Cihan University/ Sulaymaniyah

College of Health Science

Medical Laboratory Analysis

4th Stage- 1st Semester

Clinical Immunology

Lecture- 9: Immunologic Tolerance and Autoimmunity

2023- 2024

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Immunologic Tolerance

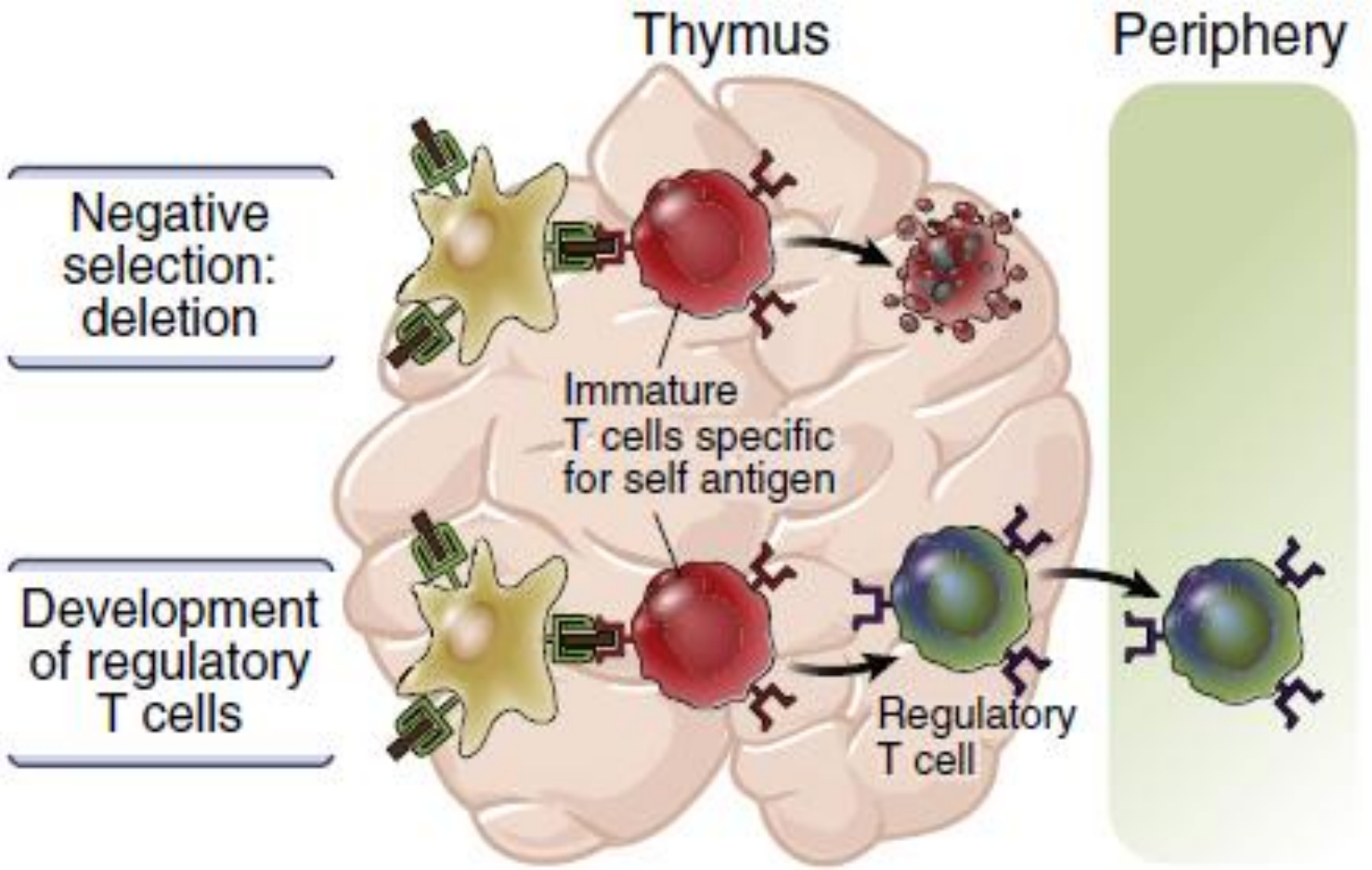
- Immunologic tolerance is a lack of response to antigens that is induced by exposure of lymphocytes to these antigens.
- The **lymphocytes** may be activated to proliferate and to differentiate into effector and memory cells, leading to a productive immune response; antigens that elicit such a response are said to be **immunogenic**.
- Or the lymphocytes may be functionally inactivated or killed, resulting in tolerance; antigens that induce tolerance are said to be **tolerogenic**.
- In some situations, the **antigen-specific lymphocytes** may not react in any way; this phenomenon has been called **immunologic ignorance**, implying that the lymphocytes simply ignore the presence of the antigen.
- Normally, **microbes are immunogenic** and **self antigens are tolerogenic**.

Central T Lymphocyte Tolerance

- Immunologic tolerance to different self antigens may be induced when **developing lymphocytes** encounter these **antigens in the generative (central) lymphoid organs**, a process called **central tolerance.**
- The **central tolerance** in T cells are **death of immature T cells** and the **generation of CD4+ regulatory T cells** .
- The **lymphocytes that develop in the thymus** consist of cells **with receptors** capable of **recognizing many antigens**, both **self** and **foreign**.
- If a **lymphocyte** that **has not completed its maturation** **interacts strongly with a self antigen**, that lymphocyte receives signals that trigger **apoptosis**. Thus, the **self-reactive cell** dies before it can become functionally competent.
- The process of **negative selection** affects **self-reactive CD4+ T cells and CD8+ T cells**, which recognize self peptides displayed by class II MHC and class I MHC molecules, respectively.

Central T cell tolerance

Strong recognition of self antigens by immature T cells in the thymus may lead to death of the cells (negative selection, or deletion), or the development of regulatory T cells that enter peripheral tissues.



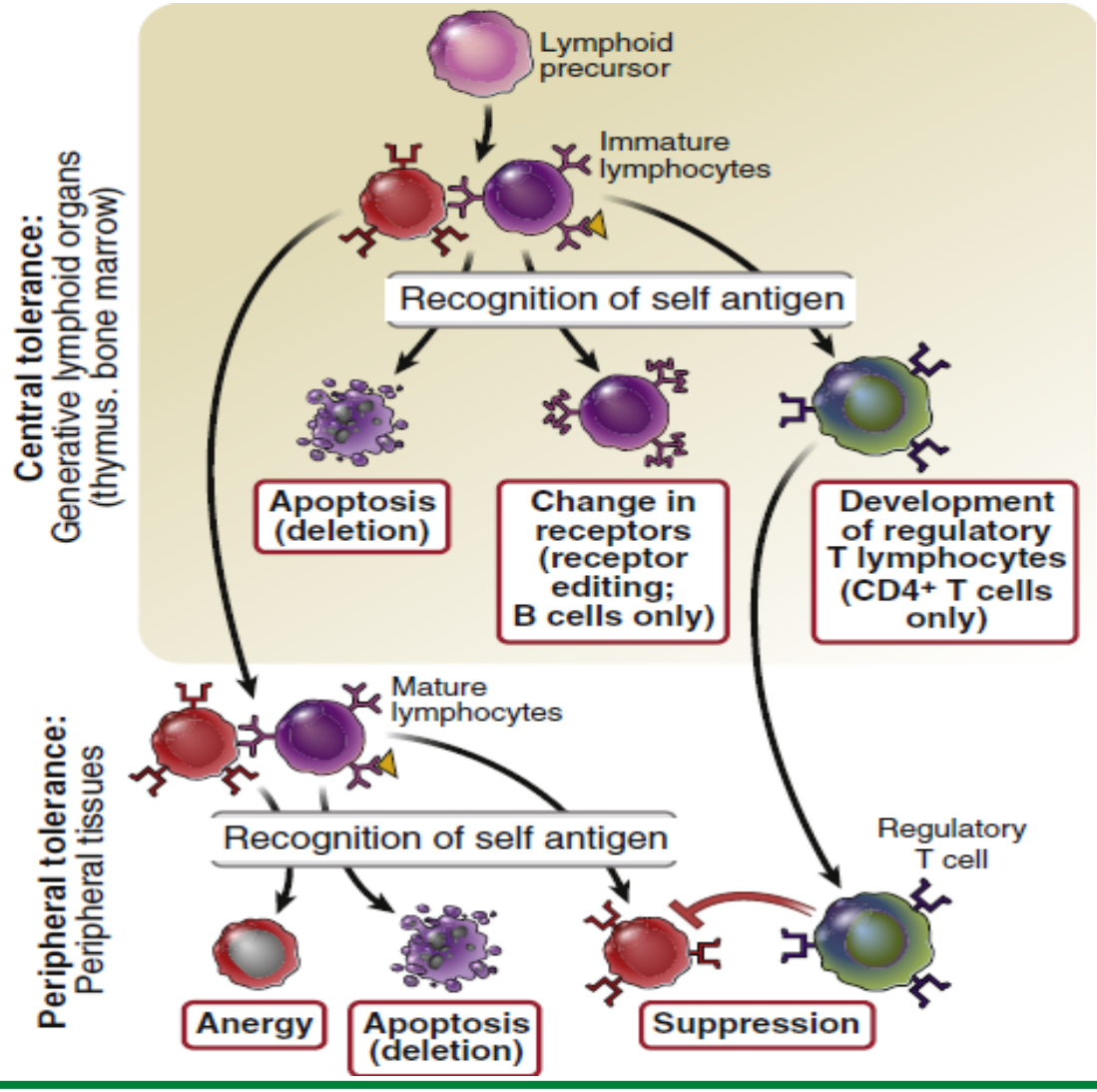
Central and Peripheral Tolerance to Self Antigens

❖ Central tolerance:

- Immature lymphocytes specific for self antigens may encounter these antigens in the generative (central) lymphoid organs and are deleted;
- B lymphocytes may change their specificity (receptor editing); and some T lymphocytes develop into regulatory T cells.
- Some self-reactive lymphocytes may complete their maturation and enter peripheral tissues.

❖ Peripheral tolerance:

- Mature self-reactive lymphocytes may be inactivated or deleted by encounter with self antigens in peripheral tissues or suppressed by regulatory T cells.

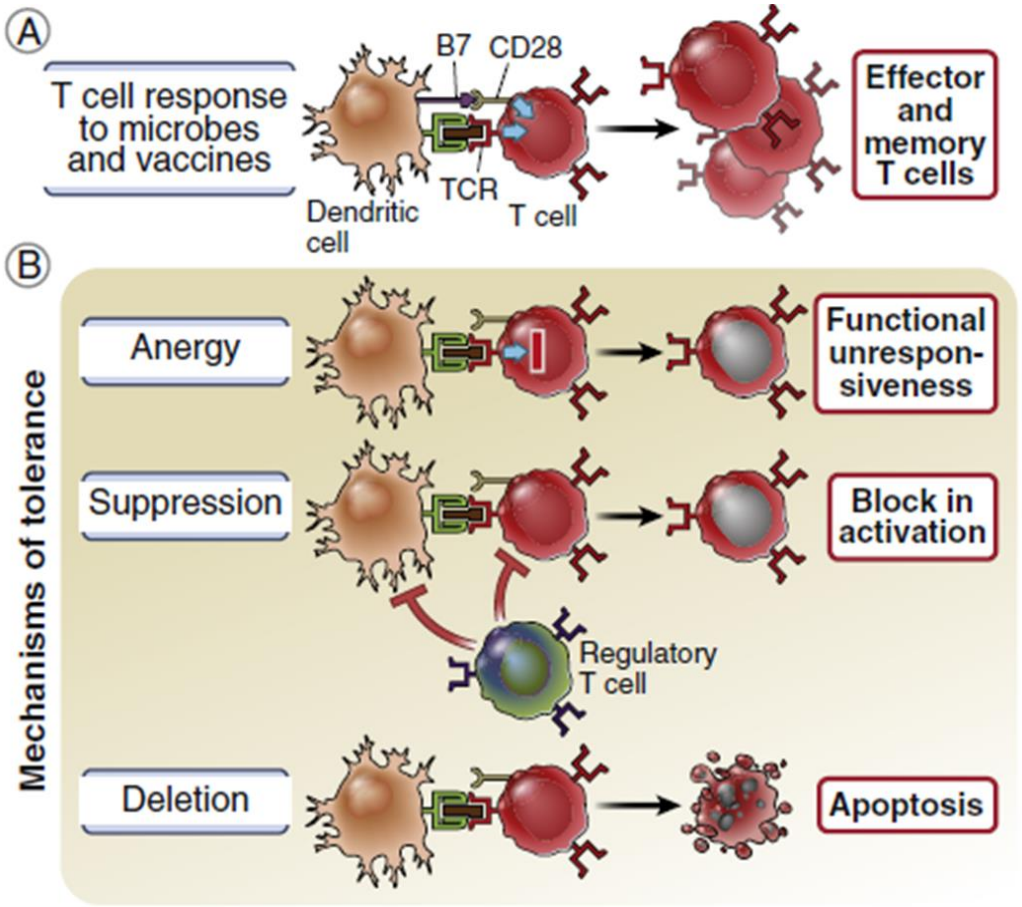


Peripheral T Lymphocyte Tolerance

- Peripheral tolerance is induced when **mature T cells** recognize **self antigens** in **peripheral tissues**, leading to **functional inactivation (anergy)** or **death**.

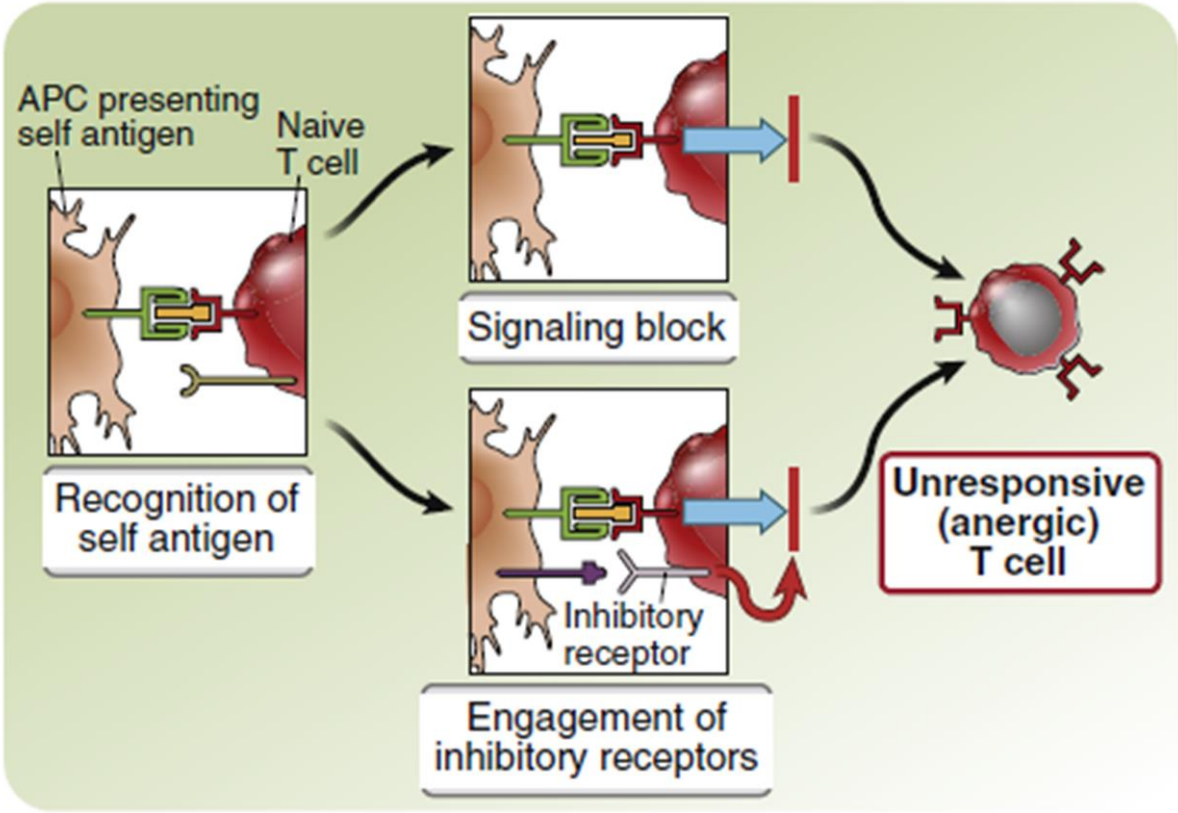
- Peripheral tolerance is clearly important for:
  1. Preventing **T cell responses** to **self antigens** that are not present in the thymus.
  2. Preventing **autoimmunity** in situations where **central tolerance to antigens** that are expressed in the thymus is **incomplete**.

- **Naive T lymphocytes** need at least two signals to induce their proliferation and differentiation into **effector** and **memory cells**:
  1. Signal 1 is always **antigen**,
  2. Signal 2 is provided by **costimulators that are expressed on APCs**.



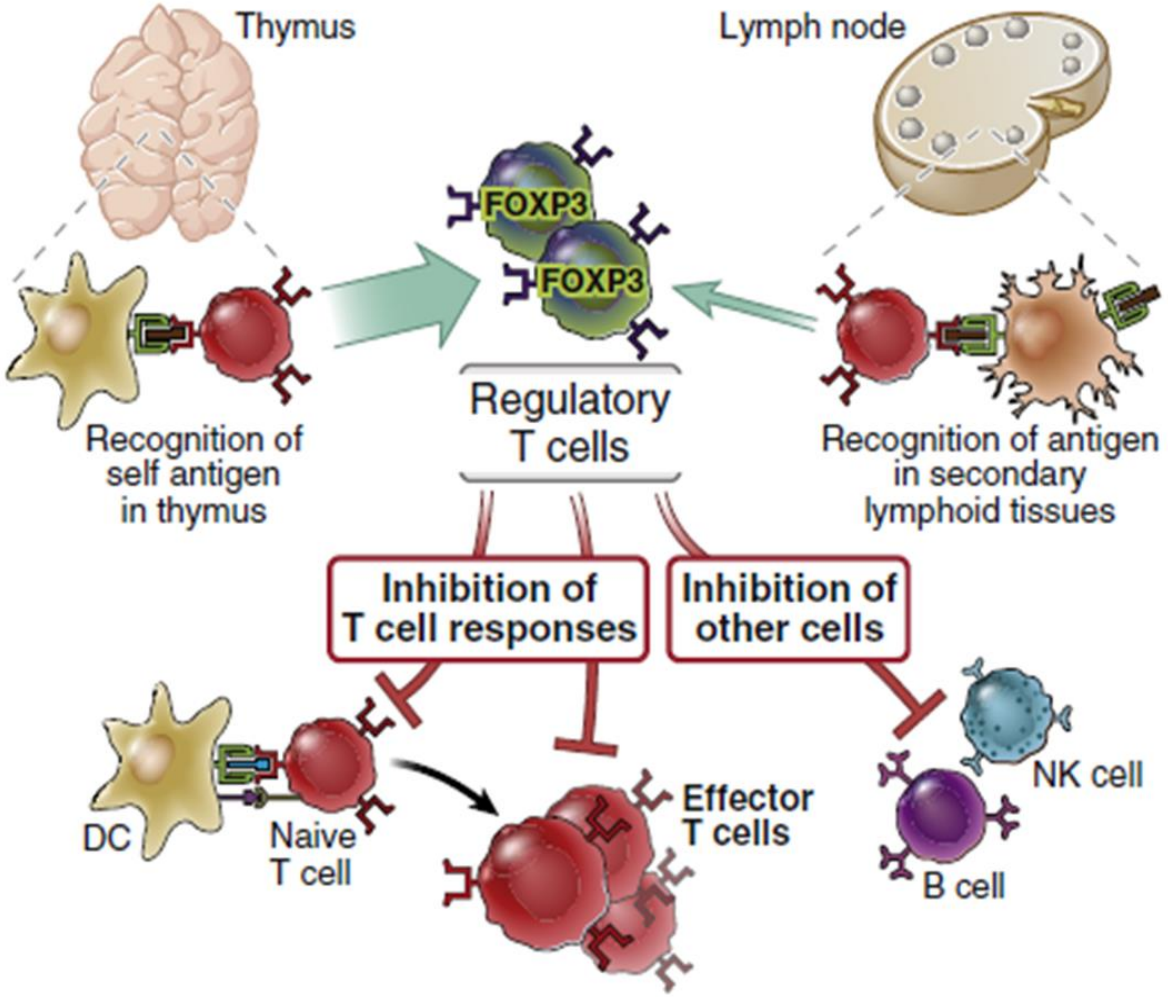
Anergy

- **Anergy** in **T cells** refers to **long-lived functional unresponsiveness** that is induced when these **cells** recognize **self antigens**.
- **Self antigens** are normally displayed with **low levels of costimulators**.
- **Antigen recognition** without adequate costimulation is thought to be the basis of **anergy induction**.
- **Anergic cells survive** but are **incapable of responding to the antigen**.
- When **T cells** recognize **antigens without costimulation**, the TCR complex may **lose its ability to transmit activating signals**.



Regulation of T Cell Responses by Inhibitory Receptors

- **Immune responses** are influenced by a **balance** between **engagement of activating** and **inhibitory receptors**.
- This idea is established for B and T lymphocytes and natural killer (NK) cells.
- In T cells, the main **activating receptors** are the **TCR complex** and **costimulatory receptors** such as **CD28** and the coinhibitors, are **CTLA-4** and **PD-1**.



Deletion: Apoptosis of Mature Lymphocytes

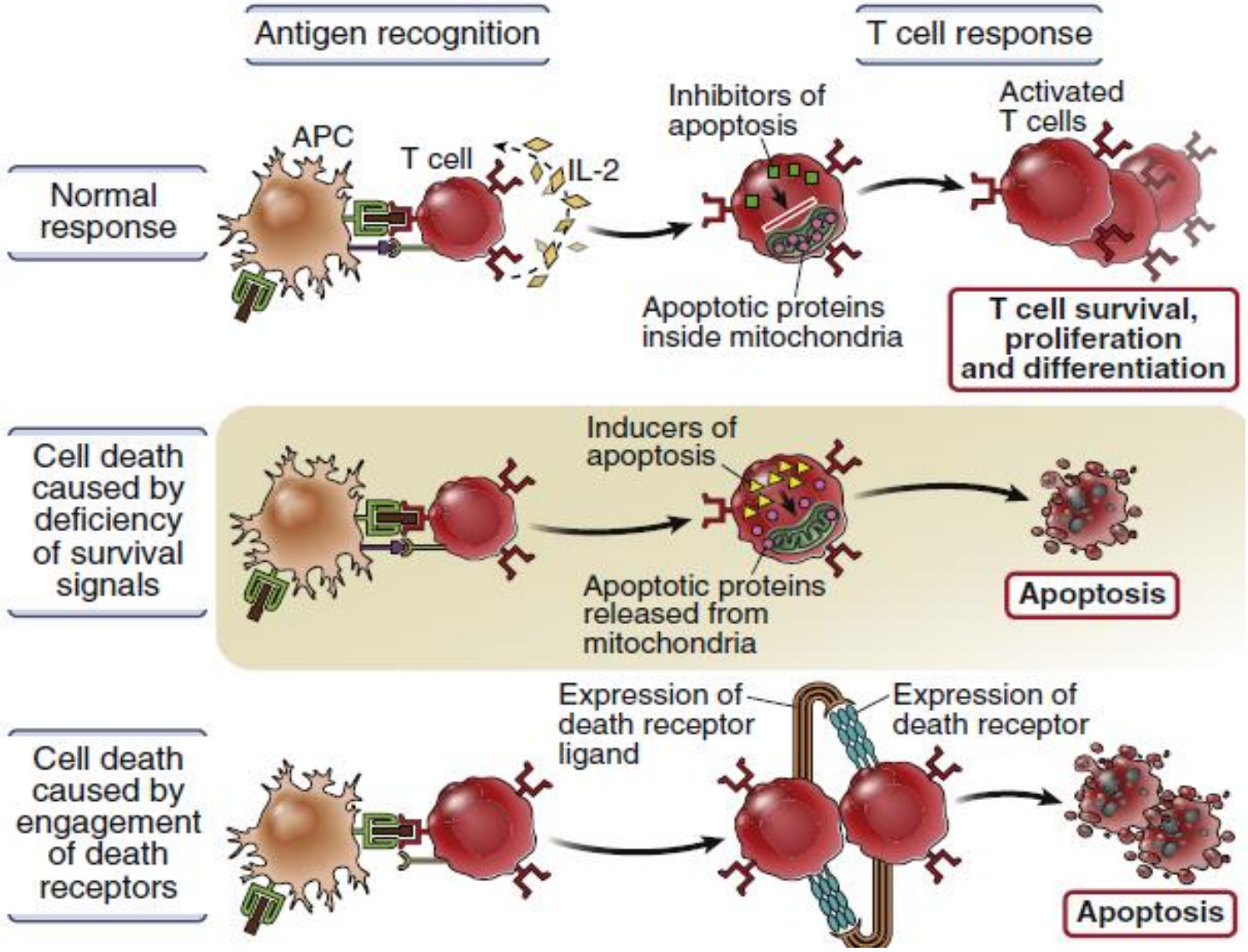
- **Recognition of self antigens** may **trigger pathways of apoptosis** that result in **elimination (deletion)** of the **self-reactive lymphocytes**.

- There are two likely mechanisms of death of mature T lymphocytes induced by self antigens:

1. **Antigen recognition** induces in **T cells** the production of **proapoptotic proteins** that cause **mitochondrial proteins**, such as **cytochrome c**, to **leak out** and **activate cytosolic enzymes** called **caspases** that **induce apoptosis**.
   - In normal immune responses, the activity of these **proapoptotic proteins** is **counteracted by antiapoptotic proteins** that are induced by costimulation and by growth factors produced during the responses.

2. **Recognition of self antigens** may lead to the coexpression of **death receptors** and **their ligands**.

Mechanisms of Apoptosis of T Lymphocytes

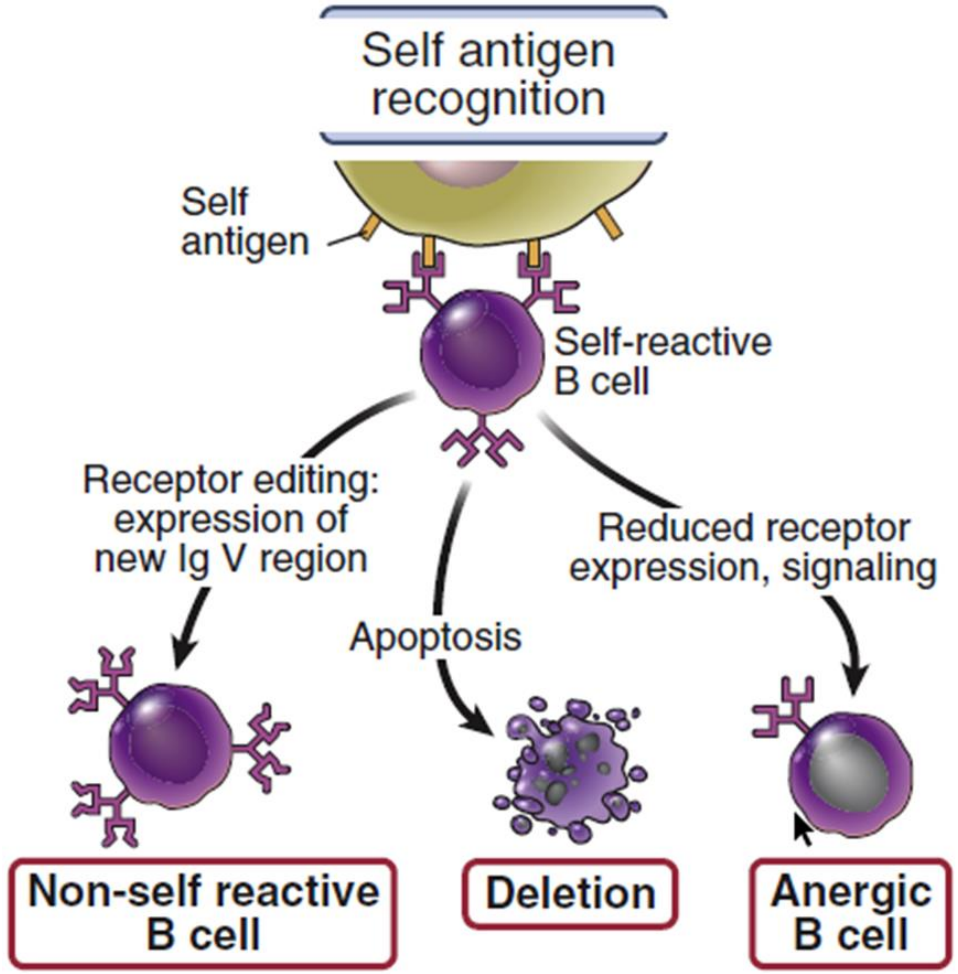


B Lymphocyte Tolerance

- **Self polysaccharides**, **lipids**, and **nucleic acids** are **T-independent antigens** that are **not recognized by T cells**.
- **These antigens** must induce tolerance in B lymphocytes to prevent **autoantibody** production.
- **Self proteins** may not elicit autoantibody responses because of **tolerance in helper T cells** and in **B cells**.
- It is suspected that **diseases** associated with **autoantibody production**, such as **systemic lupus erythematosus (SLE)**, are caused by **defective tolerance** in both **B lymphocytes** and **helper T cells**.

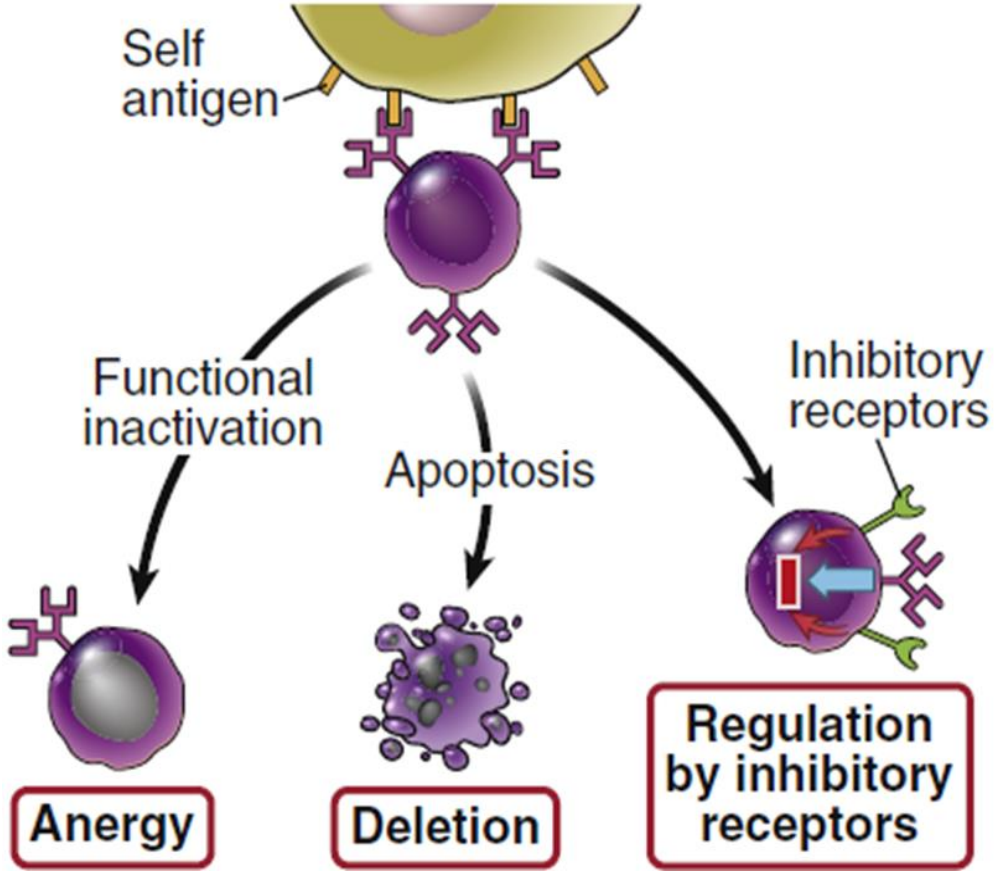
Central B Cell Tolerance

- When **immature B lymphocytes** interact **strongly** with **self antigens** in the **bone marrow**, the B cells either **change their receptor specificity (receptor editing)** or are **killed (deletion).**
- **Receptor editing. Immature B cells** are at a stage of maturation in the bone marrow when they have **rearranged their immunoglobulin (Ig) genes**, **express IgM with a heavy chain and light chain**.
- **Deletion.** If **editing fails**, **immature B cells** that strongly recognize self antigens **receive death signals** and **die by apoptosis**. This process of deletion is similar to negative selection of immature T lymphocytes.
- **Anergy. Some self antigens, such as soluble proteins**, may be recognized in the bone marrow with low avidity, **B cells specific for these antigens survive**, but **antigen receptor expression is reduced**, and the **cells become functionally unresponsive (anergic).**



Peripheral B Cell Tolerance

- **Mature B lymphocytes** that **encounter self antigens** in **peripheral lymphoid tissues** become **incapable of responding to that antigen**.
- If **B cells recognize a protein antigen** but do not receive T cell help, the **B cells become anergic** because of a **block in signaling from the antigen receptor**.
- **Anergic B cells** may **leave lymphoid follicles** and are subsequently **excluded from the follicles**.
- These **excluded B cells** may die because they do not receive necessary survival stimuli.
- **B cells that recognize self antigens** in the periphery may also **undergo apoptosis**, or inhibitory receptors on the B cells may be engaged, thus preventing activation.



Tolerance to Commensal Microbes

- There are two other types of antigens that are **not self** but are produced by cells or tissues that have to be tolerated by the immune system.
- These **are products of commensal microbes** that live in **symbiosis** with humans and paternally derived **antigens in the fetus.**
- Coexistence with these antigens **is dependent on** many of the same mechanisms that are used to maintain **peripheral tolerance to self antigens**.
- **Mature lymphocytes** in these tissues are **capable of recognizing the organisms but do not react against them**, so **the microbes are not eliminated**, and **harmful inflammation is not triggered**.

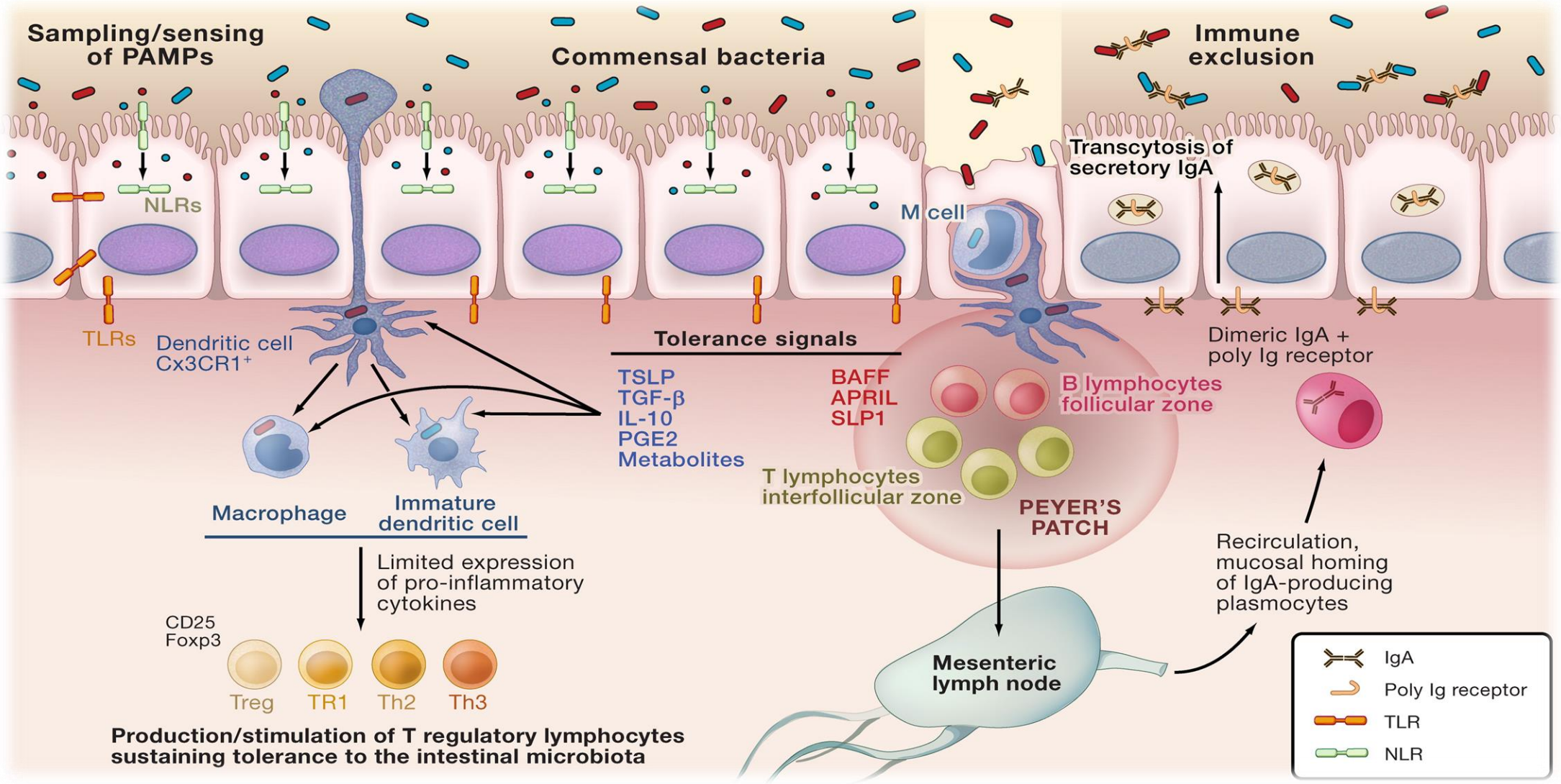
Tolerance to Commensal Microbes and Food Antigens- Cont..

- The role of the GI mucosa in establishing oral tolerance is complex.
- The GI tract sees approximately **70–100 g of protein daily**, and the immune regulation in response to this antigen load relies on a number of factors:
  - ✓**Physical barriers of the epithelium**
  - ✓**Its secreted products, luminal digestion of antigens,**
  - ✓**Suppressive immune milieu including the presence of regulatory T cells.**
- The barrier function of the GI tract includes a **hydrophobic layer of mucin oligosaccharides** that trap antigen and **secretory IgA** that **prevents absorption of food proteins across the intestinal epithelium**.
- As food proteins pass through the stomach and duodenum, **gastric acid and other digestive enzymes destroy their conformational and linear epitopes and break them down into di- and tripeptides**, rendering them **less immunogenic** while **simultaneously permitting absorption of peptides and amino acids as nutrients**.

Tolerance to Commensal Microbes and Food Antigens- Cont..

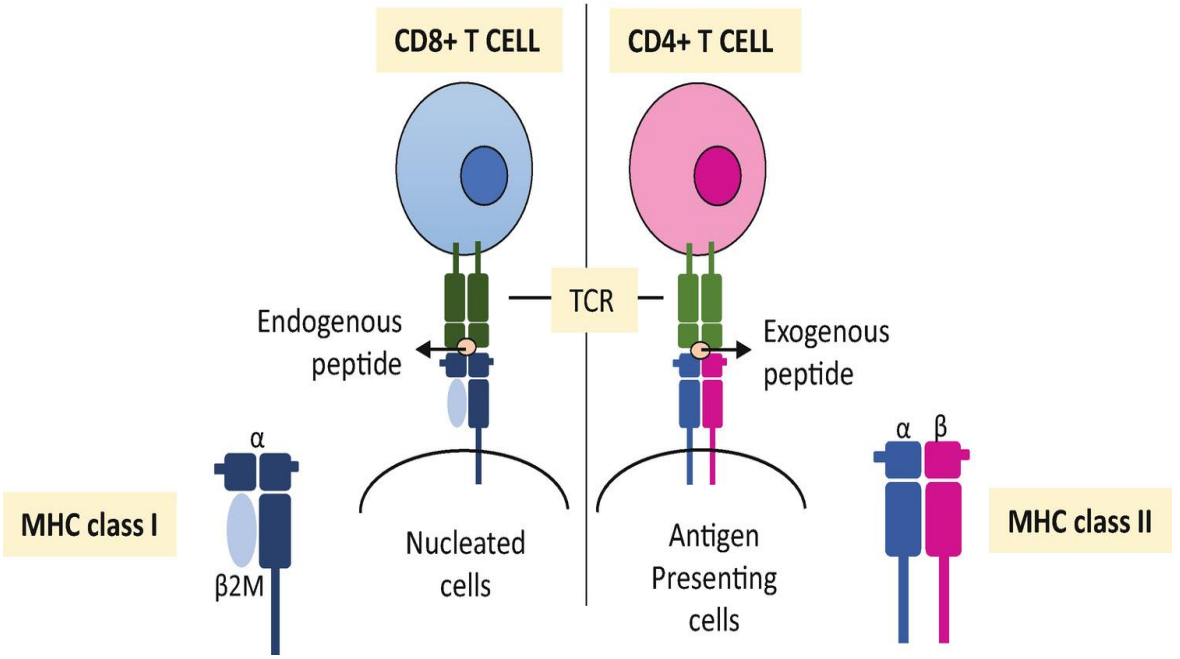
- **Three different types of cells in the intestinal mucosa can sample proteins that escape digestion.**
- Specialized epithelial cells called **microfold (M) cells** are found in the dome epithelium overlying **Peyer's patches**.
- They can take up particulate antigen due to their limited glycocalyx, their sparse cytoplasm, and their high endocytic activity, allowing for efficient delivery to the underlying immune cells.
- **Intestinal epithelial cells (IECs)** can also transport soluble antigens by a transcellular mechanism,
- **Dendritic cells (DCs)** can directly sample antigen by **extending dendrites into the intestinal lumen**.
- Once antigen has been check out, it **generates the production of regulatory T cells** that **suppress effector T-cell responses in an antigen-specific manner**.
- Feeding of antigen induces regulatory CD4+ and CD8+ T cells that can transfer tolerance to a naïve animal.

Tolerance Mechanism of Commensal Bacterial



Major Histocompatibility Complex (MHC)

- They are **group of genes** that **code for proteins** found on **the surfaces of cells** that help the immune system **recognize foreign substances**.
- **MHC proteins** are found in **all higher vertebrates**.
- In human beings the complex is also called the **human leukocyte antigen (HLA) system**.



MHC Classes

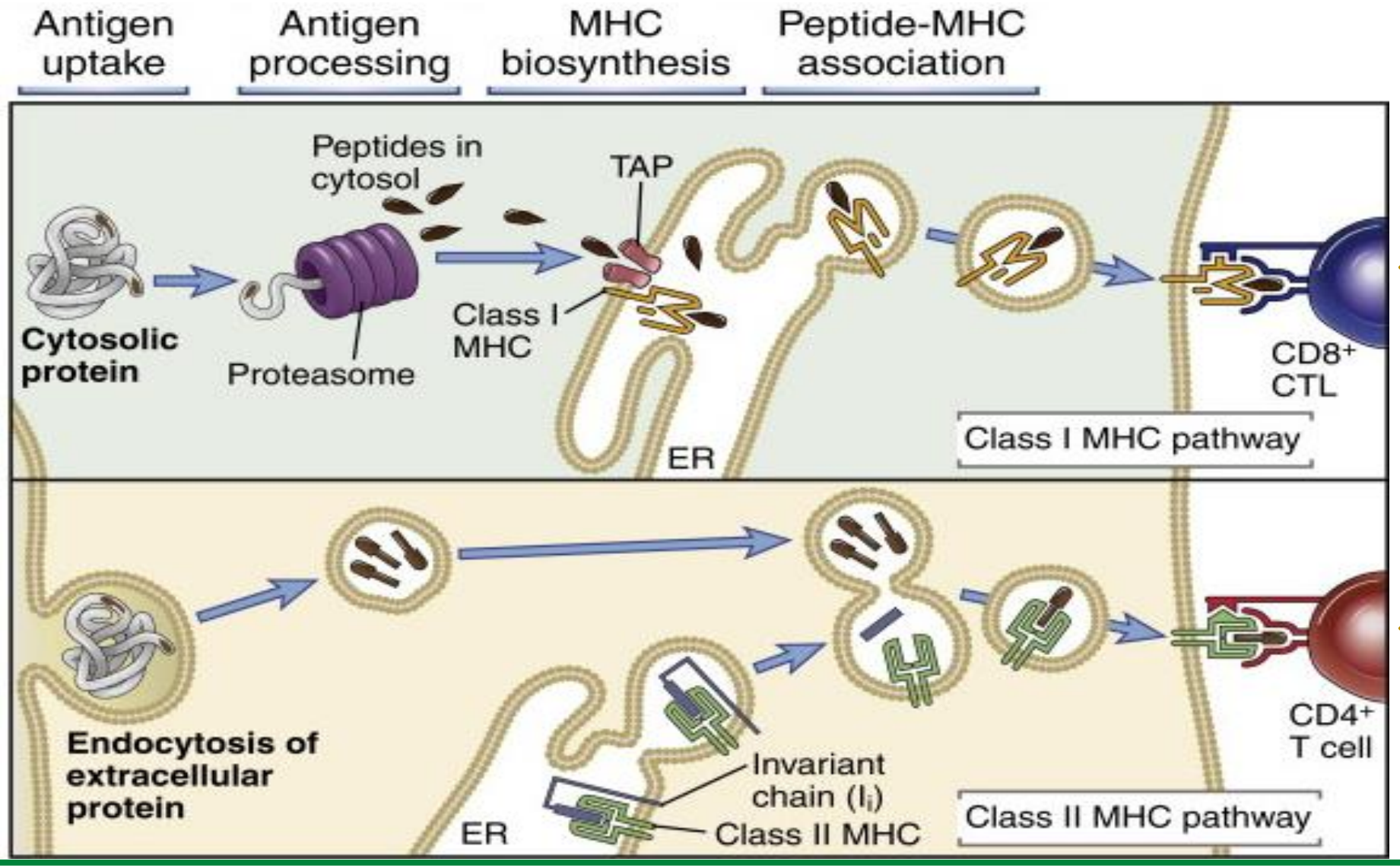
1. Class I MHC Genes

- **MHC Class 1** mediates immune responses against **endogenous antigens**, antigens that are **already found in the cell**.
- Usually, these **cells that are expressing MHC class 1** are **viral-infected** or are **tumor cells**.
- MHC Class 1 **presents peptides** that are **8–10 amino acids** in size, which will then be **recognized by the cytotoxic (CD8) T cells**.
- MHC Class 1 is found on all nucleated cells.

2. Class II MHC Genes

- **MHC class 2** mediates immune responses against **exogenous antigens**, antigens that are found **outside of the cell**, **in the cytosol**.
- **MHC class 2** will **bind with amino acid** residues that are **13–18 in size** and will be **recognized by (CD4)T helper cells**.
- The MHC class 2 protein is found on cells like the B lymphocytes, macrophages, monocytes, dendritic cells.
- These **cells are phagocytic** and can **engulf an extracellular antigen**.

Antigen Processing



MHC-I PATHWAY

MHC-II PATHWAY

T cell receptor (TCR)

- TCR receptor (antigen recognition) is associated with complex of CD3 proteins important for signal transmission
- In the process of antigen recognition TCR cooperate with CD4 and CD8 coreceptors
- TCR recognize only MHC proteins with antigen peptides fragments.
- For full activation – T cell must recognize the antigen on the cell surface of APC.

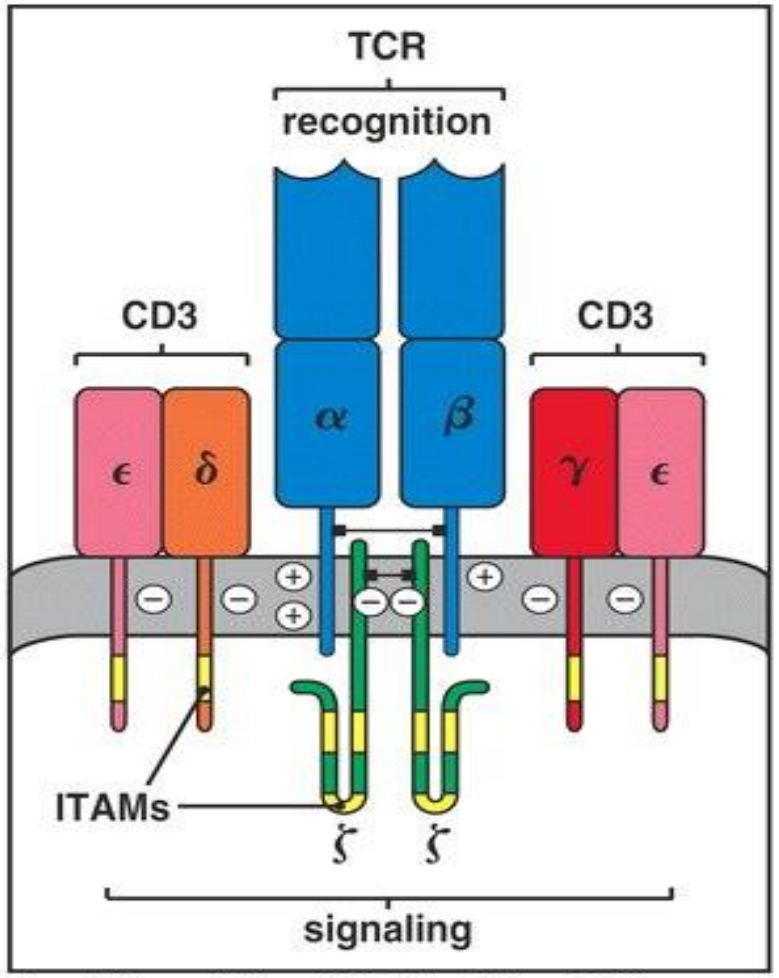


Figure 6-9 Immunobiology, 6/e. (© Garland Science 2005)

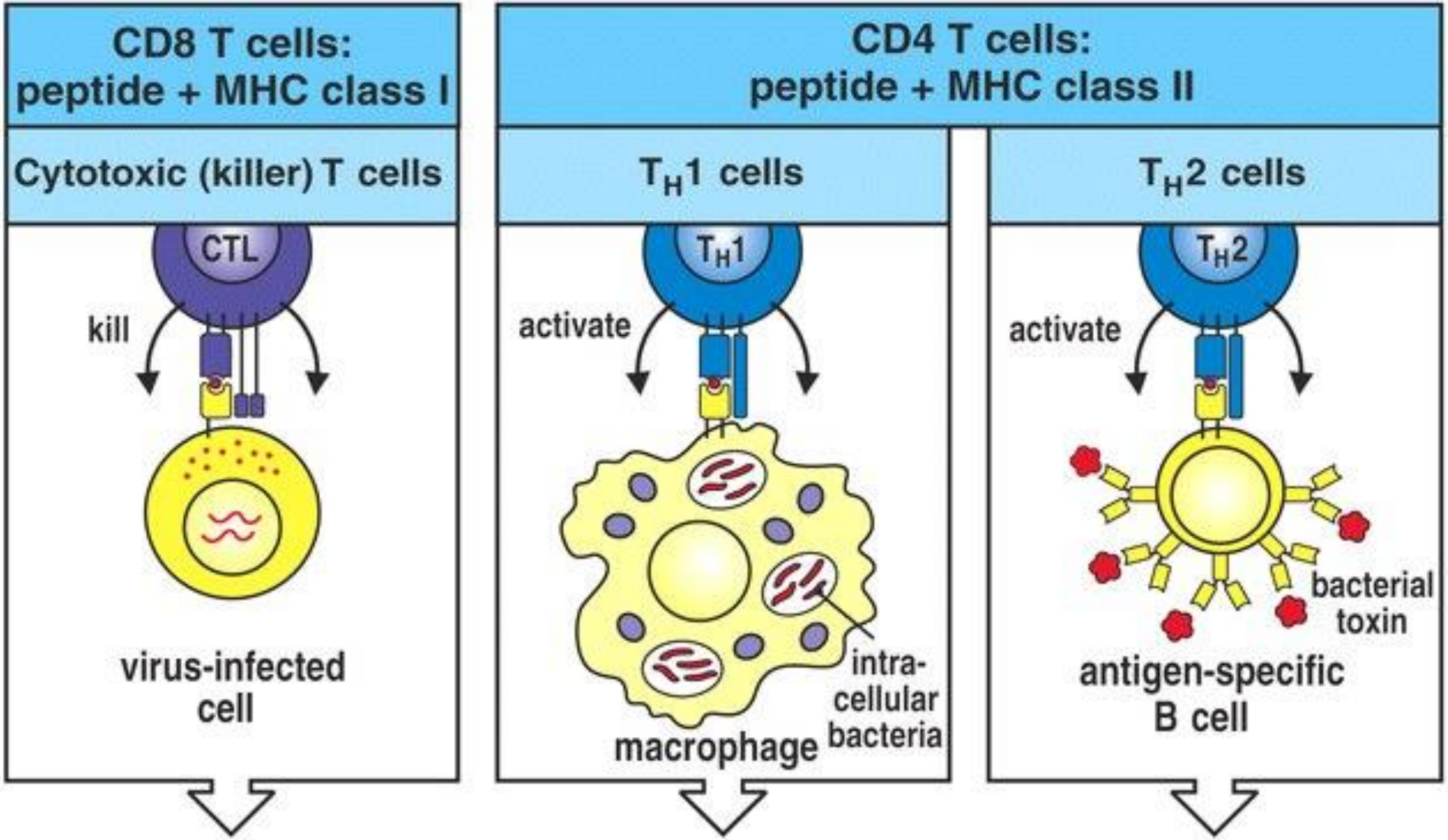


Figure 8-27 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

Helper T cells are MHC II restricted

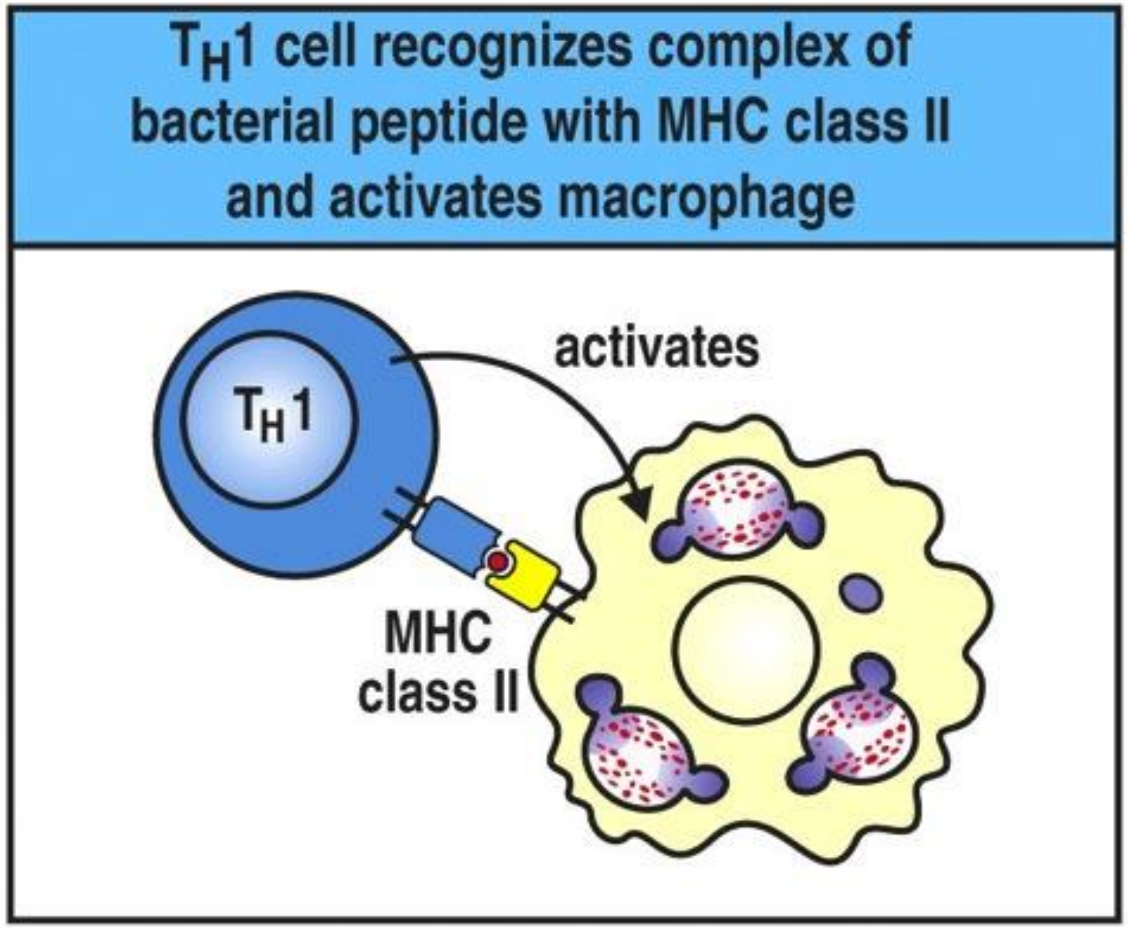


Figure 1-31 Immunobiology, 6/e. (© Garland Science 2005)

Cytotoxic T cells are MHC I restricted

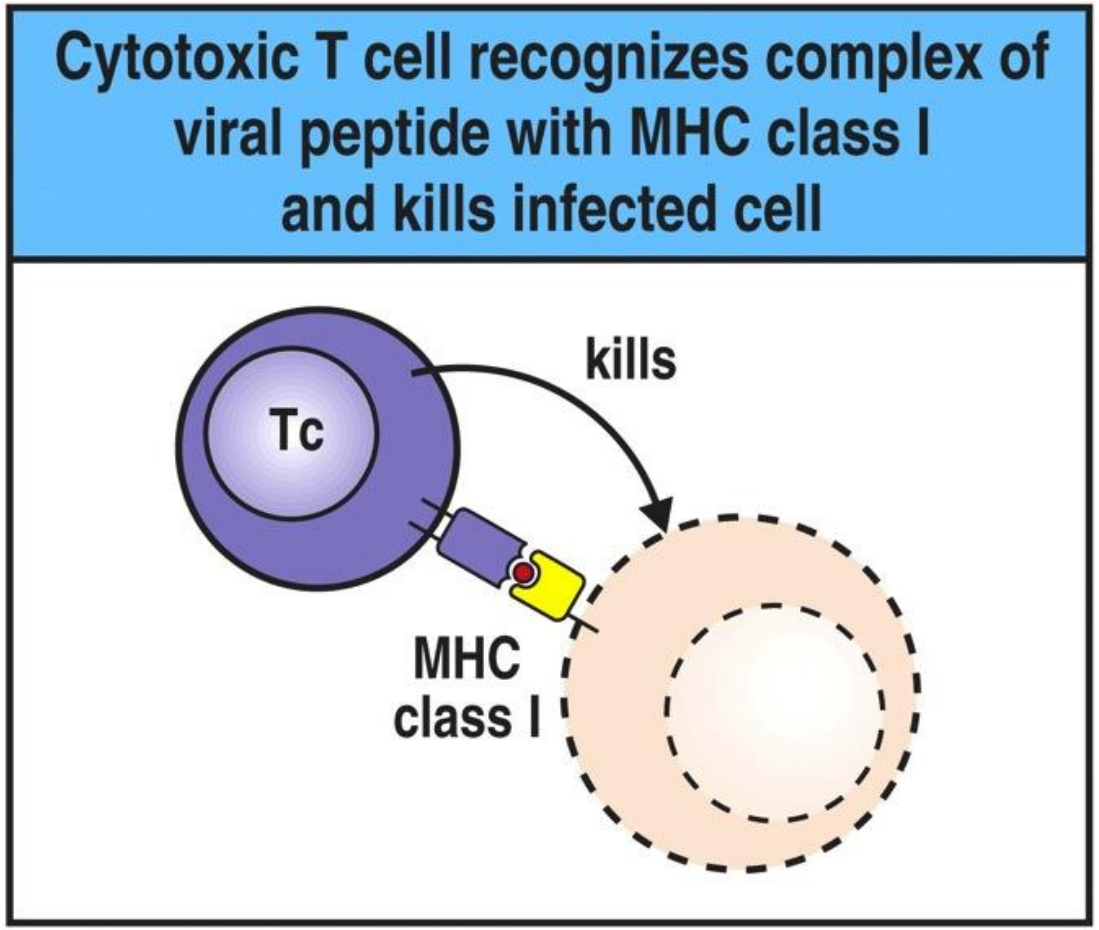


Figure 1-30 Immunobiology, 6/e. (© Garland Science 2005)

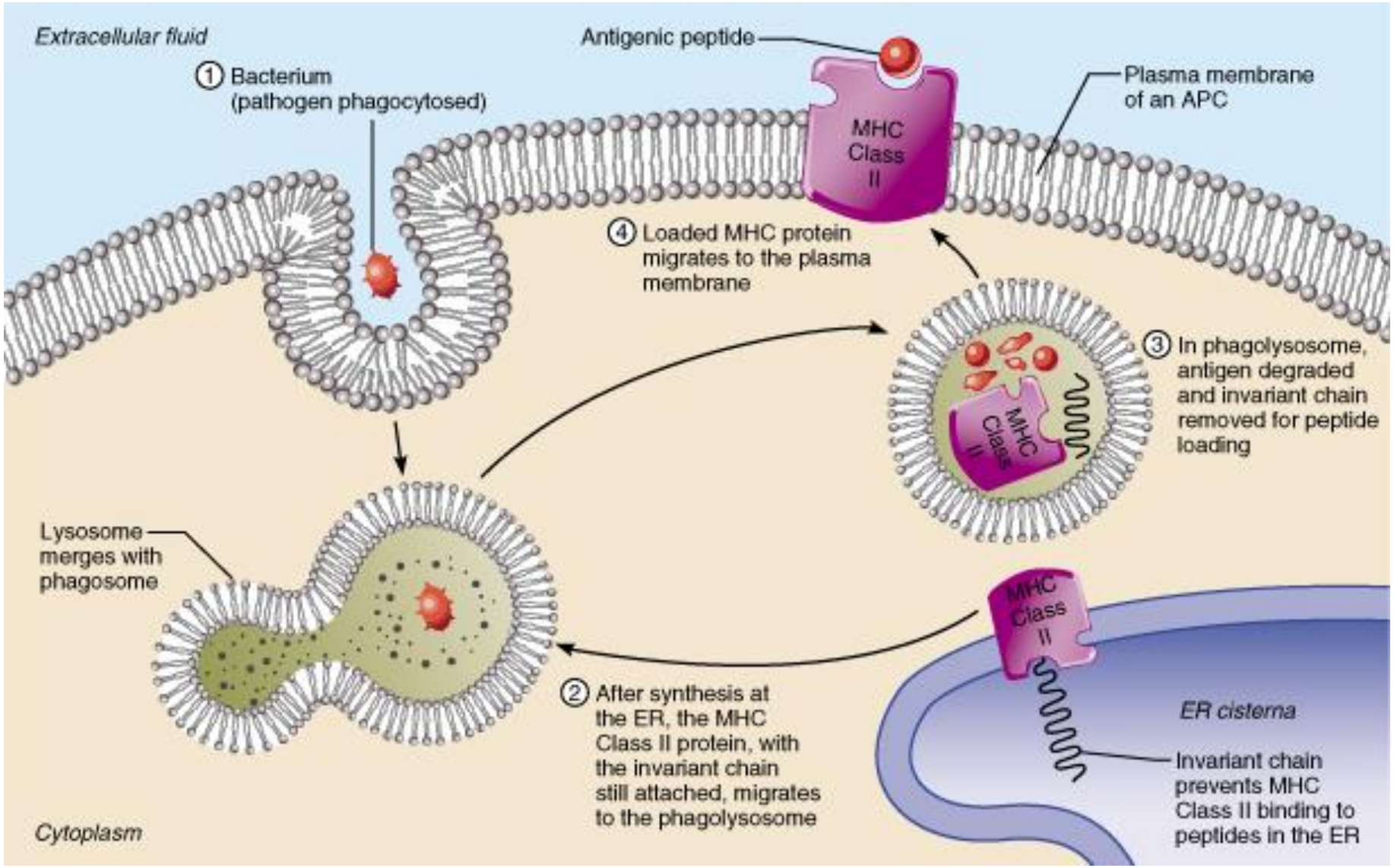
Processing and Presentation of Protein Antigens

❖There are 2 different antigen-presenting pathway to mediate responses:

A. Exogenous (Extracellular- Endocytic) antigens (Endocytic Pathway)

1. The pathway begins by **phagocytosis of a foreign agent**, an organism, bacteria, helminthic, and etc. The **antigen is now in a phagosome**.
2. A **lysosome will fuse** with the **phagosome** to become a **phagolysosome**. The **antigen will be degraded into smaller peptides**.
3. The **MHC class-II** will **migrate to the phagolysosome**, where it will **bind to components** that are **13–18 amino acids** in size. Once bound, the **MHC class-II will migrate to the membrane to display the antigen**.
4. A **helper T cell** will **recognize the complex** and trigger the appropriate response, such as **secreting cytokines** and **chemokines** to control whatever kind of infection is taking place.

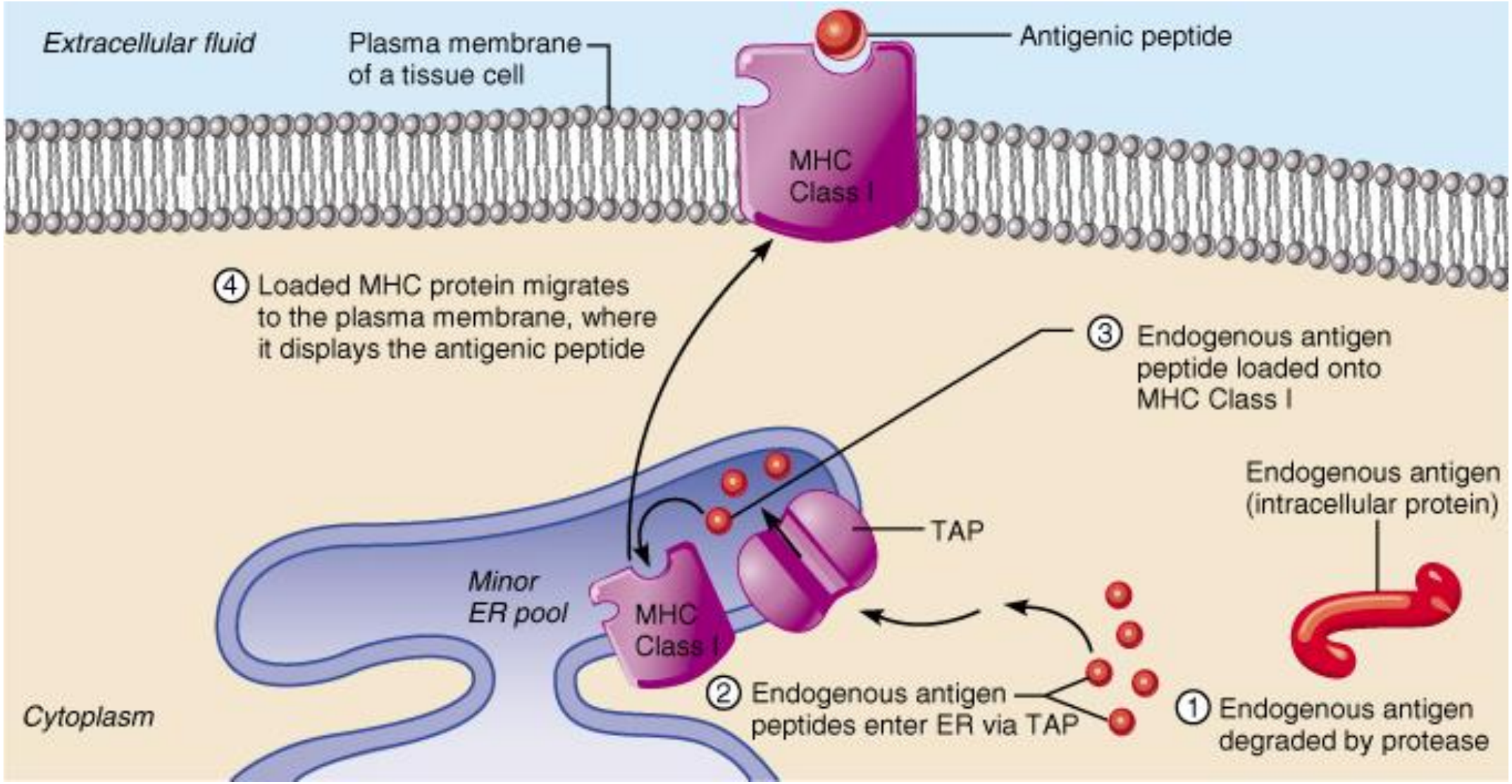
Endocytic (Exogenous) Pathway



B. Endogenous (intracellular-Cytosolic) antigens

1. **Intracellular auto-antigens**, antigens of **viruses** or other intracellular parasites or **tumorous antigens**.
2. It starts with an **antigen that's already in the cell**. It will be **broken down into smaller peptides** by a protease.
3. The **peptides** will be **transported into the endoplasmic reticulum** where **MHC-I** is located.
4. The **8– 10 amino acid residues** will **bind with MHC-I** and once that happens, the **MHC-I** and **antigen** will **migrate to the cell surface**, where it will **present the antigen**.
5. **Cytotoxic T cells** will **recognize this complex** and initiate the appropriate immune response to kill this cell.

Cytosolic (Endogenous) Pathway



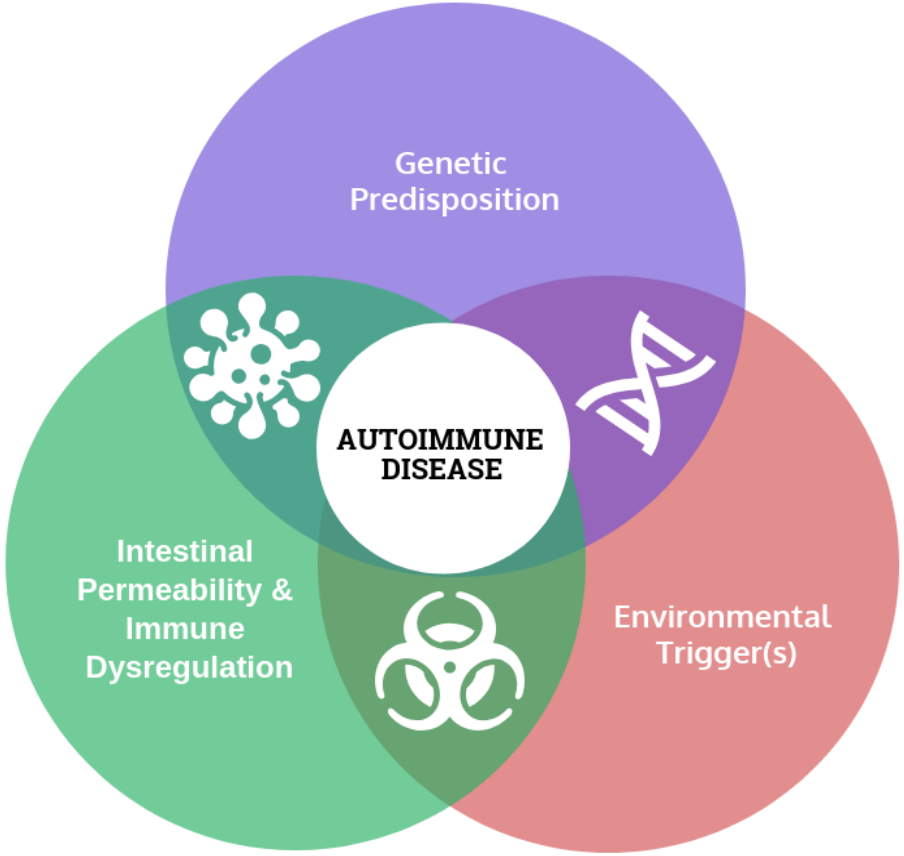
Autoimmunity

- Autoimmunity is defined as an **immune response against self (autologous) antigens**.
- It is estimated to affect 5% to 10% of the population in developed countries
- There are different autoimmune diseases may be:
  1. **Organ-specific**, affecting only one or a few organs,
  2. **Systemic**, with widespread tissue injury and clinical manifestations.
- Tissue injury in autoimmune diseases may be caused by **antibodies against self antigens** or by **T cells reactive with self antigens**.

Causes of Autoimmune Diseases

Pathogenesis: the inheritance of **susceptibility genes** and environmental triggers, such as **infections**. It is postulated that **susceptibility genes** interfere with **pathways of self-tolerance** and lead to the **persistence of self-reactive T and B lymphocytes**.

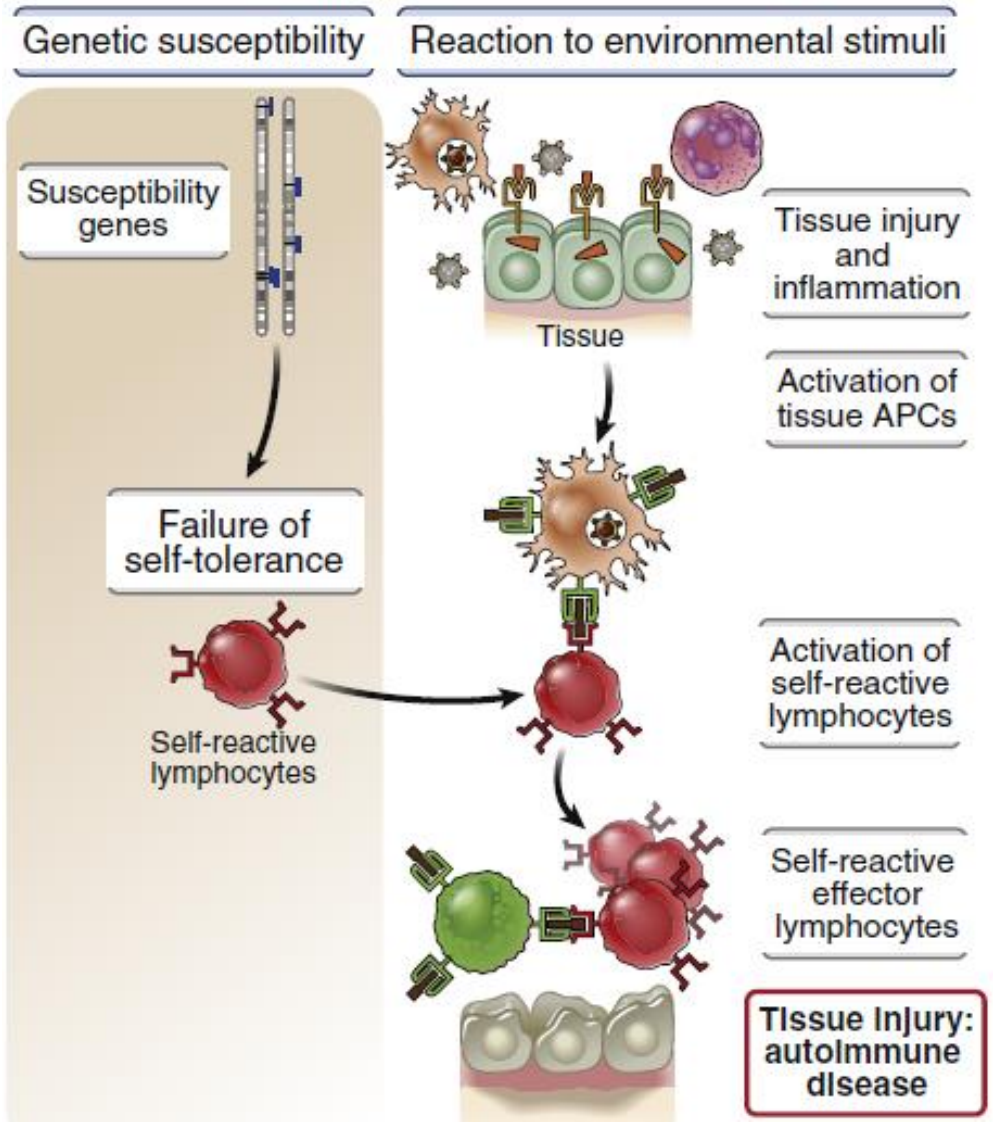
Environmental stimuli may cause **cell and tissue injury** and **inflammation.** Activating these **self-reactive lymphocytes**, resulting in the generation of **effector T cells and autoantibodies** that **are responsible** for the **autoimmune disease**.



Genetic Factors:

Inherited risk for most autoimmune diseases is attributable to multiple gene loci, of which the largest contribution is made by **MHC genes**.

Postulated Mechanisms of Autoimmunity



Common Autoimmune Diseases

Disease	Disease Mechanism	Consequence
Type 1 diabetes	the immune system attacks and destroys insulin-producing cells in the pancreas.	Destruction of pancreatic islet B cells leading to non-production of insulin.
Rheumatoid arthritis (RA)	the immune system (autoreactive T cells) attacks the joints synovium.	Joint inflammation and destruction causing arthritis.
Graves' disease	Autoantibodies against the thyroid- stimulating-hormone receptor.	Hyperthyroidism, overproduction of thyroid hormones.
Hashimoto's thyroiditis	Autoantibodies and autoreactive T cells against thyroid antigens.	Destruction of thyroid tissue leading to hypothyroidism, underproduction of thyroid hormones.
Multiple sclerosis	Autoreactive T cells against brain antigens.	Formation of sclerotic plaques in brain with destruction of myelin sheaths surrounding nerve cell axons, leading to muscle weakness, ataxia, and other symptoms.
Systemic lupus erythematosus	Autoantibodies and autoreactive T cells against DNA, chromatin proteins, and ubiquitous ribonucleoprotein antigens.	Glomerulonephritis, vasculitis, rash.
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.

Autoimmune Diseases

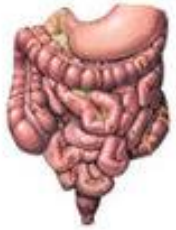
Brain
Multiple Sclerosis
Guillaun-Barre Syndrome
Autism

Thyroid
Thyroiditis
Hashimoto's Disease
Graves' Disease

Blood
Leukemia
Lupus Erythematosus
Hemolytic Dysglycemia

Bones
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica

GI Tract
Celiac's Disease
Crohn's Disease
Ulceratic Colitis
Diabetes Type I



>100 Autoimmune Diseases

Muscles
Muscular Dystrophy
Fibromyalgia

Nerves
Peripheral Neuropathy
Diabetic Neuropathy

Lung
Fibromyalgia
Wegener's Granulomatosis

Skin
Psoriasis
Vitiligo
Eczema
Scleroderma

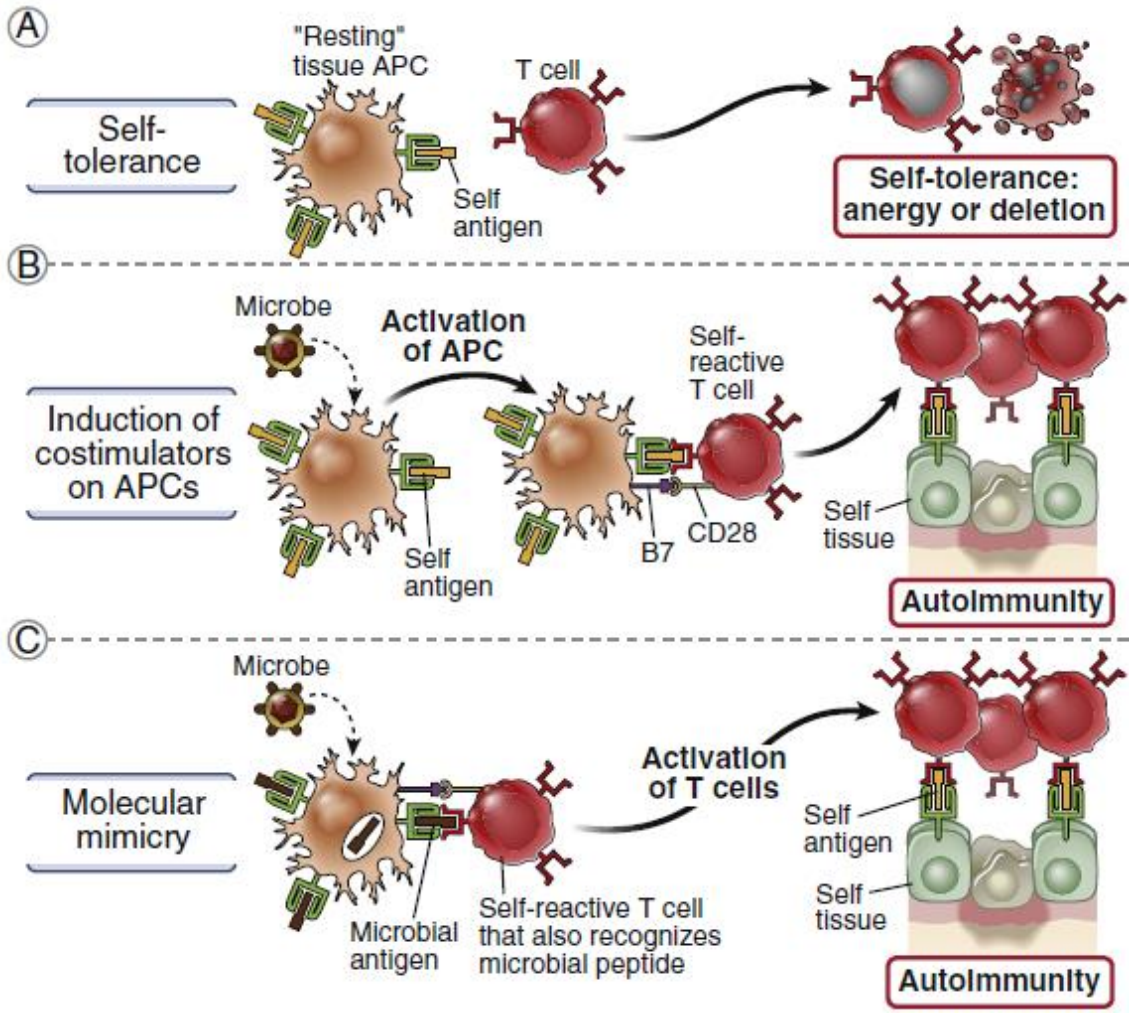
Mechanisms by Which Microbes may Promote Autoimmunity

A. Normally, an encounter of mature T cells with self antigens presented by resting tissue antigen-presenting cells (APCs) results in peripheral tolerance.

B. Microbes may activate the APCs to express costimulators, and when these APCs present self antigens, the specific T cells are activated, rather than being rendered tolerant.

C. Some microbial antigens may cross-react with self antigens (mimicry).

- Therefore, immune responses initiated by the microbes may become directed at self cells and self tissues.



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