

Society for Immunotherapy of Cancer (SITC)

Immunology 101 for the Non-Immunologist

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Advances in Cancer Immunotherapy™ - Texas
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Society for Immunotherapy of Cancer

Objectives

- Describe the different functions of the immune system
- Understand differences in two major types of immune responses (innate and adaptive)
- Define the immune cells that mediate and regulate immune responses
- Explain how immune cells recognize and respond to foreign entities
- Relate basic concepts of immunology to its applications in immunotherapy

Outline

- I. General function and responses of immune system**
- II. Structure of the immune system
(cells, molecules, organs)**
- III. Innate Immune Responses**
- IV. Adaptive Immune Responses**
- V. Role of immune system in disease**

Function of Immune Responses

- **Immune Recognition**-detects the presence of harmful and foreign entities.
- **Immune Effector Function**- contains and eliminate infection.
- **Immune Regulation**-controls immune response to prevent damage.
- **Immunological Memory**- protects against recurrent exposures to the same foreign entity.

Two General Types of Immune Responses

Innate

- Always available
- First line of defense
- Specific for general types of pathogens but not an individual pathogens
- Does not lead to lasting immunity

Adaptive

- Develops during lifetime as an adaptation to infections with pathogens

- Is antigen specific (ex. H1N1 strain of flu but not all Influenza strains)
- Confers long lasting immunity

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Immune cells are derived from stem cells in the bone marrow

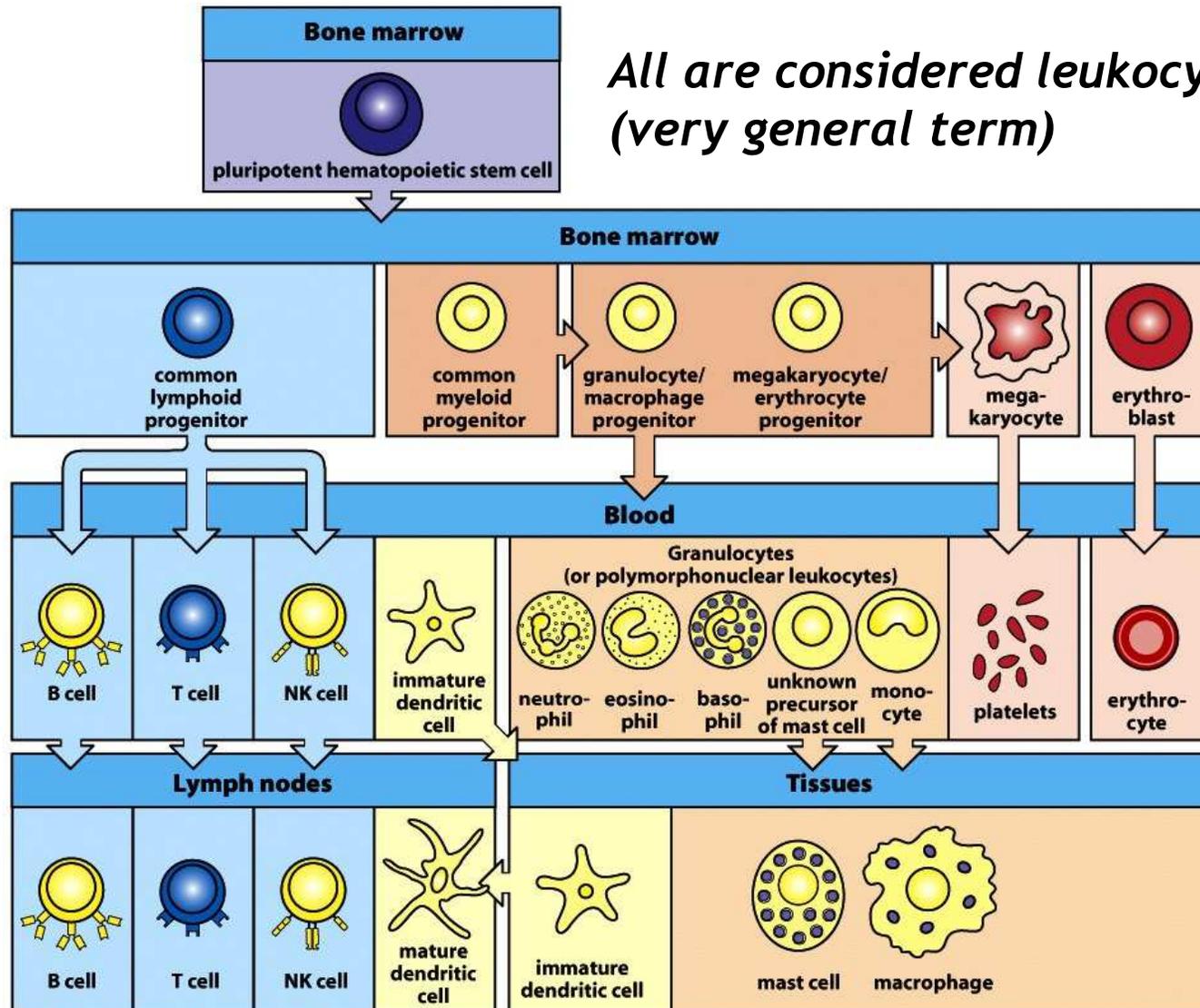
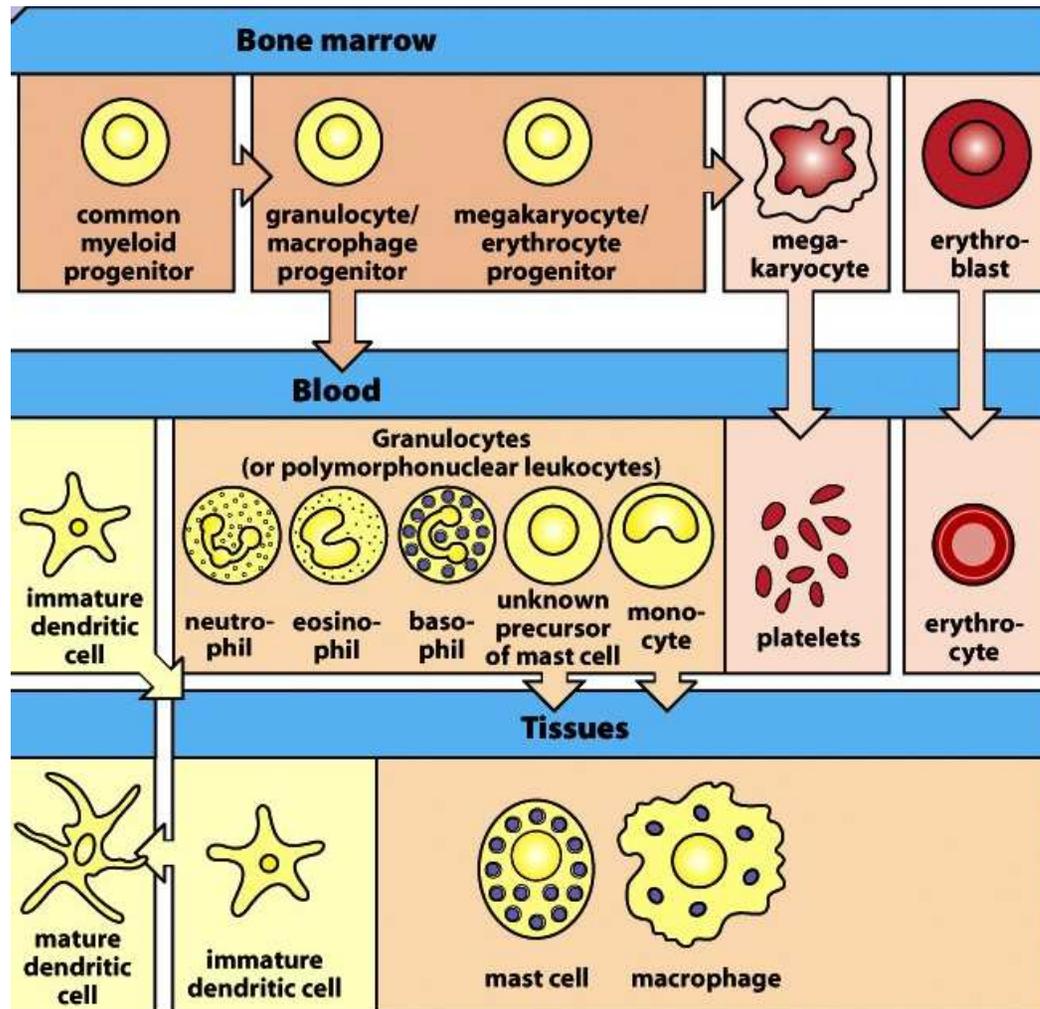


Figure 1-3 Immunobiology, 7ed. (© Garland Science 2008)

Myeloid cells



- Derived from a common progenitor
- Comprises most of the cells of the innate immune system

Granulocytes

Short lived cells that possess granules containing degradative enzymes and anti-microbial substances

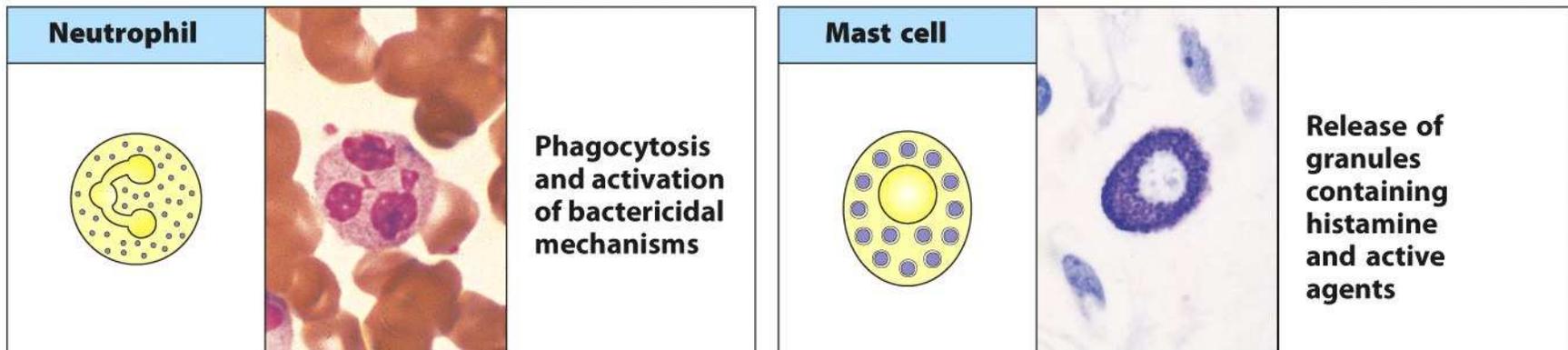
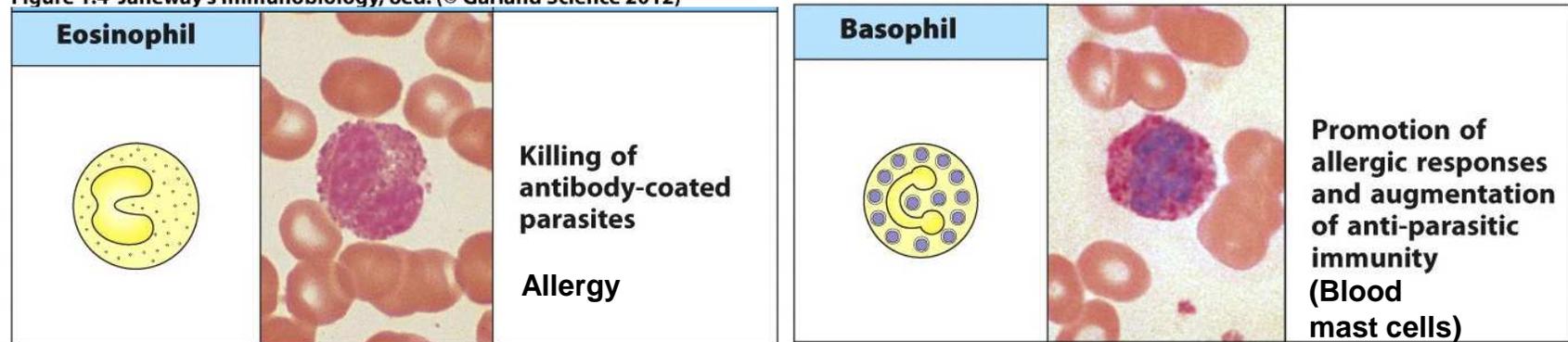


Figure 1.4 Janeway's Immunobiology, 8ed. (© Garland Science 2012)



Neutrophils, Eosinophils, Basophils are sometimes referred to as polymorphonuclear leukocytes (PMNs)

Phagocytes

Neutrophils, Macrophages, and Dendritic Cells

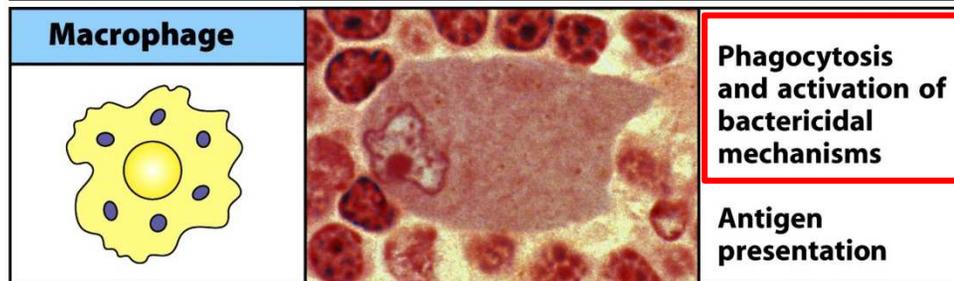


Figure 1-4 part 1 of 6 Immunobiology, 7ed. (© Garland Science 2008)

Reside in tissues



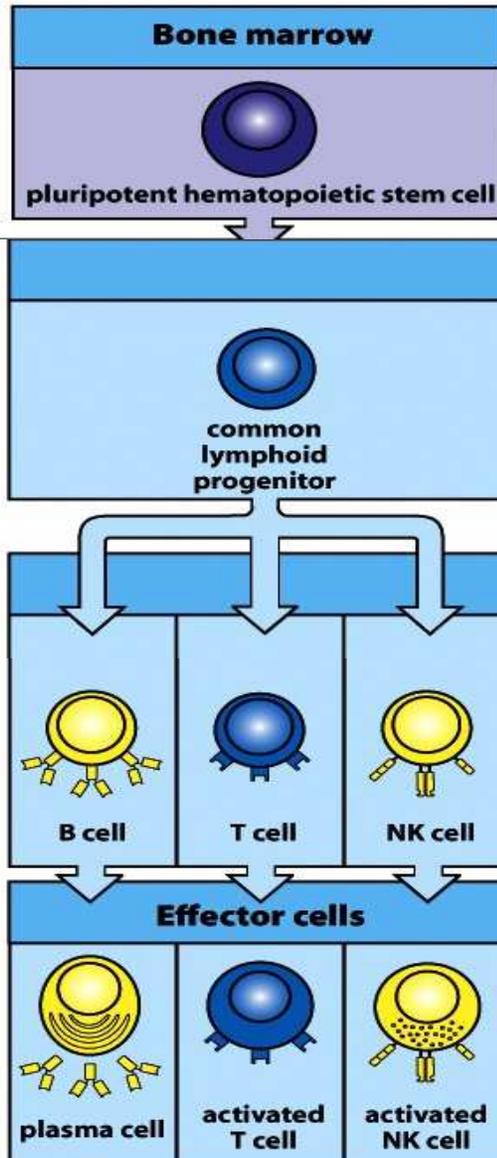
Figure 1-4 part 2 of 6 Immunobiology, 7ed. (© Garland Science 2008)

(small particles)

Main role is not clearance of pathogen but rather adaptive immune cell activation

Dendritic cells and macrophages are two types of professional antigen presenting cells (APCs)

Lymphocytes



B cells

- produce antibodies (Ab) that bind antigens

T cells

- recognize processed antigens presented on cell surfaces
- kill (CD8 T cells)
- produce cytokines (CD4 T cells)

Natural Killer (NK) cells

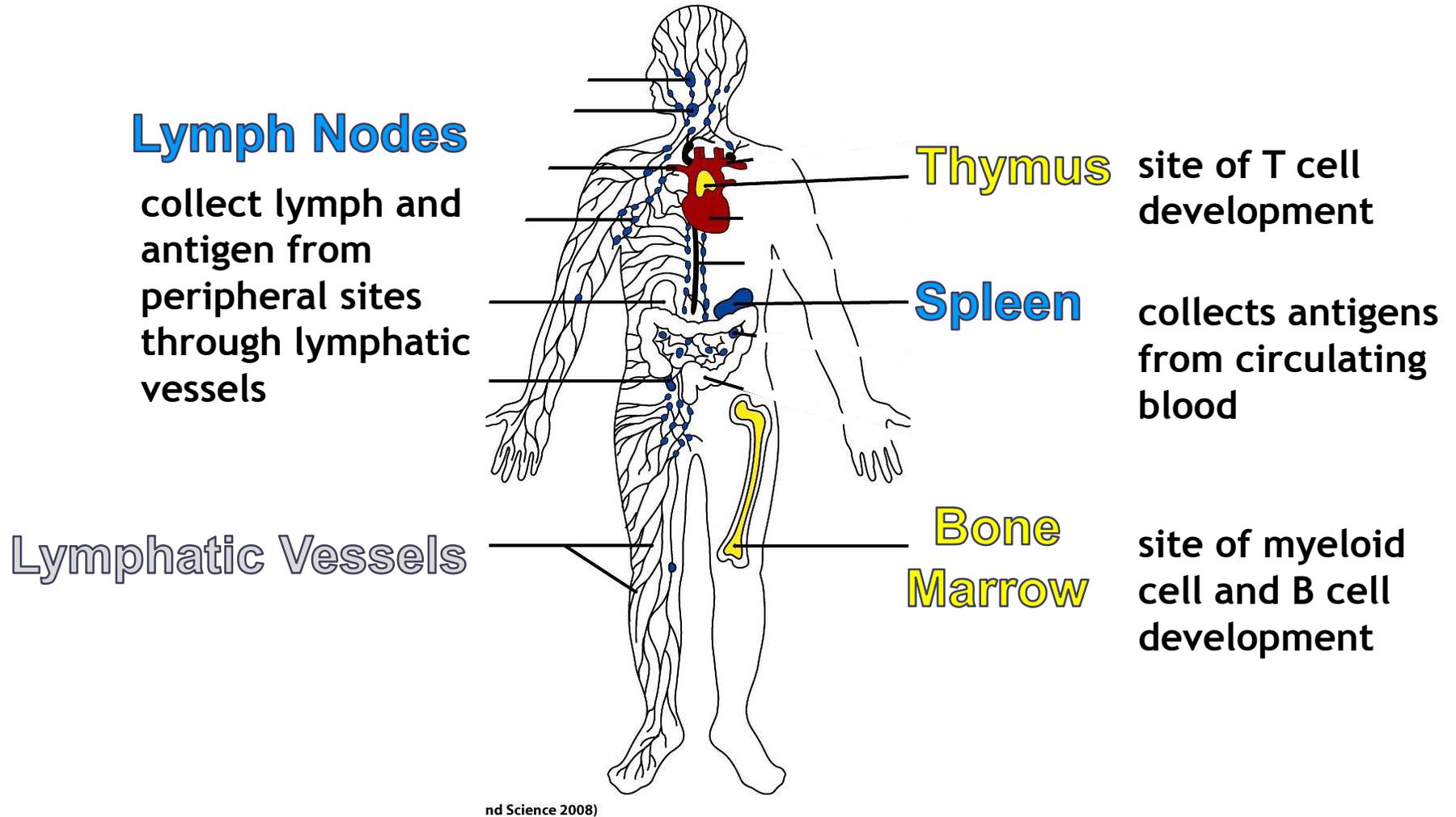
- kill tumor and virus-infected cells

Adaptive
(recognize very specific antigens)

Innate
(recognize general features)

Figure 1-3 Immunobiology, 7ed. (©

Primary and Secondary Lymphoid Organs



Note: Immune cells and lymphoid aggregates are also found throughout the body

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Infectious agents first activate innate immune cells resulting in an inflammatory response

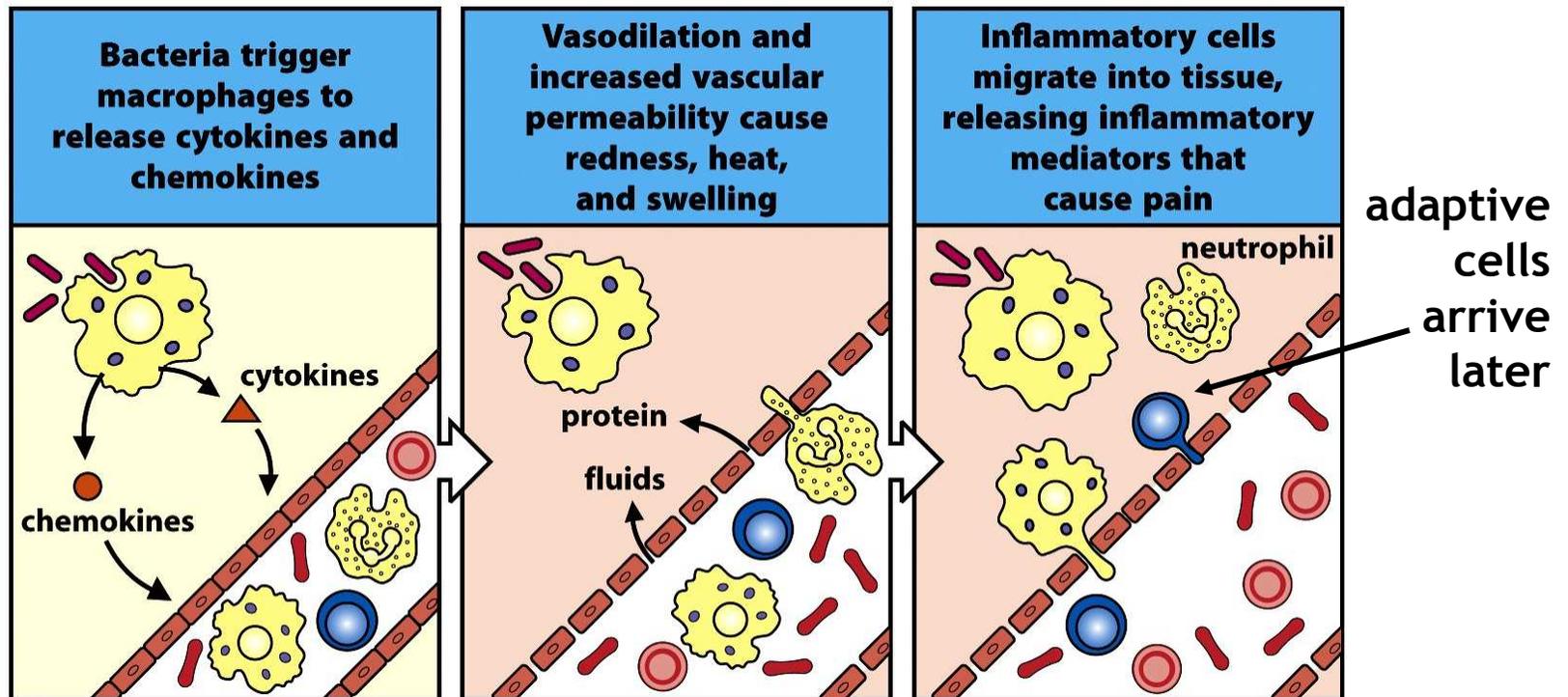


Figure 1-8 Immunobiology, 7ed. (© Garland Science 2008)

Cytokines-proteins that immune cells use to communicate/regulate other immune cells, not all cytokines are inflammatory

Chemokines- group of cytokines that attract other immune cells

Innate responses are initiated upon recognition of “danger signals” by pattern recognition receptors (PRRs)

“Danger Signals”

- A. Pathogen associated molecular patterns (PAMPs)
- *Bacteria proteins*
 - *Viral DNA/RNA*
- B. Damage-associated molecular patterns (DAMPs)
- *Products of dying cells*

Receptors can be on the cell surface or intracellular

Types of PRRs

- Toll like receptors (TLR)
- C type lectin receptors
- NOD-like receptors (NLRs)
- RIG-I like receptors

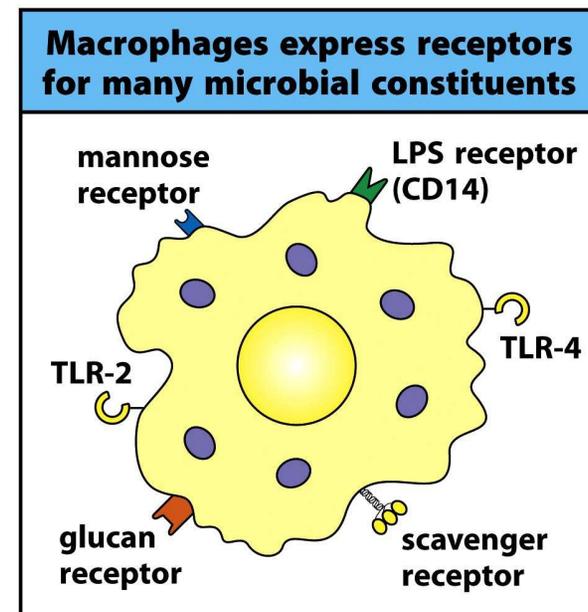


Figure 1-10 Immunobiology, 7ed. (© Garland Science 2008)

Stimulation of PPRs are responsible for effectiveness of vaccine adjuvants

Purified proteins → poorly immunogenic

killed bacteria or
bacterial extracts
+
purified protein → Obtain response
to purified protein

Bacterial proteins stimulate DCs making them efficient APCs for lymphocytes

Antigen Processing and Presentation

Professional APCs present Ag to naïve T cells and induce activation

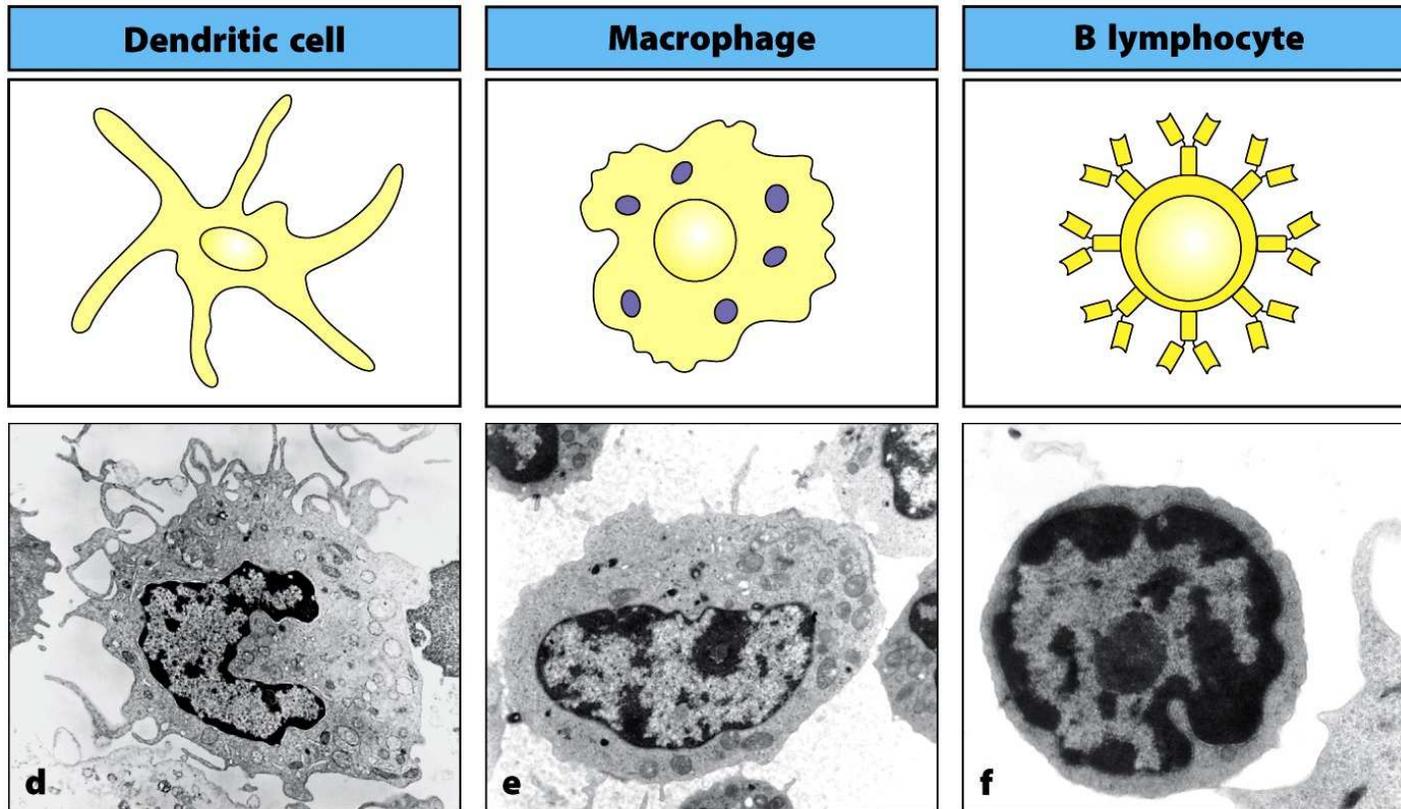


Figure 1-22 part 2 of 3 Immunobiology, 7ed. (© Garland Science 2008)

Immature DCs
very efficient at
Ag processing (in tissues)



Mature DCs
very efficient at
Ag presentation (in LNs)

MHC Class I presents peptide antigens to CD8 T cells

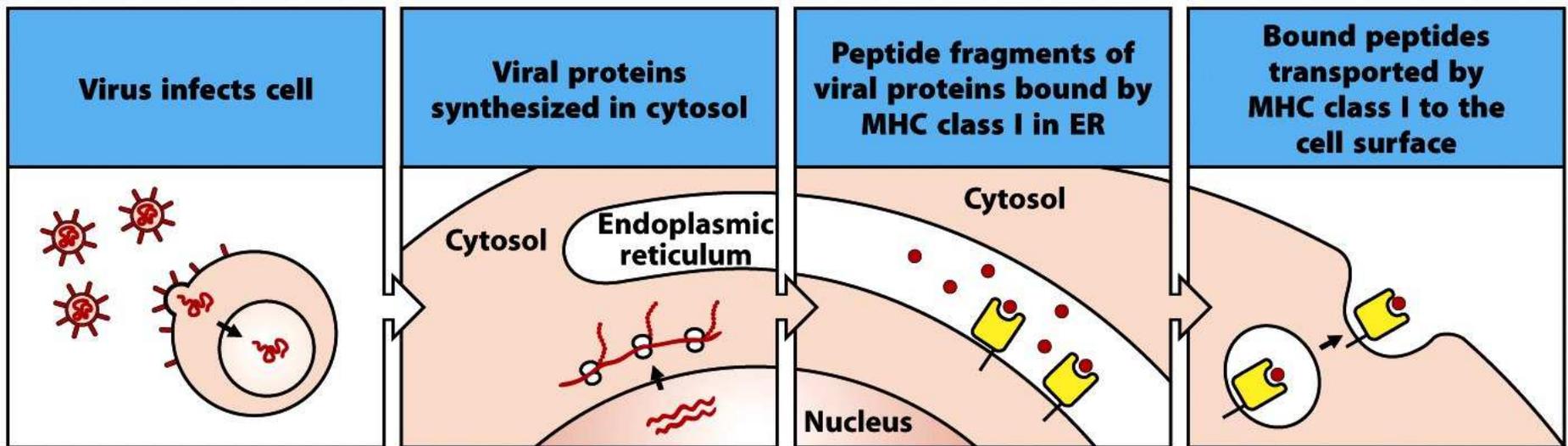


Figure 1-30 Immunobiology, 7ed. (© Garland Science 2008)

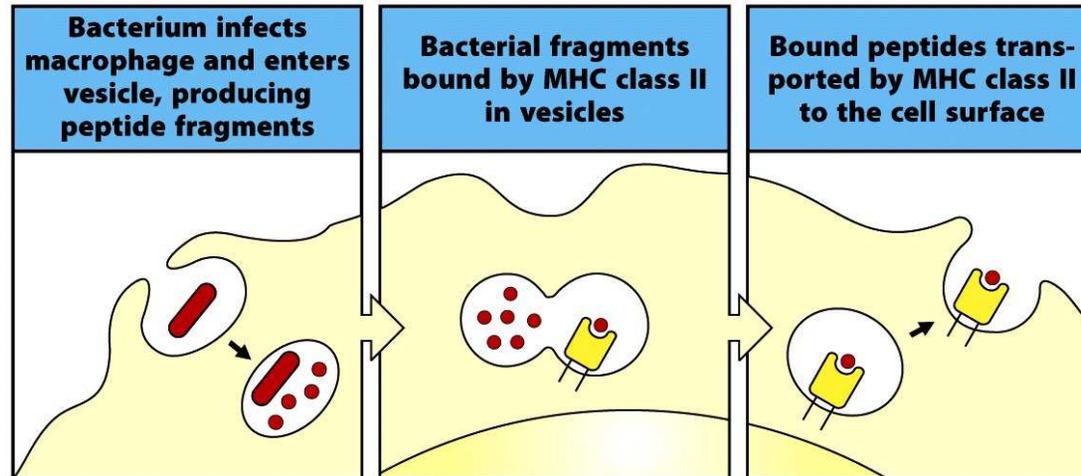
MHC Class I

- expressed by all nucleated cells
- presents peptides derived from endogenous proteins
- MHC Class I proteins are also recognized by NK cells

(MHC= Major Histocompatibility Complex)

MHC Class II presents peptide antigens to CD4 T cells

Macrophages:



B cells:

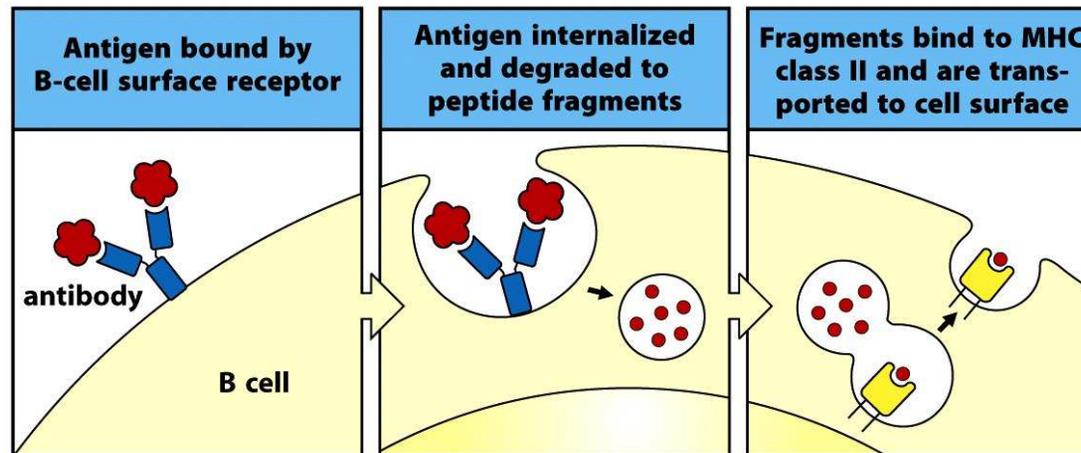


Figure 1-31 Immunobiology, 7ed. (© Garland Science 2008)

MHC Class II -typically expressed by professional APCs
-presents peptides derived from exogenous proteins

DCs are important for initiating adaptive immune responses

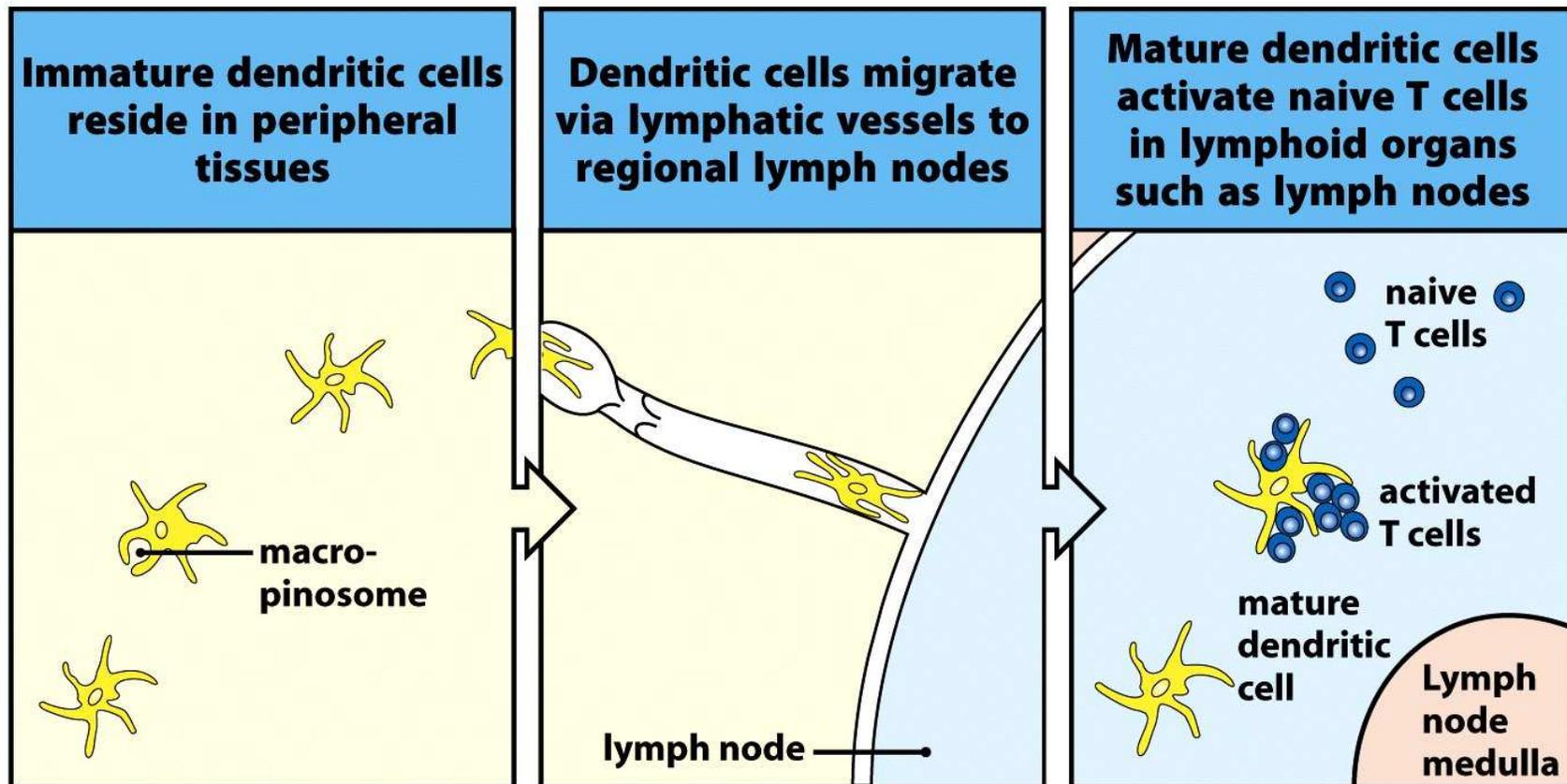


Figure 1-9 Immunobiology, 7ed. (© Garland Science 2008)

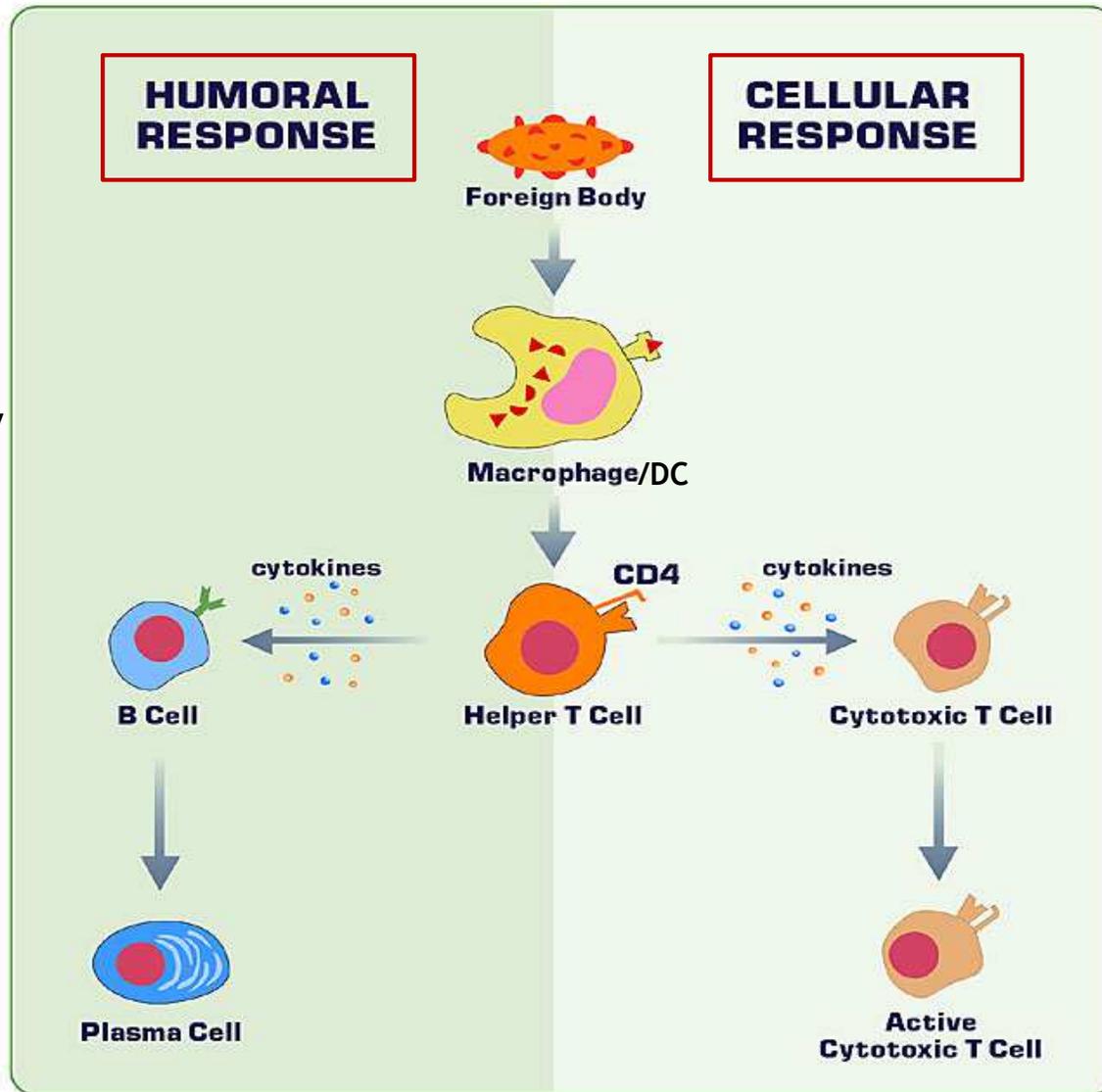
This is an important bridge between innate and adaptive responses; a failure to stimulate innate immune cells can lead to poor T cell and B cell responses.

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Adaptive Immune Responses

Antibodies present in blood allow immunity to be transferred via proteins

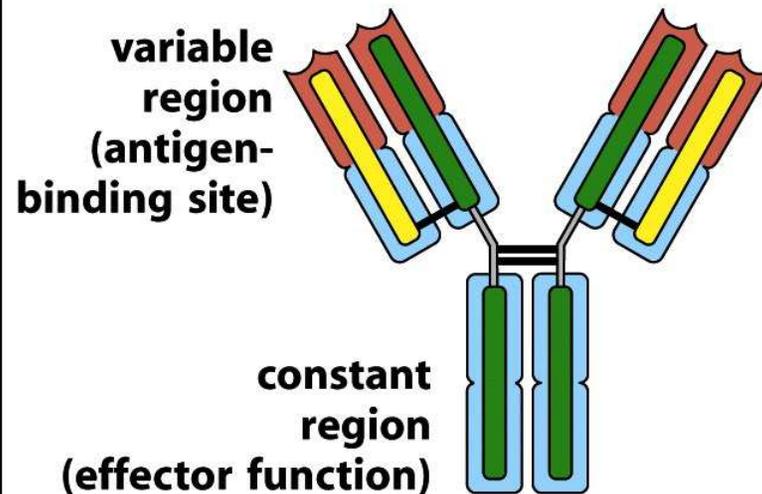


Immunity is mediated by T cells

Antigen Receptors

Antibody (Ab)

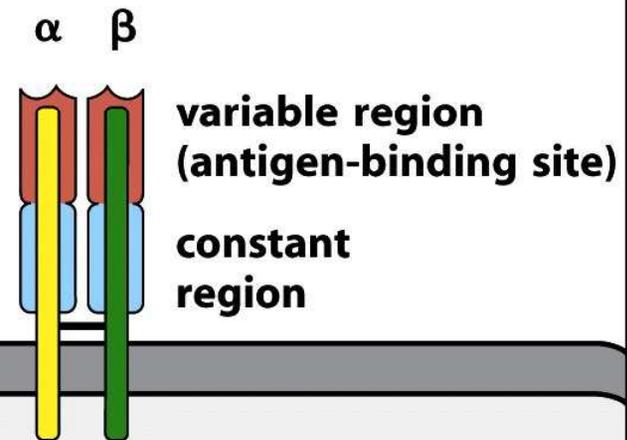
Schematic structure of an antibody molecule



(Cell surface and secreted)

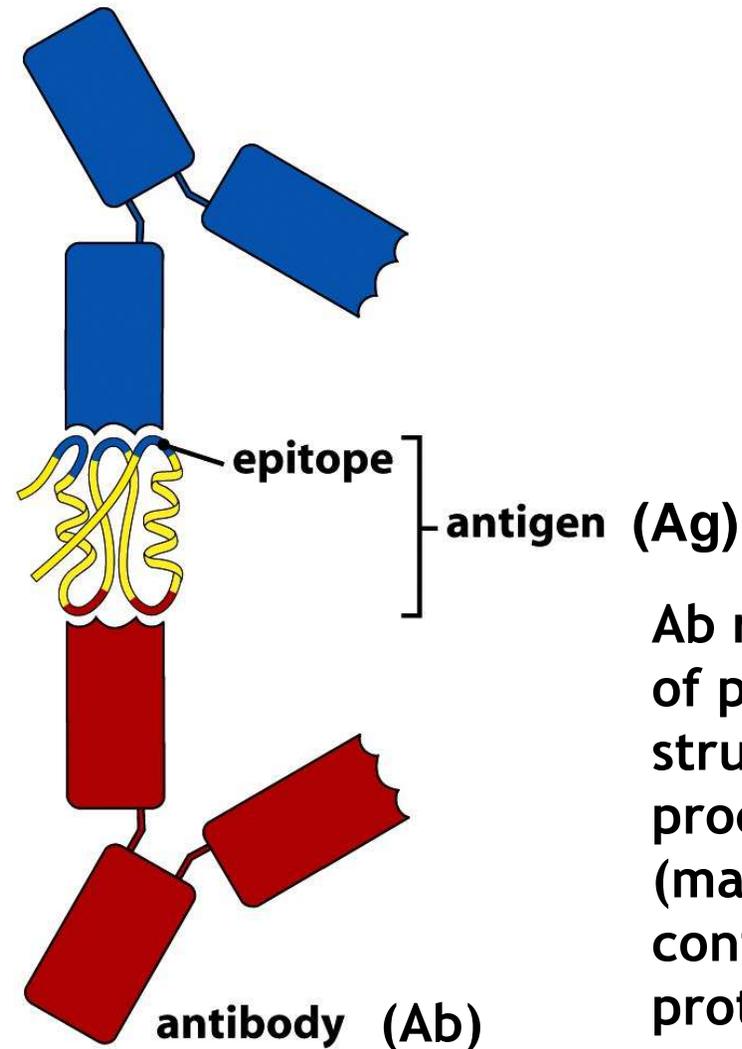
T cell Receptor (TCR)

Schematic structure of the T-cell receptor



(Cell surface only)

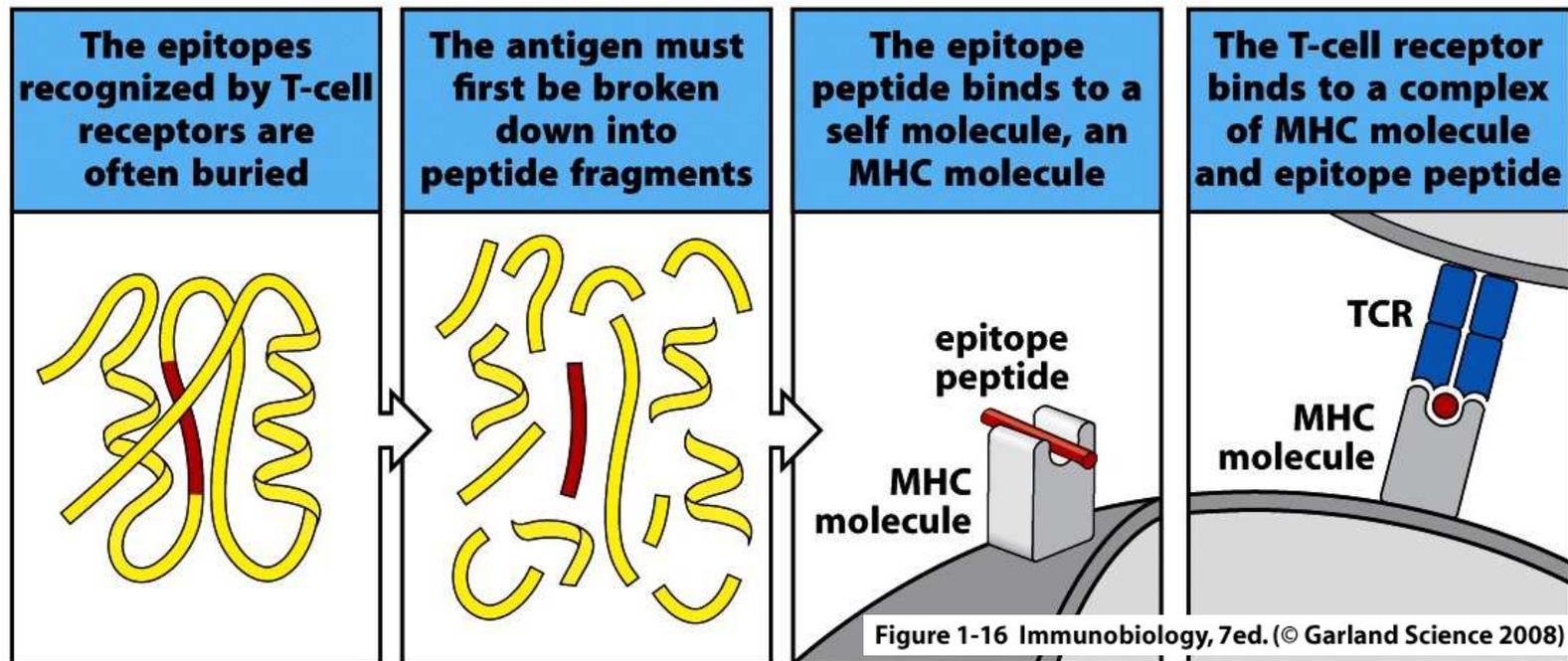
Antigen Recognition by Antibodies



Ab recognize portions of proteins in native structures, not processed proteins (may not be continuous portion of protein)

Figure 1-15 Immunobiology, 7ed. (© Garland Science 2008)

T cell Receptor (TCR) recognize processed proteins presented by MHC



(MHC= Major Histocompatibility Complex)

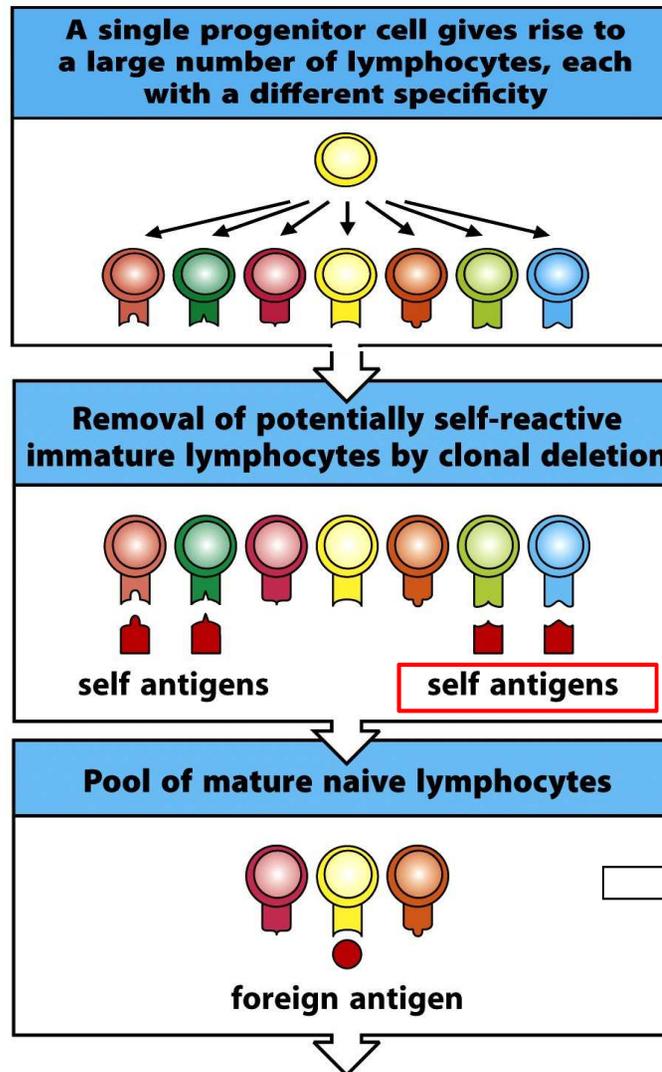
Generating lymphocytes that each have a unique specificity

1. Generating of vast pool of cells

2. Eliminating cells that can recognize self Ags



Mechanism of **Central Tolerance**

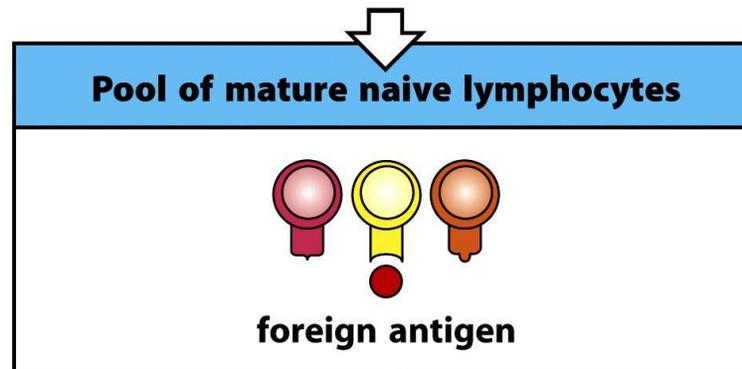


Immature cells
(non-functional)

One barrier to inducing responses against tumor cells

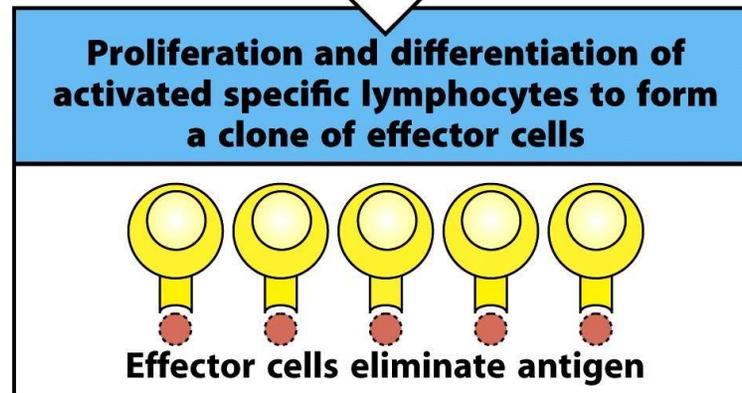
Lymphocyte Activation

“Naive”



Cells that recognize a specific Ag are very rare

“Activated” or “Effectors”

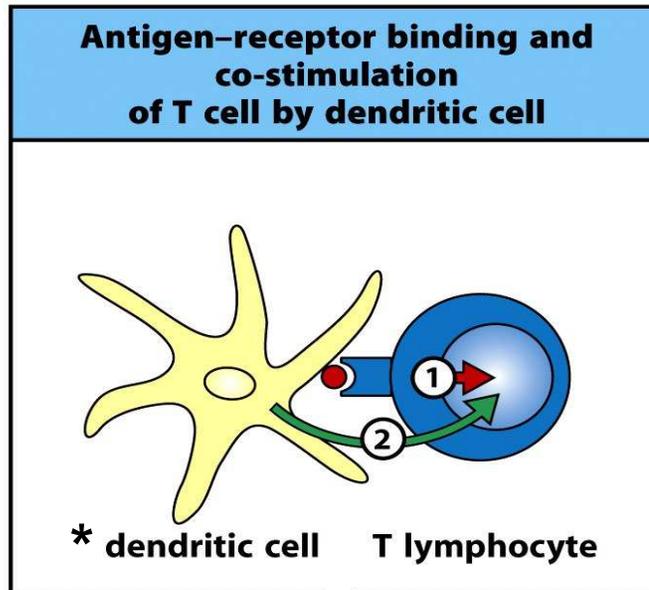


Results in:
1. Expansion
2. Acquisition of effector functions

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

Lymphocyte Activation

T Cells

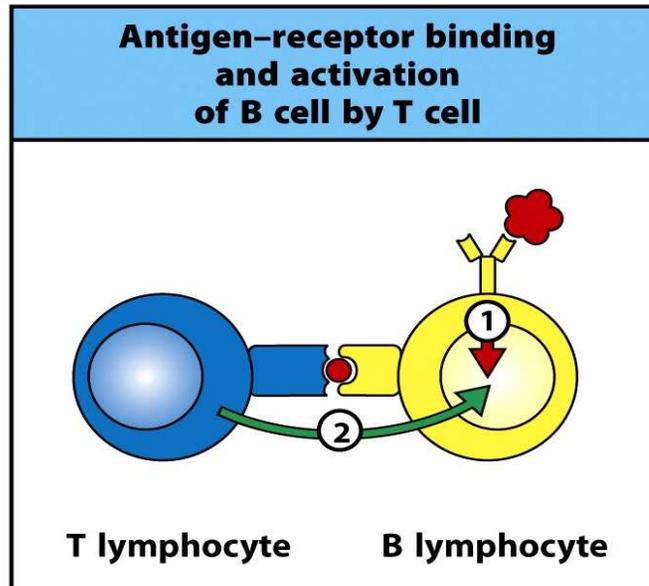


**Must be mature DC*

Activation of T and B cells requires stimulation thru:

1. antigen receptor (Signal 1)
2. costimulatory molecules (Signal 2)

B Cells



Absence of costimulation leads to unresponsiveness



peripheral tolerance

Effector Mechanisms of Adaptive Immunity

CD8+ T Cells (Cytotoxic T cells)

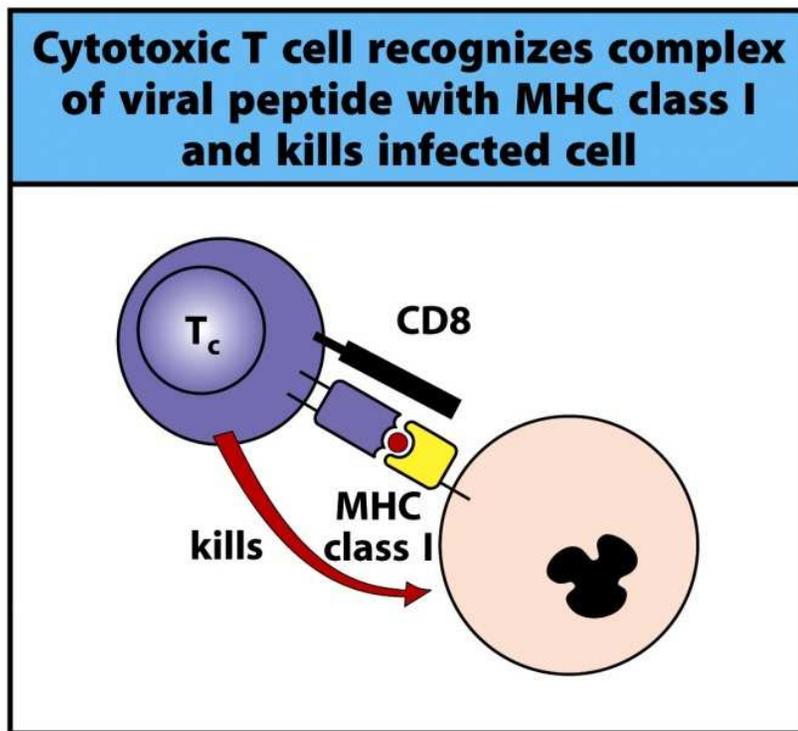
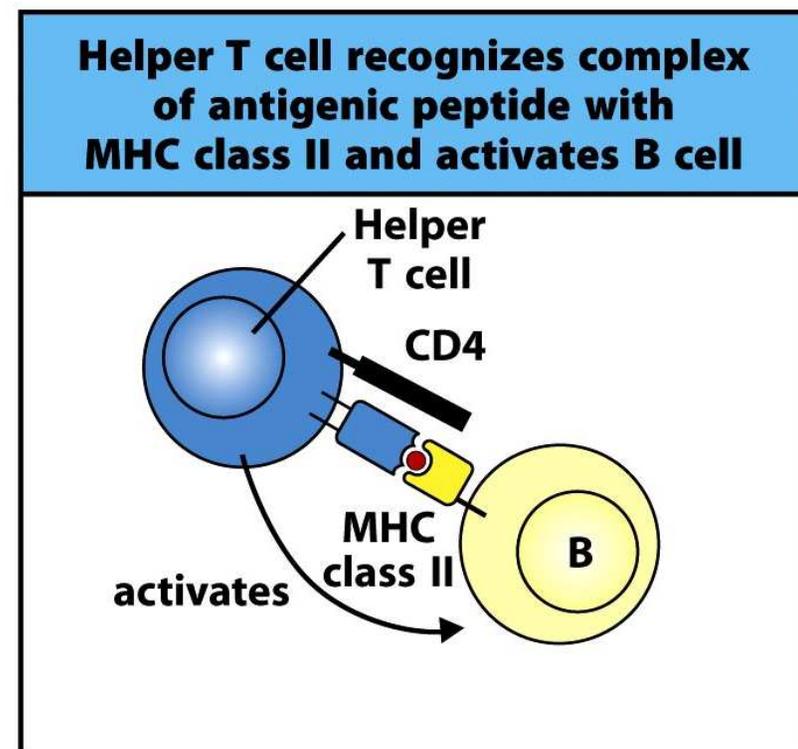


Figure 1-32 Immunobiology, 7ed. (© Garland Science 2008)

(Produce proteins that lyse cells)

CD4+ T Cells (Helper T cells)



Different subtypes:
Th1, Th2, Th17, Tregs

Effector Mechanisms of Adaptive Immunity

B Cells

Ab functions:

1. Neutralize
2. Block protein functions
3. Promote engulfment
4. Induce complement-mediated cell lysis

Different classes (isotypes) of Ab: IgM, IgG, IgE, IgA

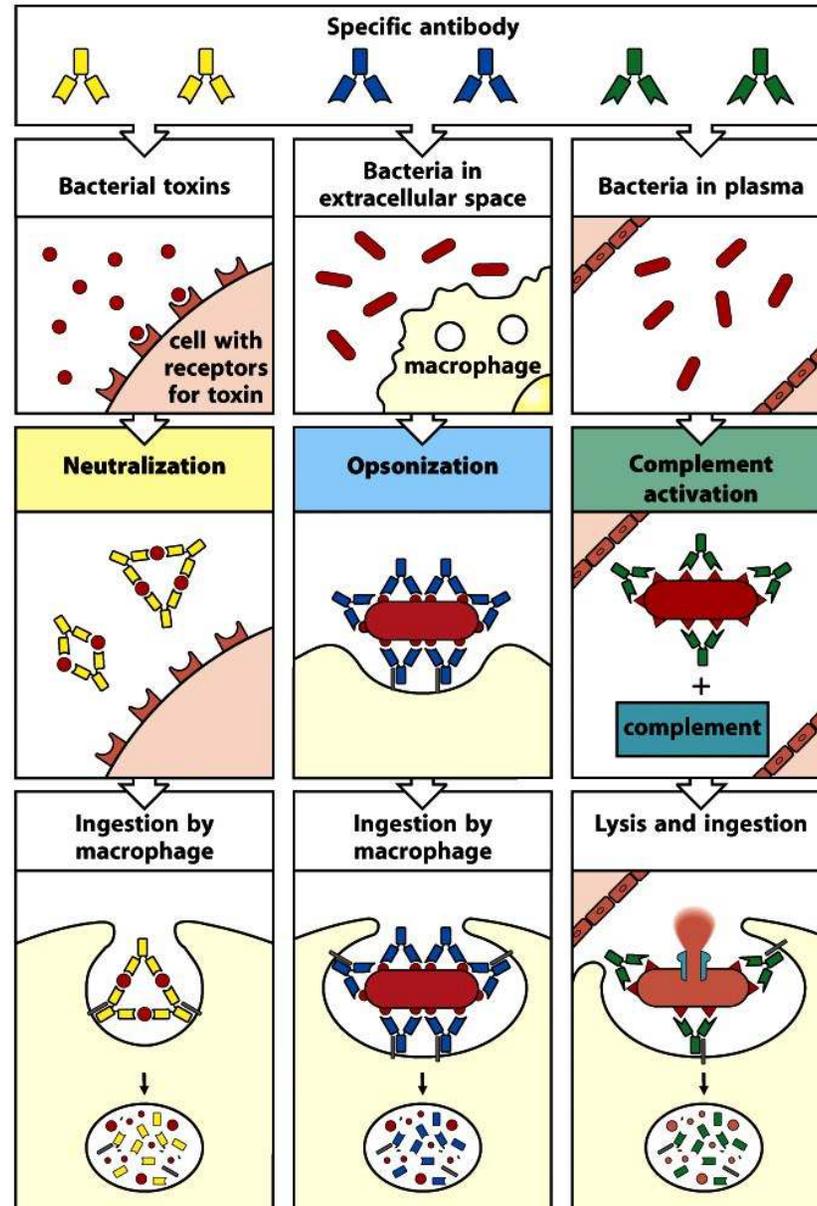


Figure 1-26 Immunobiology, 7ed. (© Garland Science 2008)

Lymphocyte Activation

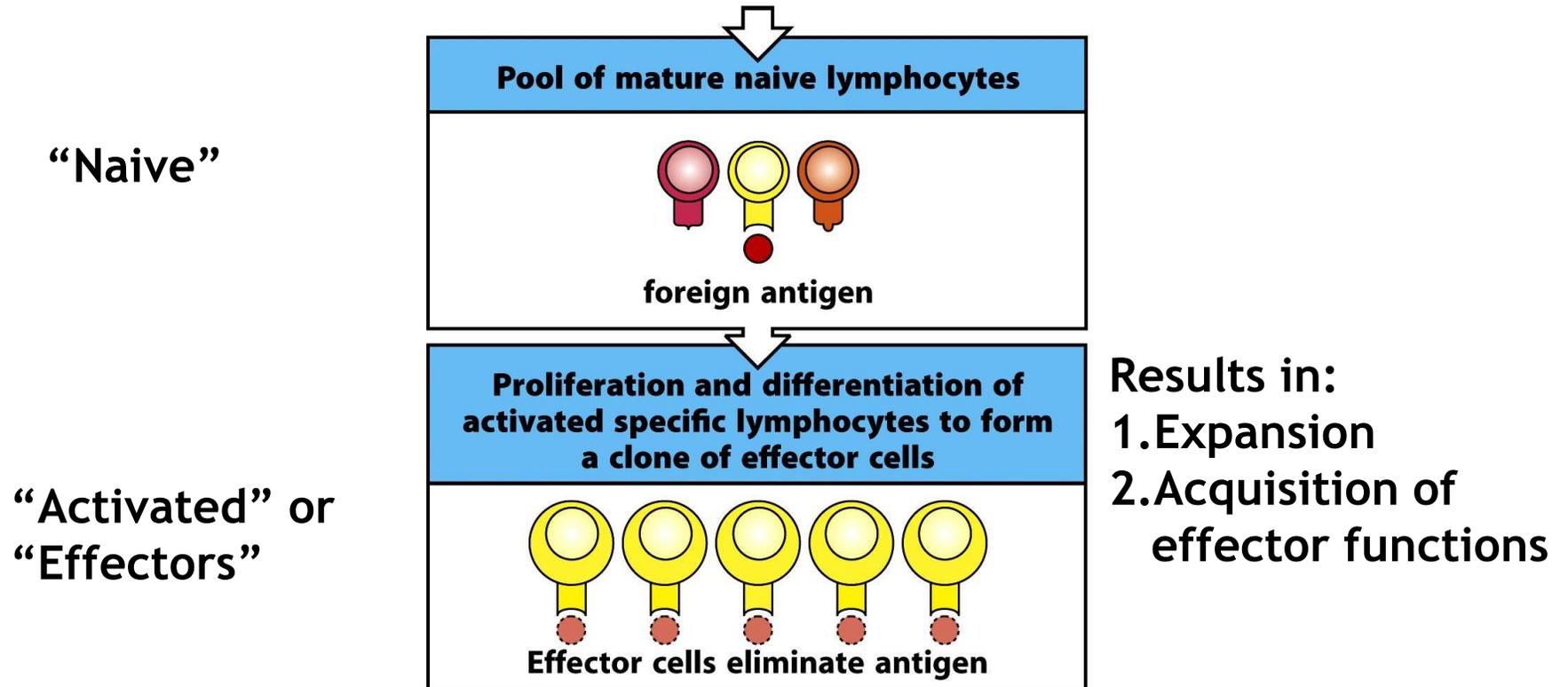


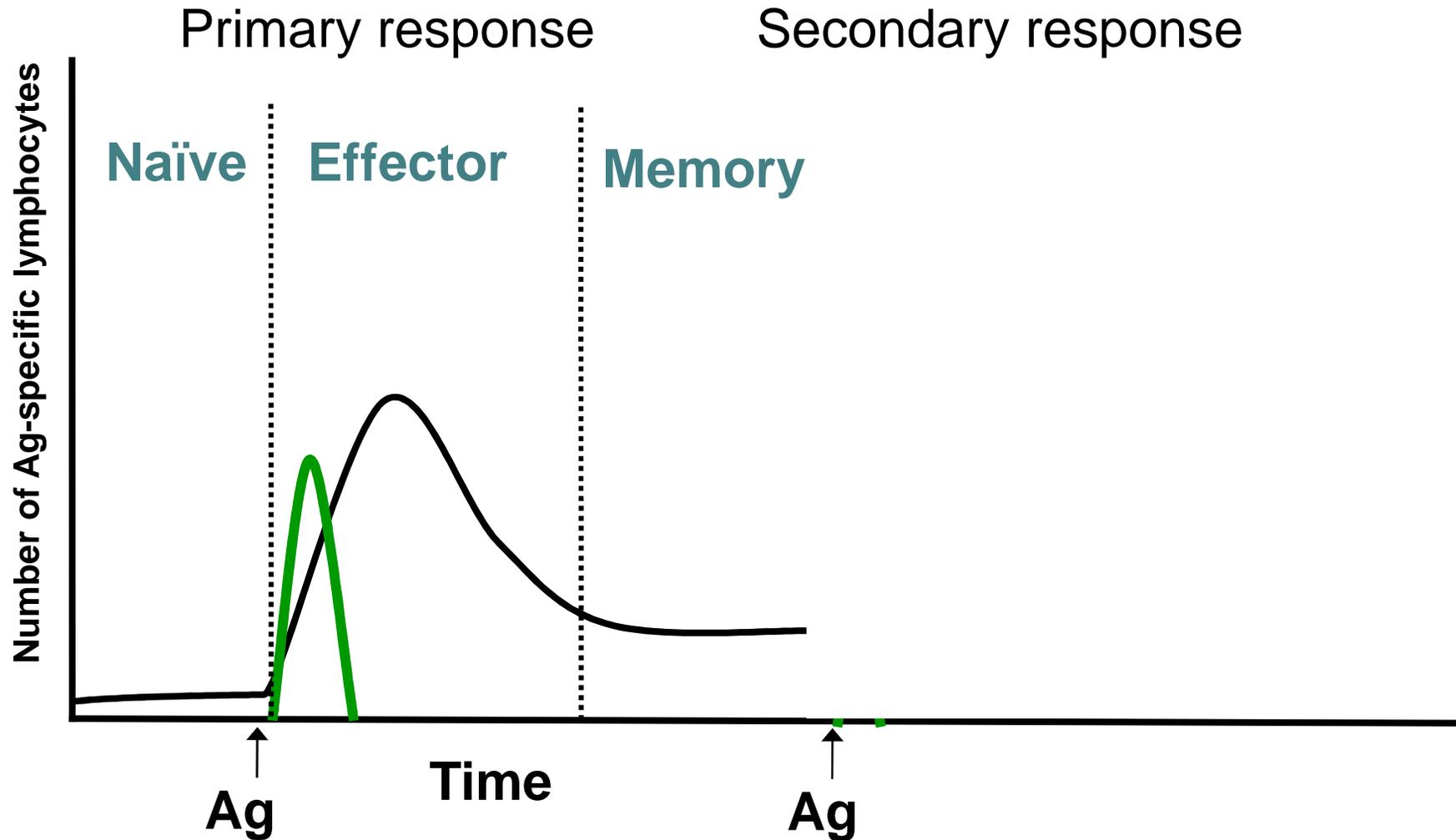
Figure 1-11 part 3 of 3 Immunobiology, 7ed. (© Garland Science 2008)

What happens to T cells and B cells after immune response?



Differentiate into long-lived memory lymphocytes

Significance of Immunological Memory



The memory phase can last for decades

Secondary immune response larger, faster, and more effective

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Immune responses can be beneficial or harmful

Antigen	Effect of response to antigen	
	Normal response	Deficient response
Infectious agent	Protective immunity	Recurrent infection
Innocuous substance	Allergy	No response
Grafted organ	Rejection	Acceptance
Self organ	Autoimmunity	Self tolerance
Tumor	Tumor immunity	Cancer

Figure 1.32 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Effectiveness of mechanisms mediating immune tolerance and regulation

Immune Regulation

Myeloid-derived Suppressor cells

- Heterogeneous, immature myeloid phenotype
- Produce immunosuppressive cytokines, IL-10 and TGF- β
- Expand during inflammation, infection, and cancer
- Enriched in the tumor microenvironment

T regulatory cells

- Inhibit or suppress other adaptive immune responses
- Recognize self Ag
- Produce TGF- β and IL-10
- Different subsets: generated during development or induced from naïve T cells in the periphery
- Enriched in the tumor microenvironment

Lessons and Take Home Messages

Lessons learned:

Immune Recognition

Various immune cells use different mechanisms to recognize foreign entities- PRR, Ab, TCR

Immune Effector Function

Phagocytosis, Ab neutralization, cytolysis, cytokines

Immunological Memory

T cells and B cells provide long term protection against recurrences

Immune Regulation

*Central and peripheral Tolerance
Tregs, myeloid-derived suppressor cells*

Lessons and Take Home Messages

Key Points

- *There are numerous ways the immune system recognizes and eliminate foreign entities*
- *Innate immune responses can be immediately elicited while adaptive responses need to be induced*
- *Responses to foreign entities by adaptive immune cells can be highly specific, very efficient, and long lasting*

Impact on field

The immune system can be elicited to eliminate cancers, leading to long term, durable responses