TRANSPLANTATION IMMUNOLOGY.

Learning Objectives.

- Describe the genetic variation in transplantation
- Understand the immunological barriers that must be considered in transplantation.
- Understand the basis of rejection of transplants
- Describe donor tissues and privileged organs in transplantation.

Introduction.

- Transplantation is the introduction of biological material - organs, tissue, cells, fluids - into an organism.

- **We can distinguish 3 critical relationships between the transplanted material and the recipient.**

- **syngeneic** transplants - from genetically identical individuals, usually the **same individual** *(these are similar to grafts between identical twins or isogenic strains of experimental animals). Referred to as autologous in the ABO blood groups, skin grafts.*

- **allogeneic** transplants - from one individual to another of the **same species**
- **xenogeneic** transplants - between individuals of **different species**.

- Unsurprisingly syngeneic transplants (same individuals) do not usually generate any immunological problems, but **allogeneic** and **xenogeneic** transplants are almost always destroyed by immunological processes unless some action is taken to impair the immunological process.

- Basically therefore transplantation presents 2 key problems.

➢ Genetic variation between donor and recipient.

➢ Immunological recognition of the variation.

1. Genetic variation between donor and recipient.

- Genetic variation between individuals that results in protein sequence differences is at the heart of the transplant problem.
- In an essentially out-bred species like *Homo sapiens* the extent of this allelic polymorphism is considerable.
- Obviously the variation is even greater between individuals from different species.

2. Immunological recognition of the variation.

- Genetic differences between donor and recipient are only of significance in transplantation if they cause incompatibility.
- Almost ubiquitous in allogeneic transplants is immunological rejection.
- Early experimental work on allotransplantation in mice identified a very clear distinction between one chromosomal region and the remainder of the genome.

- Non-identity at this special region always led to **very rapid rejection of the transplanted** tissue, even if this was the only genetic difference between the donor and recipient.
- This region was therefore termed the **Major Histocompatibility Complex (MHC)**.
- MHC, which exists in all vertebrates is highly polymorphic, so that in out-bred populations 2 individuals will almost certainly differ at this region unless they are monozygotic.

- However the parallel is NOT true, that is, even if identical at the MHC, transplants between individuals are likely to be rejected due to **minor histocompatibility loci**.
- The key distinction is that **individually** these minor H loci are less 'strong' and in particular the strength varies between allelic differences.

Recognition and rejection mechanisms.

- There are 3 basic types of 'recognition' which allows the host to know that the transplanted tissue is foreign.
- recognition by Antibody
- recognition of foreign MHC by T cells (**direct recognition**)
- recognition of minor H loci by T cells (**Indirect recognition**).

- As implied above these 3 recognitions may lead to very different time scales of destruction of the transplanted cells/tissue and trigger distinct effector mechanisms. We distinguish 3 types of rejection.

Types of rejection.

- Hyper-acute rejection
- Acute rejection
- Chronic rejection

1. Hyperacute rejection.

- Occurs very rapidly, resulting in necrosis of the transplanted tissue within minutes or a few hours of contact.
- It always results from the reactivity of the donor cells with **pre-existing** antibody.
- The most common situation in which this occurs is in ABO blood group incompatible transplants, therefore let us briefly review the ABO system.

Blood Groups.

- Blood groups arise from genetic variations within a species. Blood transfusion is the oldest form of transplantation and today we should be careful to distinguish what component of blood we are transplanting; **what we call blood groups are genetically variable (polymorphic) structures present on red blood cells**.
- It is important to note that some of these structures are only present on red blood cells and thus incompatibility at these loci only affects the transplantation of RBC (blood transfusion), whereas others are present on many tissue cells and therefore affect other types of transplantation.

Non-ABO antibodies can also cause hyperacute rejection.

- These could be from previous transplants (transfusions)
- Particular problems in xenotransplants
  - humans lack Gal alpha 13 Gal structures **and** make natural antibody to this (**both IgG and IgM**).
  - many species express this structure in abundance on their cell surfaces (e.g Pigs).
  - Transplants from one species to another where there is natural antibody are termed **discordant.**

2. Acute Graft Rejection

- This is the main immunological barrier to allotransplantation (same species, **BUT** different individuals).
- It is caused by **T cell recognition of the transplanted tissue**.
- It is not a significant problem in red cell transfusion

a. because the cells survive only short periods

b. human rbc do not express MHC antigens.

- There are 2 quite distinct modes of recognition

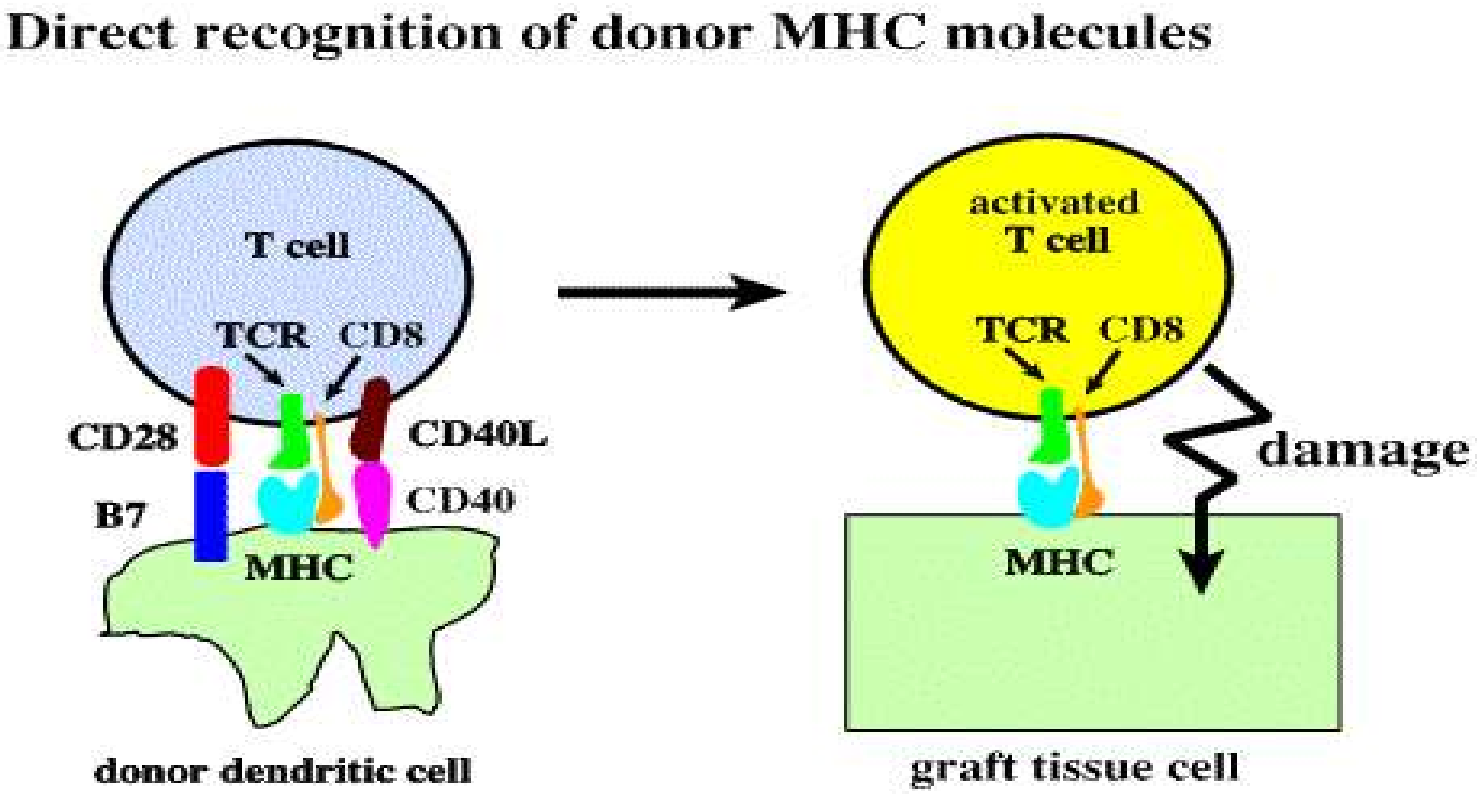
A. Direct recognition of allo MHC.

As referred to earlier, experimental transplantation showed that a single major gene cluster, the MHC, had a dominant role in histocompatibility.

In the context of transplantation the key attributes of the MHC are

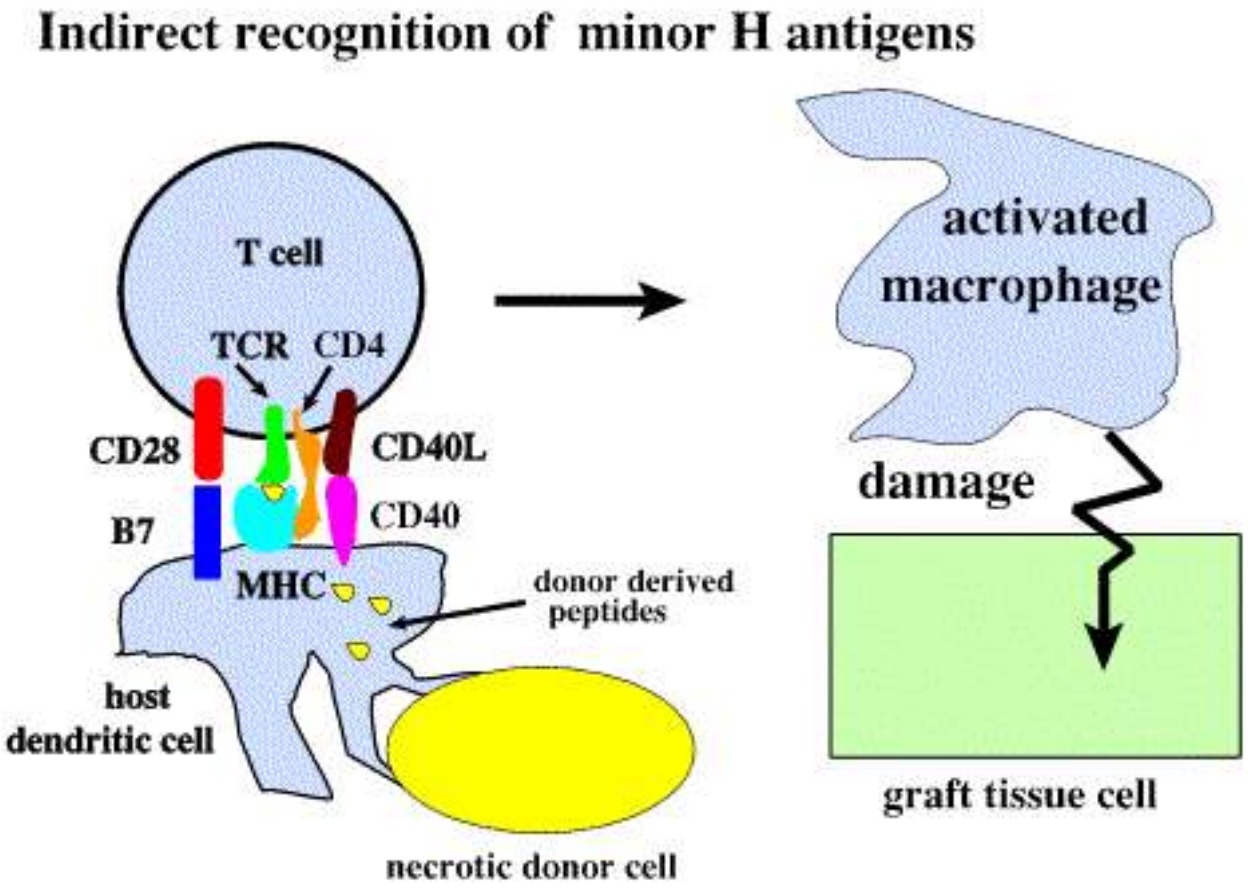
- rapid rejection of MHC non-identical transplants
- reproducible, consistent rejection rates.

modes of recognition: **Direct recognition of allo MHC**



- **Why do the products of the MHC cause such reproducible and rapid graft rejection?**
  The basic answer to this question is that naive individuals have high-frequency of T cells reactive with alloMHC products. More complex is to explain why this high frequency exists.
- It is undoubtedly the result of T cell receptors being MHC binding.

B. Indirect recognition of minor transplantation antigens.



MHC identical grafts are still rejected acutely by T cell dependent mechanisms.

- Minor transplantation antigens are proteins which vary in sequence and where one (at least) of the allomorphs is found in a peptide which binds to the MHC of the recipient.
- In the case of indirect recognition, MHC sharing between donor and recipient increases the reactivity as donor dendritic cells can prime recipient T cells for minor H peptides bound to shared MHC
- activated T cells can be triggered by donor tissue cells (usually class I expressing)

Properties of minor antigens

- rejection is slower than for MHC
- it is additive, however; thus many minor differences combine to give rapid rejection
- rejection times (in experimental grafts) are more variable and strength is allele specific.

3. Chronic rejection.

- In stark contrast to the considerable progress in the management of acute rejection (see Immunosuppression, below) essentially no improvement in treatment in past 25 years has made a significant impact on the long-term loss of transplanted organs through chronic rejection.
- Possibly in part this is because the mechanism(s) of chronic rejection are still obscure.

Particular transplant situations.

1. Privileged sites.

- Transplants at certain anatomical sites are generally accepted without any immune rejection. The most important of these is the **cornea**.
- The absence of lymphatic drainage is probably the critical common factor.
- (some sites also lack vascularisation).

2. Vascularised solid organs.

- kidney
- lung
- liver
- heart
- pancreas

3. Haemopoietic stem cell transplants

- Often previously called bone marrow transplants, now renamed as source is frequently blood.
- 3 sources of stem cells are used, listed in order of decreasing mature T cell contamination
  - peripheral blood (enriched by cytokine administration)
  - bone marrow
  - cord blood