

## Immunology Lecture 4-8-05: Transplantation and Pregnancy

Definitions:

**Central tolerance:** A form of self-tolerance induced in generative lymphoid organs as a consequence of immature self-reactive lymphocytes recognizing self antigens leading to their death or inactivation.

**Peripheral tolerance:** Physiologic unresponsiveness to self antigens that are present in peripheral tissues and usually not in the generative lymphoid organs. Peripheral tolerance is induced by the recognition of the antigens without adequate levels of the costimulators that are required for lymphocyte activation or by persistent and repeated stimulation by these self antigens.

**Graft versus host disease:** A disease occurring in bone marrow transplant recipients that is caused by the reaction of mature T cells in the marrow graft against alloantigens on host cells.

**Mixed leukocyte chimerism:** The co-existence of leukocytes from genetically distinct individuals within one person. This happens after tissue transplant. This concept is especially relevant to bone marrow transplantation, but is also applicable to transplants of other tissues.

**Autoimmunity:** The response of the adaptive immune system to self antigens that occurs when mechanisms of self tolerance fail.

**Allergy:** A form of atopy or immediate hypersensitivity disease. These conditions are related to antigen induced mast cell or basophil activation.

There are four types of transplants:

1. skin grafts
2. blood transfusions
3. bone marrow transplants
4. organ transplants

There are four ways of classifying the “foreignness” of a transplant:

1. autologous (self-transplant)
2. syngeneic (individuals with identical DNA, ie., identical twins or inbred mice)
3. allogeneic (different individuals from the same species with non-identical DNA)
4. Xenogeneic (different species)

In order to minimize graft rejection, graft and host must be histocompatible. There are three histocompatibility categories:

1. ABO blood groups: glycosphingolipids expressed on red blood cells, endothelial cells, and many other cell types.
2. Major Histocompatibility Gene Products: MHC gene products; called HLA in humans.

3. Minor Histocompatibility Proteins: allelic forms of normal cellular proteins that happen to differ between donor and recipient.

#### Graft Rejection:

Graft rejection is T cell mediated. It can be caused by both minor and major histocompatibility antigens.

Rejection is classified into one of three types:

1. Hyperacute Rejection: This takes place within minutes of transplant and is mediated by antibodies and complement. It involves thrombosis of graft vessels and ischemic necrosis of the graft. Hyperacute rejection is no longer a common problem because of the use of crossmatching: testing for antibodies against cells of the donor.
2. Acute Rejection: This takes place within days to weeks of transplant and is mediated by T cells and antibodies. T cells may directly destroy graft cells or react against graft vessels. Current immunosuppressive therapy is designed to prevent or reduce acute T cell mediated rejection
3. Chronic Rejection: This may take place years after transplant and is mediated by macrophages and T cells. It involves the progressive loss of graft function and occurs through fibrosis of the graft or gradual narrowing of graft vessels.

Allogeneic MHC can be recognized either directly or indirectly:

1. Direct: T cell recognizes unprocessed allogeneic MHC molecule on graft antigen presenting cells.
2. Indirect: T cell recognizes processed peptide of allogeneic MHC molecule bound to self MHC molecule on host antigen presenting cell.

Modern immunosuppression has been very successful in reducing acute rejection of allogeneic grafts. A list of currently used drugs and their mechanisms follows: (This list is in the lecture handout with a couple of additions underlined)

1. Cyclosporine and FK506: Blocks T cell cytokine production by inhibiting activation of the NFAT transcription factor.
2. Mycophenolatemofetil: Blocks lymphocyte proliferation by inhibiting guanine nucleotide synthesis in lymphocytes.
3. Rapamycin: Blocks lymphocyte proliferation by inhibiting IL-2 signaling.
4. Corticosteroids: Reduce inflammation by inhibiting macrophage cytokine secretion. Corticosteroids also induce regulatory T cells.
5. Anti-CD3 monoclonal antibody: Depletes T cells by binding to CD3 and promoting phagocytosis or complement-mediated lysis (used to treat acute rejection).
6. Anti-IL-2 receptor antibody: Inhibits T cell proliferation by blocking IL-2 bonding. May also opsonize and help eliminate activated IL-2R-expressing T cells.
7. CTLA4-Ig: Inhibits T cell activation by blocking B7 costimulator binding to T cell CD28; used to induce tolerance (experimental) can induce tolerance of infectious particles.

8. Anti-CD40 ligand: Inhibits macrophage and endothelial activation by blocking T cell CD40 ligand binding to macrophage CD40 (experimental).

#### Graft Versus Host Disease:

- Transplant of bone marrow can prompt an immune response against the recipient
- If mature allogeneic T cells are transplanted with marrow cells, these mature T cells can attack the recipient's tissues.
- GVHD was more common in early bone marrow transplants before HLA matching improved to today's standards.

#### Graft Tolerance:

- The mechanism of graft tolerance is currently unknown.
- Some current ideas include regulatory T cells and balance of mixed leukocyte chimerism.

#### Mixed Leukocyte Chimerism:

- Chimerism can be demonstrated in all graft types (although it was previously thought that the concept applied only to bone marrow transplants).
- Leukocytes survive from both the donor and the recipient
- Grafts contain passenger hematopoietic stem cells.
- Mechanism of successful engraftment thought to involve "reciprocal clonal exhaustion, followed by peripheral clonal deletion" of lymphocytes.

#### Pregnancy:

- The fetus is an allograft that is not rejected.
- It carries MHC from the father and other foreign antigens, but is not rejected by the mother even when the mother bears multiple children to the same father.
- Some clues as to why can be seen in mice:
  - I. If pregnant mice have T cells specific for paternal alloantigen, they will have fewer of these specific T cells during pregnancy and will not reject a tumor bearing this alloantigen.
  - II. After pregnancy, they will once again reject a tumor bearing this alloantigen.
  - III. Fetus appears to be protected by physical barriers and local immunosuppression.

#### Physical Barriers: Trophoblast

- I. Trophoblast is of fetal origin
- II. Trophoblasts have reduced MHC I and a ligand for NK cell KIR's
- III. Trophoblast restricts free access of T cells and kills infiltrating T cells

#### Suppression of T cells:

- I. Trophoblasts make indoleamine 2,3-dioxygenase (IDO)
- II. IDO catabolizes tryptophan
- III. This reduction in tryptophan prevents proliferation and induces apoptosis of T cells
- IV. Blockade of IDO causes miscarriage of allogeneic fetuses but not syngeneic fetuses
- V. Trophoblasts have Fas-L, which induces apoptosis of T cells

VI. Trophoblasts secrete cytokines that prevent TH1 function and enhance regulatory T cell function.