



IMMUNOPATHOLOGY

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LEC.4





Rejection of Tissue Transplants:

-Allografts transplantation of organs from one individual to another of the same species.

xenografts: organ transplantation from one species to another (still an experimental procedure)

transplant rejection:

is a complex phenomenon in which recipient's immune system recognizes the graft as being foreign and attacks it.

This process involves both cell- and antibody-mediated reactions that destroy the graft.

Because **HLA genes** are highly polymorphic, there are always some differences between individuals (except, of course, identical twins)

Immune Recognition of Allografts

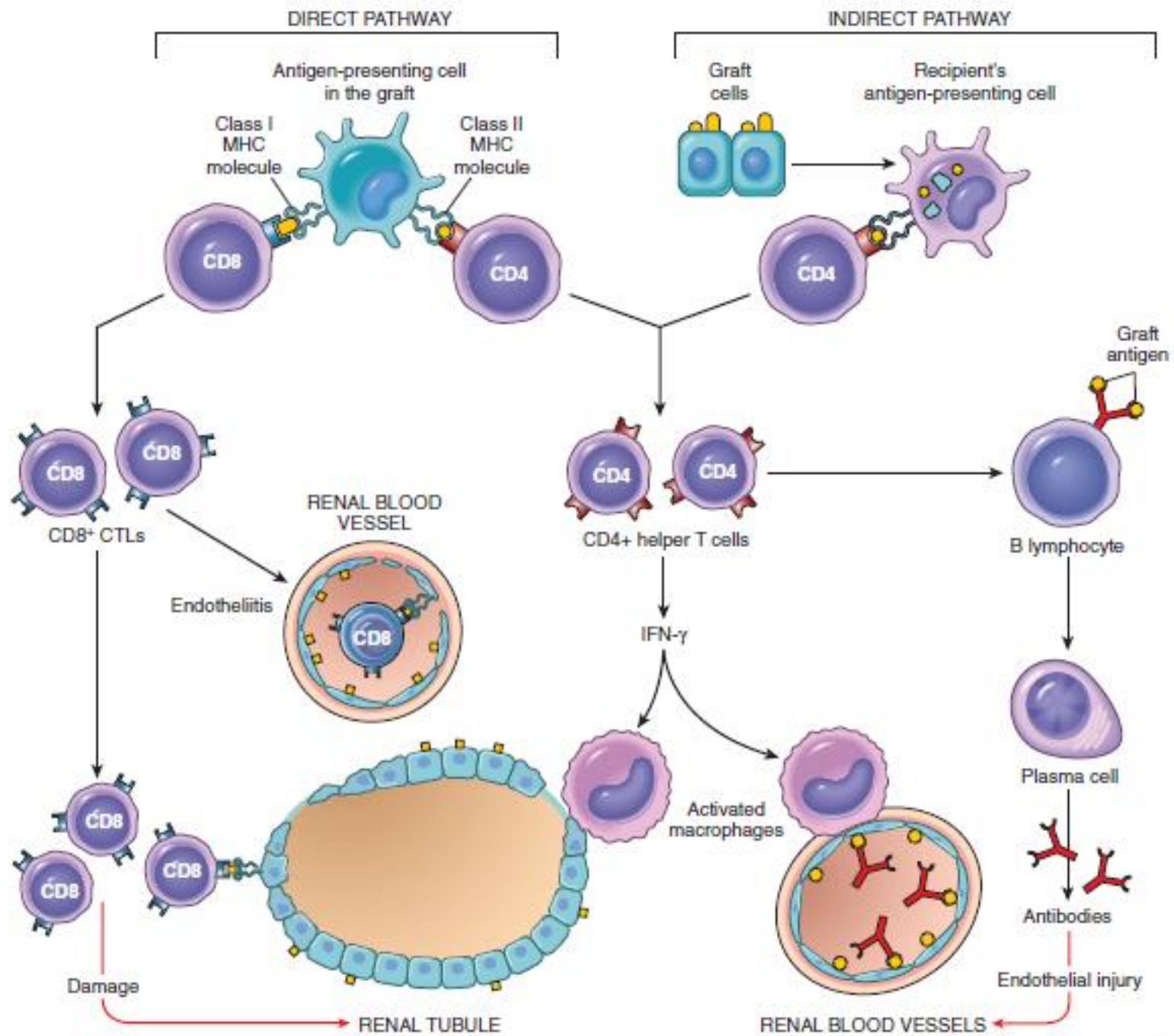
- *Rejection of allografts is a response mainly to MHC molecules.*
- There are two main mechanisms by which the host immune system recognizes and responds to the MHC molecules on the graft:

1. Direct pathway:

Host T cells recognize donor HLA on APC derived from the donor .

dendritic cells carried in the donor organs are the most important APCs for initiating the antigraft response, because they express high levels of class I and II MHC molecules and costimulatory molecules (e.g., B7-1 and B7-2) leading to activation of CD4+ and CD8+ cells.

2. Indirect pathway: Host T cells recognize donor HLA after processing and presenting on host APC (similar to any other exogenous processed antigen).



Effector Mechanisms of Graft Rejection

- Direct cytotoxic T cell (CTL-) mediated parenchymal and endothelial cytolysis
- Antibody-mediated responses can also be important; these tend to induce injury to endothelial cells rather than parenchymal cells
- Macrophage-mediated damage
- Cytokine-mediated vascular and parenchymal dysfunction
- Microvascular injury also causes downstream tissue ischemia
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- Rejection reactions are classified as hyperacute, acute, and chronic

1-Hyperacute rejection:

-occurs within minutes or hours after transplantation.

- Pre-formed anti-donor antibodies bind to graft endothelium immediately after transplantation, leading to thrombosis, ischemic damage, and rapid graft failure

hyperacutely rejecting kidney rapidly becomes **cyanotic**, **mottled**, and **flaccid**, and may excrete a mere few drops of bloody urine.

Immunoglobulin and complement are deposited in the vessel wall, causing endothelial injury and fibrin-platelet thrombi.

Neutrophils rapidly accumulate within arterioles, glomeruli, and peritubular capillaries.

As these changes become diffuse and intense, the glomeruli undergo **thrombotic occlusion** of the capillaries, and **fibrinoid necrosis** occurs in arterial walls.

The kidney cortex then undergoes necrosis (infarction), and such nonfunctioning kidneys have to be removed

It occurs when the recipient has been previously sensitized to graft antigens.

Preformed, circulating antibody binds to graft endothelial HLA with an immediate (minutes to days) complement- and antibody - mediated injury.

Such antibodies may be present in :

1-a recipient who has previously rejected a transplant

2-Multiparous women who develop antibodies against paternal HLA antigens shed from the fetus may have preformed antibodies that will react with grafts taken from their husbands or children, or even from unrelated individuals who share HLA alleles with the husbands

3- prior blood transfusions can also lead to pre sensitization, because platelets and white blood cells are rich in HLA antigens and donors and recipients are usually not HLA-identical.

Hyperacute rejection was a concern in the early days of kidney transplantation, but with the current practice of cross-matching, (testing recipient's serum for antibodies against donor's cells), it is no longer a significant clinical problem.

Acute Rejection

It typically occurs within days or weeks of transplantation.

Both cellular and humoral mechanisms can contribute.

1-Acute cellular rejection :T cells destroy graft parenchyma

and vessels by cytotoxicity and inflammatory reactions.

2- Acute humoral rejection (rejection vasculitis) is mediated by newly synthesized (not preformed and produced after transplantation) anti-donor antibodies. The initial target of these antibodies in rejection is the graft vasculature leading to necrotizing vasculitis with consequent thrombosis.

Chronic Rejection

Chronic rejection occurs over months to years .

is characterized by progressive organ dysfunction.

Chronic antibody-mediated rejection usually develops insidiously, without preceding acute rejection, and primarily affects vascular components. The mechanisms of the vascular lesions are not well understood.

T cells also contribute to chronic rejection, in which lymphocytes reacting against alloantigens in the vessel wall secrete cytokines that induce local inflammation and may stimulate the proliferation of vascular endothelial and smooth muscle cells.

The vascular lesions and T-cell reactions cause parenchymal fibrosis.

Clinically : chronic renal failure

Transplantation of Hematopoietic Stem Cells(HSC)

Hematopoietic stem cell (HSC)


transplantation is used as therapy for:

1. **hematopoietic malignancies**.e.g. leukemia, lymphoma and multiple myeloma
2. **aplastic anemias**(bone marrow failure syndrome)
3. certain **inherited disorders** e.g. immune deficiency states and severe forms of **thalassemia** and **sickle cell anemia**.

Sources of Hematopoietic Stem Cells for Transplantation:

1. from donor bone marrow,
2. from the peripheral blood.
- 3. from the umbilical cord blood of newborns, a readily available rich source of HSCs

- The recipient receives chemotherapy and/or irradiation to destroy malignant cells (e.g., in leukemia) and to create a graft bed; then, HSCs are infused into the peripheral blood, from which they home to bone marrow .

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- Rejection of allogeneic HSC transplants seems to be mediated by some combination of host T cells and NK cells that are resistant to radiation therapy and chemotherapy.

Major problems complicate this form of transplantation:

1. Immune Deficiencies. Recipients are susceptible to a variety of infections, mostly viral, such as cytomegalovirus (CMV) and EBV infections.

1.graft-versus-host disease(GVHD) :

This occurs when immunologically competent T cells (or their precursors) are transplanted into recipients who are immunologically compromised.

the transferred cells recognize alloantigens in the host and attack host tissues.

-Acute GVHD (occurring days to weeks after transplantation) causes epithelial cell necrosis in three principal target organs: liver, skin, and gut.

Clinical features:

- 1- skin rash that may lead to desquamation in severe cases.
- 2- Destruction of small bile ducts gives rise to jaundice.
- 3- mucosal ulceration of the gut results in bloody diarrhea.

-Chronic GVHD may follow the acute syndrome or may occur insidiously.

Clinical features:

- 1- The patients develop extensive cutaneous injury, with destruction of skin appendages and fibrosis of the dermis. The changes may resemble systemic Sclerosis
- 2- Chronic liver disease manifested by cholestatic jaundice is also frequent.
- 3- Damage to the GIT may cause esophageal strictures.



Figure 23.8 Widespread erythematous skin rash in acute graft-versus-host disease following allogeneic stem cell transplantation.

ImmunoDeficiency Syndromes (-IDS)

PRIMARY (GENETIC) (P-IDS)

SECONDARY (ACQUIRED) (A-IDS)

IMMUNE DEFICIENCY DISEASES:

1. Primary immunodeficiencies

are usually hereditary and manifest between 6 months and 2 years of life .

2. Secondary immunodeficiencies

result from altered immune function due to infections e.g. Acquired Immunodeficiency Syndrome (AIDS), malnutrition, aging, immunosuppression, irradiation, chemotherapy, or autoimmunity.

Clinically, patients with immune deficiency present with increased susceptibility to infections as well as to certain forms of cancer.

- - The type of infections in a given patient depends largely on the component of the immune system that is affected:
- Patients with defects in immunoglobulin, complement, or phagocytic cells typically suffer from recurrent infections with pyogenic bacteria.
- - Those with defects in cell-mediated immunity are prone to infections caused by viruses, fungi, and intracellular Bacteria

Primary immunodeficiencies

(Congenital) Caused by mutations in genes involved in lymphocyte maturation or function, or in innate immunity

- **Some of these disorders are :**

- **1. X-Linked Agammaglobulinemia (XLA) Bruton Disease**

is characterized by the failure of pre-B cells to differentiate into B cells and, there is a resultant :

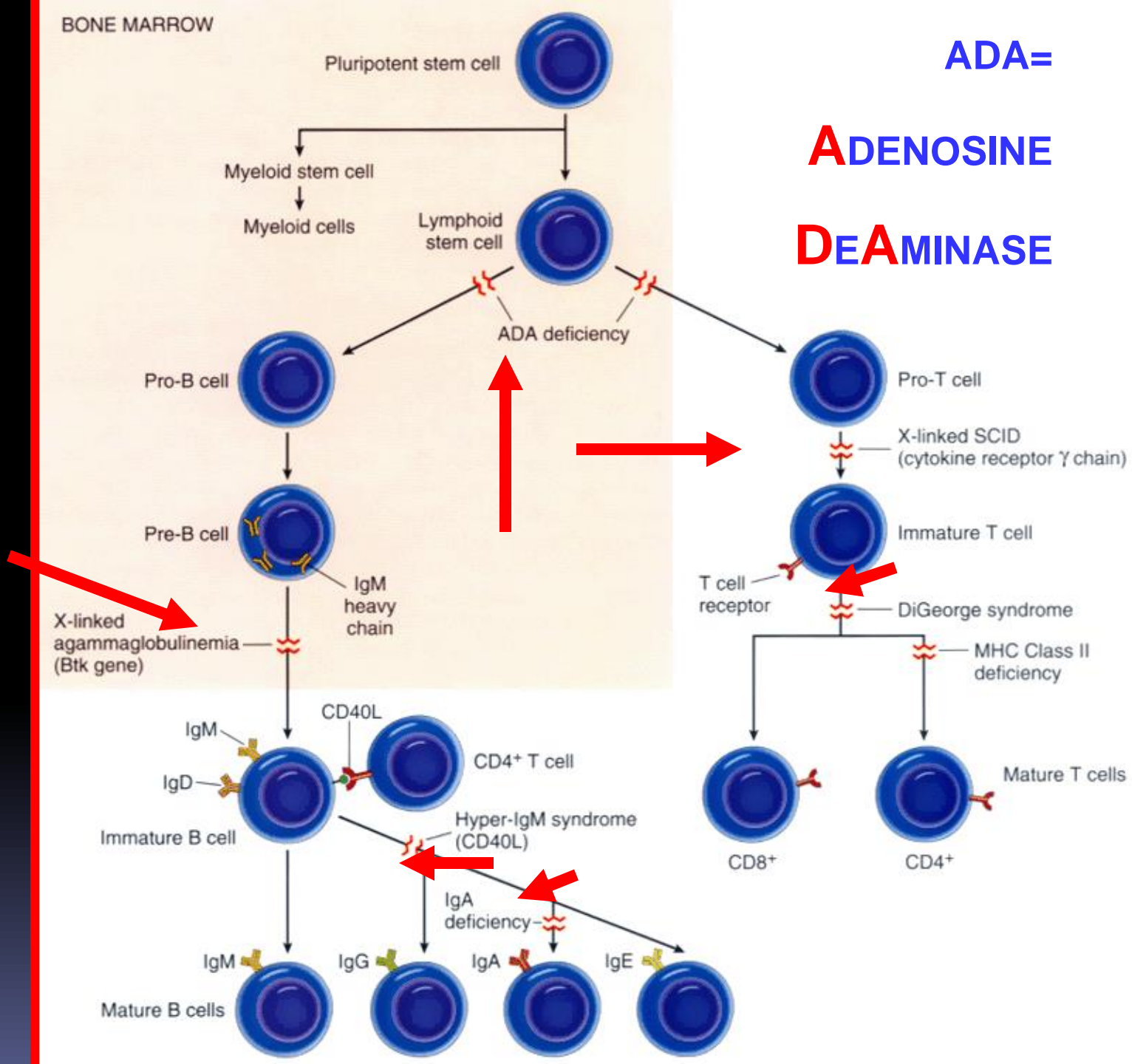
- absent or markedly decreased numbers of B cells in the circulation, with depressed serum levels of all classes of immunoglobulins.
- Normal T cell-mediated responses most intracellular viral, fungal, and protozoal infections are handled quite well by the intact T cell-mediated immunity
- XLA does not become apparent until the affected infant reach the age of approximately 6 months as maternal immunoglobulins are depleted.
- In most cases, recurrent bacterial infections such as acute and chronic pharyngitis, sinusitis, otitis media, bronchitis.
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BONE MARROW

ADA=

ADENOSINE

DEAMINASE



2. Common Variable Immunodeficiency

-Is a heterogeneous group of disorders characterized by defects in antibody Production or sometimes only hypogammaglobulinemia, resulting in impaired antibody responses to infection, and increased susceptibility to infections.

The clinical manifestations are superficially similar to those of XLA, but in common variable immunodeficiency, males and females are affected equally and the onset of symptoms is much later, in the second or third decade of life

3. Isolated IgA Deficiency The

most common of all the primary immune deficiency diseases

- Absent serum and secretory IgA
- IgA is the major immunoglobulin in mucosal secretions and is thus involved in defending the airways and the GIT.

Although most people with this condition are asymptomatic, weakened mucosal defenses predispose patients to recurrent sino-pulmonary infections and diarrhea.

Hyper-IgM Syndrome

Patients with the hyper-IgM syndrome produce normal (or even supranormal) levels of IgM antibodies to antigens but lack the ability to produce the IgG, IgA, and IgE isotypes.

the underlying defect is an inability of T cells to induce B cell isotype switching.

In 70% of patients, the disease is X-linked

-Other primary immunodeficiency diseases include:

-Severe Combined Immunodeficiency

-Thymic Hypoplasia: DiGeorge Syndrome

- Wiskott-Aldrich Syndrome :Immune Deficiency with thrombocytopenia and Eczema.

-Genetic Deficiencies of Complement Protein

-Defects in Lymphocyte Activation

-Defect in phagocyte



THANK YOU