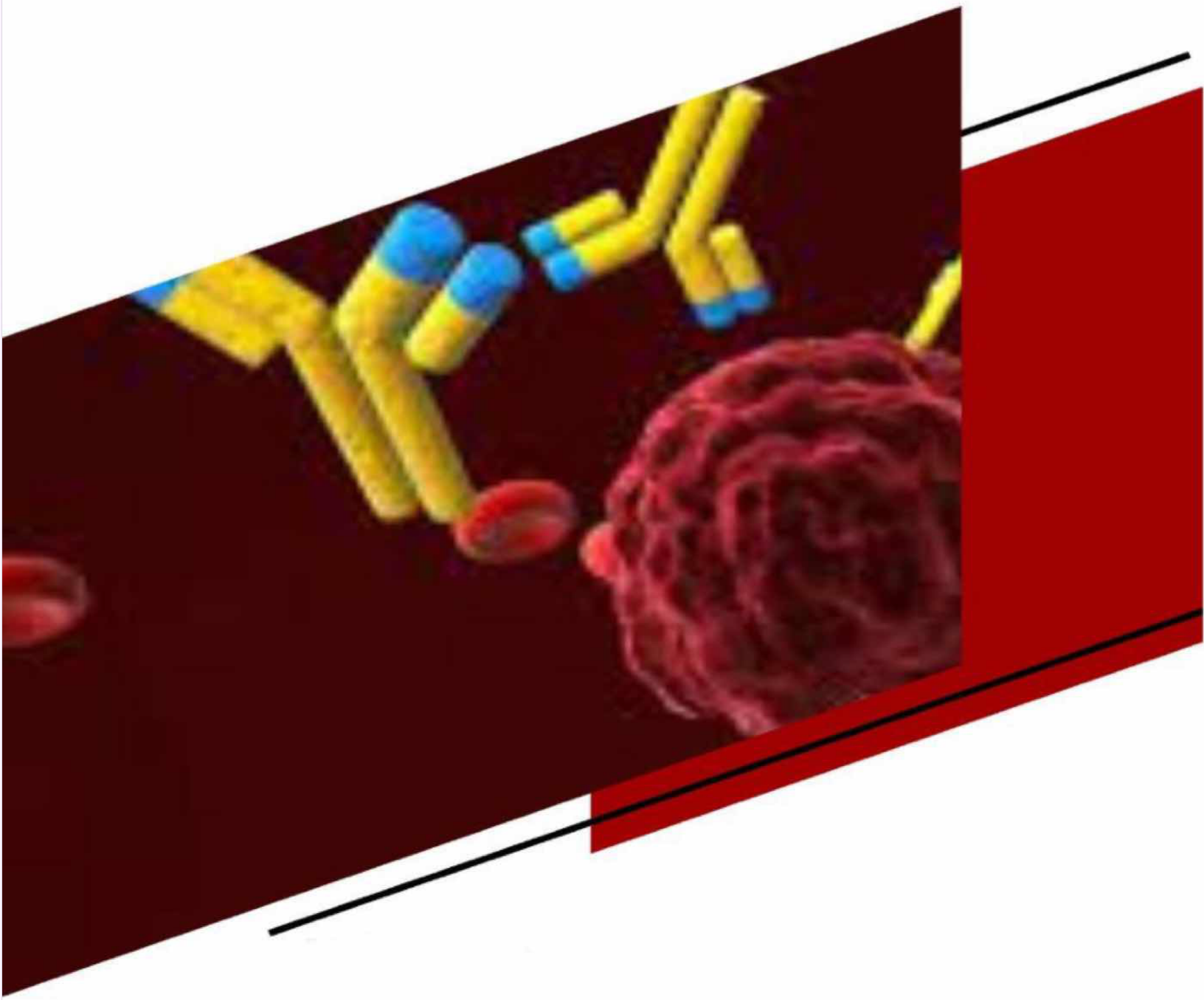
Doctor 021

IMMUNOLOGY

Sheet no.19



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•In this lecture we will discuss MHC molecules and transplantation immunology.

Major histocompatibility complex (MHC)

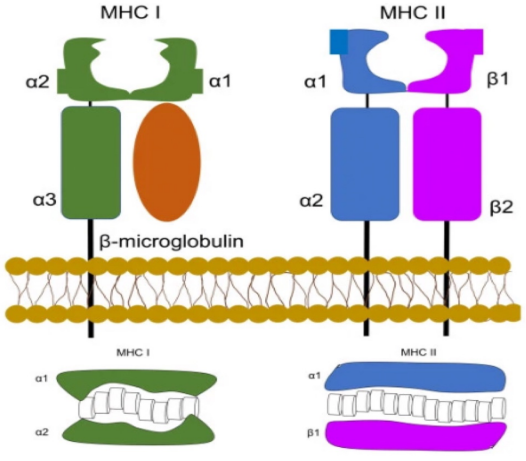
Discovery

• First it was found that individuals who had received multiple blood transfusions and patients who had received kidney transplants contained antibodies that recognized cells from the donors. and multiparous women had circulating antibodies that recognized paternal cells.Those antibodies were bound to antigens called **human leukocyte antigens (HLA)** (leukocyte because the antibodies were tested by binding to the leukocytes of other individuals). Thinking that they only exist on the surface of leukocytes. They were addressed to leukocytes due to the experiment that led to their discovery. The antigens where then renamed as **MHC** (Major Histocompatibilty Complexes). Both terms (MHC) and (HLA) are used interchangeably.

• Then, mice injected with a pathogen were found to have a variable response, better responder strains, which can mount immune responses to a particular polypeptide antigen, inherit MHC genes whose products can bind peptides derived from these antigens, forming peptide- MHC complexes that can be recognized by helper T cells.

-The MHC molecules are glycoproteins encoded in the large cluster of genes known as the major histocompatibility complex (MHC). Their most striking structural feature is a cleft running across their outermost surface, in which a variety of peptides can be bound forming **peptide-MHC complexes** that can be recognized by helper & cytotoxic T cells.

-Each class I or class II MHC molecule has a single peptide-binding cleft that binds one peptide at a time, but each MHC molecule can bind many different peptides.



The Classical MHC molecules
MHC Class I and Class II present peptides to immune cells as part of routine immune surveillance.
LEFT: MHC Class I is comprised of three alpha subunits and beta macroglobulin. The binding groove (lower left) of Class 1 is deep, with closed ends and binds peptides of 8-10 amino acids in length.
RIGHT: MHC Class II is a heterodimer of a 2-unit alpha chain and a 2-unit beta chain. The binding groove of class II is shallow and open at each end, allowing binding of peptides 13-17 amino acids in length.

-MHC molecules show great genetic variation in the population, and each individual carries up to 12 of the possible variants which increases the range of pathogen-derived peptides that can be bound. (Molecular sequencing has shown that a single serologically defined HLA allele may actually consist of multiple variants that differ slightly). Different alleles will have the same general constitution of units as a protein, but they'll differ in the cleft shape, which affects the way in which antigen peptides would bind to it, producing different **complexes** recognized differently by the T lymphocytes.

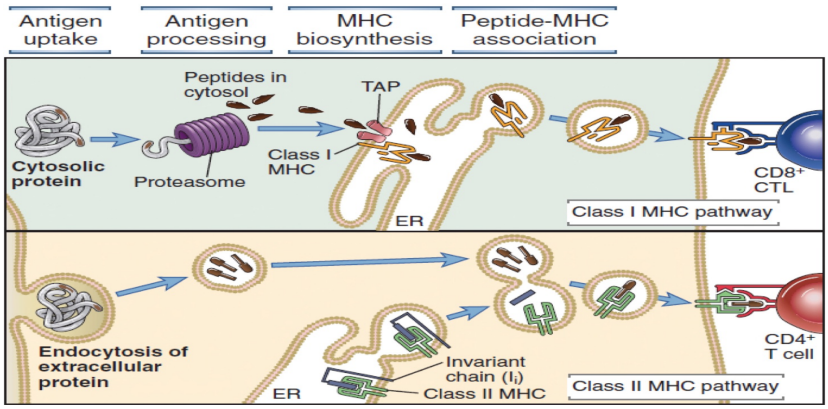


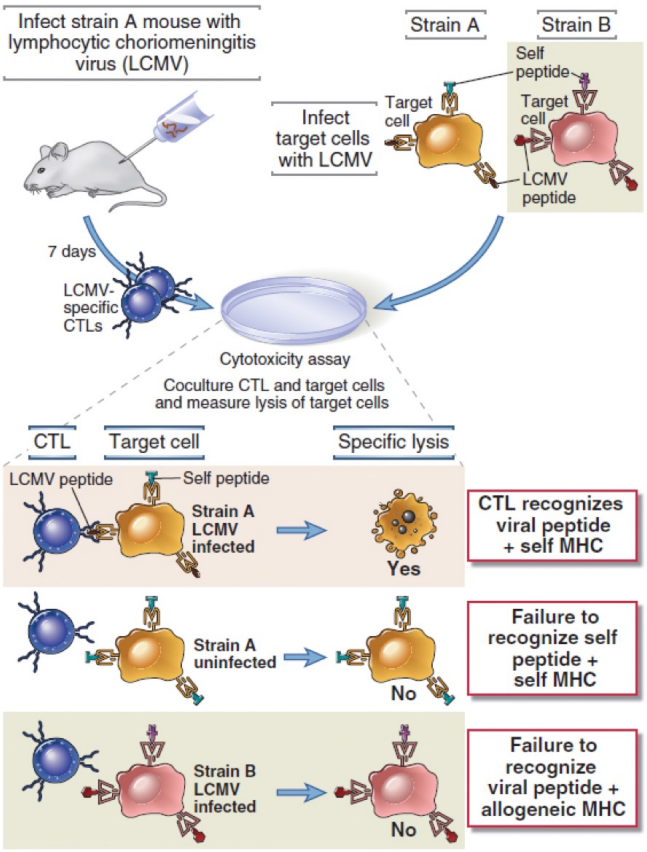
FIGURE 6–14 Pathways of antigen processing and presentation. In the class I MHC pathway *(top panel)*, protein antigens in the cytosol are processed by proteasomes, and peptides are transported into the endoplasmic reticulum (ER), where they bind to class I MHC molecules. In the class II MHC pathway *(bottom panel)*, extracellular protein antigens are endocytosed into vesicles, where the antigens are processed and the peptides bind to class II MHC molecules. Details of these processing pathways are in Figures 6-16 and 6-17.

The set of alleles that is present in each chromosome is called the MHC haplotype. In humans, each HLA allele is named with a number. For instance, for a given individual, his haplotype might be HLA-A2, HLA-B5, HLA-DR3, etc... Each heterozygous individual will have two MHC haplotypes, one each from the paternal and maternal chromosomes. MHC alleles are expressed in codominant fashion. This means the alleles (variants) inherited from both parents are expressed equally.
The MHC genes are highly polymorphic; many different alleles exist in the different individuals inside a population.
Each person carries 2 alleles of each of the 3 class-I genes, (**HLA-A, HLA-B and HLA-C**), and so can express six different types of MHC-I. one heterozygous individual can inherit six or eight functioning class-II alleles, three or more from each parent

MHC restriction

T-cell receptors recognize features both of the peptide antigen and of the MHC molecule to which it is bound. Any given T-cell receptor is specific not simply for a foreign peptide antigen, but for a **unique combination** of a peptide and a particular MHC molecule, this is known as **MHC restriction.**

-In an experiment, mice of two different strains were infected with a certain virus. After a period of time, the activated T lymphocytes of one mouse (mouse1) where extracted.
-The T Lymphocytes were then co-cultured with target cells of the two infected strains in two separate petri dishes. ***Petridish 1 (mouse1 T-cells + mouse1 infected cells) and petridish 2 (mouse1 T-cells + mouse 2 infected cells).



The whole experiment was performed to see the reaction of T Lymphocytes of an individual to different individual's MHC-peptide complex (MHC restriction).
In petridish 1, Mouse1 lymphocytes with Mouse1 infected cells reacted properly, inducing apoptosis of cells. This happened because MHC complex was recognized. On the other hand, in petridish 2, Mouse1 T Lymphocytes and Mouse2 infected cells didn't react properly. T Lymphocytes didn't recognize the MHC complex of Mouse2; therefore, no apoptosis was induced.

Transplantation Immunology

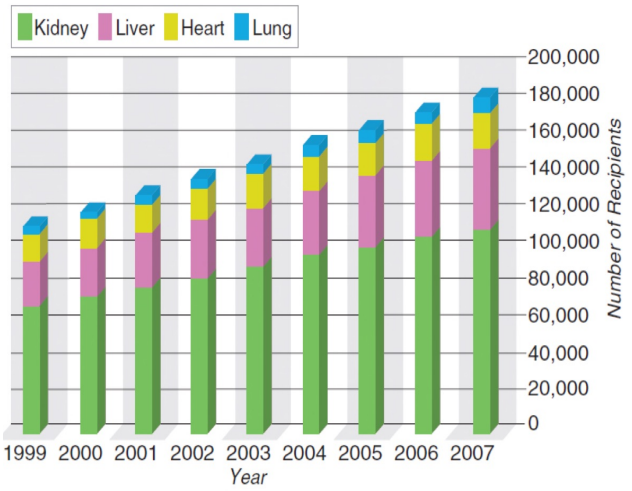
Transplantation is the process of moving cells, tissues or organs from one site to another for the purpose of replacing or repairing damaged or diseased organs and tissues.

The immune system poses a significant barrier to successful organ transplantation when tissues/organs are transferred from one individual to another. **Rejection** is caused by the immune system identifying the transplant as foreign, triggering a response that will ultimately destroy the transplanted organ or tissue. **Donor** and recipient are carefully matched prior to transplantation to minimise the risk of rejection**. Immunosuppressive drugs** are used to prevent and to treat transplant rejection by dampening the overall immune response.

**Research on the immunological mechanisms of rejection will help improve cross matching, diagnosis and treatment, as well as facilitating the discovery of novel strategies for preventing rejection.

• Clinical transplantation to treat human diseases
has increased steadily during the past 45 years, and
transplantation of kidneys, hearts, lungs, livers, pancreata,
and bone marrow is widely used today.

• Since 1990, 1-year survival of kidney allografts has been better than 90% but the 10-year survival has remained about 60% despite
advances in immunosuppressive therapy.



People in the United States living with functioning organ grafts, 1999-2007. (Data from OP

Types of transplantation

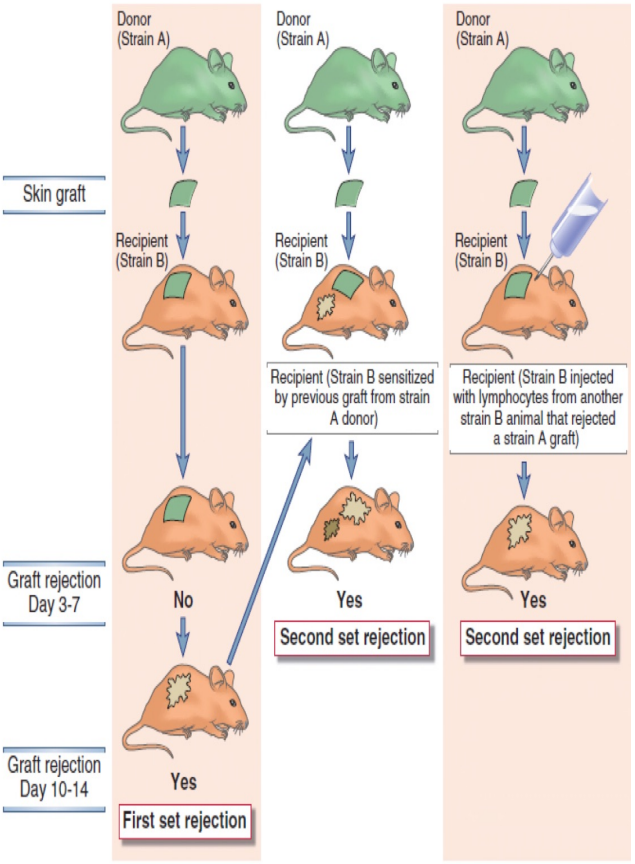
Autograft –Transplantation of cells, tissues or organs between sites within the same individual e.g. skin grafts in burn patients.

Allograft – Transplantation of organs or tissues from a donor to a non-genetically identical individual of the same species. Allografts are the most common type of transplant.

Isograft - Transplantation of organs or tissues from a donor to a genetically identical individual (i.e. identical twin). It's the best type of transplantation because the donor and the recipient have identical genetic material. We give immunosuppressive drugs for a small period of time => easily accepted.

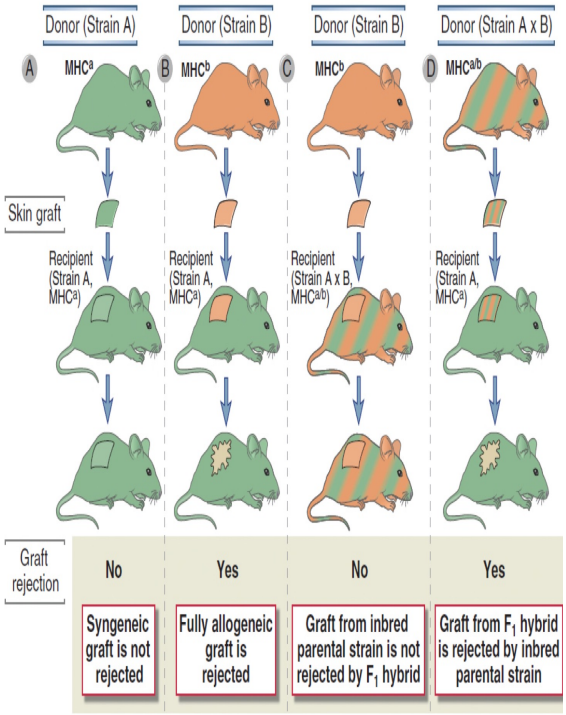
Xenograft – Transplantation of an organ or tissue between two different species. 'Pig valves', for example, are commonly used to repair or replace a defective heart valve in humans.

-An experiment was done to determine the most important factor in graft rejection.
in this experiment :
1) Skin was taken from strain (A) mouse donor and transplanted to strain (B) recipient which differs in the genetic background, in the first week, there was no sign of graft rejection, but after 10-14 days the graft was rejected.
2)Another piece of skin was transplanted to the same mouse of strain (B) from (A) and the graft got rejected faster this time (within the first week), this indicates that there is an **adaptive immune response** and memory cells playing a part in the rejection.
3) To verify the results, lymphocytes were taken from mouse (B) and injected in a mouse of the same strain which hadn't had a transplantation before and the graft got rejected within the first week since it has the first mouse lymphocytes which are already activated.



But what antigens are causing those lymphocytes to attack the graft?

Another experiment was done, here strain (A) and (B) are very similar genetically except in a locus (fixed position on a chromosome) responsible for the formation of MCH molecules.
A) A graft was taken from strain (A) and transplanted to a mouse of the same strain with similar MHCs and as expected the graft was accept and everything was fine.
B) Here we transplanted the graft to strain B which is identical in everything except for the MHC molecules and the graft was rejected.
C) A son of Strains A+B accepted the graft whether it was from the mother or the father
D) If we transplant the graft from the son to either the mother or father it'll be rejected.



• We conclude from the previous experiment that :
1) The molecules responsible for almost all strong (rapid) rejection reactions are called major histocompatibility complex (**MHC**) molecules.

2) The inheritance of MHC is **co-dominant** (both alleles are expressed) and this is why the mouse will take the graft whether it was from either parent and it's T-cells will recognize the alleles as self- alleles but if we do the opposite the father won't recognize the alleles of the mother as self and the graft will be rejected.

• Allogeneic MHC molecules of a graft may be presented for recognition by the T cells of the recipient in two fundamentally different ways, called direct and indirect alloantigen presentation.

•The MHC variability between individuals causes T cells to recognize them as foreigners producing an alloreactive T cells.

-Direct Alloantigen Recognition:

T cells of the recipient recognize MHC complexes that are foreign, causing the initiation of an immune response, here the APCs are allogenic (from the donor), the MHC is allogeneic but the peptide that it shows could be from
the recipient body, even if that happens the T cell will recognize them as a foreign and we call it Alloreactive T cell.

-Indirect Alloantigen Recognition:

Dendritic cells of the recipient recognize and uptake the foreign MHC complex of the donor (Allogenic MHC) . Then, dendritic cells represent the uptaken MHC complex as a peptide on its MHC to T cells which mount an immune response against the donor cells.

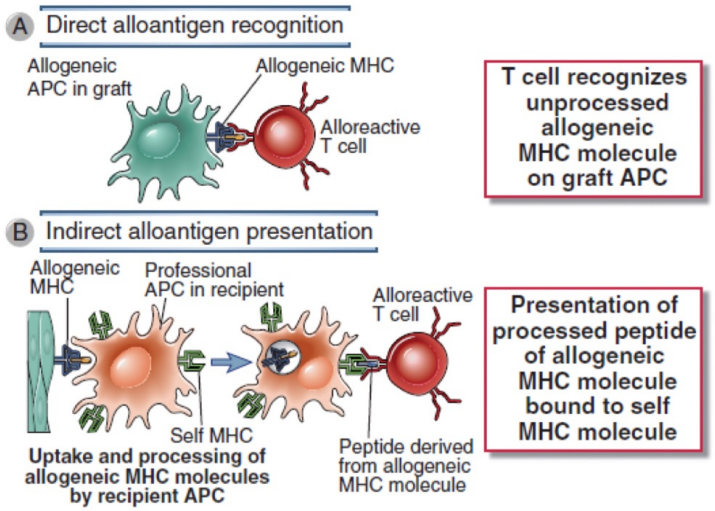


FIGURE 16–4 Direct and indirect alloantigen recognition. A, Direct alloantigen recognition occurs when T cells bind directly to an intact allogeneic MHC molecule on a graft (donor) antigen-presenting cell (APC). **B,** Indirect alloantigen recognition occurs when allogeneic MHC molecules from graft cells are taken up and processed by recipient APCs and peptide fragments of the allogeneic MHC molecules containing polymorphic amino acid residues are bound and presented by recipient (self) MHC molecules.

Rejection of graft (types/stages)

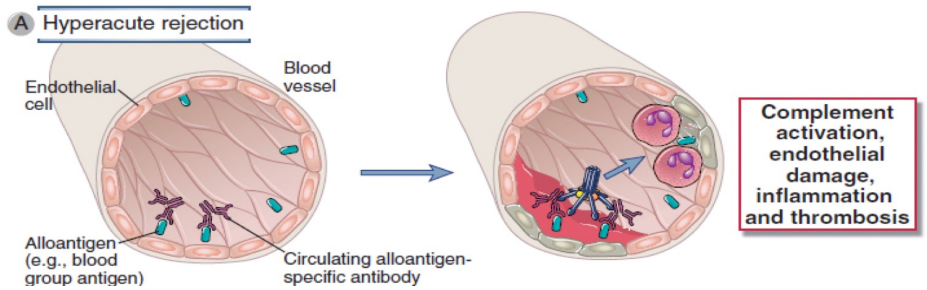
• Keep in mind that alloantibodies and alloreactive T-cells are immune components from the host that stimulate an immune response against donor alloantigens.

1) Hyperacute rejection:

• Hyperacute rejection occurs within minutes or hours after a transplantation and is caused by the presence of **preexisting antibodies** of the recipient, that match the foreign antigens of the donor (blood groups for example), triggering an immune response against the transplant.

• The antibodies react with cells in the blood vessels of the graft, causing blood clots to form, which will prevent blood supply from reaching the graft resulting in immediate rejection of the transplant.

• The binding of the antigen will activate the complement system and will draw WBC into the endothelium, damaging the blood vessel, causing thrombosis and clots.



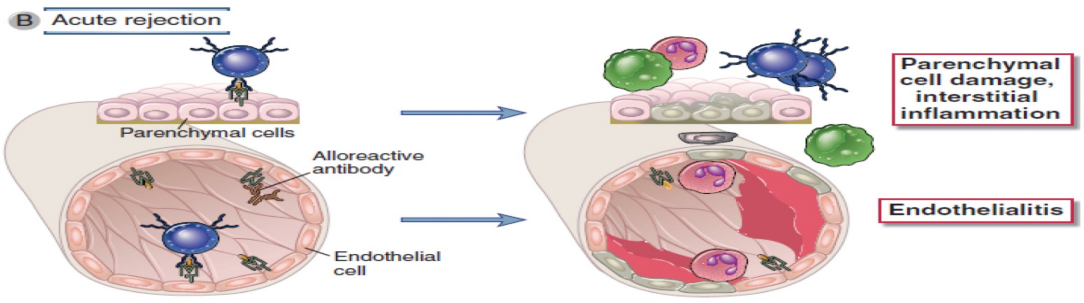
2) Acute rejection:

• Acute rejection usually takes several days-weeks, and occurs within the first 6 months after transplantation. Some degree of acute rejection will occur in all transplantations, except between identical twins.

• In addition to direct killing of the graft cells by CTLs, activated CD4+ helper T cells and CTLs produce cytokines that recruit and activate inflammatory cells, which also injure the graft.

• Alloantibodies cause acute rejection by binding to alloantigens, mainly HLA molecules, on vascular endothelial cells, causing endothelial injury and intravascular thrombosis that results in graft destruction.

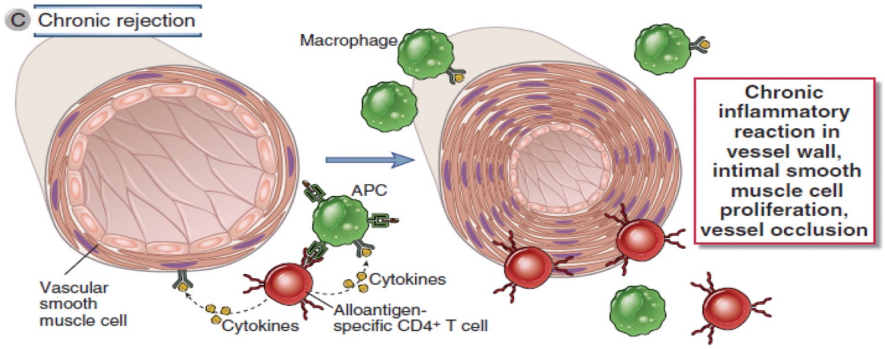
• Acute rejection is a process of injury to the graft parenchyma and blood vessels mediated by alloreactive T cells and antibodies.



3) Chronic rejection:

• Repeated episodes of acute rejection can ultimately lead to chronic rejection of the graft and failure of the transplant. Chronic rejection commonly manifests as scarring of the tissue or organ which can occur months to years after acute rejection has subsided.

• A dominant lesion of chronic rejection in vascularized grafts is arterial occlusion as a result of the proliferation of intimal smooth muscle cells, and the grafts eventually fail mainly because of the resulting ischemic damage.



Compatibility testing (matching)

Rejection can be minimised by carefully matching the donor and recipient for compatibility prior to transplantation. The better matched the donor and recipient are the more successful the transplantation is likely to be. Several tests are commonly done including:

ABO blood group compatibility – The donor and recipient are tested for compatible blood groups.

Tissue typing – A blood sample is taken from the recipient to identify the HLA antigens present on the
surface of the their cells to help find a compatible donor. **Siblings** offer the best donors usually.

Cross matching (after we determine the donor) – Blood samples are taken from both the recipient and donor, and the cells of the donor are mixed with the blood serum of the recipient. If the recipient's antibodies attack the donor cells, they are considered a positive match and transplantation will not be suitable due to increased risk of hyper-acute rejection.

Panel reactive antibody test – The blood serum of patients awaiting transplantation are tested for reactive antibodies against a random panel of cells. The more HLA antibodies present, the higher he panel reactive antibody (PRA) level denoted to the patient, and the greater the chance of graft rejection.

• In kidney transplantation, the larger the number of MHC alleles that are matched between the donor and recipient, the better the graft survival

• Past clinical experience with older typing methods had shown that of all the class I and class II loci, matching at **HLA-A, HLA-B, and HLA-DR** is most important for predicting survival of kidney allografts.

• Zero-antigen mismatches predict the best survival of living related donor grafts, and grafts with one-antigen mismatches do slightly worse.

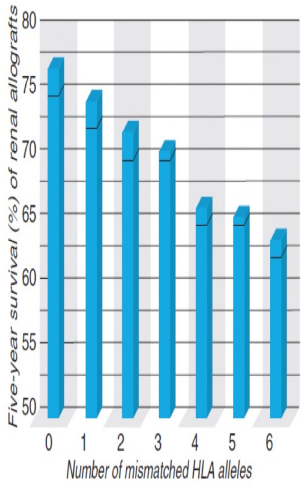


FIGURE 16-12 Influence of MHC matching on graft survival. Matching of MHC alleles between the donor and recipient significantly improves renal allograft survival. The data shown are for deceased donor (cadaver) grafts. HLA matching has less of an impact on survival of renal allografts from live donors, and some MHC alleles are more important than others in determining outcome. *(Data from Organ Procurement and Transplantation Network/Scientific Registry annual report, 2010.)*

Immunosuppressive drugs

• To reduce the risk of transplant rejection, patients are treated with immunosuppressive drugs that will dampen their immune response.

• Immunosuppressive drugs are given in two phases; an initial induction phase involving a high dose, and a later maintenance phase which involves using the drug in the long term at a lower dose.

• The combination of drugs, and dosage given, will vary depending on the type of transplant and the chosen treatment regime.

• Examples include: The calcineurin inhibitors cyclosporine and tacrolimus, steroids, Target of Rapamycin Inhibitors, Azathioprine.

Graft vs host disease (GVHD)

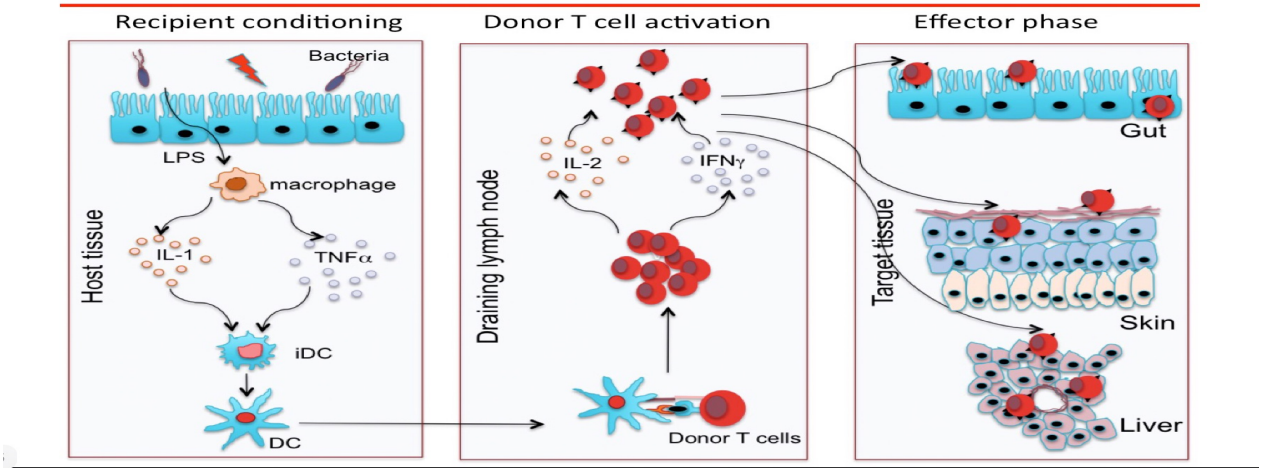
• Allogeneic hematopoietic stem cell transplantation (HSCT) is used for treatment of several hematological malignancies as well as immune disorders.

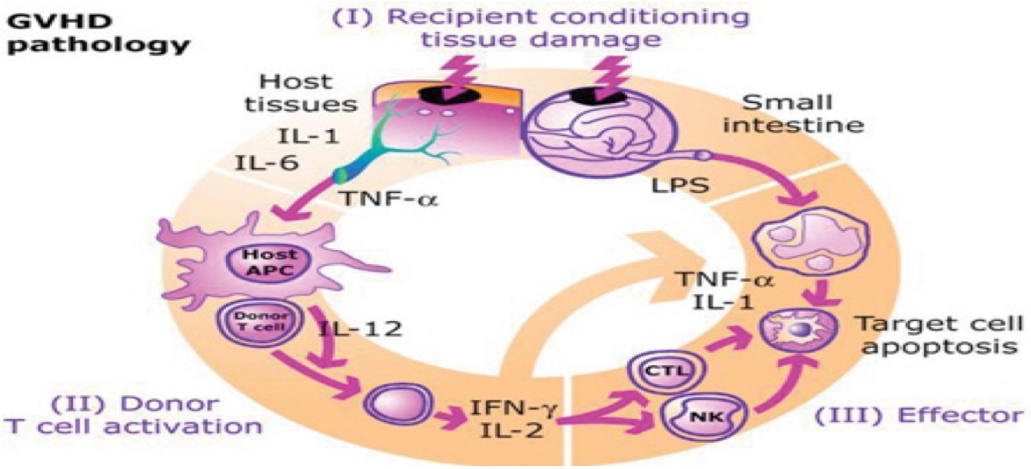
• GVHD is initiated by mature donor CD4+and/or CD8+ T cells that accompany allogenic hematopoietic stem cell transplantation (HSCT). And it occurs when those T-cells stimulate an immune response against host cells when the immune system is activated against a certain pathogen.

• GVHD can occur in **HLA identical** individuals, due to differences in minor histocompatibility antigens
(miHA). Many miHA are encoded on the Y chromosome.

• Diagnosis of GVHD is based on signs and symptoms the affected tissue.

Patho-physiology of GVHD





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