# Outline

Autoimmunity

- Regulatory mechanisms
- Development of autoimmunity
- Autoimmune diseases

# Common Autoimmune Diseases

| Disease | Disease mechanism | Consequence | Prevalence |
|---|---|---|---|
| Psoriasis | Autoreactive T cells against skin-associated antigens | Inflammation of skin with formation of scaly patches or plaques | 1 in 50 |
| Rheumatoid arthritis | Autoreactive T cells and autoantibodies against antigens localized to joint synovium | Joint inflammation and destruction causing arthritis | 1 in 100 |
| Graves' disease | Autoantibodies against the thyroid-stimulating-hormone receptor | Hyperthyroidism: overproduction of thyroid hormones | 1 in 100 |
| Hashimoto's thyroiditis | Autoantibodies and autoreactive T cells against thyroid antigens | Destruction of thyroid tissue leading to hypothyroidism: underproduction of thyroid hormones | 1 in 200 |
| Systemic lupus erythematosus | Autoantibodies and autoreactive T cells against DNA, chromatin proteins, and ubiquitous ribonucleoprotein antigens | Glomerulonephritis, vasculitis, rash | 1 in 200 |
| Sjögren's syndrome | Autoantibodies and autoreactive T cells against ribonucleoprotein antigens | Lymphocyte infiltration of exocrine glands, leading to dry eyes and/or dry mouth; other organs may be involved, leading to systemic disease | 1 in 300 |
| Crohn's disease | Autoreactive T cells against intestinal flora antigens | Intestinal inflammation and scarring | 1 in 500 |
| Multiple sclerosis | Autoreactive T cells against brain and spinal cord antigens | Formation of sclerotic plaques in brain and spinal cord with destruction of myelin sheaths surrounding nerve cell axons, leading to muscle weakness, ataxia, and other symptoms | 1 in 700 |
| Type 1 diabetes (insulin-dependent diabetes mellitus, IDDM) | Autoreactive T cells against pancreatic islet cell antigens | Destruction of pancreatic islet β cells leading to nonproduction of insulin | 1 in 800 |

Figure 15.1 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Autoimmunity

Autoimmunity is the consequence of the loss of self-tolerance

## Types of tolerance:

- Central tolerance
  - Thymus (positive and negative selection)
- Peripheral tolerance
  - Periphery/circulation (lack of co-stimulation, regulatory T cells)

# Central Tolerance

## T-Cells tolerate tissue specific antigens

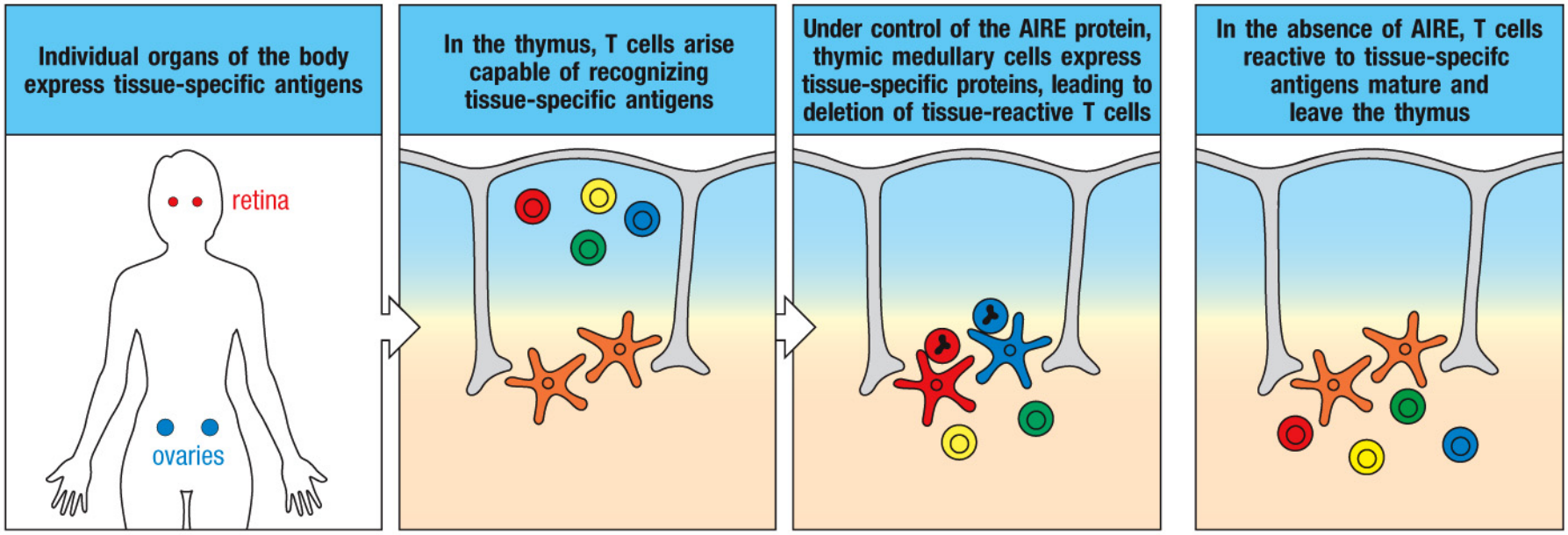



Figure 15.4 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Central Tolerance

Auto-reactive B cells are deleted in the bone marrow

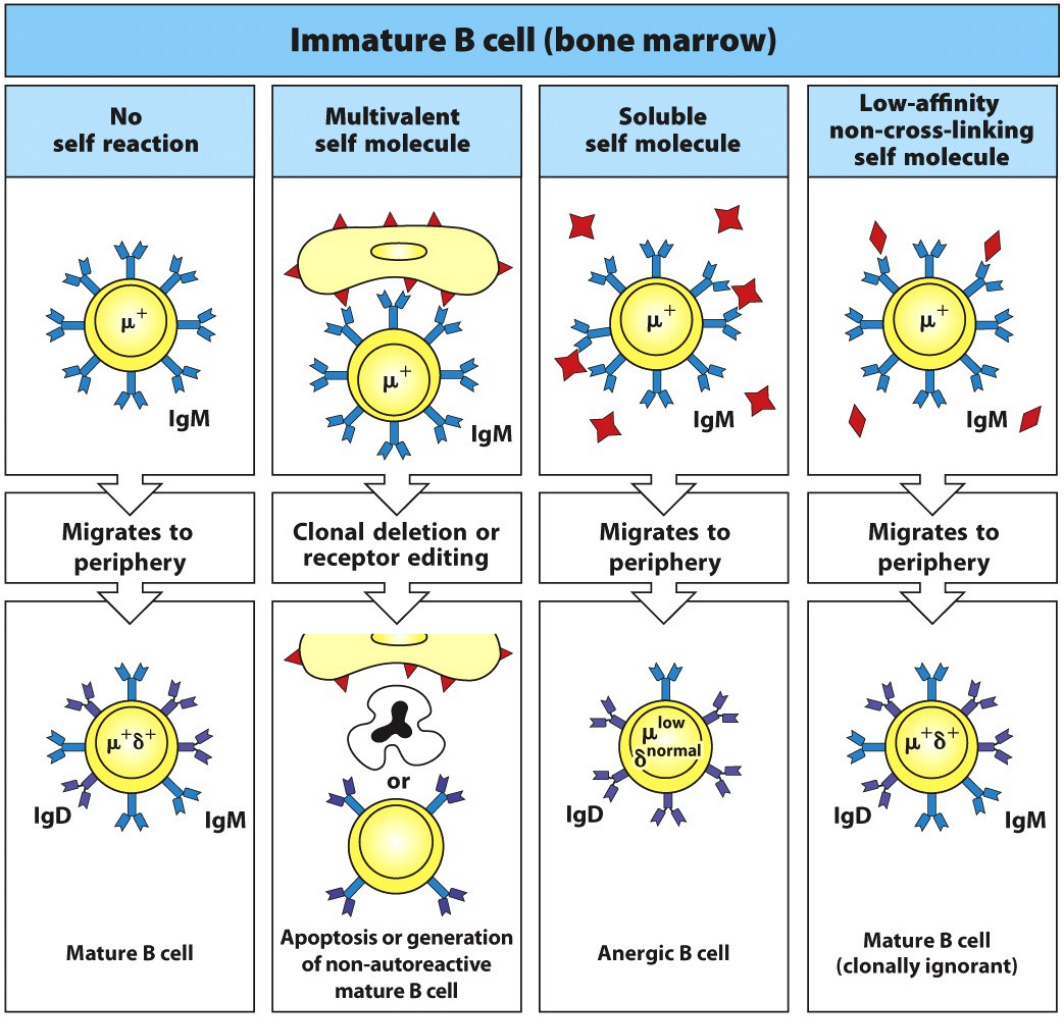



Figure 8.12 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

# Mechanisms of Peripheral Tolerance

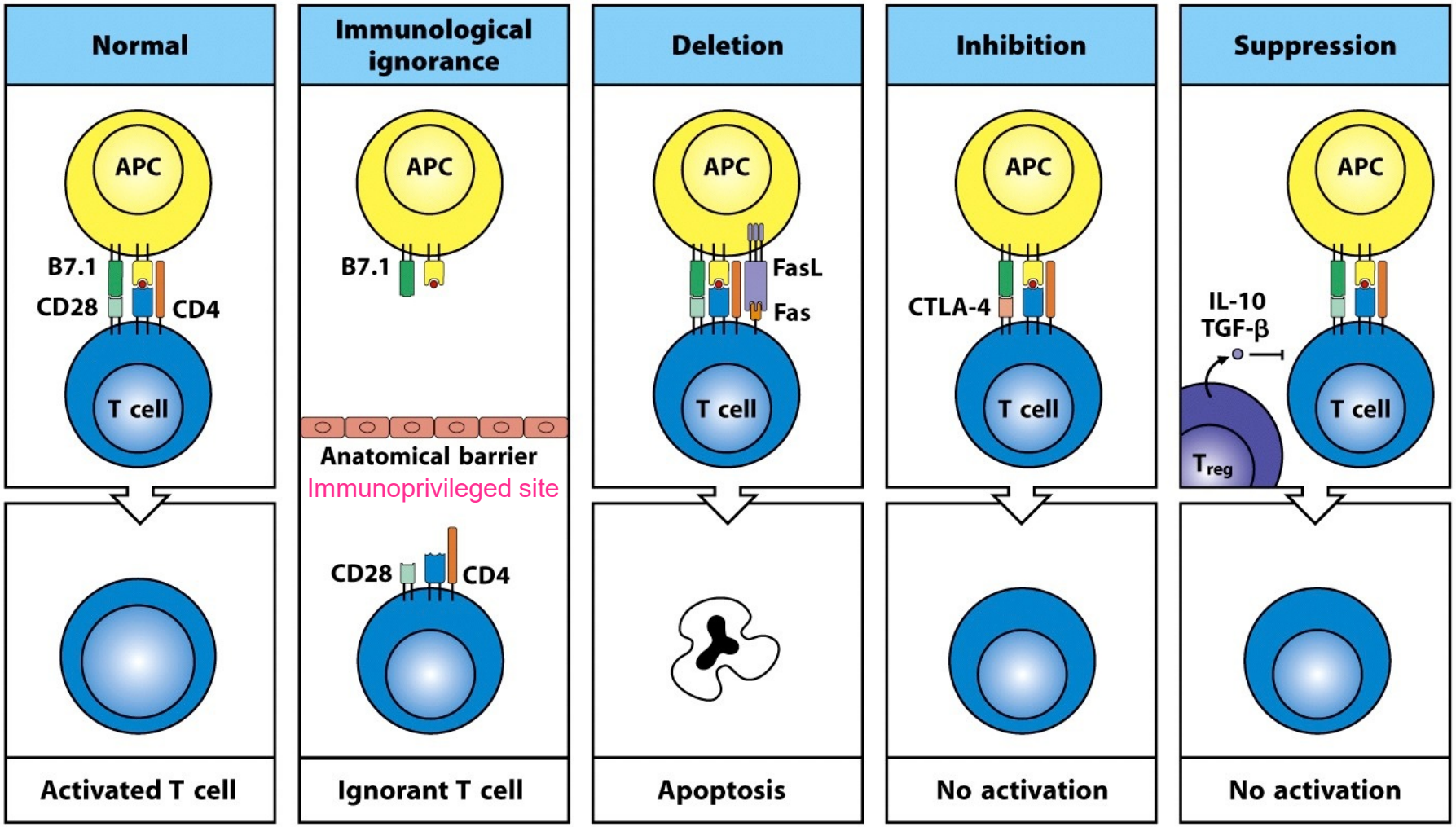



Figure 25-1 Case Studies in Immunology, 5ed. (© Garland Science 2008)

# Immunologically Privileged Sites

| Immunologically privileged sites |
| --- |
| Brain |
| Eye |
| Testis |
| Uterus (fetus) |

Figure 15.7 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Regulation:

1. Physical barrier
   - Extracellular fluid does not pass through lymphatics
   - Tissue barriers which exclude naïve lymphocytes
2. Soluble factors (cytokines)
   - TGFβ induces Treg
3. FasL expression
   - Apoptosis of Fas bearing lymphocytes

# Damage Induced Auto-Immunity

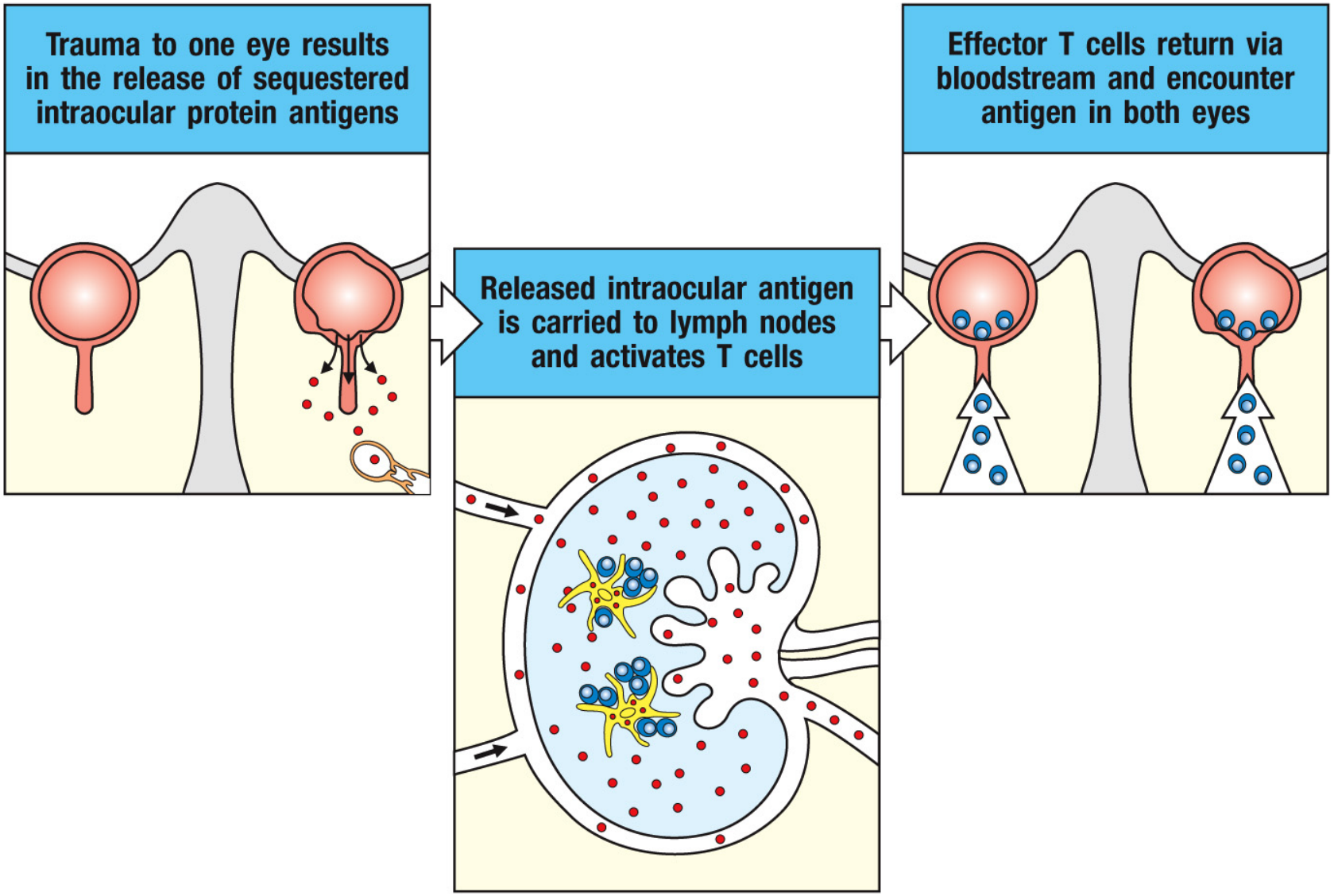



Figure 15.8 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Regulatory Tolerance

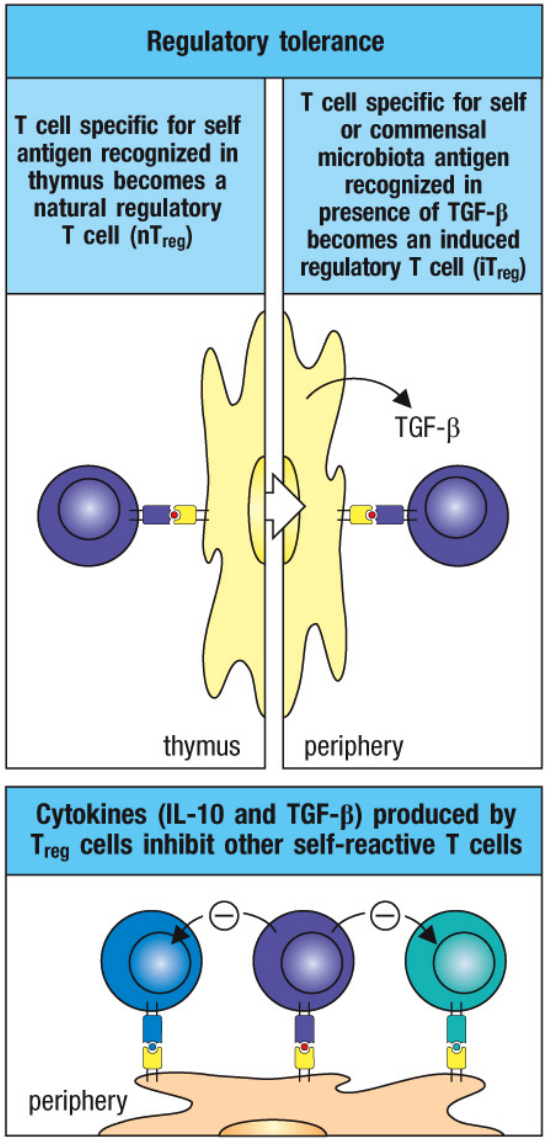
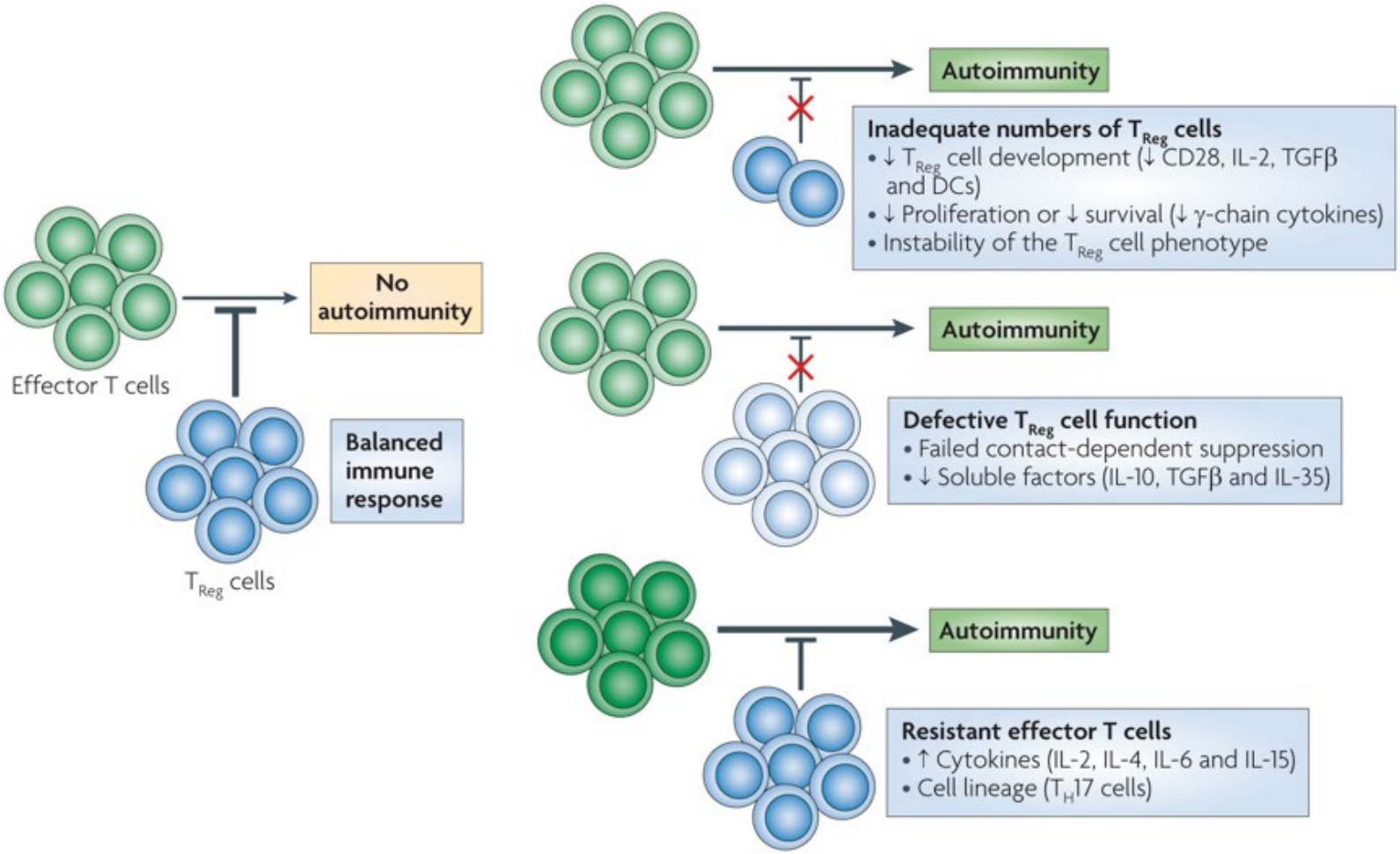



Figure 15.9 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Regulatory Tolerance

## Impairment of $T_{Reg}$ responses stimulates autoimmunity




Nature Reviews Immunology 10, 849-859 (2010)

# Outline

Autoimmunity

- Regulatory mechanisms
- Development of autoimmunity
- Autoimmune diseases

# Autoimmunity: Contributing Factors

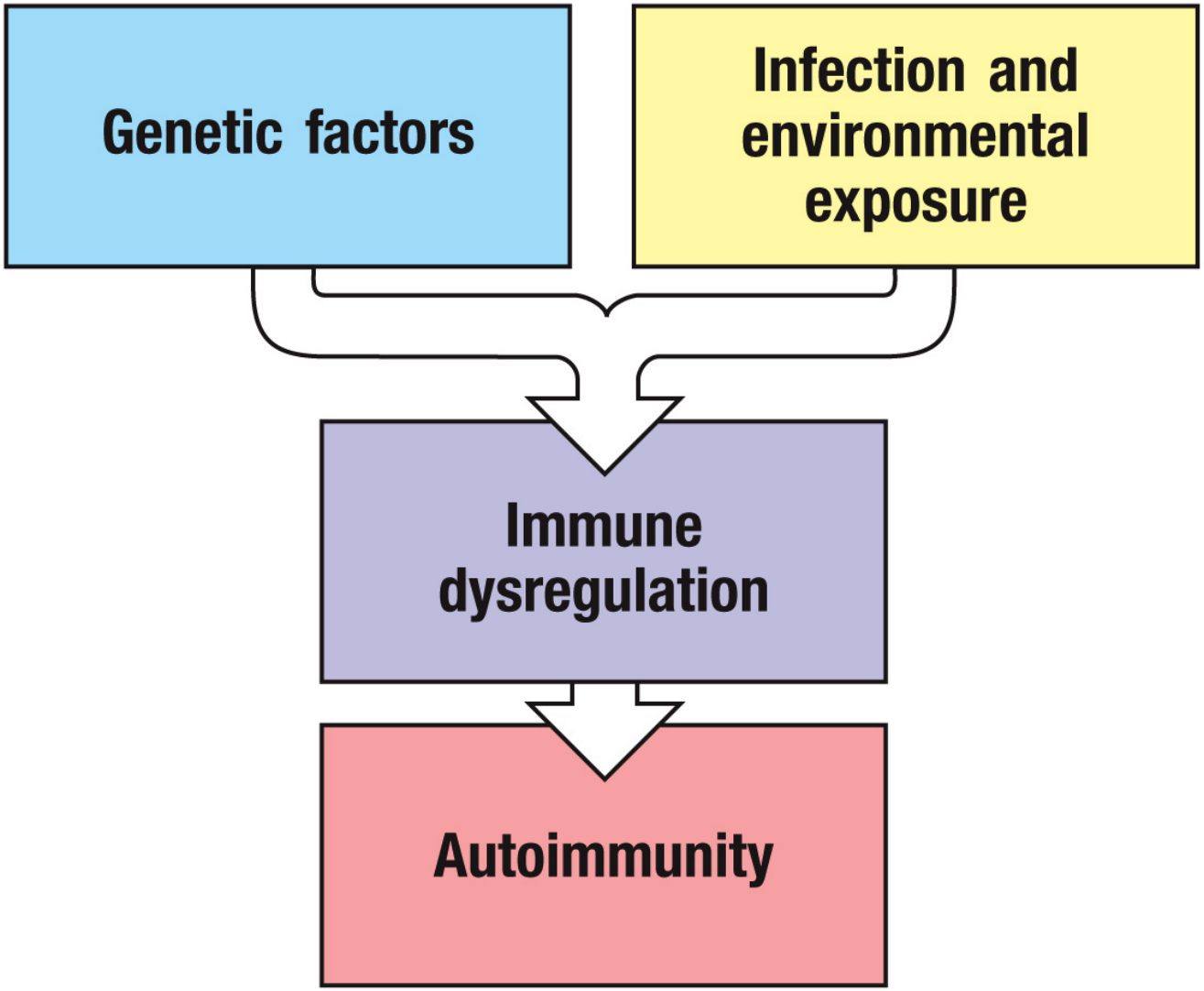



Figure 15.3 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Develop of Auto-Immune Disease

- Auto Immunity arise spontaneously in genetically autoimmune-prone individual
  - Unknown triggers
- Self antigen targets can be identified
- Infection is a trigger for autoimmune
  - Molecular mimicry
  - Damage tissue barrier
    - DAMP provide costimulation to Naïve B cells
  - Pro-inflammatory environment
    - Presentation of self antigen
    - Present self antigen in a immunological active form
    - Activation of self reactive cells- cytokines
      - Suppression of Treg

# Infections Can Induce Autoimmunity

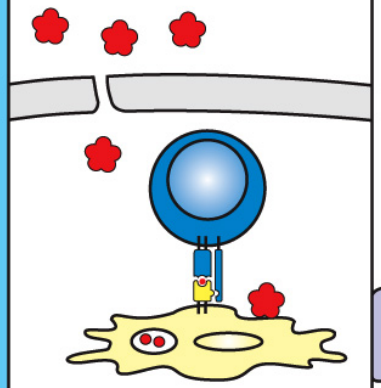
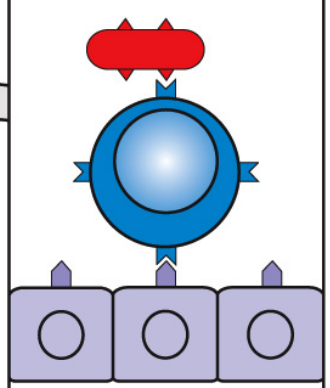
| | | |
|---|---|---|
| Mechanism | Disruption of cell or tissue barrier | Molecular mimicry |
| Effect | Release of sequestered self antigen; activation of nontolerized cells | Production of cross-reactive antibodies or T cells |
| Example | Sympathetic ophthalmia | Rheumatic fever<br>Reactive arthritis<br>Lyme arthritis |
| |  |  |

Figure 15.42 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Molecular Mimicry

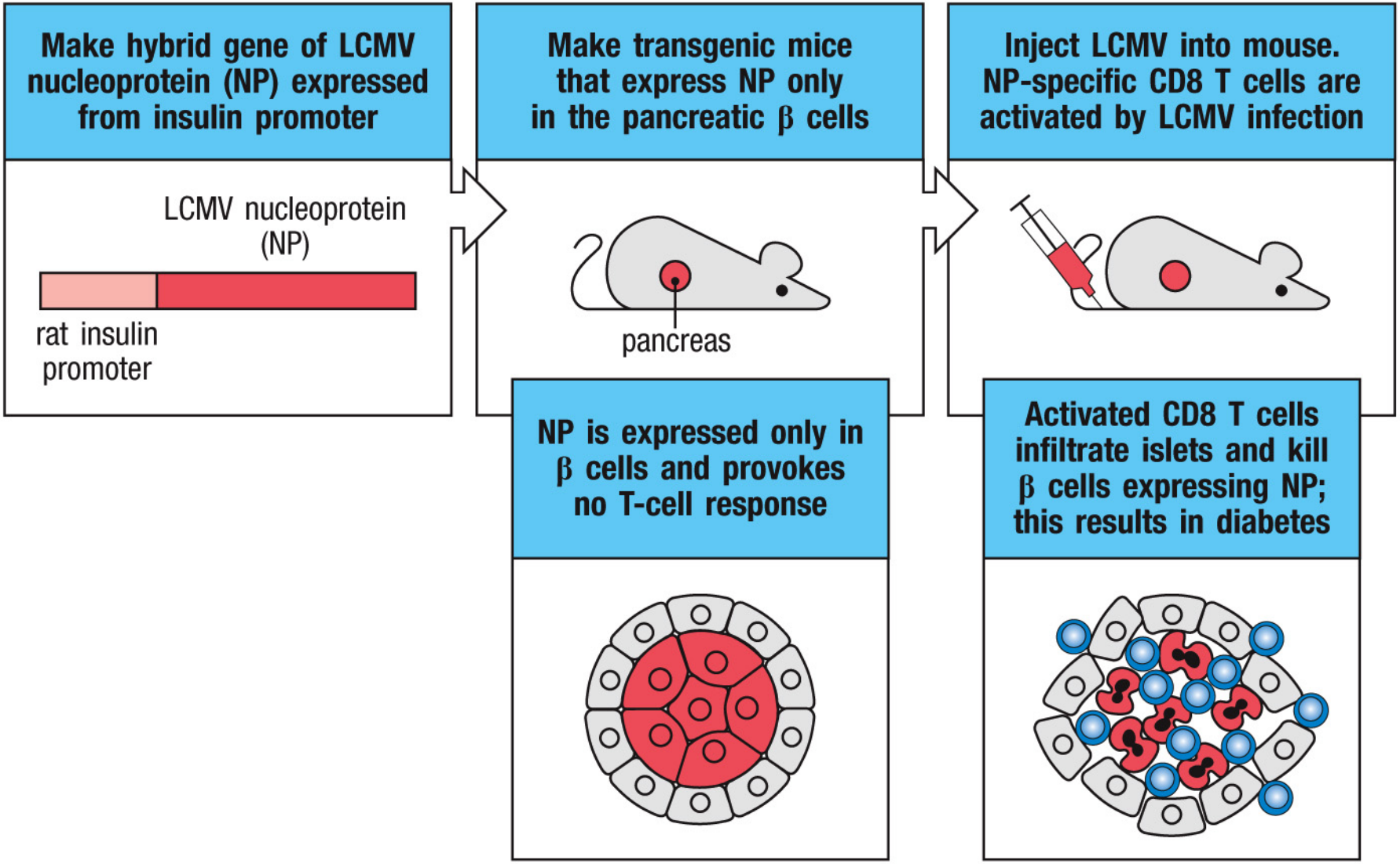



Figure 15.43 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Molecular Mimicry

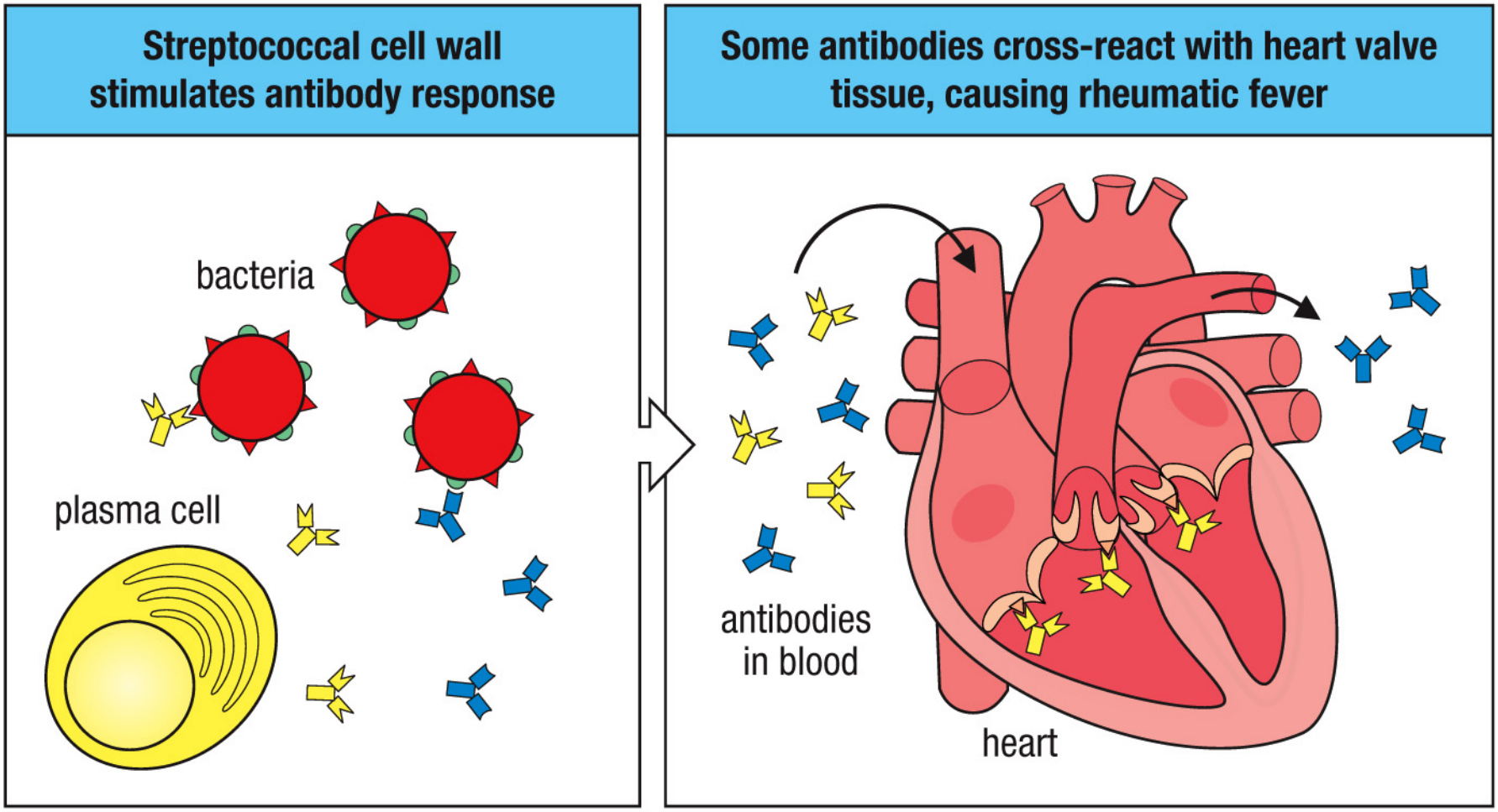



Figure 15.44 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# A Defect in a Single Gene Can Cause Autoimmunity

| Single-gene traits associated with autoimmunity | | | |
|---|---|---|---|
| **Gene** | **Human disease** | **Mouse mutant or knockout** | **Mechanism of autoimmunity** |
| *AIRE* | APECED (APS-1) | Knockout | Decreased expression of self antigens in the thymus, resulting in defective negative selection of self-reactive T cells |
| *CTLA4* | Association with Graves' disease, type 1 diabetes, and others | Knockout | Failure of T-cell anergy and reduced activation threshold of self-reactive T cells |
| *FOXP3* | IPEX | Knockout and mutation (*scurfy*) | Decreased function of CD4 CD25 regulatory T cells |
| *FAS* | ALPS | *lpr/lpr; gld/gld* mutants | Failure of apoptotic death of self-reactive B and T cells |
| *C1q* | SLE | Knockout | Defective clearance of immune complexes and apoptotic cells |
| *ATG16L1* | IBD | Hypomorph | Defective autophagy/clearance of bacteria by innate cells in intestines |
| *IL10RA, IL10RB* | IBD | Knockout | Defective IL-10 signaling; impaired anti-inflammatory response |
| *INS* | Type 1 diabetes | None | Decreased expression of insulin in thymus; impaired negative selection |

Figure 15.36 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

APECED, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy;
APS-1, autoimmune polyglandular syndrome 1;
IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome;
ALPS, autoimmune lymphoproliferative syndrome;
SLE, systemic lupus erythematosus;

# HLA Serotype Bias in Autoimmunity

| HLA- and gender-associated risk for autoimmune disease | | | |
|---|---|---|---|
| **Disease** | **HLA allele** | **Relative risk** | **Sex ratio (♀:♂)** |
| Ankylosing spondylitis | B27 | 87.4 | 0.3 |
| Type 1 diabetes | DQ2 and DQ8 | ~25 | ~1 |
| Goodpasture's syndrome | DR2 | 15.9 | ~1 |
| Pemphigus vulgaris | DR4 | 14.4 | ~1 |
| Autoimmune uveitis | B27 | 10 | <0.5 |
| Psoriasis vulgaris | CW6 | 7 | ~1 |
| Systemic lupus erythematosus | DR3 | 5.8 | 10–20 |
| Addison's disease | DR3 | 5 | ~13 |
| Multiple sclerosis | DR2 | 4.8 | 10 |
| Rheumatoid arthritis | DR4 | 4.2 | 3 |
| Graves' disease | DR3 | 3.7 | 4–5 |
| Hashimoto's thyroiditis | DR5 | 3.2 | 4–5 |
| Myasthenia gravis | DR3 | 2.5 | ~1 |
| Type I diabetes | DQ6 | 0.02 | ~1 |

Figure 15.37 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# HLA Bias in Type I Diabetes

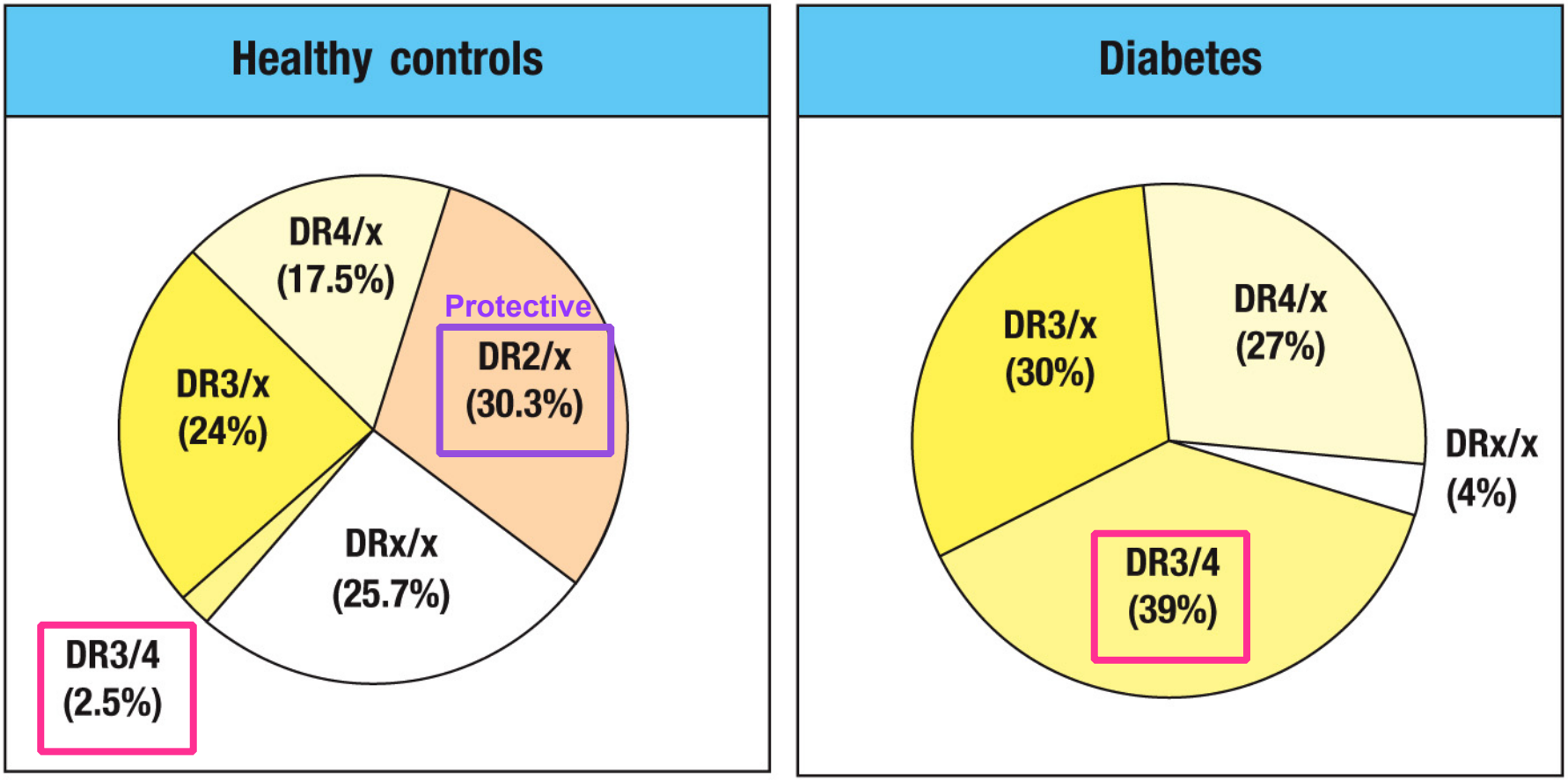
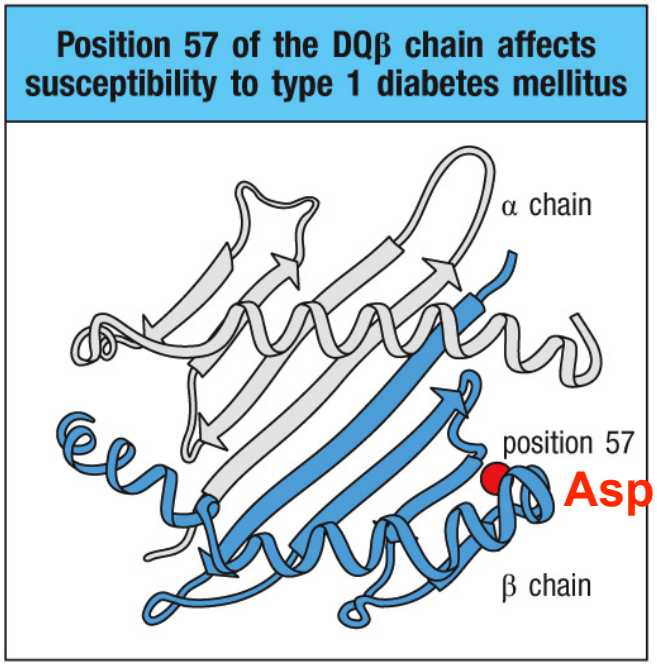
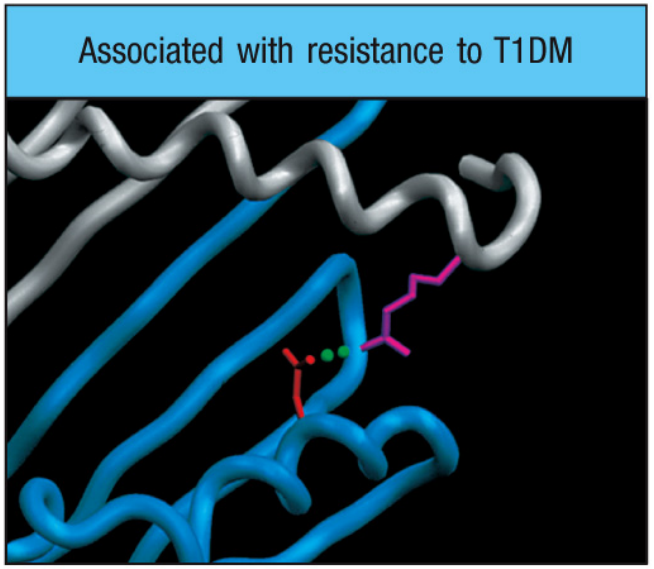



Figure 15.38 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Amino Acid Changes MHC II Correlate with Susceptibility to And Protection From Diabetes



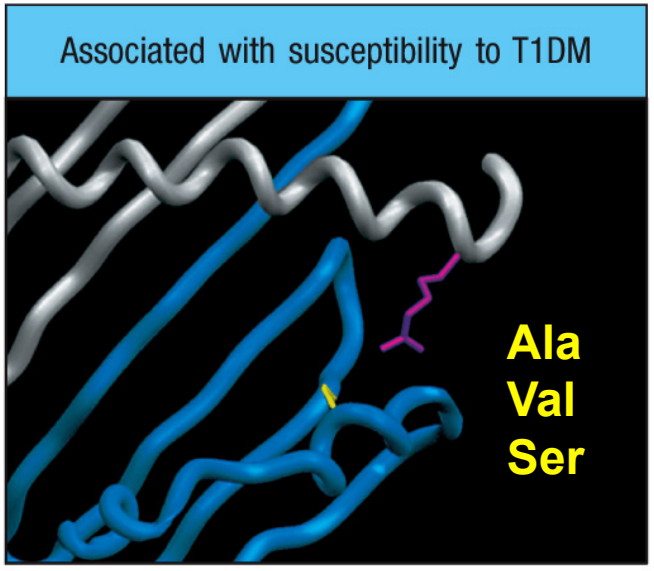




Figure 15.40 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Immune Deficiency and AutoImmune

Failure to keep microbiota in check causes Crohn's disease

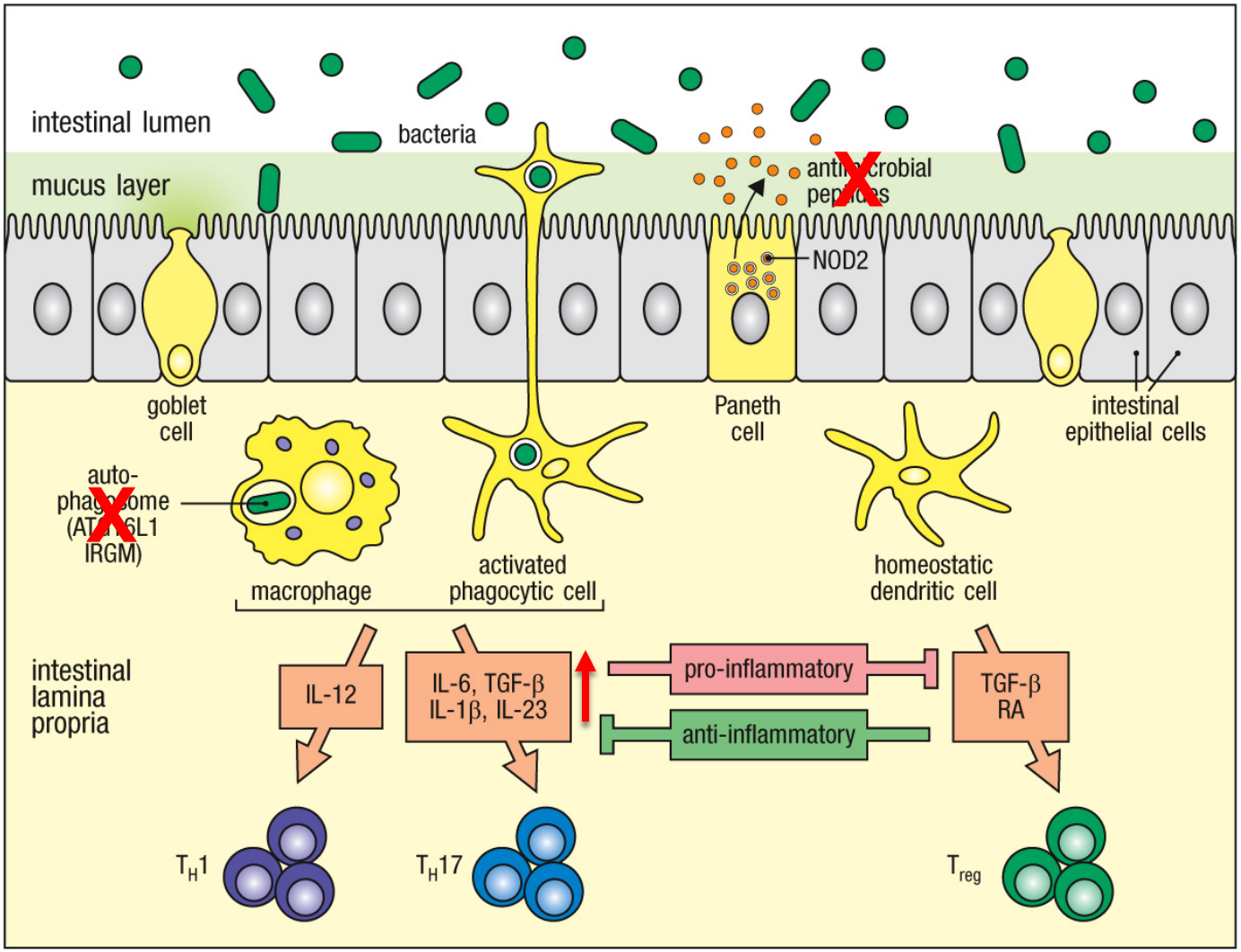



Figure 15.41 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Defects in Cytokine Production Can Cause Autoimmunity

| Defects in cytokine production or signaling that can lead to autoimmunity | | |
|---|---|---|
| **Defect** | **Cytokine, receptor, or intracellular signal** | **Result** |
| Overexpression | TNF-α | Inflammatory bowel disease, arthritis, vasculitis |
| | IL-2, IL-7, IL-2R | Inflammatory bowel disease |
| | IL-3 | Demyelinating syndrome |
| | IFN-γ | Overexpression in skin leads to SLE |
| | IL-23R | Inflammatory bowel disease, psoriasis |
| | STAT4 | Inflammatory bowel disease |
| Underexpression | TNF-α | SLE |
| | IL-1 receptor agonist | Arthritis |
| | IL-10, IL-10R, STAT3 | Inflammatory bowel disease |
| | TGF-β | Ubiquitous underexpression leads to inflammatory bowel disease. Underexpression specifically in T cells leads to SLE |

Figure 15.32 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Outline

Autoimmunity

- Regulatory mechanisms
- Development of autoimmunity
- Autoimmune diseases

# Origin of Autoimmune Diseases

| Autoimmune diseases involve all aspects of the immune response | | | |
|---|---|---|---|
| **Disease** | **T cells** | **B cells** | **Antibody** |
| Systemic lupus erythematosus | Pathogenic<br>Help for antibody | Present antigen<br>to T cells | Pathogenic |
| Type 1 diabetes | Pathogenic | Present antigen<br>to T cells | Present, but<br>role unclear |
| Myasthenia gravis | Help for antibody | Antibody secretion | Pathogenic |
| Multiple sclerosis | Pathogenic | Present antigen<br>to T cells | Present, but<br>role unclear |

Figure 15.15 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Autoantibodies Stimulating or Blocking Receptor Function

| Diseases mediated by antibodies against cell-surface receptors | | | | |
|---|---|---|---|---|
| **Syndrome** | **Antigen** | **Antibody** | **Consequence** | **Target cell** |
| Graves' disease | Thyroid-stimulating hormone receptor | Agonist | Hyperthyroidism | Thyroid epithelial cell |
| Myasthenia gravis | Acetylcholine receptor | Antagonist | Progressive muscle weakness | Muscle |
| Insulin-resistant diabetes | Insulin receptor | Antagonist | Hyperglycemia, ketoacidosis | All cells |
| Hypoglycemia | Insulin receptor | Agonist | Hypoglycemia | All cells |
| Chronic urticaria | Receptor-bound IgE or IgE receptor | Agonist | Persistant itchy rash | Mast cells |

Figure 15.23 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Myasthenia Gravis

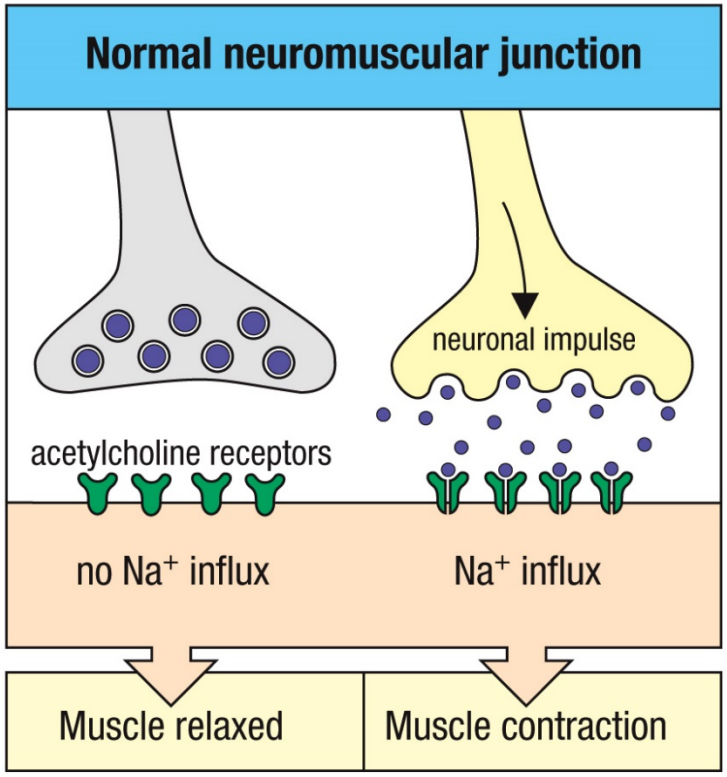



Figure 15.22 (part 1 of 2) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

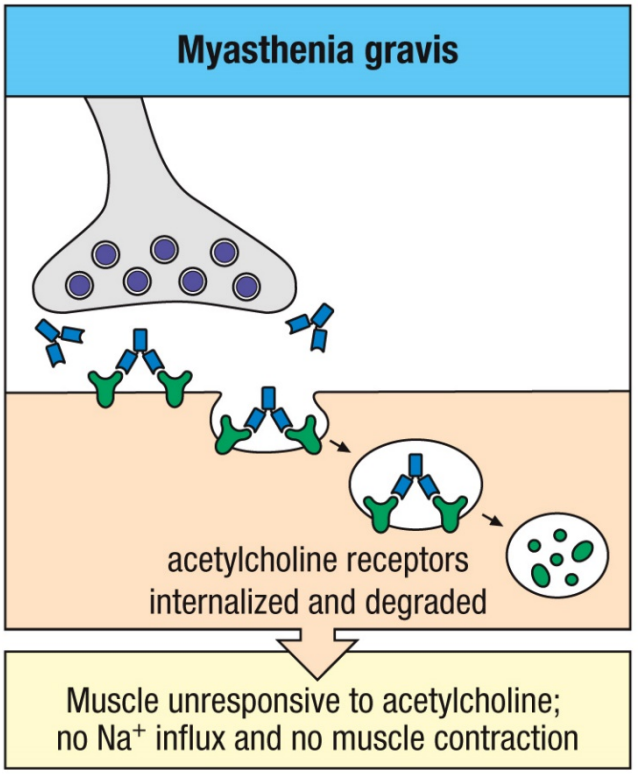



Figure 15.22 (part 2 of 2) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Autoantibodies Can Transfer Autoimmunity

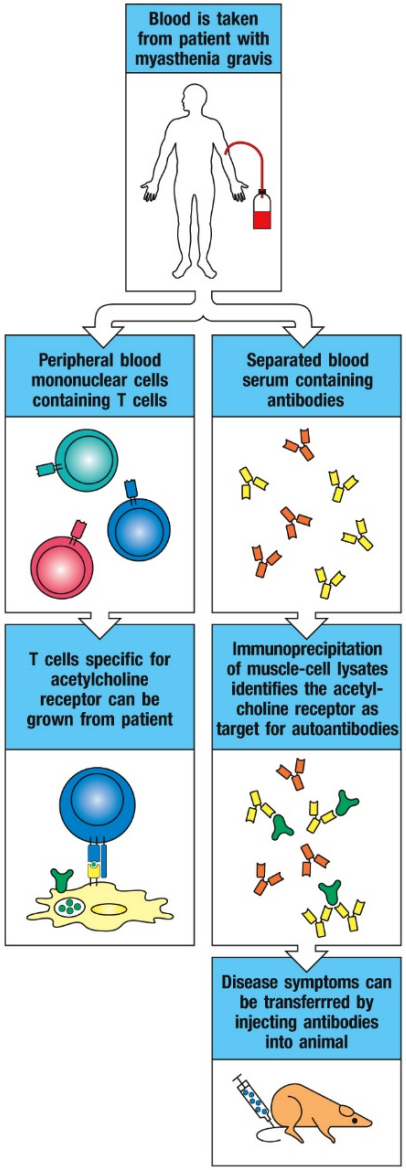



Figure 15.11 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Graves Disease

Constitutive production of thyroid hormone
- activating autoantibody

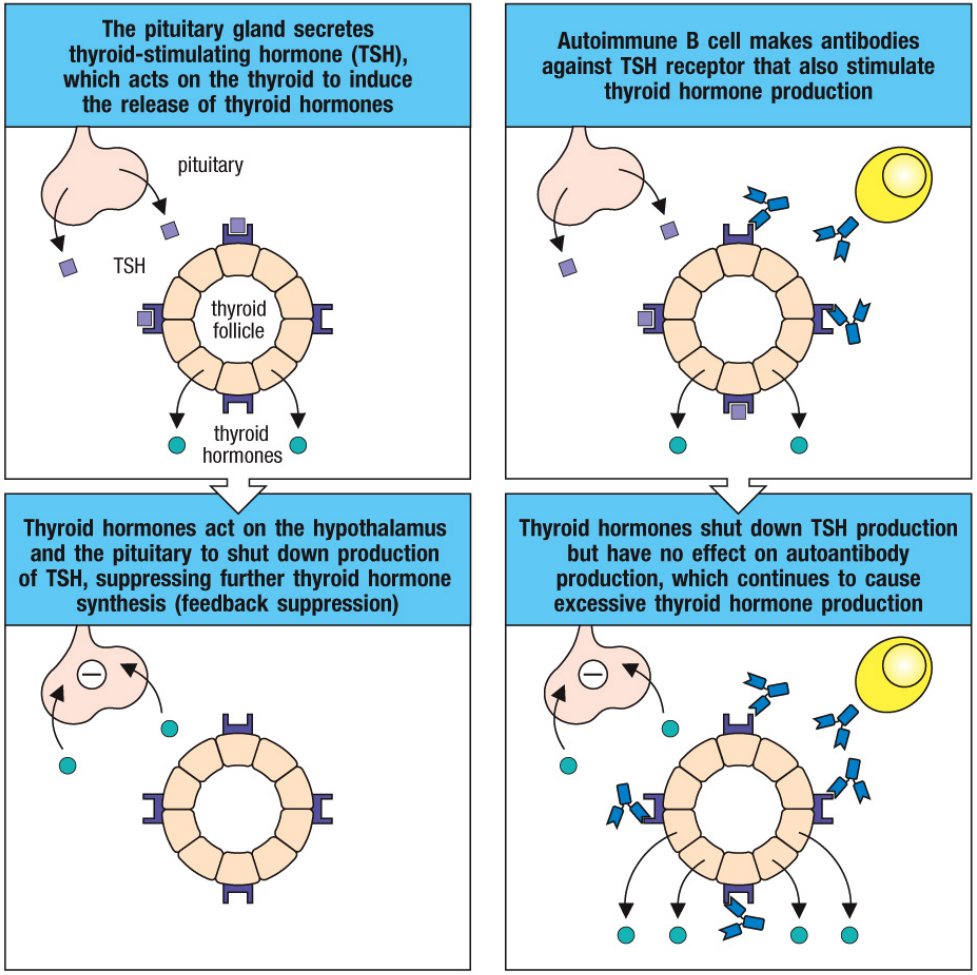



Figure 15.21 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Transplacental Antibody Transfer Can Induce Autoimmunity in Infants

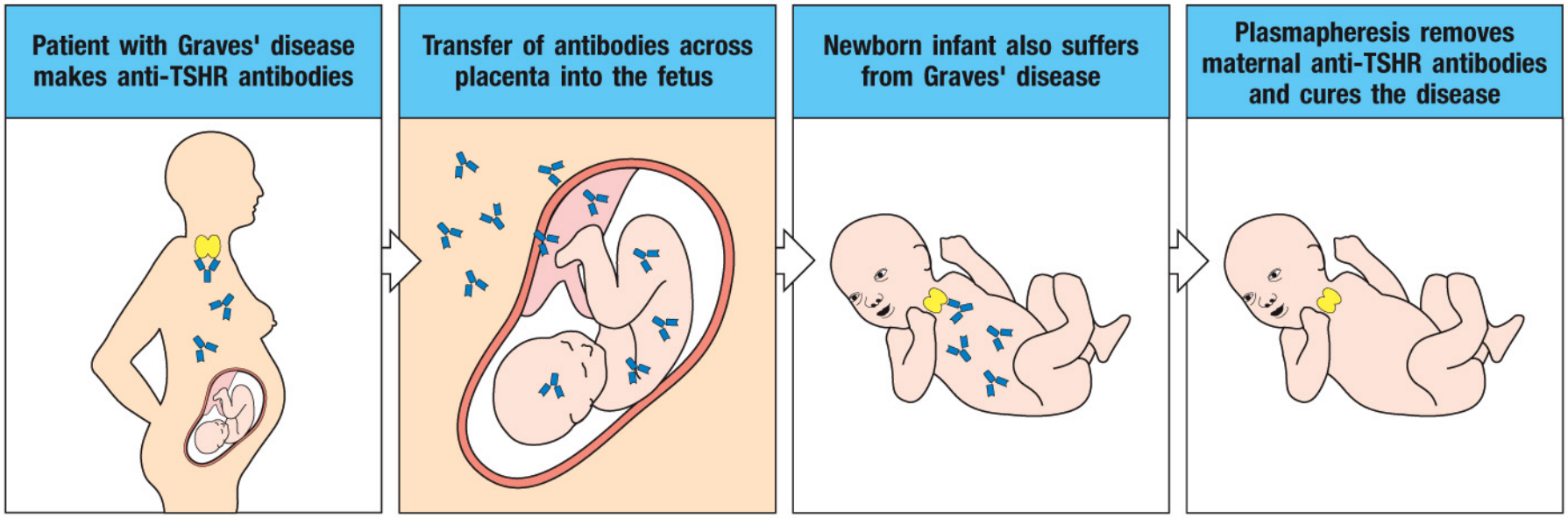



Figure 15.14 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Antibodies Specific for Cell-Surface Antigens Can Destroy Cells

Autoimmune hemolytic anemia

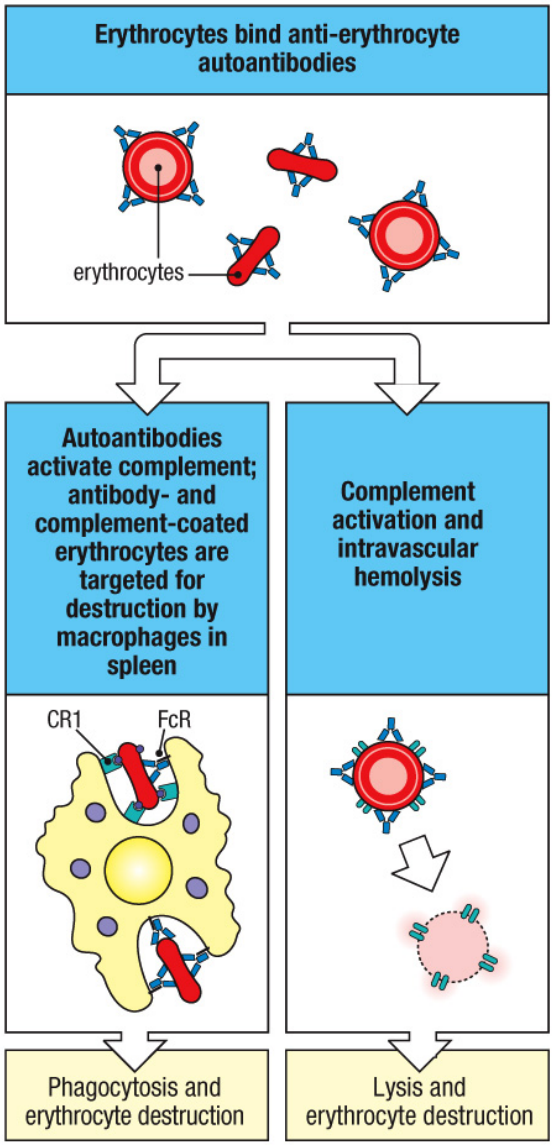



Figure 15.20 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# AutoImmune is Self Amplifying

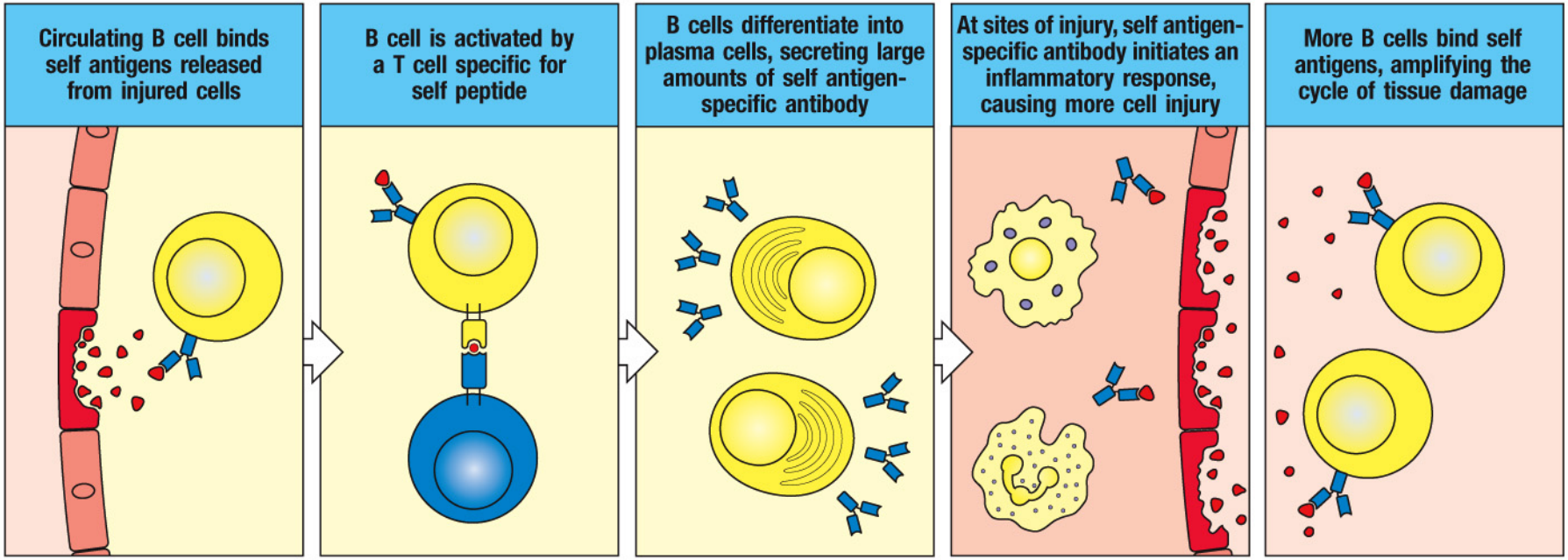



Figure 15.16 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# AutoImmune is Broadening: Epitope Spreading

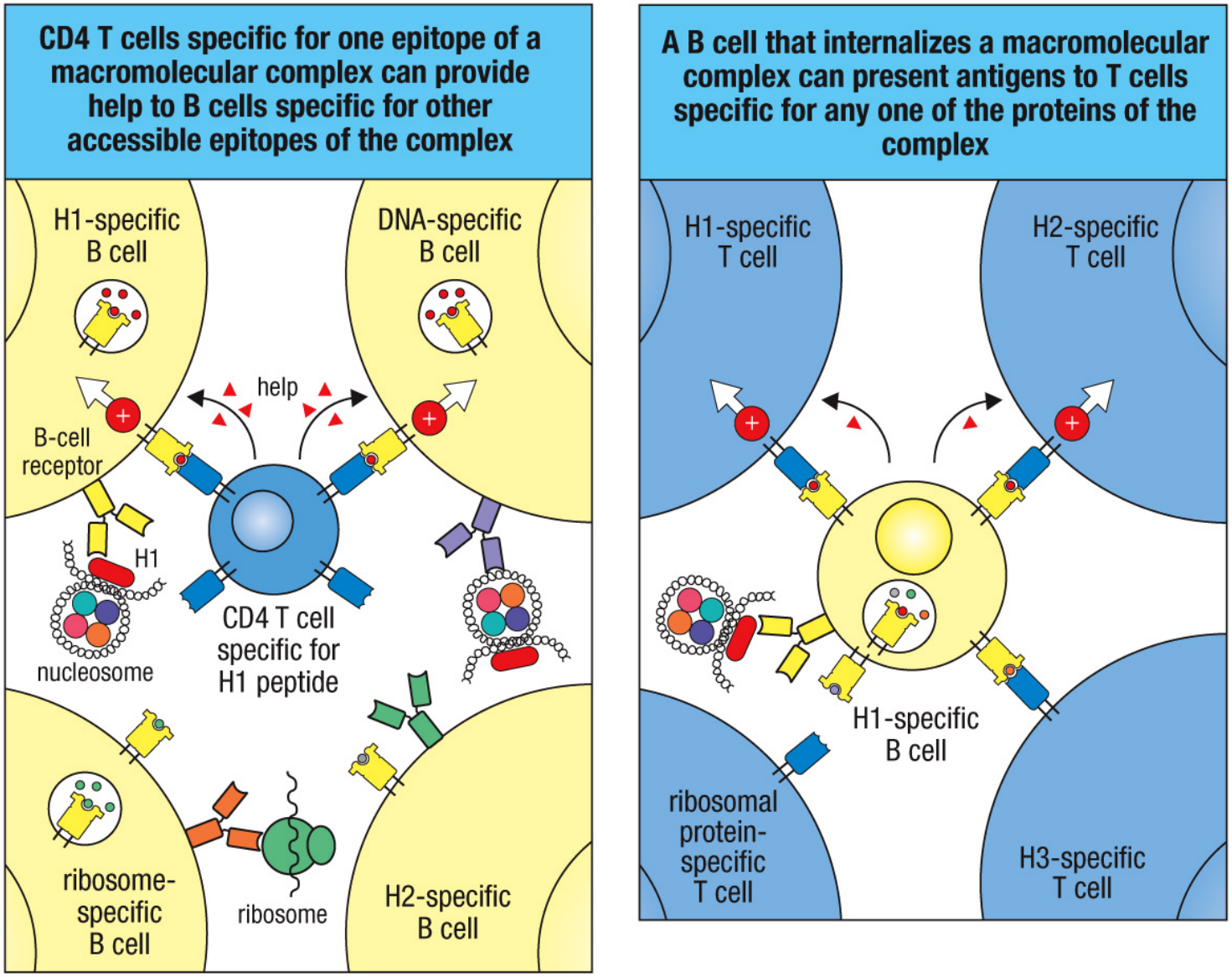
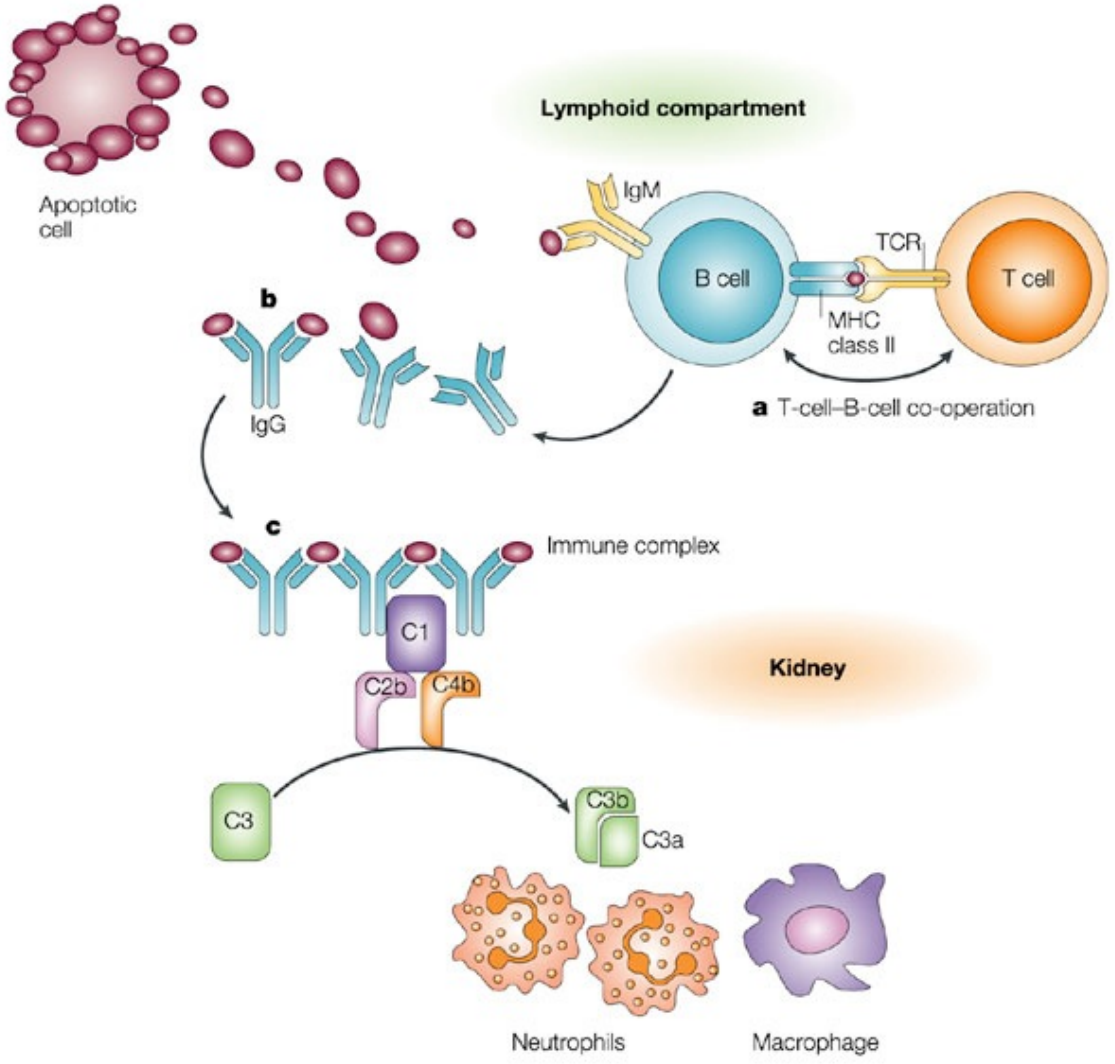



Figure 15.17 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Sometimes It Is Lupus!


http://pics.bbzzdd.com/users/gpb.atot/not-lupus.png

# Systemic Lupus Erythematosus Is Characterized by Autoantibodies to Conserved Nuclear Antigens




Nature Reviews Immunology 4, 825-831 (October 2004)

# Deposition of Immune Complexes Leads to Renal Failure-SLE

Basement membrane thickening

Anti-immunoglobulin

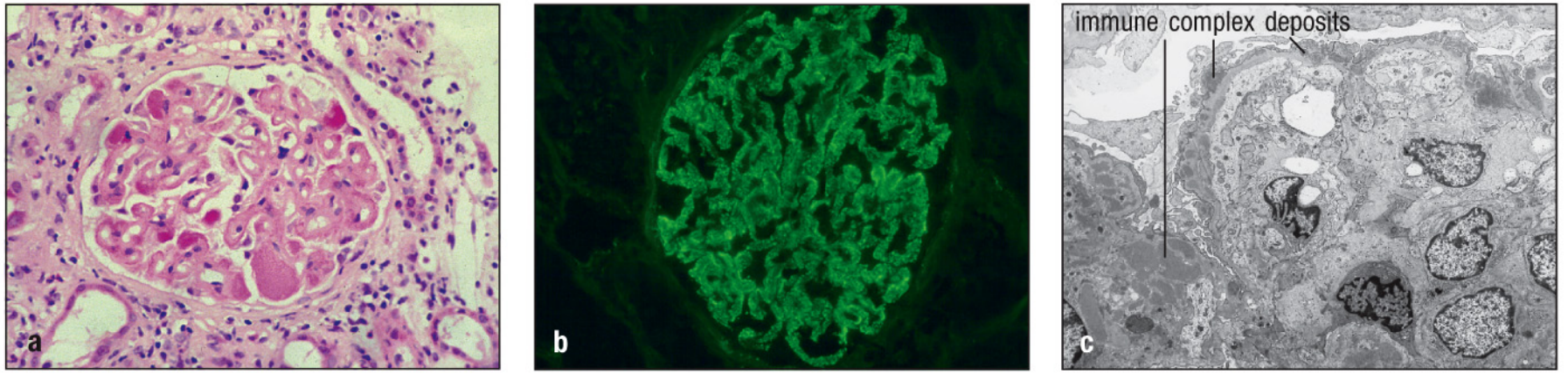



Figure 15.26 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# T Cell Mediated Disease

| Some common autoimmune diseases classified by immunopathogenic mechanism | | |
|---|---|---|
| **Syndrome** | **Autoantigen** | **Consequence** |
| **T-cell-mediated disease** | | |
| Type 1 diabetes | Pancreatic β-cell antigen | β-cell destruction |
| Rheumatoid arthritis | Unknown synovial joint antigen | Joint inflammation and destruction |
| Multiple sclerosis | Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein | Brain and spinal cord invasion by CD4 T cells, muscle weakness, and other neurological symptoms |
| Crohn's disease | Antigens of intestinal microbiota | Regional intestinal inflammation and scarring |
| Psoriasis | Unknown skin antigens | Inflammation of skin with formation of plaques |

Figure 15.19 (part 3 of 3) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Type I Diabetes

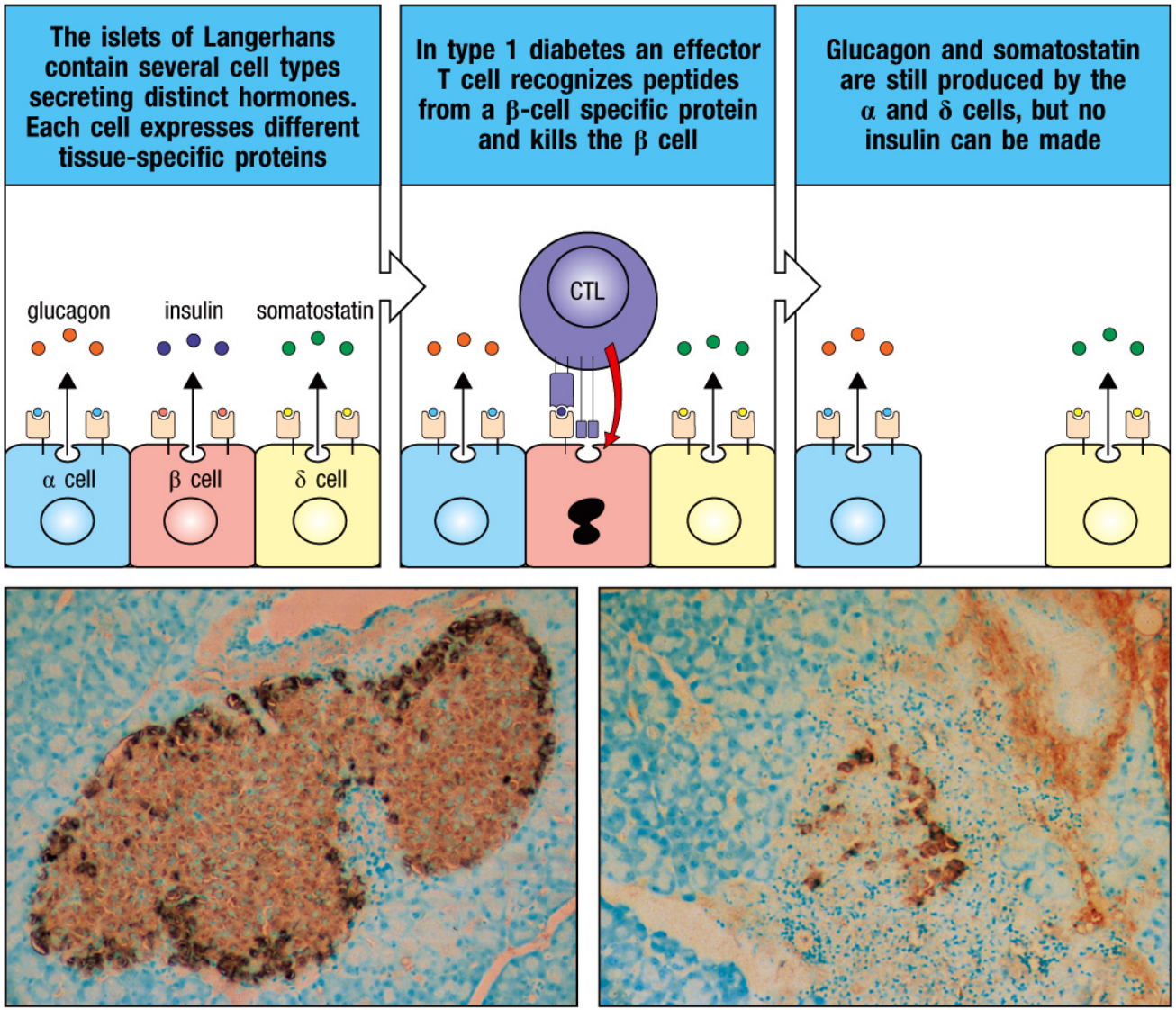



Figure 15.27 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Multiple Sclerosis

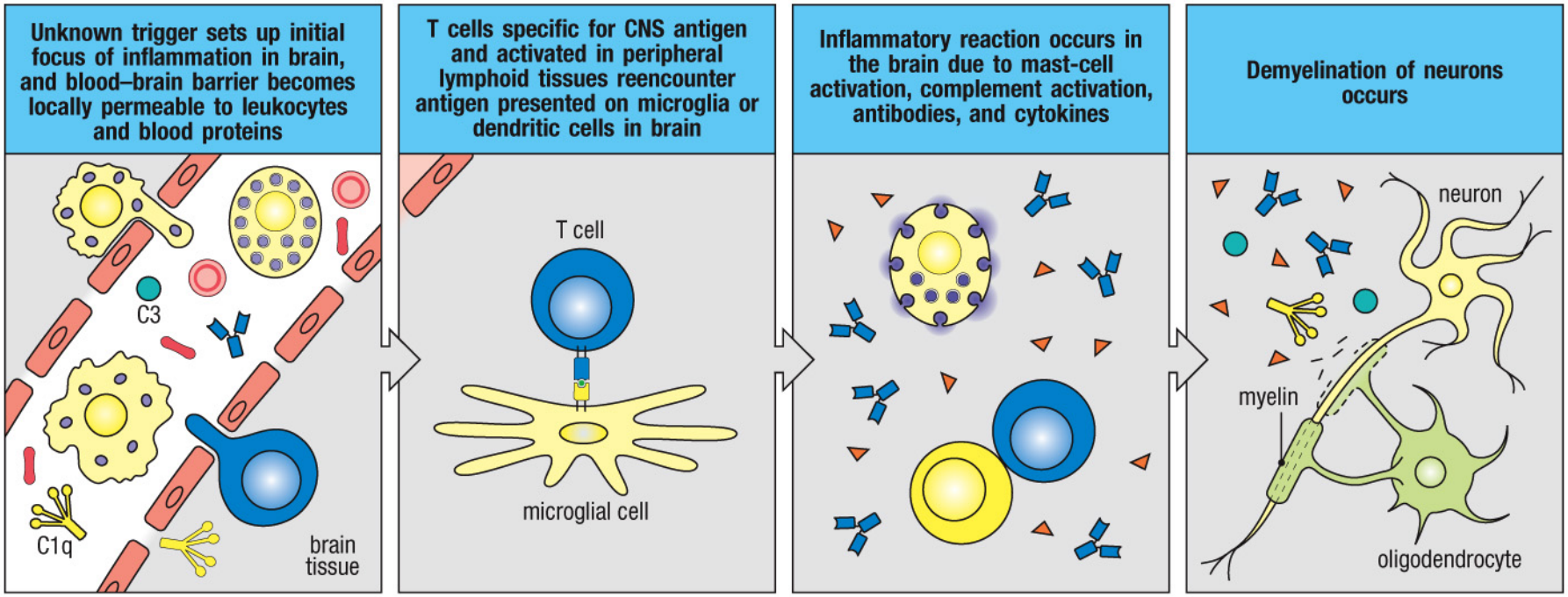



Figure 15.28 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Autoreactive T-Cells Can Transfer Autoimmunity

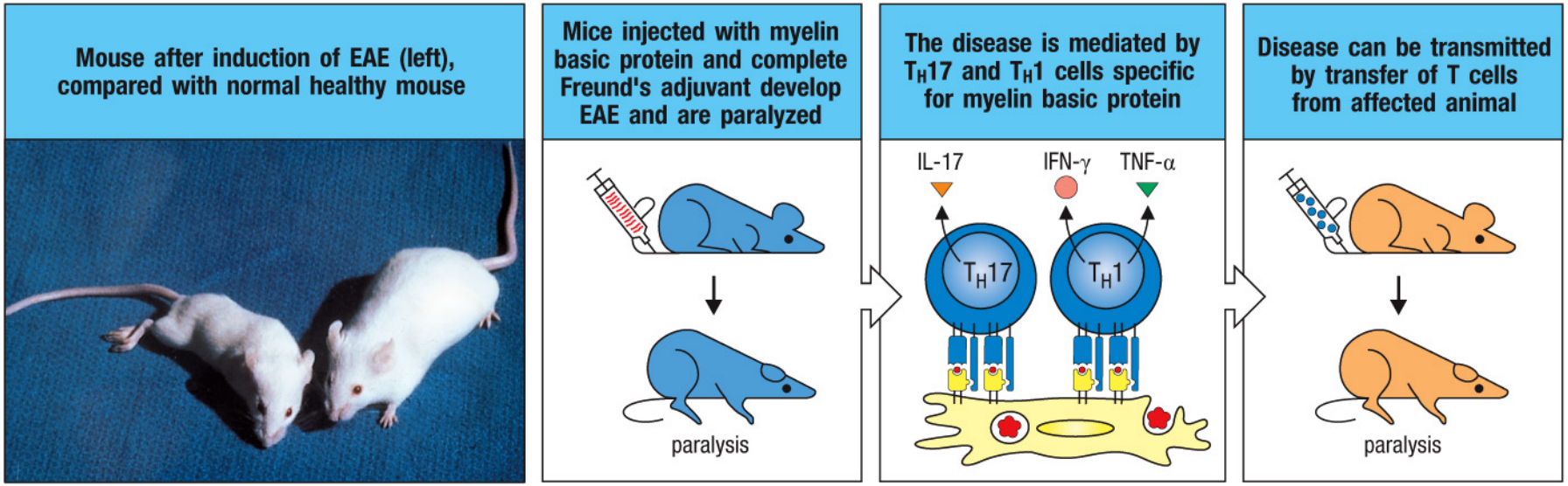
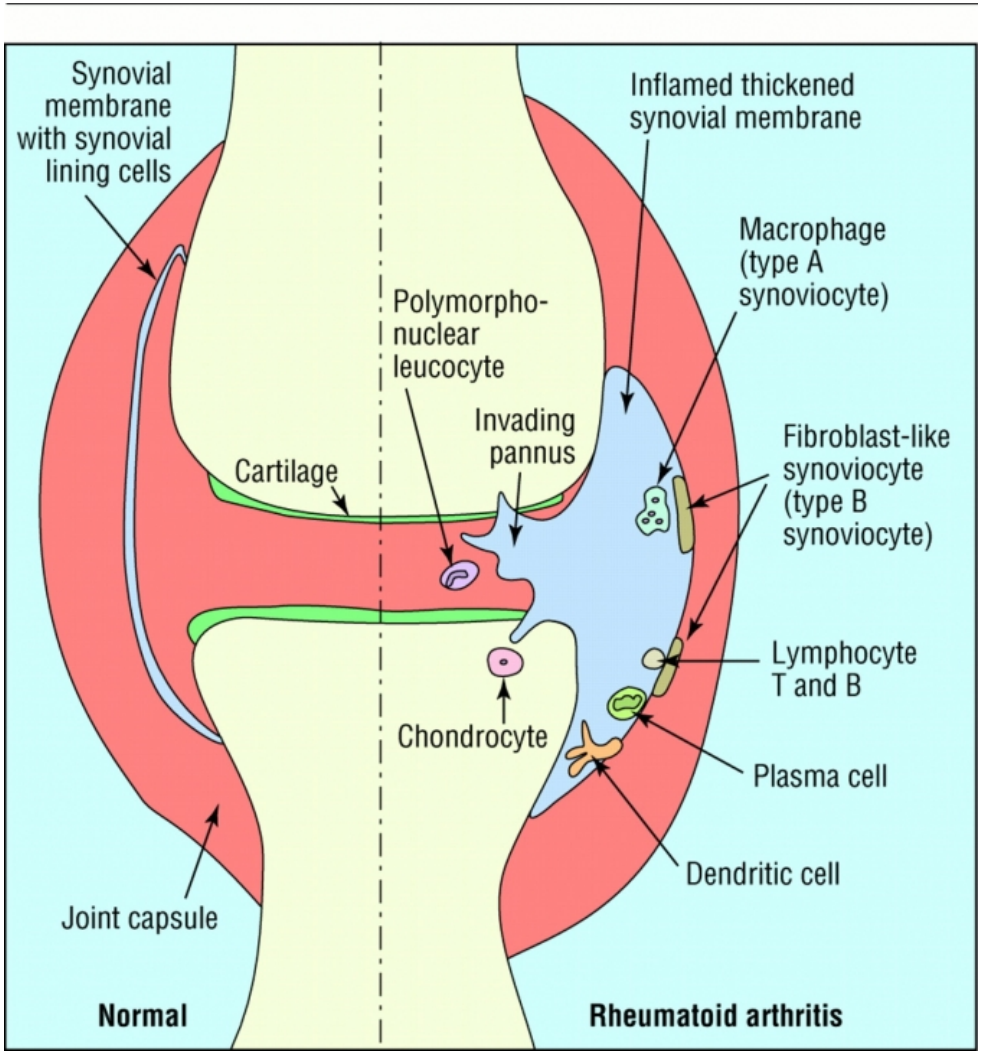



Figure 15.12 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

# Rheumatoid Arthritis



# Rheumatoid Arthritis

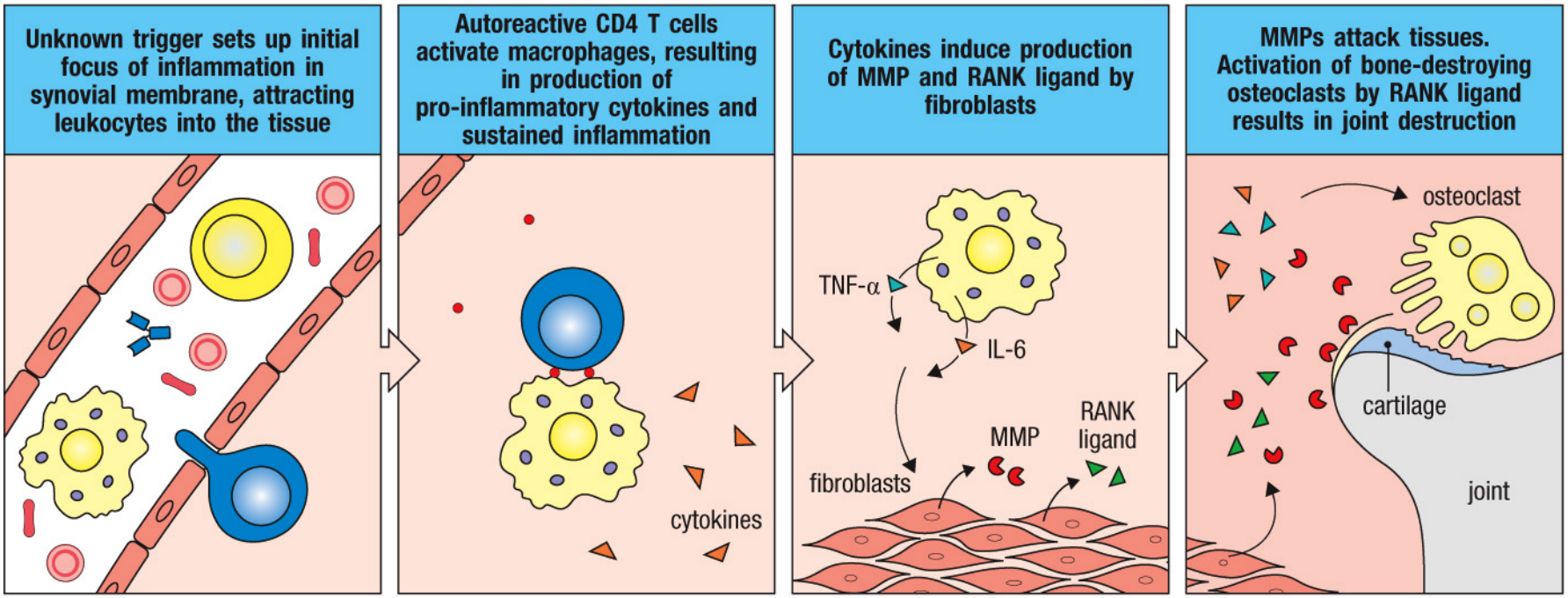



Figure 15.29 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Both B and T cells are involved in pathogenesis

# Summary

- Adaptive immunity to self antigen
- Trigger largely unknown
- Progressive and self amplifying

# Question

- What can not be used to treat autoimmune disorders?

- A) neutralizing antibodies
- B) immune suppressant
- C) Cytokines
- D) bone marrow transplantation
- E) None of the above