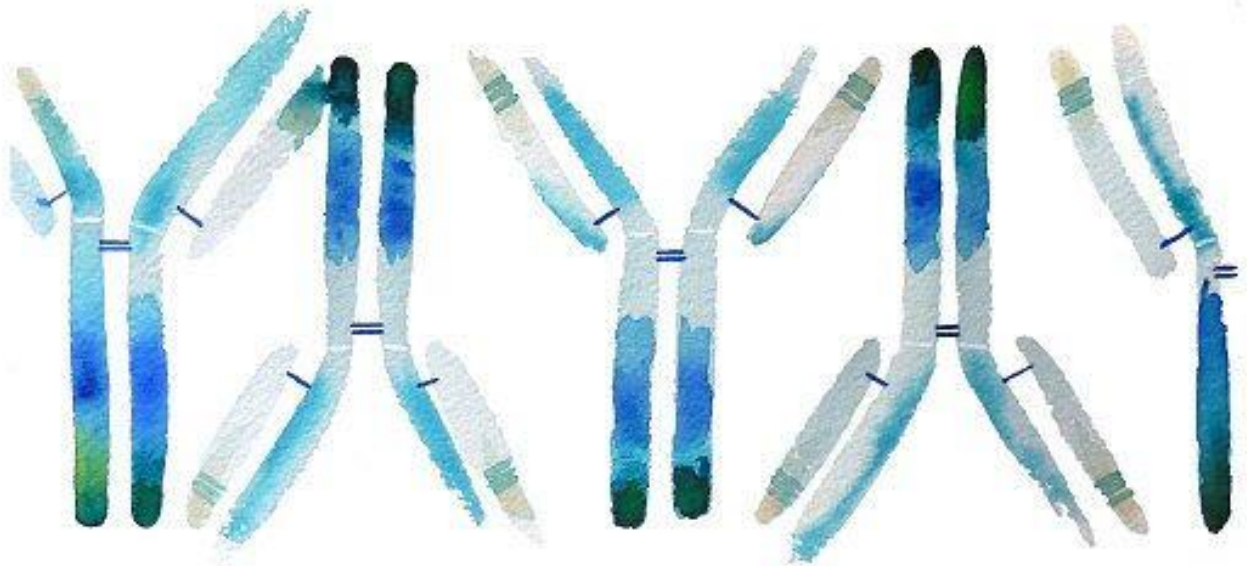
Medical Immunology



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Lecture 10

MHC molecules and transplantation

In this lecture we will discuss:

- MHC molecules
- Protein antigens
- 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 bound to antigens called **human leukocyte antigens** (HLA) (leukocyte because the antibodies were tested by binding to the leukocytes of other individuals).

- 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.

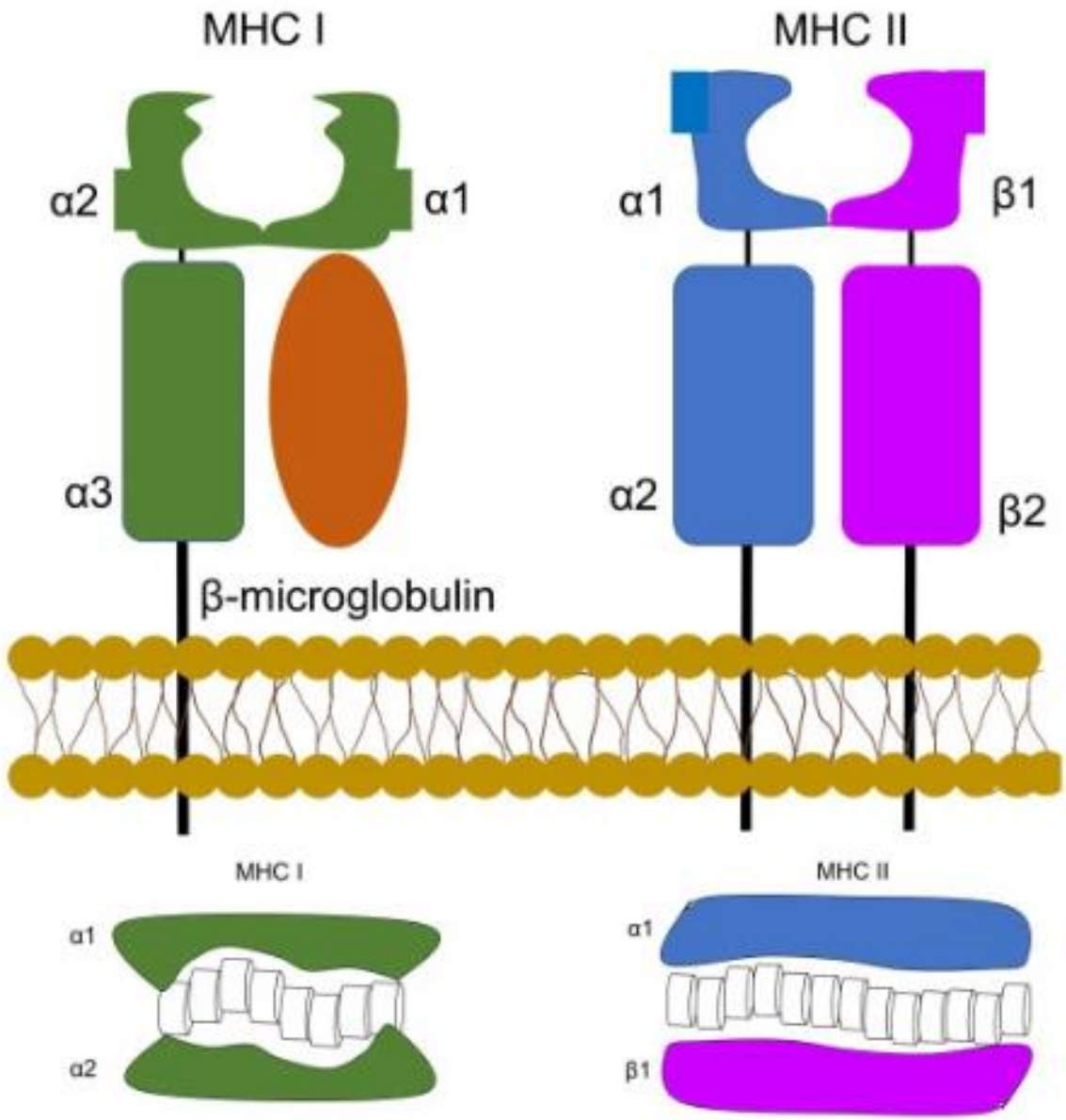
Major histocompatibility complex (MHC)

- 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.**

- 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.**

- 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).

Major histocompatibility complex (MHC)



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.

Major histocompatibility complex (MHC)

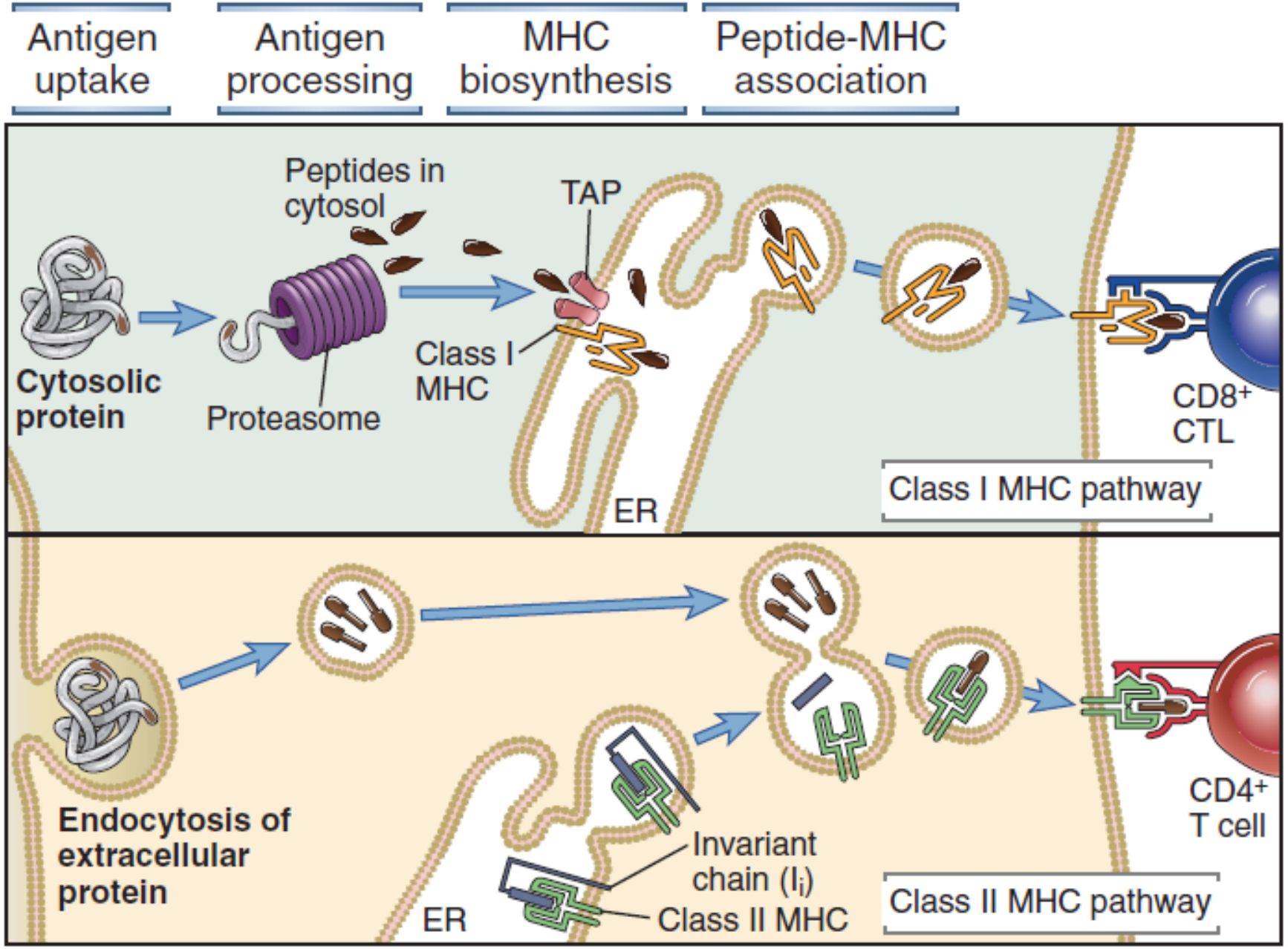


FIGURE 6–14 Pathways of antigen processing and presentation. In the class I MHC pathway *(top panel)*, protein antigens in the cytosol are processed by proteasomes, and peptides are transported into the endoplasmic reticulum (ER), where they bind to class I MHC molecules. In the class II MHC pathway *(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.

Major histocompatibility complex (MHC)

- 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.**

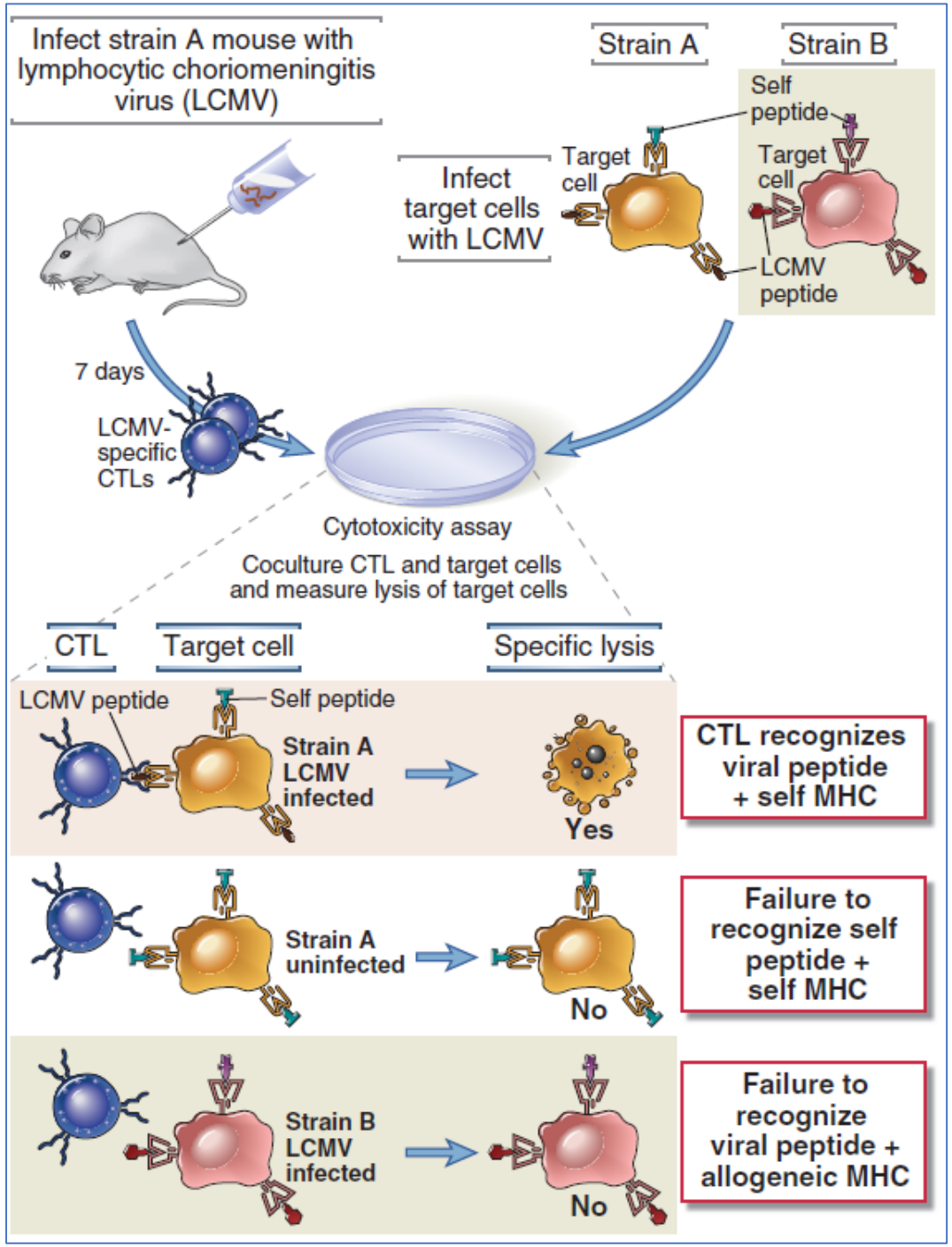


FIGURE 6–6 Experimental demonstration of the phenomenon of MHC restriction of T lymphocytes. Virus-specific cytotoxic T lymphocytes (CTLs) generated from virus-infected strain A mice kill only syngeneic (strain A) target cells infected with that virus. The CTLs do not kill uninfected strain A targets (which express self peptides but not viral peptides) or infected strain B targets (which express different MHC alleles than does strain A). By use of congenic mouse strains that differ only at class I MHC loci, it has been proved that recognition of antigen by $CD8^+$ CTLs is self class I MHC restricted.

Cross presentation

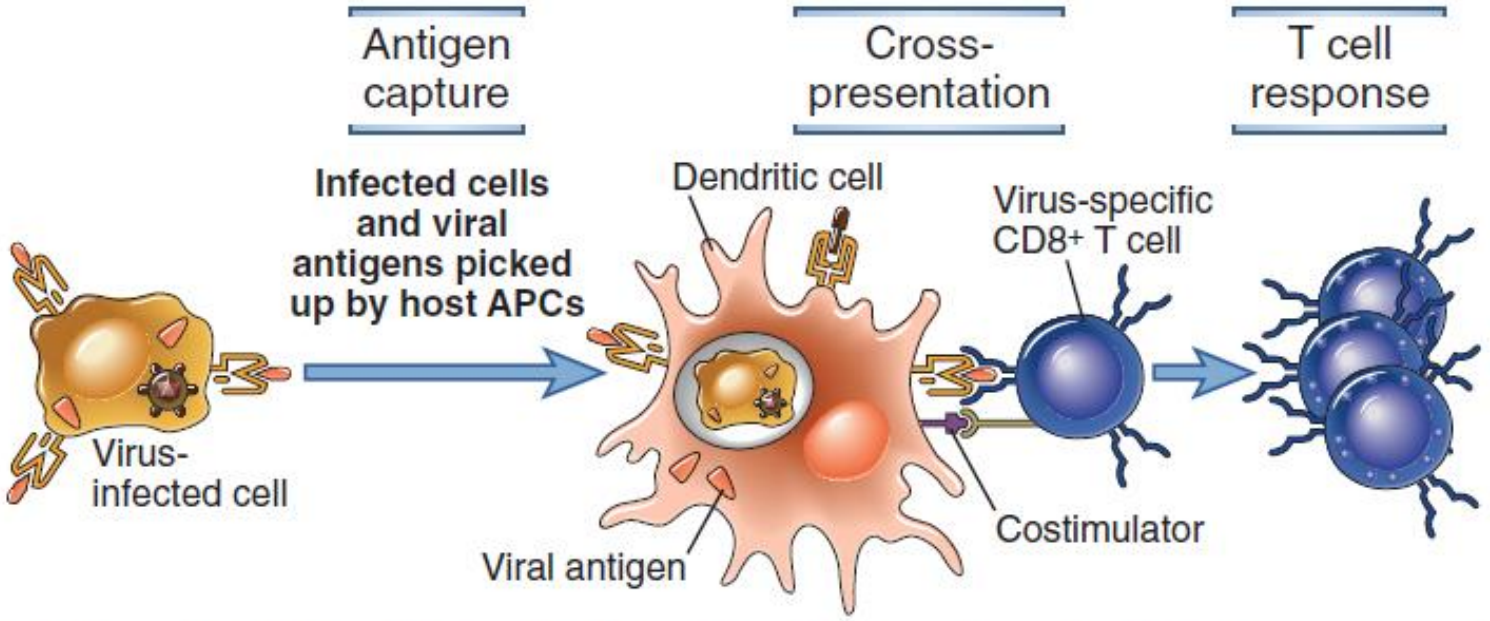
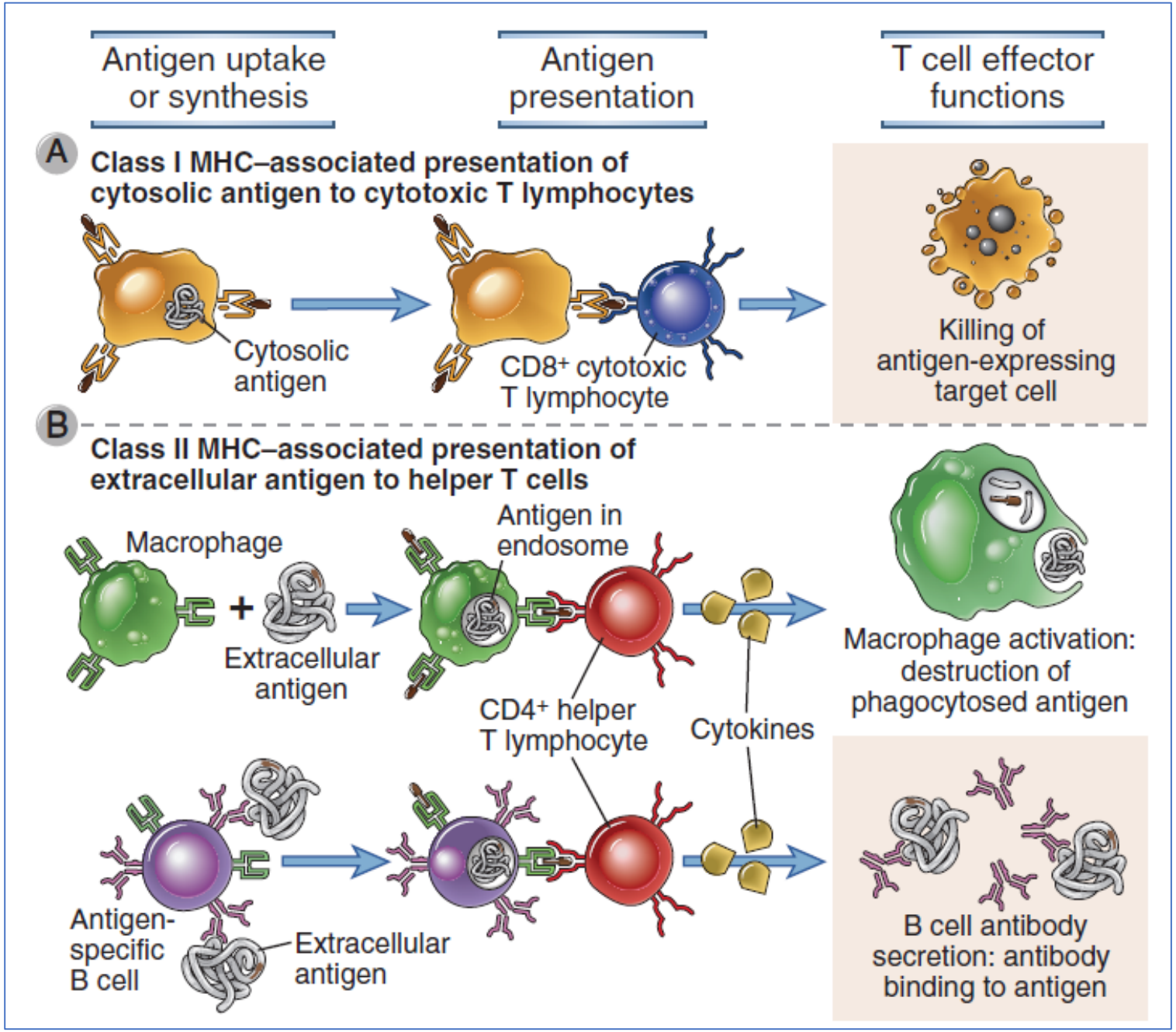


FIGURE 6–20 Cross-presentation of antigens to CD8$^+$ T cells. Cells infected with intracellular microbes, such as viruses, are ingested by dendritic cells, and the antigens of the infectious microbes are processed and presented in association with class I MHC molecules to CD8$^+$ T cells. Thus, dendritic cells are able to present endocytosed vesicular antigens by the class I pathway. Note that the same cross-presenting APCs may display class II MHC–associated antigens from the microbe for recognition by CD4$^+$ helper T cells.

- Some dendritic cells have the ability to capture and to ingest virus-infected cells or tumor cells and present the viral or tumor antigens to naive CD8+ T lymphocytes.

- This process is called **cross-presentation**, or cross-priming, to indicate that one cell type (the dendritic cell) can present antigens from another cell (the virus-infected or tumor cell) and prime, or activate, T cells specific for these antigens.

Major histocompatibility complex (MHC)



Lymphocyte recognition of antigens

TABLE 3-3 COMPARISON OF ANTIGEN RECOGNITION BY T CELLS AND B CELLS

Characteristic	B cells	T cells
Interaction with antigen	Involves binary complex of membrane Ig and Ag	Involves ternary complex of T-cell receptor, Ag, and MHC molecule
Binding of soluble antigen	Yes	No
Involvement of MHC molecules	None required	Required to display processed antigen
Chemical nature of antigens	Protein, polysaccharide, lipid	Mostly proteins, but some lipids and glycolipids presented on MHC-like molecules
Epitope properties	Accessible, hydrophilic, mobile peptides containing sequential or nonsequential amino acids	Internal linear peptides produced by processing of antigen and bound to MHC molecules

PROTEIN ANTIGENS

- The epitopes of complex proteins that elicit the strongest T cell responses are the peptides that are generated by proteolysis in APCs and bind most avidly to MHC molecules.

- The majority of the responding T cells are specific for only one or a few linear amino acid sequences of the antigen. These are called the **immunodominant epitopes** or determinants. Understanding the basis for this can help in vaccine production.

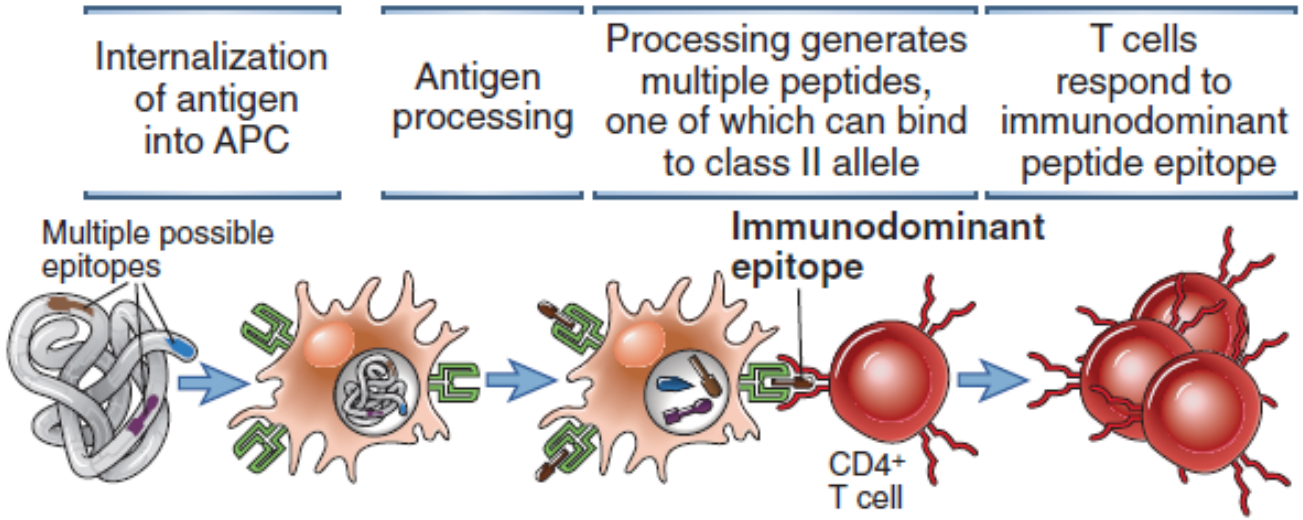


FIGURE 6–22 Immunodominance of peptides. Protein antigens are processed to generate multiple peptides; immunodominant peptides are the ones that bind best to the available class I and class II MHC molecules. The illustration shows an extracellular antigen generating a class II–binding peptide, but this also applies to peptides of cytosolic antigens that are presented by class I MHC molecules.

PROTEIN ANTIGENS

- Although all antigens are recognized by specific lymphocytes or by antibodies, only some antigens are capable of activating lymphocytes. Molecules that stimulate immune responses are called **immunogens**

- The spatial arrangement of different epitopes on a single protein molecule may influence the binding of antibodies in several ways.

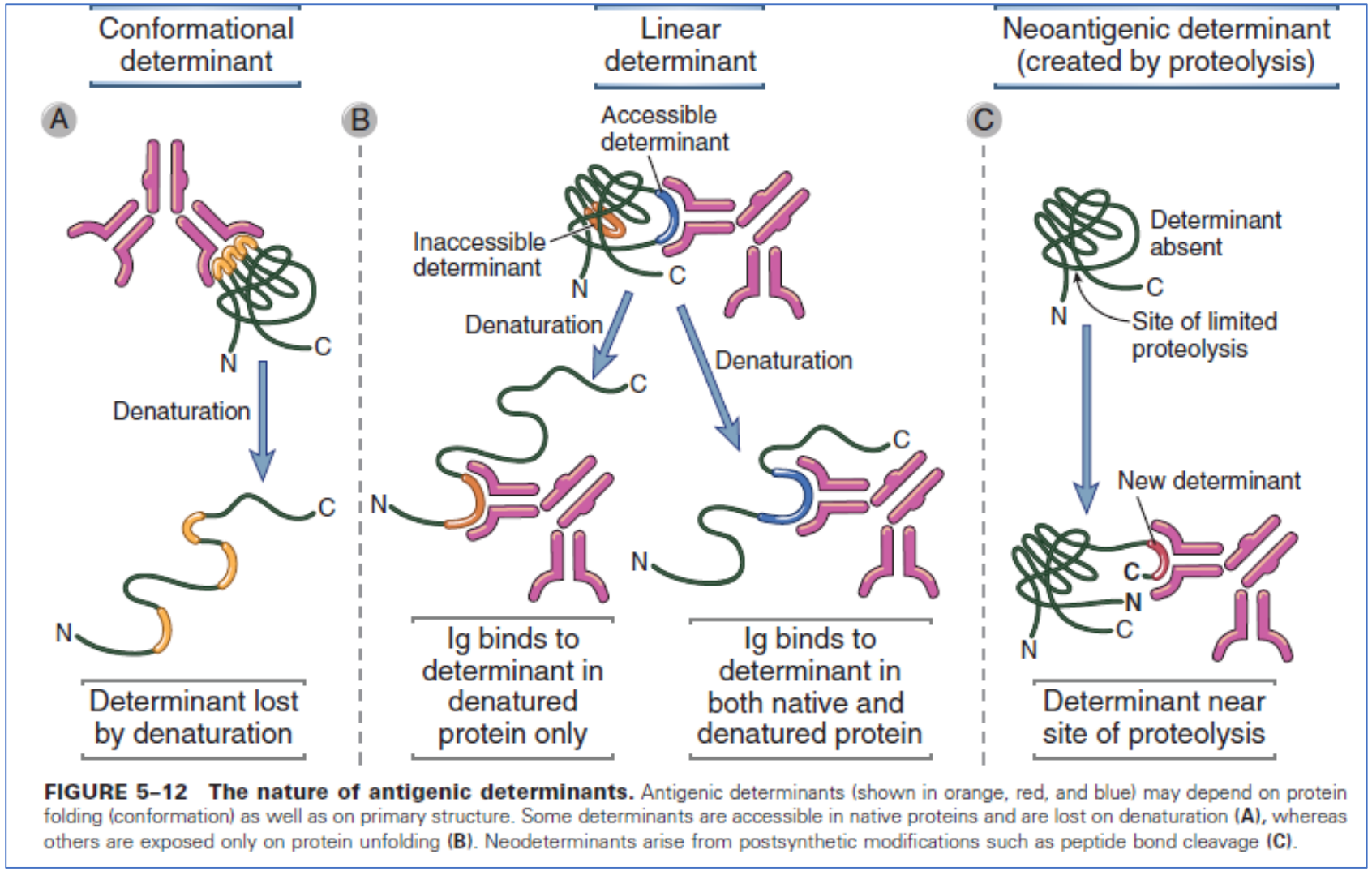


FIGURE 5–12 The nature of antigenic determinants. Antigenic determinants (shown in orange, red, and blue) may depend on protein folding (conformation) as well as on primary structure. Some determinants are accessible in native proteins and are lost on denaturation **(A)**, whereas others are exposed only on protein unfolding **(B)**. Neodeterminants arise from postsynthetic modifications such as peptide bond cleavage **(C)**.

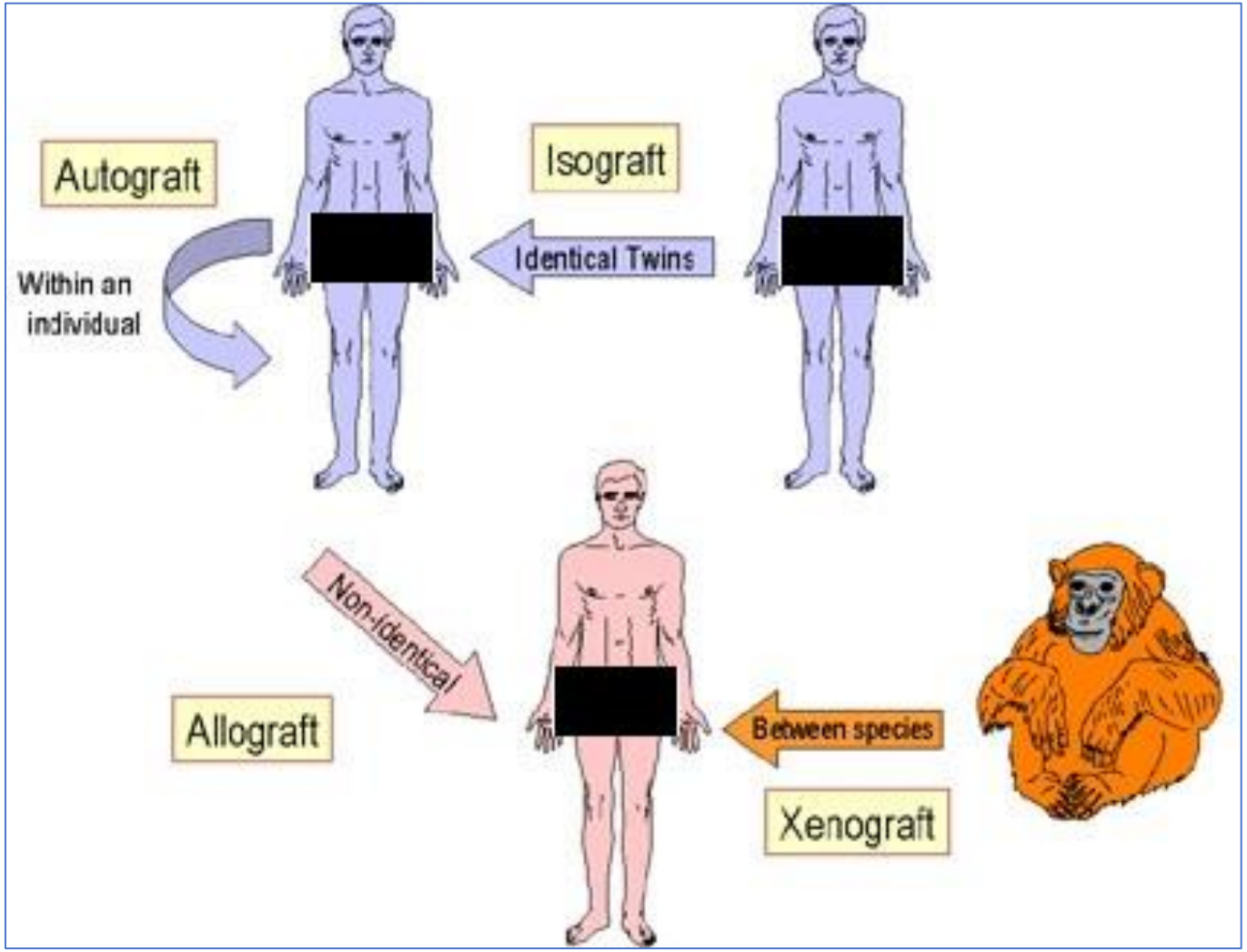
Transplant Immunology

- **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.

Transplants - yearly summary	2011	2012	2013	2014	2015	2016	2017
Heart	14	16	21	22	19	28	19
Heart/Kidney	1	0	2	0	0	0	1
Kidney (deceased donor)	93	111	107	101	161	173	225
Kidney (living donor)	98	83	127	104	110	95	97
Liver/Kidney	0	0	0	0	3	1	0
Liver (deceased donor)	49	58	58	60	76	74	80
Liver (living donor)	7	7	3	3	3	0	0
Lung	12	25	21	24	35	40	52
Pancreas, pancreas/islet, pancreas/kidney	11	6	7	12	15	12	5
Total	**285**	**306**	**346**	**326**	**422**	**423**	**479**

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).
- **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.



Transplant Immunology

- 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

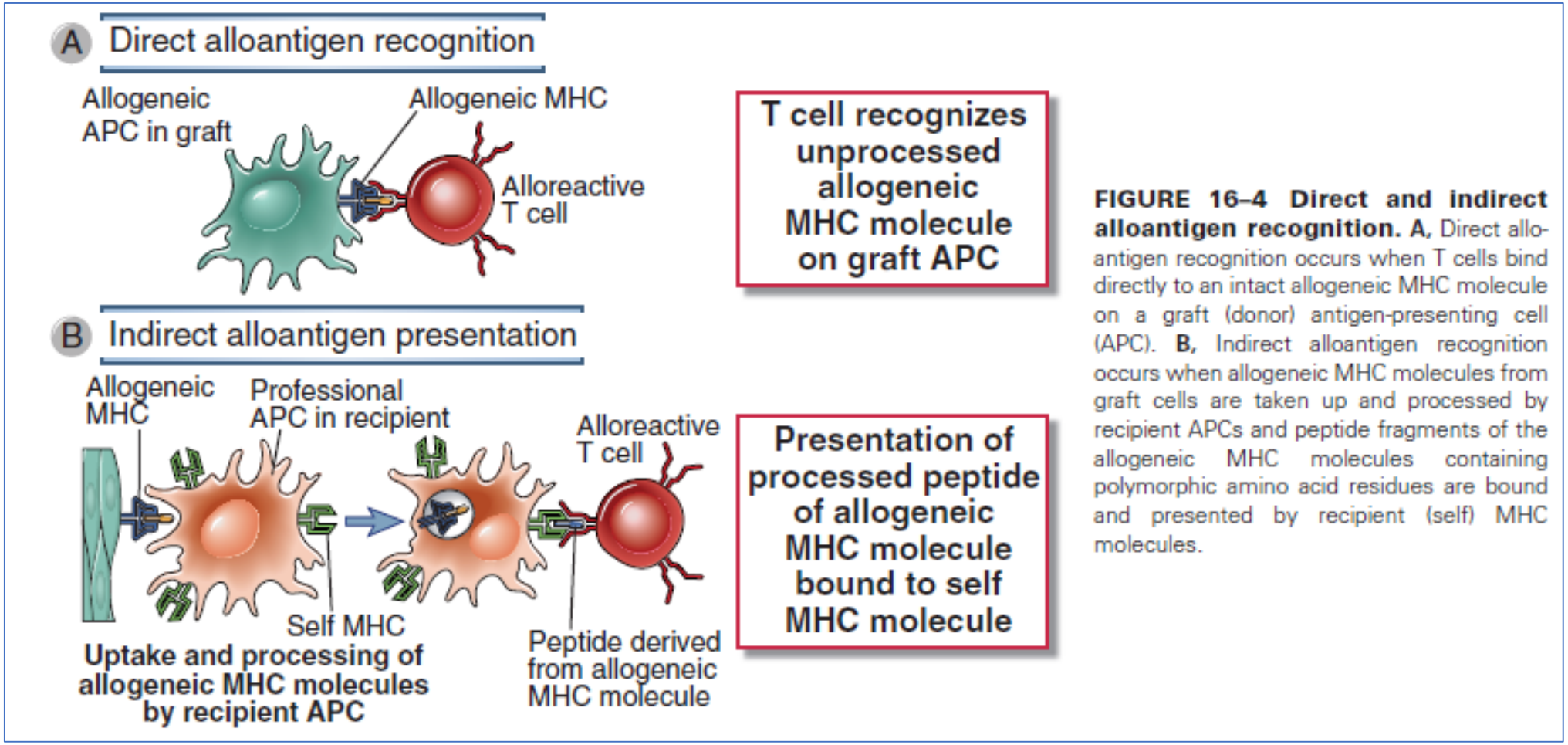
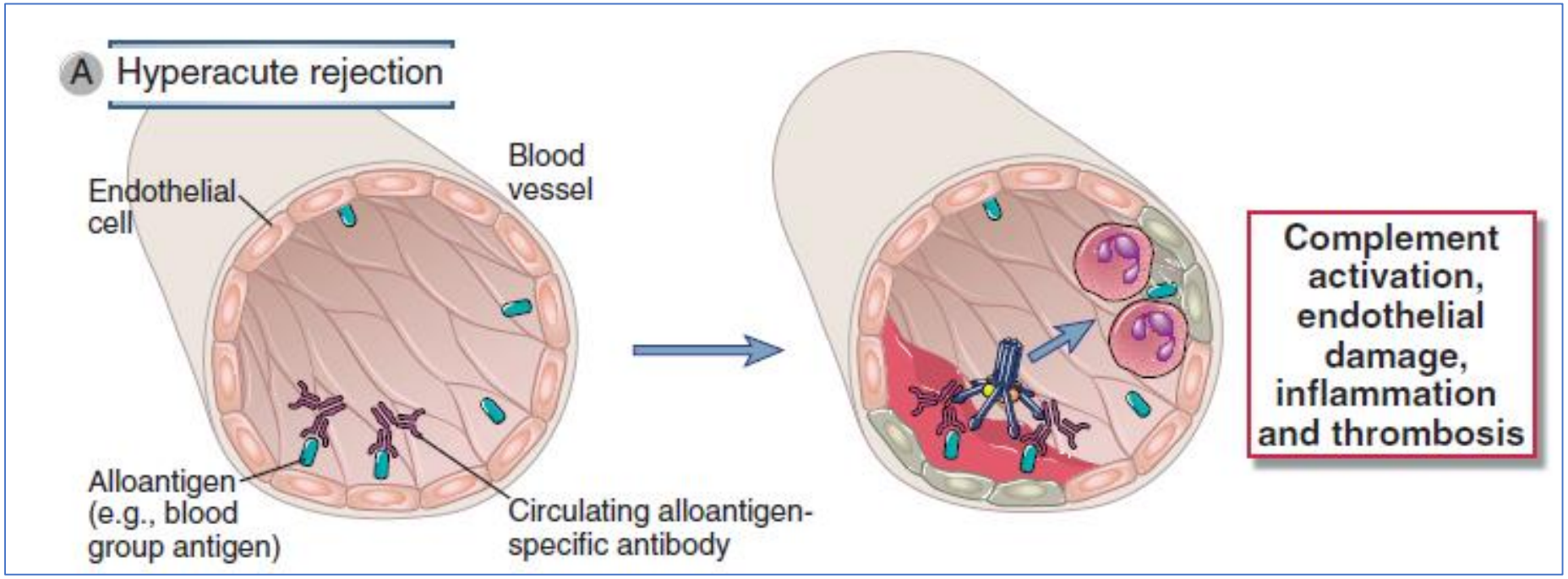


FIGURE 16–4 Direct and indirect alloantigen recognition. A, Direct alloantigen recognition occurs when T cells bind directly to an intact allogeneic MHC molecule on a graft (donor) antigen-presenting cell (APC). **B,** Indirect alloantigen recognition occurs when allogeneic MHC molecules from graft cells 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)

- **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, 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



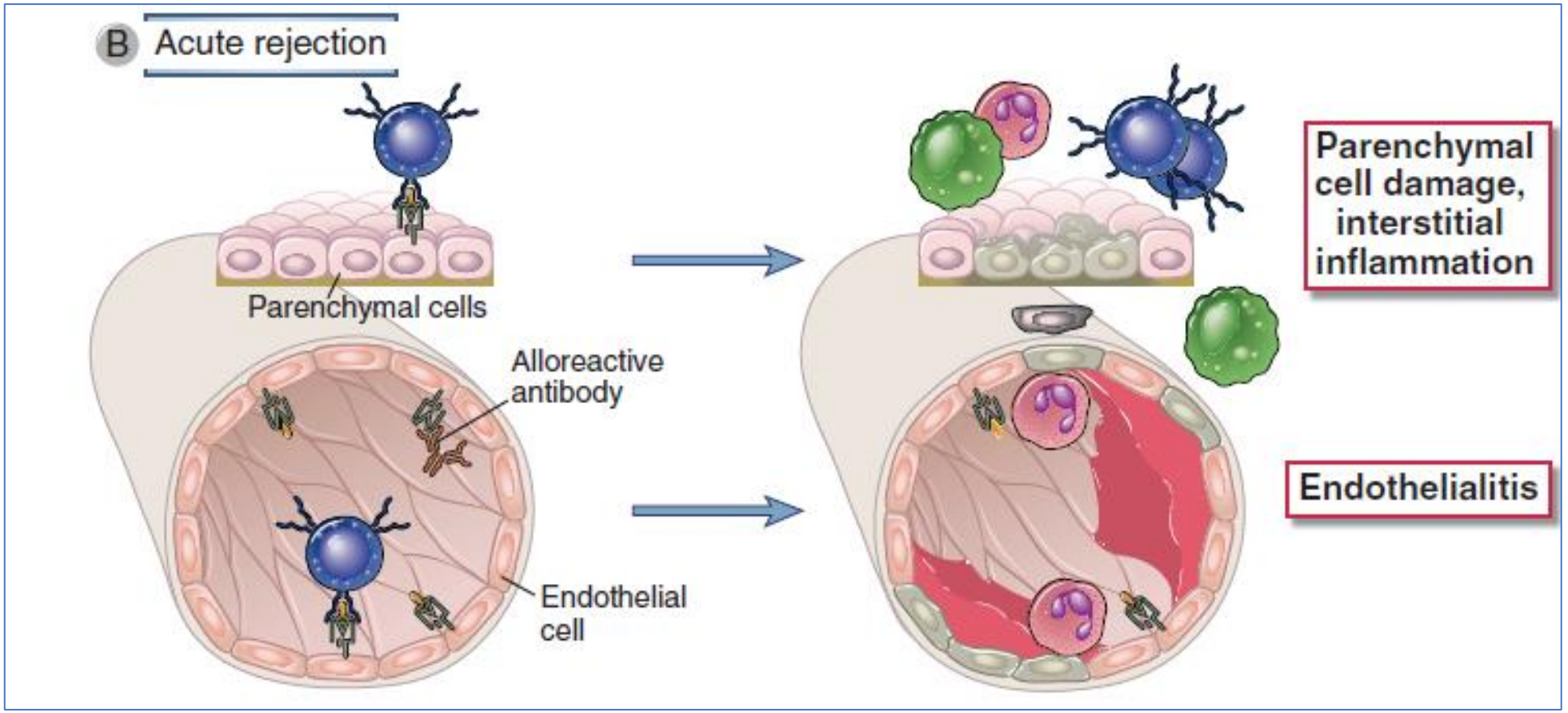
Rejection of graft (types/stages)

- **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.

Rejection of graft (types/stages)

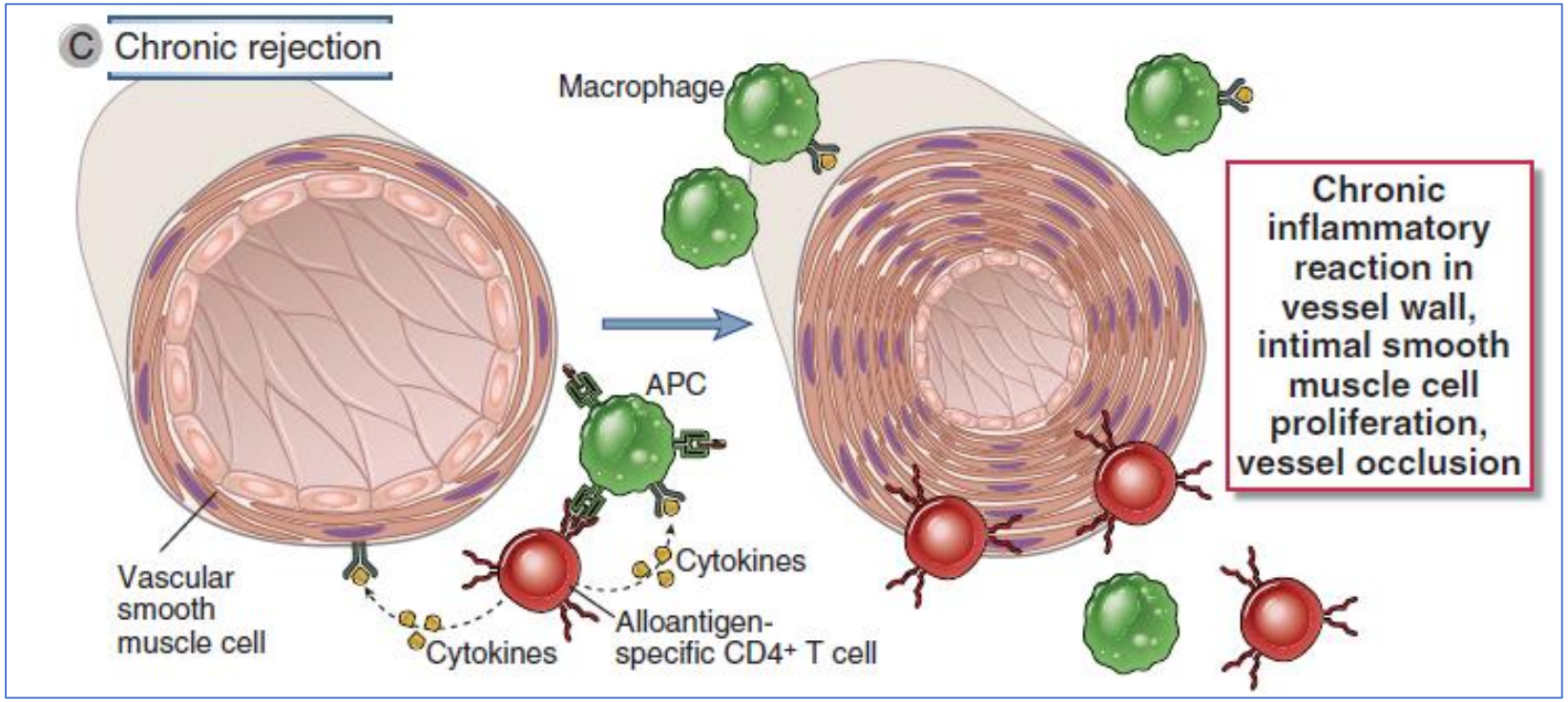


Acute rejection is a process of injury to the graft parenchyma and blood vessels mediated by alloreactive T cells and antibodies

Rejection of graft (types/stages)

- **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** – 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.

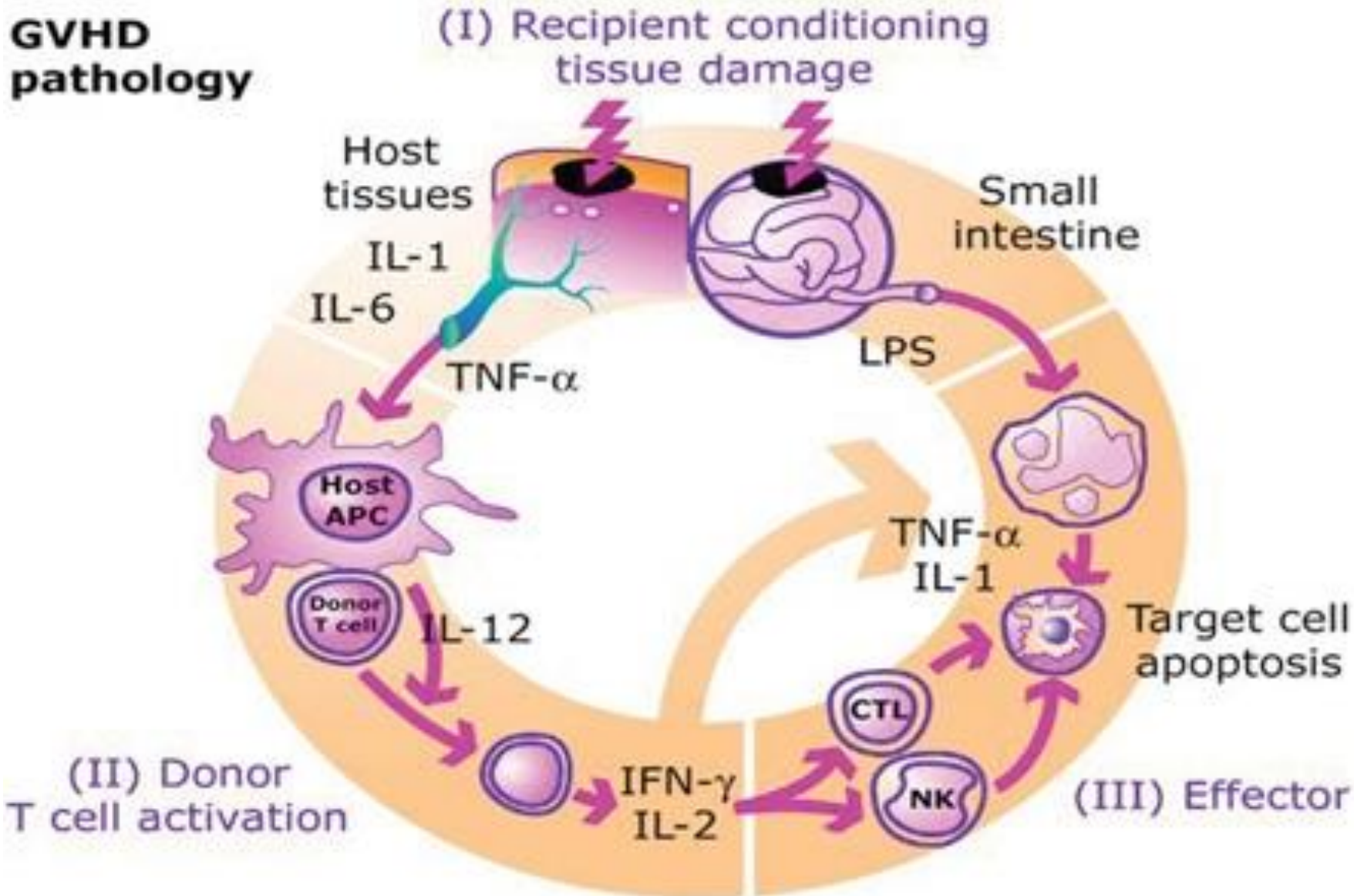
Immunosuppressive drugs

- 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 $CD4^+$and/or $CD8^+$ **T cells** that accompany **allogeneic HSCT**.
- 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.

GVHD pathology



Further reading:

- Cellular and Molecular Immunology. 7th Edition..

Chapter 6. Major histocompatibility complex molecules ….

Chapter 16. Transplantation immunology