IMMUNOLOGY

Transplantation

Transplantation

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Learning Objectives

- ❑❑ Solve problems concerning definitions
- ❑❑ Use knowledge of mechanisms of graft rejection
- ❑❑ Answer questions about graft versus host disease

Transplantation

OVERVIEW

Transplantation is the process of taking cells, tissues, or organs (a **graft**) from one individual (the **donor**) and implanting them into another individual or another site in the same individual (the **host** or **recipient**). **Transfusion** is a special case of transplantation and the most frequently practiced today, in which circulating blood cells or plasma are infused from one individual into another. As we have seen in previous chapters, the immune system is elaborately evolved to recognize minor differences in self antigens that reflect the invasion of harmful microbes or pathologic processes, such as cancer. Unfortunately, it is this same powerful mechanism of self-protection which thwarts tissue transplantation because tissues derived from other individuals are recognized as **"altered-self"** by the educated cells of the host's immune system.

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Types of Graft Tissue

Several different types of grafts are used in medicine:

- Autologous grafts (or **autografts**) are those where tissue is moved from one location to another in the same individual (skin grafting in burns or coronary artery replacement with saphenous veins).
- **Isografts (or syngeneic grafts)** are those transplanted between genetically identical individuals (monozygotic twins).
- **Allogeneic** grafts are those transplanted between genetically different members of the same species (kidney transplant).
- **Xenogeneic** grafts are those transplanted between members of different species (pig heart valves into human).

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MECHANISMS OF GRAFT REJECTION

The recognition of transplanted cells as self or foreign is determined by the extremely polymorphic genes of the major histocompatibility complex, which are expressed in a **codominant** fashion. This means that everyone inherits a complete set or **haplotype** from each parent and virtually assures that 2 genetically unrelated individuals will have distinctive differences in the antigens expressed on their cells. The net result is that all grafts except autografts are ultimately identified as foreign invading proteins and destroyed by the process of **graft rejection**. Even syngeneic grafts between identical twins can express recognizable antigenic differences due to somatic mutations that occur during the development of the individual. For this reason, all grafts except autografts must be followed by some degree of lifelong immunosuppression of the host to attempt to avoid rejection reactions.

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The time sequence of allograft rejection differs depending on the tissue involved but always displays specific ty and memory. As the graft becomes vascularized, CD4+ and CD8+ cells that migrate into the graft from the host become sensitized and proliferate in response to both major and minor histocompatibility differences. In the **effector phase** of the rejection, Th cytokines play a critical role in stimulating macrophage, cytotoxic T cell, and even antibody-mediated killing. Interferons and TNF-α and -β all increase the expression of class I MHC molecules in the graft, and IFN-γ increases the expression of class II MHC as well, increasing the susceptibility of cells in the graft o MHC-restricted killing.

Four different classes of allograft rejection phenomena are classified according to their time of activation and the type of effector mechanism that predominates.

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Hyperacute Graft Rejection

- Occurs within minutes to hours
- Due to pre-formed antibodies due to transfusions, multi-parity, or previous organ transplants (type II cytotoxic hypersensitivity)
- Antibodies bind to the grafted tissue and activate complement and the clotting cascade resulting in thrombosis and ischemic necrosis
- Rare because of cross-matching blood, **but common vignette**

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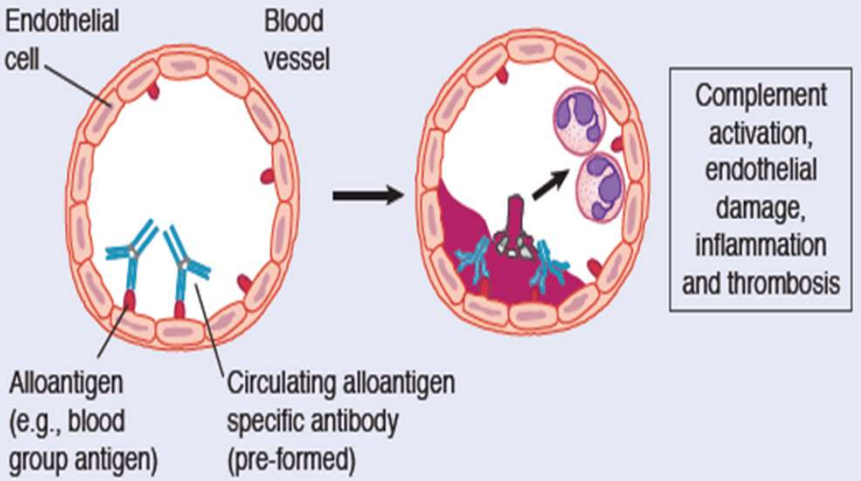
Hyperacute Reaction

Type of Rejection	Time Taken	Mechanism & Pathogenesis
Hyperacute rejection	Minutes to hours	

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Acute Graft Rejection

- Occurs within days to weeks; the timing and mechanism are similar to a primary immune response
- Induced by alloantigen (predominantly MHC) in the graft
- Both CD4 and CD8 T cells play a role as well as antibodies (think normal immune response)
- Immunosuppressive therapy works to prevent this type of graft rejection mainly

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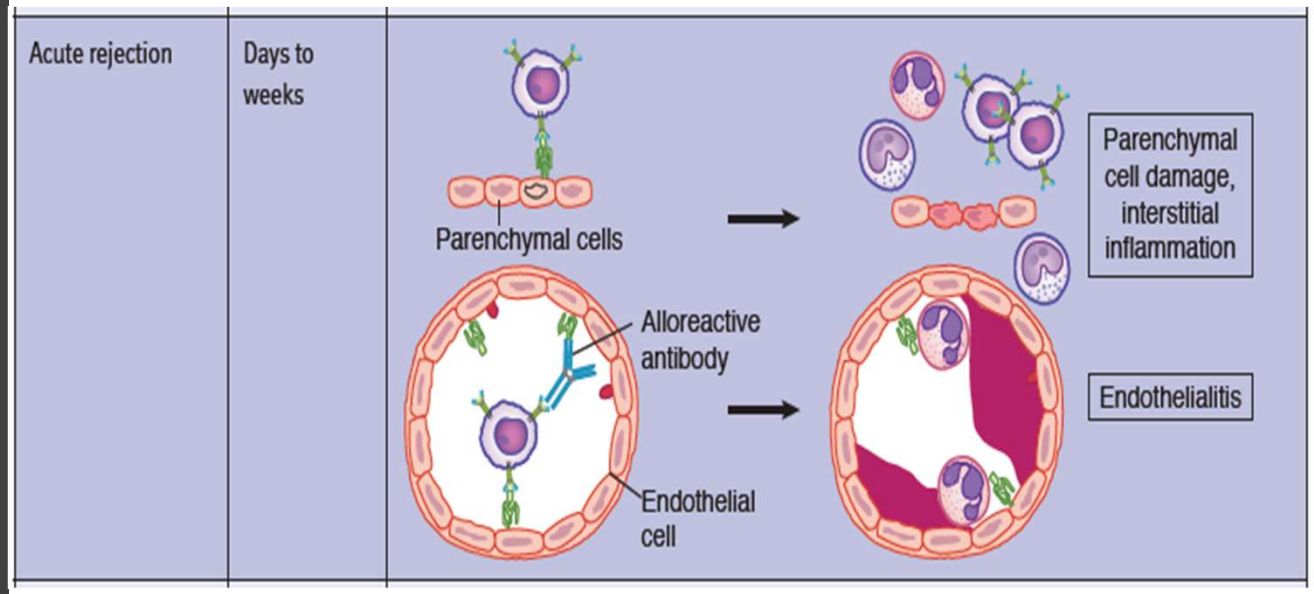
Acute graft rejection



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Accelerated Acute Graft Rejection

• Occurs within days; the timing and mechanism are like a memory response, mediated by memory cell responses

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Chronic Graft Rejection

- Occurs within months to years
- Predominantly T cell mediated
- Difficult to treat and usually results in graft rejection
- Etiology not well understood, possibly triggered by viral infections

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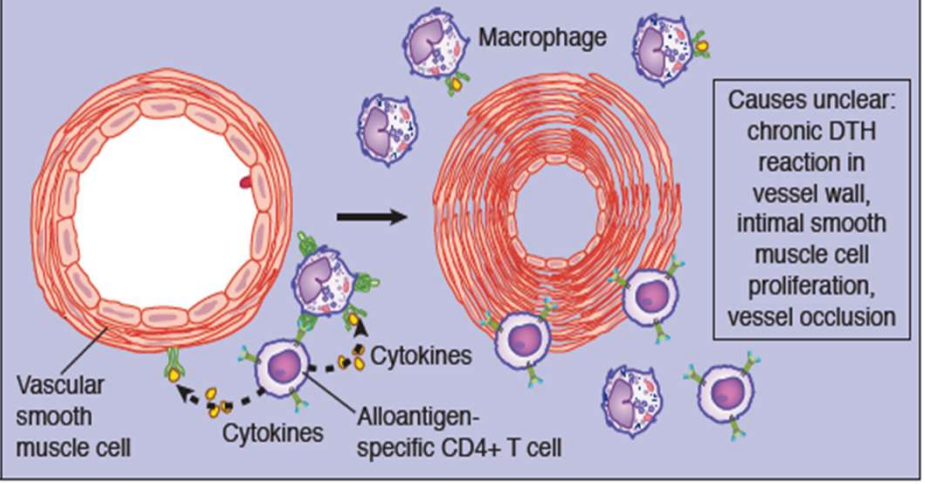
Chromic Graft Rejection

Chronic rejection	Months to years	

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GRAFT VERSUS HOST DISEASE

A special case of tissue transplantation occurs when the grafted tissue is bone marrow.

Because the bone marrow is the source of pluripotent hematopoietic stem cells, it can be used to reconstitute myeloid, erythroid, and lymphoid cells in a recipient who has lost these cells as a result of malignancy or chemotherapeutic regimens. Because the bone marrow is a source of some mature T lymphocytes, it is necessary to remove these cells before transplantation to avoid the appearance of **graft- versus-host disease** in the recipient. In this special case of rejection, any mature T cells remaining in the bone marrow inoculum can attack allogeneic

MHC-bearing cells of the recipient and cause widespread epithelial cell death accompanied by rash, jaundice, diarrhoea, and gastrointestinal haemorrhage.

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Clinical Correlate

Monoclonal antibodies are used in the treatment and prevention of graft rejection along with the classic therapies (corticiosteroids, cyclosporine A, rapamycin, etc.).

Drug/Target Mechanism of Action

Daclizumab, Basiliximab (anti-IL-2 receptor antibody)

- Blocks T cell proliferation via blocking the binding of IL-2, opsonization of IL-2R bearing cells

Muromonab (anti-CD3) Blocks T cell activation by causing apoptosis

Belatacept (CTLA-4-Ig) Inhibits T cell activation by blocking the B7 costimulatory molecule binding to CD28

Alemtuzumab (anti-CD52)* Depletes pool of T cells by binding to them and causing complement mediated lysis

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Chapter Summary

In transplantation, tissues are taken from a donor and given to a host or recipient.

• During graft rejection, MHC allele products are recognized as foreign by CTLs, macrophages, and antibodies, and the graft is destroyed.

— Graft rejection is hyperacute when preformed anti-donor antibodies and complement destroy the graft in minutes to hours.

— Graft rejection is acute when T cells are activated for the first time and destroy the graft in days to weeks.

— Graft rejection is accelerated when sensitized T cells are reactivated to destroy the graft in days

— Graft rejection is chronic when antibodies, immune complexes, or cytotoxic cells destroy the graft in months to years.

• Graft-versus-host disease occurs when mature T cells inside bone marrow transplants become activated against the MHC products of the graft recipient.