UNIVERSITATEA DE STAT DE MEDICINĂ
ȘI FARMACIE „NICOLAE TESTEMIȚANU”
DIN REPUBLICA MOLDOVA

Transplant immunology

Brocovschii Victoria
Associate professor
Pneumology and Allergology Department
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Transplantation

- Transplantation is widely used for replacing nonfunctioning organs and tissues with healthy organs or tissues.

- Transplantation is the process of taking cells, tissues, or organs, called a **graft**, from one individual and placing them into a (usually) different individual.

- The individual who provides the graft is called the **donor**, and the individual who receives the graft is called either the **recipient** or the **host**.

- **Transfusion** refers to the transfer of circulating blood cells or plasma from one individual to another

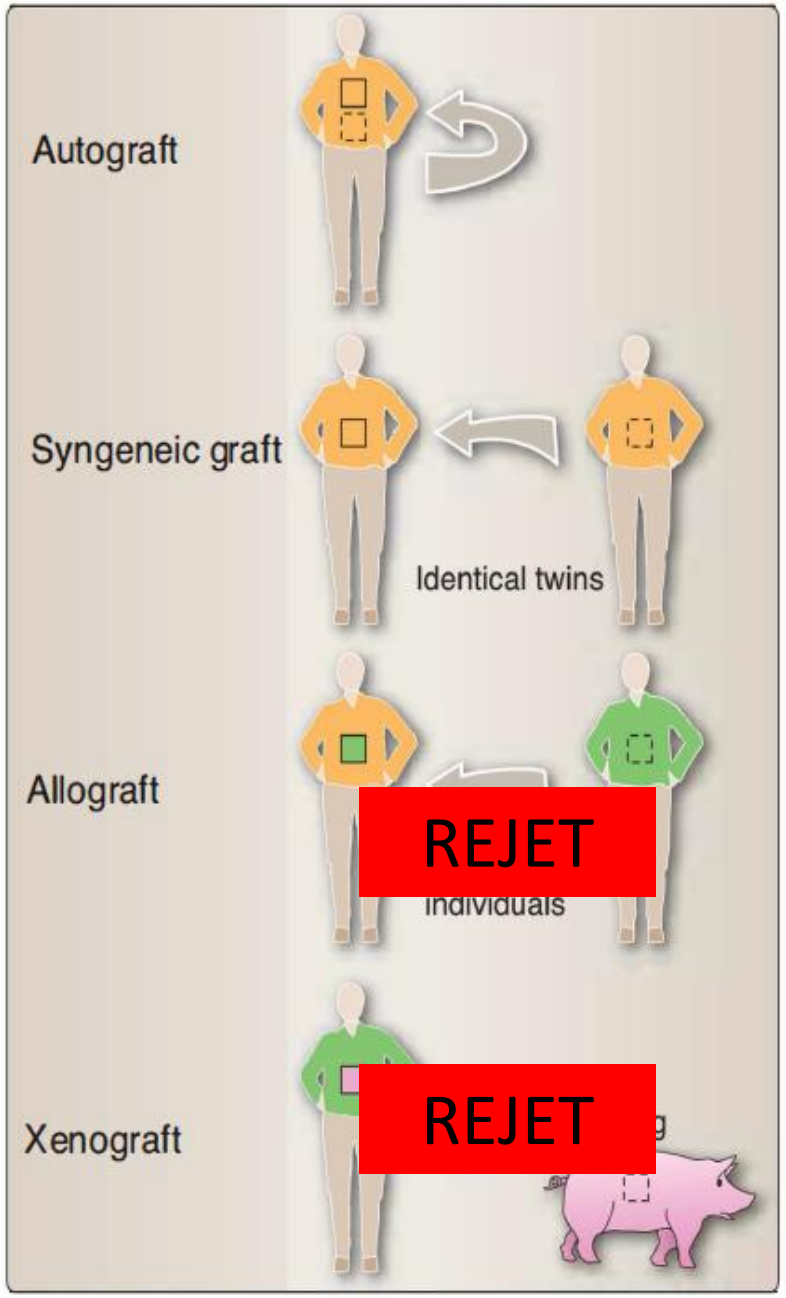
Types of grafts
(donor-recipient genetic relationship)

- **Autografts** - transferred from one part of an individual to another location on that same individual

- **Syngeneic grafts** - transferred between different individuals who are genetically identical or nearly so (identical twins or members of an inbred strain)

- **Allogeneic grafts (or allografts)** are transferred between two genetically disparate individuals of the same species (brother and sister, parent and child, or totally unrelated individuals)

- **Xenogeneic grafts (or xenografts**) are those exchanged between members of different species (the placement of primate hearts into human recipients)



Transplantation Immunology

- A host can recognize as foreign and mount a response against any histocompatibility antigen not encoded within its own cells

- The biggest obstacle to transplantation remains the immune system

- Normally the immune system will seek to destroy any foreign (non-self) structure

- Non-self cells will be recognised immediately, by recognising MHC membrane antigens, encoded by major histocompatibility complex genes

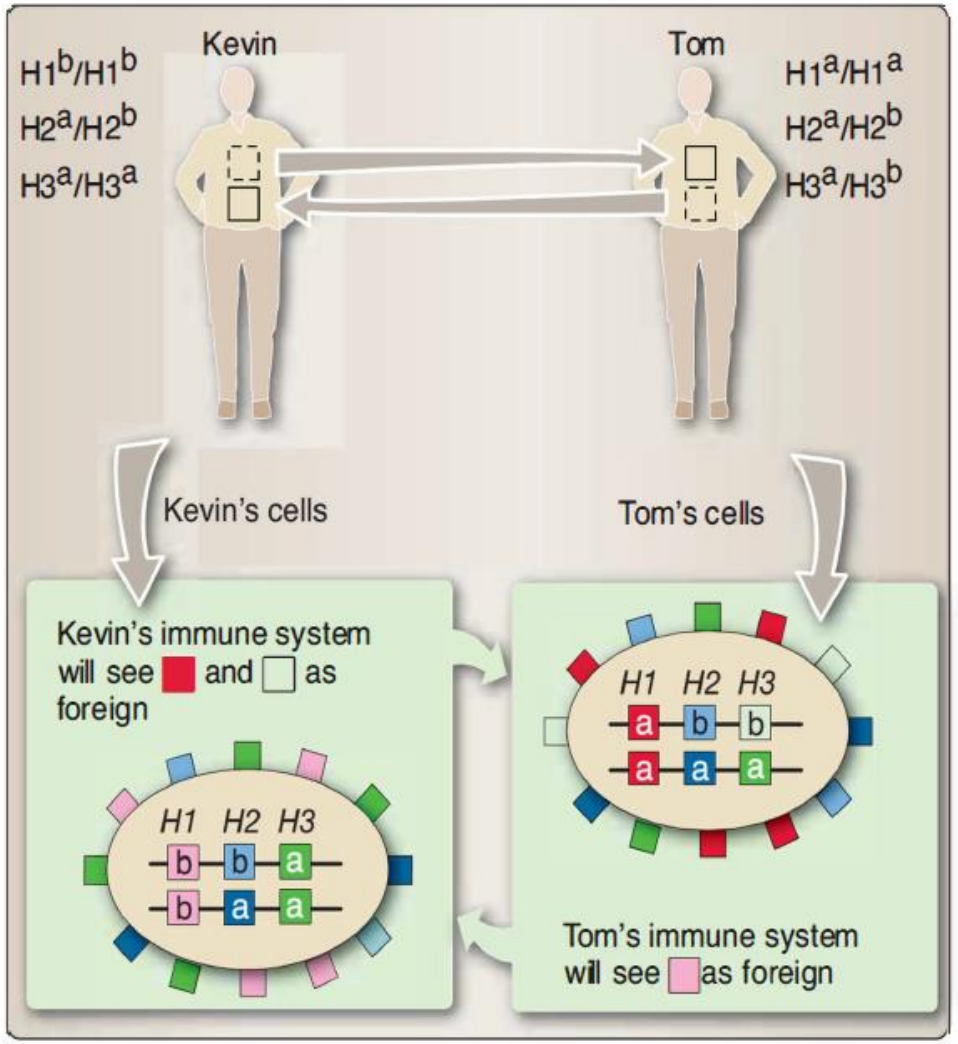
- These mechanisms are involved in the rejection/rejection of transplanted organs, as they are recognised as non-self by the recipient's immune system

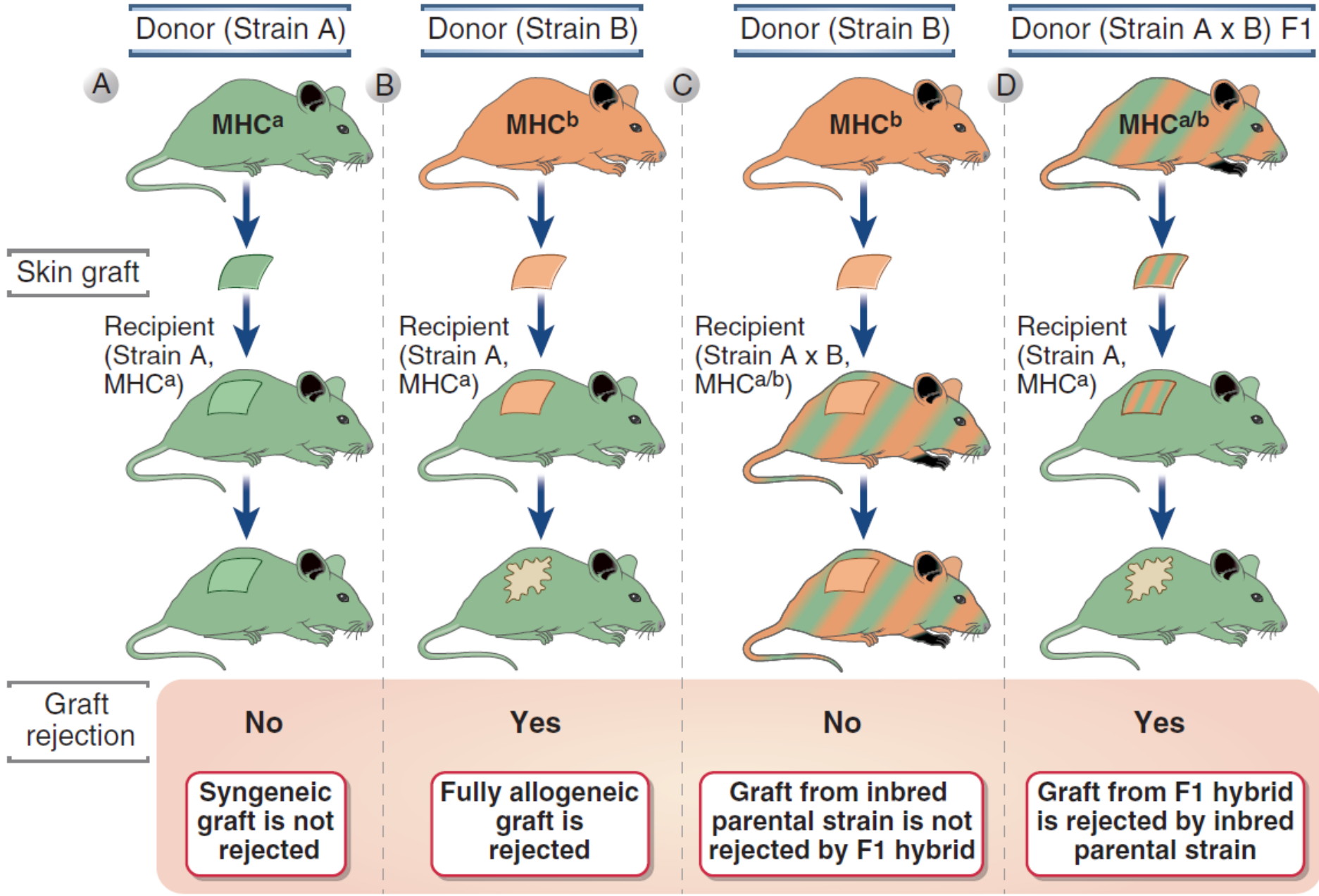
The laws of transplantation

- Grafts exchanged between individuals of the same species who are completely different (homozygous for different alleles) at a histocompatibility locus can potentially be rejected.

- Each member in the exchange will recognize the allelic form of the histocompatibility antigen expressed by the other as foreign

- Heterozygous recipients will see nothing foreign on grafts received from homozygous parental donors.




Donor (Strain A)
Donor (Strain B)
Donor (Strain B)
Donor (Strain A x B) F1
A
B
C
D
MHC^a
MHC^b
MHC^b
MHC^a/b
Skin graft
Recipient (Strain A, MHC^a)
Recipient (Strain A, MHC^a)
Recipient (Strain A x B, MHC^a/b)
Recipient (Strain A, MHC^a)
Graft rejection
No
Yes
No
Yes
Syngeneic graft is not rejected
Fully allogeneic graft is rejected
Graft from inbred parental strain is not rejected by F1 hybrid
Graft from F1 hybrid is rejected by inbred parental strain

Antigene de transplant

- Antigenele responsabile pentru declanșarea răspunsului imun împotriva unui transplant se numesc *antigene de transplant* (sau *aloantigene*).

Deosebim 3 tipuri de antigene:

- antigene de grup sanguin
- antigene de histocompatibilitate majore
- antigene de histocompatibilitate minore

Antigenele de histocompatibilitate

- La om, MHC se numește sistemul antigen leucocitar uman (HLA);
- Funcția fiziologică a moleculelor MHC este aceea de prezentare a antigenelor limfocitelor T (limfocitele T recunosc antigenele doar dacă sunt prezentate într-un complex alături de molecule MHC);
- tipul I de MHC este responsabil de prezentarea de antigene intracelulare (antigene virale, tumorale sau antigene self) limfocitele CD8+;
- clasa II de MHC prezintă antigene extracelulare (antigene bacteriene) limfocitele CD4+.

Condiții pentru stabilirea compatibilității pre-transplant
Antigene de transplant

I. **Compatibilitate după grupele de sânge (AB0) (***incompatibilitatea minoră și majoră***)**

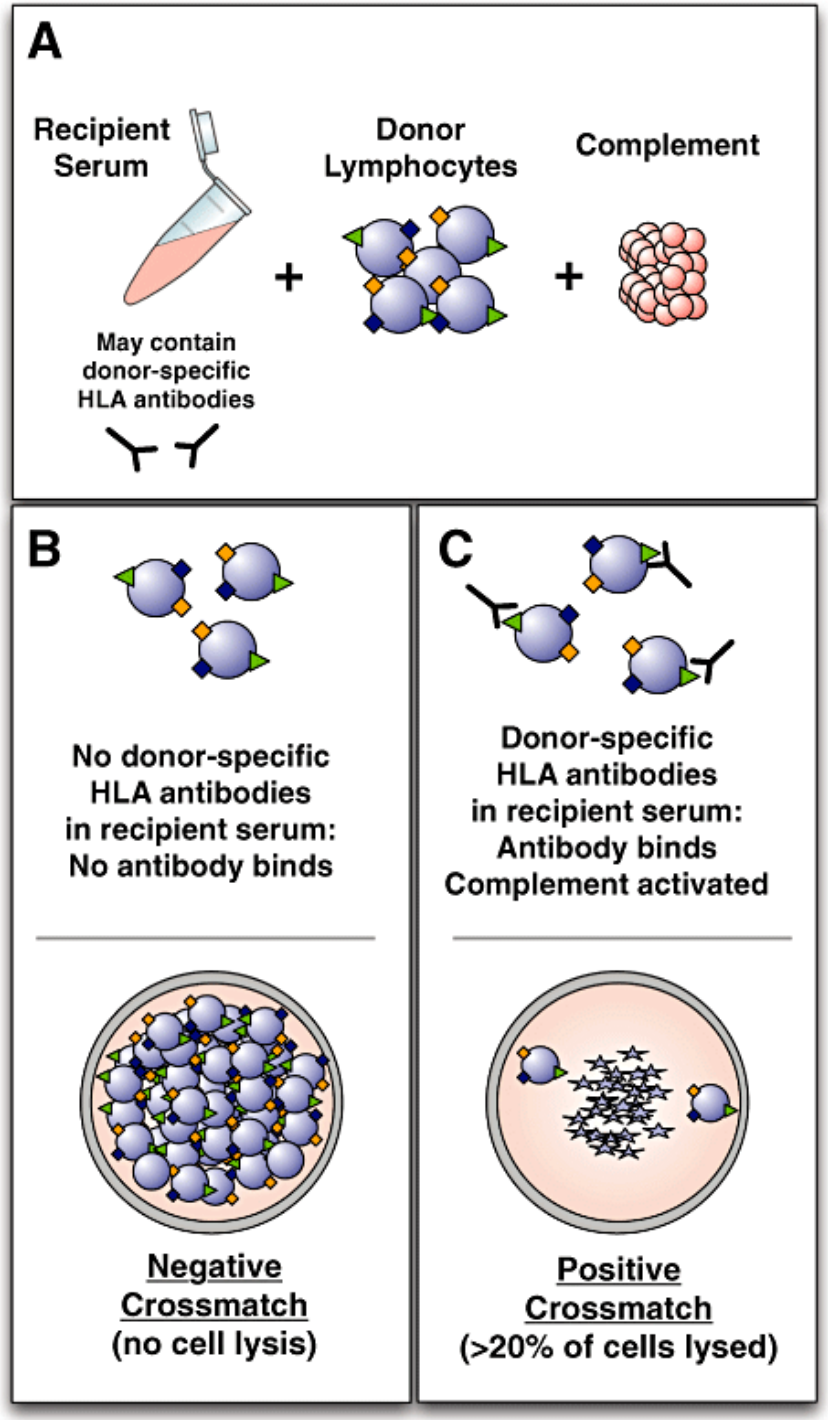
II. **Compatibilitatea HLA (tipizarea HLA-A, HLA-B, HLA-DR) -** genotiparea HLA

Condiții pentru compatibilitate

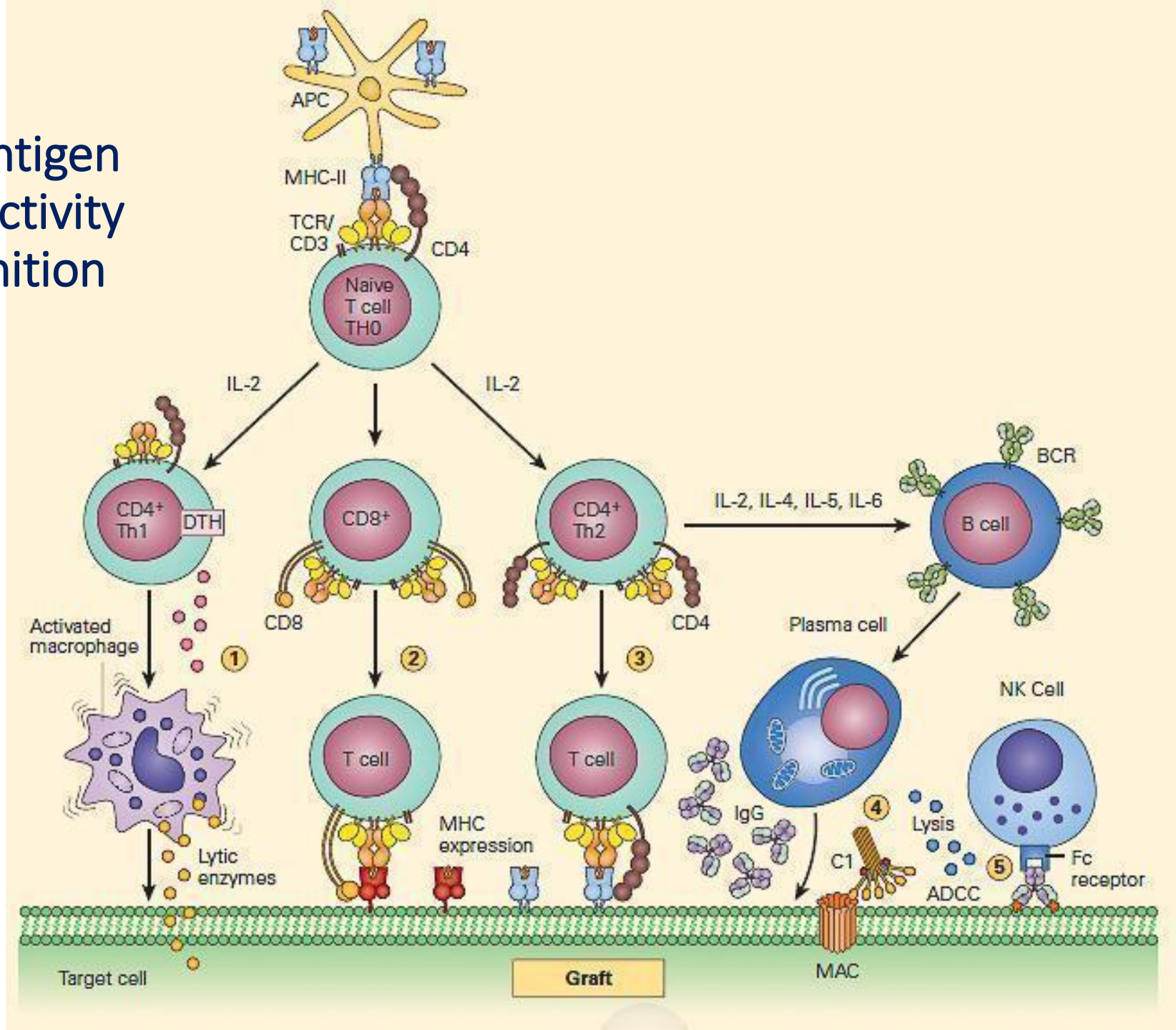
Se testează cel puțin 3 locusuri: HLA-A; HLA-B; HLA-DR, 6 Ag HLA, dintre care cel puțin 4 Ag trebuie să fie similare, condiție obligatorie în transplantologie

III. **Absența în serul pacientului a unor Ac anti-donator (testul *cross-match*)** (testarea sanguină încrucișată) constă în detectarea Ac preformați în serul recipientului împotriva Ag HLA de pe suprafața limfocitelor. Este o tehnică de citotoxicitate dependentă de complement, care apreciază compatibilitatea sau incompatibilitatea serologică între donator şi recipient

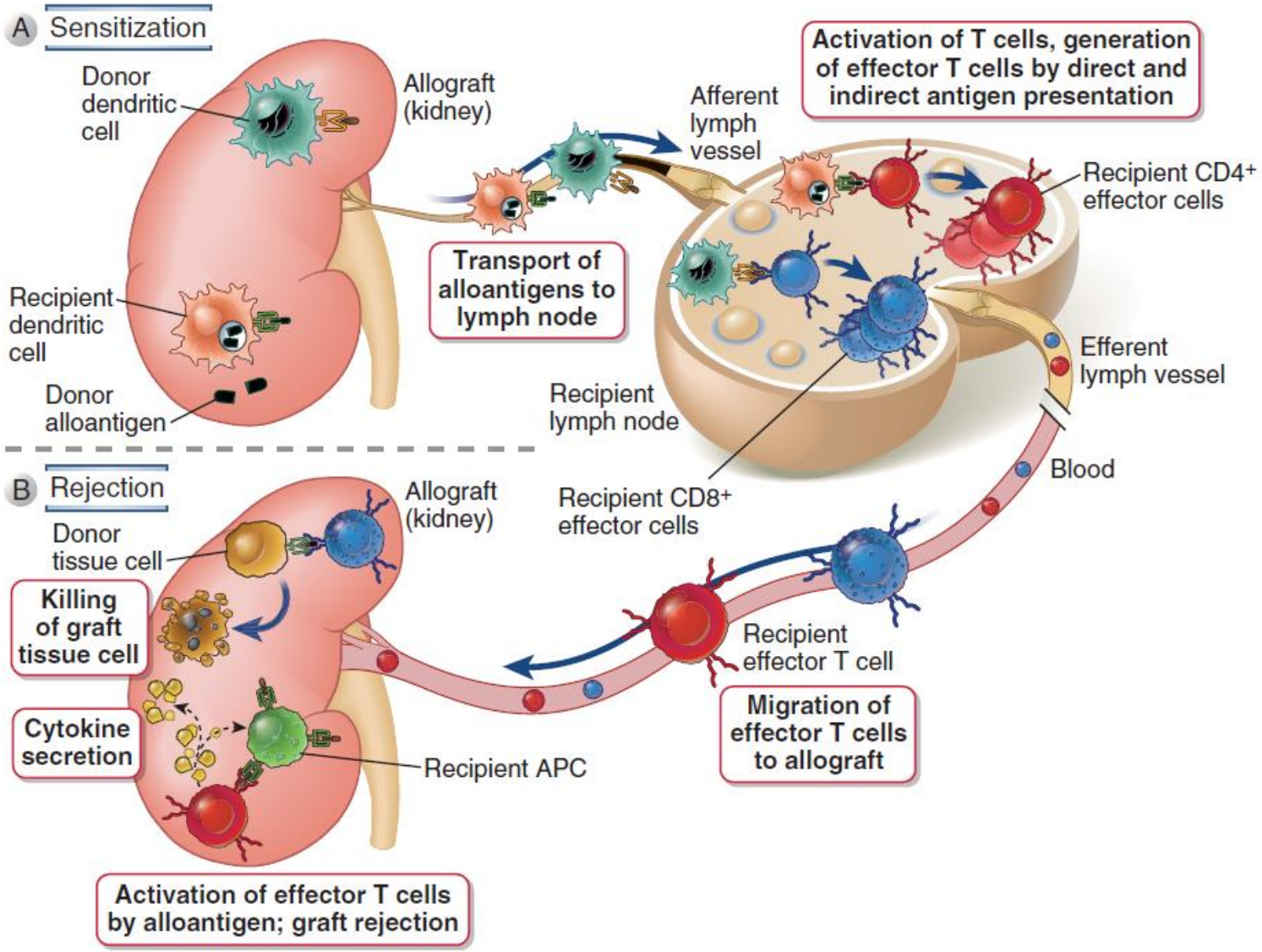
testul *cross-match*



Cellular events involved in antigen recognition and immune reactivity associated with graft recognition



Activation of alloreactive T cells

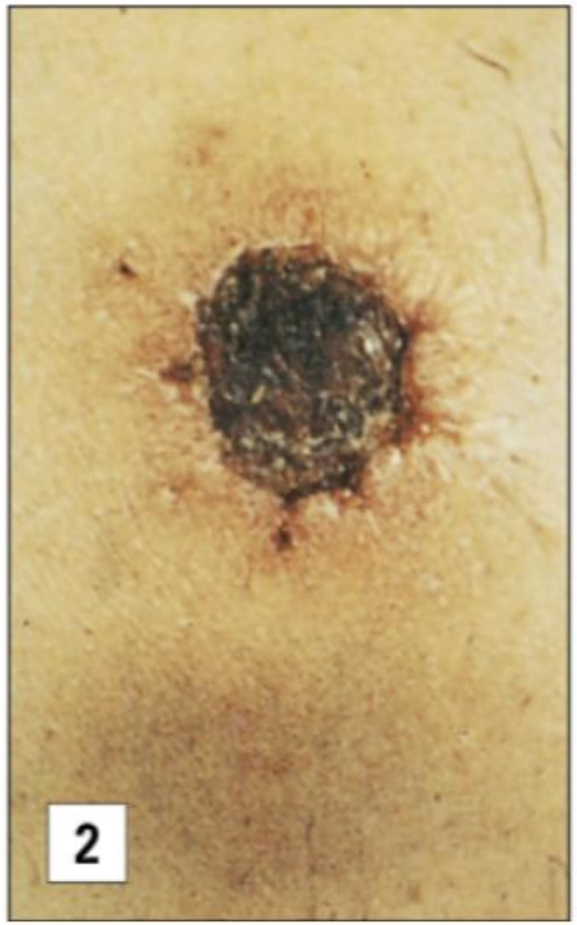


PATTERNS AND MECHANISMS OF ALLOGRAFT REJECTION

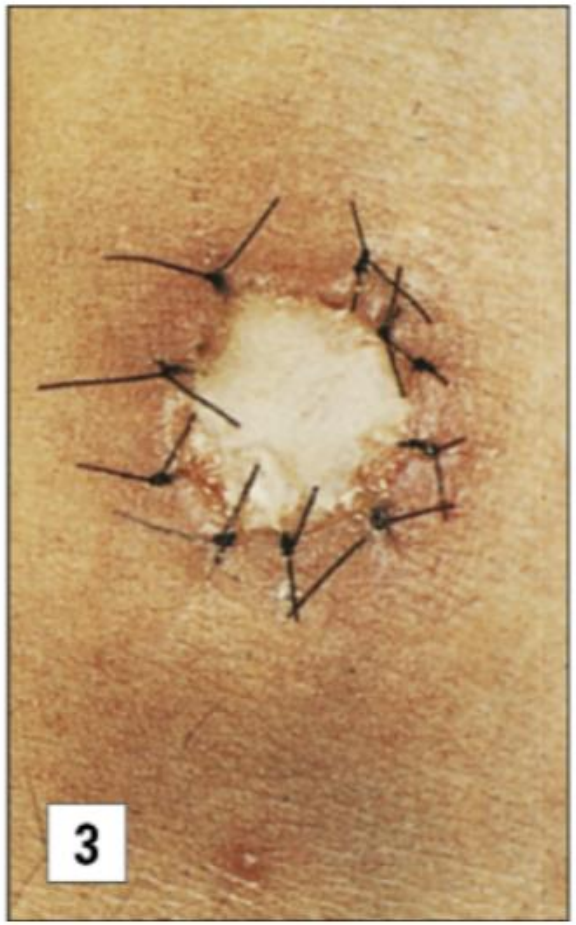
- Rejection responses fall into three general categories - chronic, acute, and hyperacute
- Depending on timing and intensity.
- Each type involves particular sets of immune responses and is determined in part by the genetic mismatch between donor and recipient.

Rejetul autografei

Alograft de piele în ziua 5, complet vascularizat



Același alograft în ziua 12 este complet distrus – rejet acut



Al doilea alograft nu se vascularizează și este distrus rapid – rejet hiperacut

Hyperacute rejections

- Hyperacute rejections are the most rapid type of rejection.
- They are initiated and completed within a few days of graft placement, usually before the grafted tissue or organs can establish connections with the recipient vasculature.
- The immune attack is typically directed at the vasculature of the graft and is mediated (in various situations) by complement, natural killer (NK) cells, and/or preexisting antibodies.
- Hyperacute rejections have also been called "white grafts" because in the case of skin, the fai l u re to establish a vascular connection gives the engrafted skin a blanched appearance

PERMISSIBLE ABO HOST–DONOR COMBINATIONS

Recipient Phenotypes	Can Accept Erythrocytes from Donors of Phenotypes
A	A, O
B	B, O
AB[a]	AB, A, B, O
O	O[b]

[a]Because they can safely accept erythrocytes from all donor types, type AB individuals are called *universal recipients*.

[b]Because they can safely donate erythrocytes to all recipient types, type O individuals are called *universal donors*.

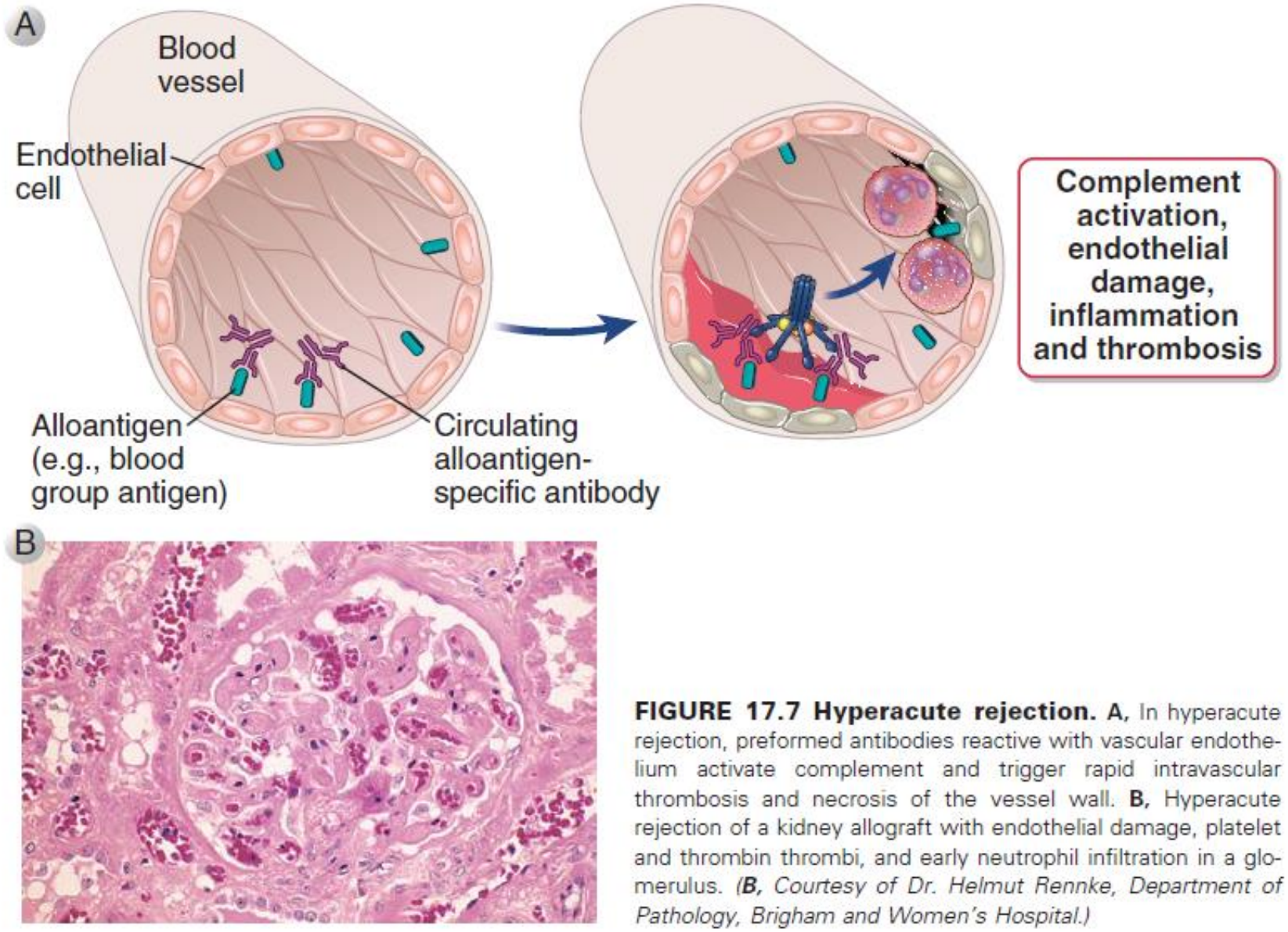
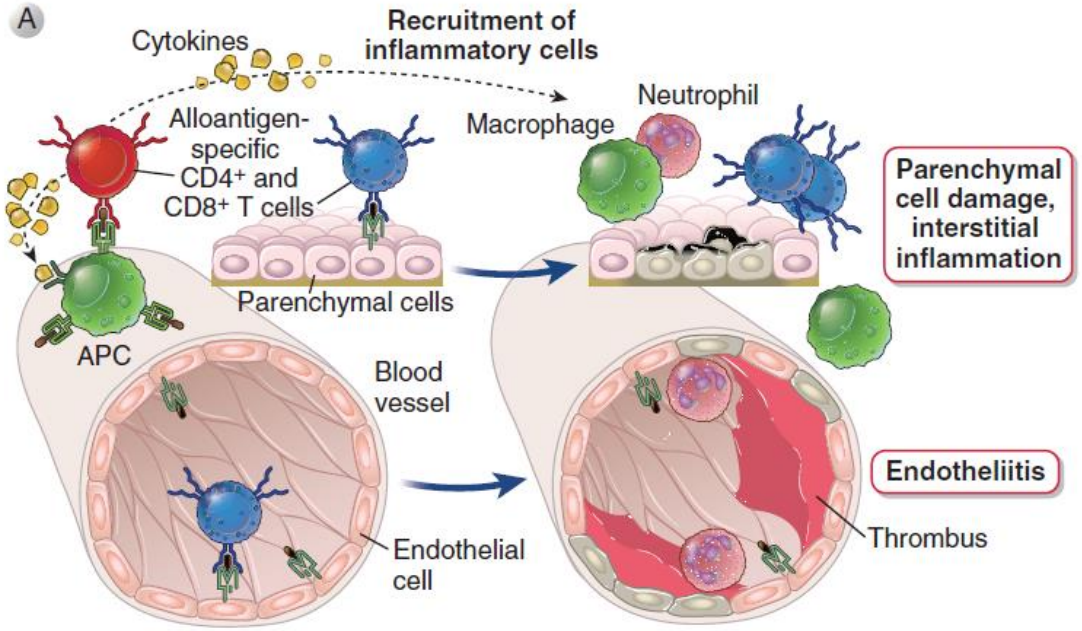


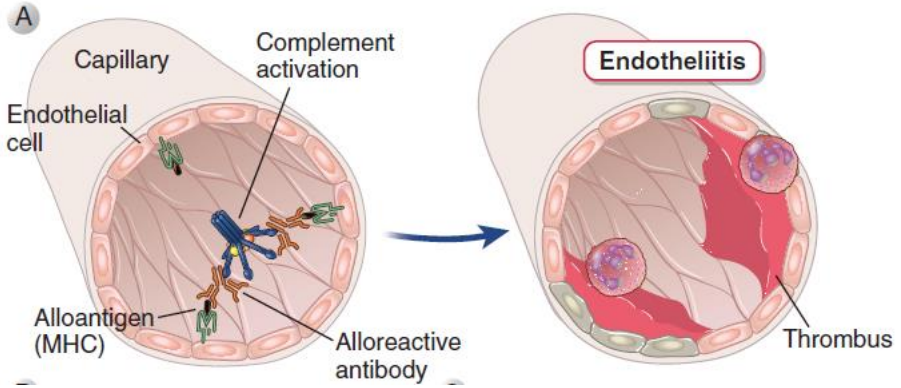
FIGURE 17.7 Hyperacute rejection. A, In hyperacute rejection, preformed antibodies reactive with vascular endothelium activate complement and trigger rapid intravascular thrombosis and necrosis of the vessel wall. **B,** Hyperacute rejection of a kidney allograft with endothelial damage, platelet and thrombin thrombi, and early neutrophil infiltration in a glomerulus. *(**B,** Courtesy of Dr. Helmut Rennke, Department of Pathology, Brigham and Women's Hospital.)*

Acute rejections

- Acute rejections occur much sooner after graft emplacement than do chronic rejections.
- The grafts establish vascular connections and function normally for a relatively short period (2 to 4 weeks) before the first signs of rejection appear.
- acute rejections proceed rapidly once underway.
- The grafts become edematous and inflamed, with an influx of blood and mononuclear cell infiltrates, and complete destruction and sloughing of the grafted tissues may take only a very few days following the first signs of deterioration.
- Acute rejections are commonly seen when the donor and recipient differ at MHC histocompatibility genes, especially those involving the MHC class I loci .



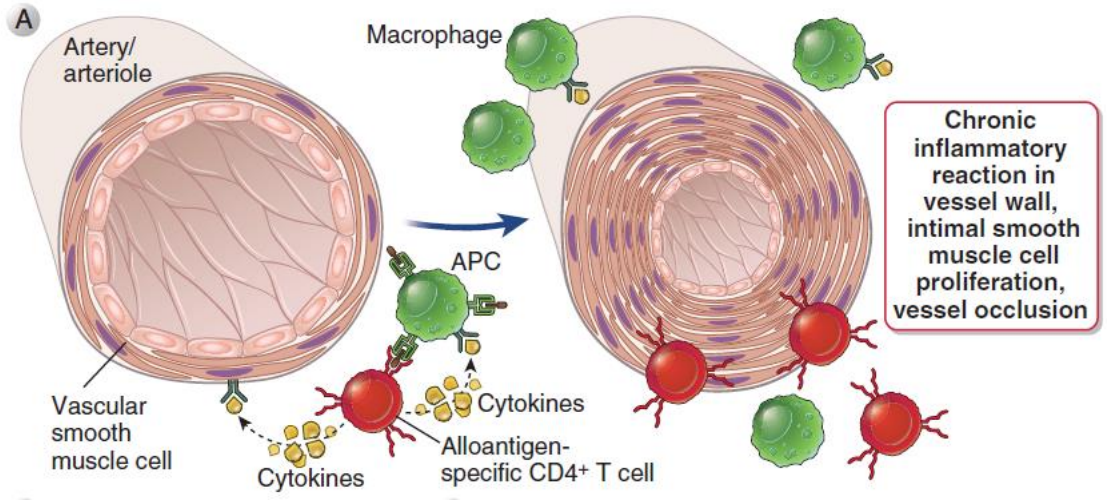
In acute cellular rejection, CD4+ and CD8+ T lymphocytes reactive with alloantigens on endothelial cells in blood vessels and parenchymal cells mediate damage to these cell types.



Acute antibody mediated rejection. **A,** Alloreactive antibodies formed after engraftment may contribute to parenchymal and vascular injury

Chronic rejections

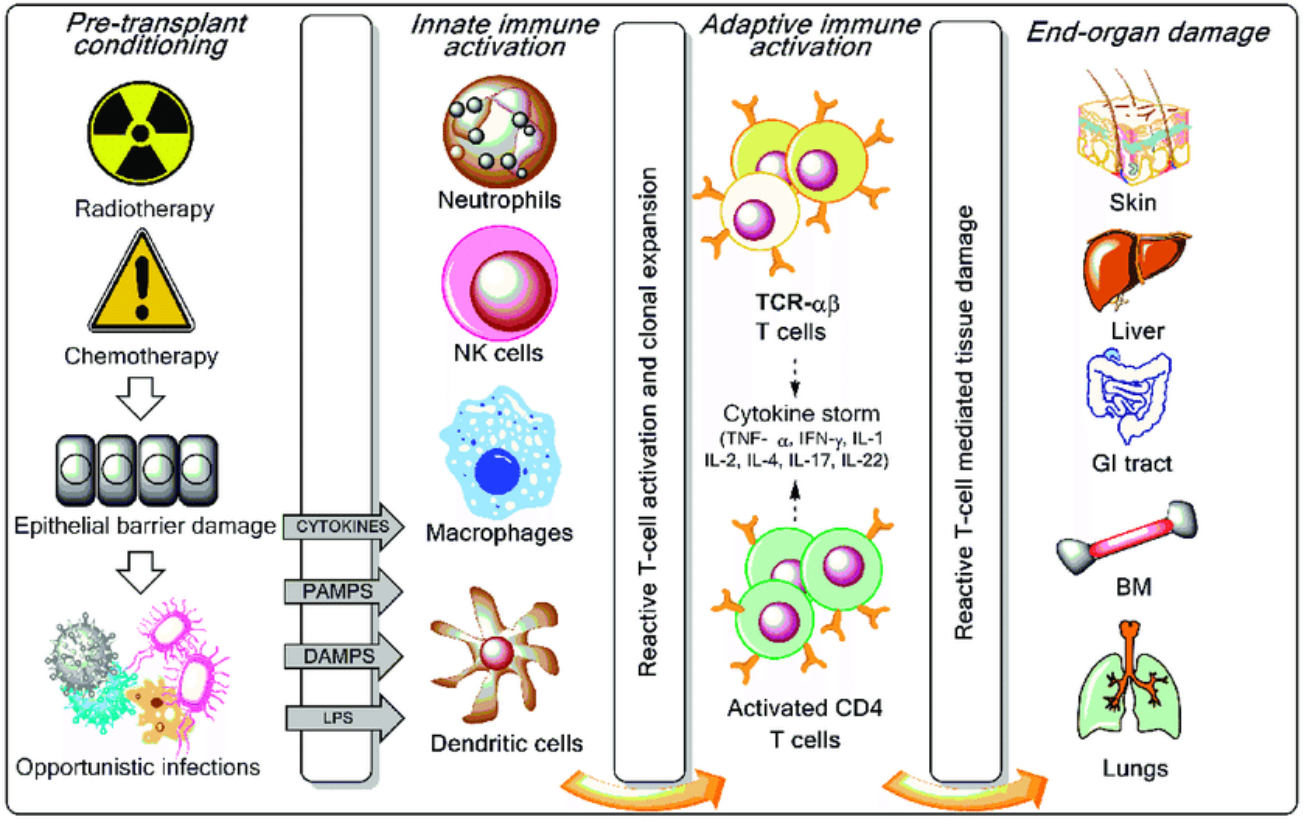
- Chronic rejections are the slowest and the least vigorous type of rejection.
- The transplanted tissues or organs establish a vascular connection and proceed to function for weeks, months, and even years before signs of deterioration due to immune attack become evident.
- Even after the first signs of rejection appear, the graft destruction proceeds slowly and gradually as the graft tissue is replaced by intracellular matrix and scar tissue.
- Chronic rejections are typical of situations in which the donor and recipient differ by only non-MHC histocompatibility gene differences, although there are exceptions.



In chronic rejection with graft arteriosclerosis, injury to the vessel wall leads to intimal smooth muscle cell proliferation and luminal occlusion.
This lesion may be caused by a chronic inflammatory reaction to alloantigens in the vessel wall

Immunologic Complication of Hematopoietic Stem Cell Transplantation - ***Graft-Versus-Host Disease***

- ***GVHD is caused by the reaction of grafted mature T cells in the HSC inoculum with alloantigens of the host***.
- It occurs when the host is immunocompromised and therefore unable to reject the allogeneic cells in the graft.
- In most cases, the reaction is directed against minor histocompatibility antigens of the host because bone marrow transplantation is not usually performed when the donor and recipient have differences in MHC molecules.

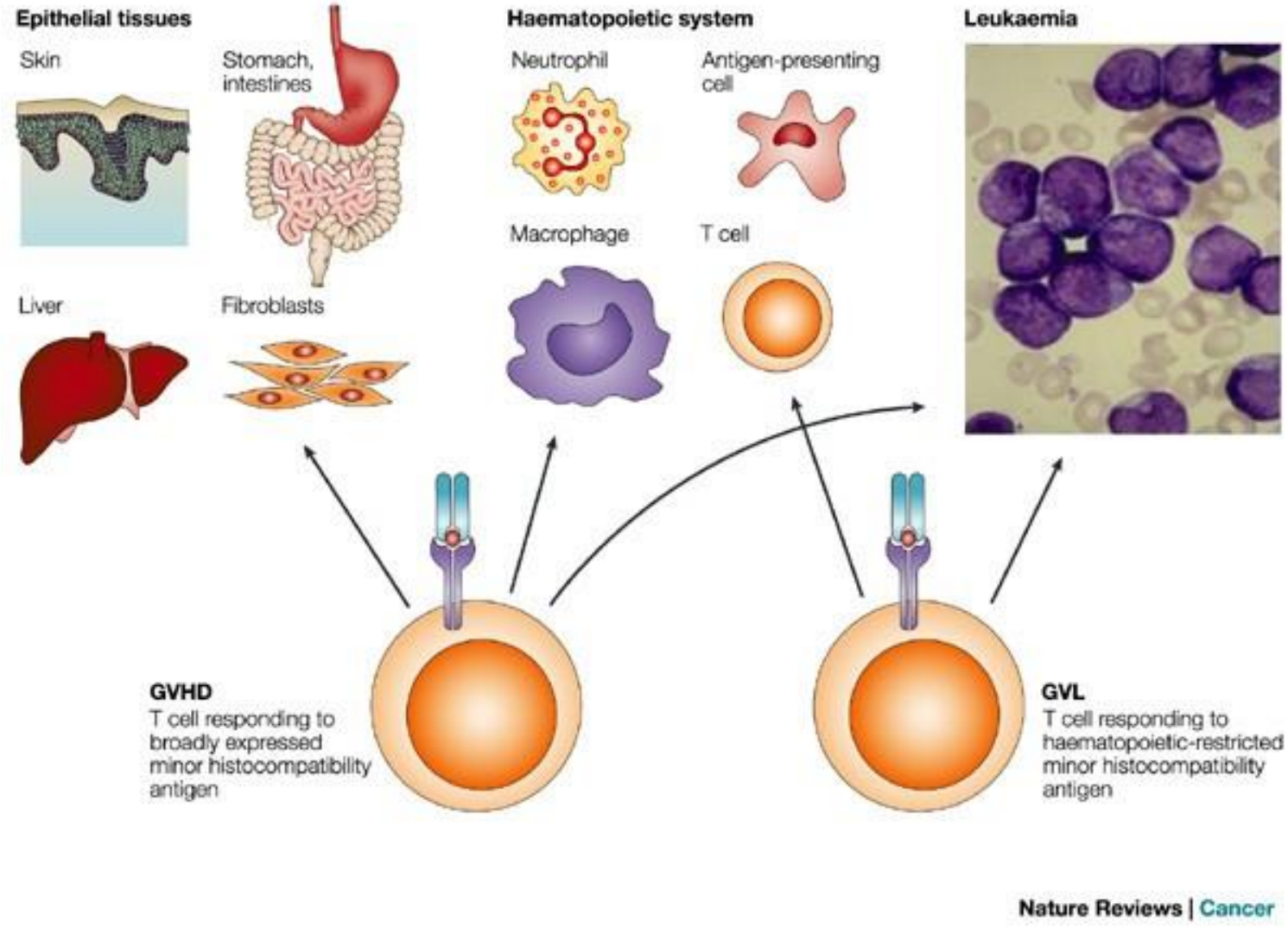


GVHD may also develop when solid organs that contain significant numbers of T cells are transplanted, such as the small bowel, lung, or liver.

GVHD is the principal limitation to the success of bone marrow transplantation.

Graft versus leukemia

- the ability of donor immune cells to eliminate host leukemic cells after allogeneic HSCT



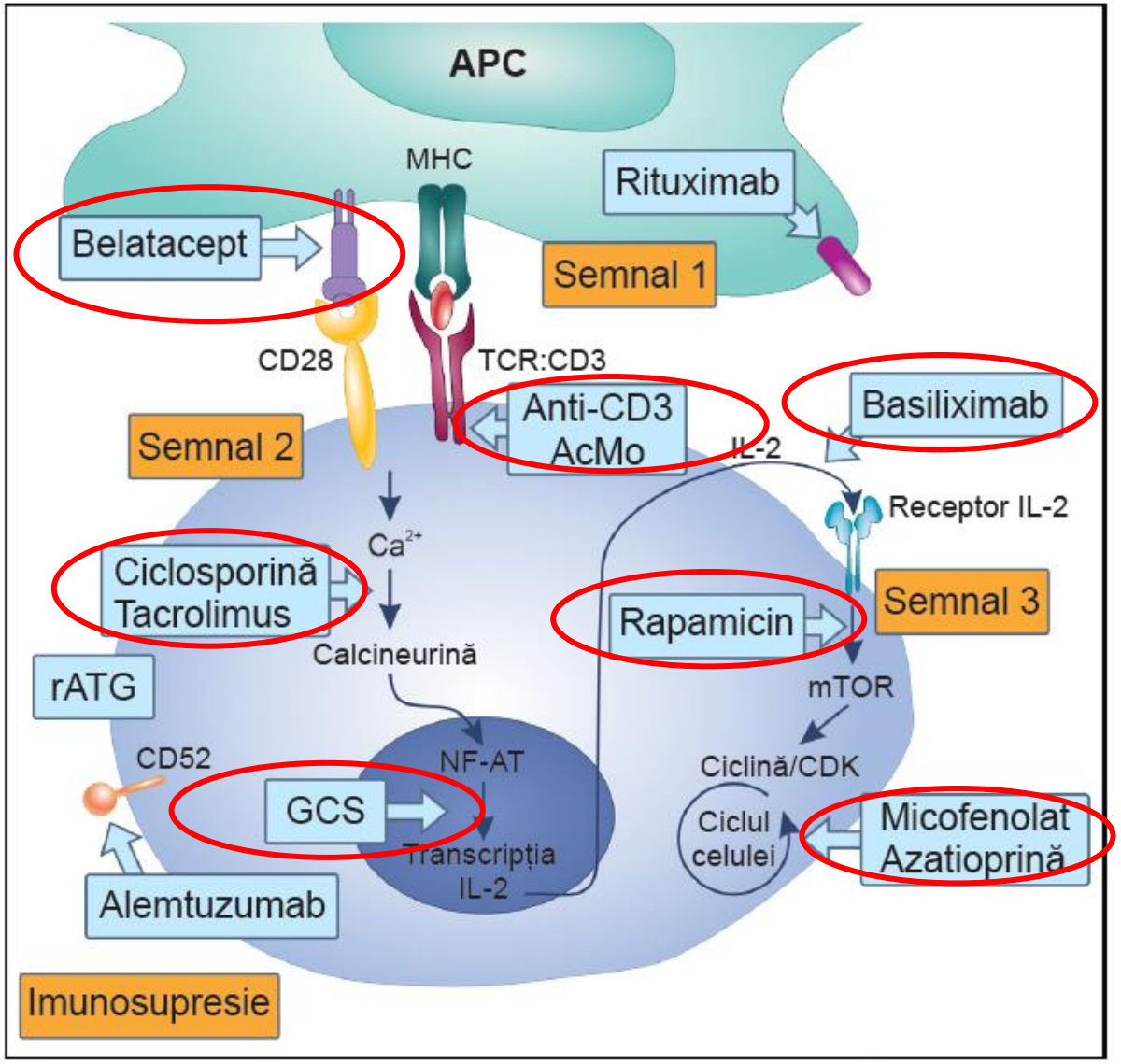
Mechanisms of action of immunosuppressive drugs

- The main goal of immunosuppression is to avoid triggering the alloimmune response by preventing activation of LT and subsequent release of cytokines and cell proliferation
- Immunosuppression is indicated in all transplant patients

- Exception:

- monozygotic twins
- corneal transplant (immune-privileged organ)

In the absence of immune suppression allografts are rejected



Immunosuppressive agents relevant to transplantation

Agent	Affected Cells	Mode of Action
Azathioprine	Multiple cell types	Inhibition of nucleotide synthesis
Corticosteroids (e.g., prednisone)	Multiple cell types	Inhibition of transcription for numerous cytokines and other products involved in inflammation
Cyclophosphamide	Multiple cell types	Inhibition of nucleotide synthesis
Cyclosporine	Lymphocytes	Inhibition of transcription for multiple cytokines (e.g., IL-2, IL-4)
Mycophenolate mofetil	Lymphocytes	Inhibition of lymphocyte nucleotide synthesis and proliferation
Sirolimus (rapamycin)	T cells	Inhibition of some signal transduction induced by cytokines (e.g., IL-2)
Tacrolimus (FK506)	T cells	Inhibition of gene transcription in lymphocytes, inactivation of calcineurin
Antibodies against the IL-2 receptor	T cells	Inhibition of IL-2 mediated activation of lymphocytes
Irradiation	Many cell types	Induction of DNA damage, especially in rapidly proliferating cells
Antibodies against lymphocytes or against T cells	Lymphocytes, T cells	Destruction or inhibition of lymphocytes or lymphocyte subsets
Anti-CD4 antibodies, anti-CD8 antibodies	$CD4^+$ T cells, $CD8^+$ T cells	Interference with TCR binding
Anti-MHC I/II antibodies	Antigen-presenting cells	Interference with antigen presentation and T-cell activation by blockading

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