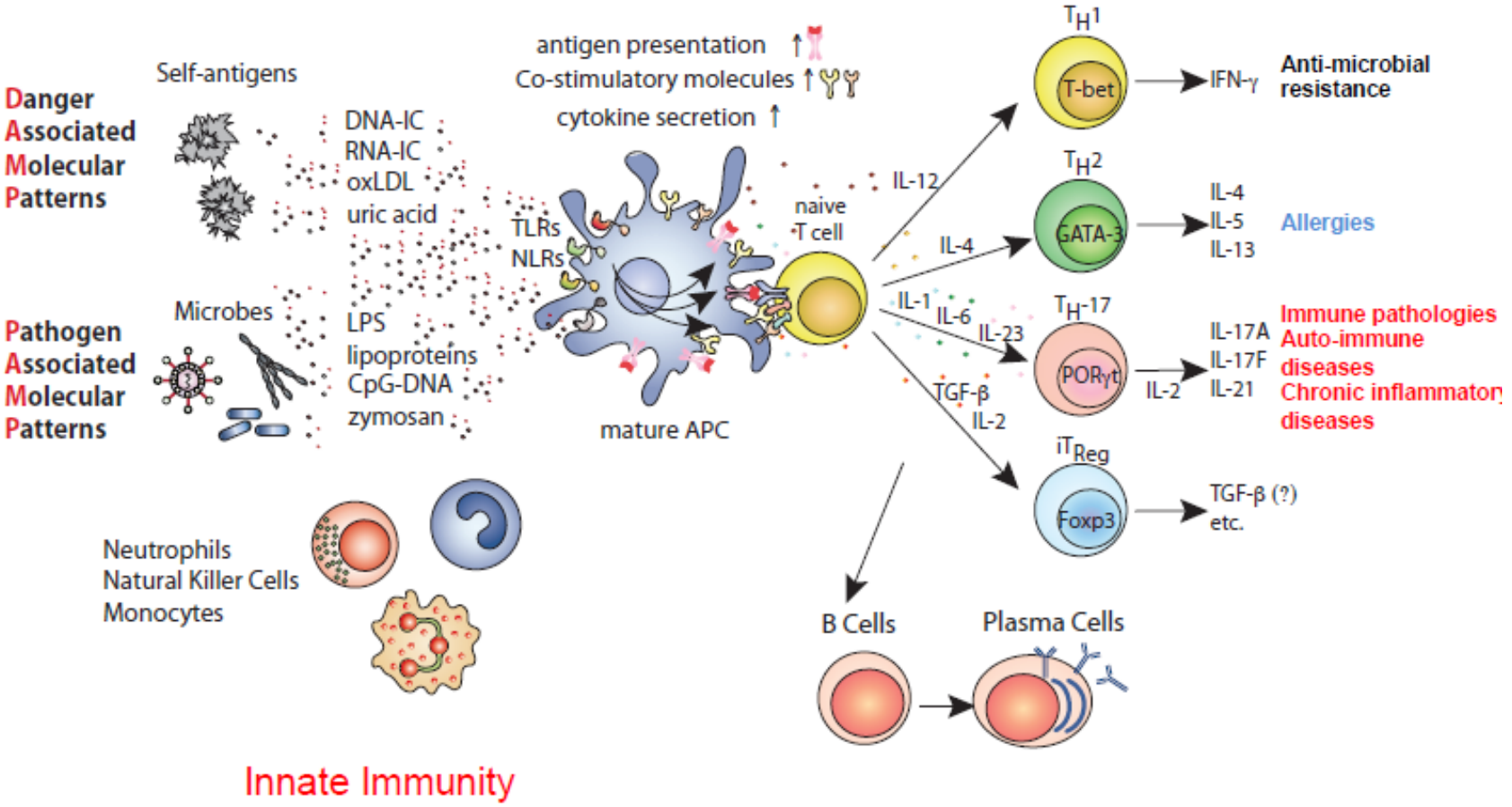
Pattern Recognition

- Pattern Recognition Receptors (PRR)
  - Toll-like receptors (TLRs)
  - NOD-like receptors (NLRs)
- Pathogen Associated Molecular Patterns (PAMPs)
- Death Associated Molecular Patterns
- (DAMPs)

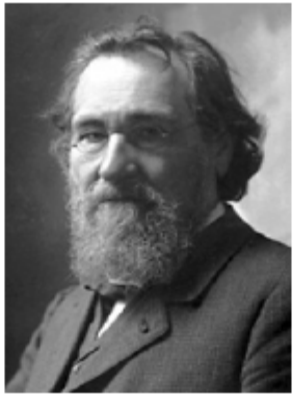
Recognizing Danger



Origins of Innate Immunity ?

Late 1880's: Discovery of phagocytosis and phagocytes
cellular immunity

"mobile white corpuscles of the blood which absorb microbes and destroy them"



Ilya Mechnikov

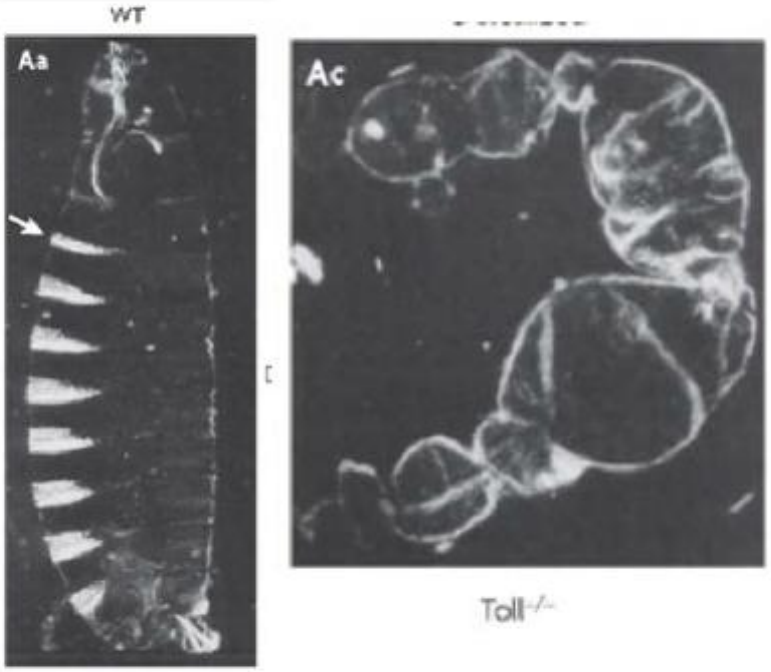
The Nobel Prize in Physiology or Medicine 1908
Ilya Mechnikov, Paul Ehrlich

"in recognition of their work on immunity"

*"It has been shown that the white corpuscles (phagocytes) entertain no fear of **microbial poisons** (endotoxins, dead microbes and nucleic acids) and are well fitted to absorb them and make them harmless."*

How do phagocytes recognizes these danger signals?

"Toll" a gene important in embryogenesis in establishing the dorsal-ventral axis



Christiane Nüsslein-Volhard

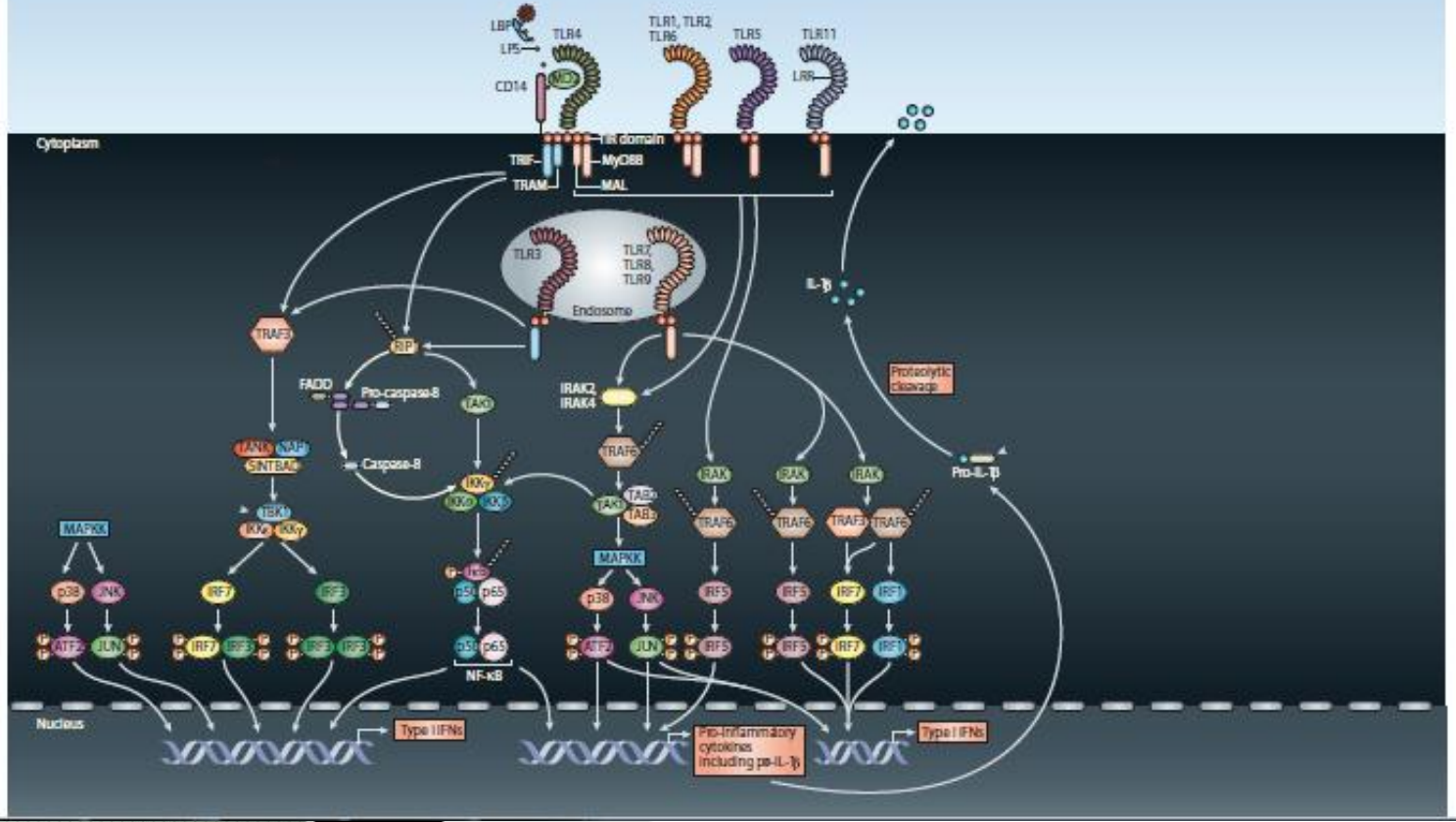
"Das ist ja toll!"

The Nobel Prize in Physiology or Medicine 1995
Edward B. Lewis, Christiane Nüsslein-Volhard, Eric F. Wieschaus

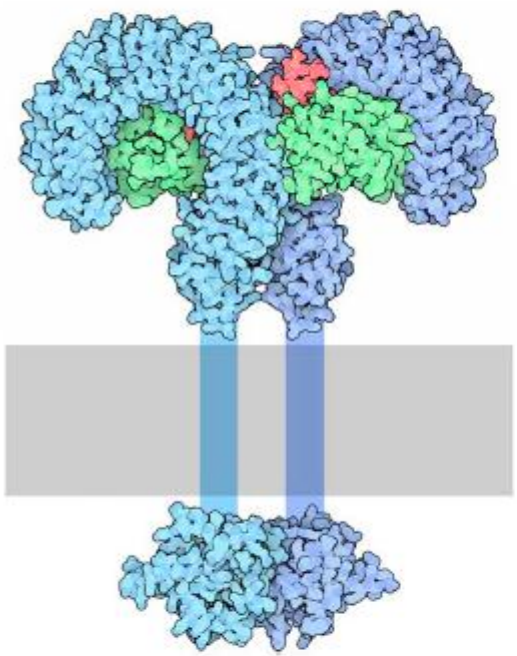
"the genetic control of early embryonic development"

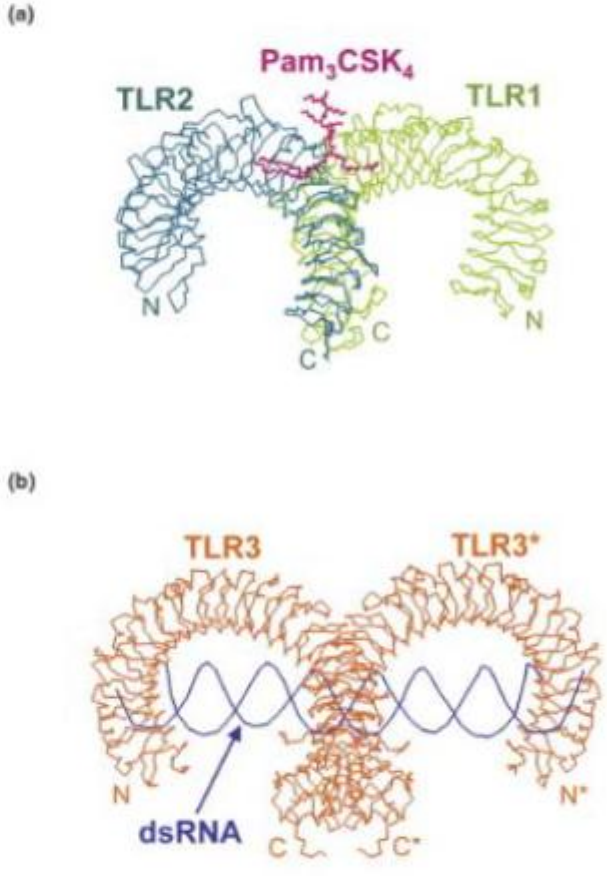
Toll-like receptor (TLR) family

- 13 TLRs identified in mammals (11 expressed in humans)
- Cell surface and endosomal TLRs
- Recognizing a diverse range of ligands



TLR dimerization





Antigen & Immunogen

- An antigen is any agent capable of binding specifically to components of the immune system, such as the B cell receptor (BCR) on B lymphocytes and soluble antibodies.

- An immunogen is any agent capable of inducing an immune response and is therefore ***immunogenic.***

- There are many compounds that are incapable of inducing an immune response, yet they are capable of binding with components of the immune system that have been induced specifically against them.

- Thus all immunogens are antigens, but not all antigens are immunogens.

Antigens

◆**Most are proteins or large polysaccharides from a foreign organism.**

- **Microbes:** Capsules, cell walls, toxins, viral capsids, flagella, etc.

- **Non-microbes**: Pollen, egg white , red blood cell surface molecules, serum proteins, and surface molecules from transplanted tissue**.**

- **Lipids and nucleic acids are only antigenic when combined with proteins or polysaccharides.**

Haptens

- A hapten is a compound that, by itself, is incapable of inducing an immune response (non-immunogenic) but against which an immune response can be induced when conjugated to a carrier.

Requirements for immunogenicity

- Foreignness
- High molecular size
- Complexity of structure
- Degradability
- Antigenic determinants
- Others, conformation, charge, dosage, route

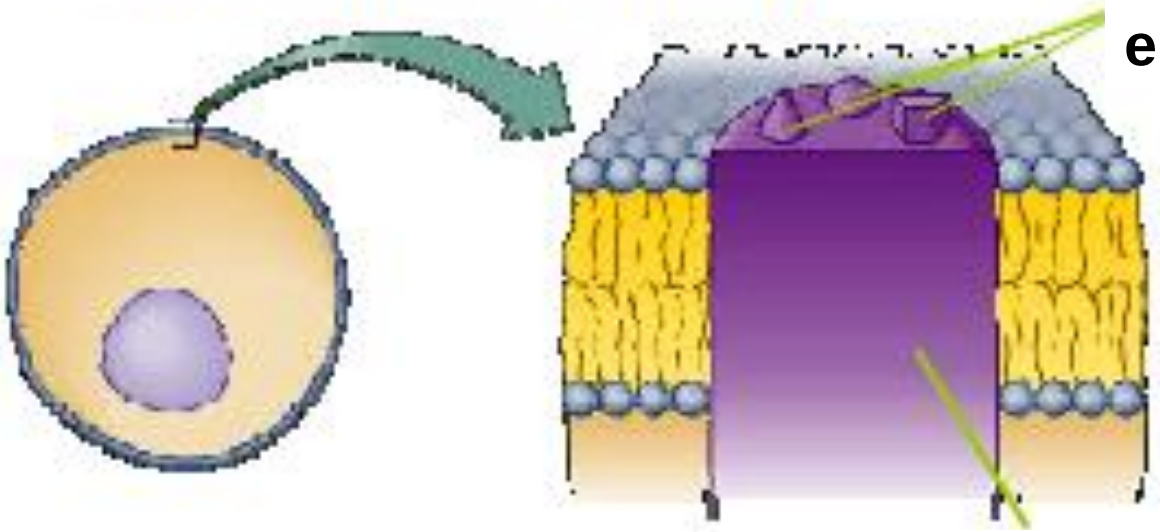
Epitope

Small part of an antigen that interacts with an antibody.

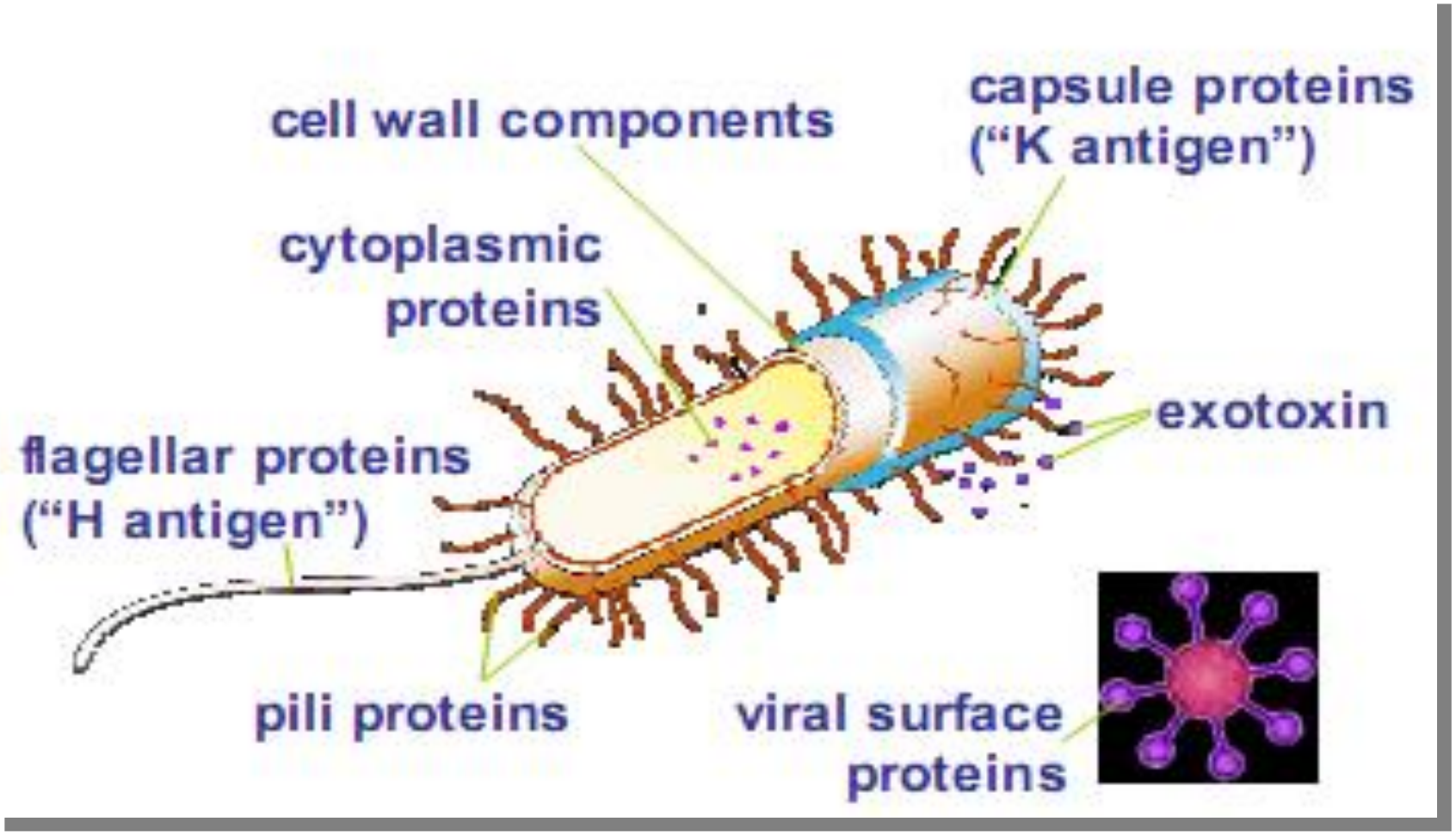
- Any given antigen may have several epitopes.
- May be Linear or Conformational
- Each epitope is recognized by a different antibody.

Antigens/Epitopes

surface molecules of sufficient size, structural complexity



Microbial antigens/epitopes

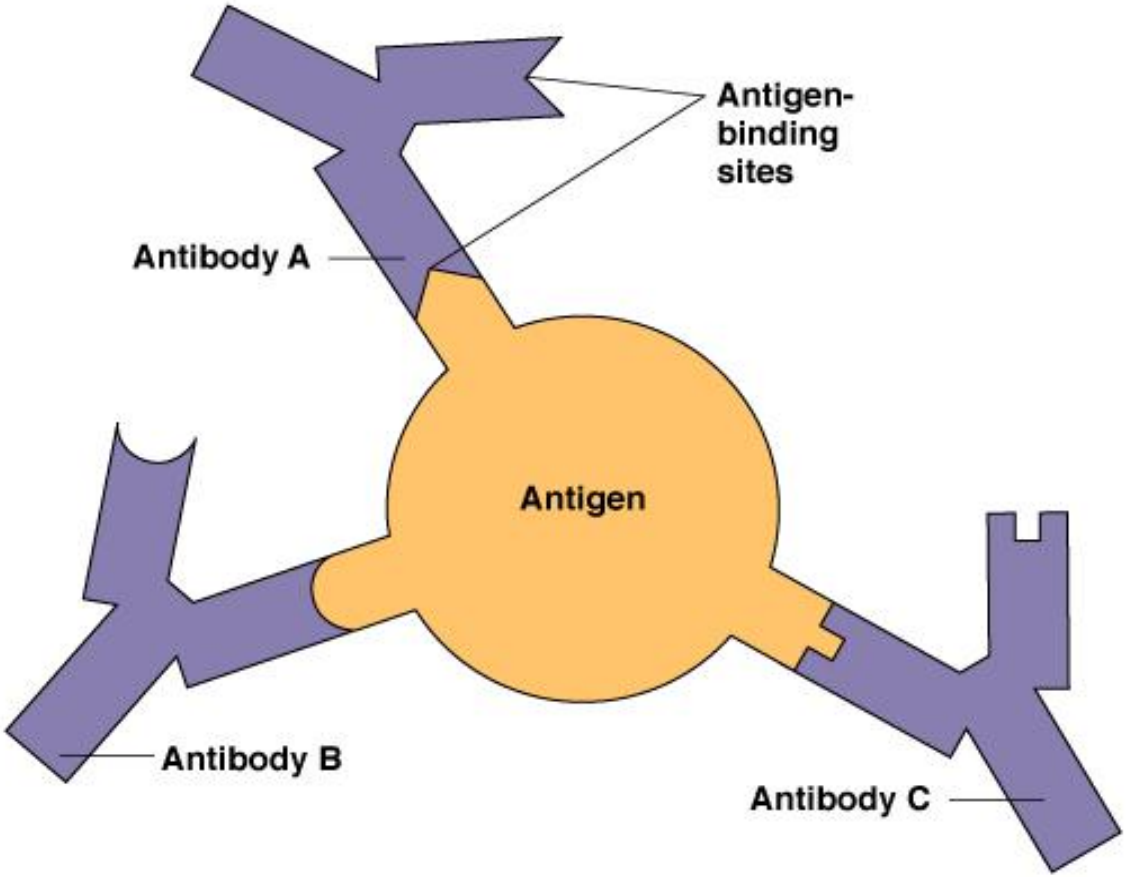


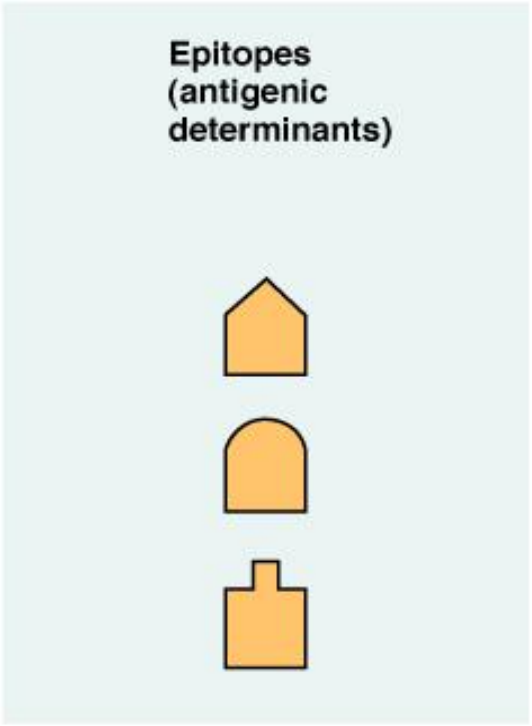
Antibodies

- **Made in response to exposure to the antigen, and react specifically to that antigen**
- **Proteins that recognize and bind to a particular antigen with very high *specificity*.**
- **One virus or microbe may have several *antigenic determinant sites*, to which different antibodies may bind.**
- **Each antibody has at least two identical sites that bind antigen: *Antigen binding sites*.**

- **Valence of an antibody: Number of antigen binding sites. Most are bivalent.**
- **Belong to a group of serum proteins called immunoglobulins (Igs).**
- **Antigen-antibody reactions**
  - **Antiserum: serum that contains a large amount of antibodies that bind to a particular antigen**
- **Natural antibodies**
  - **Igs which react specifically to antigens of no known exposure.**
  - **Usually of low titre but may confer resistance to certain infections.**

Epitopes: Antigen Regions that Interact with Antibodies





Antibodies work in three ways:

1. **Neutralisation**. blocking the biological activity of their target molecule e.g a toxin, by binding to it's receptor
2. **Opsonisation**. interact with special receptors on various cells, including macrophages, neutrophils, basophils and mast cells allowing them to "recognise" and respond to the antigen
3. **Complement Activation**. cause direct lysis by complement complement recruitment also enhances phagocytosis

4. **Neutralization:** IgG inactivates viruses by binding to their surface and neutralize toxins by blocking their active sites.

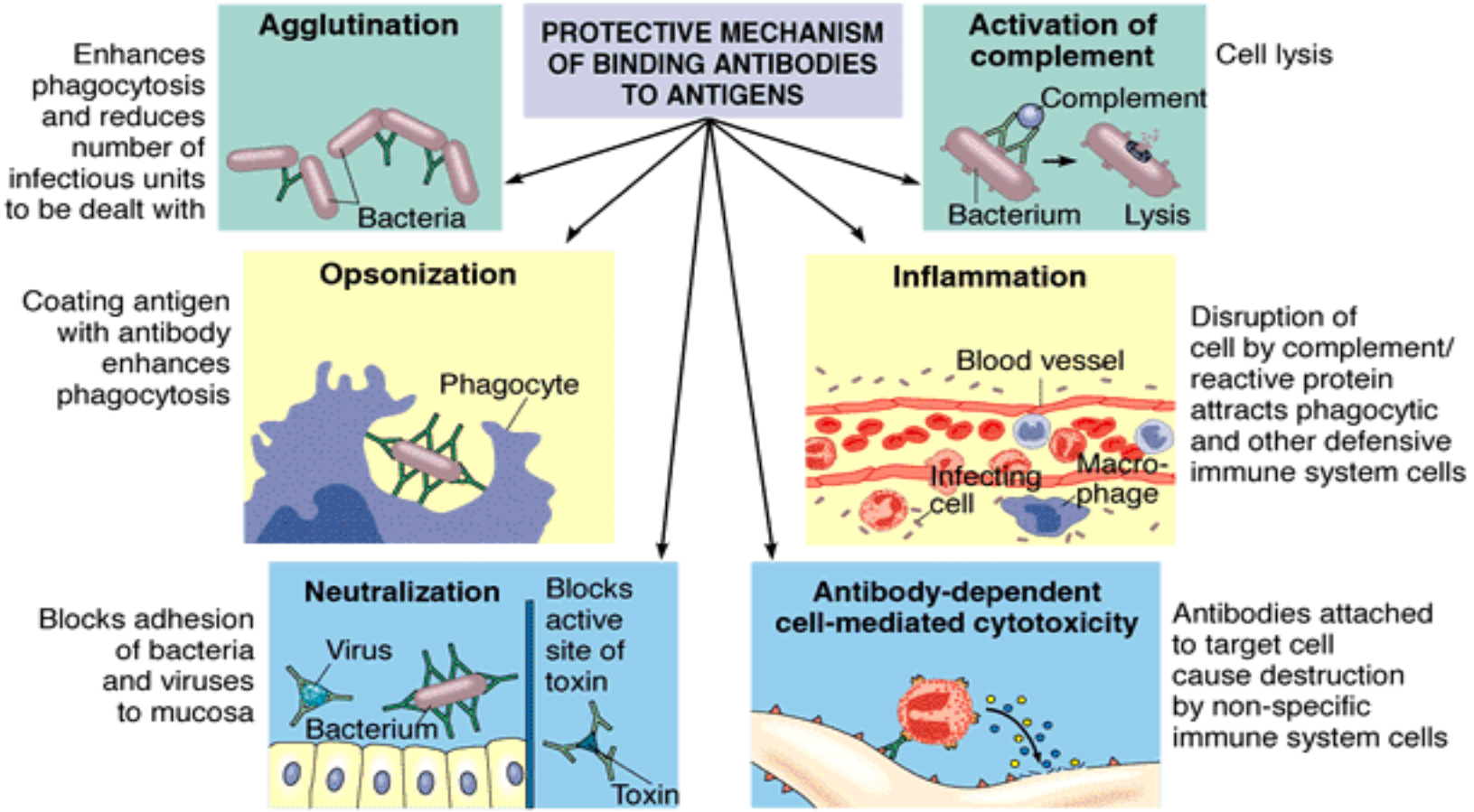
5. **Antibody-dependent-cell-mediated cytotoxicity:** Used to destroy large organisms (e.g.: worms). Target organism is coated with antibodies and bombarded with chemicals from nonspecific immune cells.

6. **Complement Activation:** Both IgG and IgM trigger the complement system which results in cell lysis and inflammation.

All the interactions between antigen and antibody are non-covalent interactions:

- ionic interactions, eg. like attraction of opposite charges on amino acids;
- hydrogen bonds;
- hydrophobic interactions.

Protective Mechanisms of Antigen-Antibody Binding



Types of antigens

- Exogenous antigens (Mostly expressed by extracelluar pathogens ie. parasites)
- Endogenous antigens (Expressed by intracellular pathogens, viruses & some bacteria)

- T-dependent antigens
- T- independent antigens

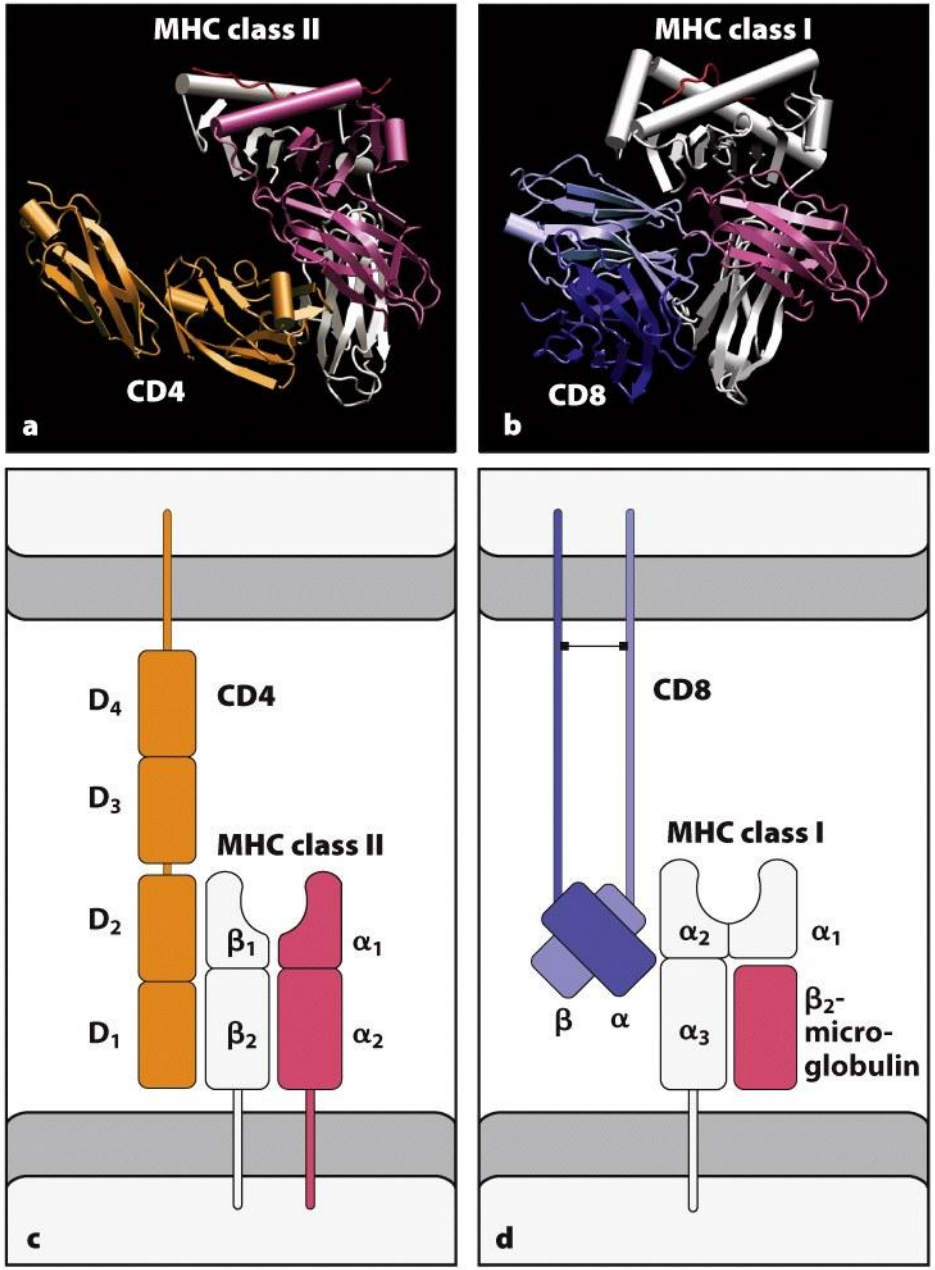


Figure 4.25 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

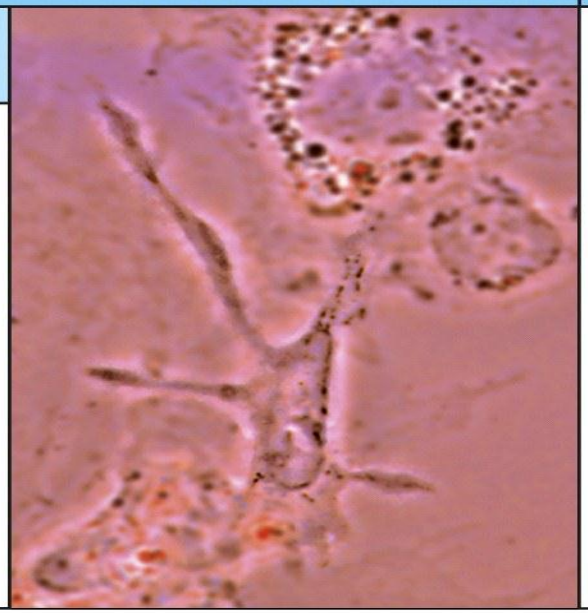
Antigen Processing and Presentation

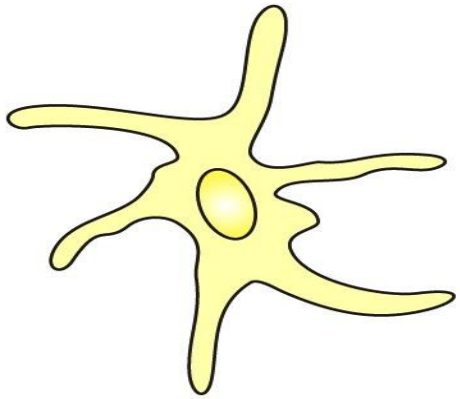
- Why is it needed? What is the purpose?
- How does it happen? & What are the components

- How are the pathways of endogenous and exogenous antigen kept apart?
- What are the consequences?
- (What happens after presentation & processing)

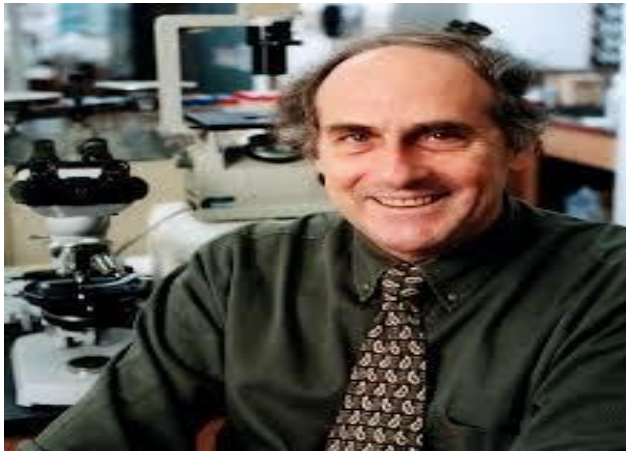
Antigen Presenting Cells

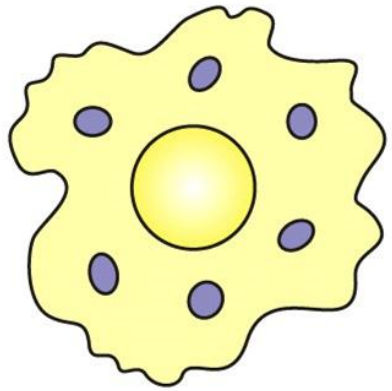
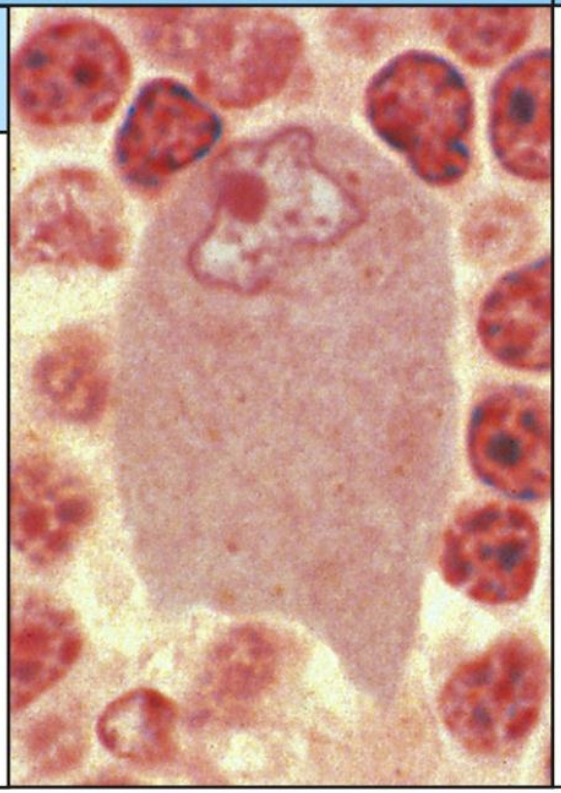
- Dendritic cells
- Monocytes/Macrophages
- B-cells

Cell		Activated function
Dendritic cell		Antigen uptake in peripheral sites Antigen presentation



DCs were first characterized by Ralph Steinman. Dr. Steinman was awarded a share in the 2011 Nobel Prize in Physiology or Medicine for his seminal work.



Cell		Activated function
Macrophage		
		**Phagocytosis and activation of bactericidal mechanisms** **Antigen presentation**

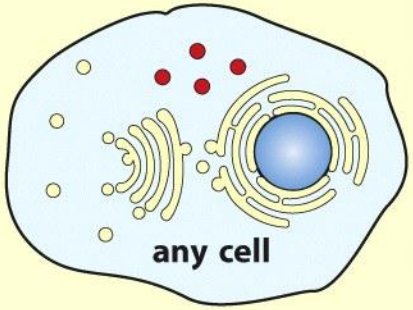
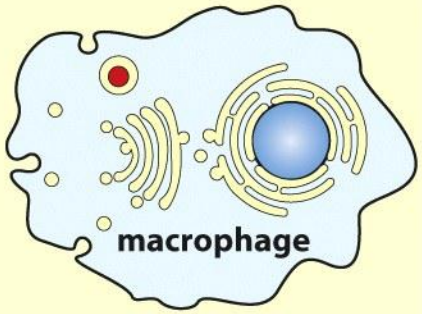
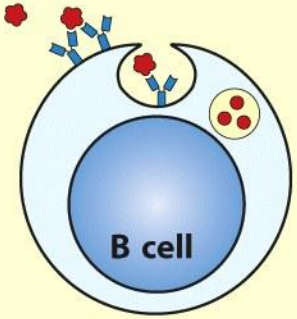
	Cytosolic pathogens	Intravesicular pathogens	Extracellular pathogens and toxins
			
Degraded in	Cytosol	Endocytic vesicles (low pH)	Endocytic vesicles (low pH)
Peptides bind to	MHC class I	MHC class II	MHC class II
Presented to	Effector CD8 T cells	Effector CD4 T cells	Effector CD4 T cells
Effect on presenting cell	Cell death	Activation to kill intravesicular bacteria and parasites	Activation of B cells to secrete Ig to eliminate extracellular bacteria/toxins

Figure 6.2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

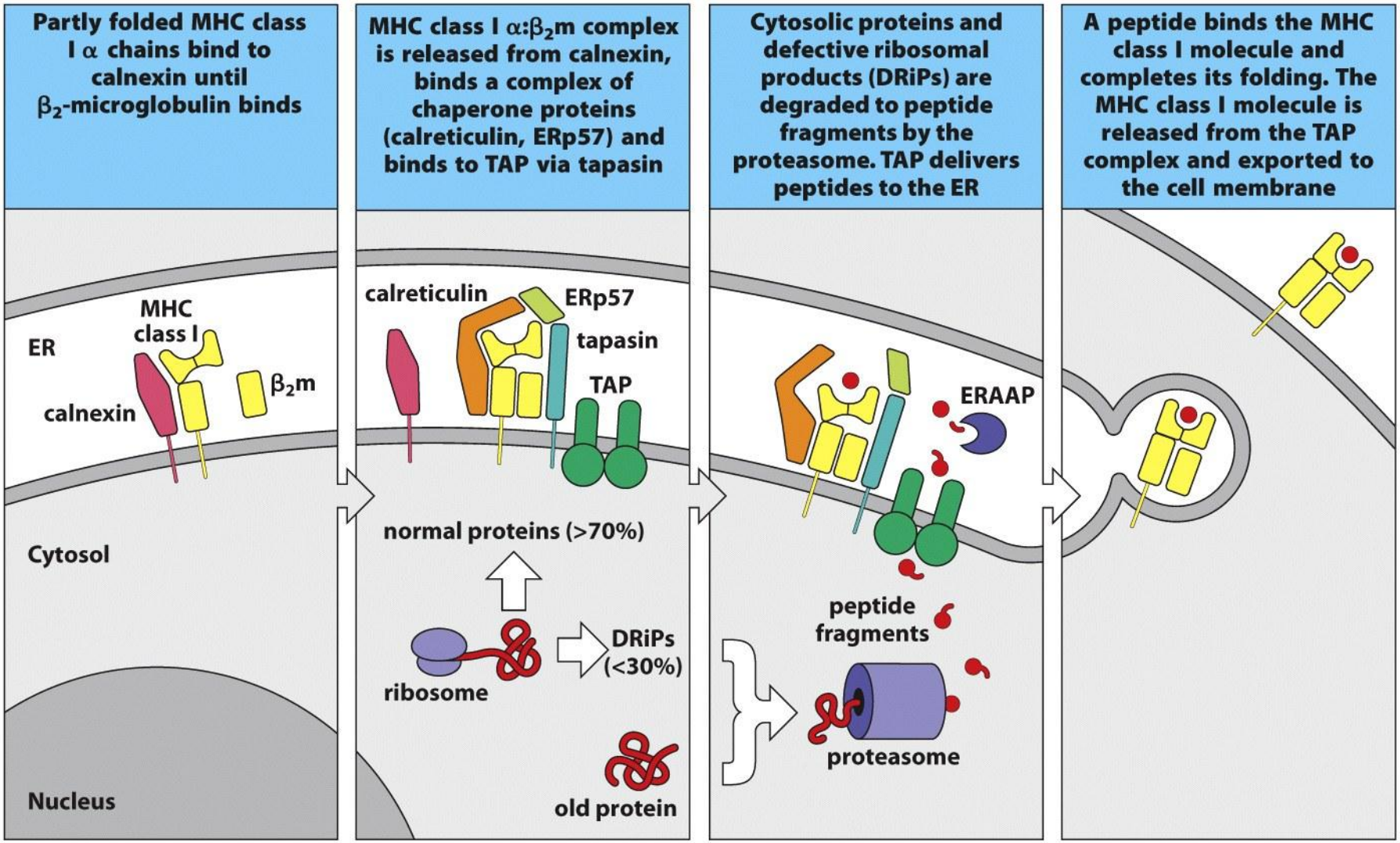


Figure 6.5 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

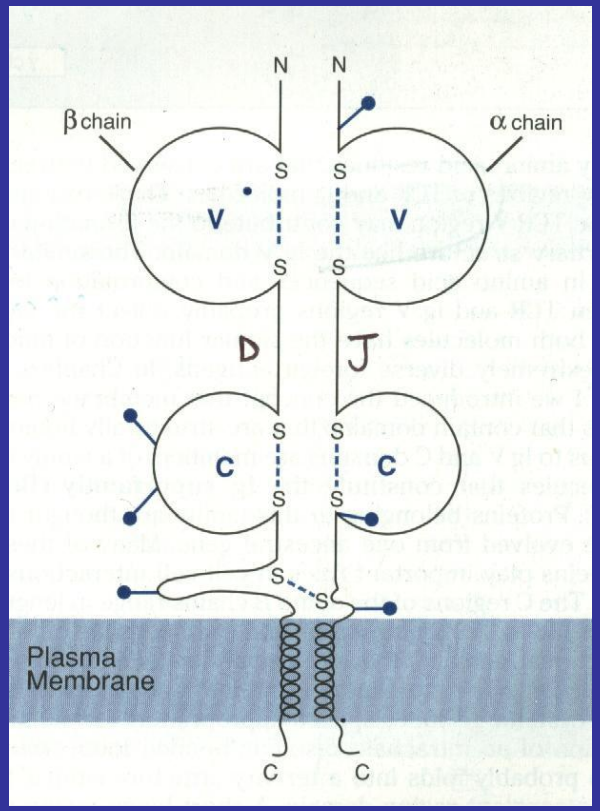
T cell receptor: antigen receptor of T cells

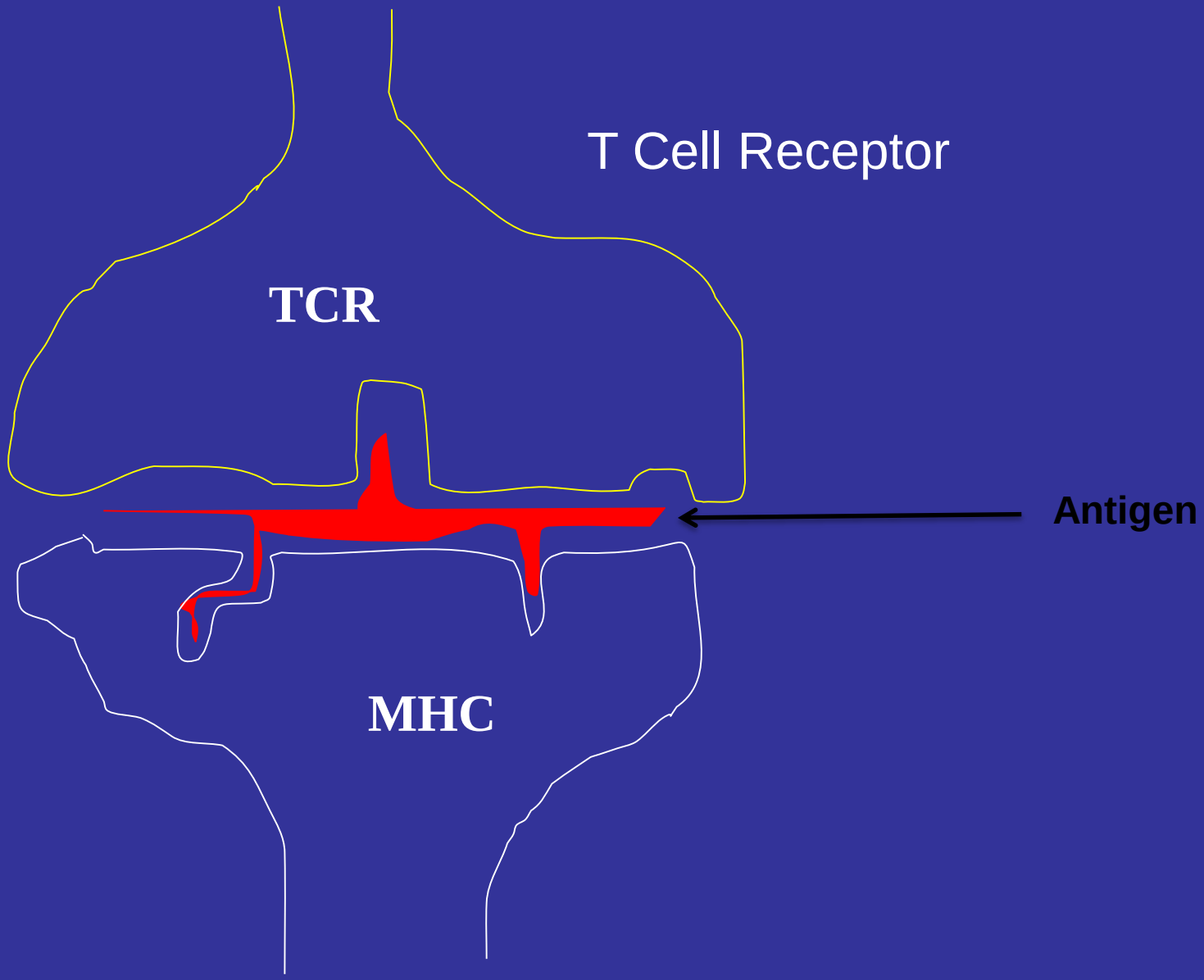
- Cannot recognise antigen in solution

- Must have the antigen processed and presented to it

- Specialised molecules present antigens to T cells:

  - Antigen presentation cells (APC's)
  - MHC molecules





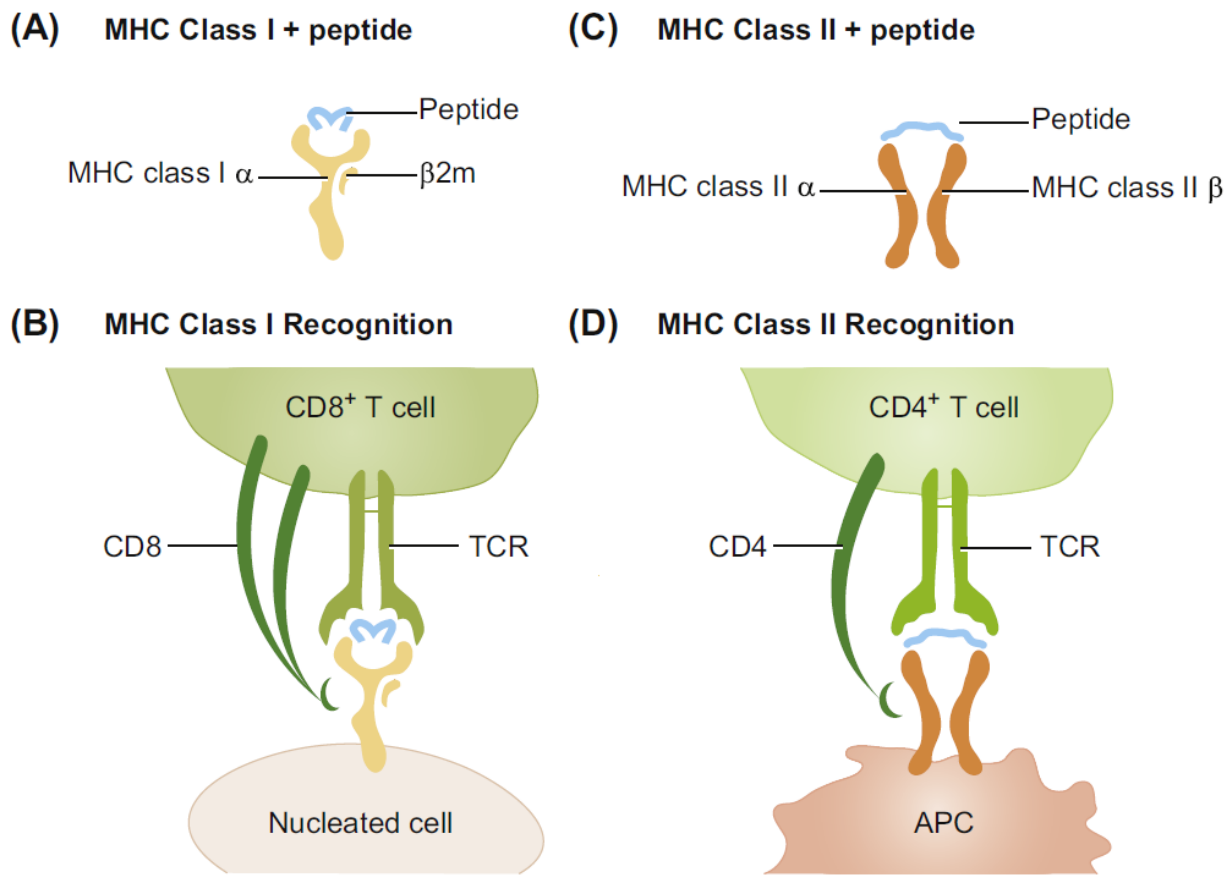
Major Histocompatibility Complex

Antigen presentation by MHC molecules

- Two types of MHC molecules
  - MHC class I
  - MHC class II
- Two types of T cells
  - CD4 T helper cells
  - CD8 T cytotoxic cells
- Two types of antigen
  - Endogenous (from within the cell)
  - Exogenous (from outside the cell)

MHC Class I Pathway

MHC Class II Pathway



Type of T cell activated

- MHC class I activate CD8 T cytotoxic cells
- Present endogenous (eg viral) antigens
- Target cell is killed by CD8 cell
- Any cell can become virally infected/neoplastic

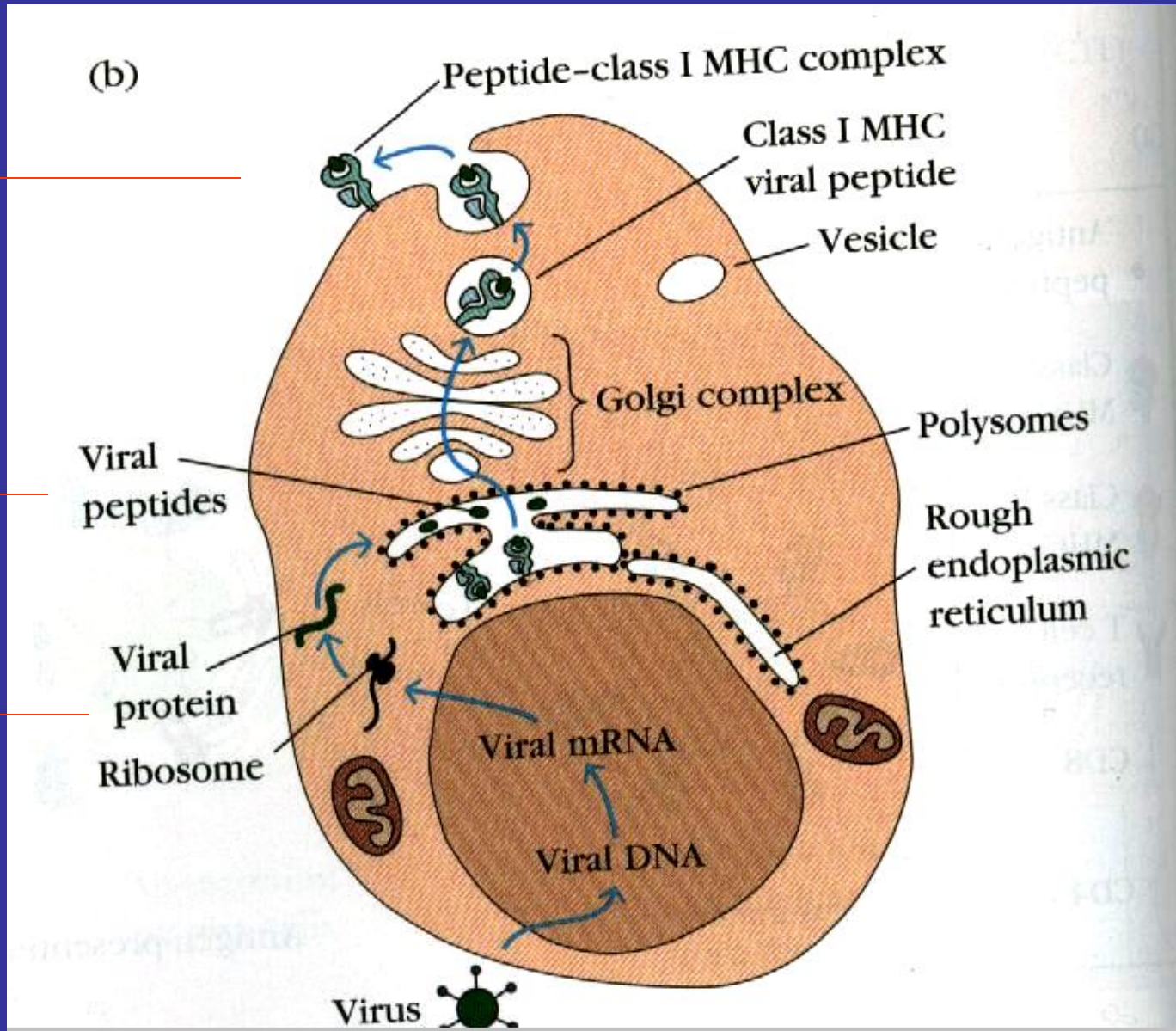
- Therefore: MHC class I is on all nucleated cells

Endogenous antigen presentation

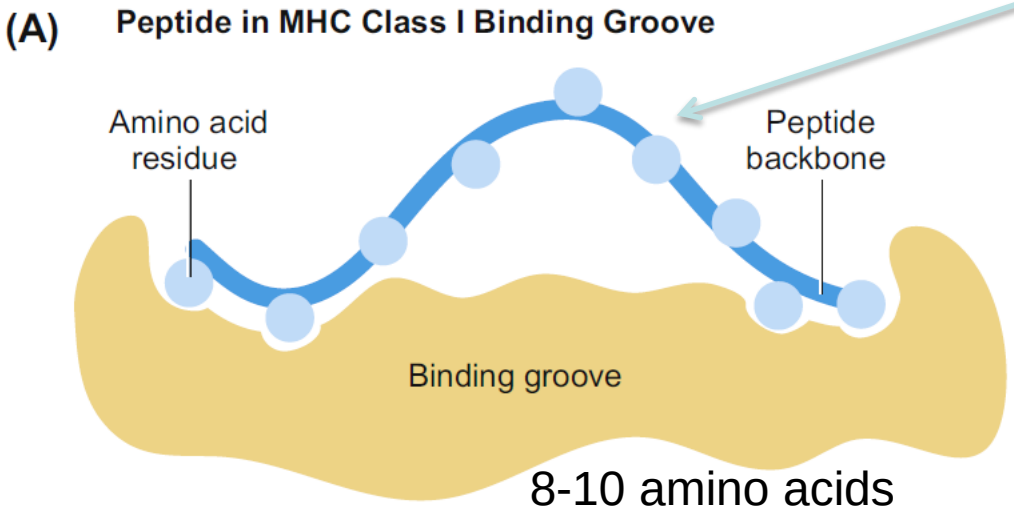
3

2

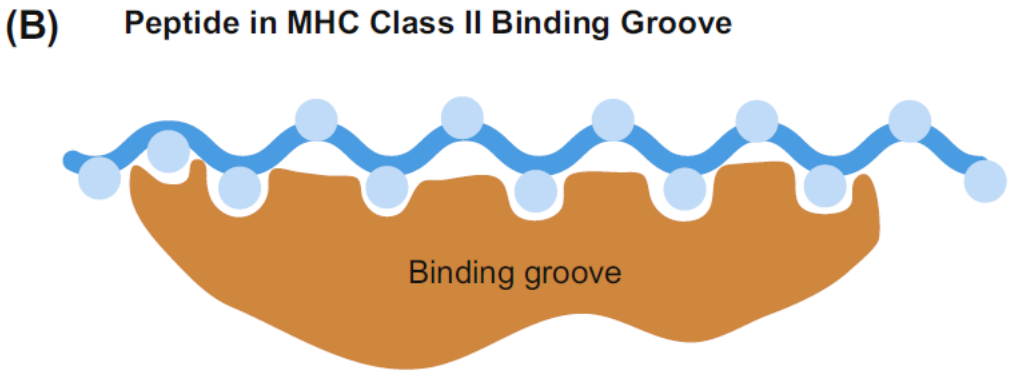
1



Peptide within groove



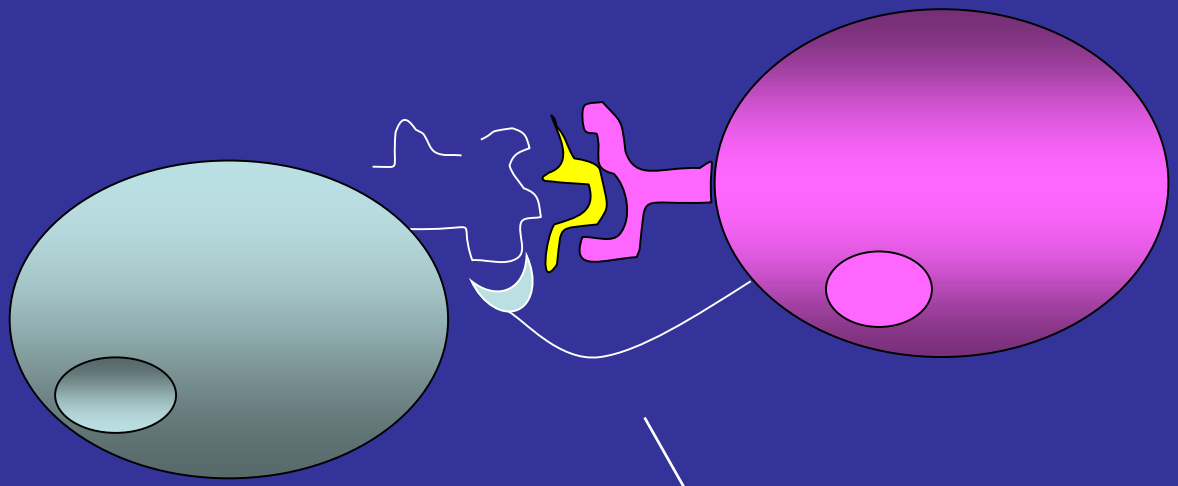
8-10 amino acids



15-20 amino acids

Peptides extends beyond groove

MHC class I Ag presentation to CD8 T cell



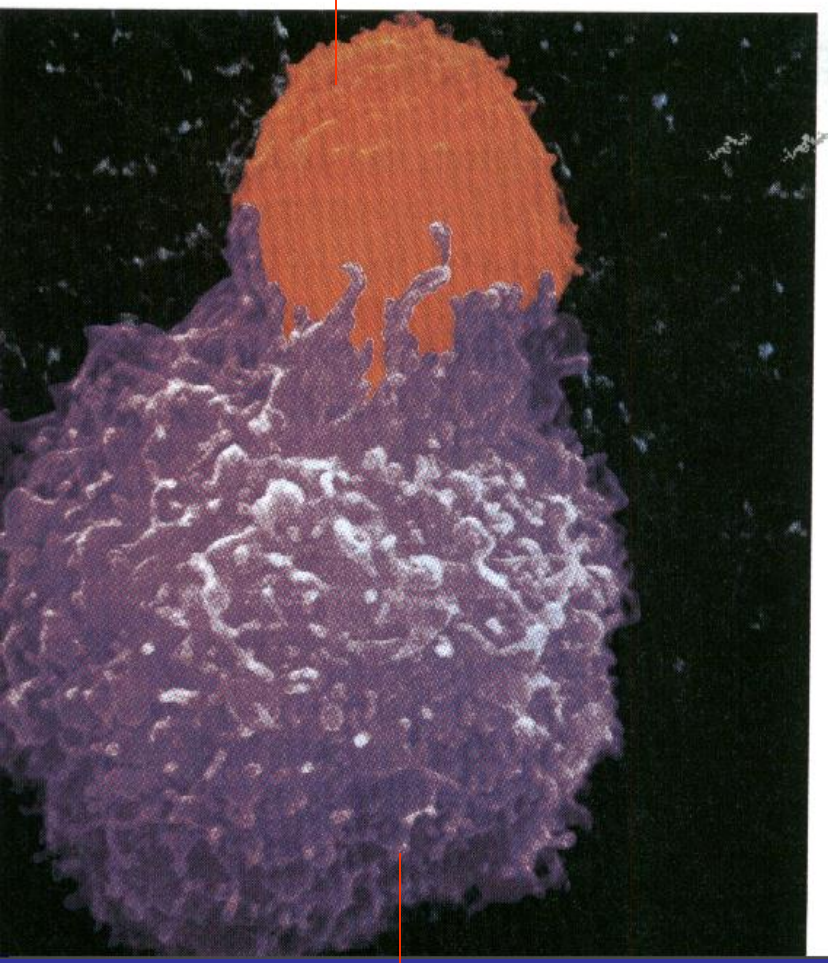
Cell expressing MHC class I

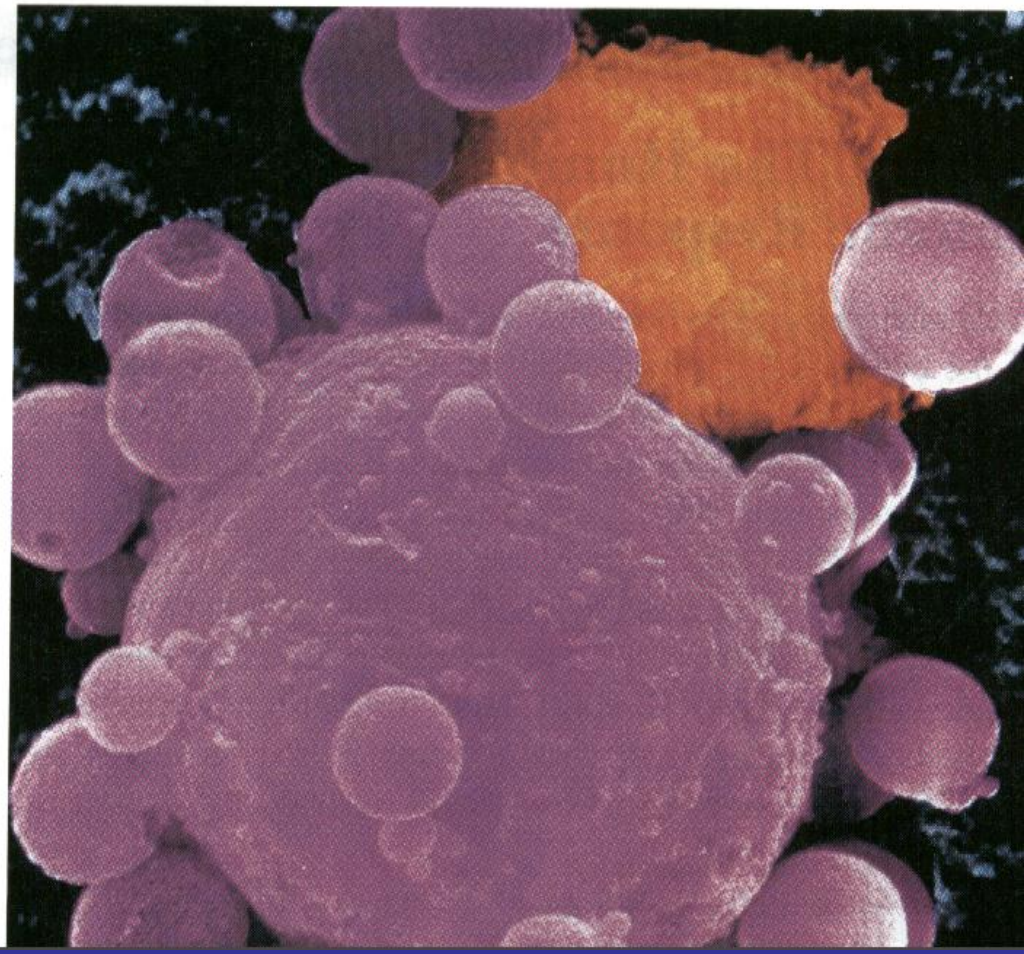
CD8+ T cell

CD 8 binds α3 domain
Stabilises interaction

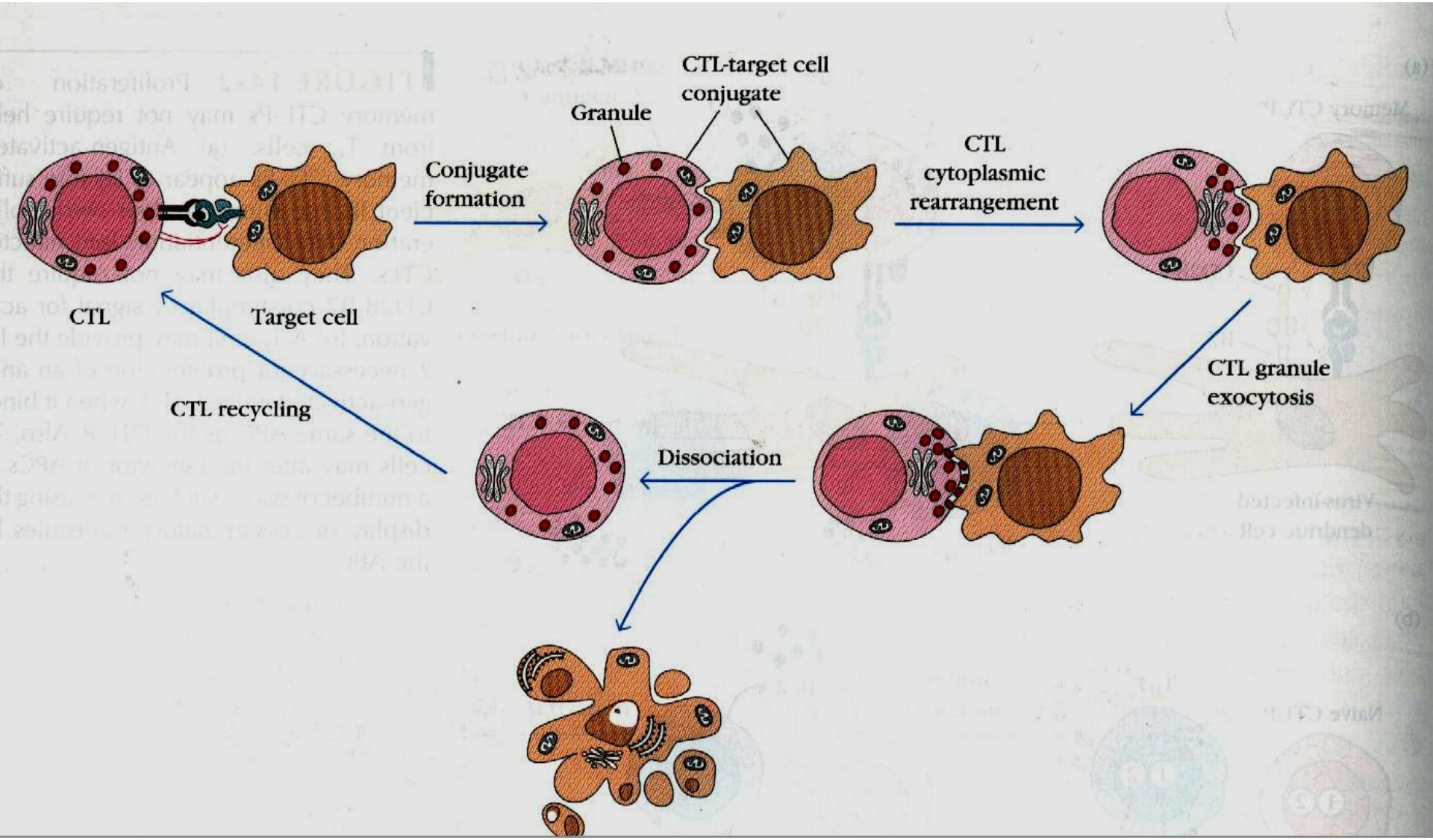
Death of target cell

CD8 CTL





Tumour cell


CTL-target cell conjugate
Granule
Conjugate formation
CTL cytoplasmic rearrangement
CTL
Target cell
CTL granule exocytosis
CTL recycling
Dissociation

Some Effector Molecules of CTLs

Protein in granules of cytotoxic T cells	Actions on target cells
Perforin	Aids in delivering contents of granules into the cytoplasm of target cell
Granzymes	Serine proteases, which activate apoptosis once in the cytoplasm of the target cell
Granulysin	Has antimicrobial actions and can induce apoptosis

Type of T cell activated

- MHC class II activate CD4 T helper cells
- Present exogenous (eg bacteria) antigens

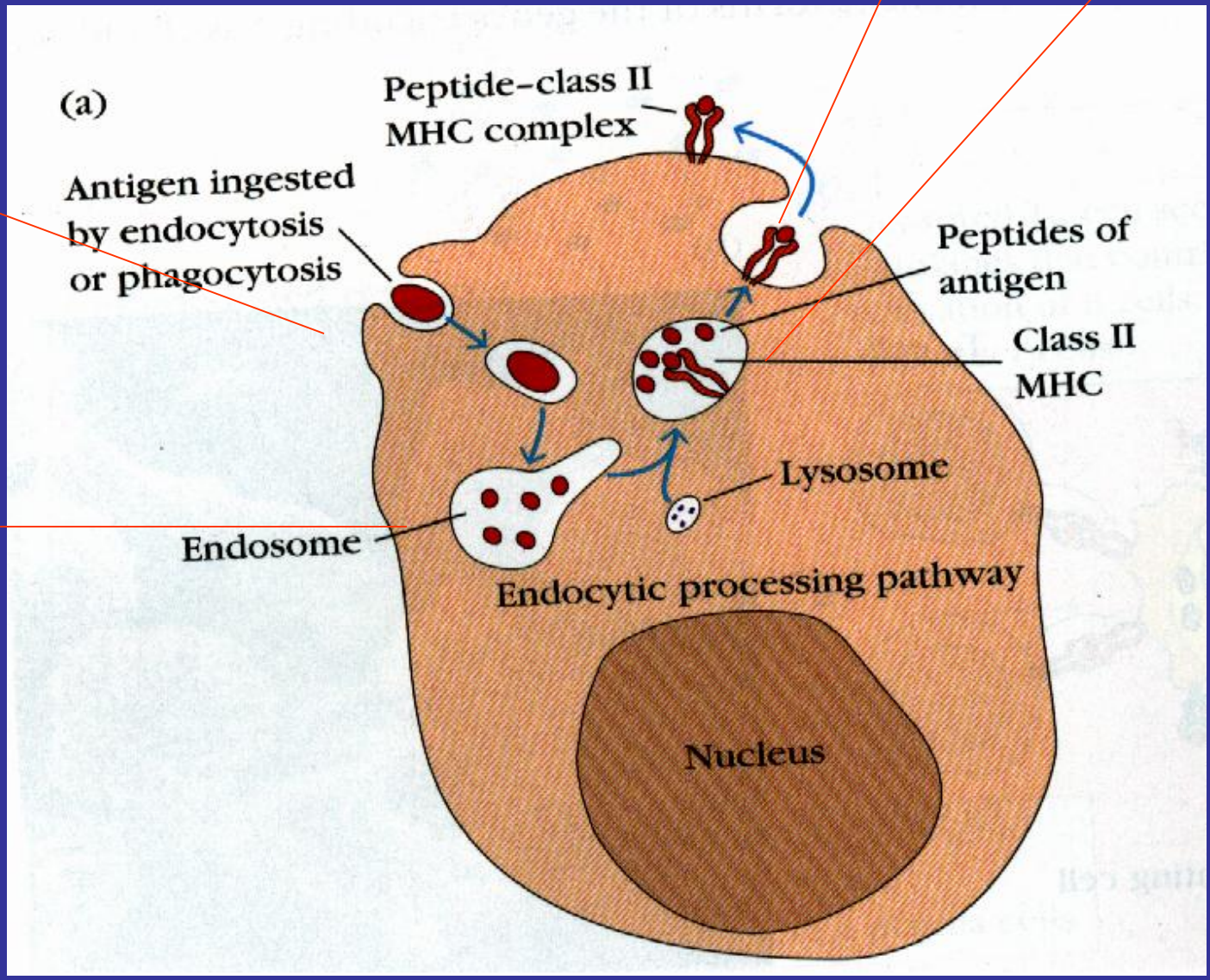
- CD4 T cells upregulate all immune functions

- MHC class II found only on cells that sample the extracellular environment

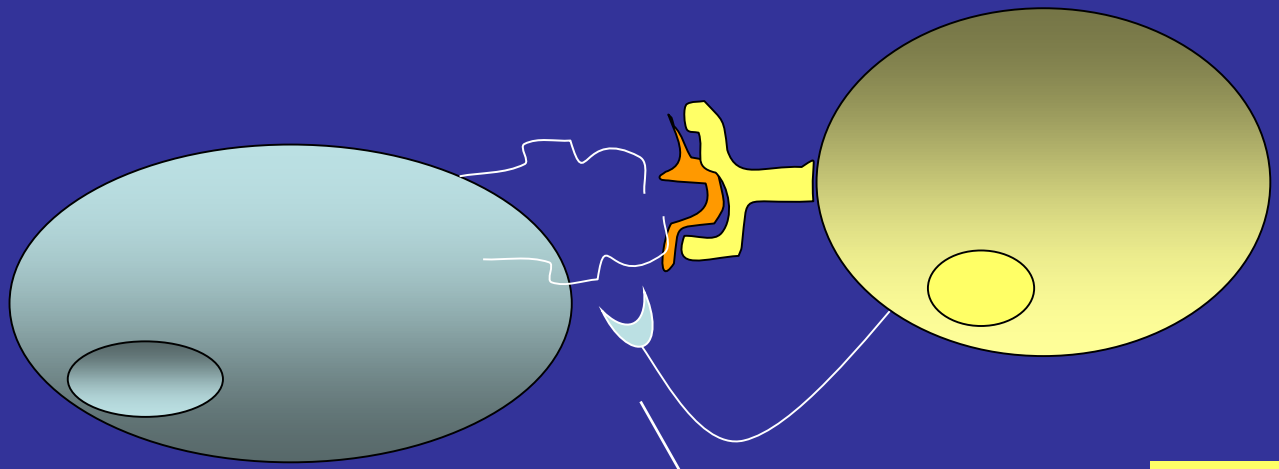
MHC class II-CD4 T cell activation

- CD4 T helper cells up regulate immune function
- Stimulate Mϕ activation and phagocytosis, B cell antibody production
- Help to clear exogenous antigen (ie. parasites)

Exogenous antigen presentation



MHC class II Ag presentation to CD4 T cell



Cell expressing MHC class II

CD4+ T cell

CD 4 binds mainly β2 domain
Stabilises interaction

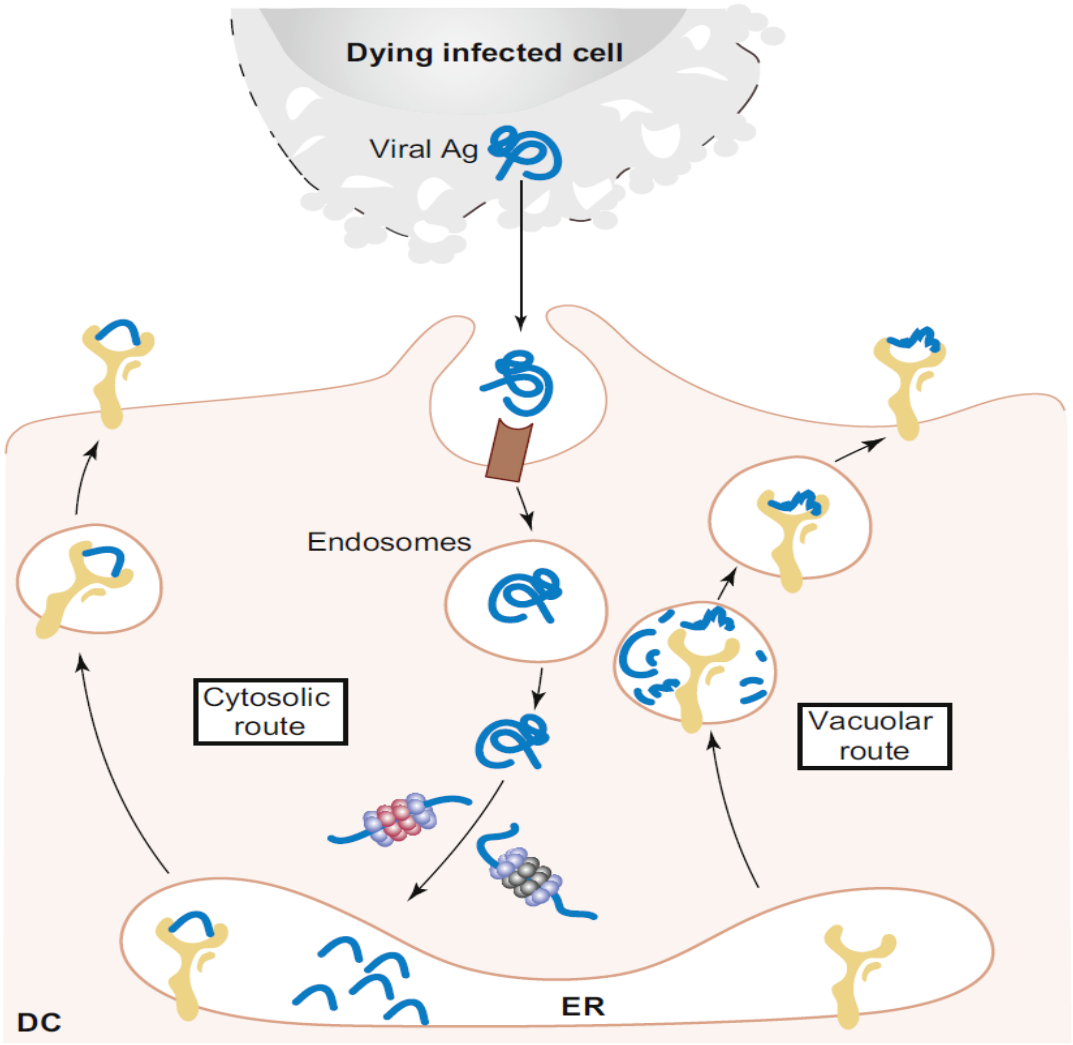
Upreglation of
Immune responses

A question of language

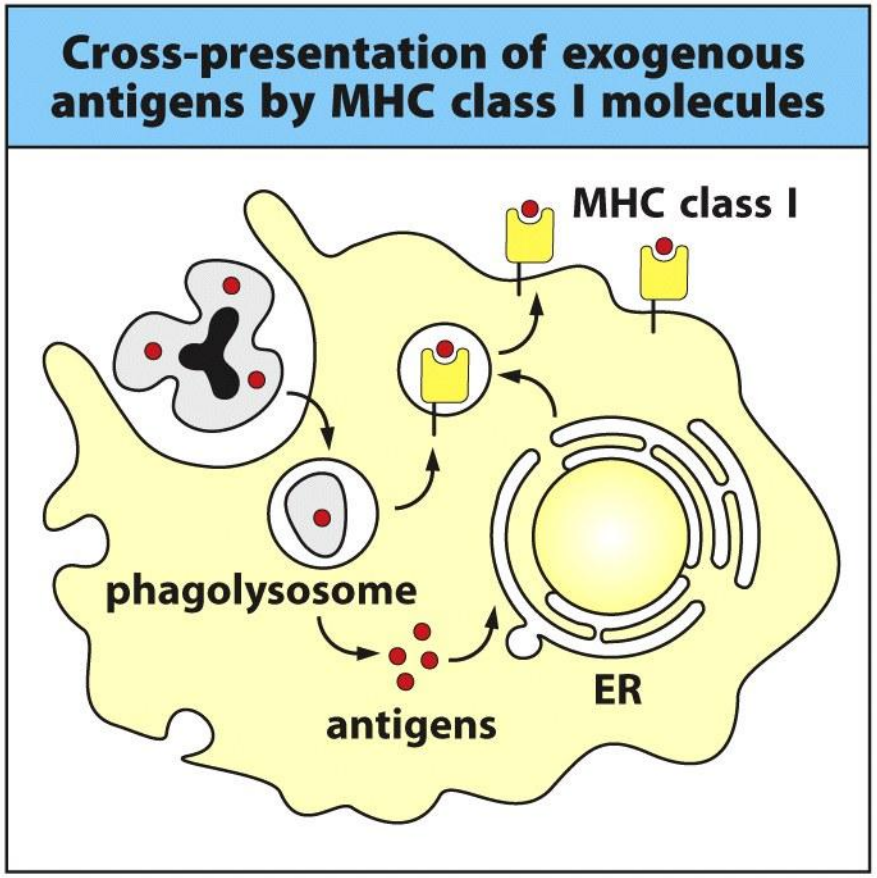
- Cells that express MHC class I, present endogenous ag
  - Are killed by CD8+ cells
  - Are called **Target cells**
- Cells that express MHC class II, present exogenous ag
  - Activate the CD4 T cell response
  - Are called **Antigen presenting cells**

- Target cells:
  - All nucleated cells express MHC class I
  - Can be a target cell if virally infected/neoplastic
- Antigen presenting cells
  - Limited number of cells express MHC class II
  - Must sample extracellular environment
  - Monocytes, MΦ, B cells

Cross Presentation



1. Cytosolic route
2. Vacuolar route



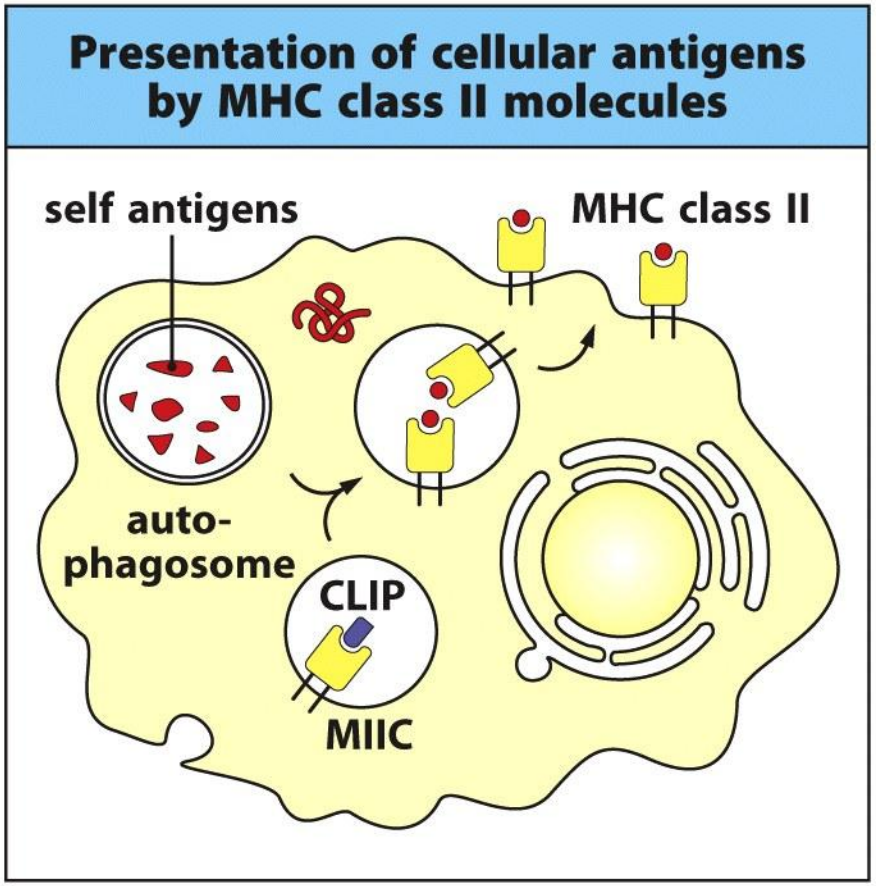
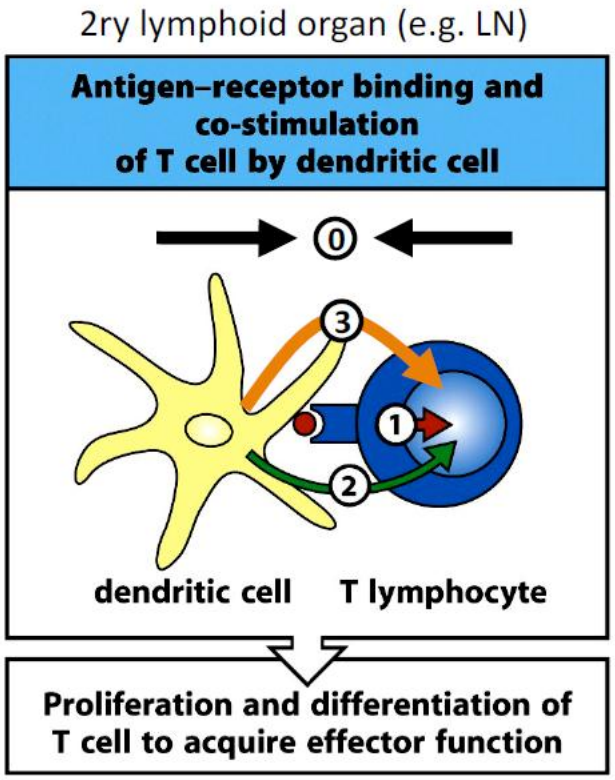


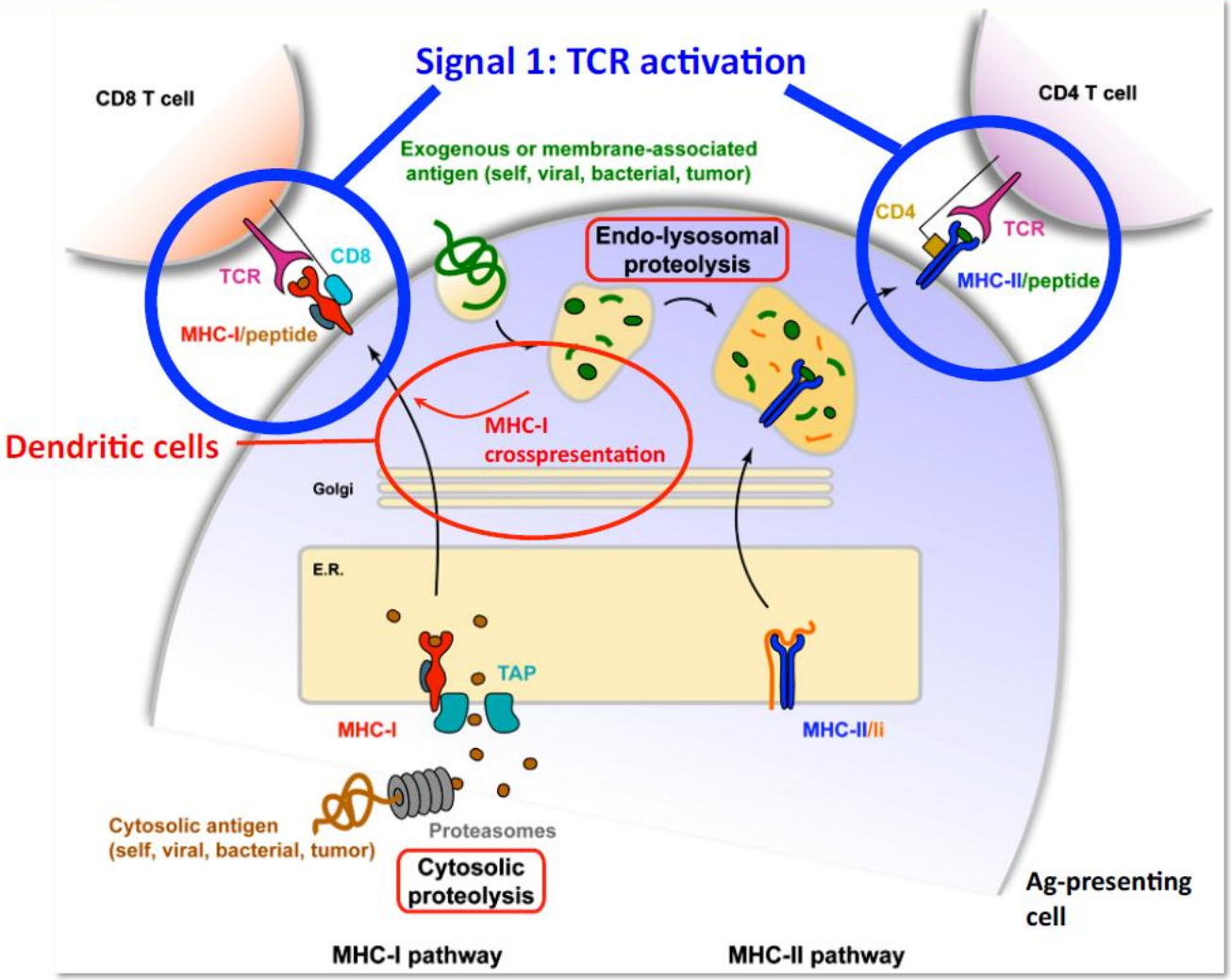
Figure 6.13 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Dendritic cells activate T cells in an antigen-specific manner: Three-signal model

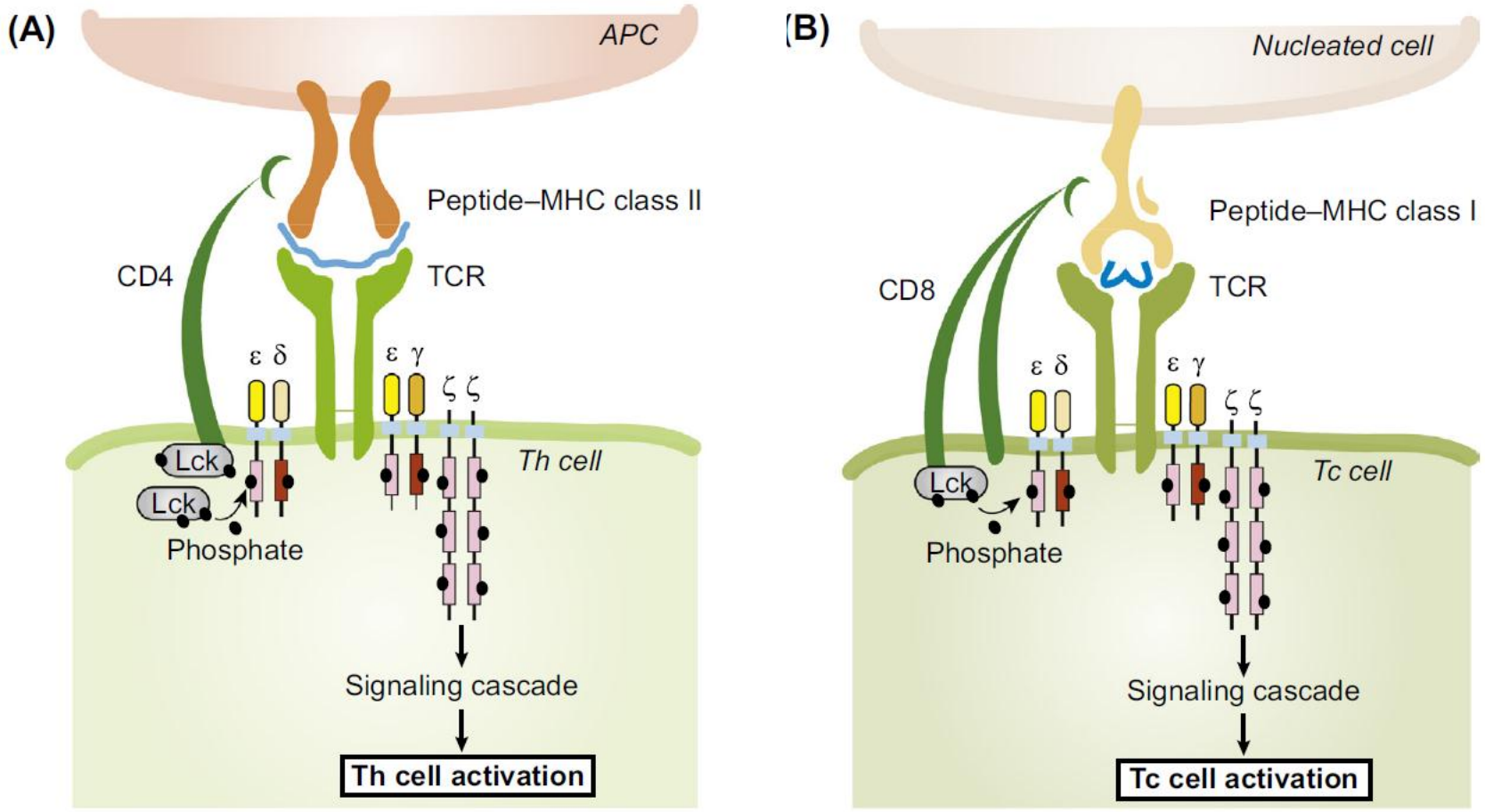


Signal 0: DCs and T cells come together
Signal 1: Ag-specific T cell activation
Signal 2: T cell survival
Signal 3: T cell differentiation

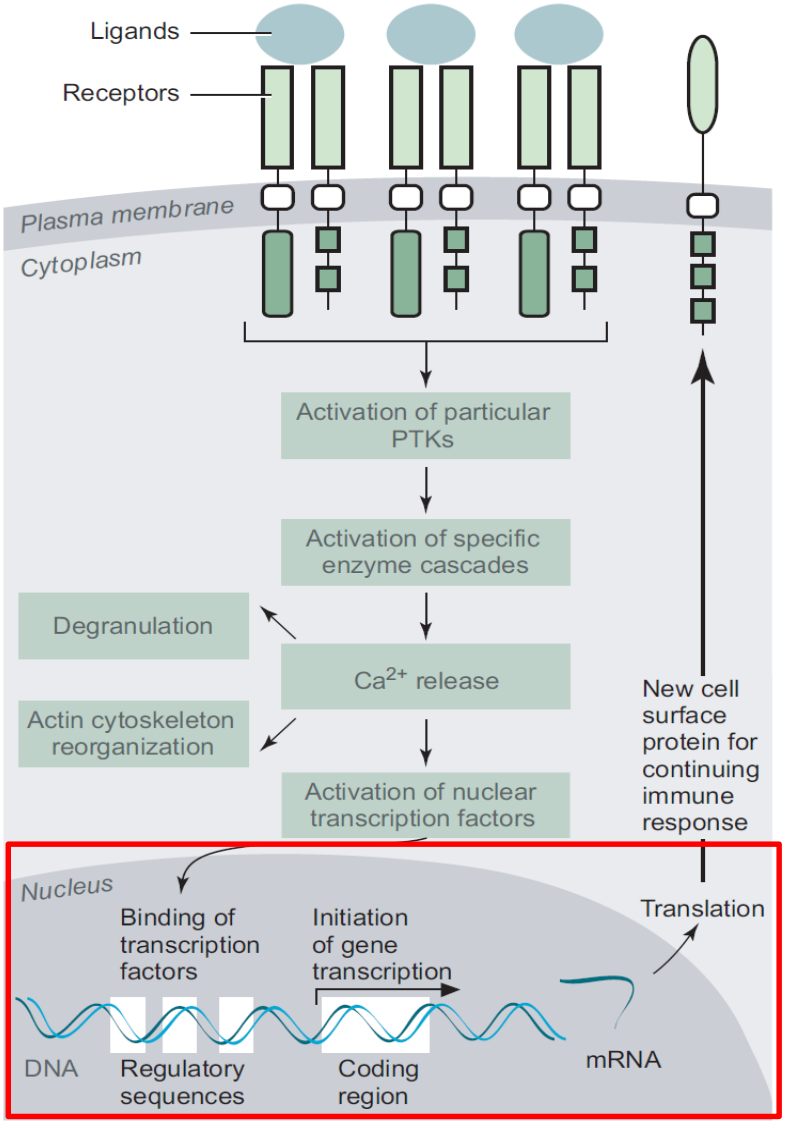
Antigen presentation: display of cell's proteome on MHC molecules for T cell recognition



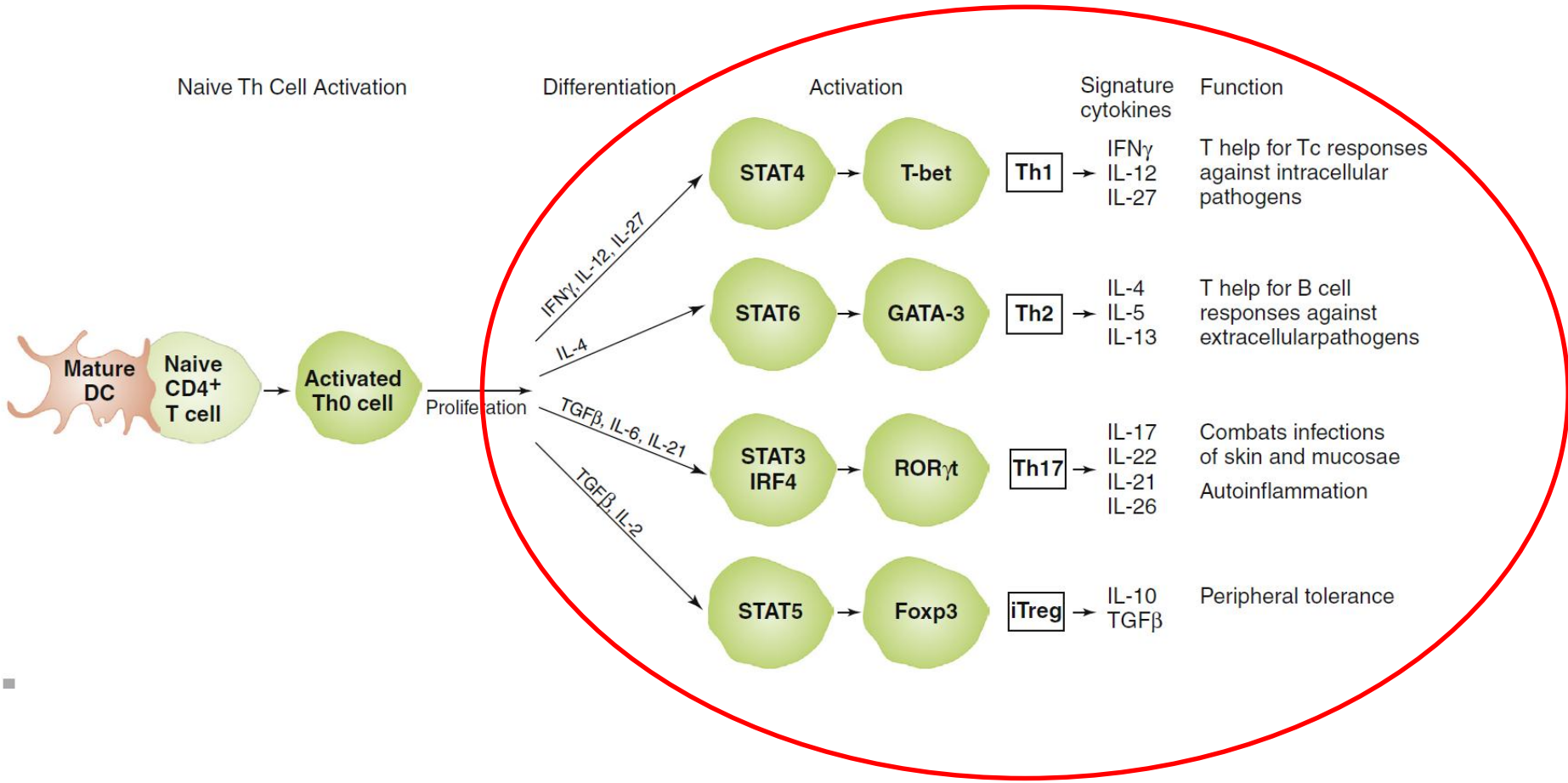
Role of coceptors in TCR signalling



Intracellular signalling Pathway



Effector T cell Differentiation



It takes 3 not 2!!!

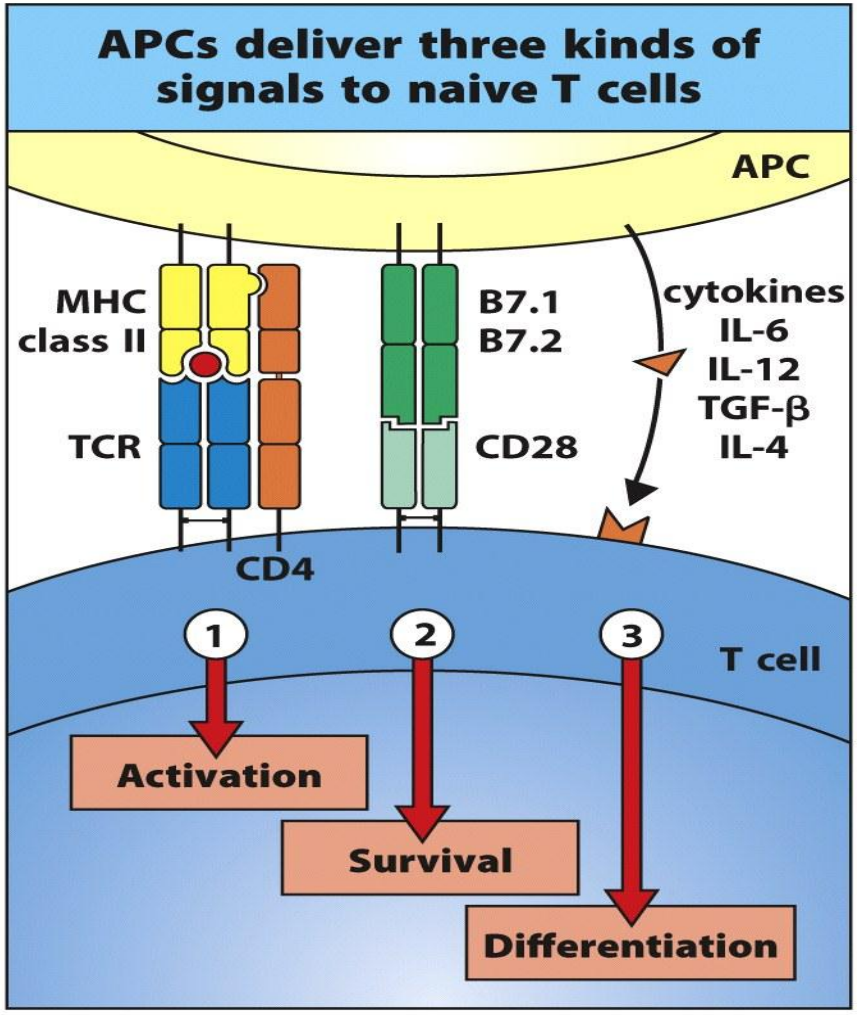


Figure 9.19 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Applying The Brakes

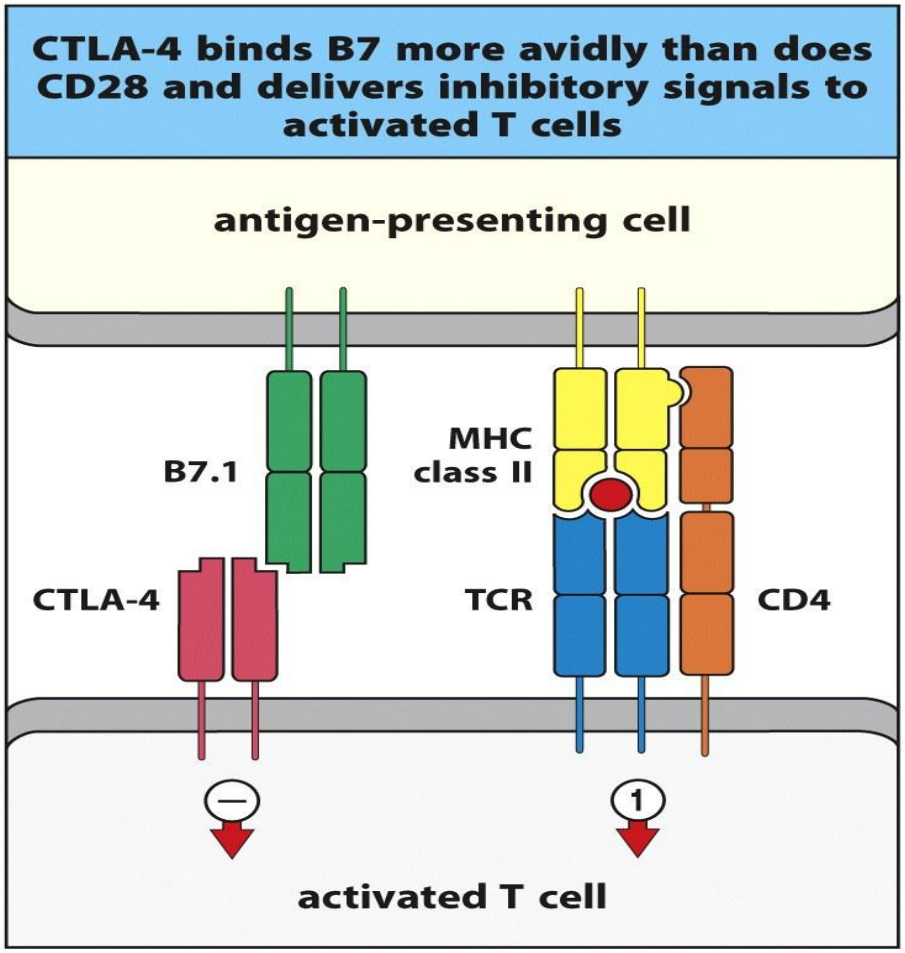


Figure 9.22 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

We never walk alone: LFC

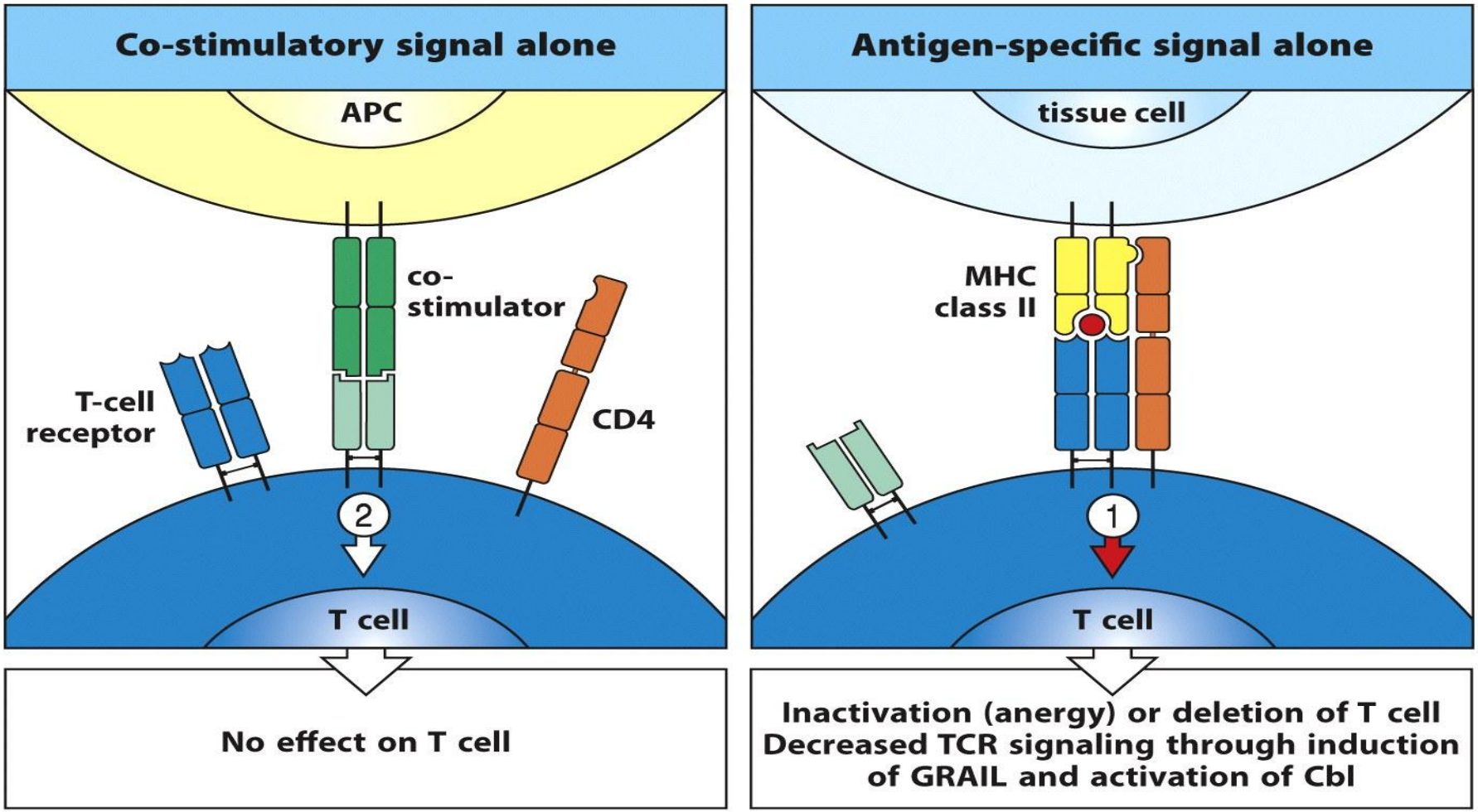


Figure 9.23 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Functional Activities of CD4+ T cells

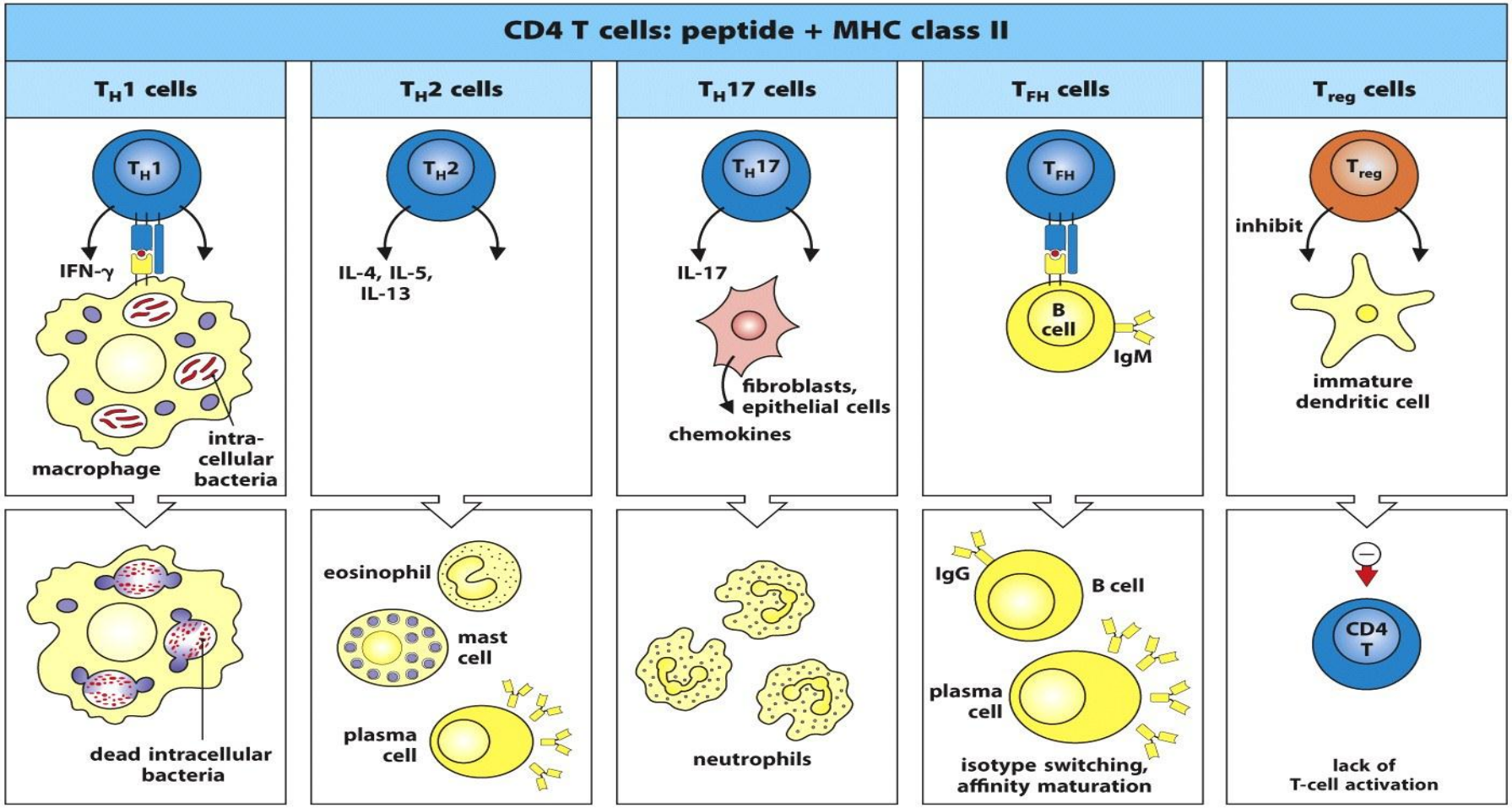


Figure 9.28 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Transcriptional Factors

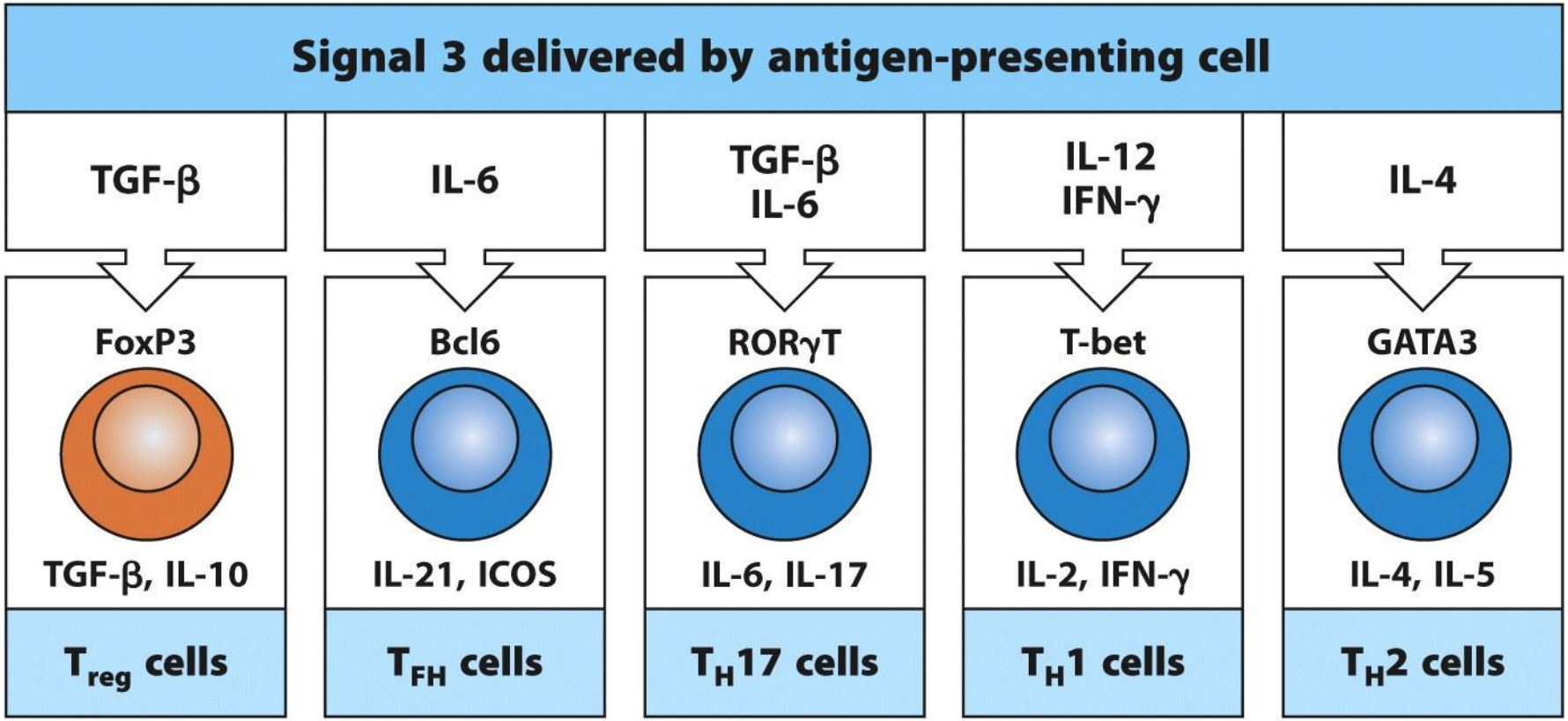
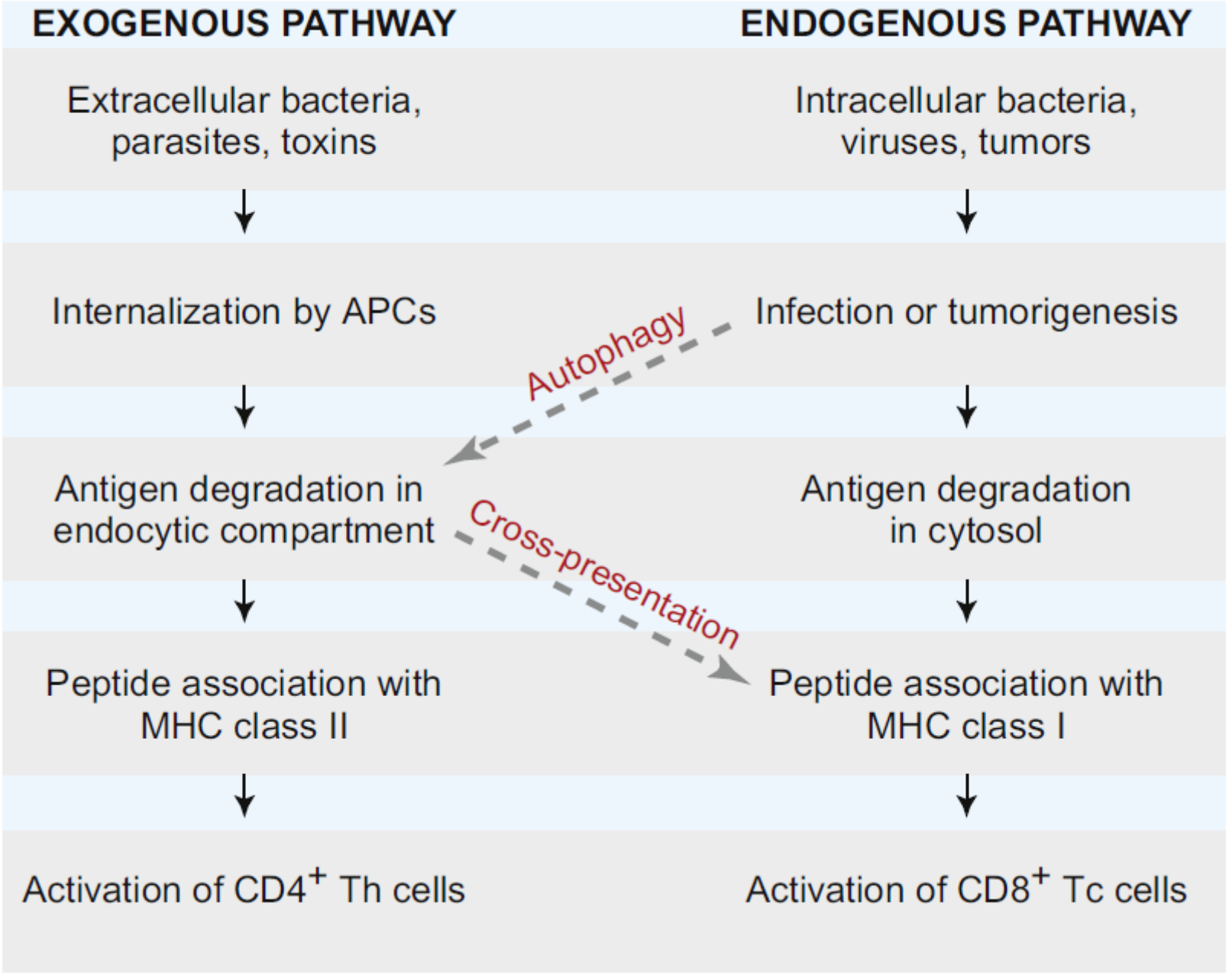


Figure 9.29 Janeway's Immunobiology, 8ed. (© Garland Science 2012)


EXOGENOUS PATHWAY
ENDOGENOUS PATHWAY
Extracellular bacteria, parasites, toxins
Intracellular bacteria, viruses, tumors
Internalization by APCs
Infection or tumorigenesis
Autophagy
Antigen degradation in endocytic compartment
Cross-presentation
Antigen degradation in cytosol
Peptide association with MHC class II
Peptide association with MHC class I
Activation of CD4+ Th cells
Activation of CD8+ Tc cells