Transplantation Immunology & Immunodeficiency

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Learning outcome

By the end of this lecture the students will be able to:

1	Distinguish between types of grafts.
2	Describe immunology of graft rejection.
3	List the procedures to improve graft survival.
4	Classify the types of primary and secondary immunodeficiency disorders.
5	Plan the treatment of immunodeficiency disorders.

Lecture outline

- Types of grafts.
- Genetics base of transplantation and immunology of graft rejection.
- Procedures to enhance graft survival.
- Definition and classification of immunodeficiency.
- Primary (congenital) Immunodeficiency disorders.
- Secondary immunodeficiency disorders.
- Immunodeficiency disorders treatment.

Case scenario, Clinical Correlate, Practice points:

A 32-year-old woman was admitted to Hospital for renal transplantation from her 27-yrs-old friend. Ten days following transplantation, the serum creatinine concentration was **1.3 mg/dl**, and the patient was discharged on a regimen of prednisone (60 mg/day) and azathioprine (100 mg/day). One day following discharge, the patient noted blood-tinged urine, mild graft site tenderness, and decreased urine output. Two days later, fever developed and the patient was readmitted to the hospital.

The renal graft site was no longer tender, and there was no obvious swelling. Results of urine analysis revealed 20 white blood cells/high power field and two to three coarse granular casts. The serum creatinine concentration was **3.1 mg/dl**.

- What is your probable diagnosis?
- Mention underlying immunological mechanism?

Transplantation Immunology

Def: Transplantation is the **transfer** of cells, tissues or organs from one part of the body to another or from one individual to another.

Types of Grafts

1. Autografts

Such as bone transplanted from one location to another.

2. Isografts

Grafts between members of the same species with identical genetic makeup **(identical twins).**

3. Allografts

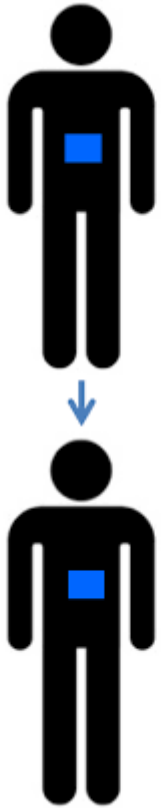
From members of the same species **(human to human).**

4. Xenografts

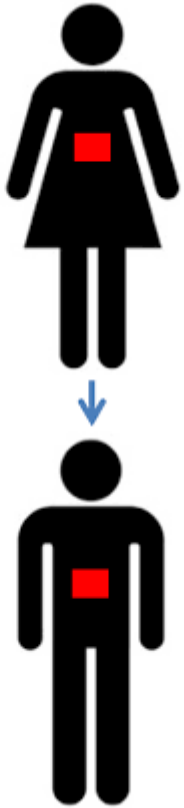
From members of different species; **(animal to human).**

1. Autografts

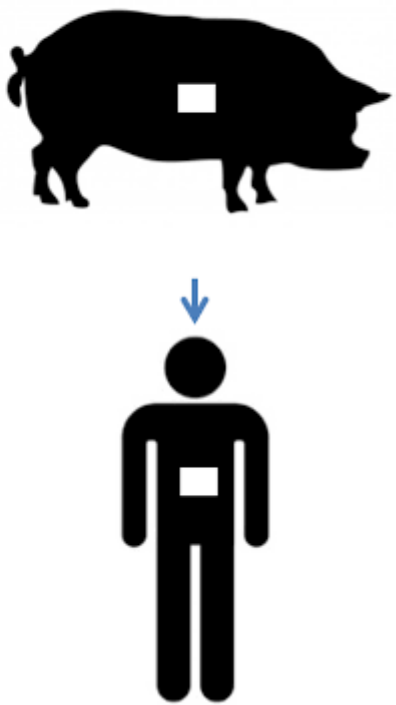
Type	Mnemonic
Autograft	*(self)*
Isograft (Syngeneic)	*(same)*
Allograft	*You can get it from All-o people*
Xenograft	*You can get it from X-tra species*



2. Isografts



3. Allografts



4. Xenografts

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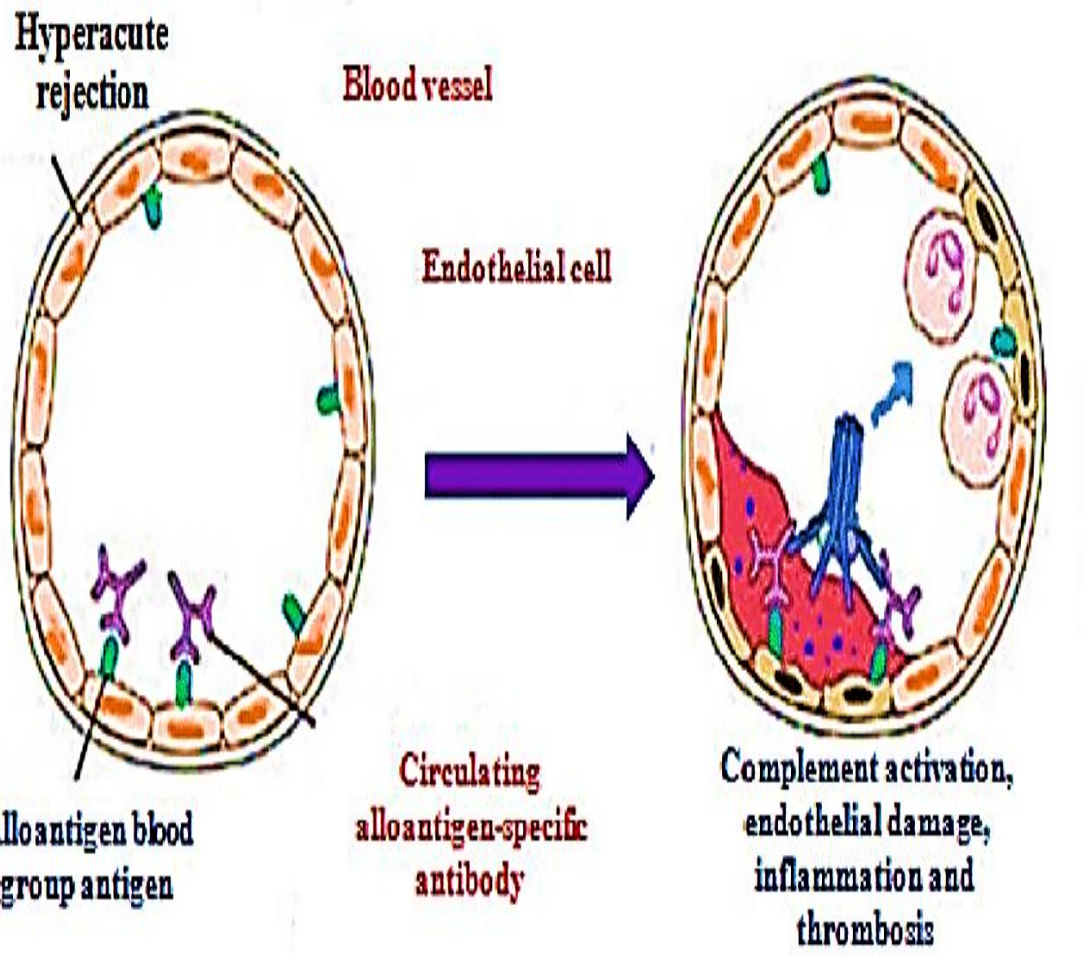
Grafts between members of the same species with identical genetic makeup is:

A. Autografts.
B. Isograft
C. Allograft
D. Xenograft
E. Alloplast

Types of graft rejection

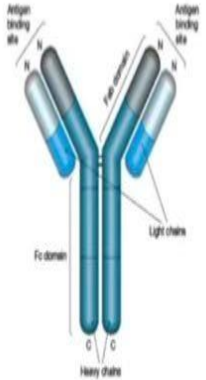
1. Hyper acute rejection (typeII hypersensitivity)	2. Acute rejection (typeIV hypersensitivity)	3. Chronic rejection (type II and IV hypersensitivity
Occurs **minutes to few hours** after transplantation.	Occurs in **weeks** following transplantation.	Occurs after extended periods (**months or years**).
It is due to **preformed antibodies**, either: ▪ Natural antibodies to blood type Ag. ▪ Anti-MHC antibodies formed in response to Blood transfusions, Previous transplants, During pregnancy to the baby's paternal MHC Ag.	Due to: Grafts contain passenger leukocytes, (APC) that travel to the draining lymph nodes and activate recipient T cells.	Comes from uptake of graft Ag by recipient Ag presenting cells and presentation on Host (recipient) MHC on recipient Ag presenting cells.
Antibodies react with antigens on vascular endothelial cells and activate complement.	Effectors are primarily Cytotoxic T lymphocytes (CD8 T cells). These cells migrate to the graft causing tissue damage. It is reversible with medications.	Effectors are usually Th1 cells that activate macrophages to cause tissue injury, vasculitis and scarring.
Resulting damage blocks blood vessels (thrombosis) causing ischemia and damages the organ. It is irreversible.		Chronic rejection and organ failure are due to: Arteriosclerosis of graft vessels, Chronic toxicity of anti-rejection drugs. It is irreversible.

Hyperacute rejection(typeII)

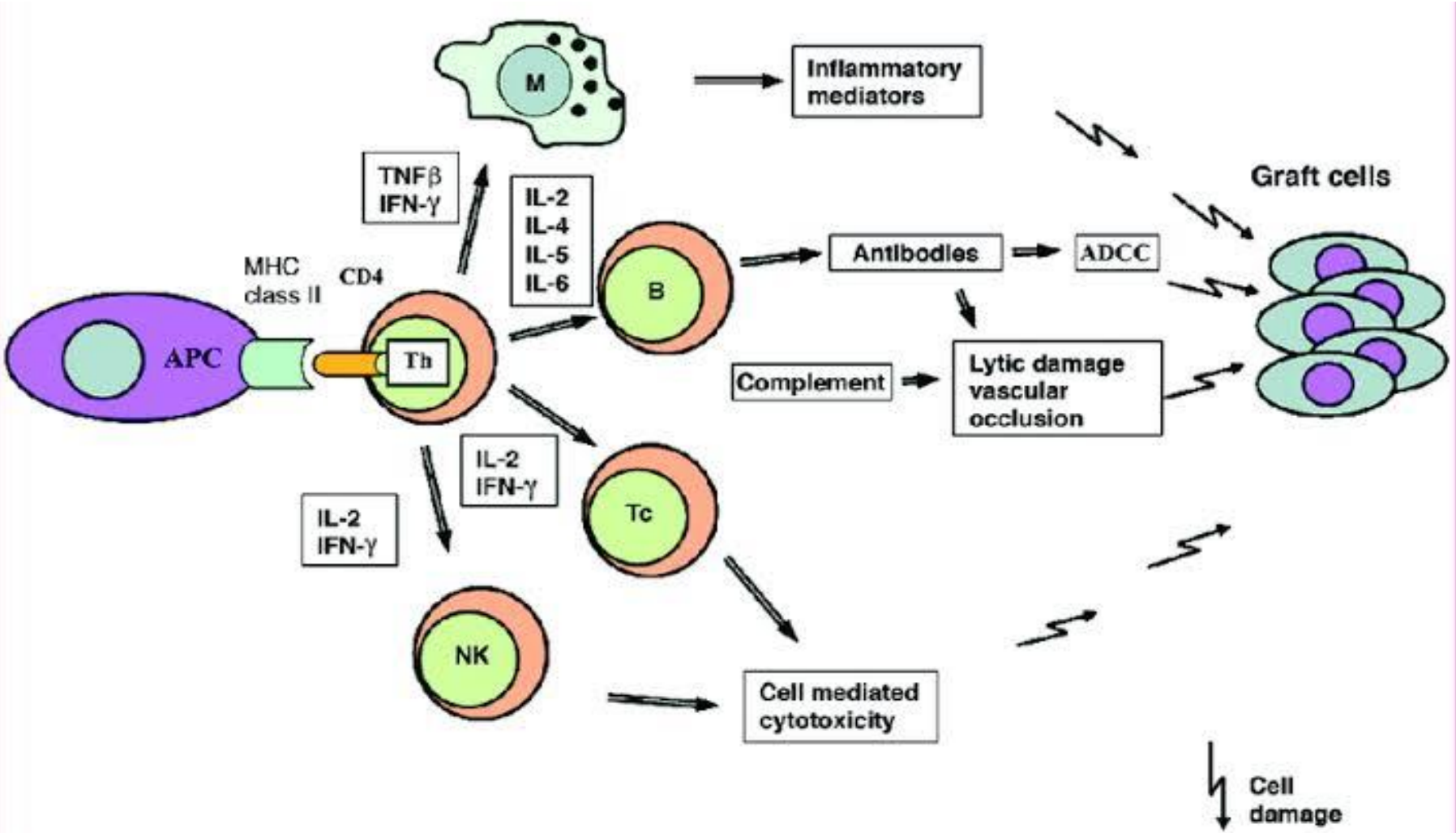


"*Hyper* children eat *Tic Tacs*"

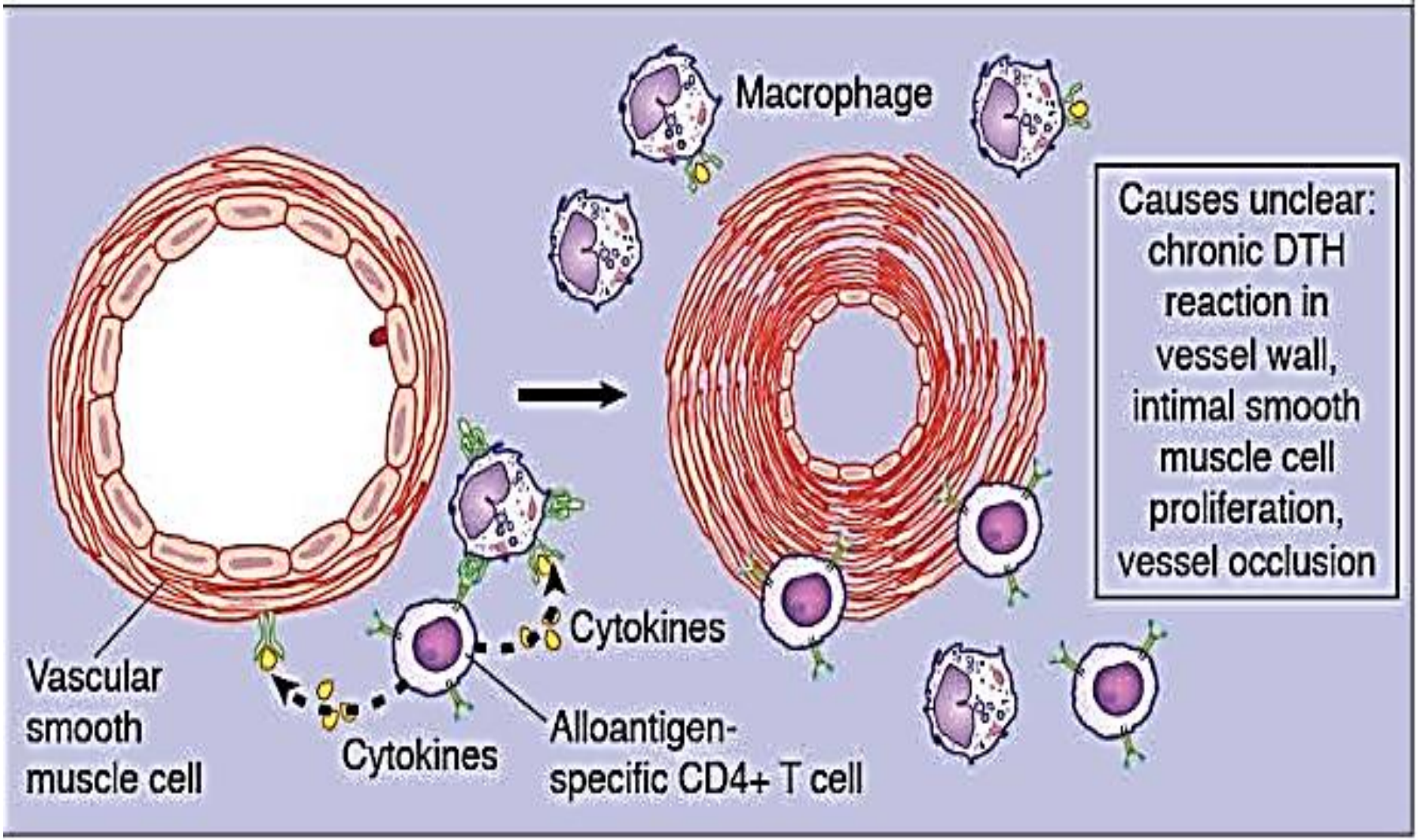
- Hyper = fast (minutes)
- Tic Tacs look like antibody light chain
- Tic = Thrombosis
- Tic Tac = Type Two



Acute rejection (typeIV)



Chronic rejection(typeII &IV)



"Hyper children eat Tic Tacs"

(this leads to)

"Weak rotting T-eeth that require medication"

(so)

"Months later, they have 24 KAVITY's"

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Which of the following is a character of hyperacute graft rejection:

A. It Occurs few days after transplantation

B. B. It is due to new formed antibodies

C. Antibodies react with antigens on vascular endothelial cells and activate complement

D. No serious damage of organ occurs.

E. Effectors are usually Th1 cells that activate macrophages to cause tissue injury and scarring.

Chronic rrejection

"**Months** later, they have **24 KAVITY**'s"

- **Months** = month
- **24** = Type II and Type IV Hypersensitivity
- **KAVITY's:**
  - **K**idney injury (Nephropathy)
  - **A**ccelerated Arteriosclerosis
  - **V**anishing Bile Duct Syndrome
  - **I**nterstitial Fibrosis
  - **T**-cell mediated cytokine production
  - **Y**ucky lung (Bronchiolitis Obliterans)

List the procedures to enhance graft survival

1. Donner selection

- The most important is the **MHC identity** with the recipient; an **identical twin** is the ideal.
- Grafts from an **HLA-matched** sibling have 95-100% chance of success.
- Organs from a two or one DR matched cadaver have been used also with some success.
- In every case, an ABO compatibility is essential.

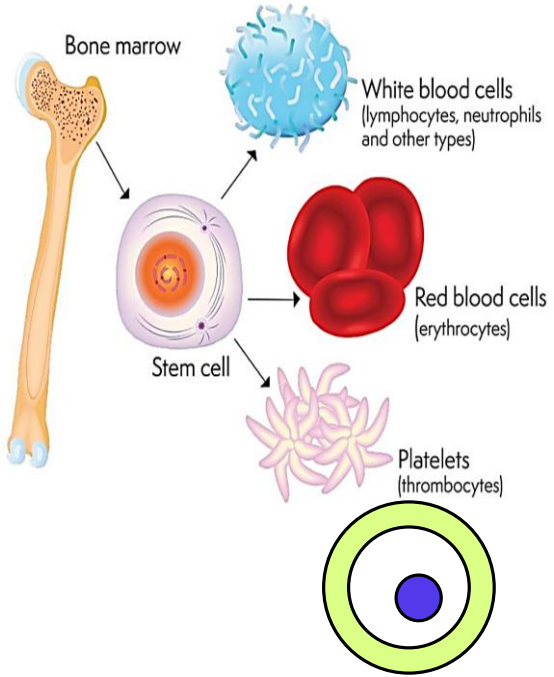
2. Recipient preparation

- Immune suppression increases the risk of infection so protect the recipient by isolation and prophylactic antibiotics.

Stem cell Transplantation

Stem cell transplant is a treatment

To try to cure some types of leukemia, lymphoma and other conditions affecting the bone marrow, such as myeloma.

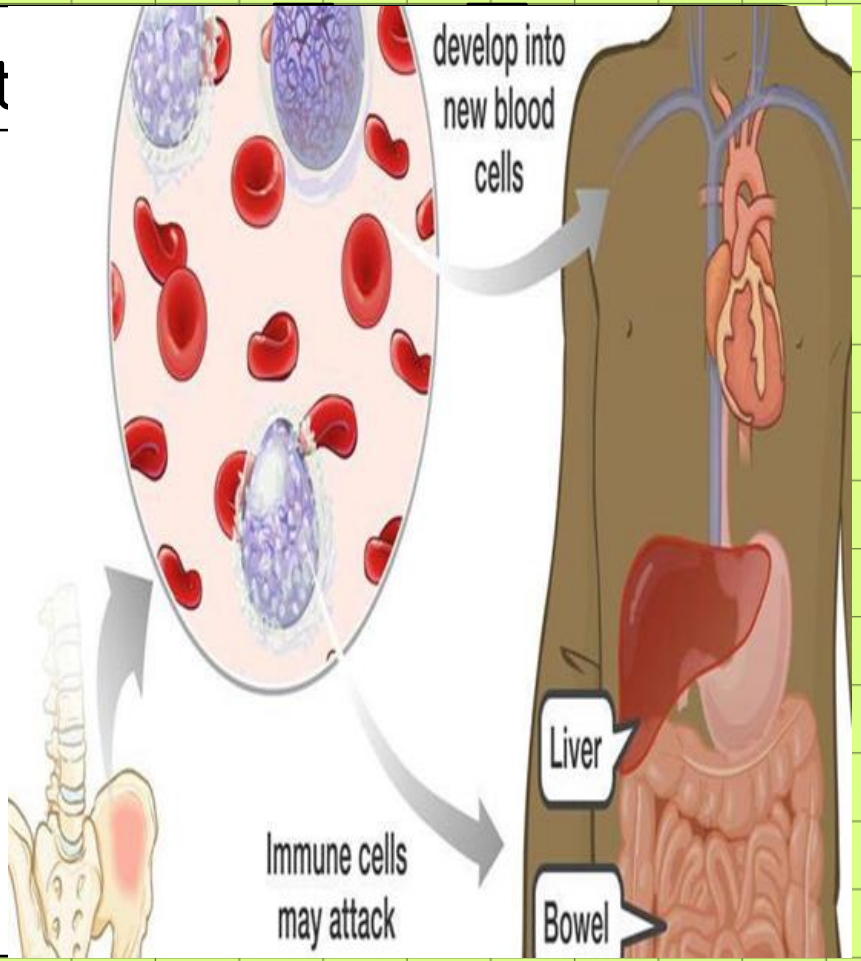


Graft-versus-host disease (GVHD)

This occurs in **bone marrow transplantation** (Stem cell transplants) where the graft contains immunologically competent cells

GVHD responses occur to both MHC and minor H antigens.

Symptoms of GVHD include rashes, diarrhea, and pneumonitis.



the newly transplanted donor cells attack the recipient's body. This happens because the donor's immune cells recognize the recipient's tissues as foreign

1.Conditioning regimen: Before a stem cell or bone marrow transplant, recipients typically undergo a conditioning regimen, which may involve chemotherapy, radiation therapy, or both. This regimen aims to suppress the recipient's immune system . This conditioning can also damage the recipient's tissues, releasing inflammatory signals and creating an environment that promotes immune cell activation.

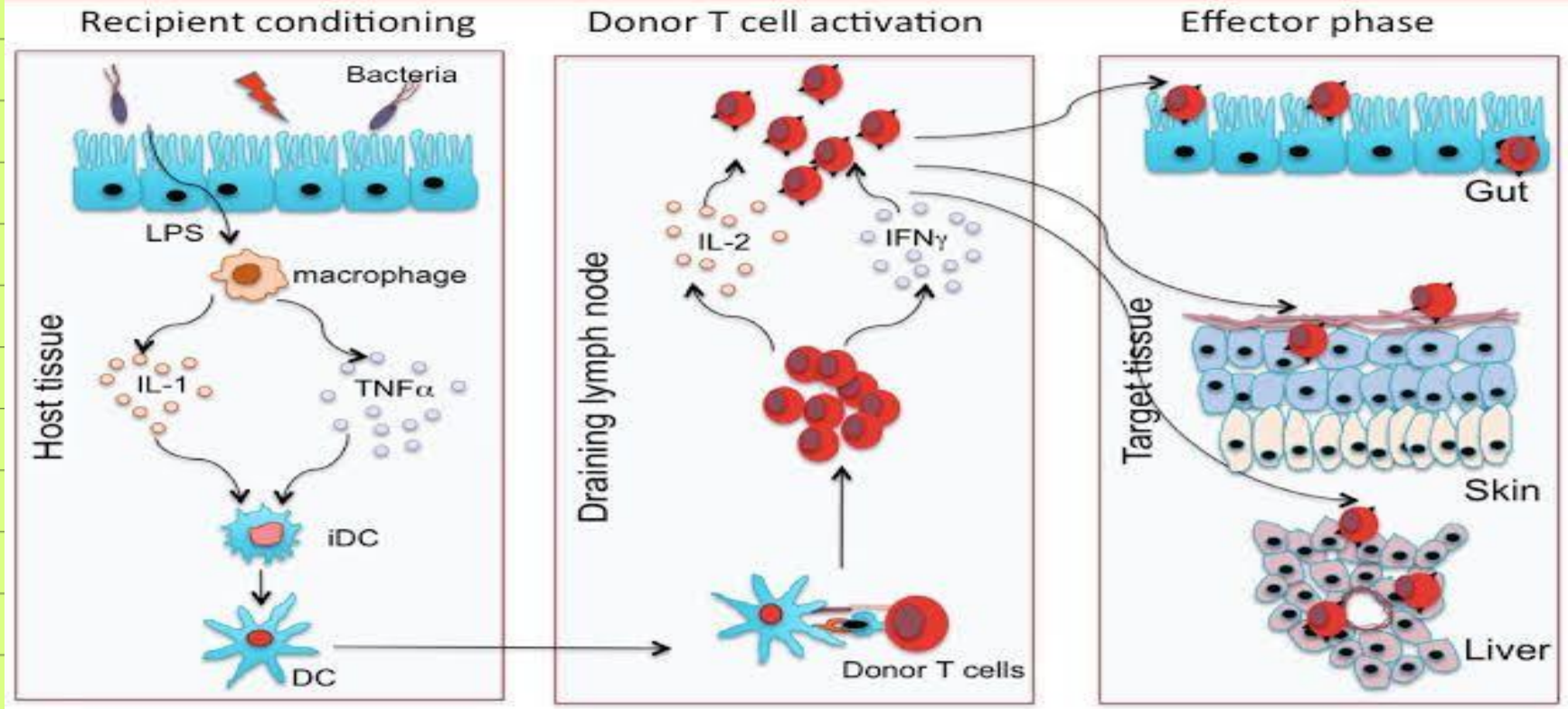
2.Activation of donor immune cells: After transplantation, donor immune cells (T cells) in the graft recognize the recipient's tissues as foreign. This recognition occurs through interactions between antigens on the recipient's cells (called major and minor histocompatibility antigens) and receptors on the donor T cells. These interactions trigger the activation and

1.Migration to target tissues: Activated donor T cells migrate to various tissues and organs in the recipient's body. This migration is facilitated by chemokines that guide the T cells to sites of inflammation and tissue damage.

2.Attack on host tissues: Once in the target tissues, donor T cells recognize and attack recipient cells expressing foreign antigens. This attack leads to tissue damage, inflammation, and dysfunction in affected organs, such as the skin, gastrointestinal tract, liver, and lungs.

3.Cytokine release: During the immune response, donor T cells release pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and interleukins (IL-1, IL-2, IL-6, IL-12). These cytokines further amplify the immune response, recruit other immune cells, and contribute to tissue damage and inflammation.

Patho-physiology of GVHD



Immunodeficiency

Def:

Failure of the immune system to protect against disease or malignancy.

Types of immunodeficiency:

A. Primary immunodeficiencies:	B. Secondary immunodeficiencies:
▪ They are inherited defects of the immune system. ▪ Individuals with primary immunodeficiency are susceptible to a variety of infections. ▪ The type of infection depends on the nature of immunodeficiency.	▪ The loss of immune function as a result of exposure to disease agents, environmental factors, immunosuppression, or aging.

Types of primary immunodeficiency

1) B-cell defects.

2) T-cell disorders.

3) Combined B- and T-cell defects.

4) Defect in macrophage and NK.

B-cell defects

1. Account for **50 to 60%** of primary immunodeficiency.
2. Causing antibody deficiencies.
3. Serum antibody titers decrease, predisposing to infections.
4. The most common B-cell disorder is selective IgA deficiency.

T-cell disorders

1. Account for about 5 to 10% of primary immunodeficiency
2. Predispose to infection by viruses, fungi, other opportunistic organisms, and many common pathogens.
3. **T-cell disorders also cause Ig deficiencies** because the B-and T-cell immune systems are interdependent.
4. The most common T-cell disorders are **DiGeorge syndrome (absent thymus).**

Combined B- and T-cell defects

1. Account for about 20% of primary immunodeficiency.
2. The most important form is **severe combined immunodeficiency (SCID).**

Severe combined immunodeficiency

Q

Most common cause of 1ry immune deficiency:

A. B cell defect.
B. T cell defect.
C. Combined B and T cell defect.
D. NK defect.
E. Macrophage.

Causes of secondary immunodeficiency

1) Immune deficiency associated with infection as viral and bacterial infection.
2) Immunological deficiency associated with **AIDS** due to decrease T helper below <200/cmm.
3) Immunodeficiency associated with **aging** due to reduction size of thymus.
4) Immunodeficiency associated with **malignancies** as leukemia and lymphomas.
5) Immunodeficiency associated with **metabolic disorders** as DM.

Treatment of immunodeficiency disorders

1. Treatment of infection
2. Intravenous gamma globulin
3. Bone marrow transplantation
4. Gene therapy in SCID

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References or further readings

Medical Microbiology and Immunology: Textbook by staff members of medical Microbiology and Immunology Department; 2018-2019 , volume I, II and III.

Basic Immunology: functions and disorders of the immune system, fifth edition; Abul K. Abbas, Andrew H. Lichtman and Shiv Pillai

Immunology: 7th edition; David Male, Jonathan Brostoff, David Roth and Ivan Roitt

THANKS