OVERVIEW OF ADAPTIVE IMMUNITY

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Presenter Disclosure Information

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The following relationships exist related to this presentation:

No Relationships to Disclose

OVERVIEW OF ADAPTIVE IMMUNITY

OBJECTIVES: At the end of the presentation, you should be able to:

1.Differentiate between innate and adaptive immunity

2. Describe the cell types and steps involved in T cell activation

3. Explain the structural differences between MHC class I and MHC class II

4. Describe how MHC class I and class II peptides are generated and presented

5. Describe the effector functions of the various T lymphocyte subsets

6. Discuss the differences between antigen recognition by B cells and T cells

7. Describe the effector mechanisms of the antibody response

CHARACTERISTICS OF INNATE AND ADAPTIVE IMMUNITY

- INNATE
- Exists prior to antigenic exposure
- Resistance not enhanced by repeated exposure to antigen
- Not antigen-specific
- Lacks a memory component

- ADAPTIVE
- Developed in response to antigen exposure
- Resistance improved by repeated exposure to antigen
- Response is antigen-specific
- Memory is established

DISTINGUISHING FEATURES OF THE ADAPTIVE IMMUNE RESPONSE

- SPECIFICITY:
- Response is directed only against the stimulating antigen.

- ADAPTIVENESS:
- Responses can be made against an immense variety of antigens some of which may not be naturally occurring.

- SELF/NON-SELF DISCRIMINATION:
- Responses are made against foreign (“non-self”) antigens and not usually against “self” antigens.

- MEMORY:
- Ability to recall previous contact with a foreign antigen and to respond in a learned way by initiating a rapid and vigorous response following re-exposure to the antigen.
-

Activation of lymphocytes constitutes the major part of the adaptive immune response to an infection. Participation of numerous cell types is necessary for the development of an effective immune response.

▪LYMPHOCYTES

▪**B lymphocytes** make antibodies which act as antigen receptors.

▪**T lymphocytes** express T cell receptors (TCRs) which bind antigen (peptides) and can be subdivided into:

- 1. T helper (T_h) cells: secrete lymphokines, activate dendritic cells and assist B lymphocytes in producing antibodies.

  2. Th17 cells: recruitment of neutrophils

- 3. T cytotoxic (T_c) cells:destroy virus-infected cells and tumor cells.

- 4. T regulatory (T_{reg})cells: regulate immune responses

ANTIGEN-PRESENTING CELLS

Dendritic cells, Macrophages,

B lymphocytes:

Ingest, process and present antigen in the form of peptides recognizable by T lymphocytes

Lymphocytes are activated by antigen to give rise to clones of antigen-specific cells that mediate adaptive immunity

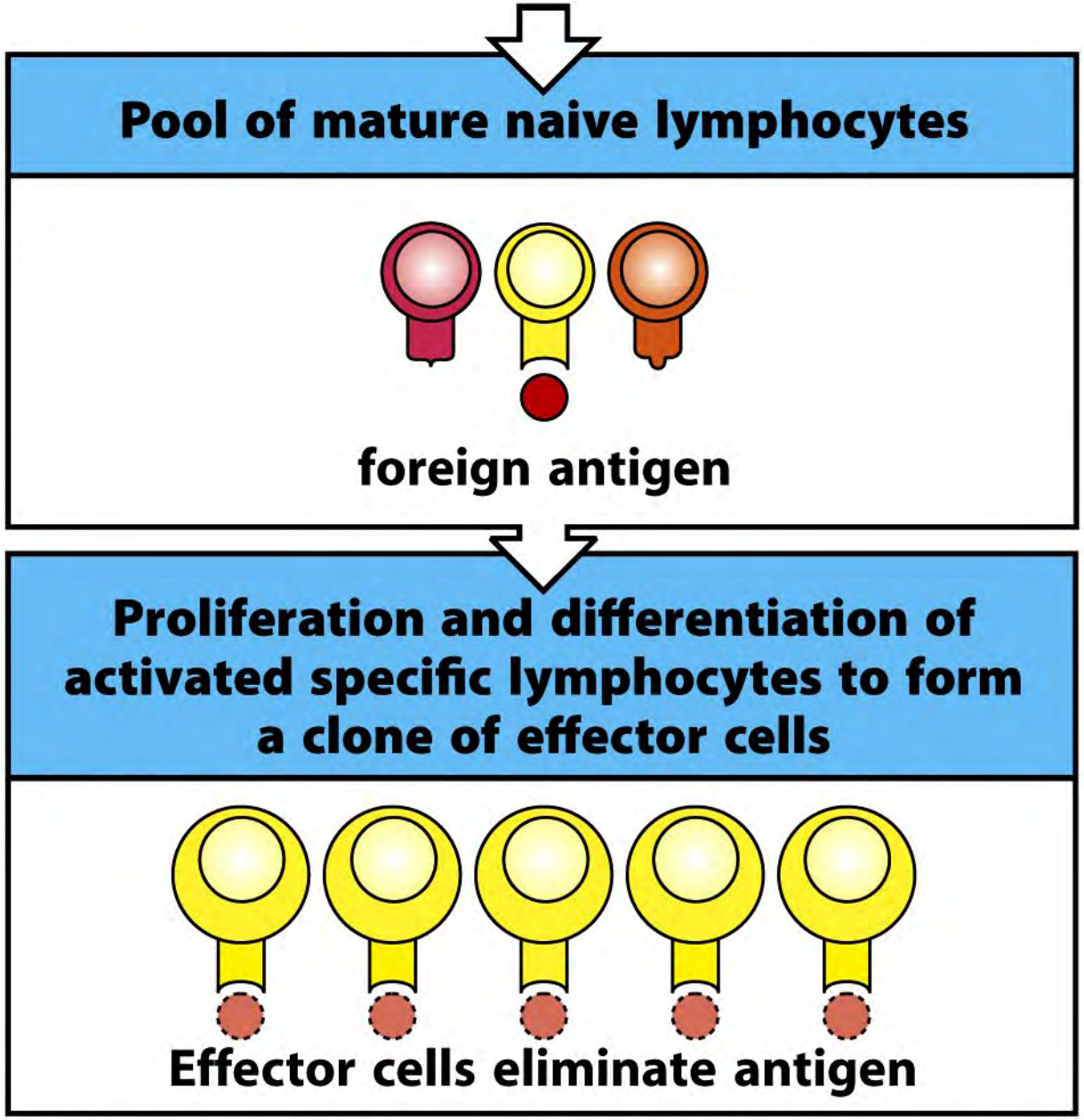


Figure 1-11 part 3 of 3 Immunobiology, 7ed. (© Garland Science 2008)

THE ADAPTIVE IMMUNE RESPONSE

- Exposure for the first time to an immunogen (priming immunization) gives rise to a **primary** immune (antibody or T cell) response.

- Subsequent re-exposure to the same immunogen (secondary immunization) results in a **secondary** (anamnestic or memory) immune response.

Interaction with another cell as well as antigen is necessary for lymphocyte activation

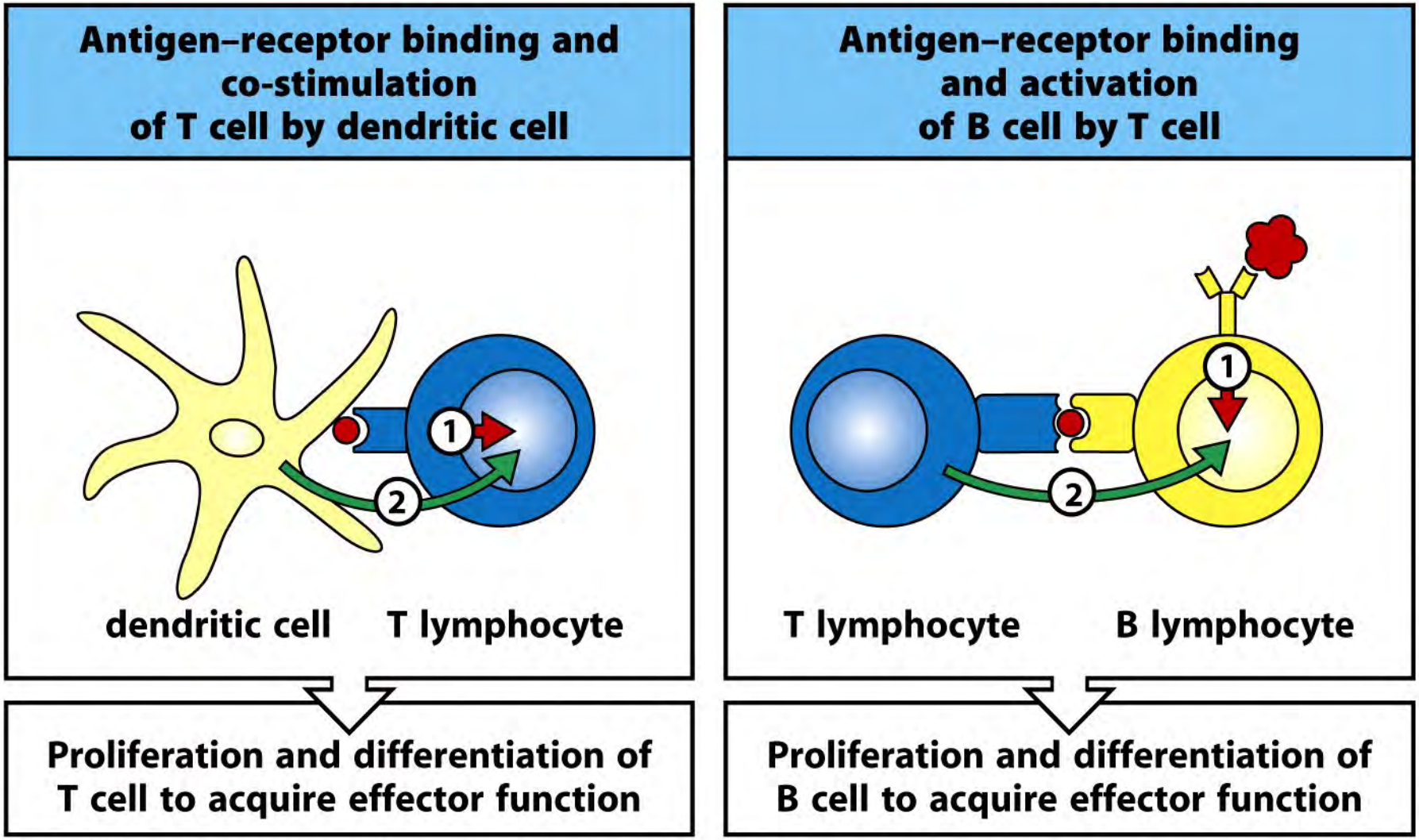


Figure 1-21 Immunobiology, 7ed. (© Garland Science 2008)

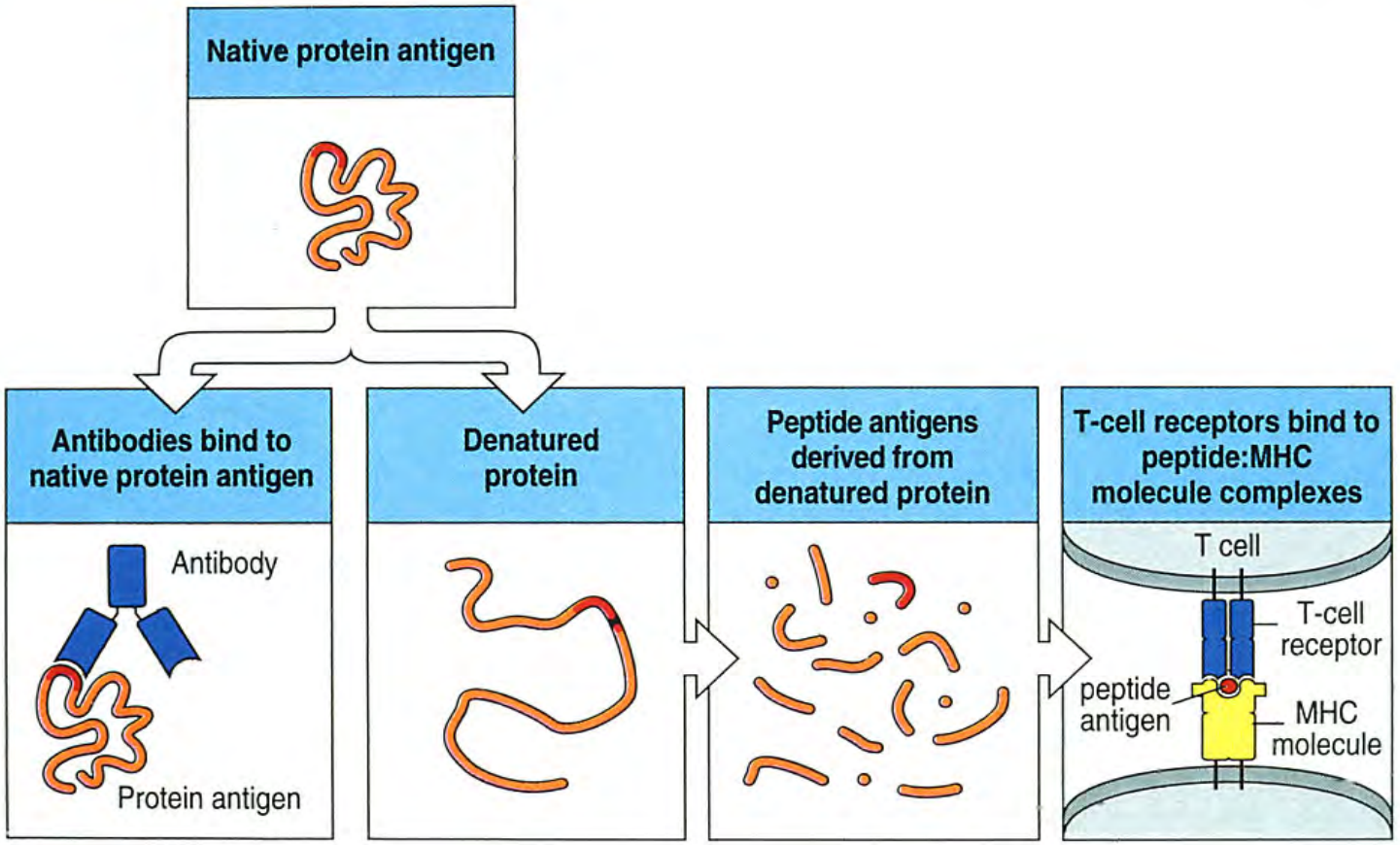
Two signals are required for T lymphocyte activation:

Signal 1: engagement of the TCR with the MHC-peptide complex or BCR with antigen

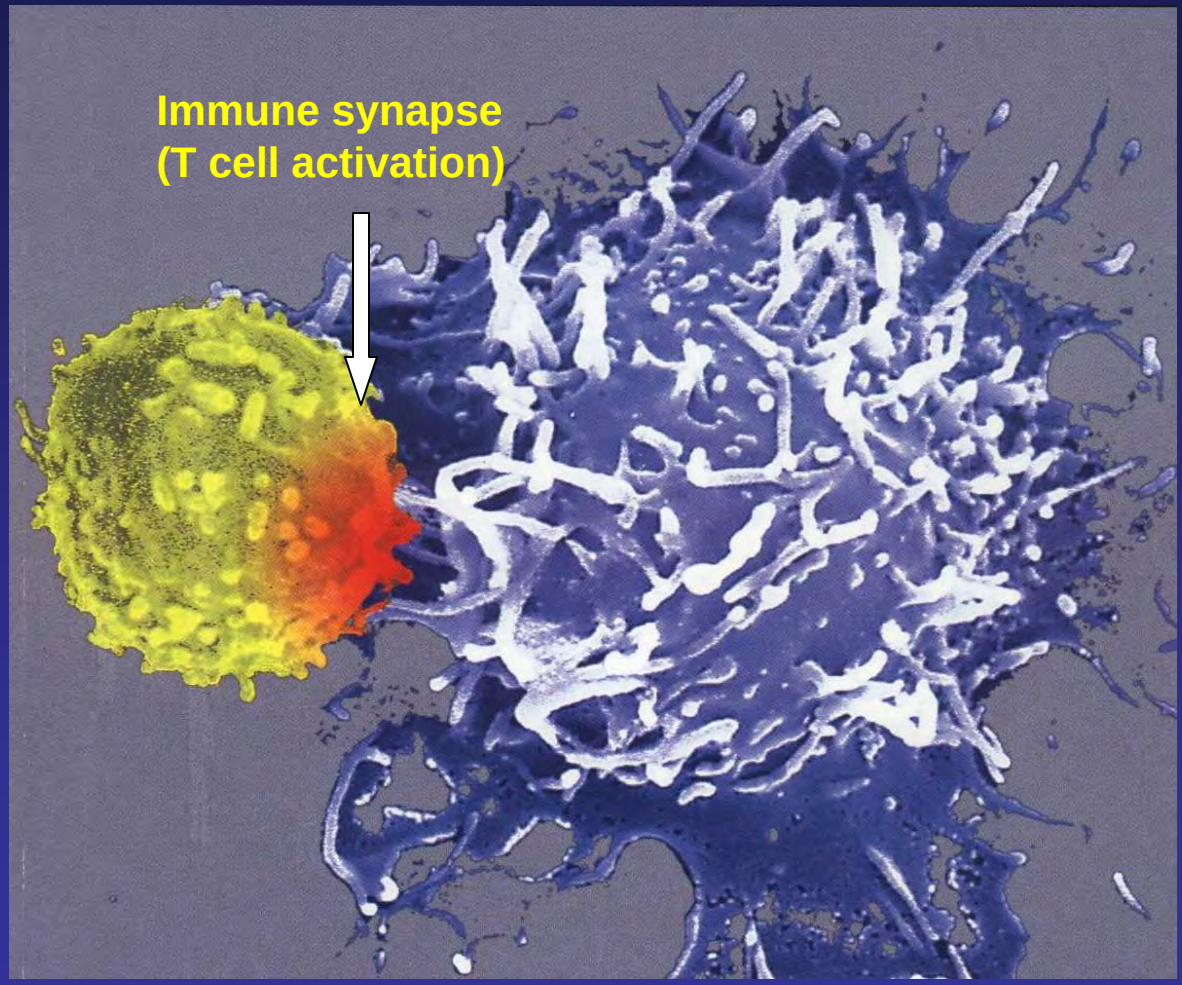
Signal 2: engagement of co-stimulatory molecules (CD40, CD80, CD86) on APC with CD40L or CD28 on T cells

The T cell response

B cells recognize intact pathogens, whereas T cells recognize pathogen-derived peptides bound by major histocompatibility complex (MHC) molecules.



T Cell Recognition of Dendritic Cell



Scanning Electron Micrograph, adapted from Nature Immunology Vol. 2, October, 2001

The dendritic cell as APC

- Capture antigen in peripheral tissues, process it for display and migrate to secondary lymphoid organs to present processed peptides to naïve T cells

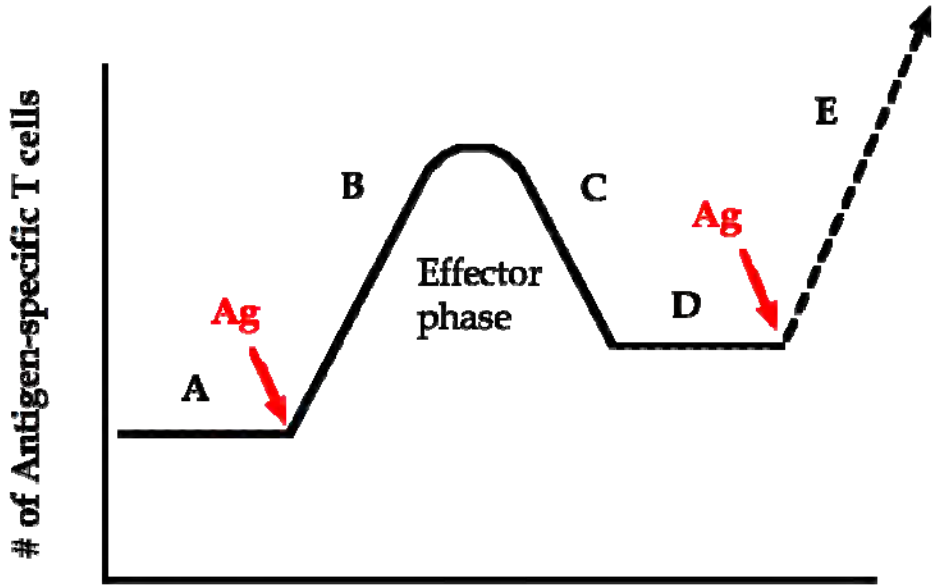
- In immature state they are characterized by high phagocytic and endocytic activities and expression of chemokine receptors (e.g.CCR1, CCR2, CCR5) that recognize inflammatory chemokines

- In response to local inflammation (e.g. during infection, tumor growth), DC mature, down-regulate phagocytic activity, receptors for inflammatory chemokines, increase cell surface MHC class II expression, up-regulate CCR7 and migrate to secondary lymphoid organs to prime naïve T cells

- Activated DC (via TLRs, cytokines (IL-1, TNF-a, type I interferons) upregulate co-stimulatory molecules (e.g.CD80/CD86, CD40). CD28:CD80/CD86 signaling induces expression of CD40L on T cells, which binds to CD40 on APC and induces further up-regulation of CD80/86 leading to signal amplification between T cells and DC.

- **T cells recognize foreign antigens as peptide fragments bound to proteins of the major histocompatibility complex (MHC**)

- Cytotoxic or helper T cells recognize their targets by binding to peptide fragments (derived from the antigen) which are bound to MHC proteins expressed on APCs, B cells or infected host cells.



A: priming and activation phase
B: expansion and effector phase
C: contraction phase
D: memory phase
E: expansion phase

Two major classes of MHC molecules are known (classical MHC) : Class I and Class II. Peptides are loaded onto MHC molecules in the cells and are then transported to the surface where they are presented to the T cell.

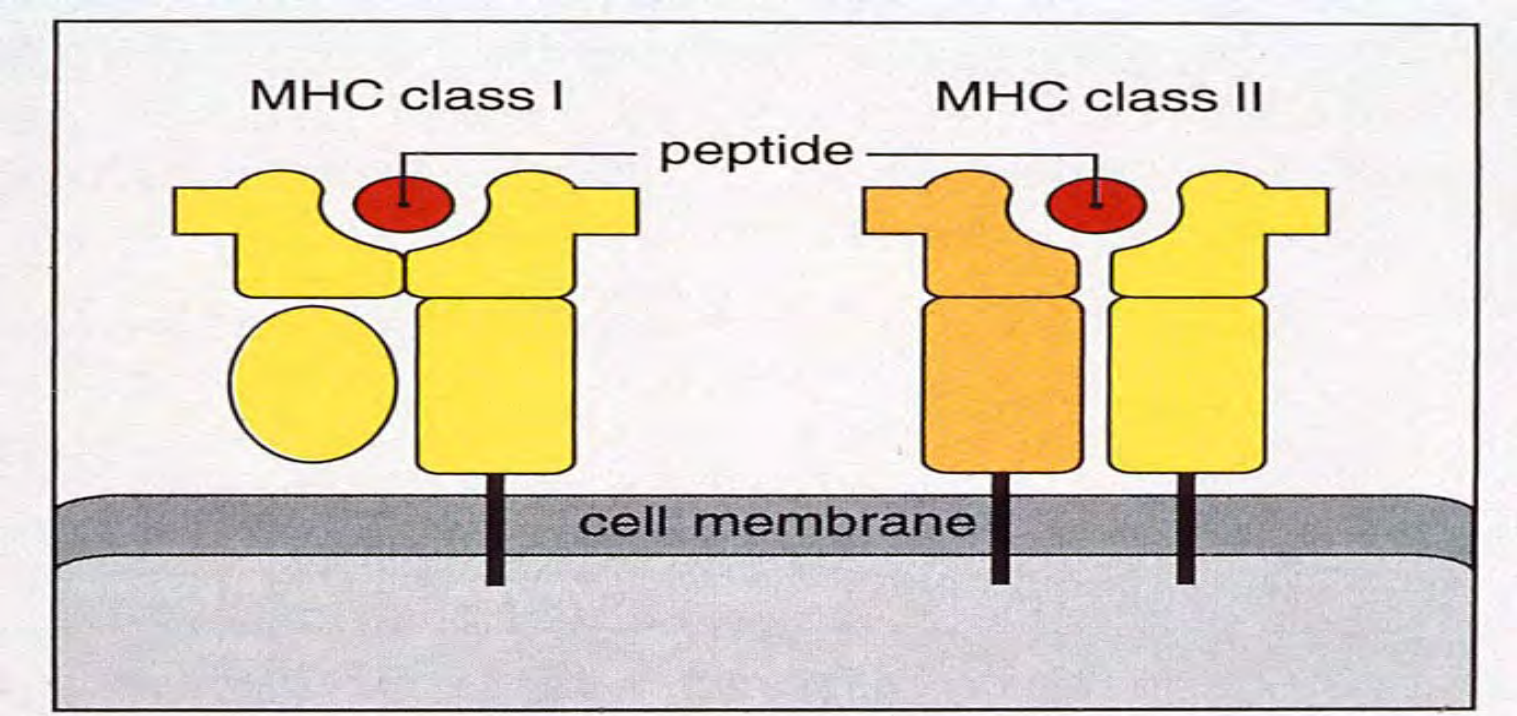


Figure 1.20 There are two types of MHC molecule, MHC class I and MHC class II.

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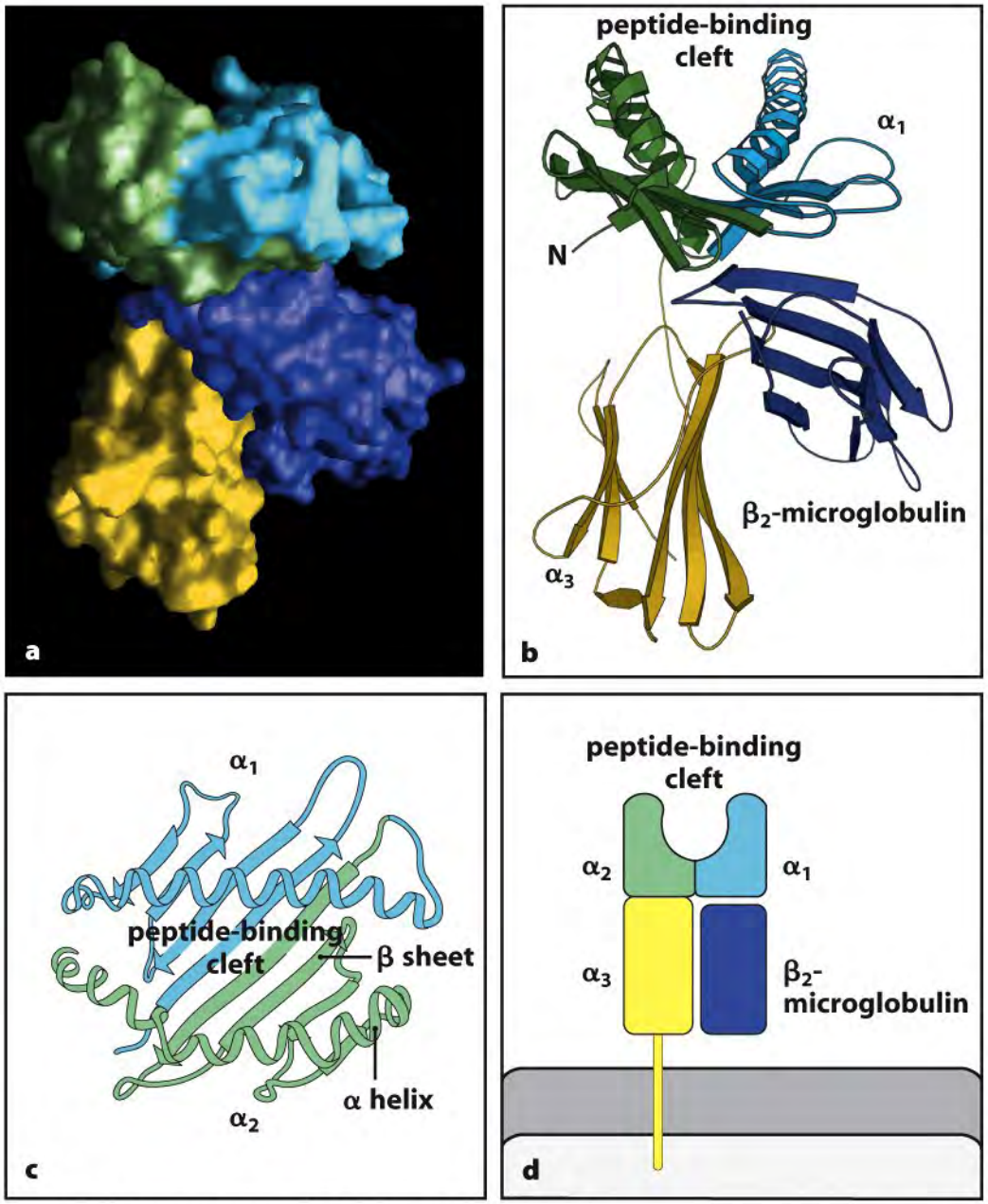


Figure 3-15 Immunobiology, 7ed. (© Garland Science 2008)

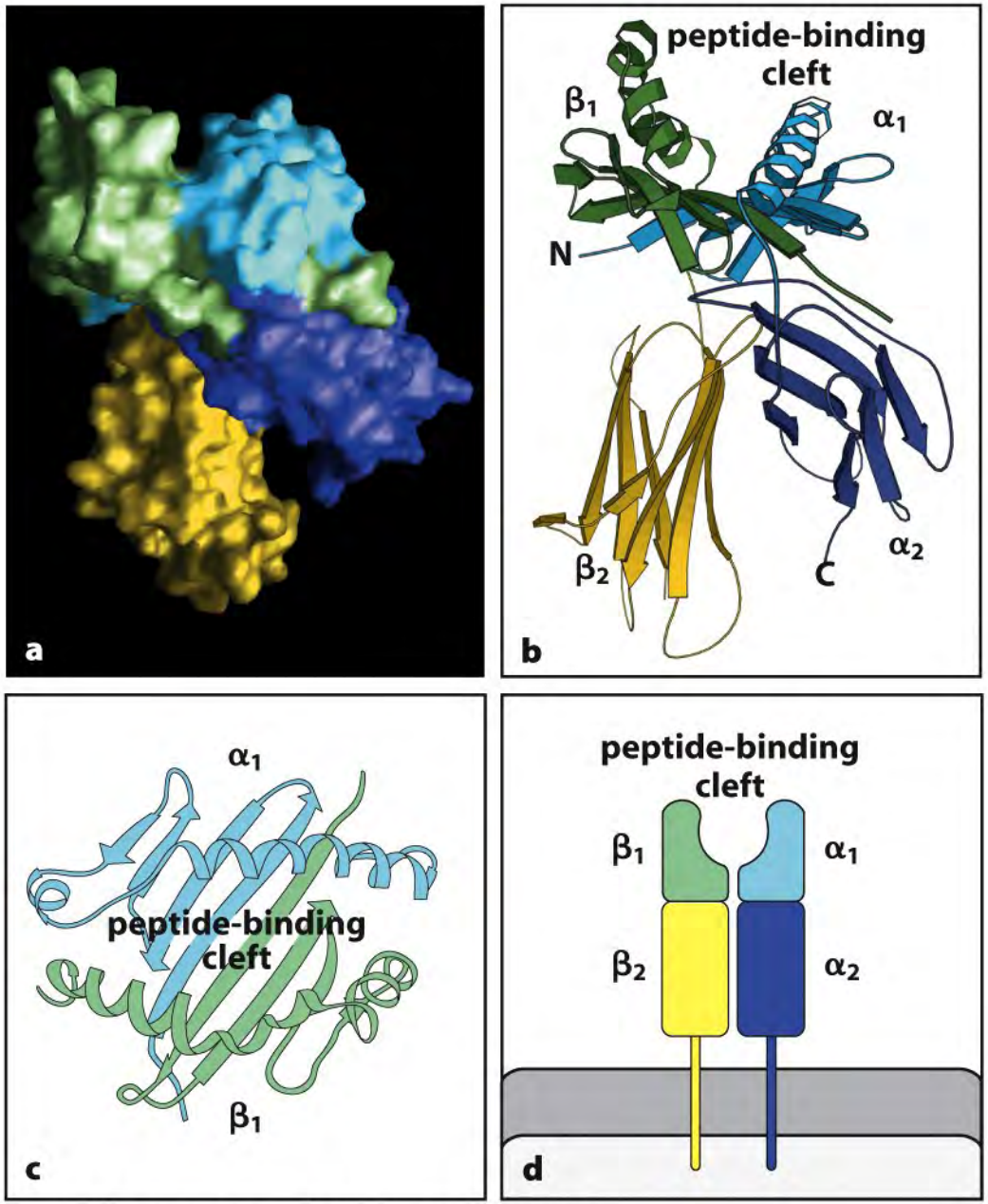
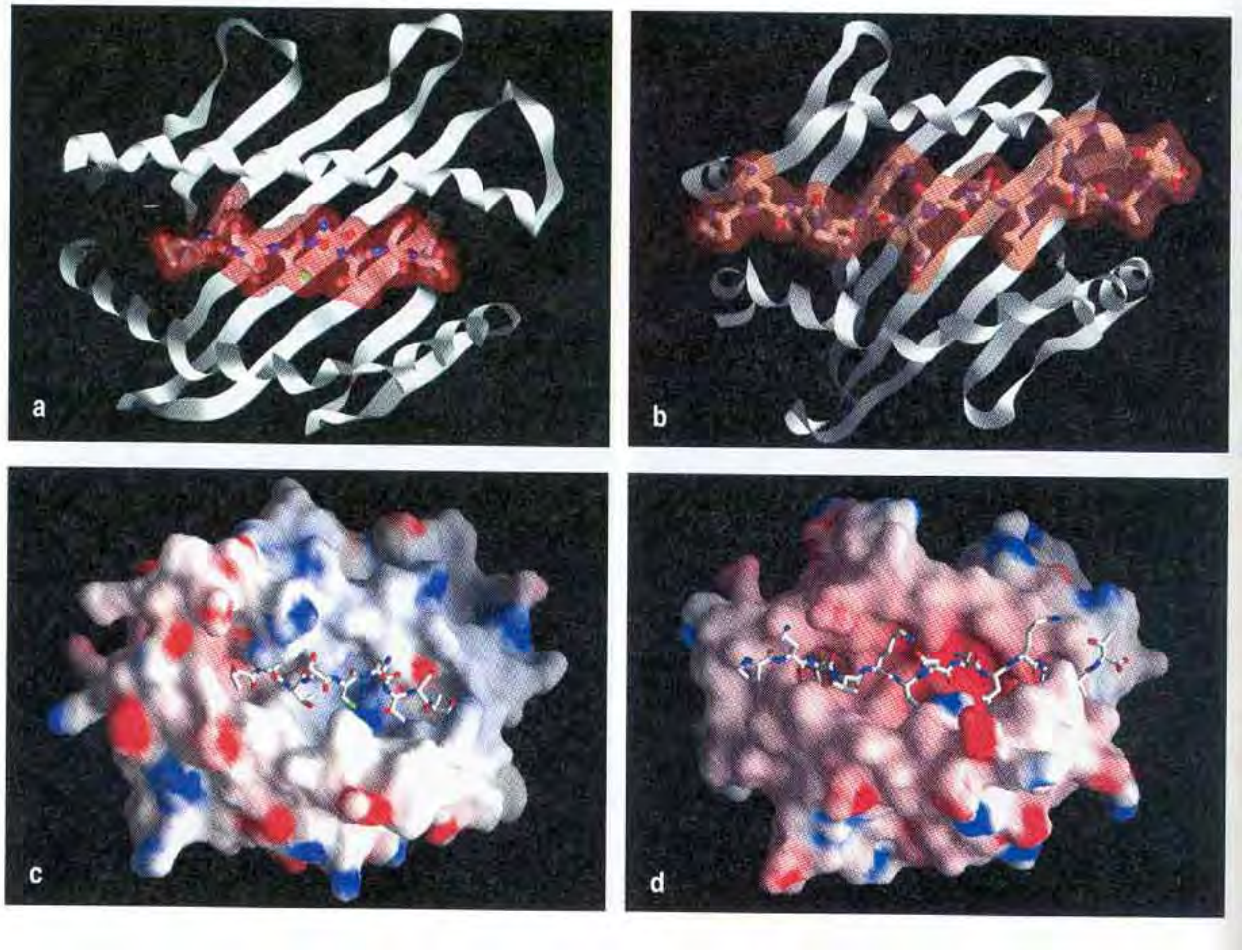
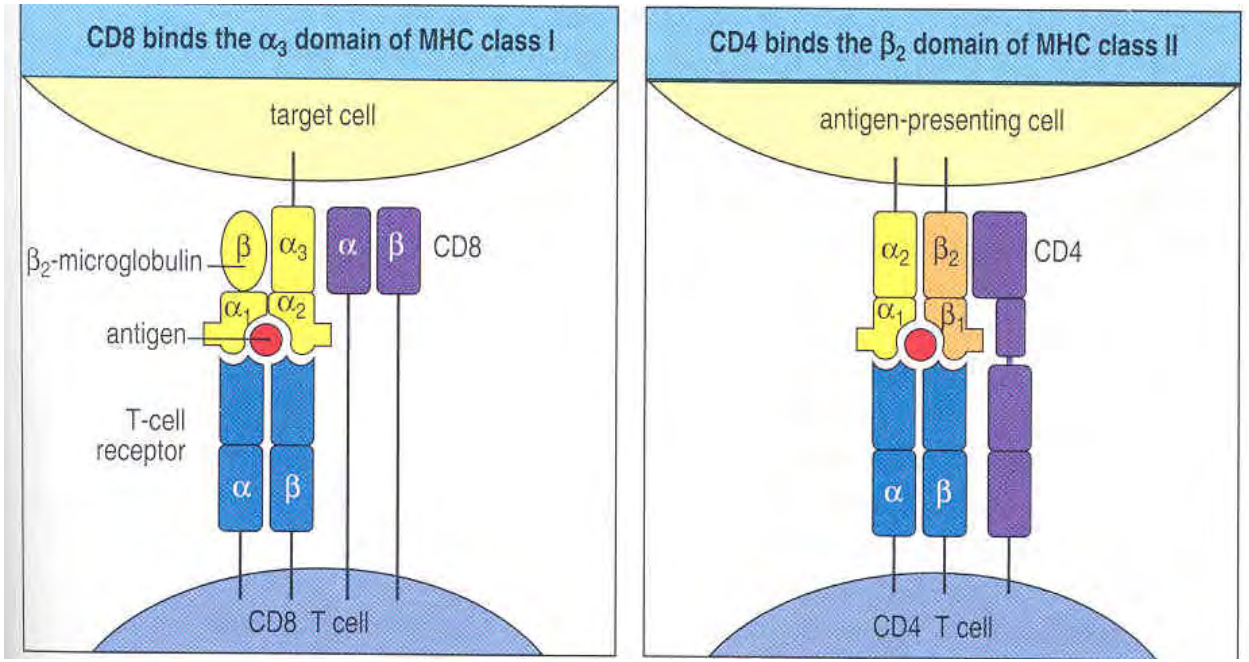


Figure 3-16 Immunobiology, 7ed. (© Garland Science 2008)

Fig. 3.22 MHC molecules bind peptides tightly within the cleft. When MHC molecules are crystallized with a single synthetic peptide antigen, the details of peptide binding are revealed. In MHC class I molecules (panels a and c) the peptide is bound in an elongated conformation with both ends tightly bound at either end of the cleft. In the case of MHC class II molecules (panels b and d), the peptide is also bound in an elongated conformation but the ends of the peptide are not tightly bound and the peptide extends beyond the cleft. The upper surface of the peptide:MHC complex is recognized by T cells, and is composed of residues of the MHC molecule and the peptide. In representations c and d, the electrostatic potential of the MHC molecule surface is shown, with blue areas indicating a positive potential and red a negative potential.





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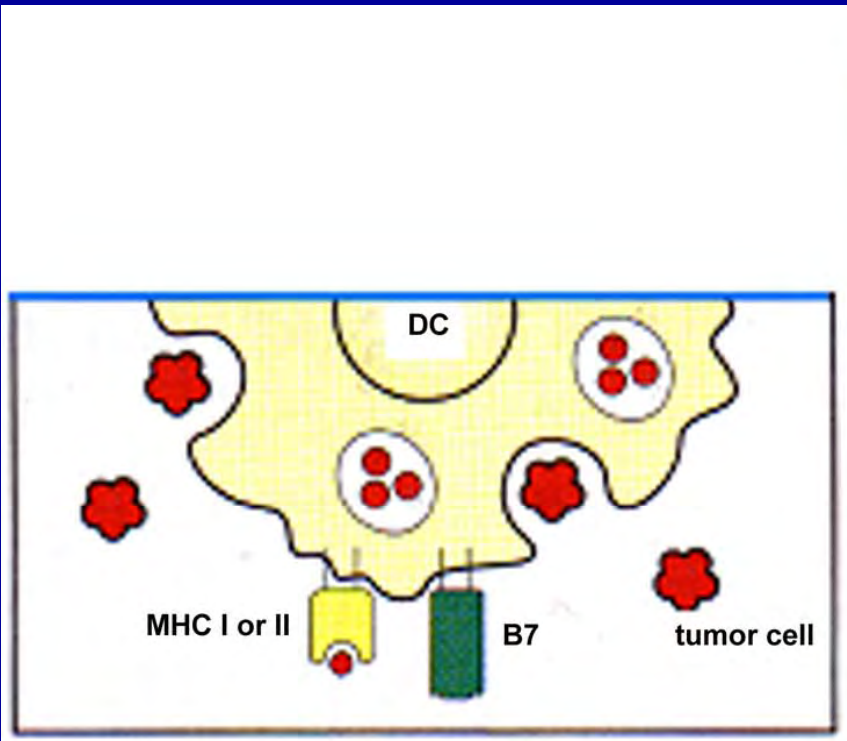
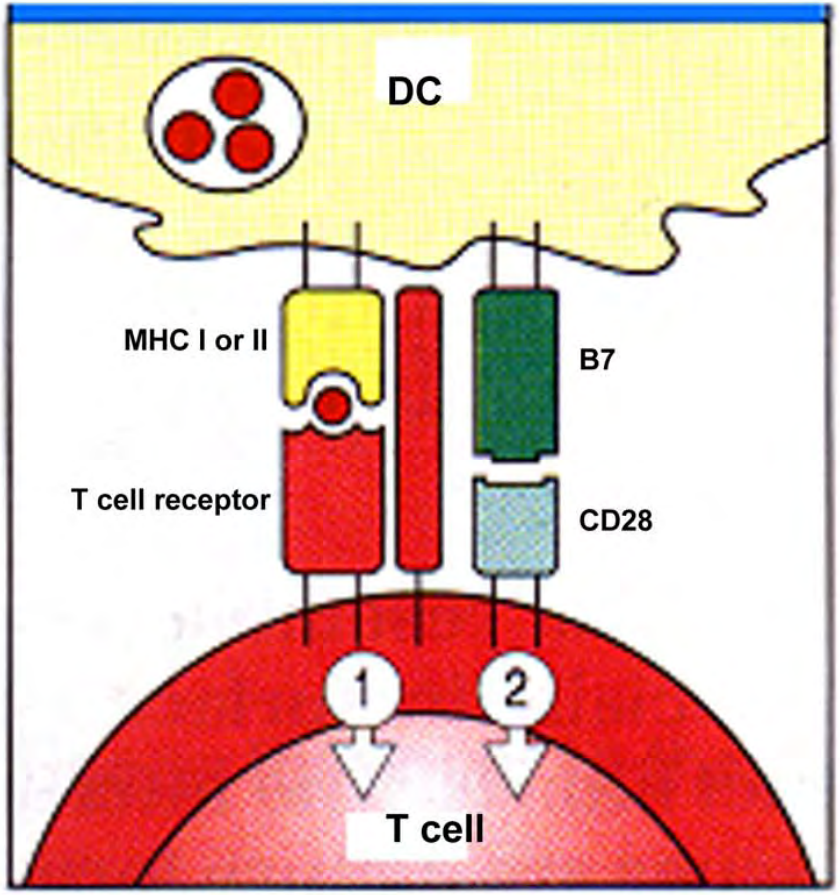
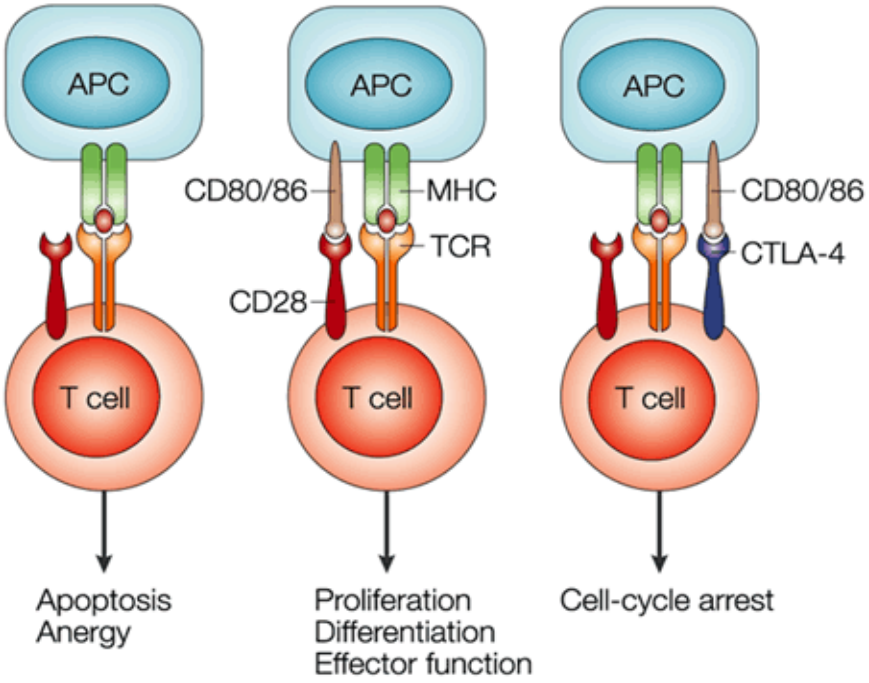
Priming of antigen (tumor)-specific T cells





T-cell Fate under Different Conditions of TCR Engagement*



One signal Two signals

*Alegre, M-L, Frauwirth, KA, Thompson, CB. T-cell regulation by CD28 and CTLA-4, Nat Rev Immunol *1*: 220-228.

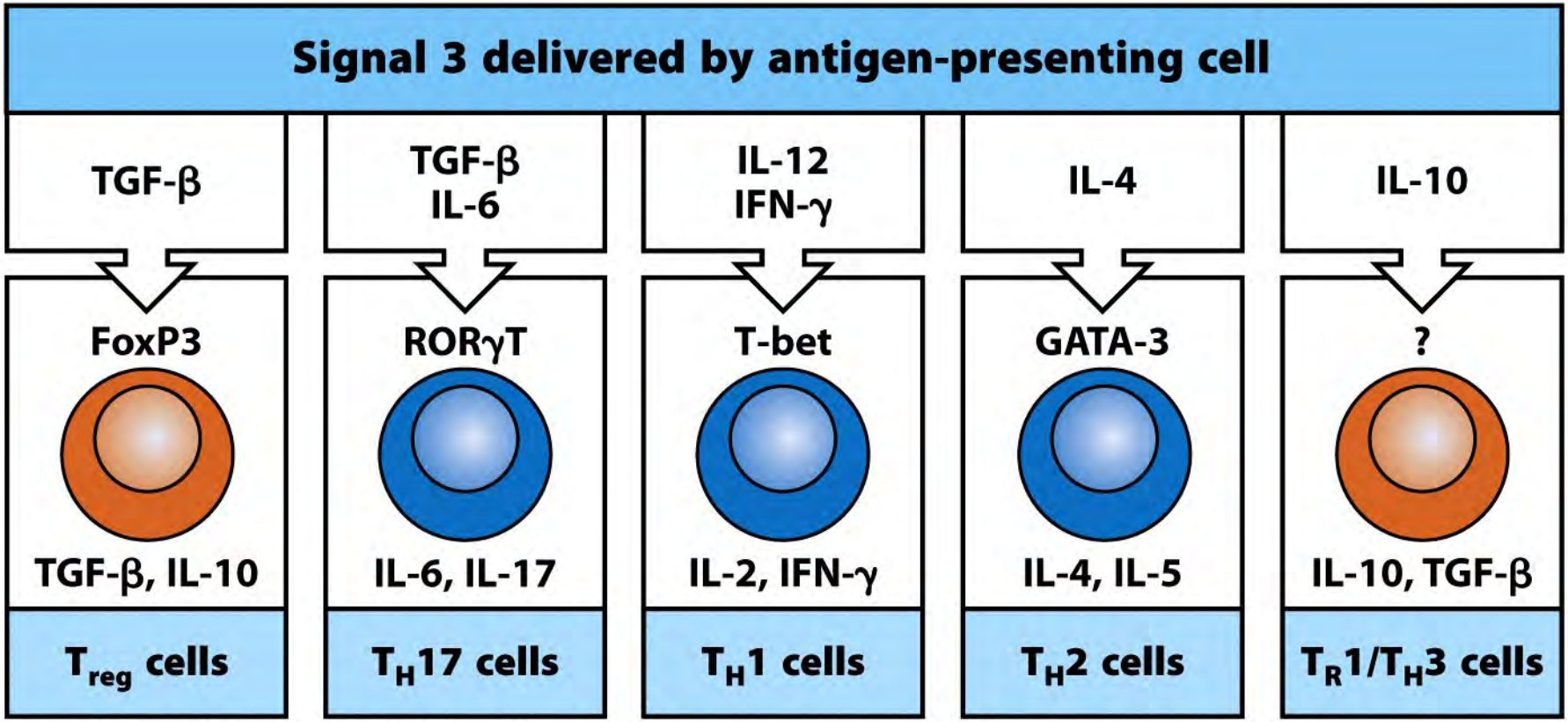
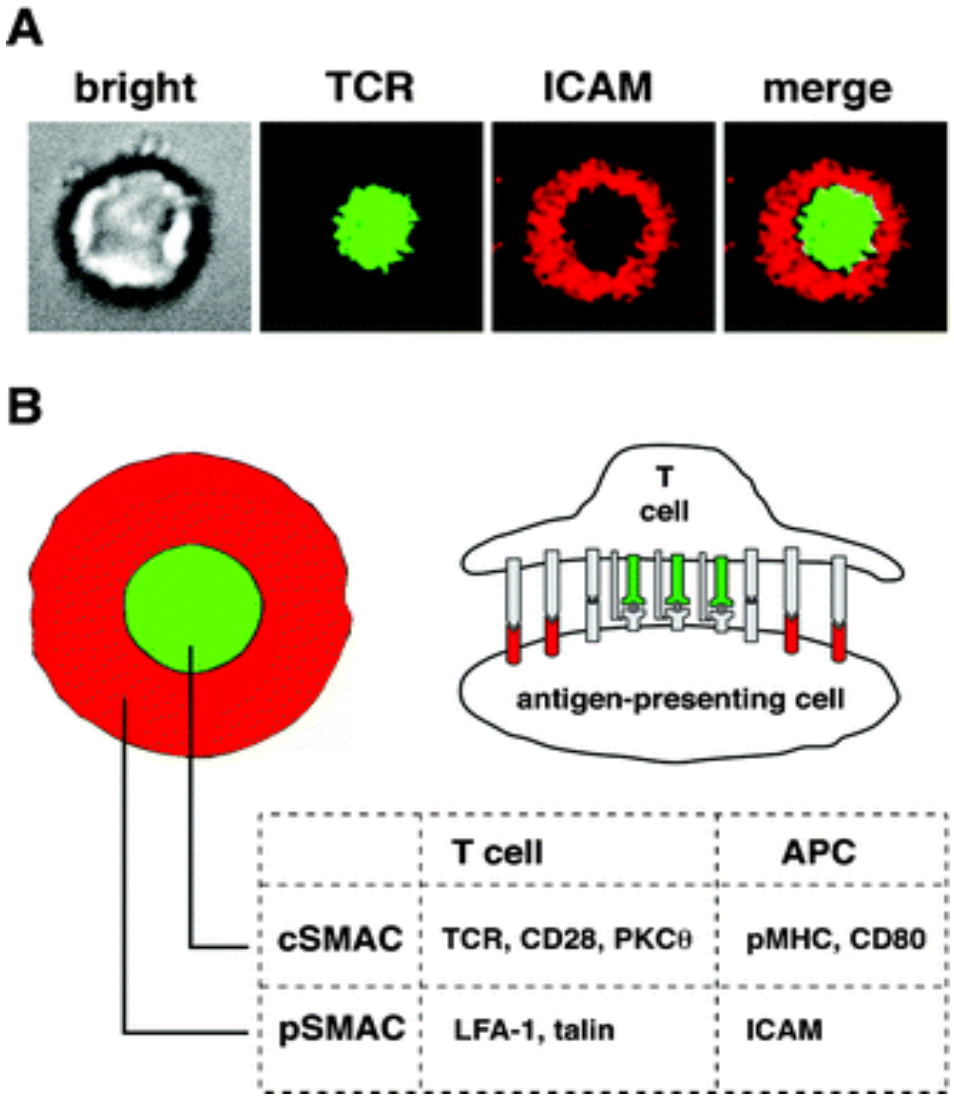


Figure 8-29 Immunobiology, 7ed. (© Garland Science 2008)

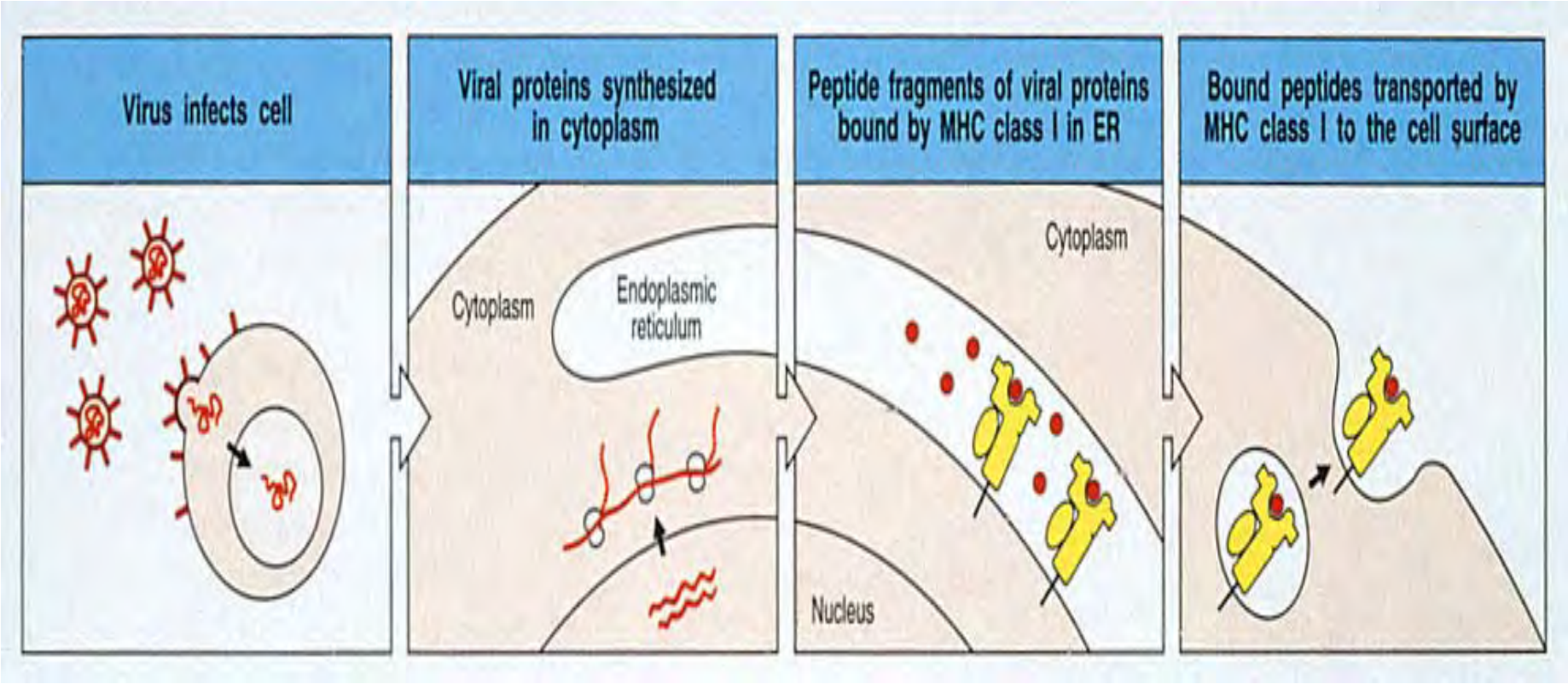
Immunological Synapse



Chem. Soc. Rev., 2007, 36, 46–54

In general:

MHC class I molecules present peptides derived from proteins in the cytosol.



MHC class I pathway for presenting antigens derived from intracellular infections

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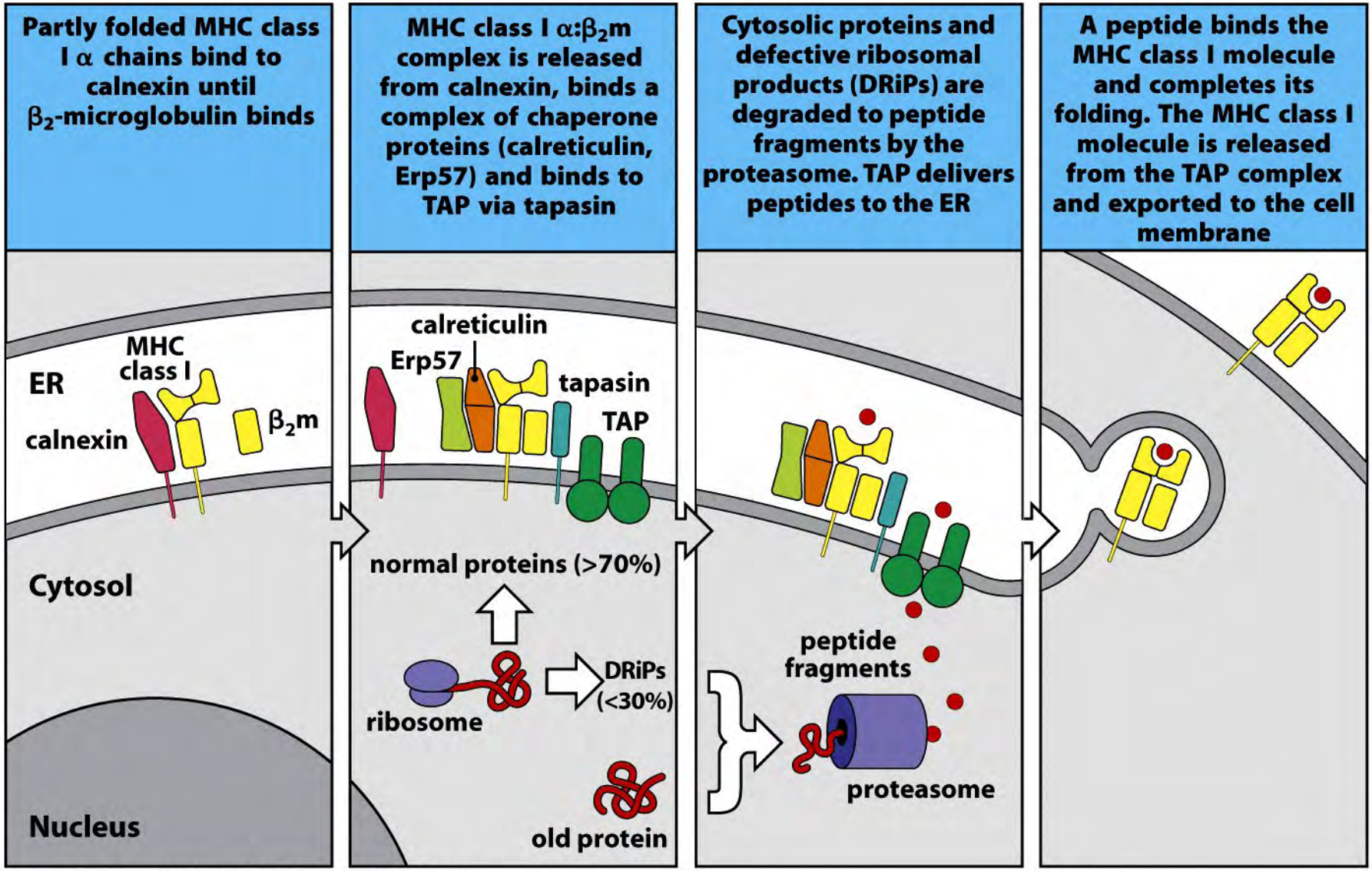


Figure 5-5 Immunobiology, 7ed. (© Garland Science 2008)

Heath, William R., Belz, Gabrielle T., Behrens, Georg M. N., Smith, Christopher M., Forehan, Simon P., Parish, Ian A., Davey, Gayle M., Wilson, Nicholas S., Carbone, Francis R. & Villadangos, Jose A. Cross-presentation, dendritic cell subsets, and the generation of immunity to cellular antigens. *Immunological Reviews* **199** (1), 9-26.

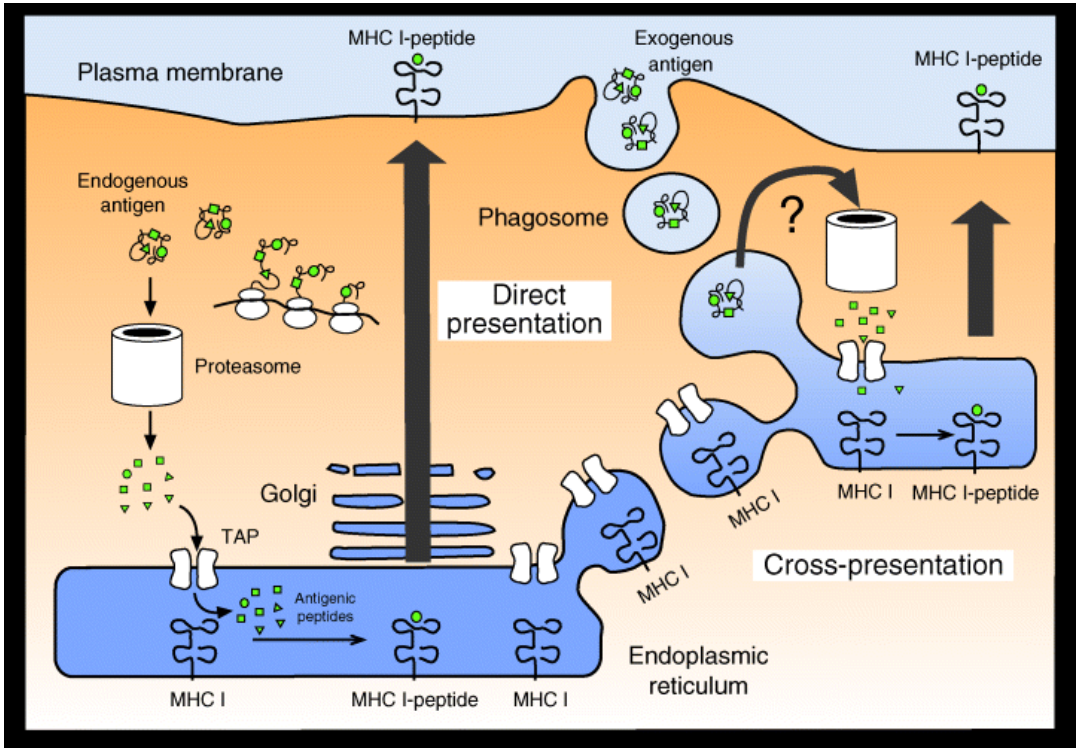
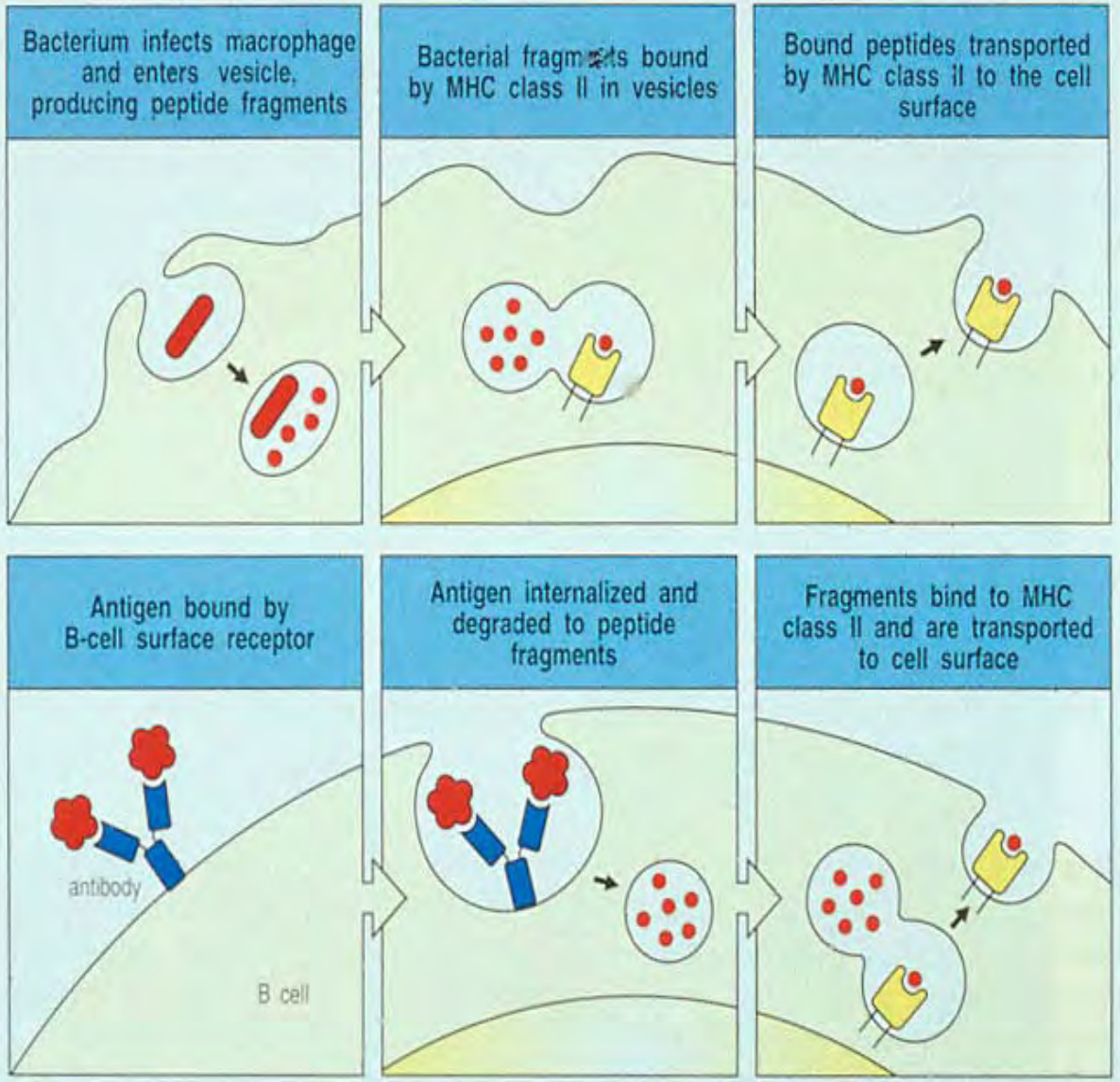


Fig. 1. Major histocompatibility complex (MHC) class I presentation pathways. Direct presentation involves the processing of endogenously synthesized antigens by the proteasome to break them down into peptides that are transported by the transporter associated with antigen presentation (TAP) complex into the endoplasmic reticulum (ER) for loading onto newly synthesized MHC class I molecules. These MHC class I molecules are then transported through the Golgi to the cell surface. Recent evidence (1–3) suggests that cross-presentation may involve the fusion of ER with early phagosomes to form organelles with all the required class I-processing machinery. Phagocytosed proteins are retrotransported out of the phagosome to be degraded by closely associated proteasomes. Peptides are then transported back into the phagosome by the TAP complex and loaded onto newly formed, or perhaps recycled, MHC class I molecules for transport to the cell surface.

Fig. 1.27 **MHC class II molecules present antigen originating in intracellular vesicles.** Some bacteria infect cells and grow in intracellular vesicles. Peptides derived from such bacteria are bound by MHC class II molecules and transported to the cell surface (top row). MHC class II molecules also bind and transport peptides derived from antigen that has been bound and internalized by B-cell antigen receptor-mediated endocytosis into intracellular vesicles (bottom row).



The MHC class II pathway for presenting antigens derived from extracellular infections.

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Generation of Class II MHC-binding peptides

Extracellular pathogens taken up by phagocytosis are degraded into peptides in the endosome and phagolysosome

Newly synthesized MHC class II molecules in the ER are prevented from binding peptides in the ER due to their association with the Invariant chain (IC) which occupies the peptide-binding site

The IC-bound MHC class II is transported to endocytic vesicles where the IC is degraded permitting binding of pathogen-derived peptides to the MHC class II molecule

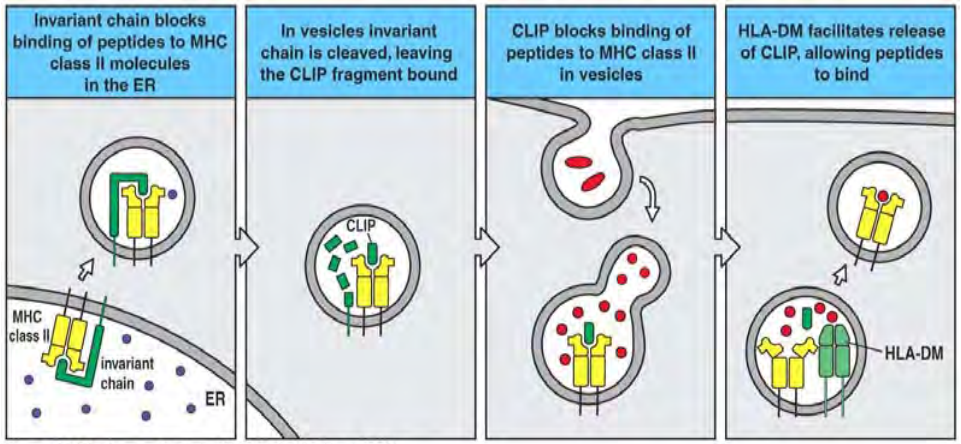

Figure 3-20 The Immune System, 2/e (© Garland Science 2005)

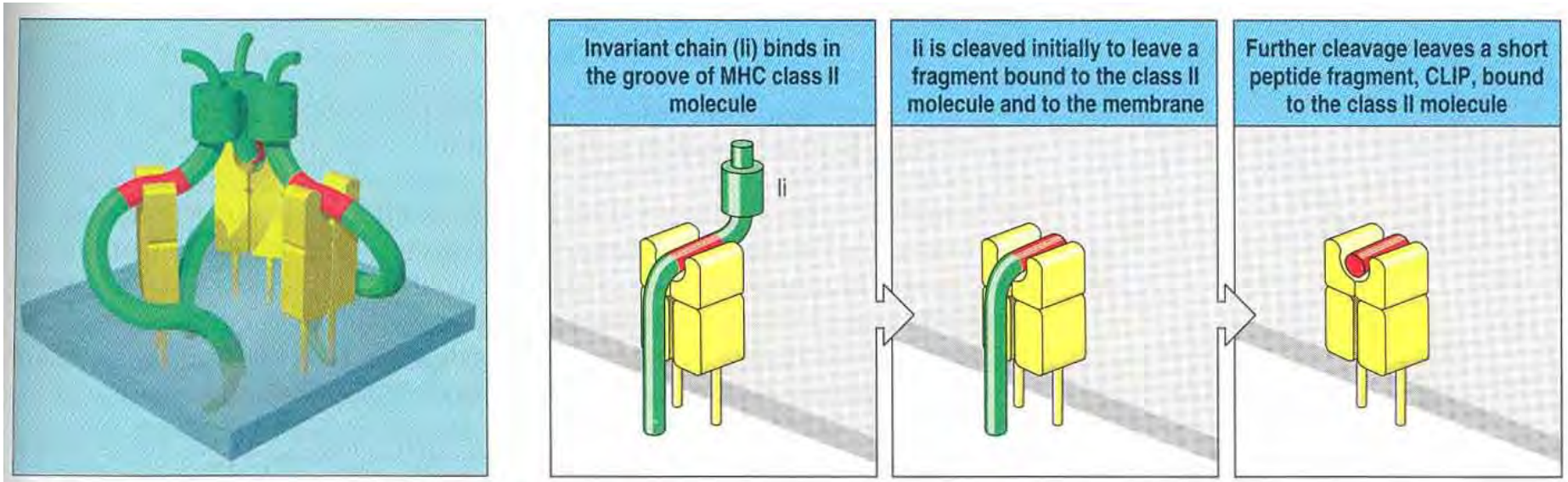

Fig. 5.7 The invariant chain is cleaved to leave a peptide fragment, CLIP, bound to the MHC class II molecule. A model of the trimeric invariant chain bound to MHC class II α:β heterodimers is shown on the left. The CLIP portion is shown in red, the rest of the invariant chain in green, and the MHC class II molecule in yellow. In the endoplasmic reticulum, the invariant chain (Ii) binds to MHC class II molecules with the CLIP section of its polypeptide chain lying along the peptide-binding groove (model and left of three panels). After transport into an acidified vesicle, Ii is cleaved, initially just at one side of the class II molecule (center panel). The remaining portion of Ii (known as the leupeptin-induced peptide or LIP fragment) retains the transmembrane and cytoplasmic segments that contain the signals that target Ii:MHC class II complexes to the endosomal pathway. Subsequent cleavage (right panel) of LIP leaves only a short peptide still bound by the class II molecule; this peptide is the CLIP fragment. Model structure courtesy of P. Cresswell.

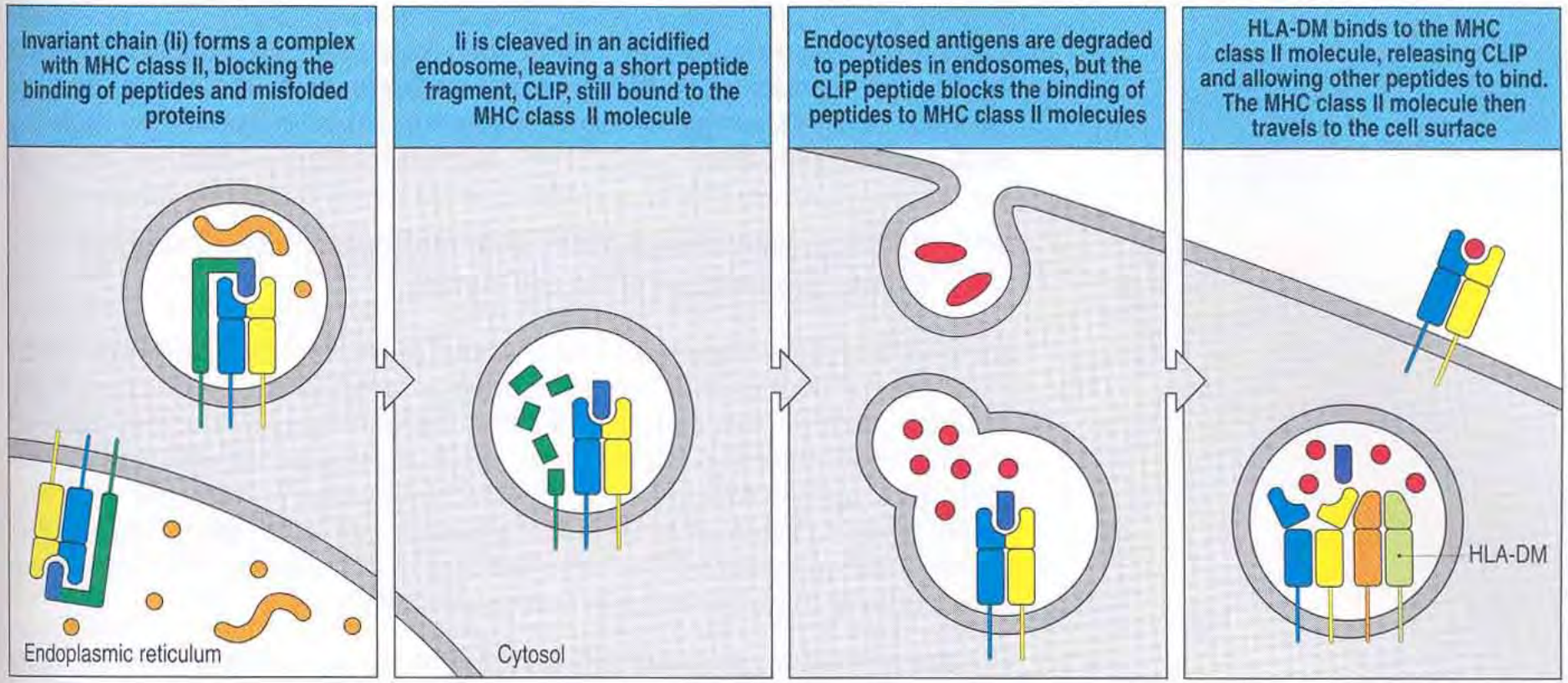

Fig. 5.9 HLA-DM facilitates the loading of antigenic peptides onto class II molecules. The invariant chain binds to newly synthesized MHC class II molecules and blocks the binding of peptides and unfolded proteins in the endoplasmic reticulum and during the transport of the MHC class II molecule into acidified endocytic vesicles (first panel). In such vesicles, proteases cleave the invariant chain, leaving the CLIP peptide bound to the MHC class II molecule (second panel). Pathogens and their proteins are broken down into peptides within acidified endocytic vesicles, but these peptides cannot bind to MHC class II molecules that are occupied by CLIP (third panel). The class II-like molecule, HLA-DM, binds to MHC class II:CLIP complexes, catalyzing the release of CLIP and the binding of antigenic peptides (fourth panel).

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Routes of antigen processing and presentation by dendritic cells

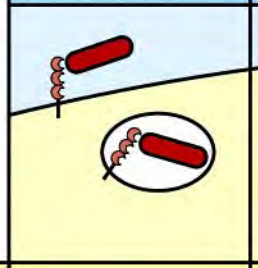
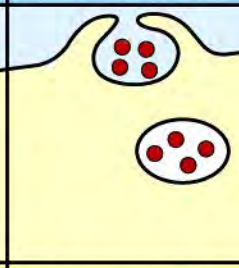
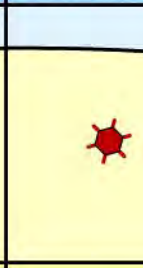
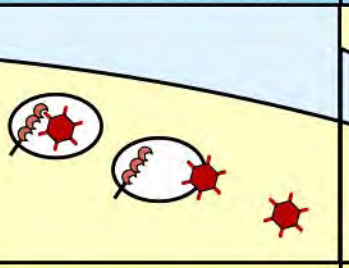
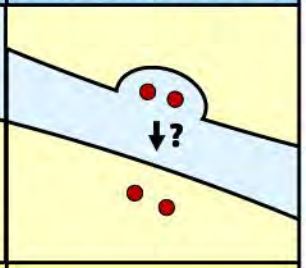
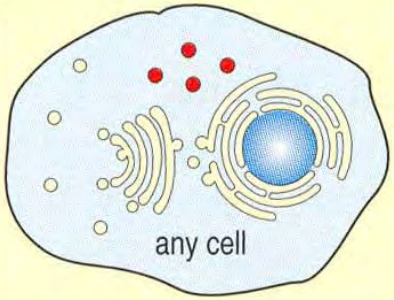
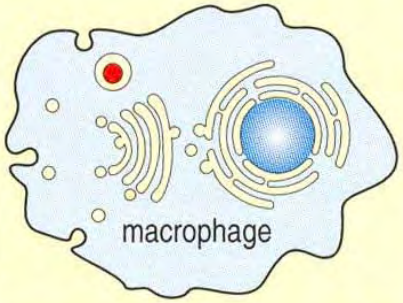
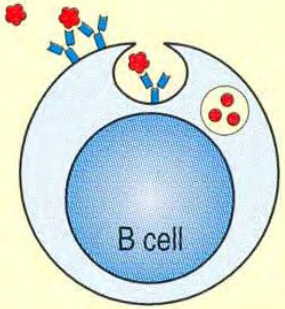
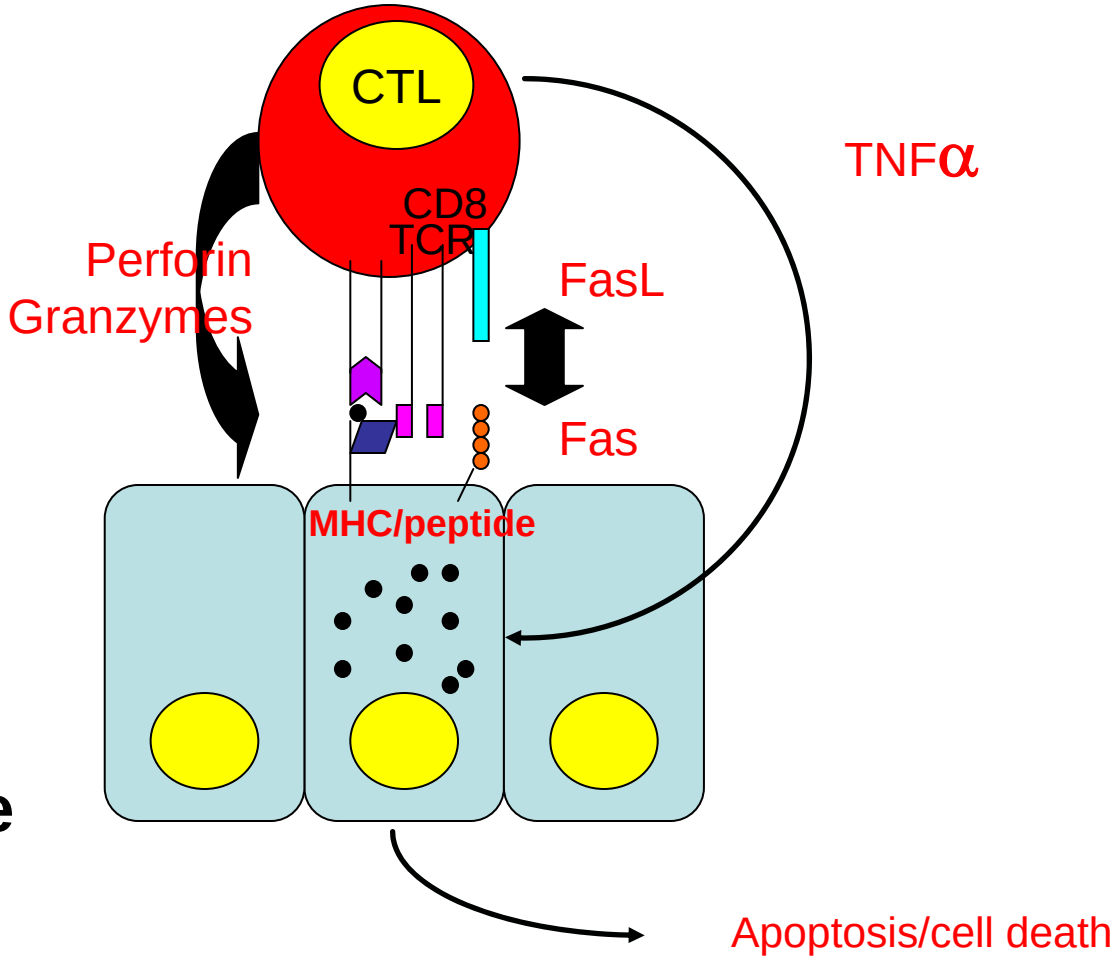
	Receptor-mediated phagocytosis	Macro-pinocytosis	Viral infection	Cross-presentation after phagocytic or macropinocytic uptake	Transfer from incoming dendritic cell to resident dendritic cell
					
Type of pathogen presented	Extracellular bacteria	Extracellular bacteria, soluble antigens, virus particles	Viruses	Viruses	Viruses
MHC molecules loaded	MHC class II	MHC class II	MHC class I	MHC class I	MHC class I
Type of naive T cell activated	CD4 T cells	CD4 T cells	CD8 T cells	CD8 T cells	CD8 T cells

Figure 8-12 Immunobiology, 7ed. (© Garland Science 2008)

	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	CD8 T cells	CD4 T cells	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

How do CTLs kill targets ?



- **Perforin/Granzyme**
- **Fas/FasL**
- **TNFα**

Cytotoxic Proteins

- **Perforin**

  Upon contact with target cell, granule contents are released, perforin polymerizes and forms pores in target cell membrane

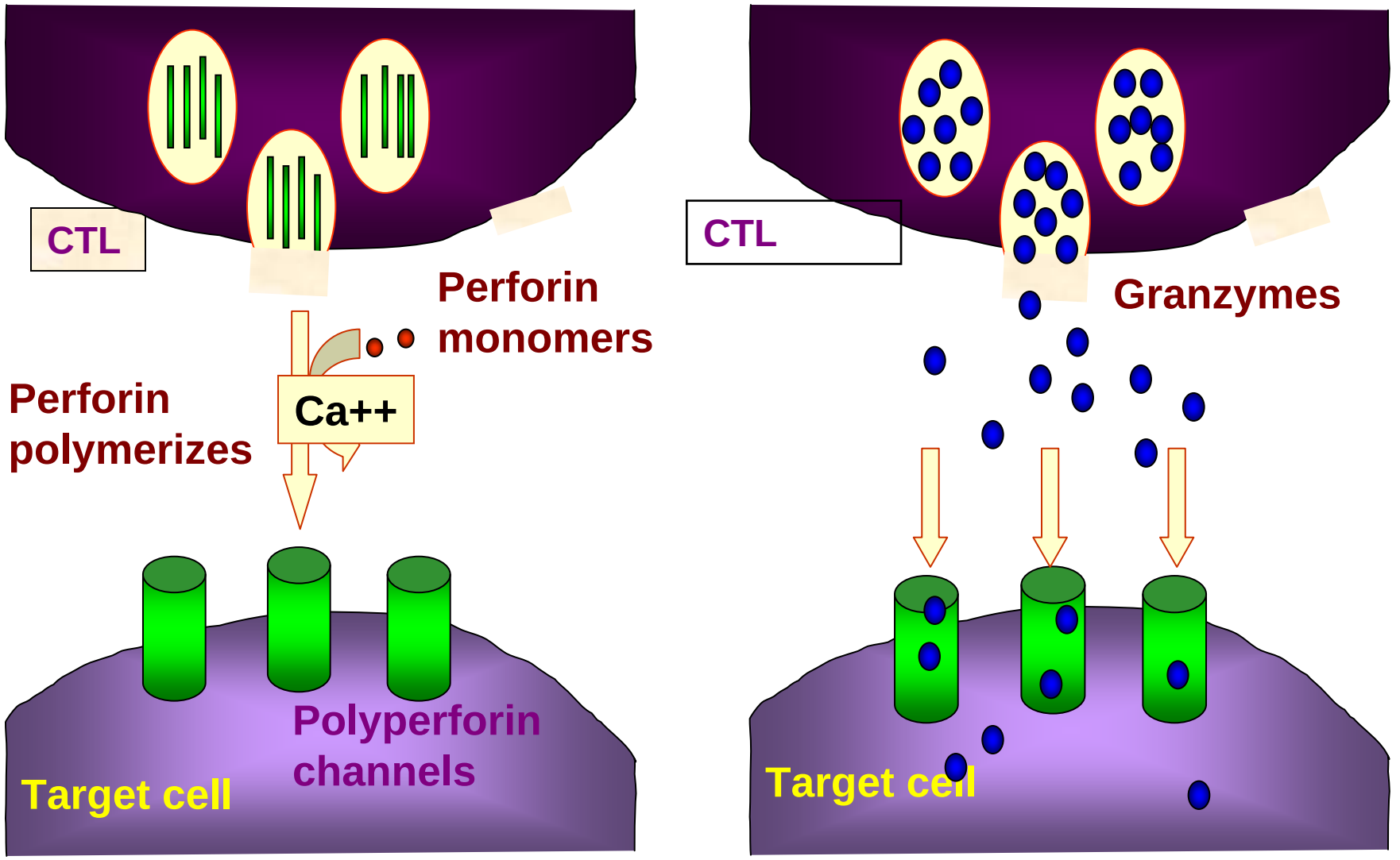
- **Granzymes**

  Granzymes (serine proteases) enter target cell through channel, activate caspases and nucleases, lead to apoptosis of target cell

- **Granulysin**

  also known as NKG5, LAG-2 ..found in granules of NK and T cells, induces apoptosis

Mechanism of Action



http://pathmicro.med.sc.edu

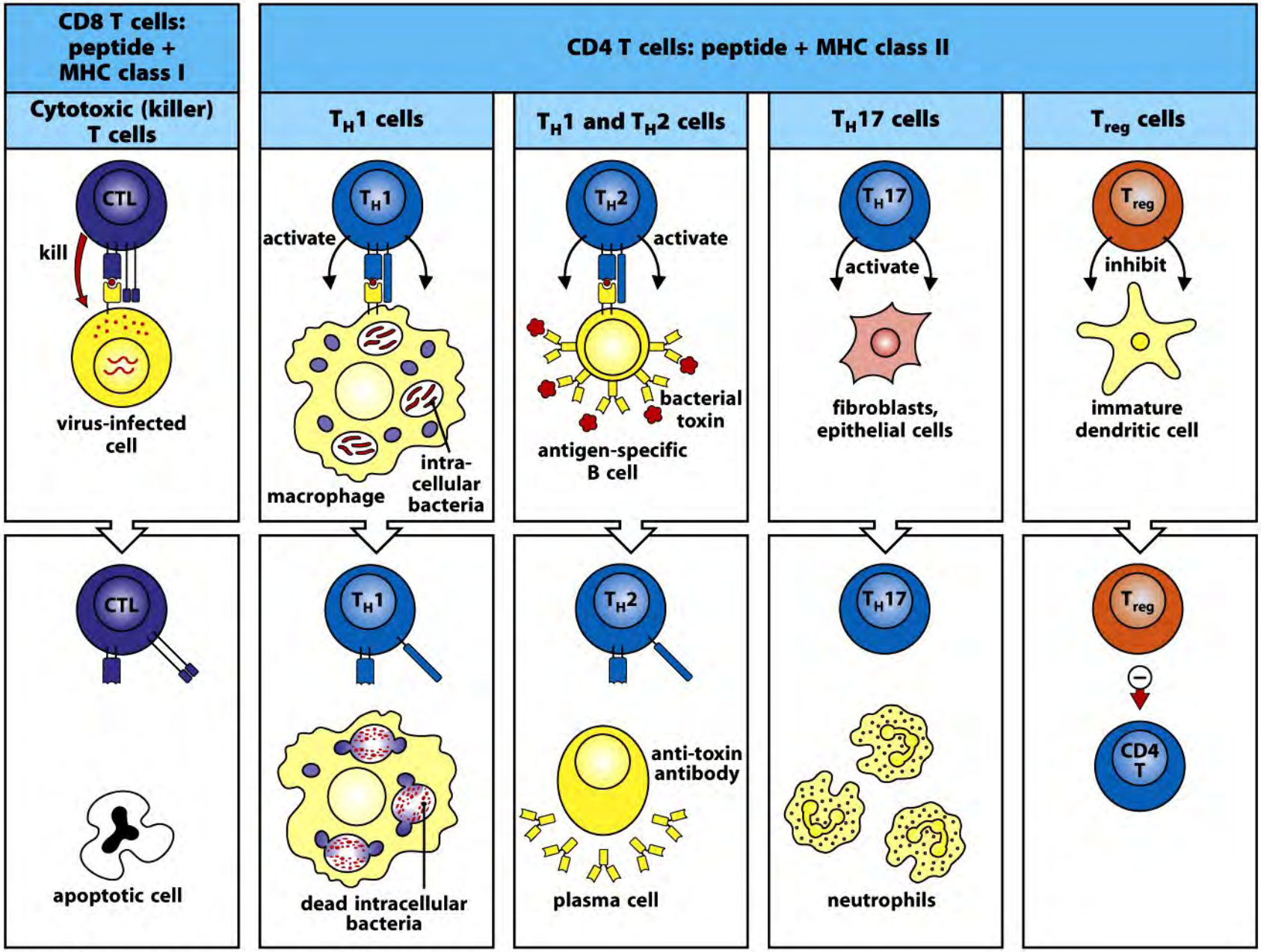


Figure 8-27 Immunobiology, 7ed. (© Garland Science 2008)

THE B CELL RESPONSE

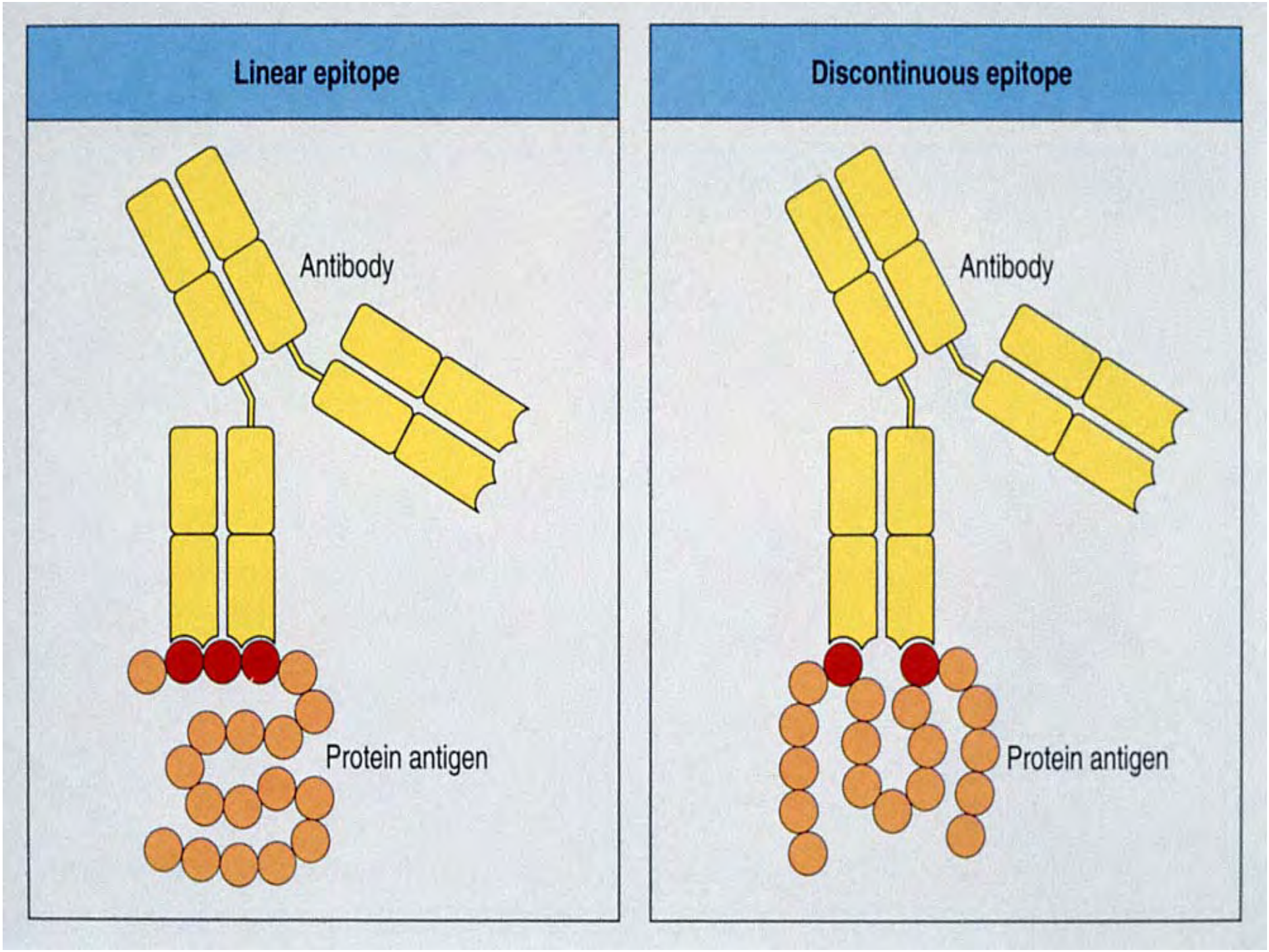
B CELLS AND T CELLS RECOGNIZE ANTIGEN DIFFERENTLY

B cells

- Receptor that binds antigen is surface Ig.
- Binding does not require MHC
- Recognize soluble antigen
- Epitopes are sequential or non-sequential
- Epitopes are accessible (outside) hydrophilic
- Recognize proteins, lipids, carbohydrates, nucleic acids

T cells

- Receptor that binds antigen is TCR
- Binding requires class I and class II MHC
- Recognize processed antigen associated with MHC
- Epitopes are sequential (linear)
- Epitopes are usually internal (amphipathic)
- Recognize only proteins


Linear epitope
Antibody
Protein antigen
Discontinuous epitope
Antibody
Protein antigen

THE ANTIBODY RESPONSE

•In the case of antibody production the following characteristics distinguish **primary** from **secondary** immune responses:

•Secondary response has a shorter lag time and extended plateau and decline of antibody levels.

• Antibody titer is higher in the secondary response (10-1000X).

•IgG is the major antibody class in secondary response whereas IgM is major antibody class in primary response. Sometimes IgG is produced later in a primary response.

•The affinity of binding of antibodies in the secondary response is higher than that of antibodies in the primary response.

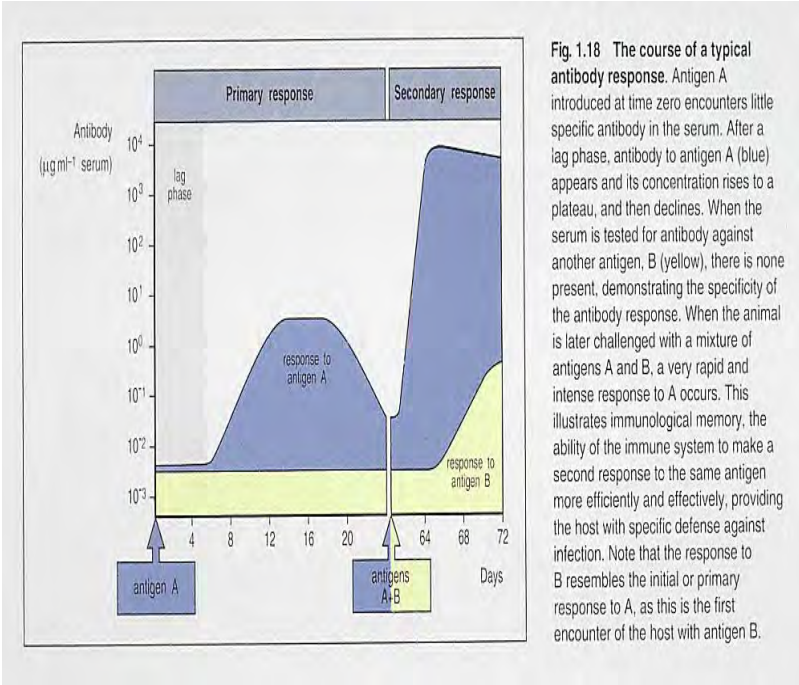
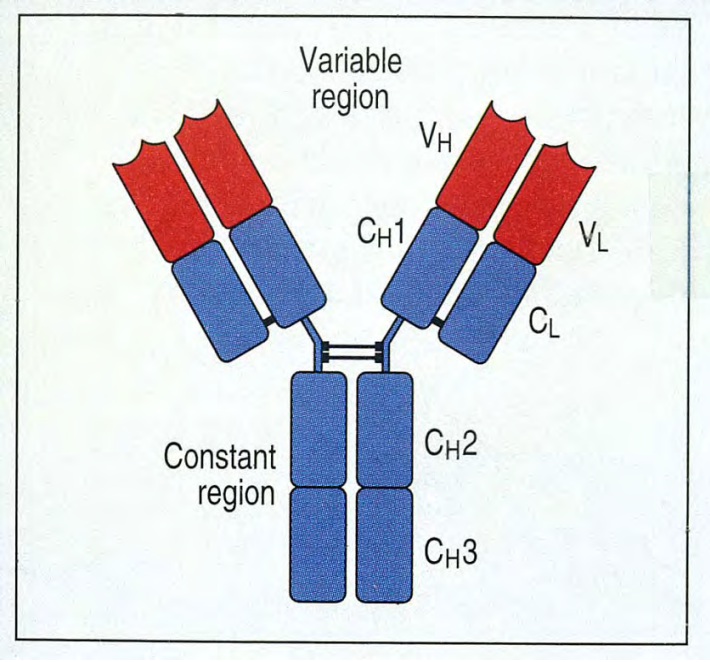


Fig. 1.18 The course of a typical antibody response. Antigen A introduced at time zero encounters little specific antibody in the serum. After a lag phase, antibody to antigen A (blue) appears and its concentration rises to a plateau, and then declines. When the serum is tested for antibody against another antigen, B (yellow), there is none present, demonstrating the specificity of the antibody response. When the animal is later challenged with a mixture of antigens A and B, a very rapid and intense response to A occurs. This illustrates immunological memory, the ability of the immune system to make a second response to the same antigen more efficiently and effectively, providing the host with specific defense against infection. Note that the response to B resembles the initial or primary response to A, as this is the first encounter of the host with antigen B.

Fundamental Structure of Immunoglobulins

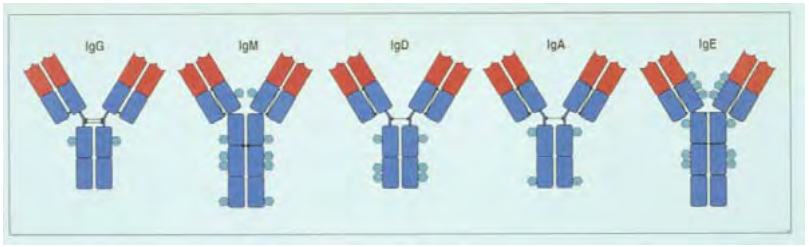
- The fundamental structure of immunoglobulins:
- Two identical Heavy (H) chains and two identical Light (L) chains.
- Each consists of variable (V) and constant (C) domains.
- All mammalian species produce only two types of L chains-kappa (κ) or lambda (λ).
- The L chains of any one immunoglobulin molecule are always either κ or λ.
- Inter- and intra-chain disulfide (S-S) bonds.
- Two antigen-binding sites (Fab).
- Hinge region - susceptible to protease digestion



Structural features of the immunoglobulin isotypes

	IgM	IgG	IgA	IgD	IgE
Size	900K	150K	165K	180K	200K
# monomers	5	1	2	1	1
Valence	10(5)	2	4	2	2
# C_H domains	4	3	3	3	4
Additional peptides	J (15K)		J,S (70K)		
% of total Ig in serum	10	70-75	15-20	<1	trace

Structural features Of an immunoglobulin determines its biological functions



The structural organization of immunoglobulin isotypes

RECOGNITION AND EFFECTOR MECHANISMS OF ADAPTIVE IMMUNITY

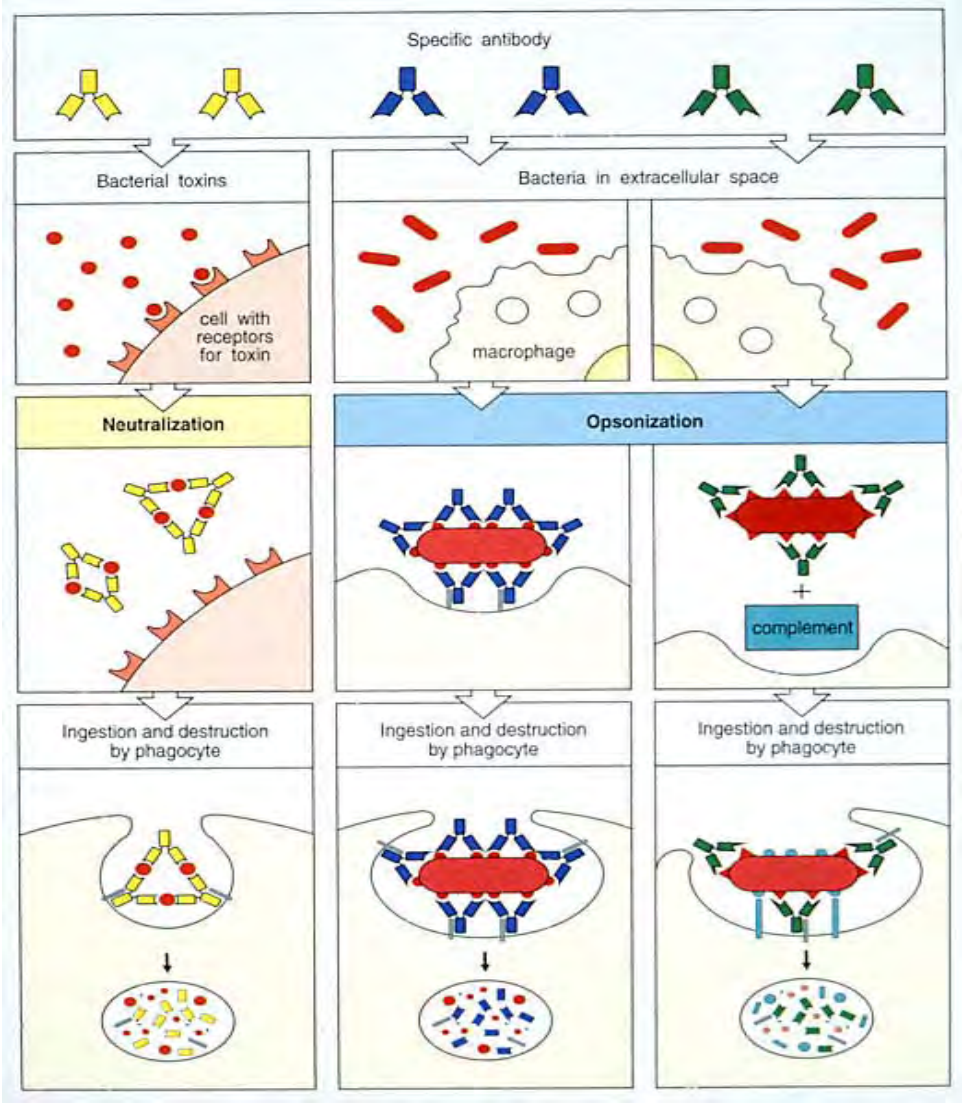
Extracellular pathogens and their toxins are eliminated by antibodies (humoral immunity)

▪**Antibodies can protect the host from pathogens by**:

• i. Neutralization of bacteria and their toxic products.

•ii. Opsonization of pathogens to facilitate phagocyte uptake and destruction.

•iii. Complement activation to cause bacterial destruction



Functional activity	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	–	++	++	++	++	++	–
Opsonization	+	–	+++	*	++	+	+	–
Sensitization for killing by NK cells	–	–	++	–	++	–	–	–
Sensitization of mast cells	–	–	+	–	+	–	–	+++
Activates complement system	+++	–	++	+	+++	–	+	–

Distribution	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Transport across epithelium	+	–	–	–	–	–	+++ (dimer)	–
Transport across placenta	–	–	+++	+	++	+/–	–	–
Diffusion into extravascular sites	+/–	–	+++	+++	+++	+++	++ (mono-mer)	+
Mean serum level (mg ml^{-1})	1.5	0.04	9	3	1	0.5	2.1	3×10^{-5}

Figure 9-19 Immunobiology, 7ed. (© Garland Science 2008)

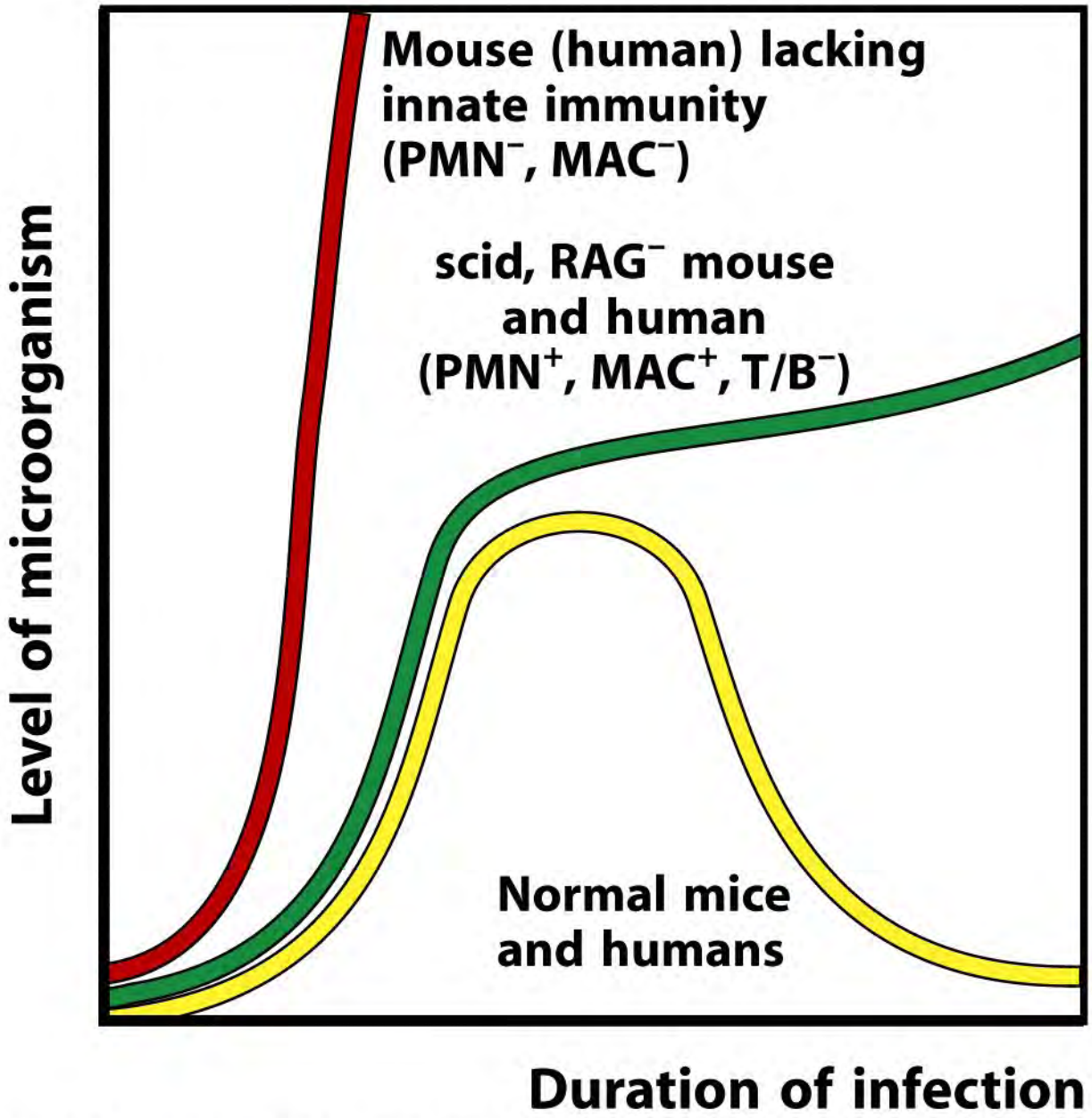
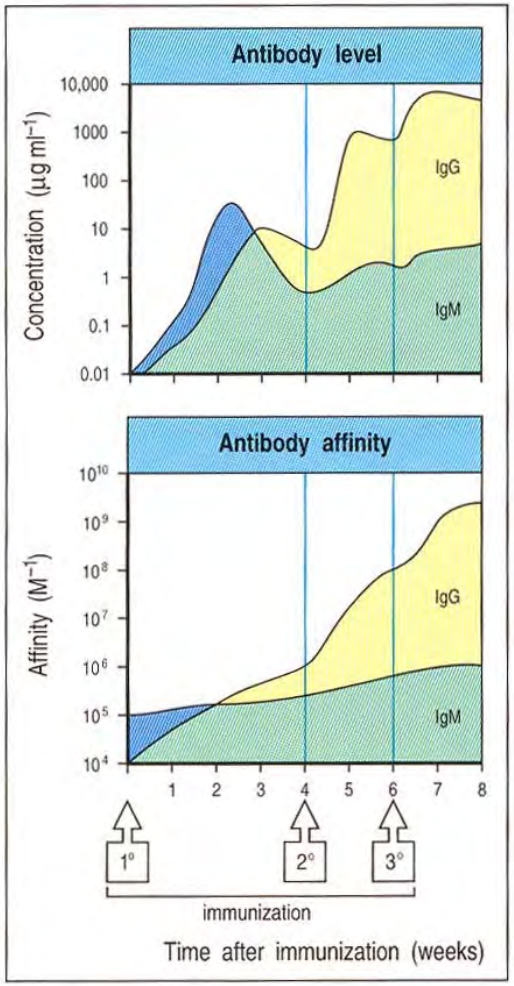


Figure 10-3 Immunobiology, 7ed. (© Garland Science 2008)

	Source of B cells	
	Unimmunized donor Primary response	Immunized donor Secondary response
Frequency of specific B cells	$1:10^4 - 1:10^5$	$1:10^3$
Isotype of antibody produced	IgM > IgG	IgG, IgA
Affinity of antibody	Low	High
Somatic hypermutation	Low	High

The generation of secondary antibody responses from memory B cells is distinct from the generation of the primary antibody response.



The affinity as well as the amount of antibody increases with repeated immunization.

Immunobiology, 5th ed (© Garland Science, 2005)