General Overview of Immunology

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

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Objectives

- Describe differences between innate and adaptive immune responses
- Describe the immune cells that mediate and regulate immune responses
- Define common terminology
- Explain how immune cells recognize and respond to foreign entities
- Relate basic concepts of immunology to its applications in immunotherapy

Immune System- Body's defense against infection

Late 1700s **Edward Jenner observed that prior history of a mild disease of cowpox (vaccinia) conferred protection against fatal smallpox**

Vaccination **inoculation of healthy people with weak or attenuated agents that cause disease.**

Disease causing agents were unknown.

Pathogens:
Viruses, bacteria, fungi, parasites

What was the mechanism of protection?

Definition: Immunity- the state of being immune from, insusceptible to, or protected from a particular disease or the like.

Immune Reponses

Innate

- Always available
- First line of defense
- Specific for general types of pathogens but not an individual pathogen
- 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

Function of Immune Reponses

- **Immune Recognition-detects the presence of infection.**

- **Immune Effector Function- contains and eliminate infection (degradative enzymes, complement, Ab, cell lysis)**

- **Immune Regulation-controls immune response to prevent damage**

- **Immunological Memory- protects against recurring disease to the same pathogen**

All are accomplished by innate and adaptive immune cells except immunological memory

Immune cells are derived from stem cells in the bone marrow

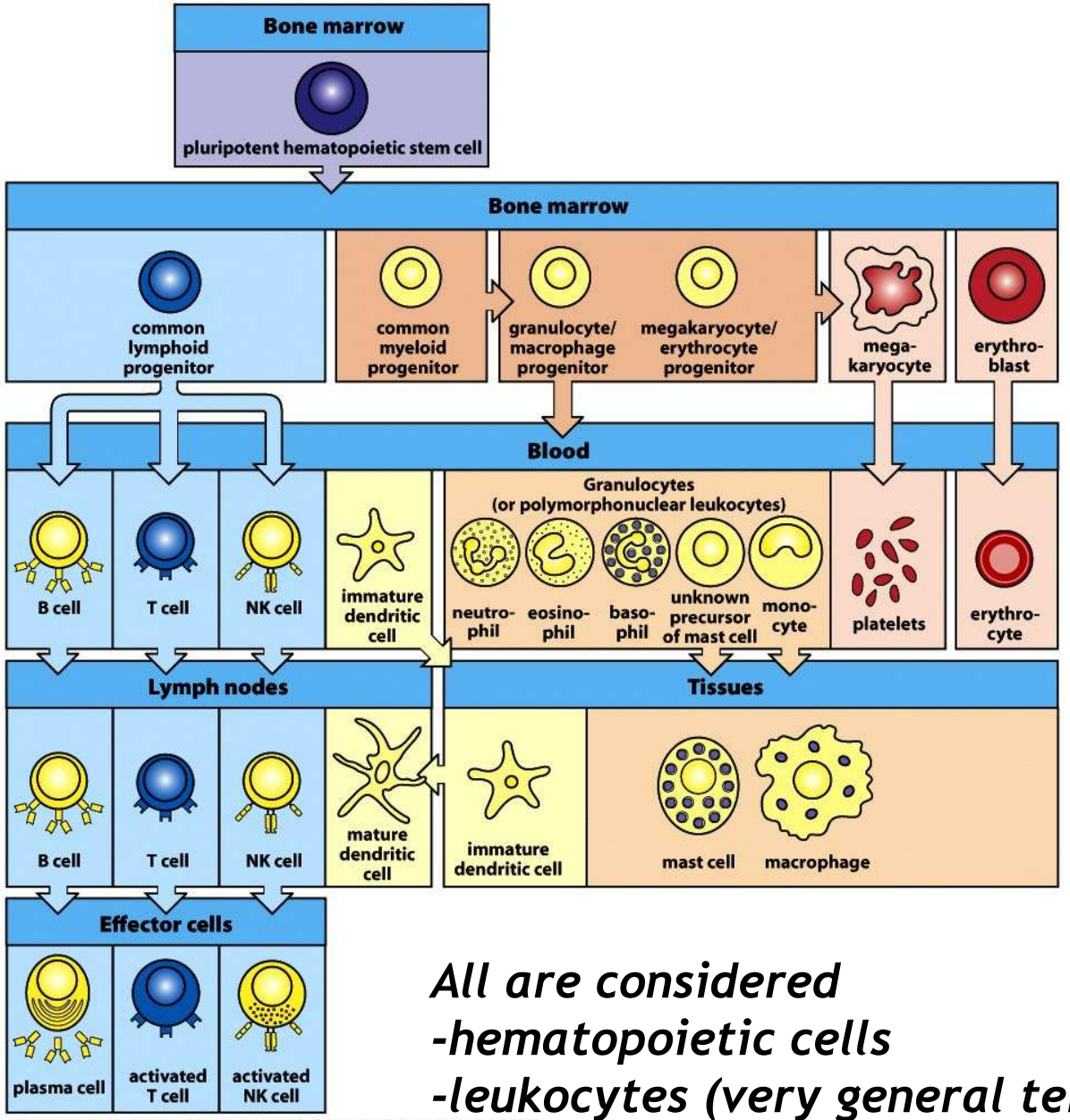
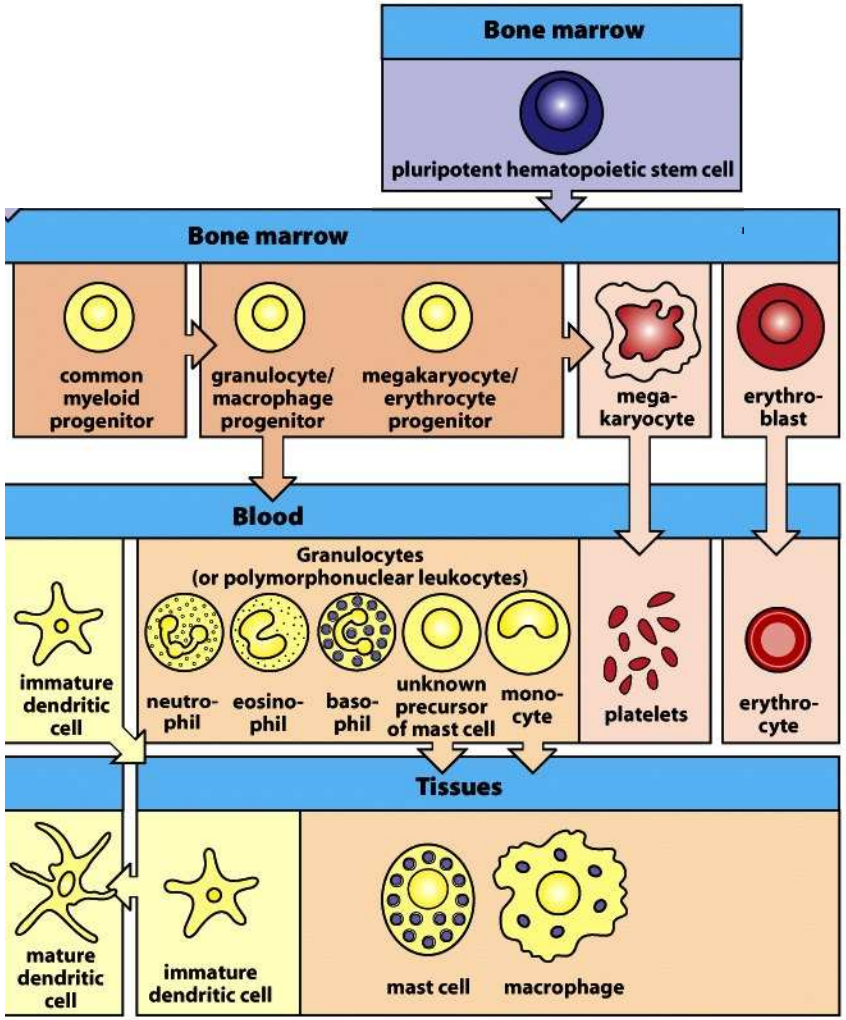


Figure 1-3 Immunobiology, 7ed. (© Garland Science 2008)

All are considered
-hematopoietic cells
-leukocytes (very general term)

The myeloid lineage comprises most of the cells of the innate immune system



Granulocytes

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

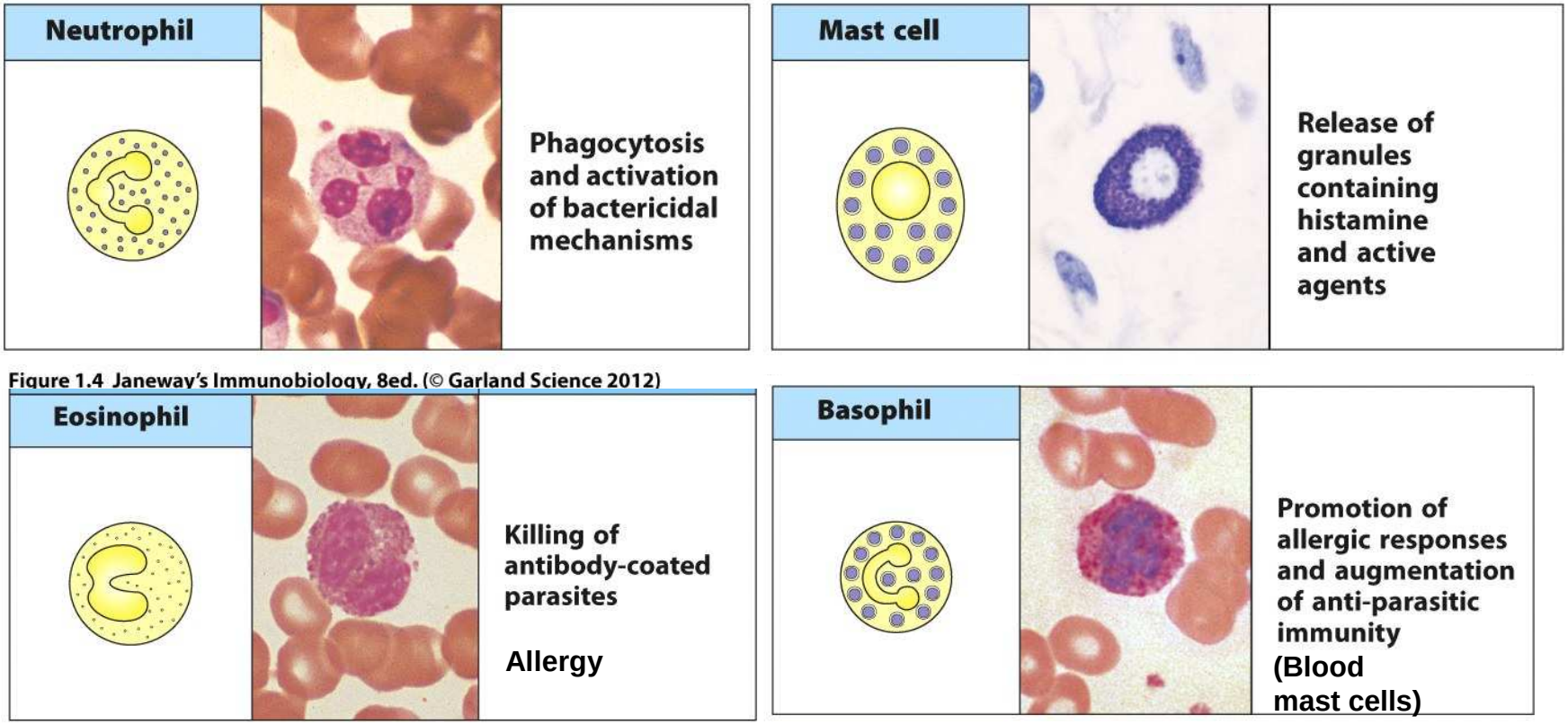


Figure 1.4 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Neutrophils, Eosinophils, Basophils are sometimes referred to as polymorphonuclear leukocytes:

Phagocytes

Neutrophils, Macrophages, and Dendritic Cells

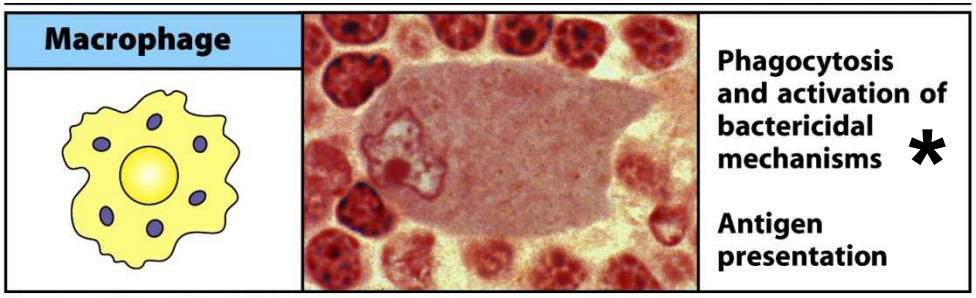


Figure 1-4 part 1 of 6 Immunobiology, 7ed. (© Garland Science 2008)

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 lymphocyte activation

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

Three Main Antigen Presenting Cells (APCs)

Professional APCs present Ag to naïve T cells and induce activation

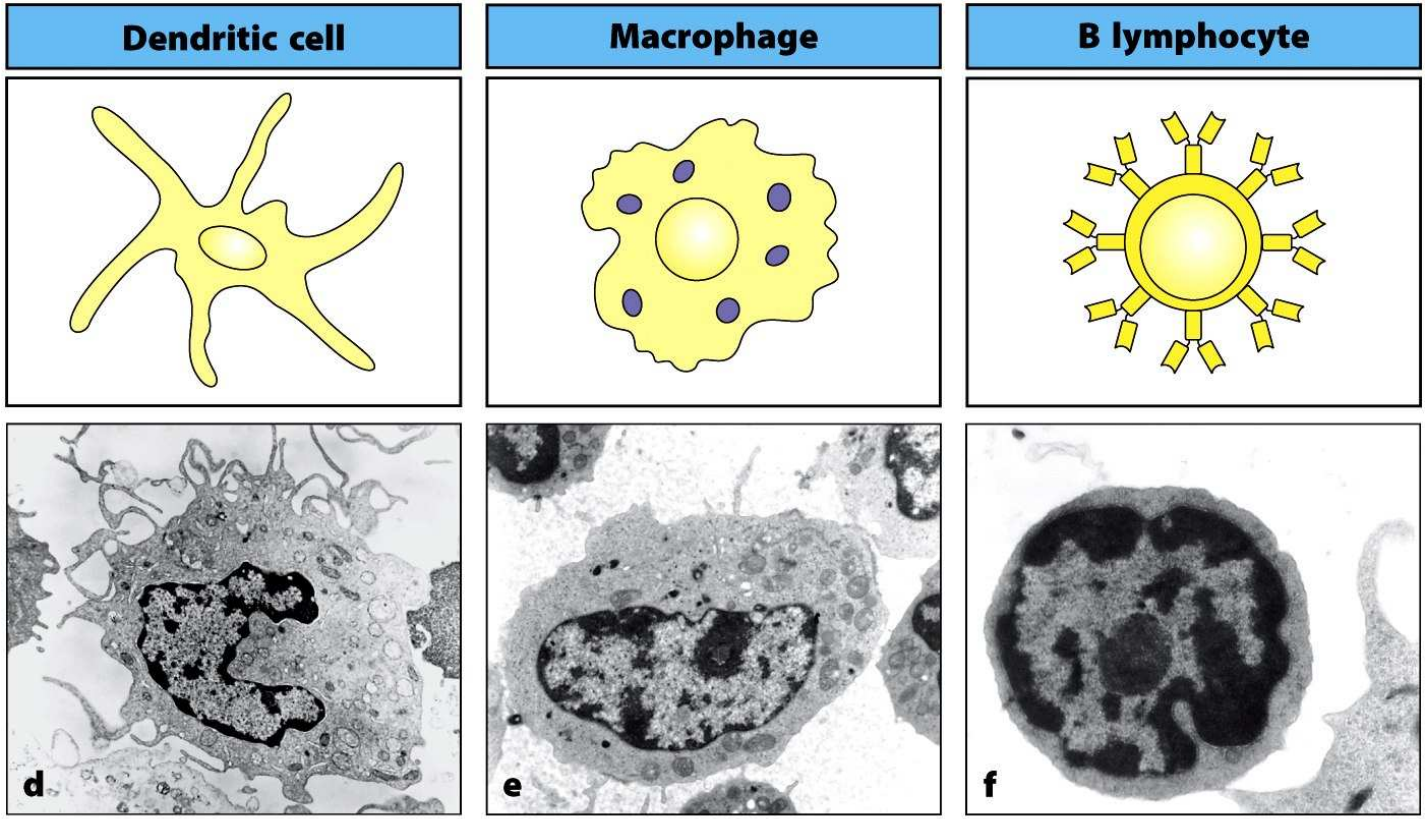


Figure 1-22 part 2 of 3 Immunobiology, 7ed. (© Garland Science 2008)

Immature DCs
very efficient at
Ag processing (in tissues)

→

Mature DCs
very efficient at
Ag presentation (in LNs)

Lymphocytes

Generally: small inactive cells

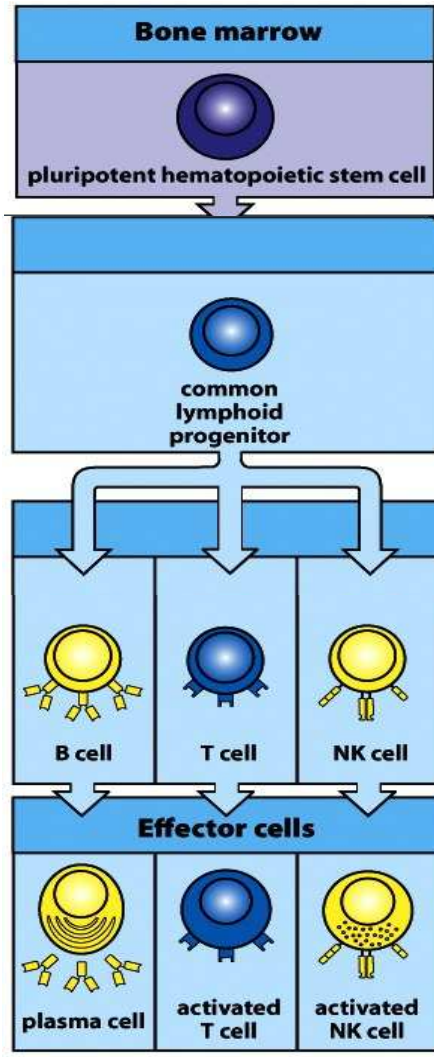


Figure 1-3 Immunobiology, 7ed. (©

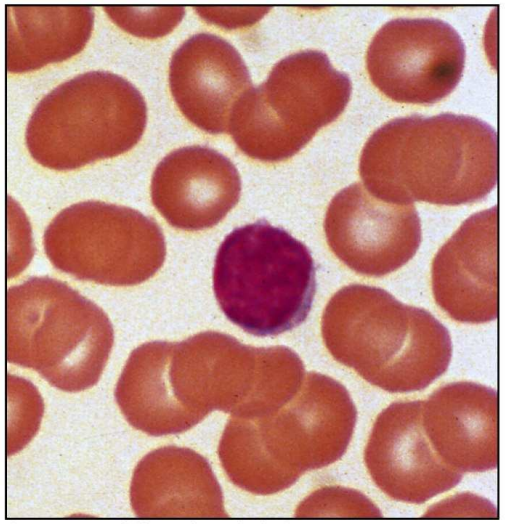
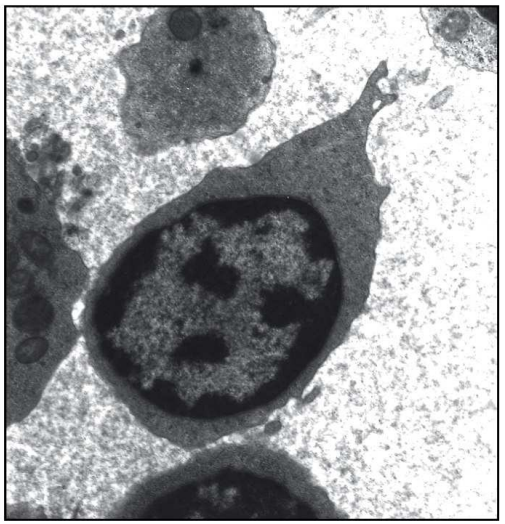


Figure 1-6 Immunobiology, 7ed. (© Garland Science 2008)



<u>3 Types:</u>

T and B cells

-mediate adaptive responses (recognize <u>very</u> specific antigens via antigen-receptors)

NK cells

-mediate innate responses (recognize general features on tumor and virus-infected cells)

Adaptive and innate immune cells in the hematopoietic lineage

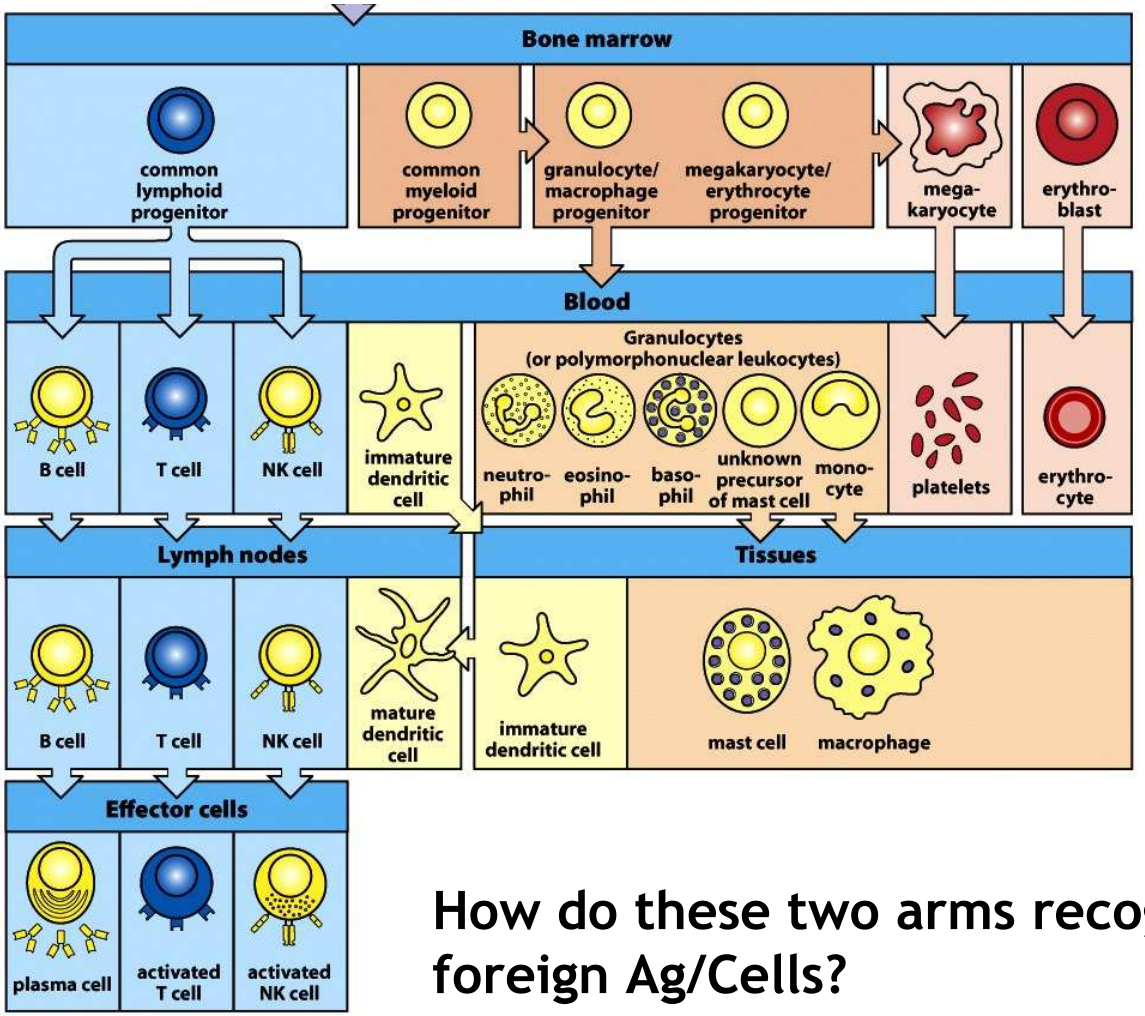


Figure 1-3 Immunobiology, 7ed. (© Garland Science 2008)

How do these two arms recognize foreign Ag/Cells?

Innate responses are initiated upon recognition of common features of pathogens (PAMPs) by pattern recognition receptors

PAMPs (Pathogen-associated molecule patterns)

-examples:
lipopolysaccride on bacterial cell walls (LPS), unmethylated CpG DNA, mannose-rich oligosaccarides

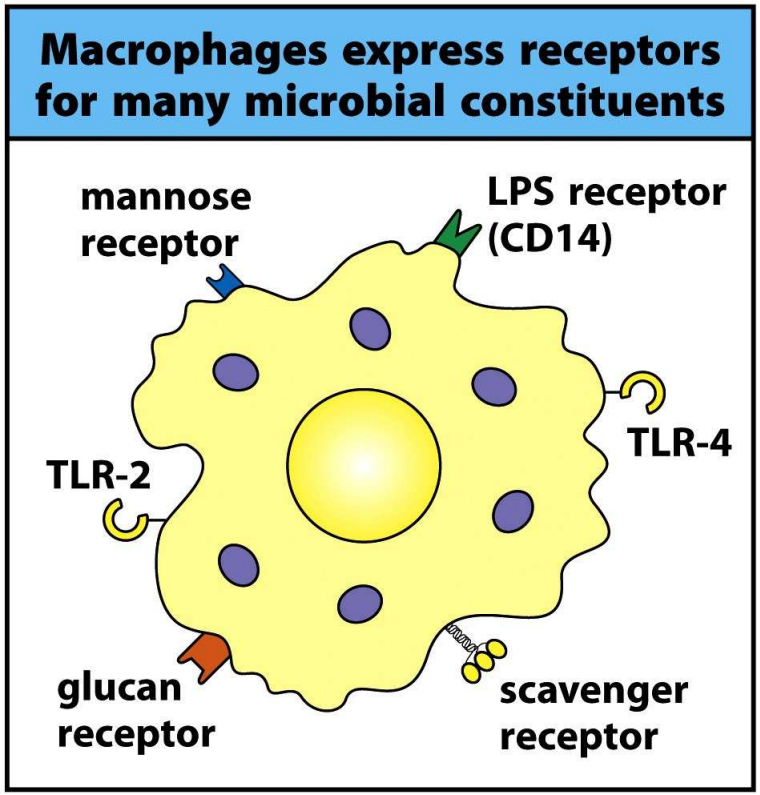


Figure 1-10 Immunobiology, 7ed. (© Garland Science 2008)

PAMP Receptors are enriched on, but are not restricted to innate immune cells

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

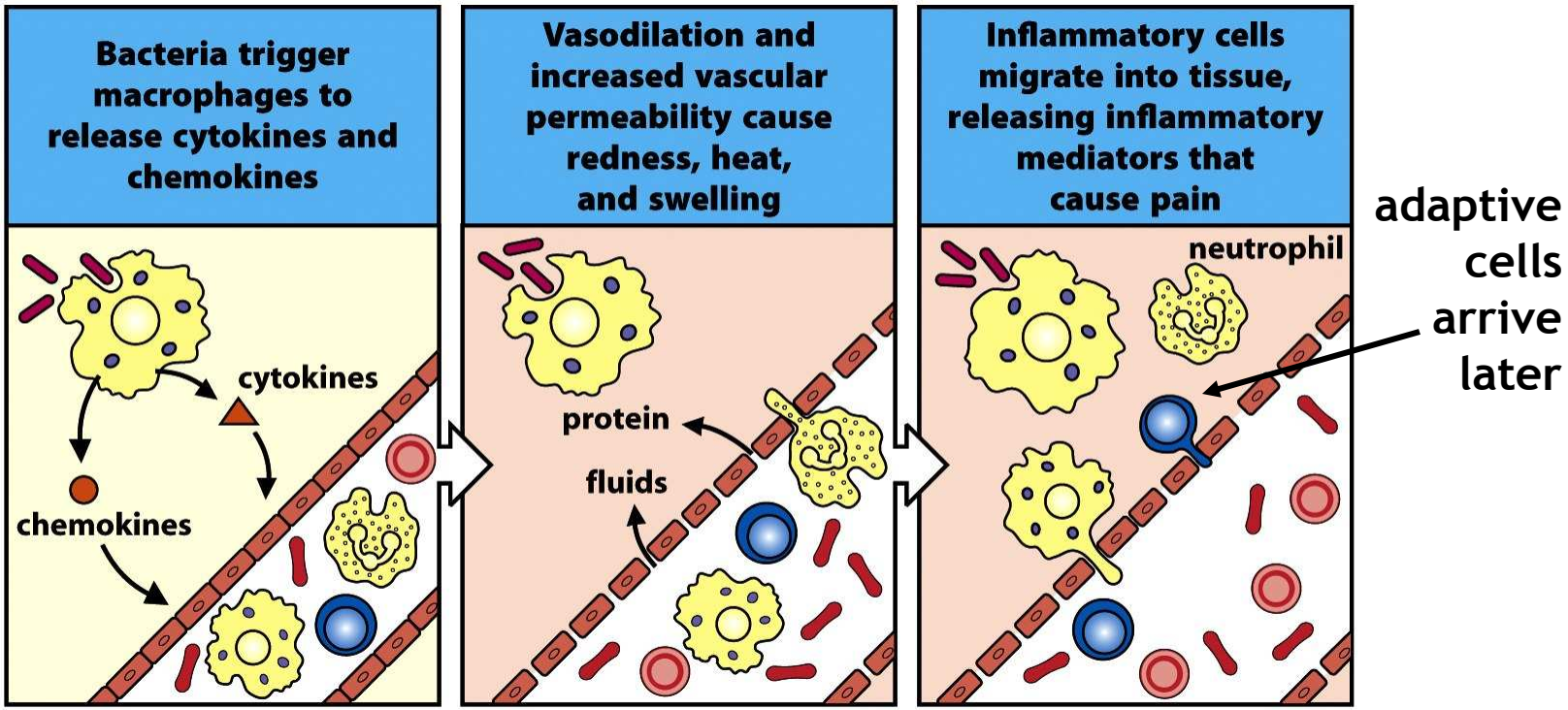


Figure 1-8 Immunobiology, 7ed. (© Garland Science 2008)

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

PAMPs are responsible for effectiveness of 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

DCs are important for initiating adaptive immune responses

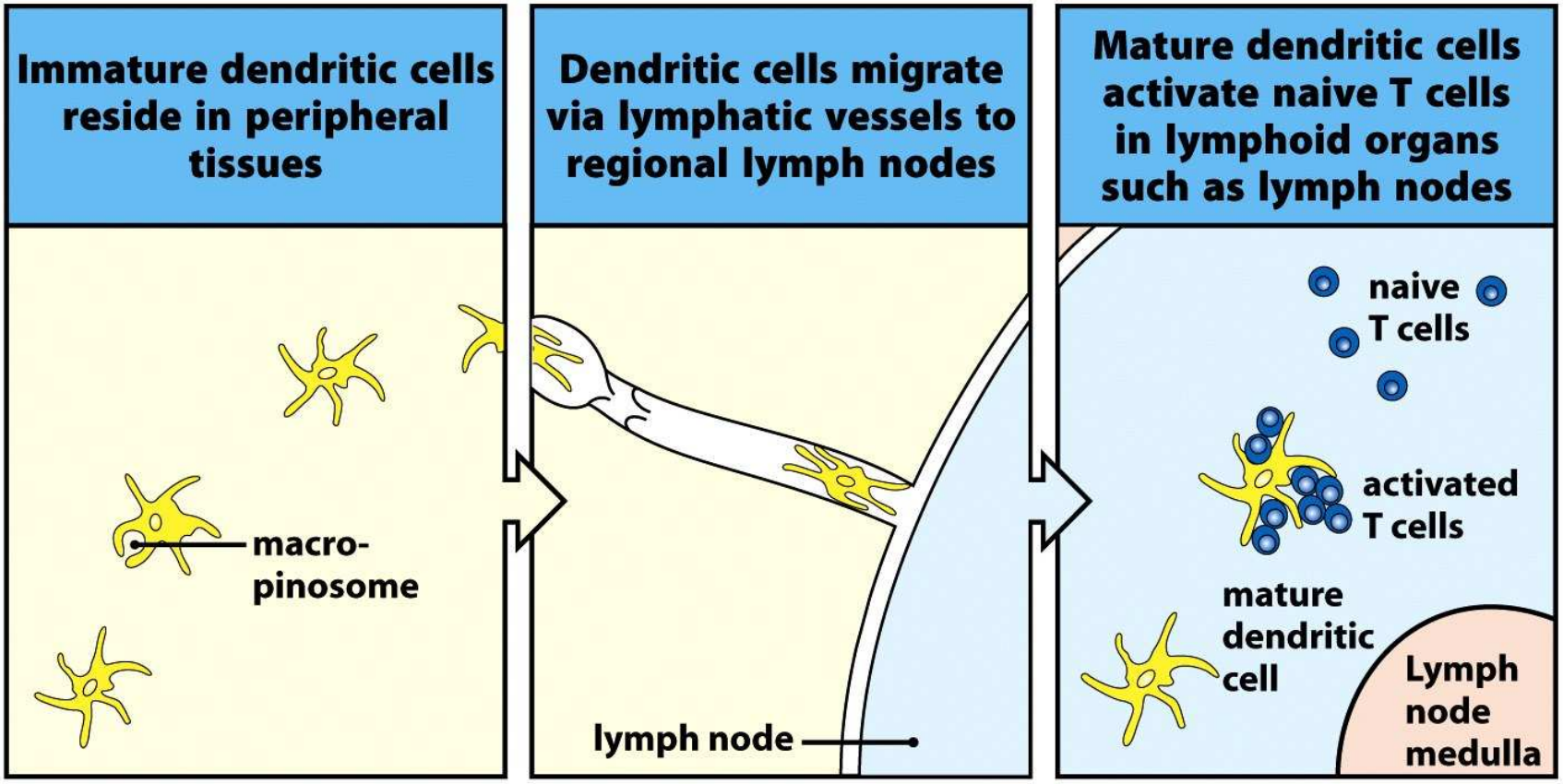
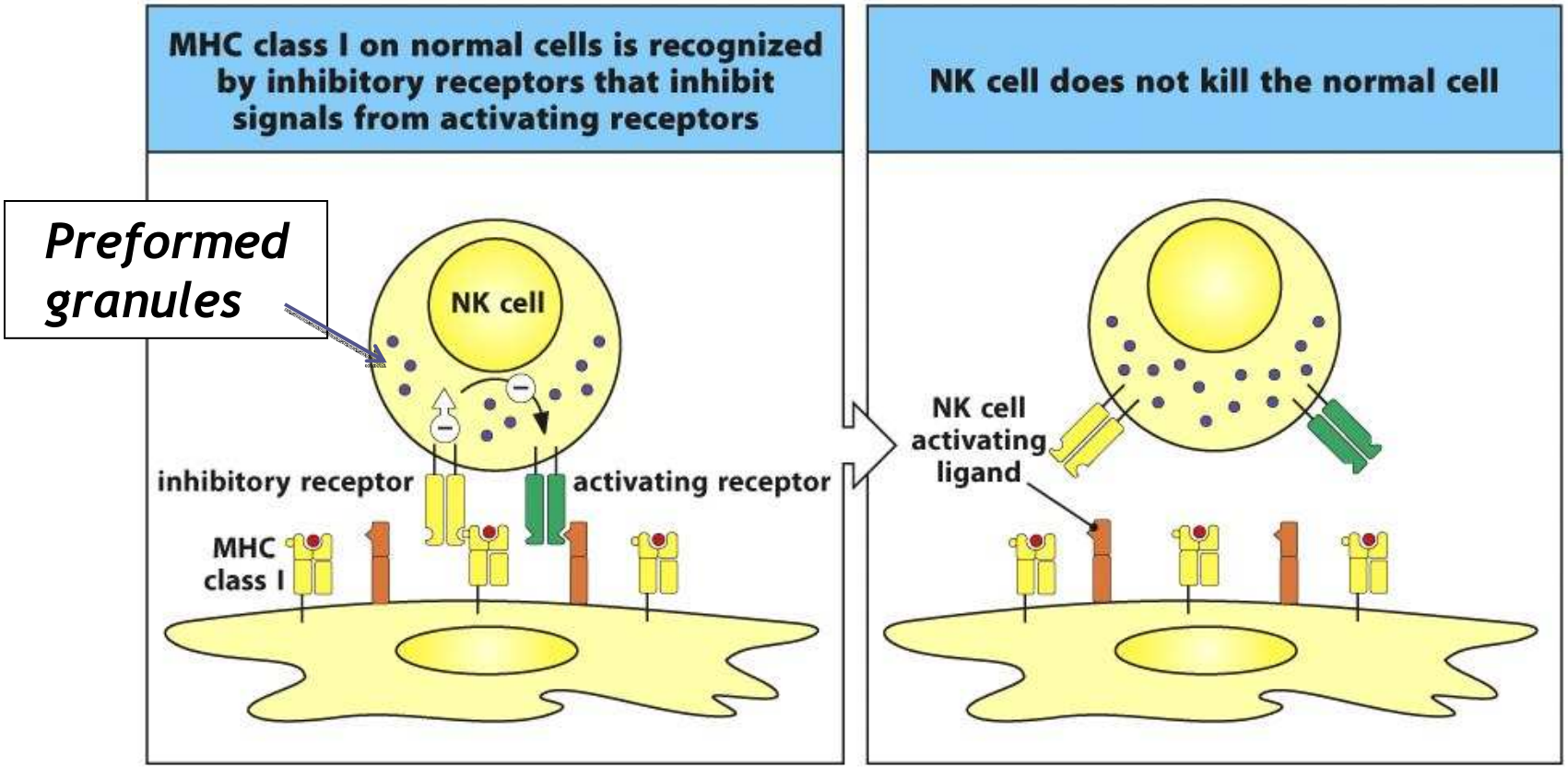


Figure 1-9 Immunobiology, 7ed. (© Garland Science 2008)

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.

Natural Killer Cells (NK cells)

No NK cell activation



NK cells express inhibitory and activating receptors that recognize self MHC class I and NK cell receptor ligands respectively

Natural Killer Cells (NK cells)

NK cell activation

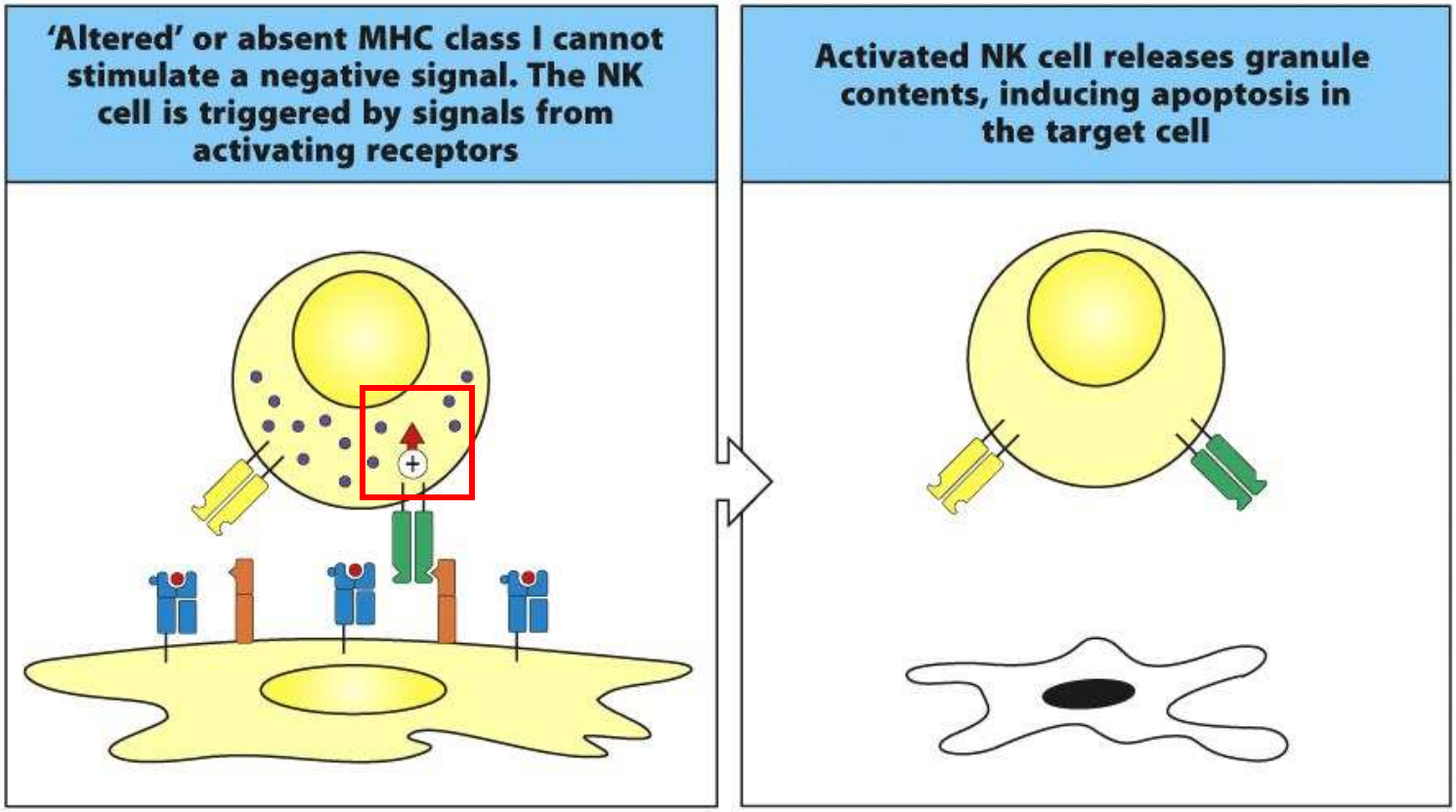
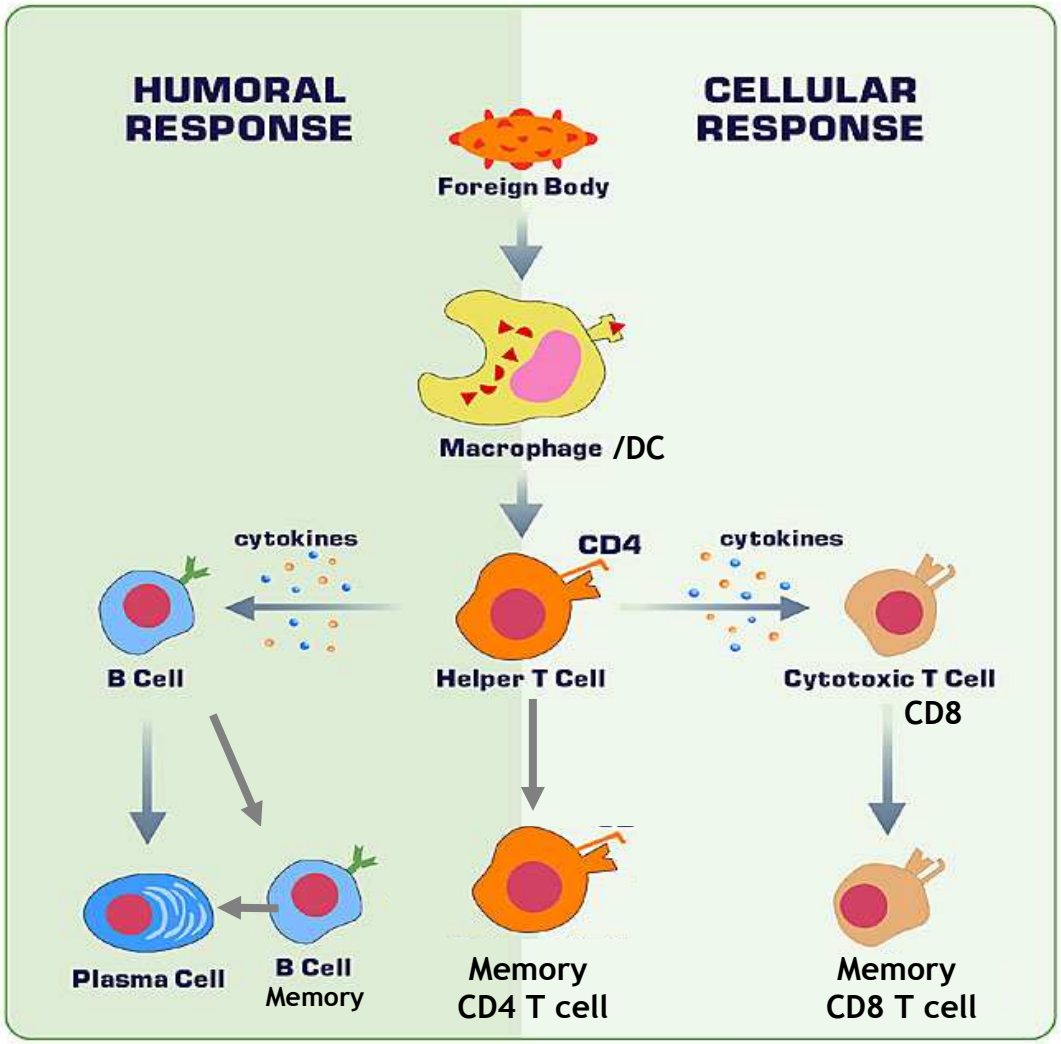


Figure 3.31 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Tumor cells, virus-infected cells, and transplanted cells are targets of NK cell killing because of decreased MHC Class I

Adaptive Immune Responses

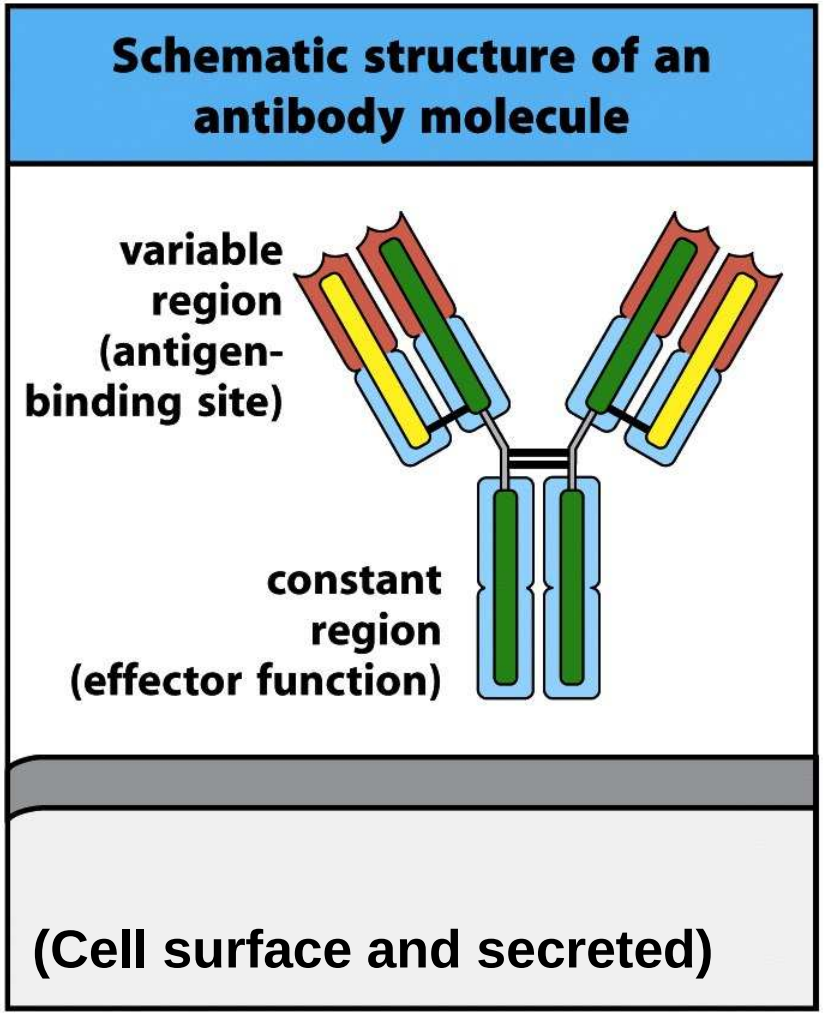
Antibodies present in blood allow immunity to be transferred via proteins



Immunity is mediated by cells

Antigen Receptors

Antibody (Ab)



T cell Receptor (TCR)

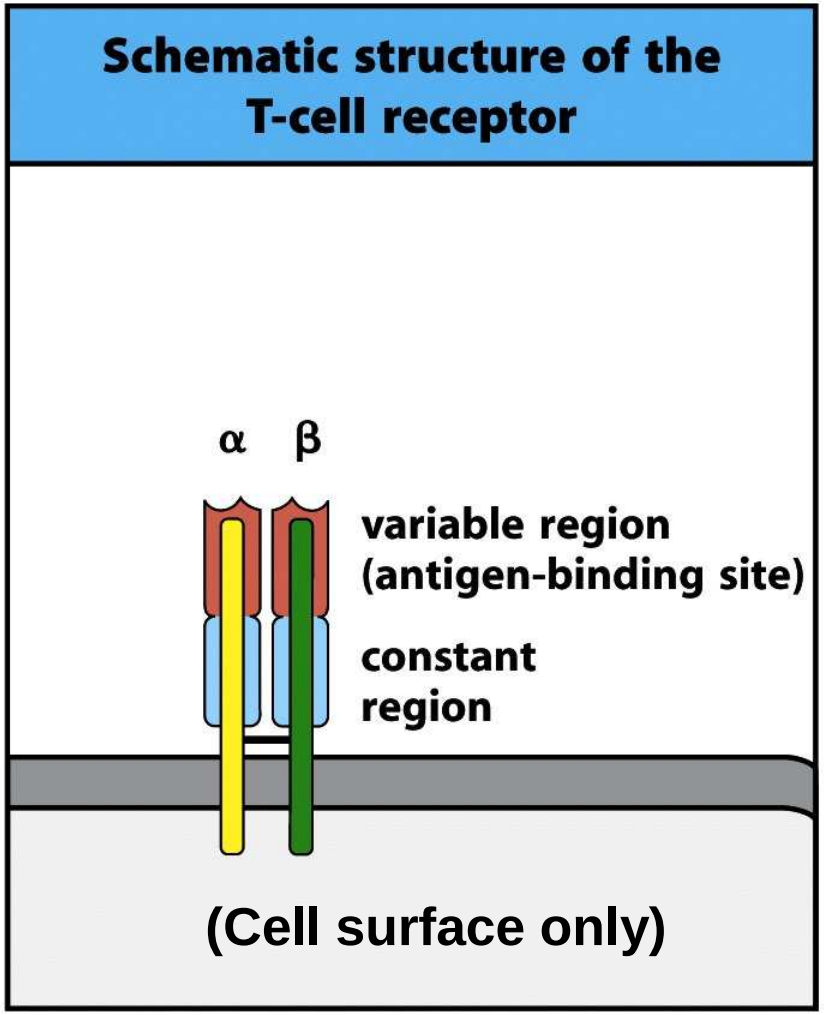


Figure 1-13 Immunobiology, 7ed. (© Garland Science 2008)

Antigen Recognition by Antibodies

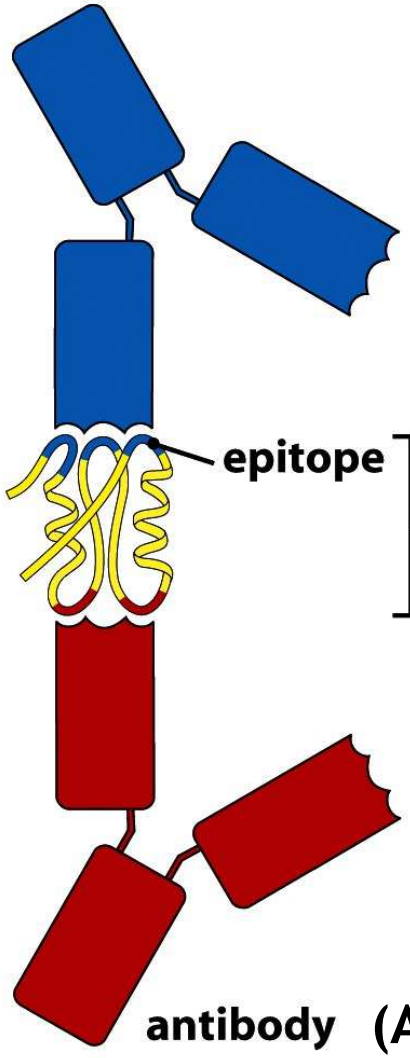


Figure 1-15 Immunobiology, 7ed. (© Garland Science 2008)

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

T cell Receptor (TCR) recognize processed proteins

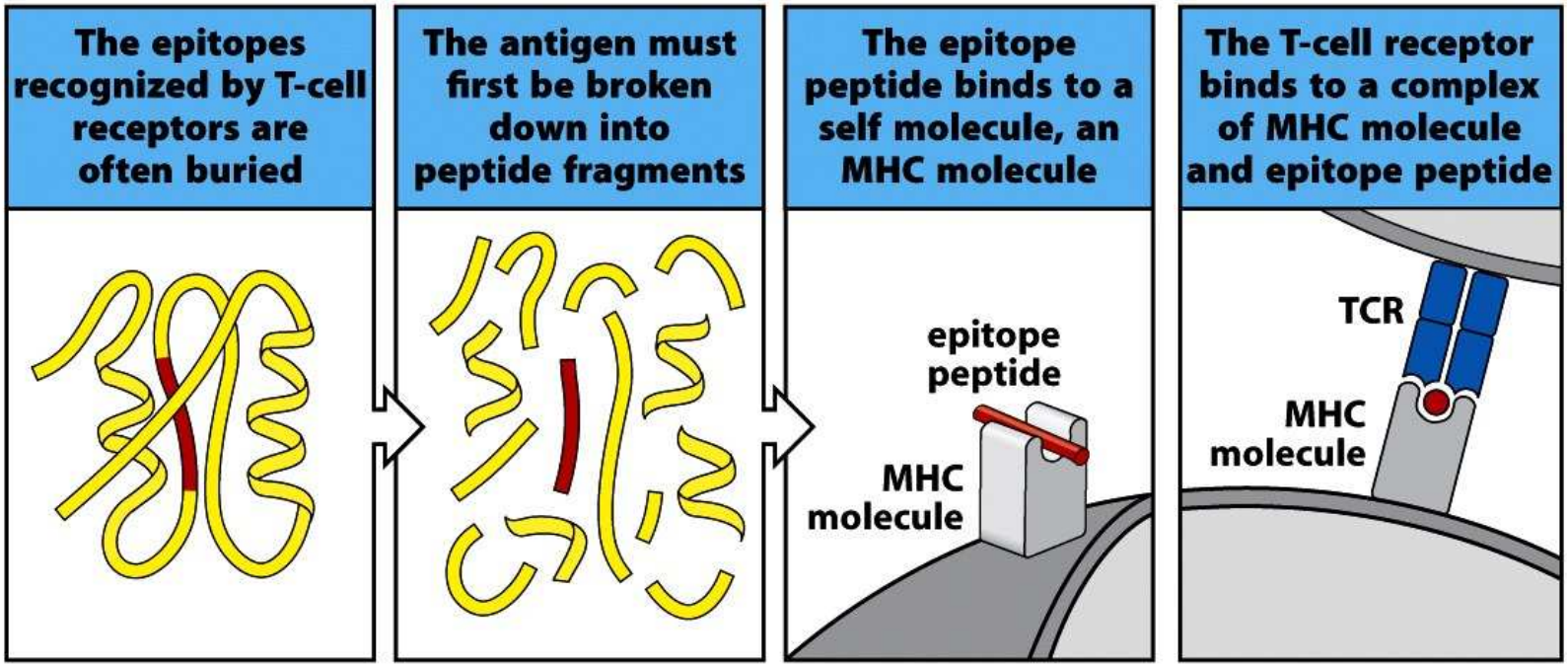
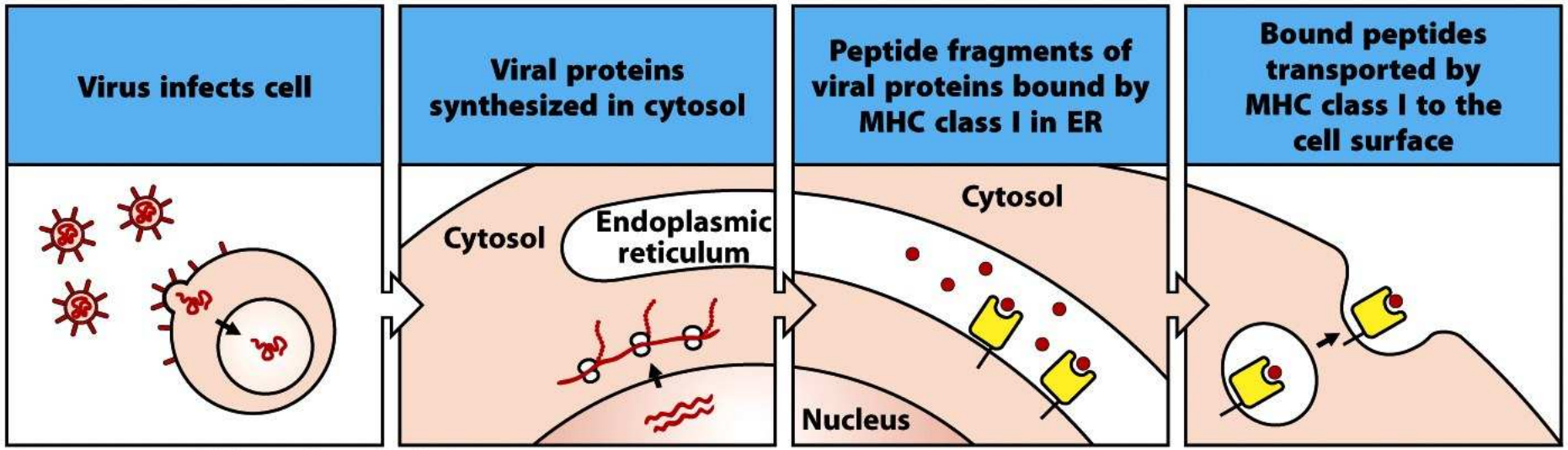


Figure 1-16 Immunobiology, 7ed. (© Garland Science 2008)

Understand what "epitope" means-
how are TCR epitopes different from Ab epitopes?

(MHC= Major Histocompatibility Complex)

MHC Class I presents peptide antigens to CD8 T cells



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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 Class II presents peptide antigens to CD4 T cells

Macrophages:

B cells:

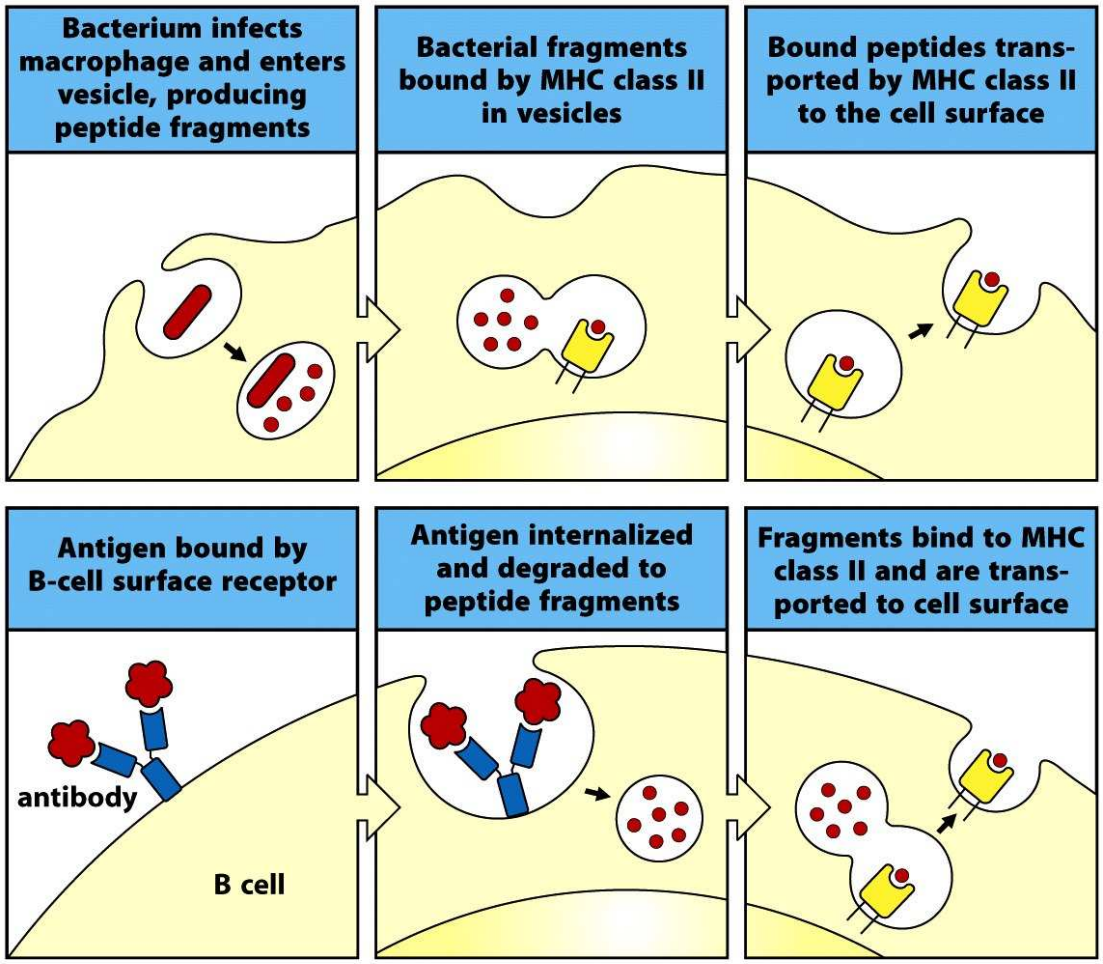


Figure 1-31 Immunobiology, 7ed. (© Garland Science 2008)

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

Each lymphocyte has a unique specificity

<u>Development</u>

-Generation of vast pool of cells

-Shaping the repertoire

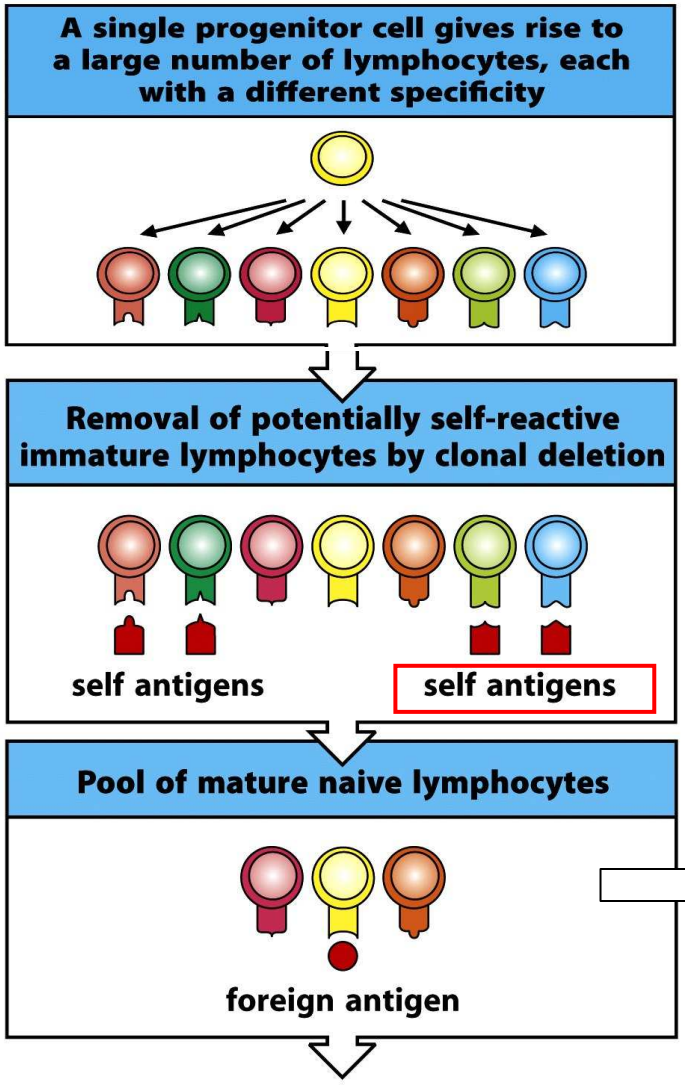


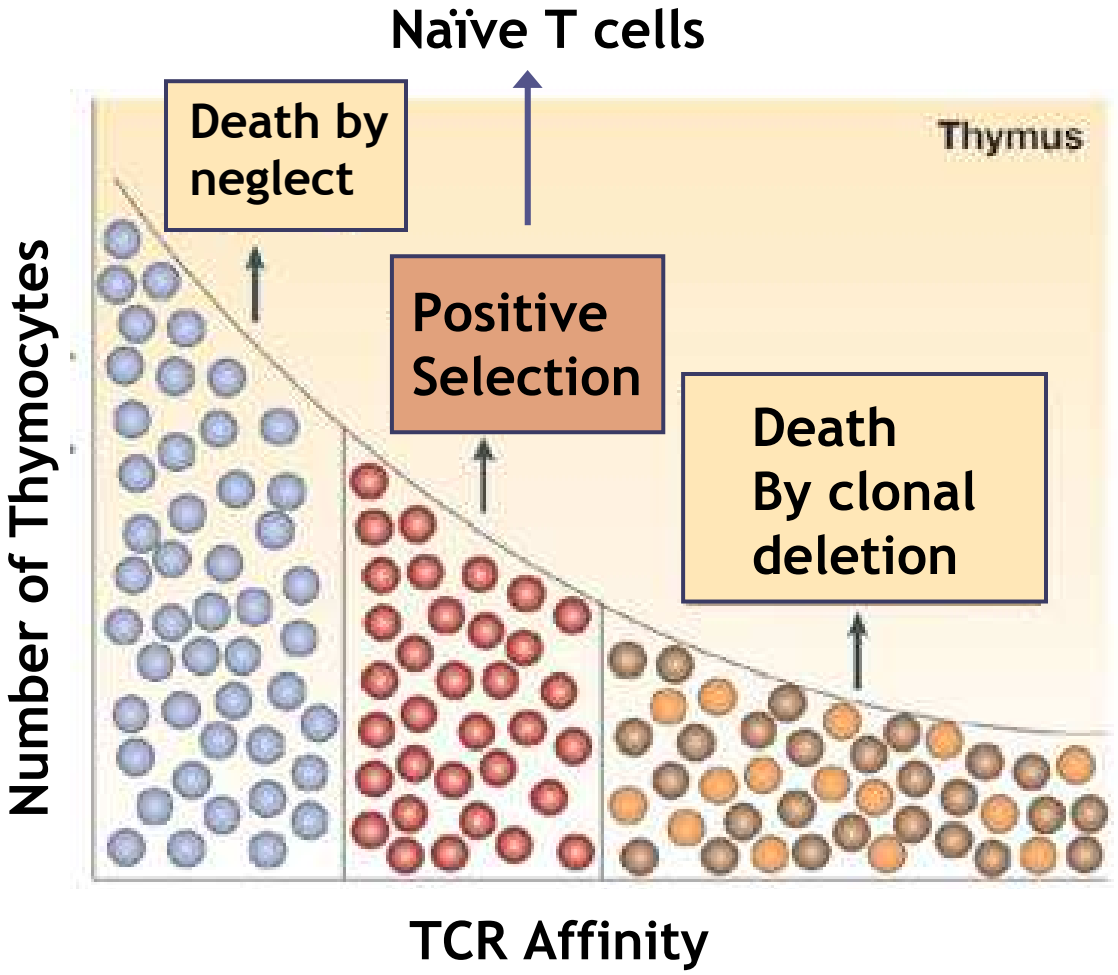
Figure 1-11 part 2 of 3 Immunobiology, 7ed. (© Garland Science 2008)

Immature cells (non-functional)

One barrier to inducing responses against tumor cells

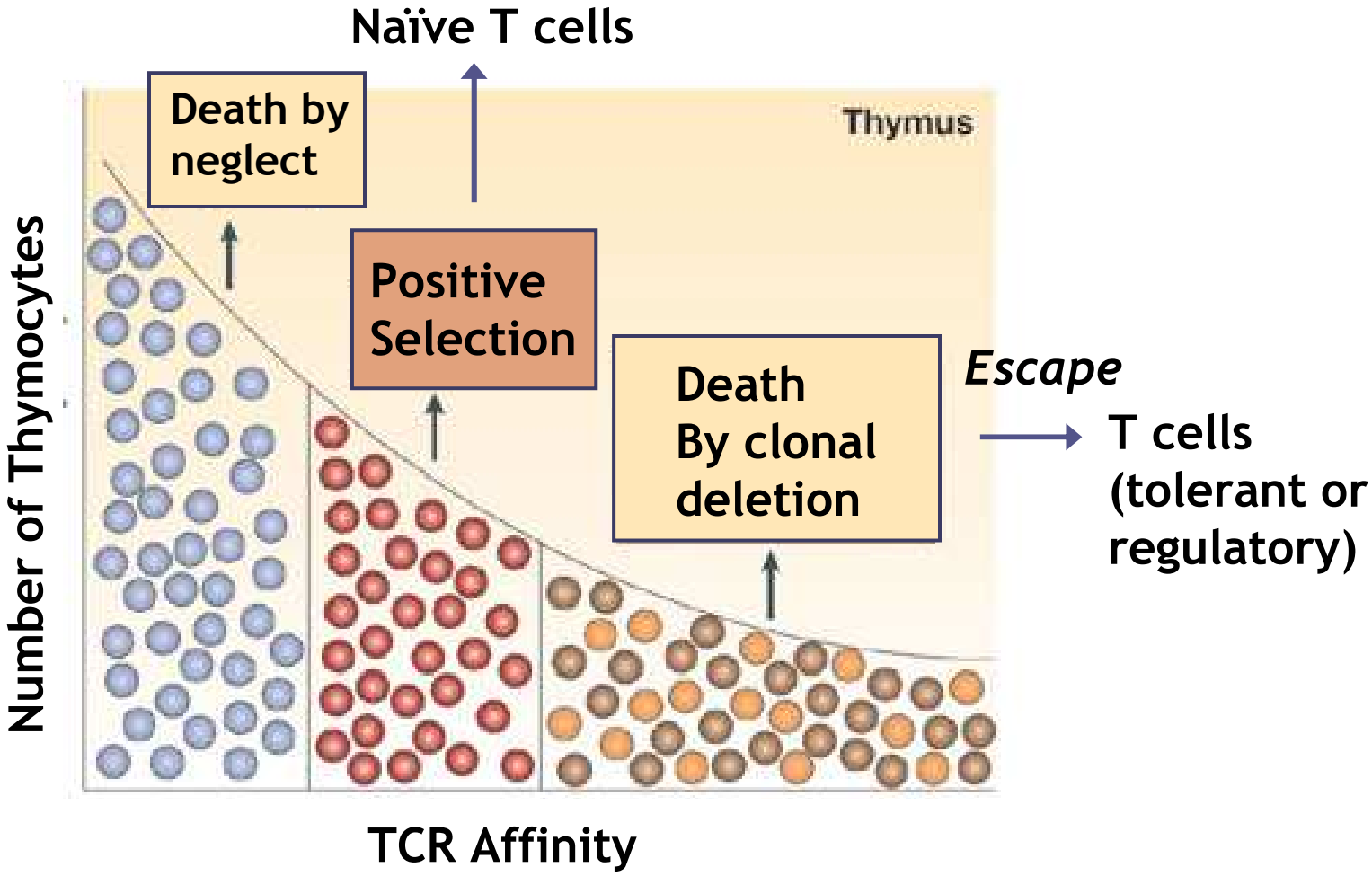
Circulating mature naïve cells

Only a small portion of thymocytes become mature T cells



Hogquist, K.A. et al 2005

Some T cells escape negative selection



Hogquist, K.A. et al 2005

Clonal Expansion

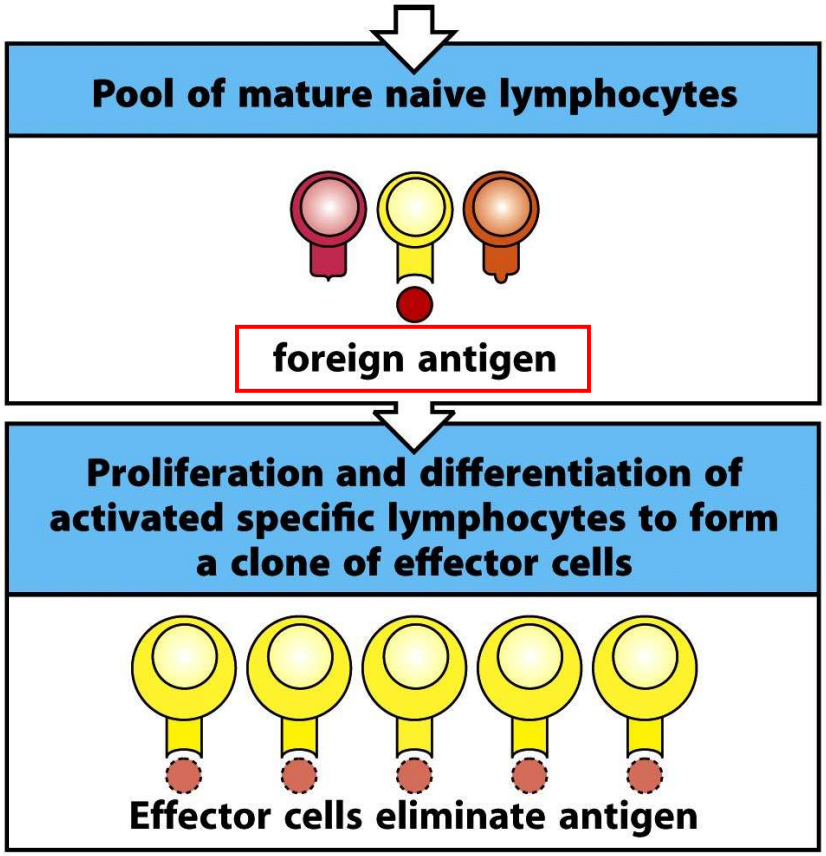


Figure 1-11 part 3 of 3 Immunobiology, 7ed. (© Garland Science 2008)

Cells that recognize a specific Ag are <u>very rare</u>

These all have the same specificity

What is the purpose of clonal expansion?

Central Principle of Adaptive Immunity

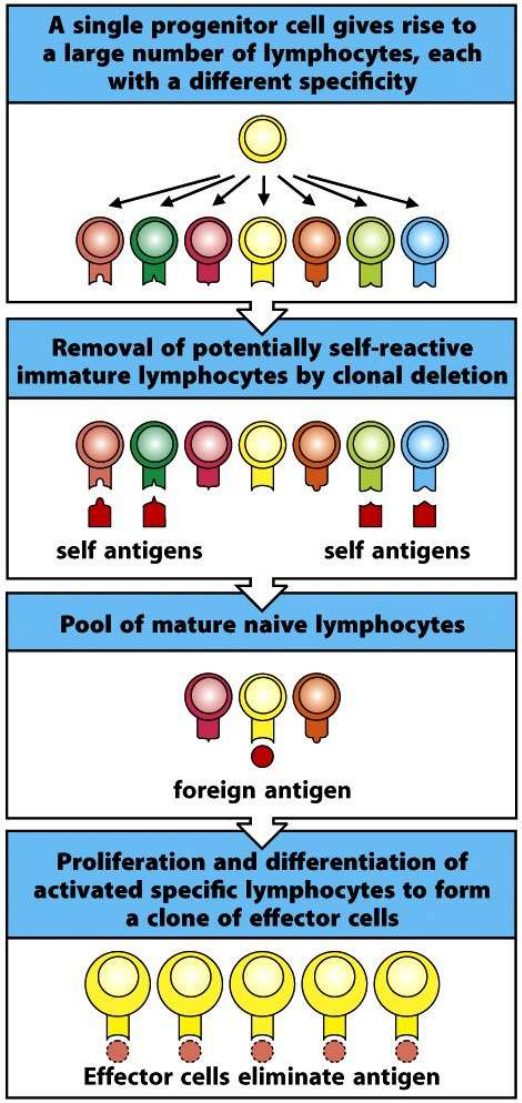


Figure 1-11 Immunobiology, 7ed. (© Garland Science 2008)

Each T/B cell has unique Ag R

T/B cells that recognize self are eliminated

Recognition of Ag lead to activation

Effectors derived from parent cell all have the same Ag R

Where does lymphocyte development and activation occur?

Primary Lymphoid Tissues

Secondary Lymphoid Tissues

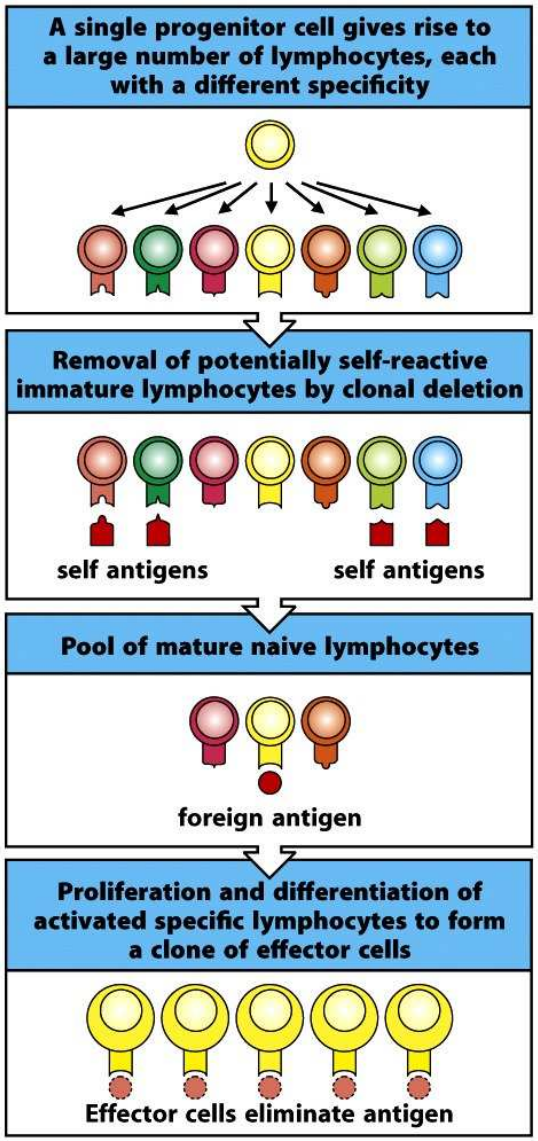


Figure 1-11 Immunobiology, 7ed. (© Garland Science 2008)

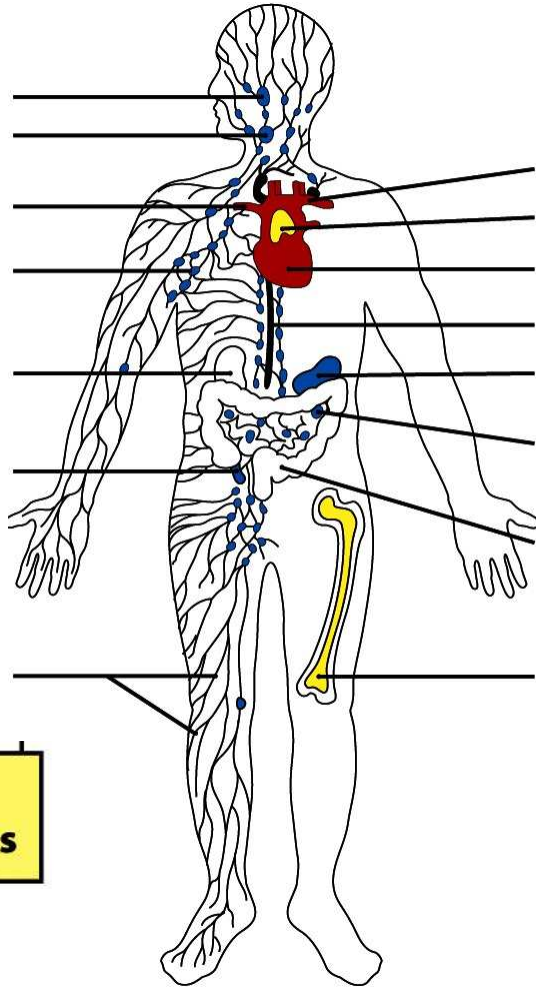
T cells develop in the Thymus

B cells develop in the bone marrow

T and B cell stimulation occur in the lymph nodes and spleen

Primary and Secondary Lymphoid Organs

Lymph Nodes collect lymph and antigen from peripheral sites



The Spleen collects antigens from circulating blood

Antigens from sites of infection reach lymph nodes via lymphatics

nd Science 2008)

LNs are prime site for lymphocyte stimulation

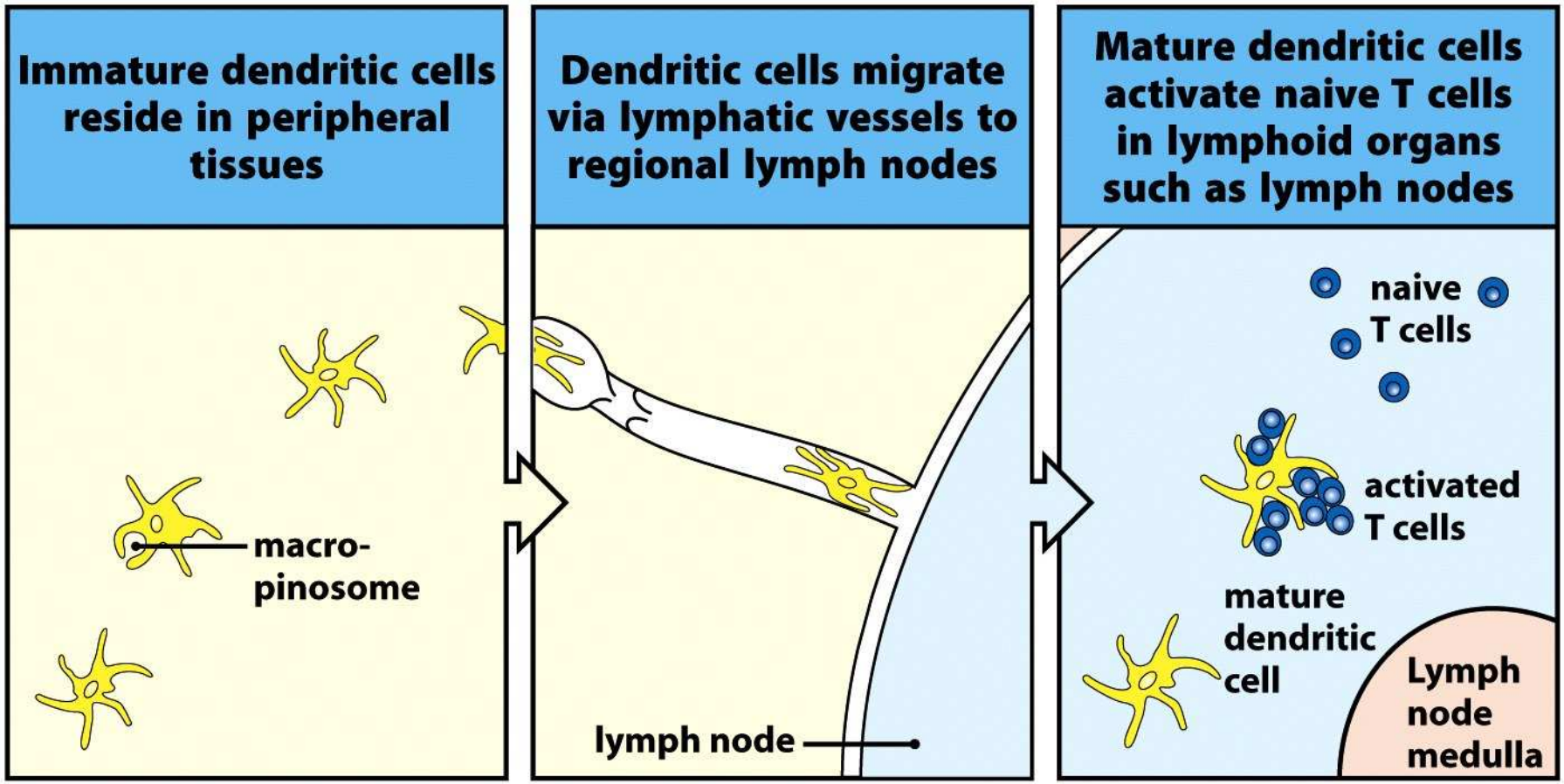


Figure 1-9 Immunobiology, 7ed. (© Garland Science 2008)

Stimulation of Lymphocytes

**Must be mature DC*

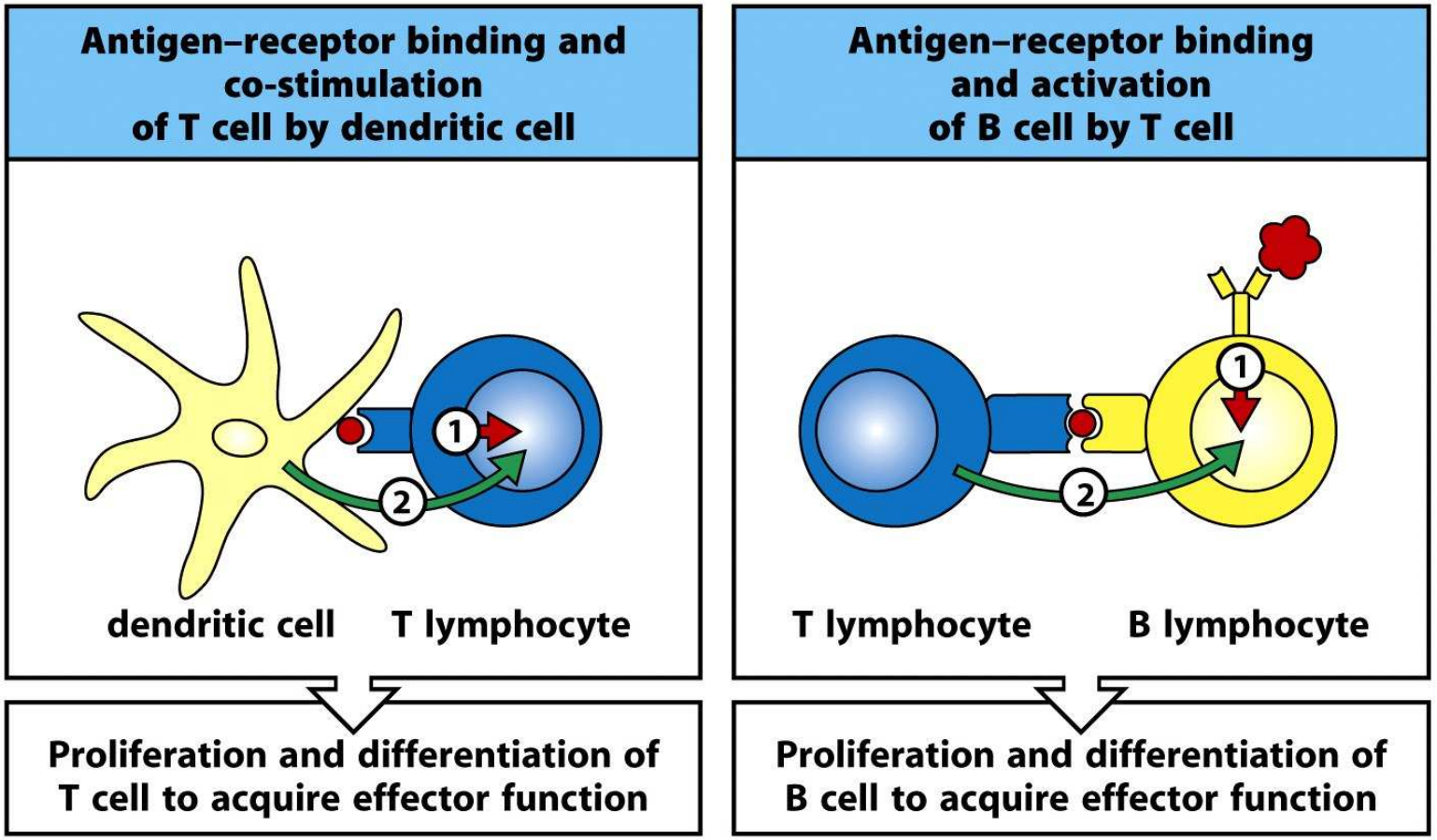


Figure 1-21 Immunobiology, 7ed. (© Garland Science 2008)

Both T and B cells require stimulation thru AgR (Signal 1) and additional costimulation (Signal 2)
Absence of costimulation leads to tolerance

T cell Activation

"Naive"

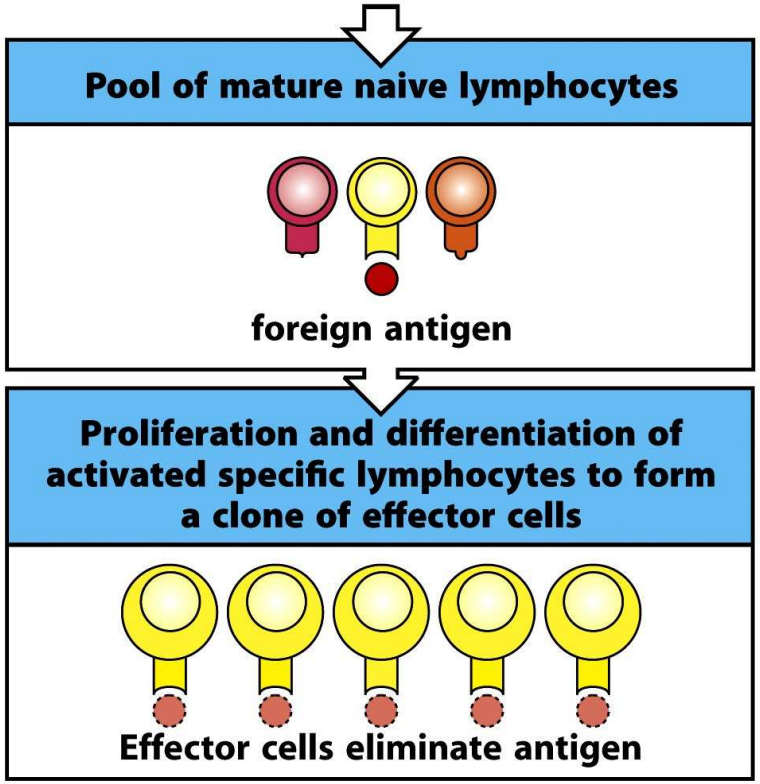


Figure 1-11 part 3 of 3 Immunobiology, 7ed. (© Garland Science 2008)

"Activated" or "Effectors"

Results in:

1. **Expansion**
2. **Acquisition of effector functions**

Effector Mechanisms of Adaptive Immunity
CD8+ T Cells (Cytotoxic T cells)

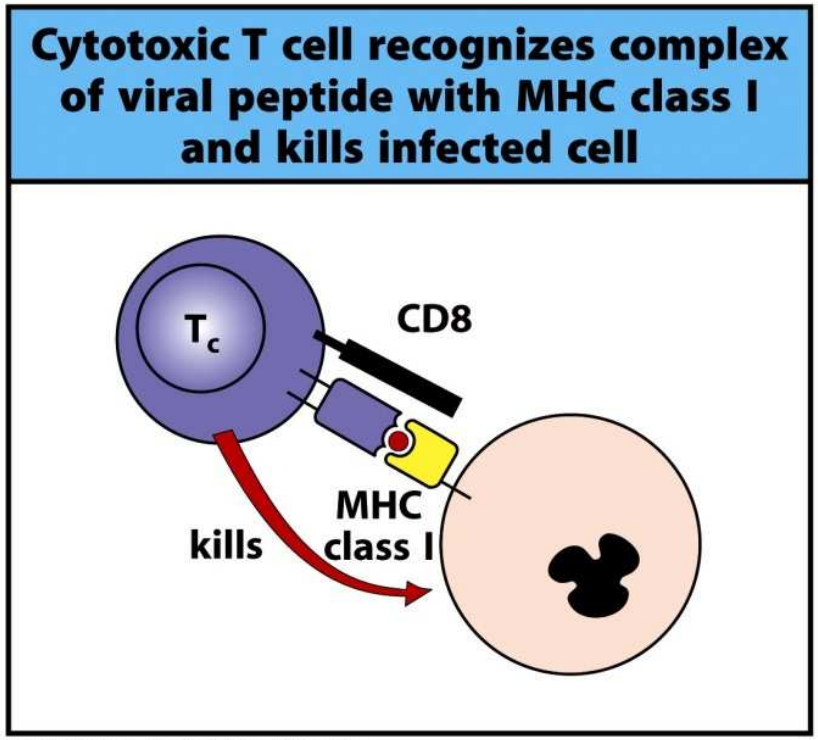


Figure 1-32 Immunobiology, 7ed. (© Garland Science 2008)

- Recognize transformed and virus infected cells
- Confer cytolytic activity
  - Release perforin, granzyme, IFN-γ, TNF-α
  - Induce apoptosis
- Majority of cancer vaccines are designed to stimulate CD8 T cell response

Effector Mechanisms of Adaptive Immunity

CD4+ Helper T Cells

Th1

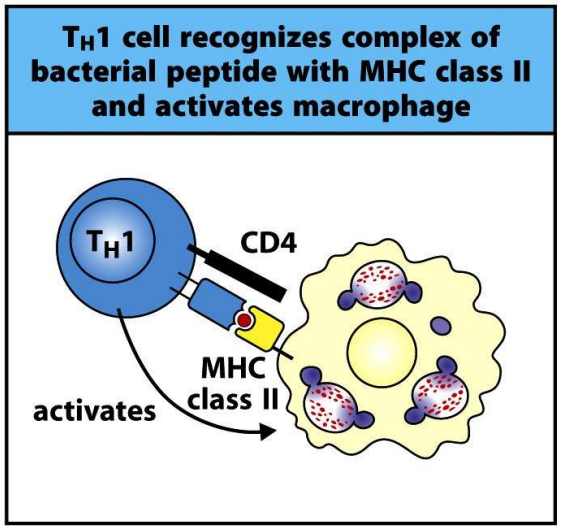
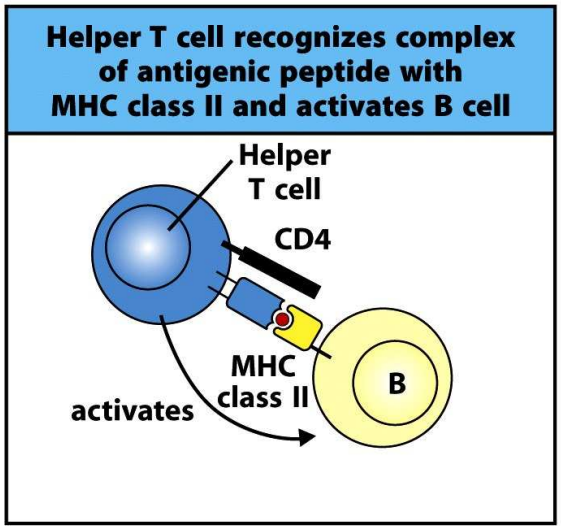


Figure 1-33 Immunobiology, 7ed. (© Garland Science 2008)

- Regulate development and persistence of cell-mediated immunity
- IL-2, INF-γ

Th2



- Enhance humoral immune responses; B cell maturation, clonal expansion, class switching
- IL-4, IL-5, IL-6, IL-10, IL-13

Effector Mechanisms of Adaptive Immunity

CD4+ Helper T Cells

Th17

- Play role in inflammation and tissue injury
- Stimulates anti-microbial responses by epithelial cells
- Recruits, stimulate Neutrophils
- May mediate regression of tumors
- IL-17, IL-22

Treg

- Recognize self Ag
- inhibit or suppress other adaptive immune responses
- IL-10, TGF-β

Effector Mechanisms of Adaptive Immunity

B Cells

Ab help eliminate extracellular pathogens

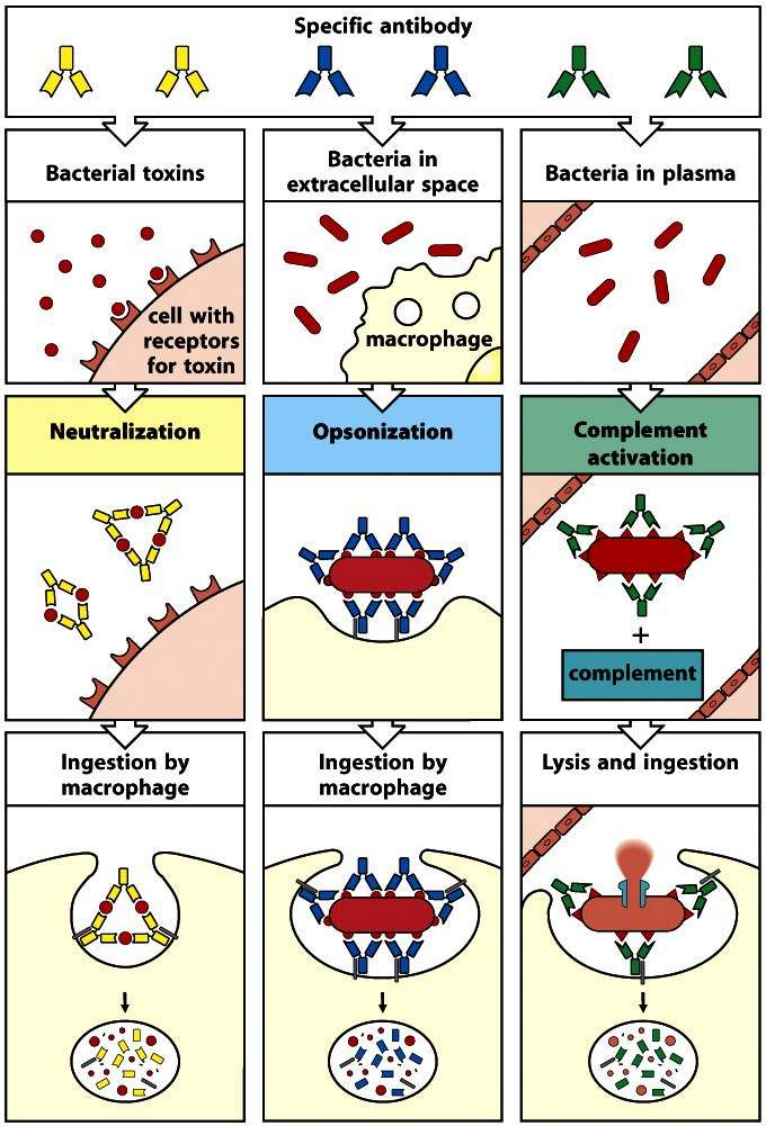


Figure 1-26 Immunobiology, 7ed. (© Garland Science 2008)

Ab can be used to eliminate large subsets of cells- Example:Rituximab = Ab against B cell cell surface molecule

Lymphocyte Activation

"Naive"

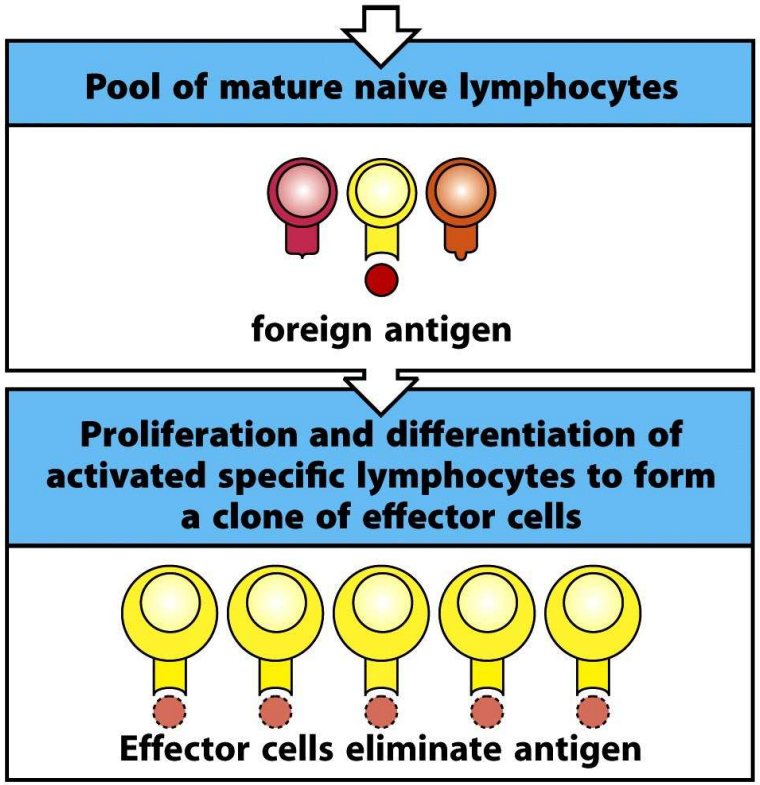


Figure 1-11 part 3 of 3 Immunobiology, 7ed. (© Garland Science 2008)

"Activated" or "Effectors"

Results in:
1. Expansion
2. Acquisition of effector functions
3. ?

What happens to T cells and B cells after antigen is gone?

Activation of B cells generates Ab-producing plasma cells and memory B cells

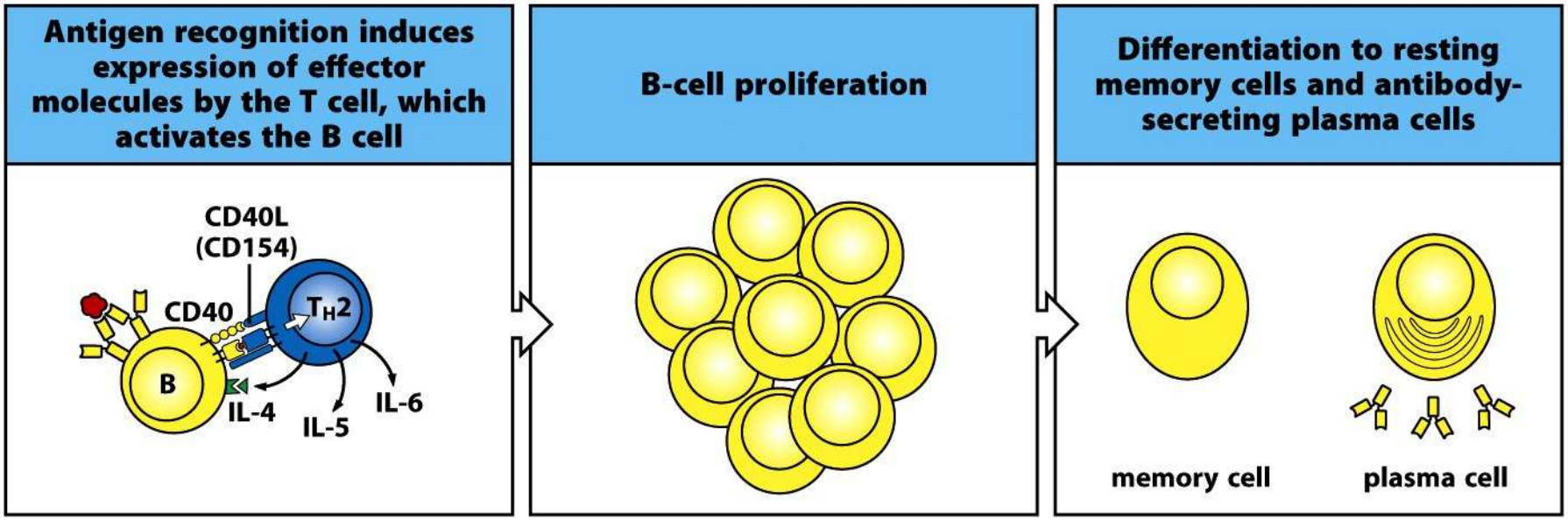


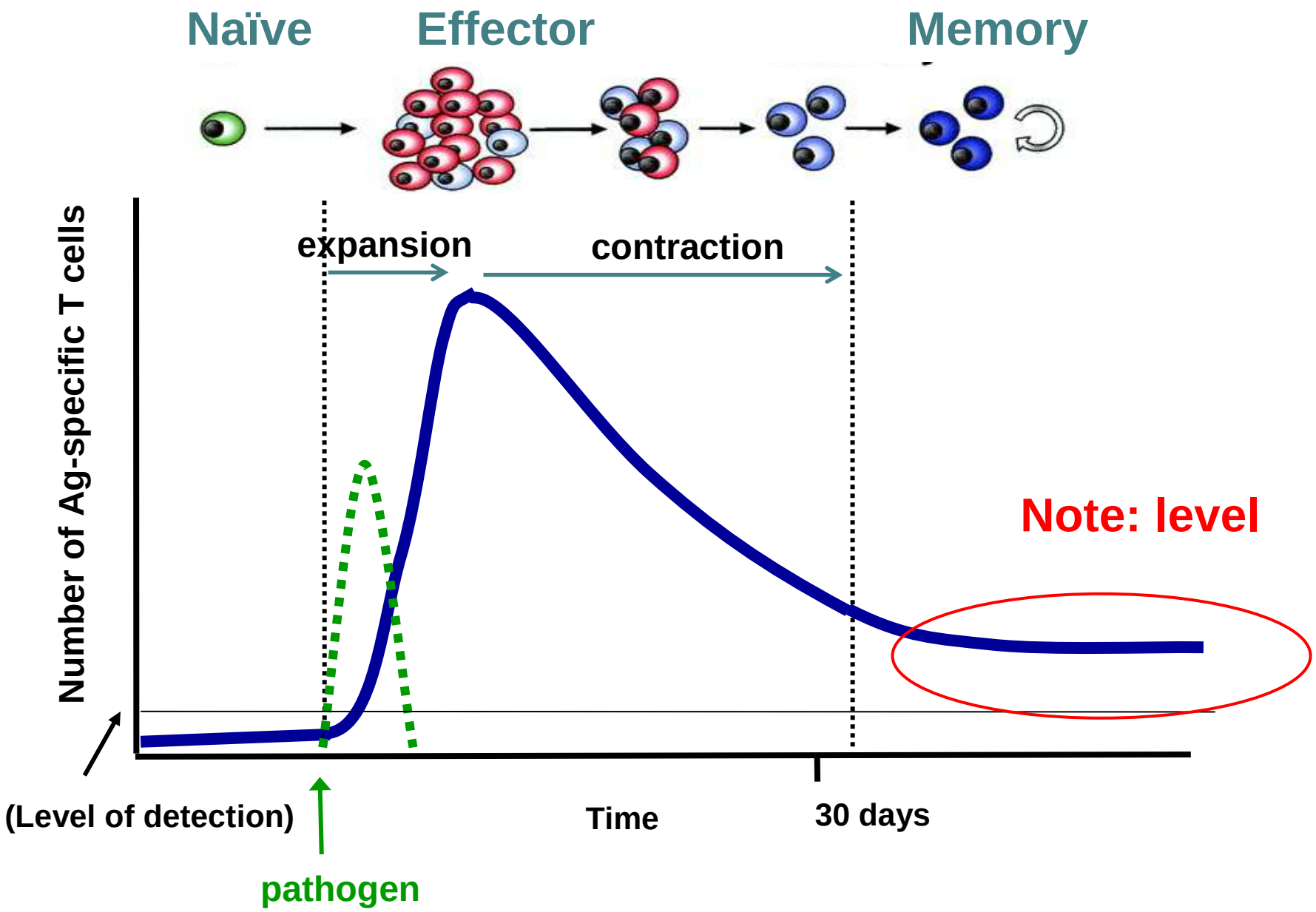
Figure 9-3 Immunobiology, 7ed. (© Garland Science 2008)

(Lymphoblast
Plasmablast)

Cytokines also induce class switching

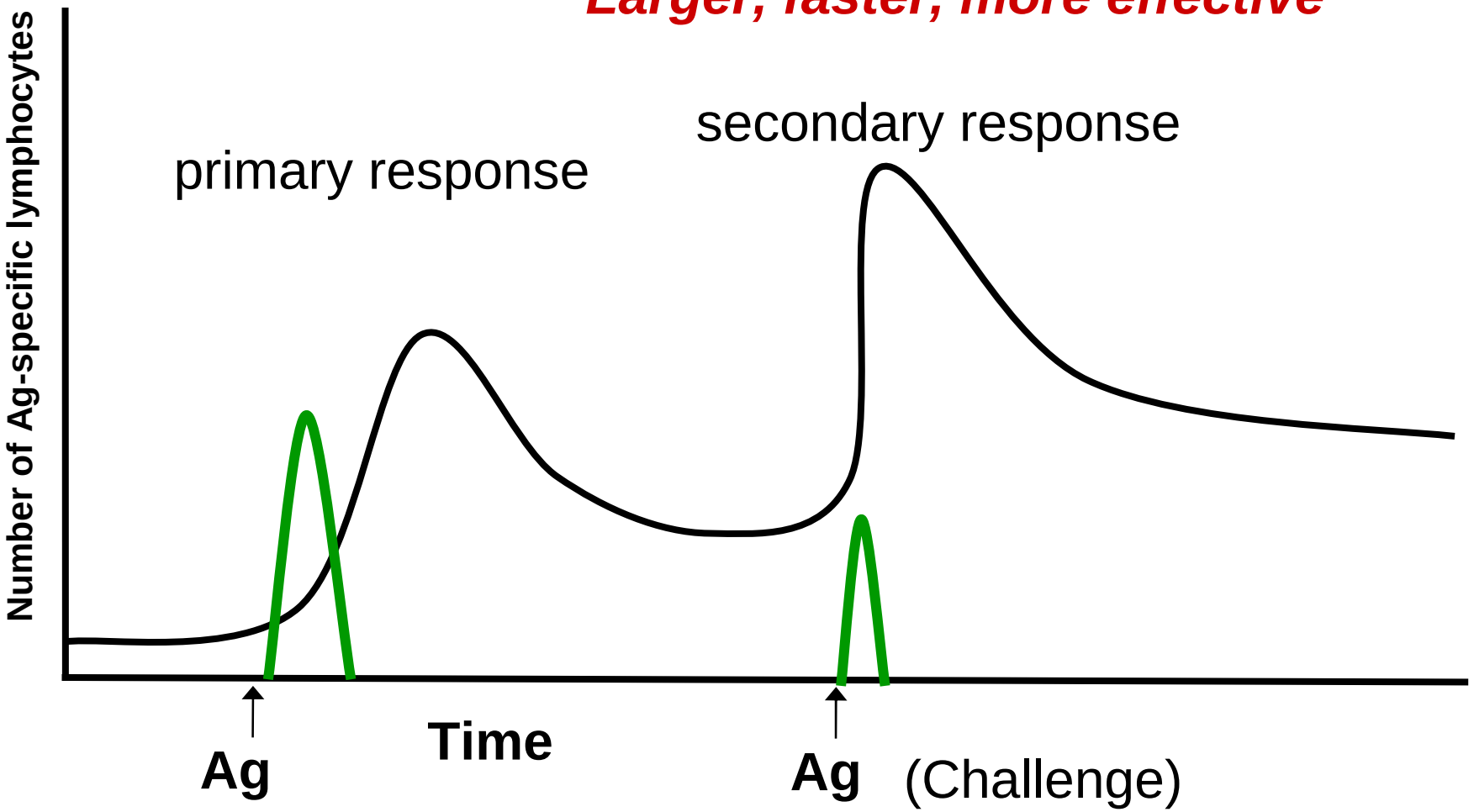
Earlier phases are dominated by IgM, later IgG and IgA are predominant

Generation of memory lymphocytes



Significance of Immunological Memory

Larger, faster, more effective

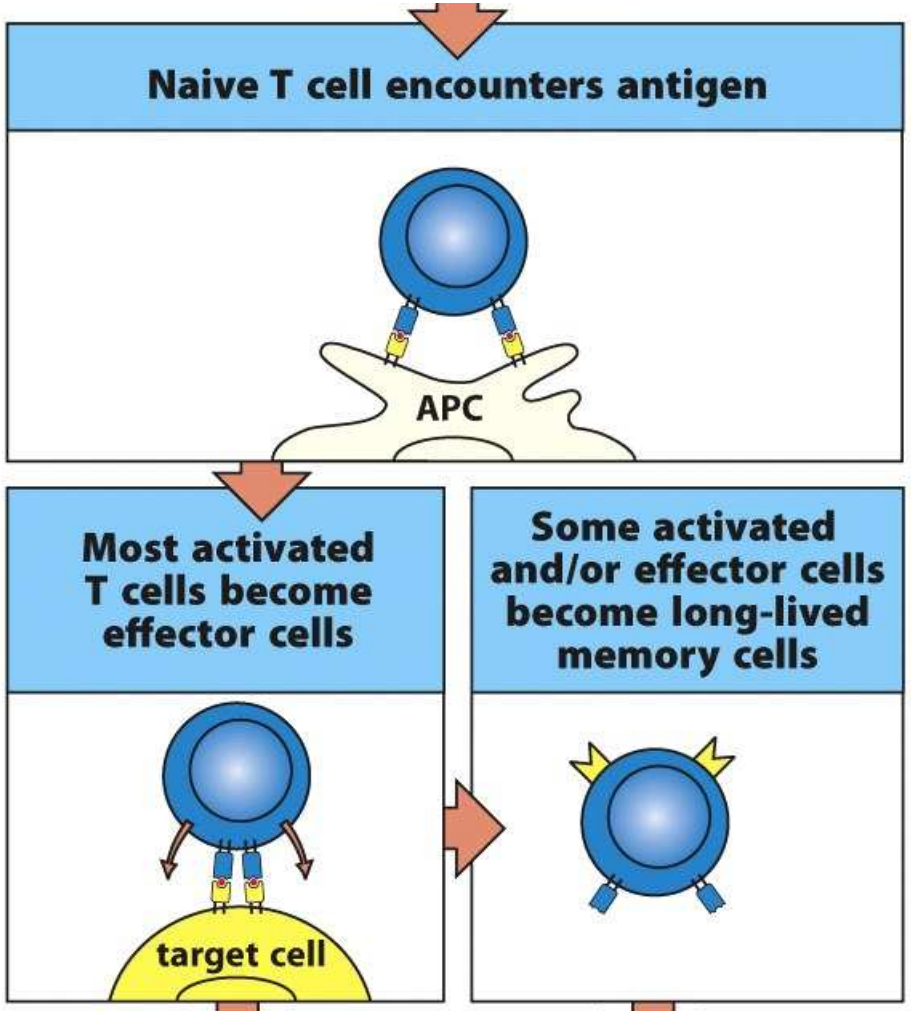


Why is a secondary immune response larger, faster, and more effective?

Efficacy of memory T cells

- Ag-specific memory T cells are present at higher levels than naive T cells
- Reactivation of memory T cells occurs within a few hours, while naïve T cell activation require days
- Memory T cells are anatomically dispersed
- Memory T cells are long-lived, self renewing, and Ag-independent

Some activated T cells become effectors while others become memory T cells



Memory T cells are heterogeneous in their migratory and functional abilities

Effector memory T cells

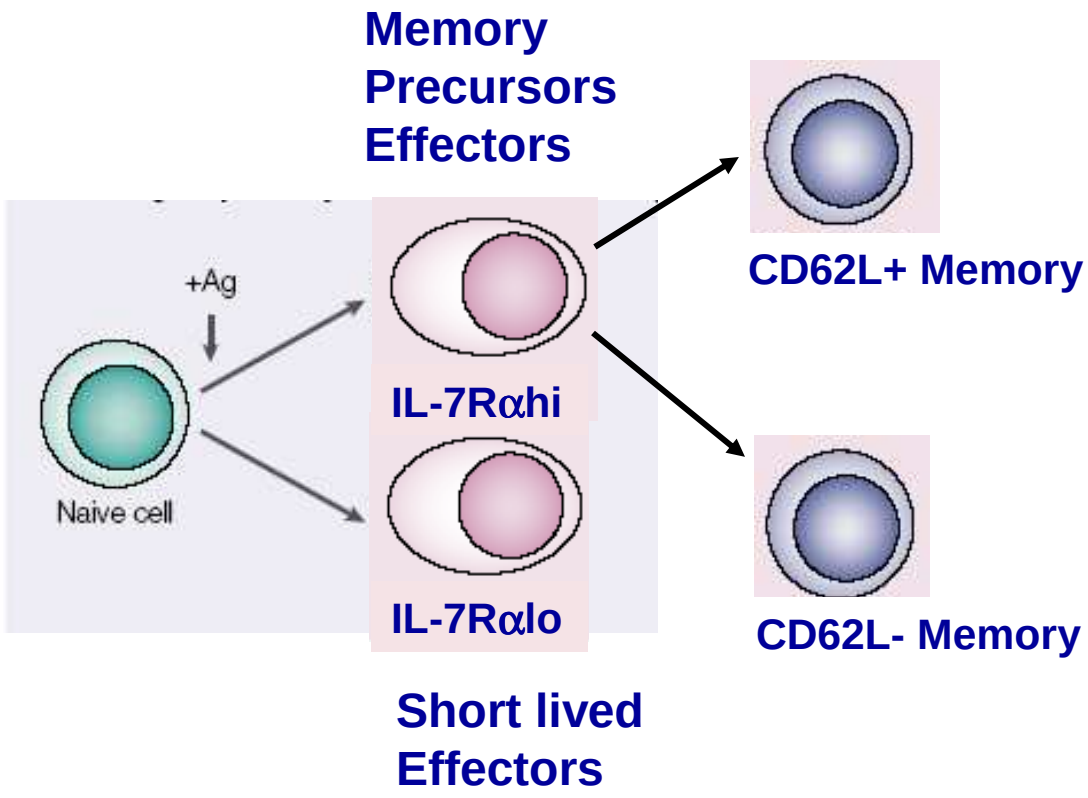
- L-selectin- CCR7-
- Preferentially migrate through tissues
- Possess immediate effector functions

Central memory T cells

- L-selectin+ CCR7+
- Preferentially migrate to secondary lymph. organs
- Respond optimally to challenge

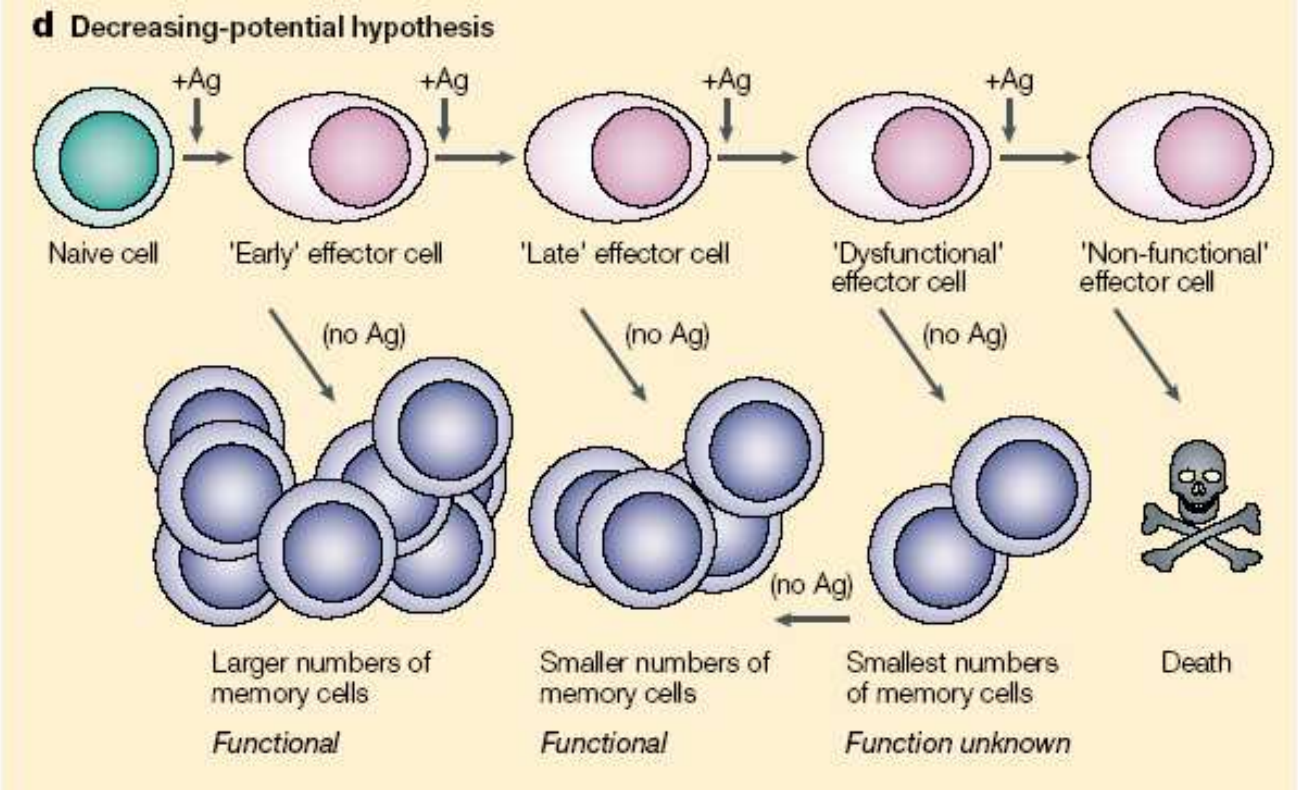
With the increased effector functions and non-lymphoid localization, effector memory T cells (Tem) are thought to act as a first line of defense; whereas central memory T cells (Tcm) may provide more long lasting protection.

Effector and central memory T cells are both derived from memory precursor



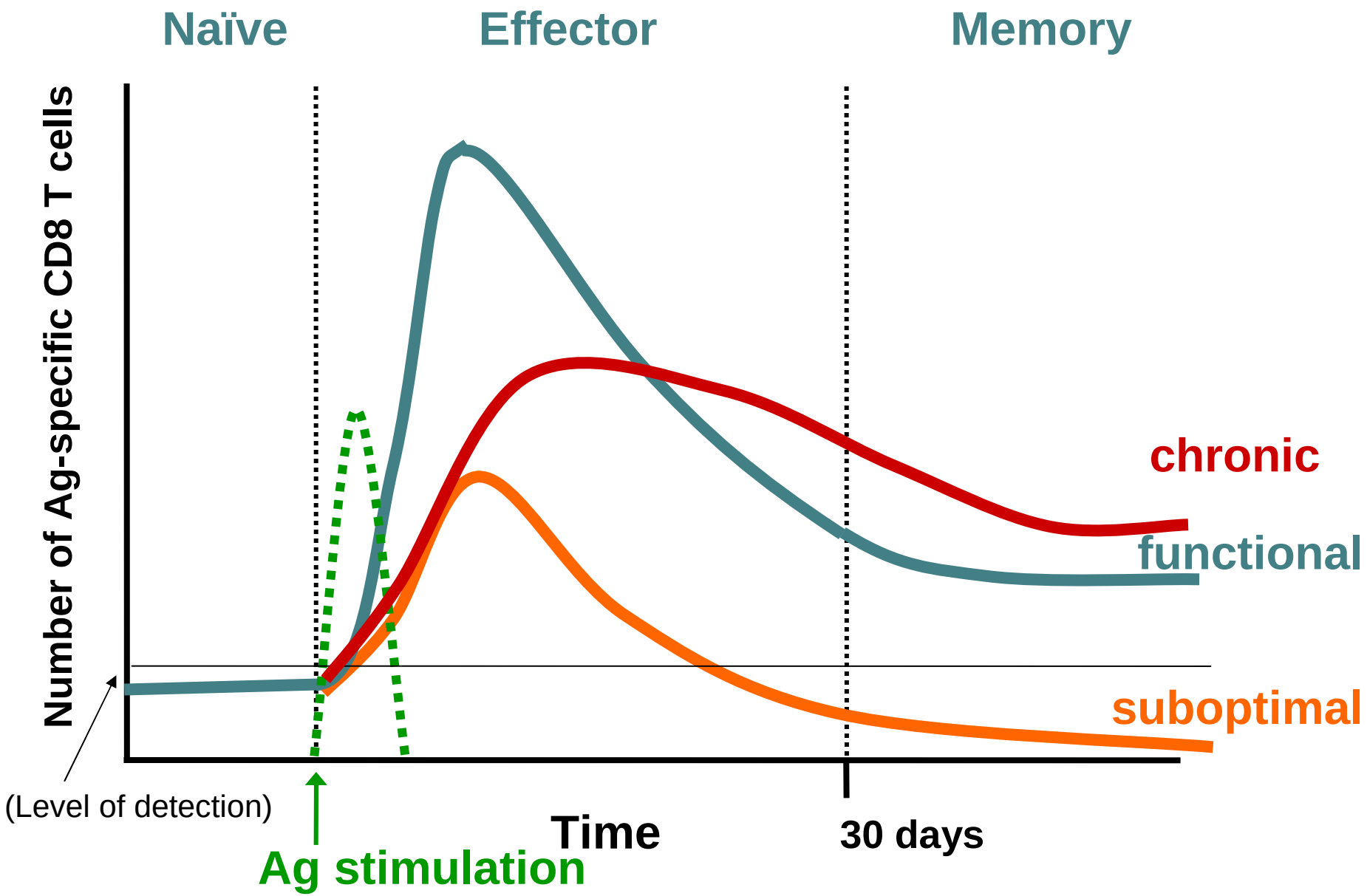
Too much Ag stimulation can lead to the generation of dysfunctional T cells or the absence of memory T cells

Observed in tumors and chronic infections



Exhausted T cells often show a specific phenotypic signature (PD-1, Tim 3, LAG-3)

Dynamics of a T Cell Response



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)

Immune Regulation

Myeloid-derived Suppressor cells

- Heterogeneous, immature myeloid phenotype
- Includes tumor-associated macrophages, which produce IL-10 and TGF-β, but not cytolytic factors
- Suppress via arginase, iNOS
- Expand during inflammation, infection, and cancer
- Enriched in the tumor microenvironment

T regulatory cells

- Inhibit or suppress other adaptive immune responses
- Multiple subsets, with different developmental origins
- CD4+Foxp3+ T regs, recognize self Ag, produce TGF-β and IL-10, are generated during development or induced from naïve T cells in the periphery
- TH3 cells- produce TGF-β and IL-10, found in mucosa
- Enriched in the tumor microenvironment

Function of Immune Reponses

- **Immune Recognition**

  Various immune cells use different mechanisms to recognize foreign entities- TLR, NK cell R, 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**

Tregs, myeloid-derived suppressor cells

Questions

1. Innate immune responses
a)are initiated after adaptive immune responses are elicited
b)become more efficient throughout one's lifetime
c)are important for successful vaccination
d)are capable of distinguishing mutated proteins expressed by tumors
e)none of the above

Questions

2. Adaptive immune responses

a)are present at birth

b)are specific for general types of pathogens

c)are capable of generating long lasting immunity

d)are mediated by NK cells and T cells

e)none of the above

Questions

3. T cells
a)each express antigen receptors with one unique specificity
b)that are specific for self-proteins are preserved during development
c)that are naive undergo activation within a few hours
d)require stimulation through only their TCR receptor for efficient activation
e)none of the above

Questions

4. Regarding Antigen Recognition:
a)T cell antigen receptors (TCR) recognize proteins in their natural structure
b)Antibodies recognize processed peptide antigens presented on the cell surface
c)TCRs recognize peptide antigens presented by MHC Class I and II molecules
d)Antibodies are expressed only as a soluble form
e)none of the above