

# Autoimmunity & Transplantation

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# Learning Objectives

**By the end of this lecture you will be able to:**

- ① Recognize the mechanisms of tolerance and autoimmunity
- ② Understand the pathophysiology of some autoimmune diseases
- ③ Describe the scenarios of transplant immunology

# Autoimmunity

- Defined as **“failure of immune tolerance”**
- The immune system loses the ability to discriminate between self and non-self
- Attacks and destroys healthy body tissue

# Central tolerance

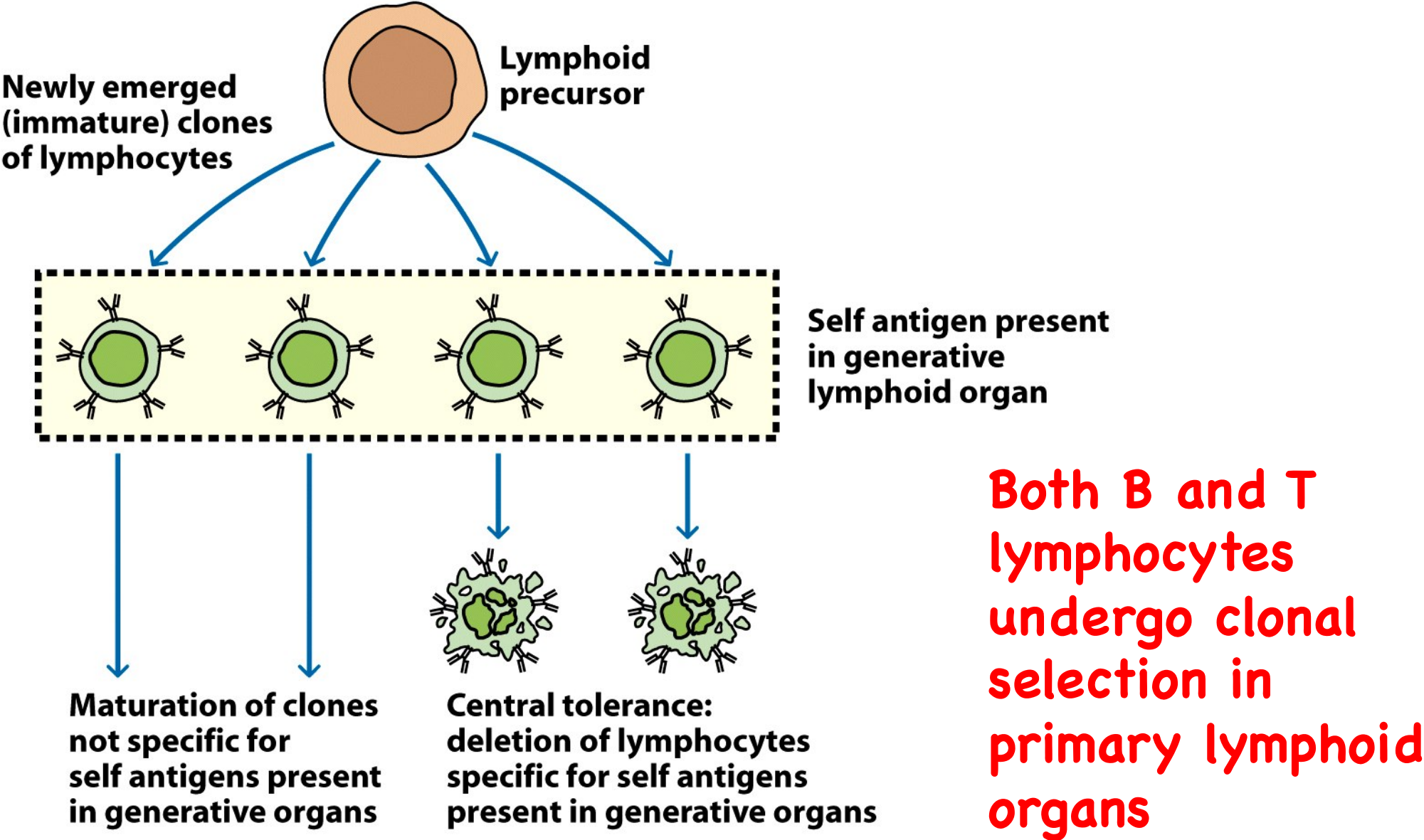
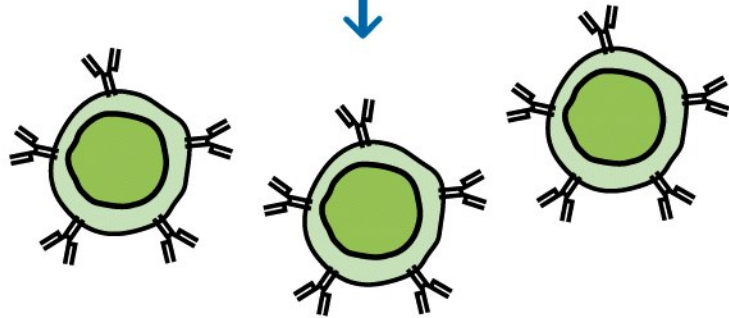
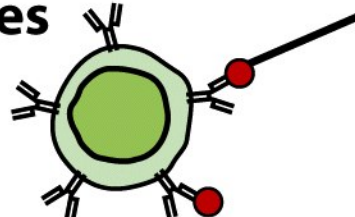


Figure 16-1a  
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# Peripheral tolerance

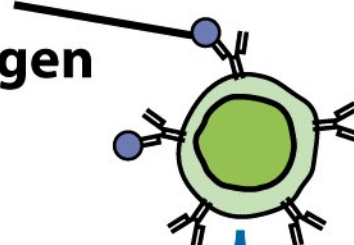
Mature lymphocytes

Foreign antigen



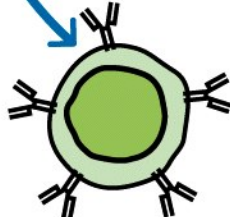
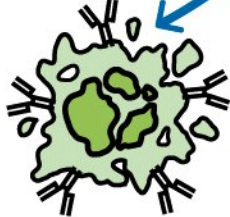
Immune response to foreign antigens

Self antigen



Apoptosis

Anergy



Peripheral tolerance: deletion or anergy of lymphocytes that recognize self antigens in peripheral tissues

Unresponsiveness to antigenic stimulus

Figure 16-1b  
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# Peripheral Tolerance

Also induced by  $T_{reg}$  cells, which is a unique subgroup of  $CD4^+$  T cells that recognize self-antigens on immune system cells and able to suppress the immune system and induce cell death in some immune cells

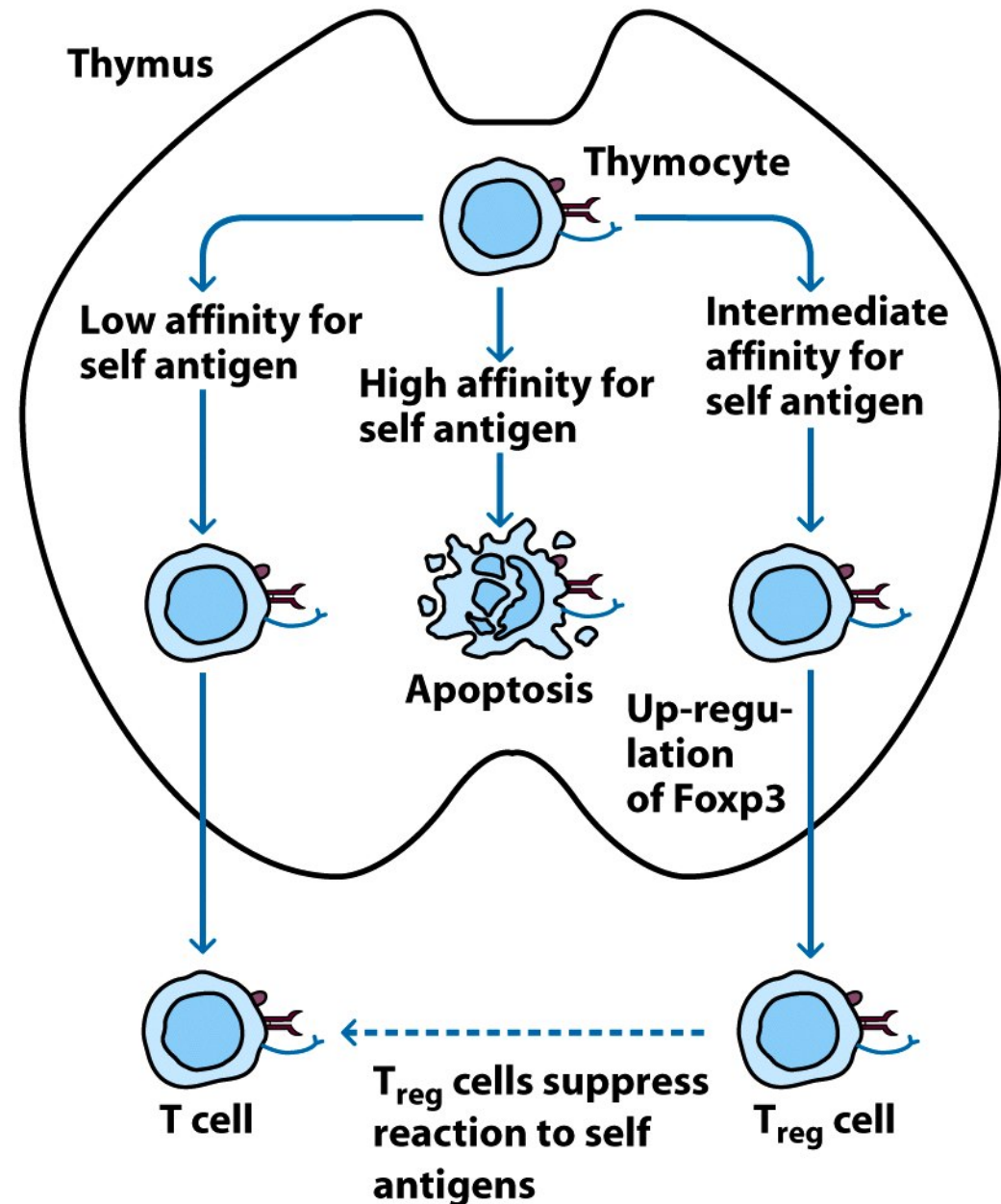
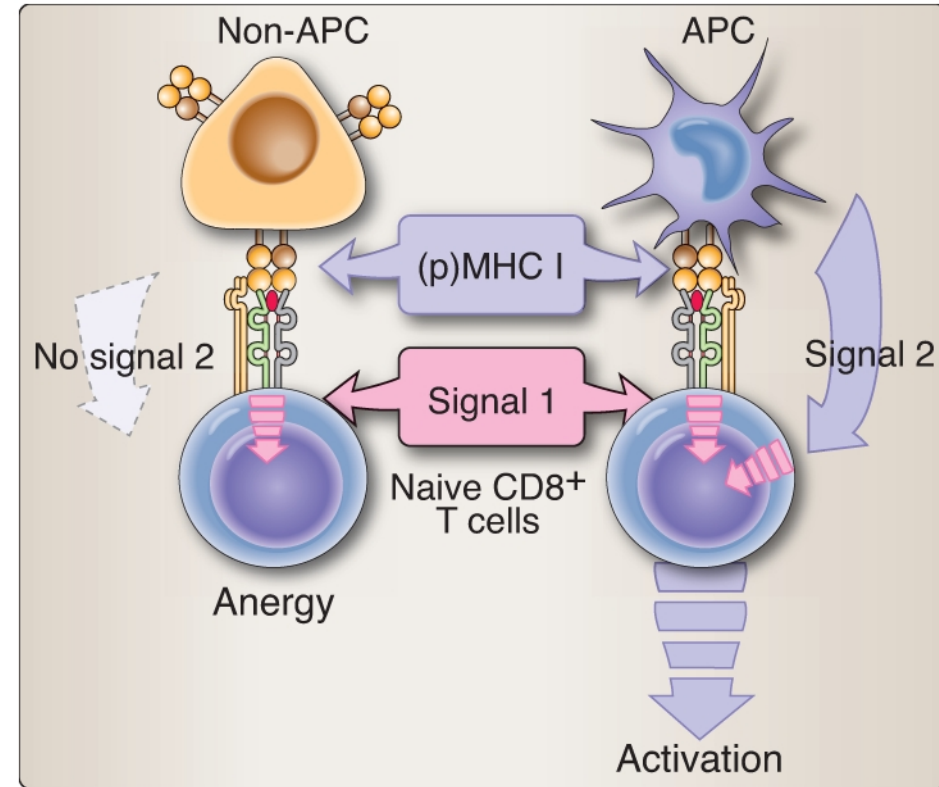


Figure 16-4  
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# Tolerogens

- High dosages of antigen
- Persistence of antigen in host
- IV or oral introduction
- Absence of adjuvants
- Low levels of co-stimulation molecules



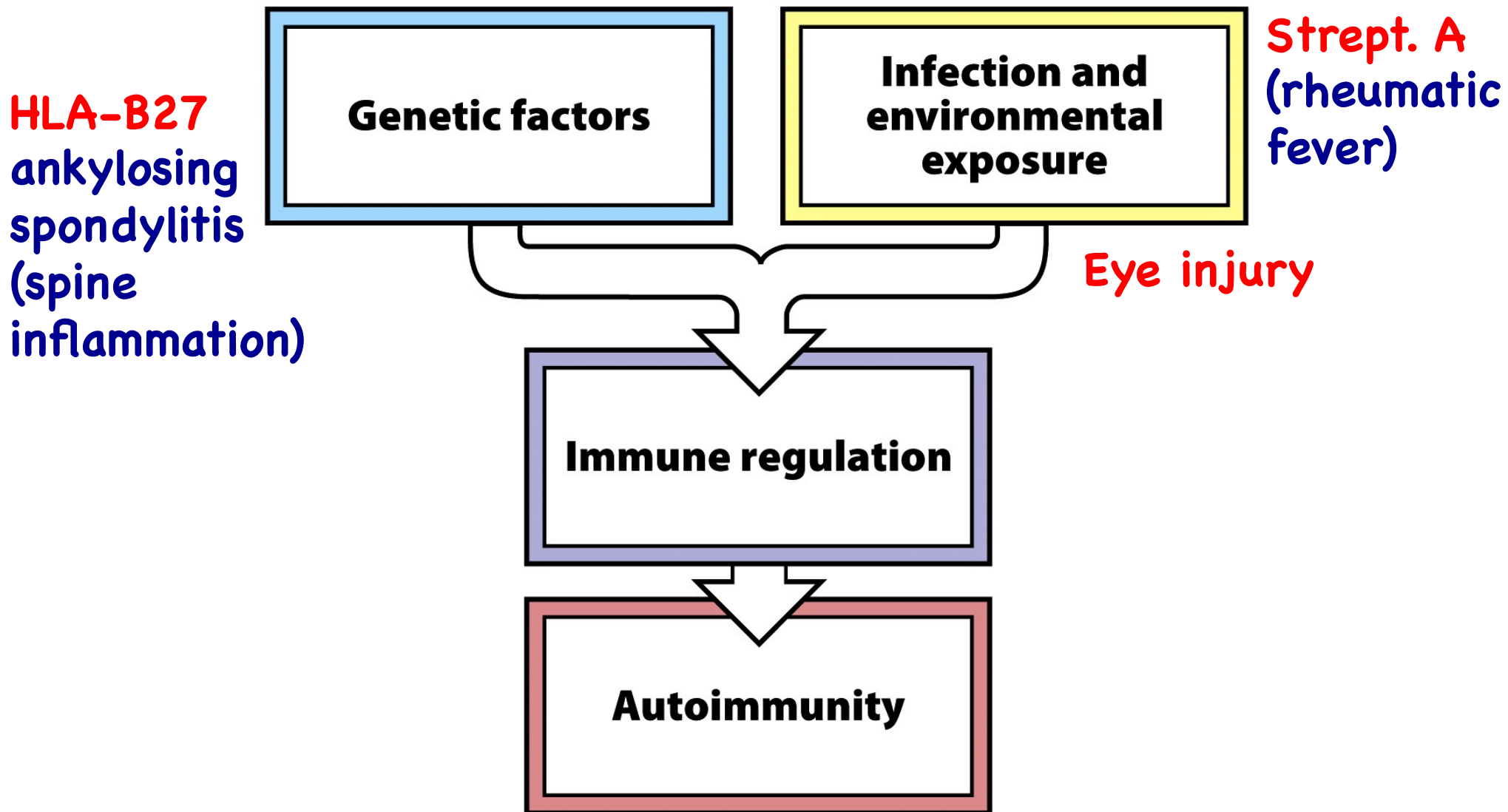


<b>Layers of self-tolerance</b>		
<b>Type of tolerance</b>	<b>Mechanism</b>	<b>Site of action</b>
<b>Central tolerance</b>	<b>Deletion Editing</b>	<b>Thymus Bone marrow</b>
<b>Antigen segregation</b>	<b>Physical barrier to self-antigen access to lymphoid system</b>	<b>Peripheral organs (e.g. thyroid, pancreas)</b>
<b>Peripheral anergy</b>	<b>Cellular inactivation by weak signaling without co-stimulus</b>	<b>Secondary lymphoid tissue</b>
<b>Regulatory cells</b>	<b>Suppression by cytokines, intercellular signals</b>	<b>Secondary lymphoid tissue and sites of inflammation</b>
<b>Cytokine deviation</b>	<b>Differentiation to <math>T_H2</math> cells, limiting inflammatory cytokine secretion</b>	<b>Secondary lymphoid tissue and sites of inflammation</b>
<b>Clonal deletion</b>	<b>Apoptosis post-activation</b>	<b>Secondary lymphoid tissue and sites of inflammation</b>

Figure 14-2 Immunobiology, 7ed. (© Garland Science 2008)



# Induction of autoimmunity

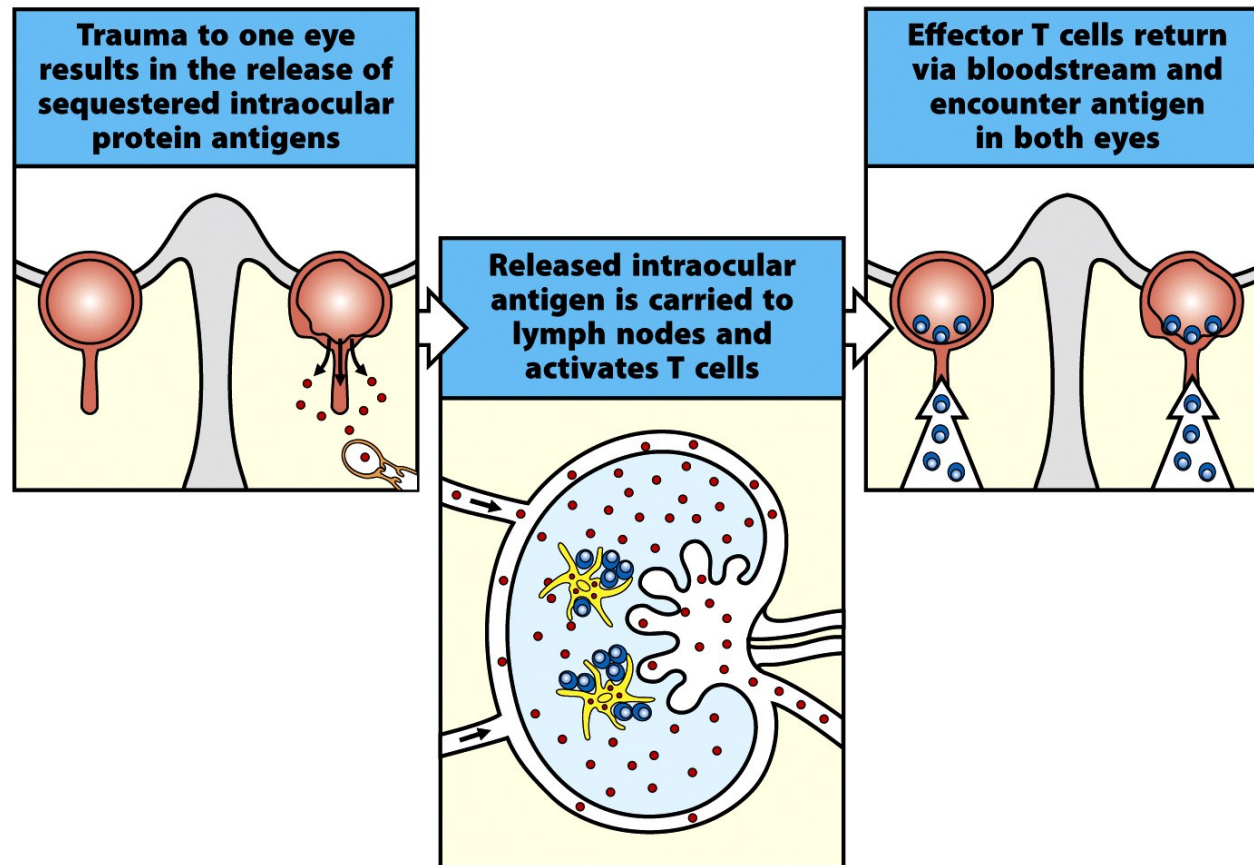


# Induction of autoimmunity

- Proposed mechanisms for induction of autoimmunity (Ag recognition) include:
  - Release of sequestered antigens
  - Molecular mimicry
  - Inappropriate expression of Class II MHC

# Release of sequestered antigens

- Some organs express antigens that are hidden from the immune system (immunologically privileged sites)



## **Immunologically privileged sites**

**Brain**

**Eye**

**Testis**

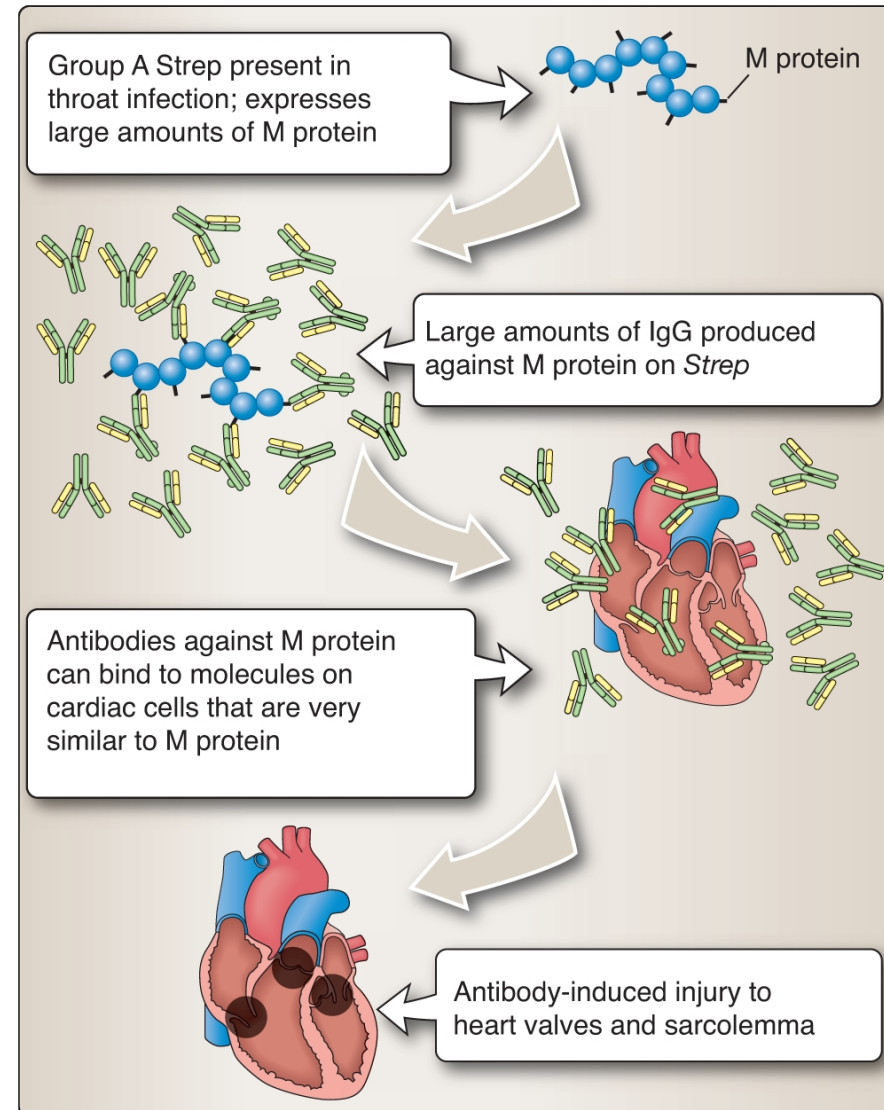
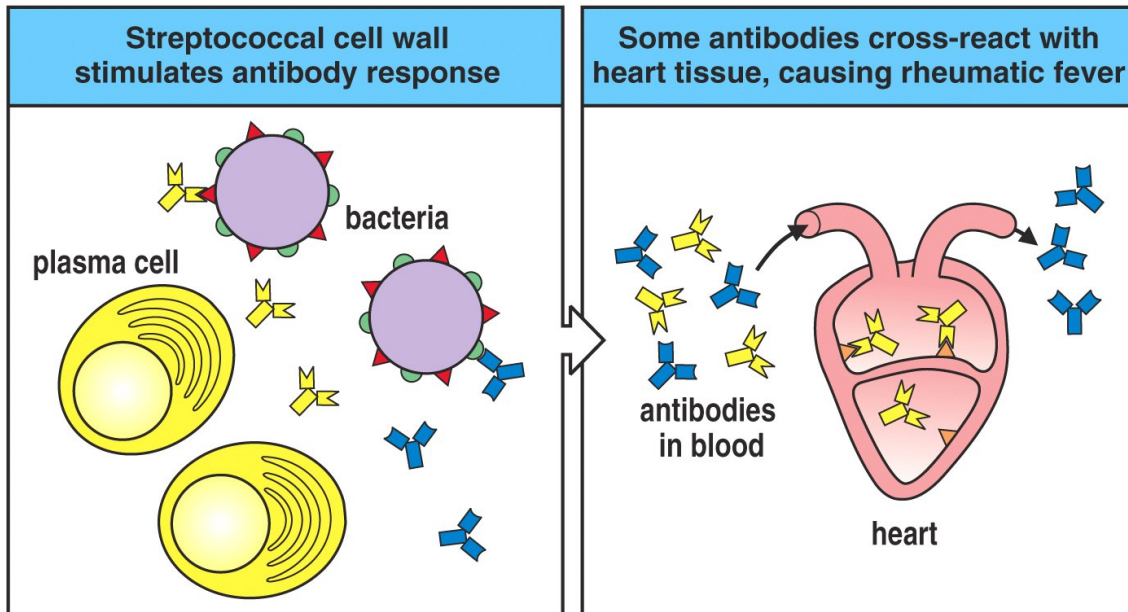
**Uterus (fetus)**



# Molecular mimicry

- When a pathogen expresses an antigen that is structurally close to a self antigen

Rheumatic fever is a post-streptococcal Group A disease





# Inappropriate expression of MHC-II

- Unusual expression of MHC-II by non-APC
- Can be caused by viral infection
- May lead to self-antigen presentation to T helper cells

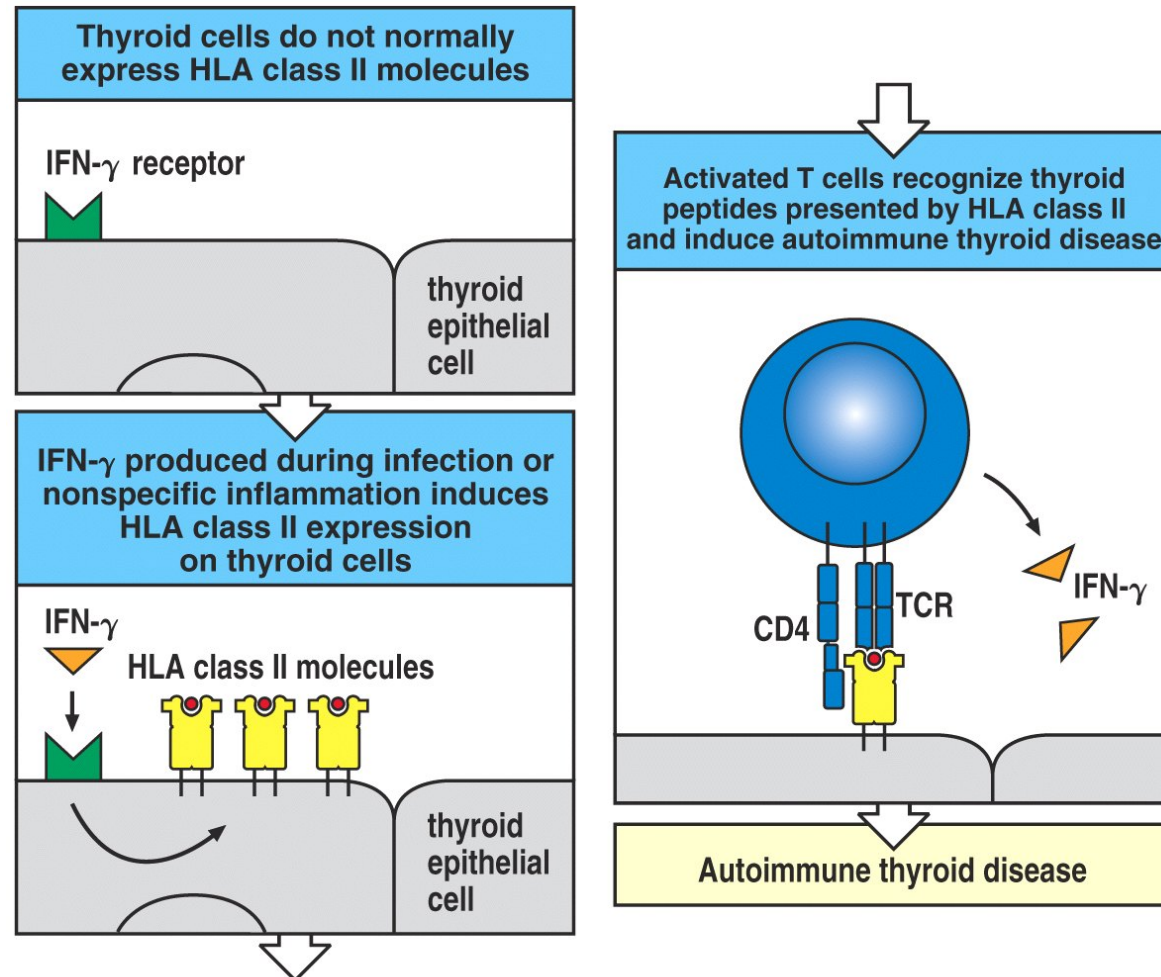


Figure 11-32 The Immune System, 2/e (© Garland Science 2005)

# Sites of autoimmune diseases

<b>Organ-specific autoimmune diseases</b>
<b>Type 1 diabetes mellitus</b>
<b>Goodpasture's syndrome</b>
<b>Multiple sclerosis</b>
<b>Graves' disease</b> <b>Hashimoto's thyroiditis</b> <b>Autoimmune hemolytic anemia</b> <b>Autoimmune Addison's disease</b> <b>Vitiligo</b> <b>Myasthenia gravis</b>

<b>Systemic autoimmune diseases</b>
<b>Rheumatoid arthritis</b>
<b>Scleroderma</b>
<b>Systemic lupus erythematosus</b> <b>Primary Sjögren's syndrome</b> <b>Polymyositis</b>

Figure 14-11 Immunobiology, 7ed. (© Garland Science 2008)



# AIHA (Type II hypersensitivity)

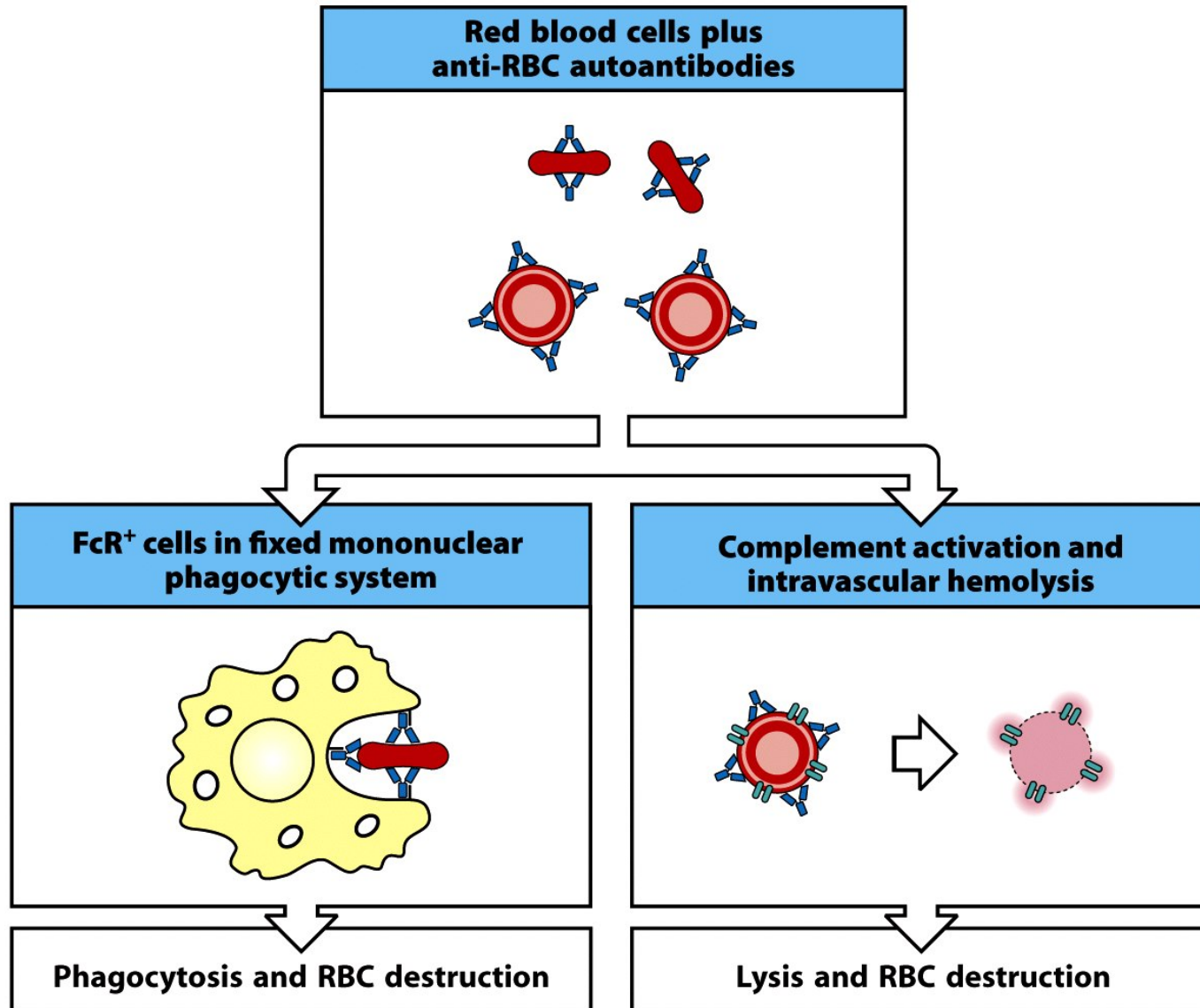


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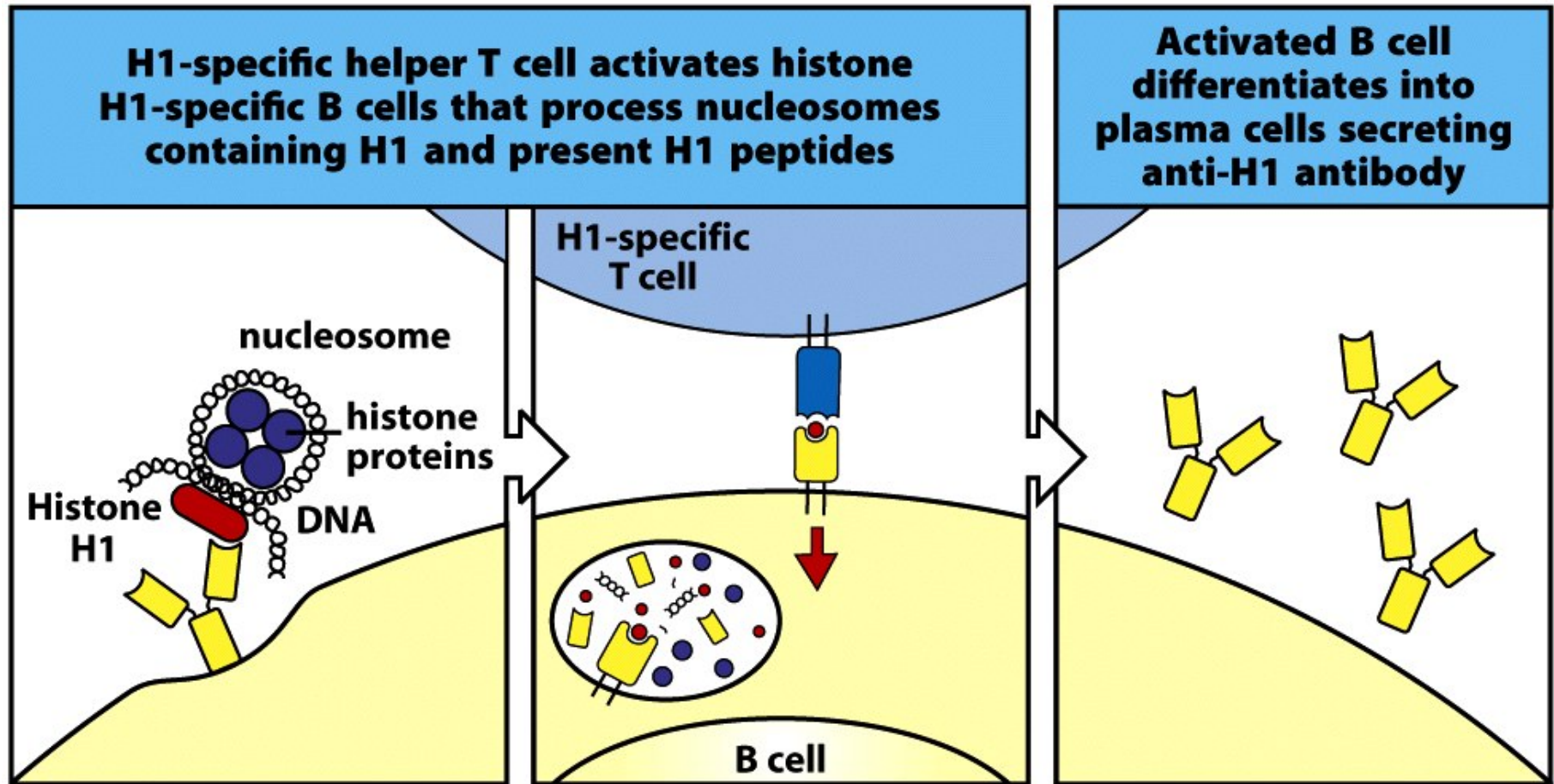
# SLE (Type III hypersensitivity)

- Typically middle-aged women
- Fever, weakness, arthritis, skin rash, kidney problems
- Produce auto-Abs to DNA, histones, platelets, leukocytes, clotting factors
- Excessive complement activation



Figure 16-10  
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# SLE (Type III hypersensitivity)





# SLE (Type III hypersensitivity)

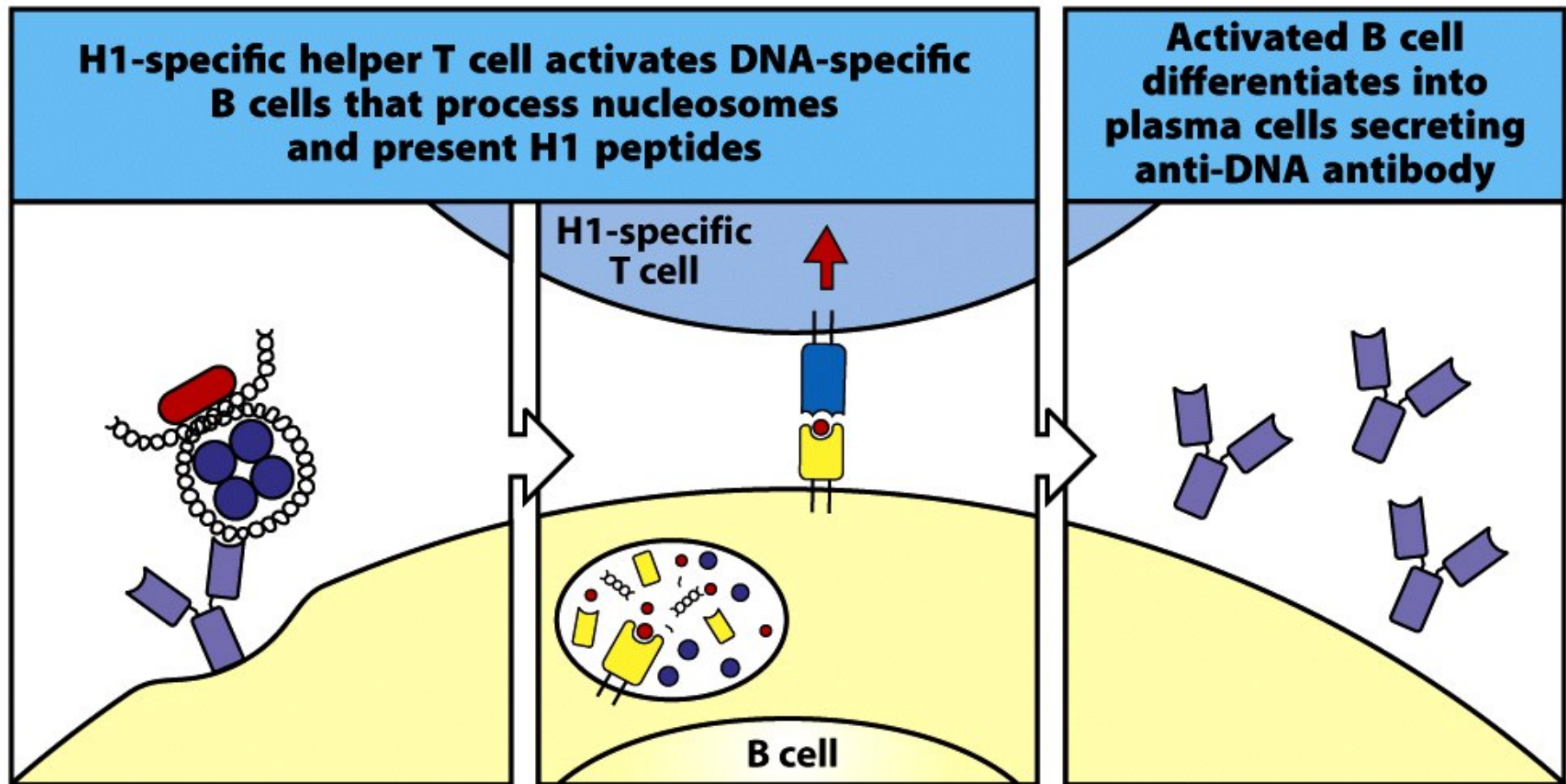
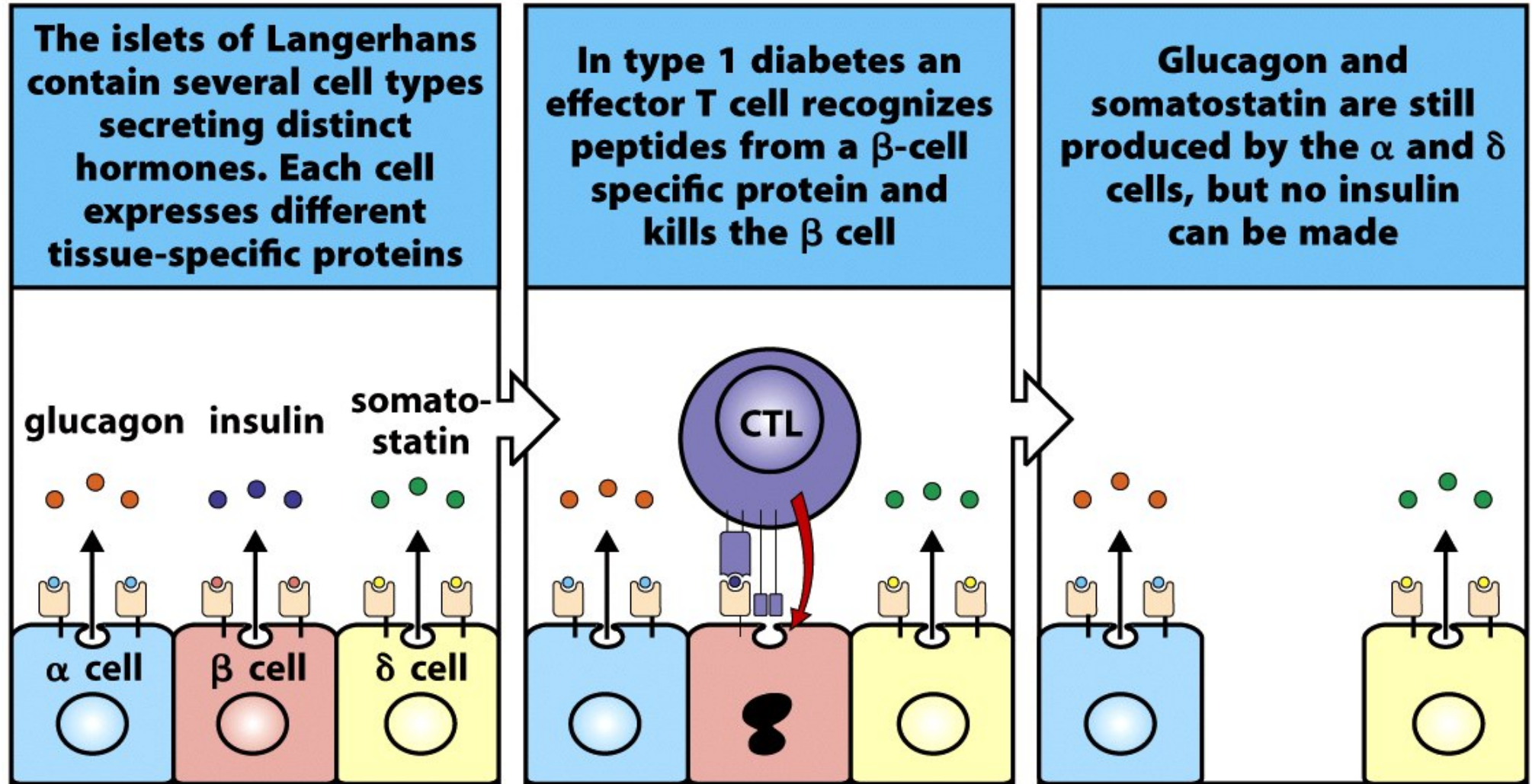


Figure 14-18 Immunobiology, 7ed. (© Garland Science 2008)

# Type 1 DM (Type IV hypersensitivity)

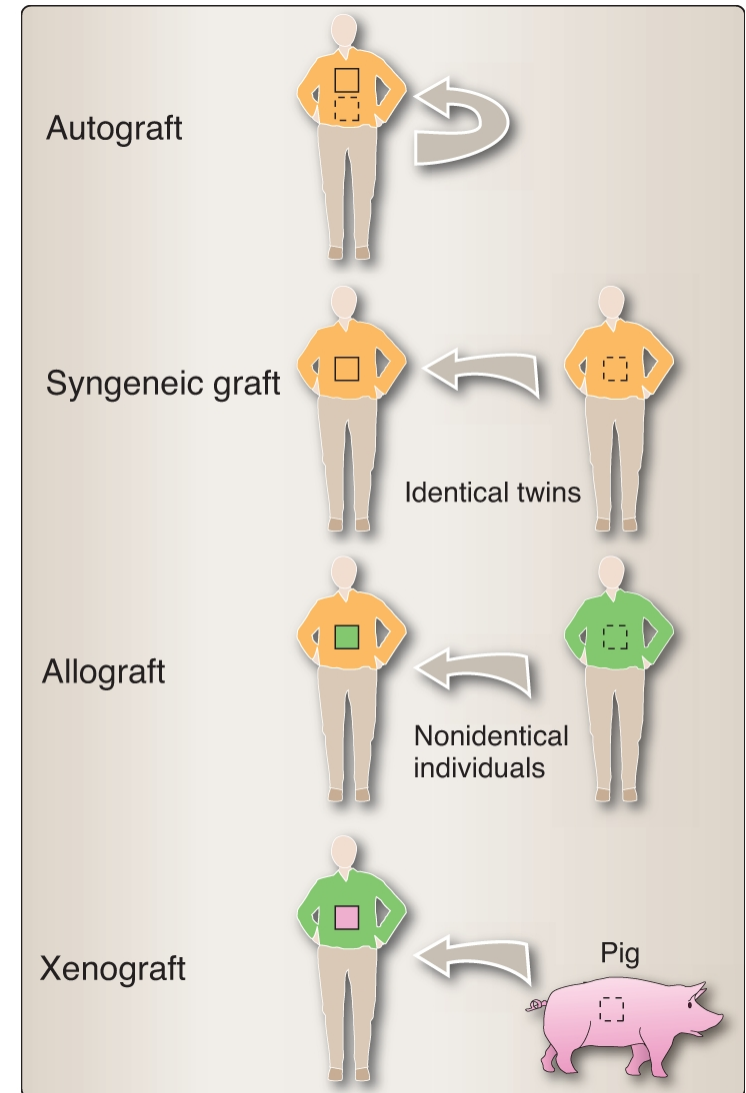


# Treatment strategies

- Immunosuppressive drugs
- Thymectomy (e.g. with myasthenia gravis)
- Plasmaphoresis (removal of extra immune complexes)
- Treating the inflammation (corticosteroids)
- Biologicals (e.g. anti-inflammatory mAbs)
- Antigen given orally can induce tolerance

# Different types of Transplants

- **Autograft**
  - Self tissue transferred from one part of body to another
- **Isograft (syngenic graft)**
  - Tissue transferred between genetically identical individuals
- **Allograft**
  - Tissue transferred between genetically different members of same species
    - Most of our transplants
- **Xenograft**
  - Tissue transferred between different species





# Recognition and Rejection

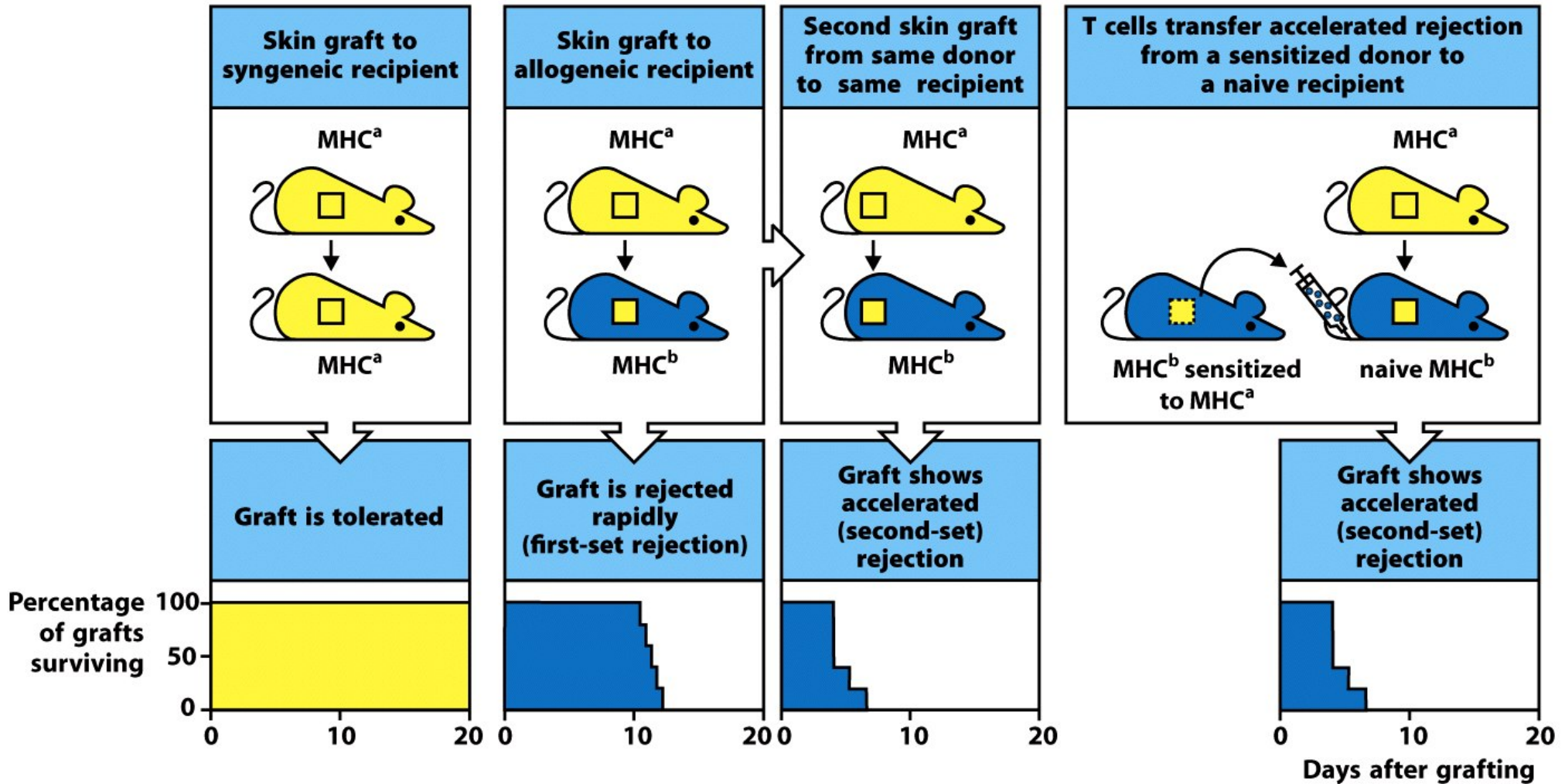


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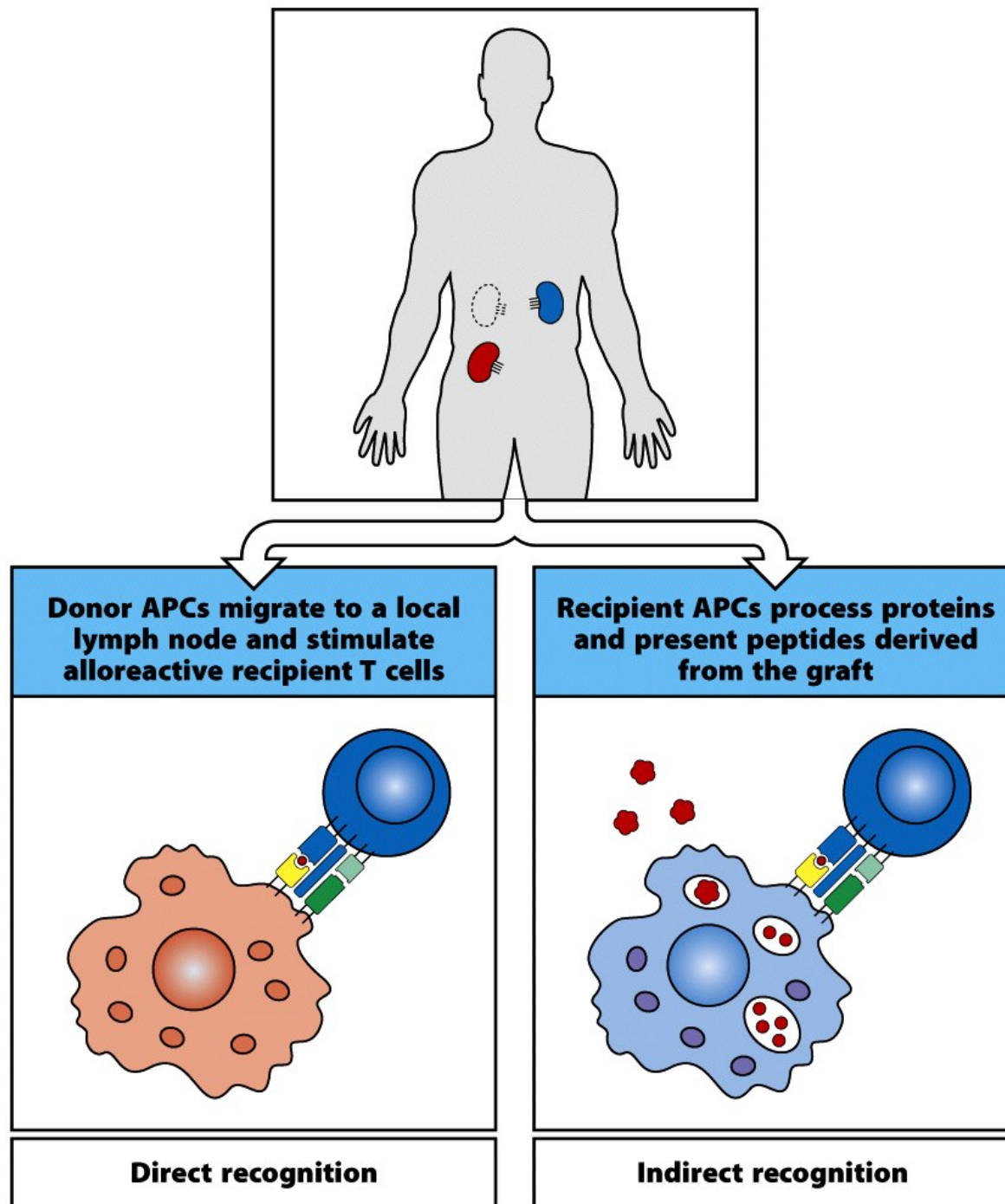


Figure 14-43 Immunobiology, 7ed. (© Garland Science 2008)

# Recognition and Rejection

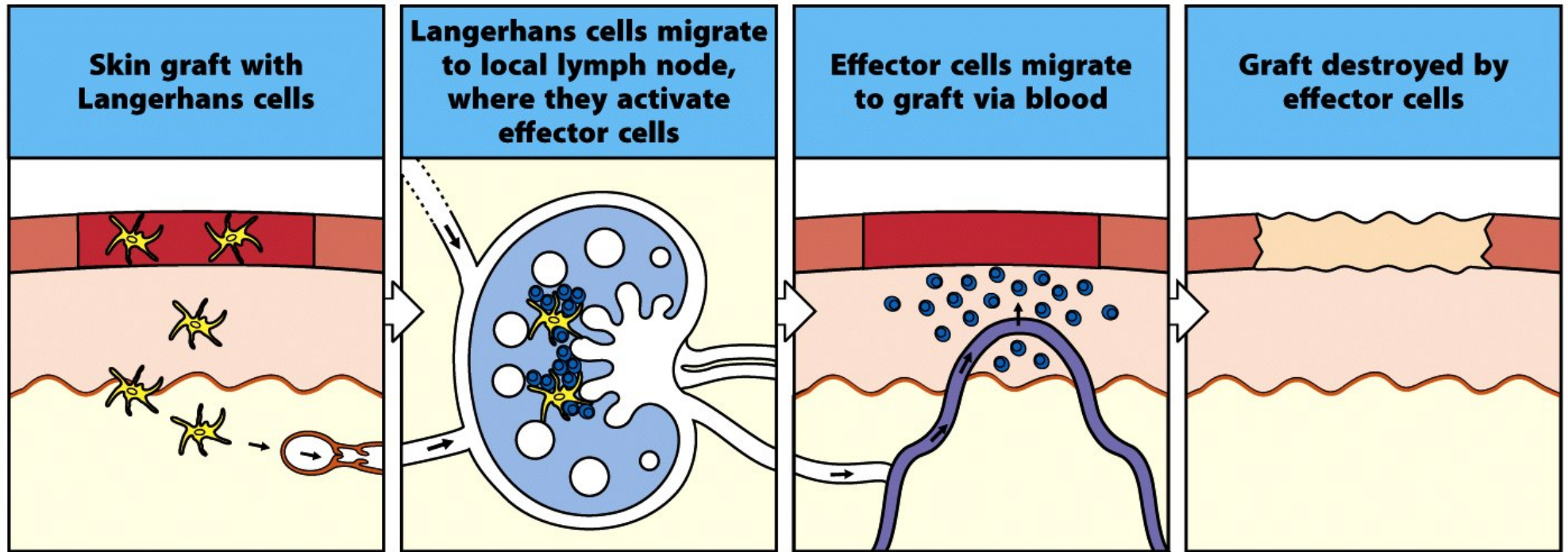


Figure 14-42 Immunobiology, 7ed. (© Garland Science 2008)

# Recognition and Rejection

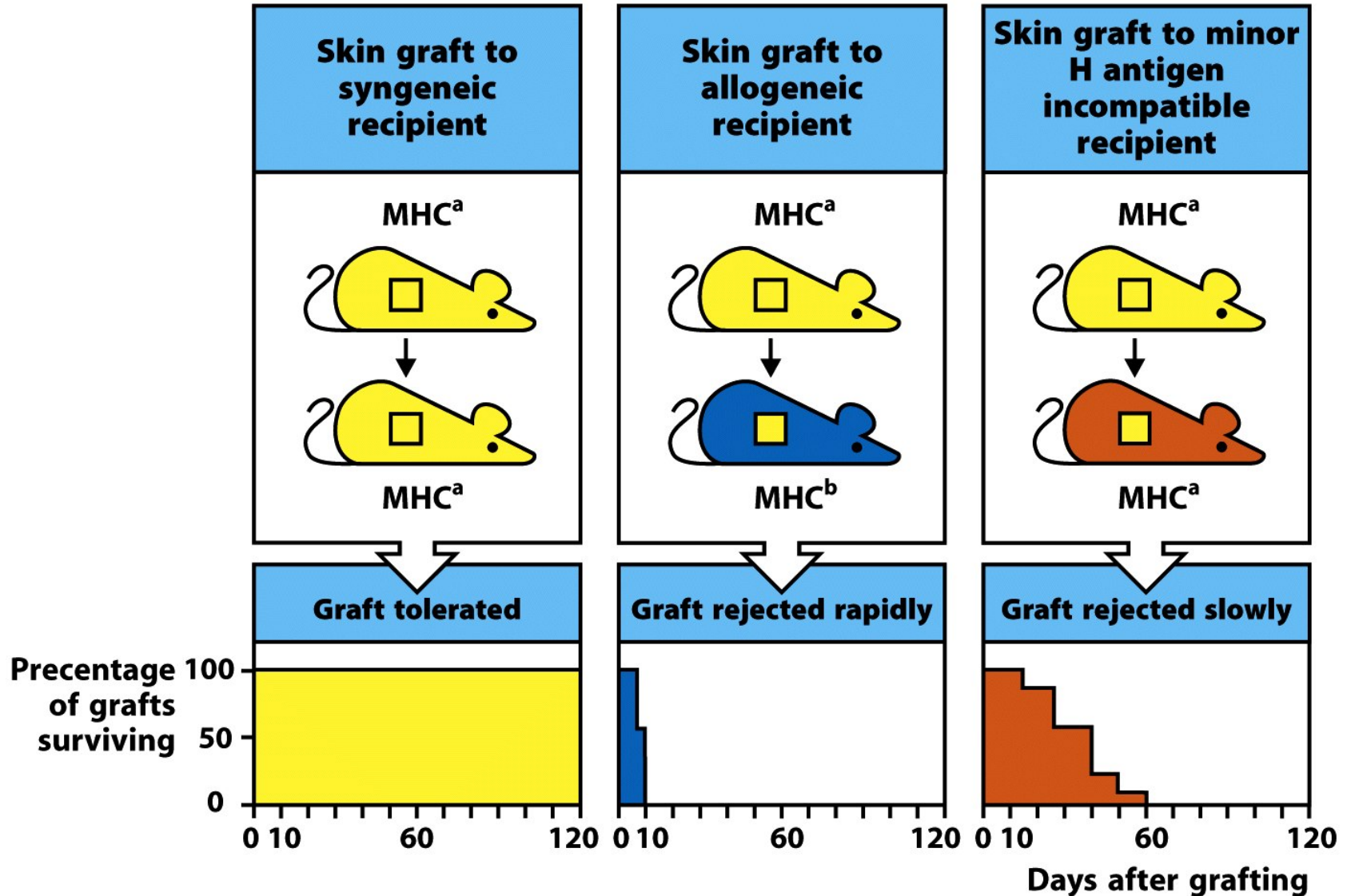
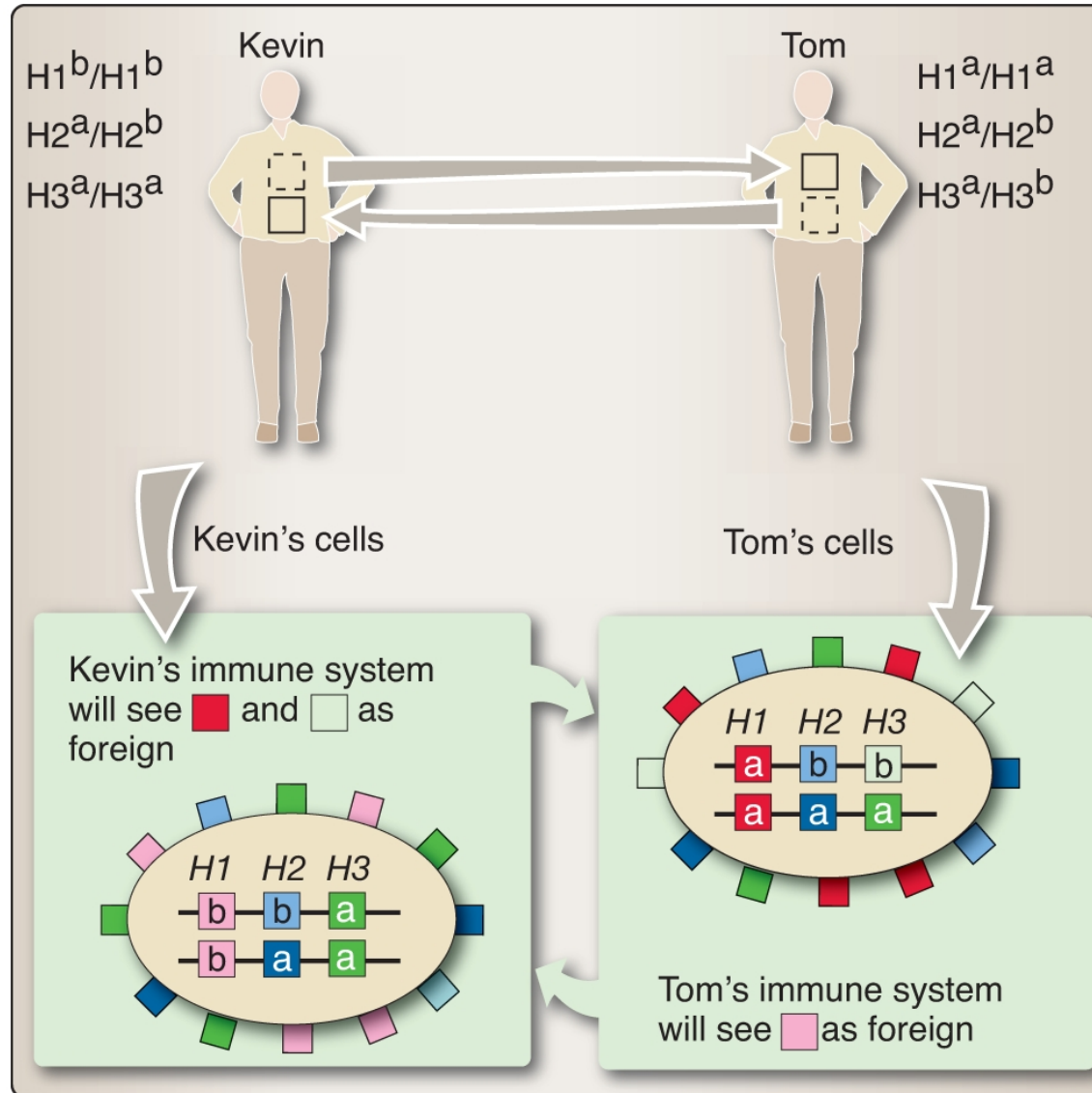


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# Histocompatibility



# Histocompatibility

- Tissues that are antigenically similar – *histocompatible*
- Mismatches with Class II MHC are more likely to lead to rejection than mismatches with Class I

- **Microcytotoxicity assay for MHC haplotypes**

- **If antigen is present on cell, complement will lyse it, and it will uptake dye (blue)**

- **Donor 1 has antigens in common with recipient**

	Antibody to different HLA-A antigens								
	1	2	3	4	5	6	7	8	9
Recipient	●	○	○	○	○	○	●	○	○
Donor 1	●	○	○	○	○	○	●	○	○
Donor 2	○	●	●	○	○	○	○	○	○

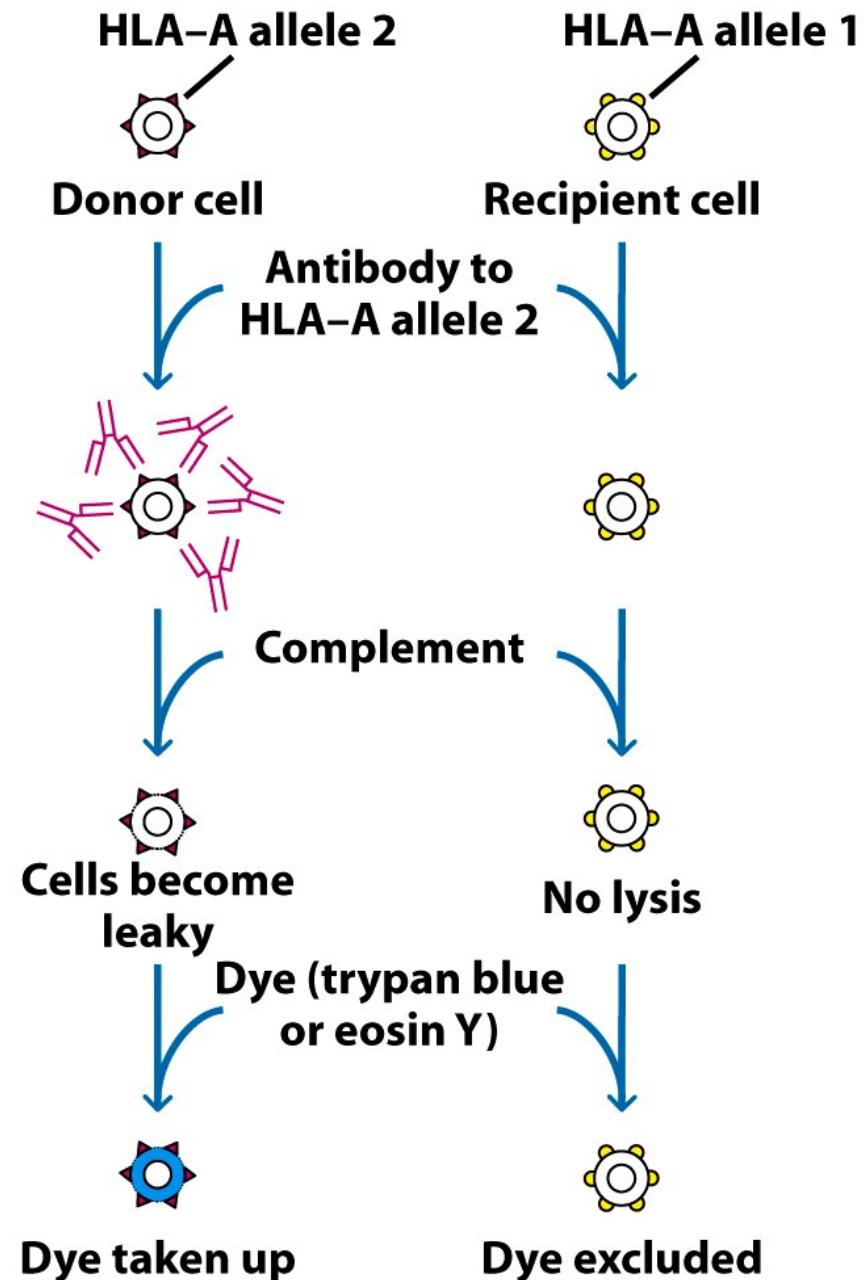
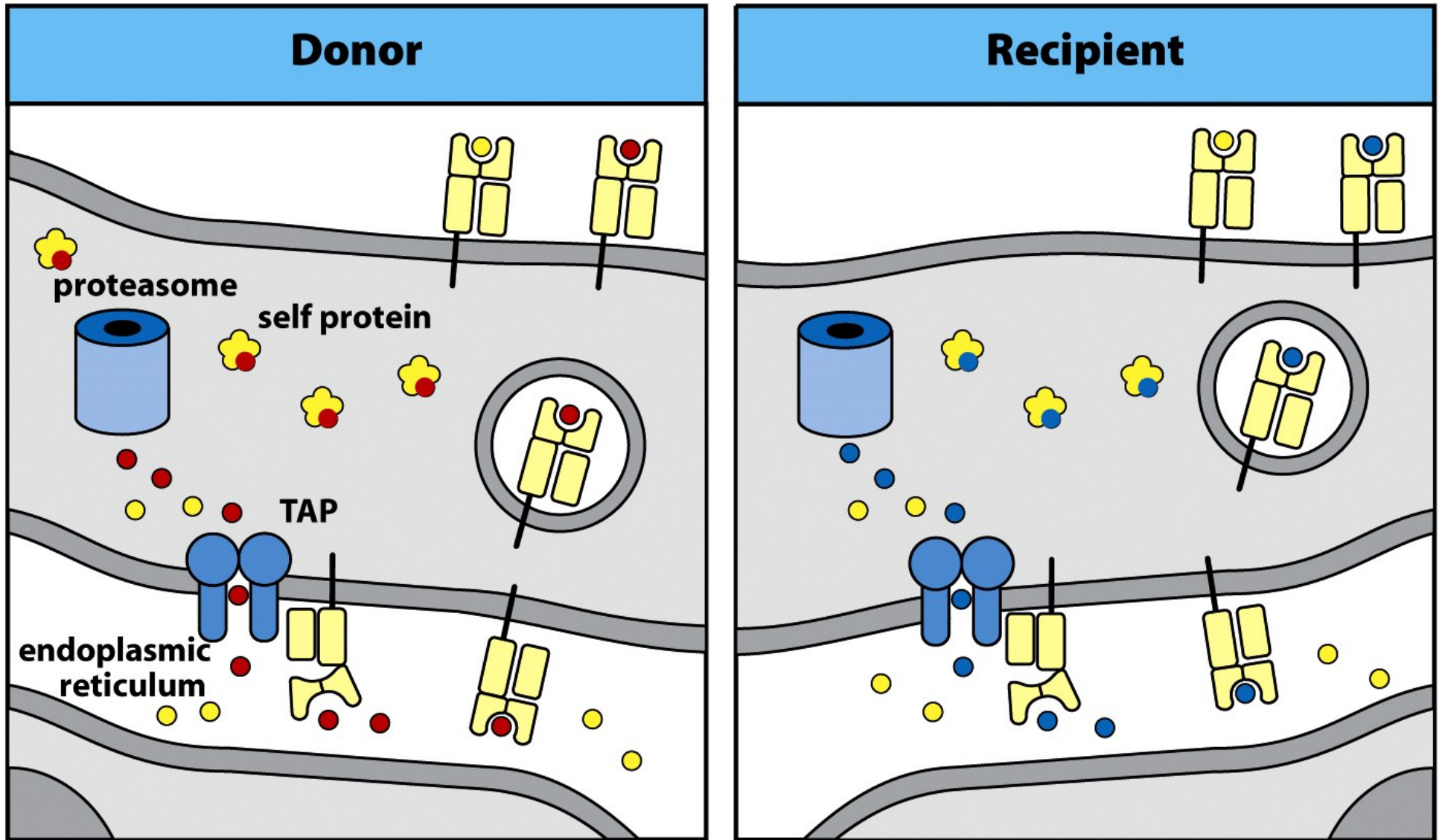


Figure 17-4a  
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**Polymorphic self proteins that differ in amino acid sequence between individuals give rise to minor H antigen differences between donor and recipient**

# Clinical Manifestations of Graft Rejections

- **Hyperacute**
  - Within hours
- **Acute**
  - Within weeks
- **Chronic**
  - Months to years

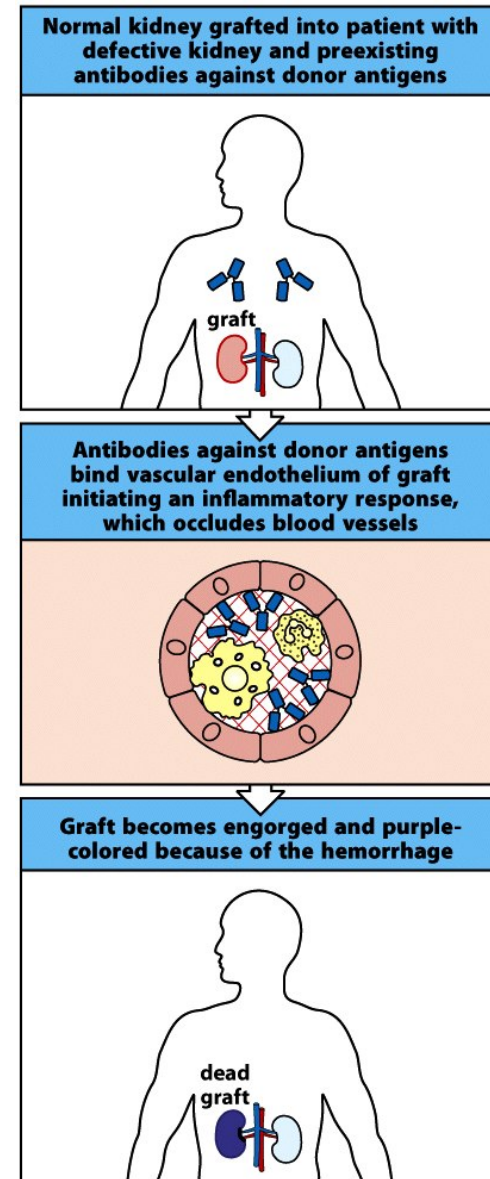


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# Graft Versus Host Disease

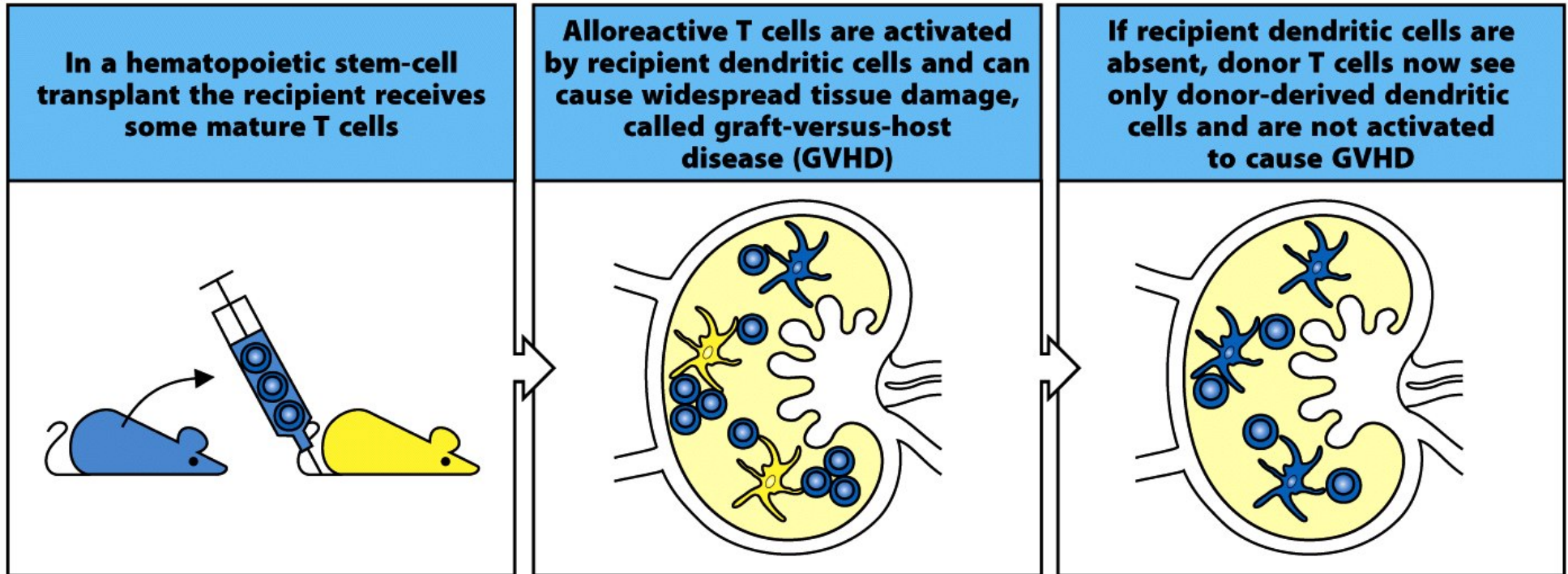


Figure 14-47 Immunobiology, 7ed. (© Garland Science 2008)

## **You are now able to:**

- ✓ Recognize the mechanisms of tolerance and autoimmunity
- ✓ Understand the pathophysiology of some autoimmune diseases
- ✓ Describe the scenarios of transplant immunology