterine NK cells which are increased in pregnancy are said to be non- cytotoxic. They are also different from the peripheral forms (which are CD56 lo) by being CD56 hi [57]. These uterine NK cells help to protect the foetus instead of attacking the paternal alloantigen in the foetus. They do this by expressing receptors for HLA-E, HLA-G and HLA-C. These receptors can be inhibitory (KIRs, LILRs) and when bound by HLA-C inhibits NK cell activating signals [12, 13].

Uterine Dendritic cells in pregnancy are usually the immature forms and tend to be tolerogenic. Like the uterine NK cells and dendritic cells, the uterine or decidual macrophages also play an immunosuppressive role in pregnancy. It is said to secrete anti-inflammatory cytokines such as IL-10 and TGF-β. It also secretes a lymphocyte inhibitory molecule known as PGE2 and B7-H1 [57, 58]

Fetal Micro-Chimerism

Microchimerism is the transmission of foetal haemopoietic cells into the maternal circulation: inherited paternal antigens (IPA).It can also occur the other way round when maternal cells are transmitted to the foetus: non-inherited maternal HLA antigens (NIMA). Apart from the fact that the cells have been found to persist in the circulation of either the mother or child several years later, it is found to induce a form of tolerance in the immune system and has been postulated to be one of the ways by which the mother is tolerant of the foetus. This mechanism was first found to be helpful in solid organ and later Stem cell transplantation, when mothers and children who had NIMA or IPA did better. It was discovered that T cells from these people show little or no response to their antigens. However, this mechanism in maternal-foetal tolerance is still controversial [59].

Assymetric Antibodies

These antibodies are asymmetrically glycosylated. They bind paternal antigens from the foetus but because of their asymmetry do not activate complement or elicit an immune response. Their binding to these paternal antigens blocks the antigens from being bound by other antibodies which can elicit an immune response. This way the foetus is protected from the humoral- mediated immune rejection [60].

V. Figures And Tables

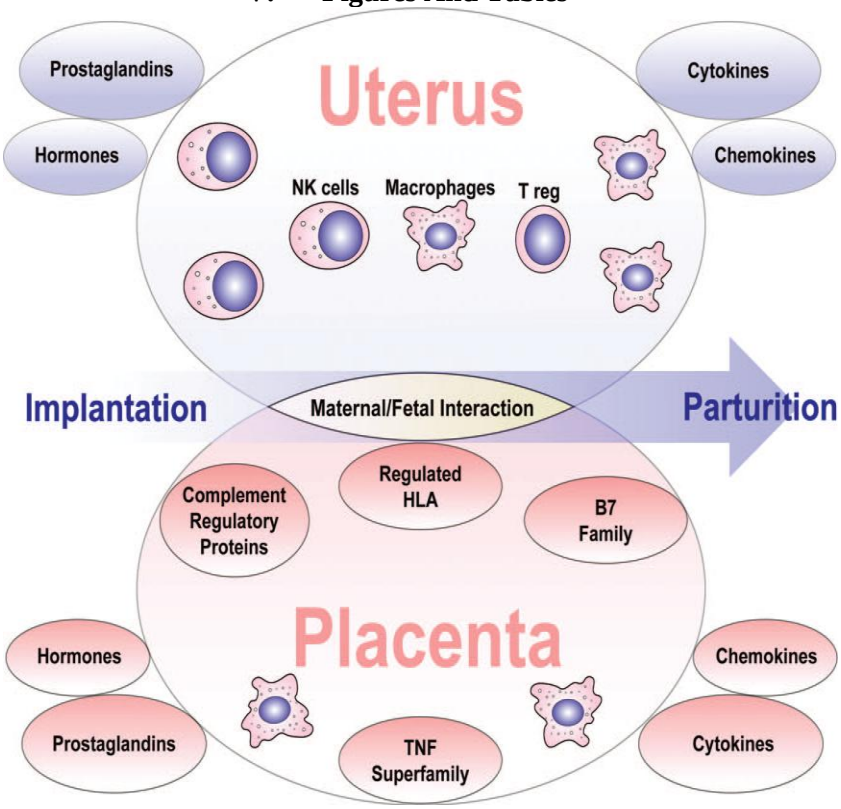

Figure 1: Maternal and foetal interactions in achieving tolerance. Uterus and placenta contribute to maternal tolerance of the foetus by expressing and secreting different molecules, receptors and hormones. TNF-tumour necrosis factor, Treg- CD4 regulatory T cells, NK cells- natural killer T cells, HLA- human leukocyte antigen. © Hunt, JS et al; 2005 (Ref. 11)

VI. Conclusion

Though the foetus is a semi-allograft, it does not suffer immunological rejection because of the mechanisms described above. The function of protection of the foetus is not left to one particular process alone. It is reported that almost a third of pregnancies are lost, and quite a number of them may be due to immune dysregulation. The maternal immune system can actually react against the foetus, and examples of these are maternal antibodies against the red blood cells and platelets of foetuses with different antigens in haemolytic disease of the newborn and neonatal immune thrombocytopenia. A lot of other findings experimentally has gone on to show that dysregulation in the mechanisms described above could result in spontaneous abortions and other disorders of pregnancy such as pre-eclampsia toxaemia (PET).

Though some of these mechanisms are still controversial, work is still on-going to elucidate fully how these mechanisms work, and probably newer mechanisms in the future may be discovered.

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