

Fetus as an Allograft: A Review

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Abstract

Allograft is a tissue or organ obtained from one member of a species and grafted to a genetically dissimilar member of the same species. Pregnant mother nourishing within itself a fetus acts as an antigenically foreign body. The foreign nature of conceptus, caused by inheritance of genes from its father that encode for proteins foreign to its mother, poses a unique problem for species that are viviparous in which mothers immune system can potentially destroy the conceptus. It requires modulation of the maternal immune system which limits fetal allograft rejection without compromising the ability of the mother to fend off infection. While as tissue (other than fetus) grafted inside uterus is instantaneously rejected by mother/dam. Host T cells responds to peptide epitopes of MHC molecules of grafted cells.

Keywords: Fetus, allograft, Immune cells

Modulation of the maternal immune system plays a vital role in maintenance of fetus within dam. It limits fetal allograft rejection without compromising the ability of the mother to fend off infection^[1]. Initial most sign of rejection is neutrophil accumulation around blood vessels at the base of graft, followed by an infiltration of mononuclear cells. Signs of tissue damage are observed in capillaries of graft. Endothelium is destroyed, resulting in formation of blood clots which results in Blood flow stoppage & tissue death follows. There are three mechanisms by which fetus evades maternal immune rejection^[2]. Firstly, the maternal immune system might not be capable of responding to fetal antigens due to mechanisms that induce anergy or tolerance in responding maternal cells. Secondly, an anatomical barrier might form between mother and fetus preventing access of maternal immune cells to fetal antigens. Thirdly, fetal cells might suppress the expression of alloantigens.

Fetus also generates site-specific immune suppression^[1]. Various types of cells plays a vital role in this mechanism (lymphocytes, monocytes, complement, cytokines).

Several theories were given from time to time in order to explain the fetal allograft tolerance by the dam. It is postulated that placenta & maternal tissue produce molecules that prevent development of antibodies against conceptus (immunosuppression theory). Another theory depicts that antibodies do not fix complement thus mask fetal antigens. MHC antigens are not expressed on regions of trophoblast in contact with the mother to prevent activation of maternal anti fetal MHC lymphocytes. While some researchers found that number of maternal T cell against fetal MHC proteins decreases during pregnancy which leads to temporary tolerance. Trophoblasts and endometrium express Fas ligands which induce apoptosis of activated T cells. Antibody mediated response is favoured

during pregnancy instead of cell mediated immunity because of preferential activation of helper T cells (TH2) over helper T cells (TH1). Lymphocytes secrete cytokines & growth factors that control growth and development of trophoblasts.

There are various types of phagocytic cells that modulate the maternal immune system during foreign tissue invasion. Important ones are Neutrophils, Macrophages, APC (antigen presenting cells), Dendritic cells, NK cells (natural killer cells) etc. Besides these, B lymphocytes helps in production of antibodies & T lymphocytes ($\alpha\beta$ T cells, $\gamma\delta$ T cells) helps in production of cytokines that play a role in the alteration of maternal immune system.

Fetal cells might evade detection and thus destruction by the maternal immune system by downregulating the expression of fetal alloantigens. The only trophoblast cells in humans to express classical MHC class I molecules are the interstitial trophoblast cells that are in contact with the maternal decidua^[3,4]. Trophoblast cells in contact with the maternal circulation do not express either MHC class I or MHC class II molecules^[4]. While the lack of expression of classical MHC molecules might help to explain the survival of the fetus,

The Fas/FasL (Fas Ligand) pathway is also thought to be important for the control of maternal immune responses at the fetal-maternal interface. The expression of FasL mRNA can be detected at the fetal-maternal interface as early as 6 days post-conception in mice and as early as 12 days post-conception in humans. CD3+ T cells produced in response to allogenic fetus undergo apoptosis due to the expression of FasL^[5].

Tryptophan catabolism is thought to prevent maternal immune responses to the fetus. Depletion of tryptophan by macrophages inhibits T cell proliferation by arresting the cells in the mid-G1 phase of the cell cycle^[6]. Indoleamine 2,3-dioxygenase protects the fetus from the maternal immune response by metabolizing

tryptophan. Catabolites of tryptophan, including kynurenine, 3-hydroxykynurenine and 3-hydroxyanthranilic acid, also prevent the activation and proliferation of T cells and B cells^[7].

The cytokine environment surrounding the fetus is essential to successful pregnancy. Pregnancy is associated with the Th2 deviation. A Th2-type response promotes successful fetal outcome while a Th1-type response induces abortion^[8].

In equine there is decreased expression of MHC class I up to attachment, except at regions next to endometrial glands^[9]. Expression stimulates lymphocyte response to that site leading to regression of endometrial cups from day 75 – 150 & is accompanied by decrease in maternal concentration of eCG. The cytotoxic antibodies are not harmful to the pregnancy because their target, MHC molecules, are withdrawn from the endometrial cup tissue by the time the antibodies start appearing in the circulation. The development of immune responses towards endometrial cups may be limited somewhat by maternal leucocytes that secrete the immunosuppressive molecule “transforming growth factor- β 2”^[10].

Progesterone, is known as hormone of pregnancy. It stimulates expression of large no. of Immuno modulatory factors like Progesterone Induced Blocking Factor, INF τ , Galectin-15 (LGALS15), Uterine Serpins, Osteopontin (OPN, SSP1). All these favour establishment of pregnancy by favouring implantation, blastocyst elongation, inhibiting NK cell activity (*in vitro*), inhibiting NK cell mediated abortion & decreasing Muc-1 protein activity. It is expressed in endometrial cells during implantation. OPN is up-regulated immensely to aid in the implantation. It helps in stromal cell proliferation and differentiation (binds to the receptor $\alpha v\beta 3$) to assist in adhesion. Along with decidualization, it encourages the successful implantation of the early embryo.

There is secretion of lymphocyte inhibitory molecules which non specifically inhibit local immune responses against conceptus antigens

without disturbing systemic immune functions. E.g, Endometrium epithelial & stromal cells produce Transforming Growth Factor- β (TGF- β) & Prostaglandin-E2 (PG-E2) respectively. There are serine proteases that are released by cytoplasmic granules within cytotoxic T cells & NK cells, called as Granzymes. These Cause immunosuppression by inducing apoptosis of T cells & NK cells.

CONCLUSION

Immunological recognition of pregnancy is important for maintenance gestation. A single mechanism does not operate for eluding of fetal rejection by dam. Progesterone dependent Immunomodulation plays a mediatory role in fetal allograft tolerance. Very low expression of fetal MHC class I proteins during early pregnancy is important for fetal allograft tolerance by mothers immune system. Shift in type of Th cells helps to reduce harmful effects to the fetus survival. Immunological recognition of fetal MHC class I around the time of parturition triggered inflammatory response contributes to the normal placental separation.

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