IMMUNE SYSTEM (I)

VU UG PHYSIOLOGY

B.Sc. General CBCS

Semester II

Core Course

DSC1BT

Virtual Class

session- 2019-2020

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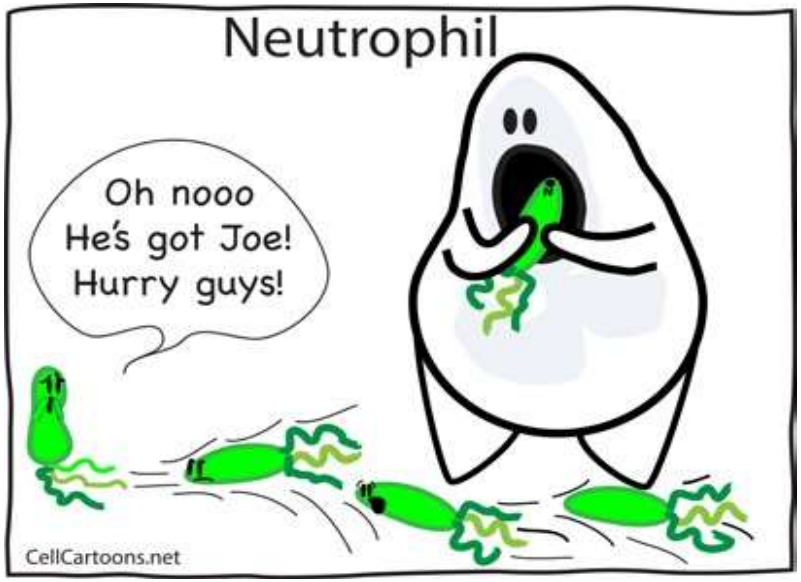
Syllabus

- **Immune System**
  Overview, properties of immune system, types of immunity : innate immunity, acquired immunity, active and passive immunity. First and second line defence. Humoral and Cell mediated immunity. Complement system. Immune Competent cells : structure and functions of neutrophil, B lymphocytes, T- lymphocytes (helper, cytotoxic and suppressor), Natural killer cells, monocytes – macrophages. Primary and Secondary lymphoid organs. Antigen and Antibody : Properties of immunogen, antigens and haptens. Classification, structure and functions of immunoglobulins. Antigen- antibody reaction, physiological effects and clinical significances. Major Histocompatibility Complex.. Brief idea of auto immunity. AIDS. Transplantation immunity. Vaccination : Immunization- Passive and active immunozation. Immunizing agents. Vaccine. Antisera. Vaccination. Toxin and Toxoids.

Immunology

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

- Immunology is the study of the ways in which the body defends itself from infectious agents and other foreign substances in its environment. The immune system protect us from pathogens. It has the ability to discriminate (differentiate) between the individual`s own cells and harmful invading organisms.



Our bodies' defenses are similar to a military defense

- The initial defence mechanisms are barriers: skin
  acid
  bile
  mucus
- These barriers inactivate and prevent entry of the foreign agents
- **Immune system has two lines of defense:**

1. Innate (non specific) immunity

2. Adaptive (specific) immunity

If these barriers are compromised or the agent gains entry in another way

- The local militia of innate responses (e.g., complement, natural killer cells, neutrophils, macrophages)

- must quickly rally to the challenge and
- prevent expansion of the invasion

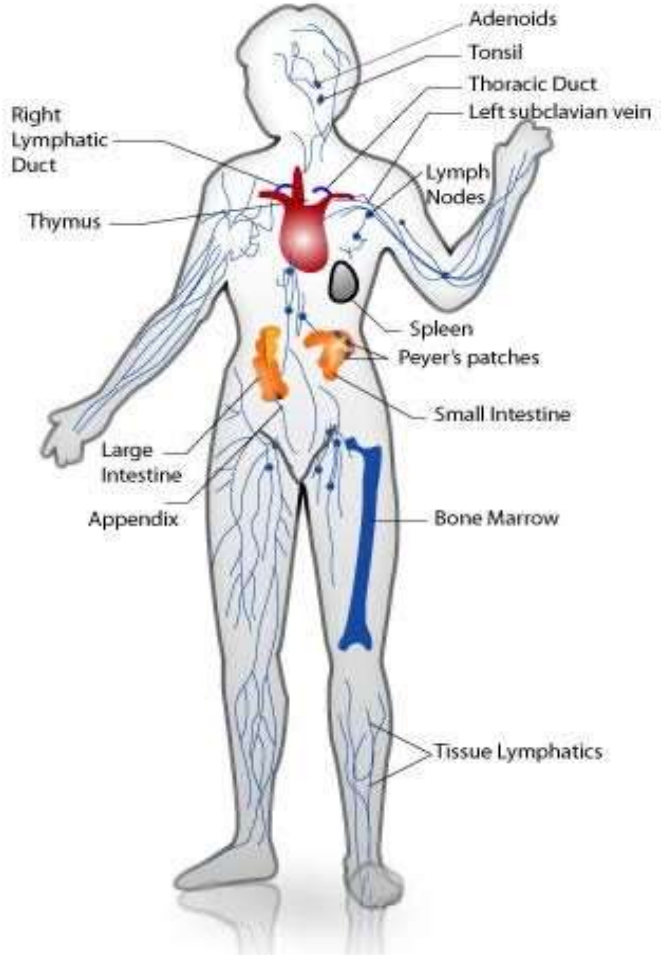
If this step is not effective

- a major campaign must be specifically directed against the invader by immune responses (antibody and T cells)
- knowledge of the characteristics of the enemy (antigens) through immunization,
- enables the body to mount a faster, more effective response (activation of memory B and T cells on rechallenge

The interactions of elements of the immune response

- The different elements of immune system interact and communicate with soluble molecules and by direct cell-to-cell interaction.
- These interactions provide the mechanisms for activation and control of the protective responses.

Functions of the immune system



Protection

Identify and destroy pathogens
Cancer

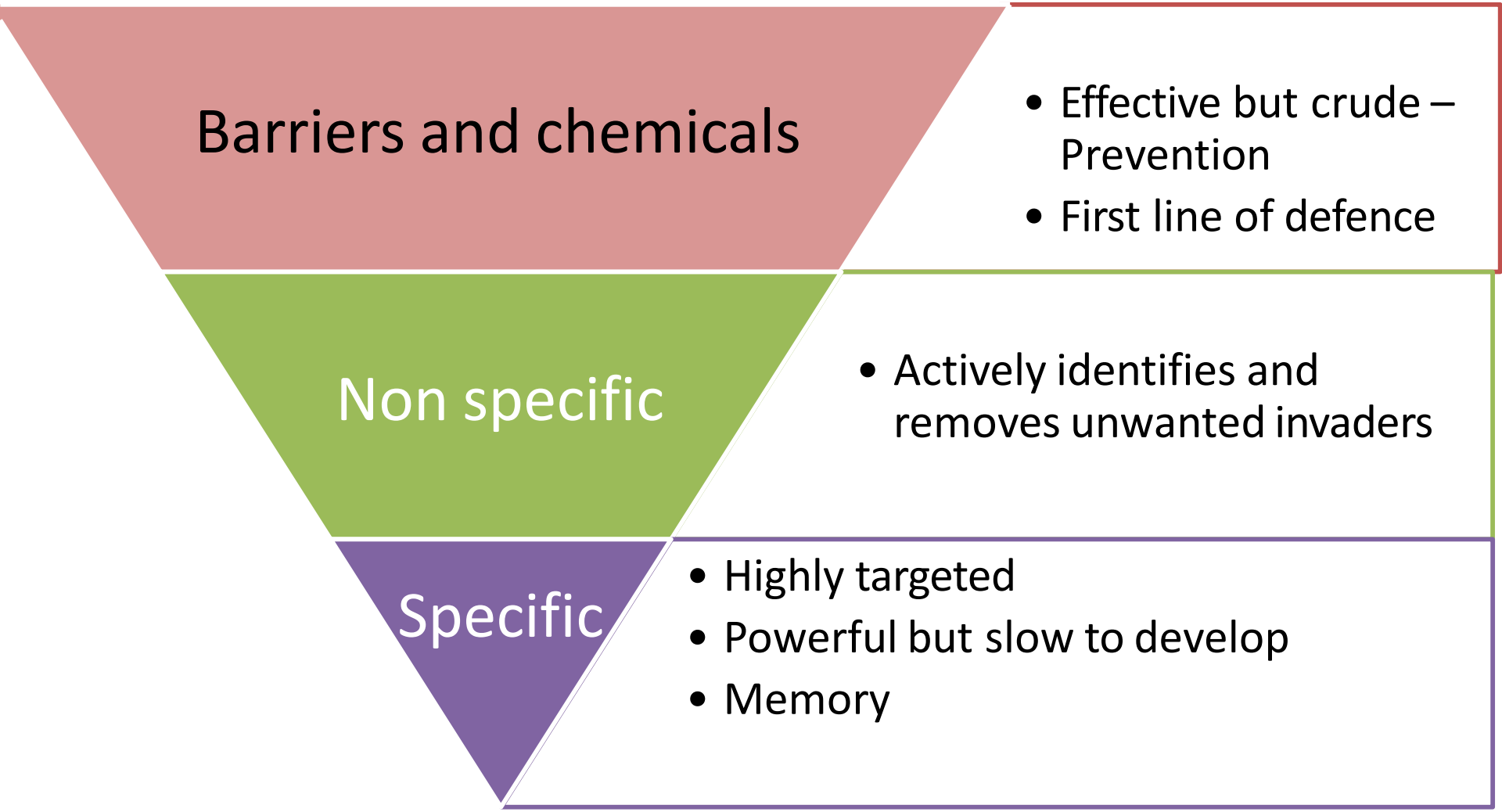
Housekeeping

Removal of debris and dead cells
Surveillance

Communication

Chemical messages
Antigen presentation
Memory

Hierarchy of defences



Self from non-self - First step to immunity

- Recognise molecular shapes
- Our own cells have a unique ‘self’ tags on them
- Learn to ignore ‘self’ in early development

Innate Immunity

- **Characters**

1. 1st line of defense
2. Rapid defense
3. The same on re-exposure to Ag
4. No memory cell
5. Recognize and react against microbes only
6. Block entry of microbes and eliminate succeeded microbes which entered the host

Innate Immunity

Components:

1 Barriers:

a. Physical barriers: protect against invasion of microbes eg epidermis & keratinocyte & epithelium of mucus membrane & cilia

b. Mechanical barrier : longitudinal flow of air and fluid & movement of mucus by cilia

c. Chemical barriers:
Skin: α & β defensin & lysozyme & RNase & Dnase
Resp Tract: β defensin
GIT: α defensin & pepsin & lysozyme
HCL of stomach: kill ingested microbes
Tears in eye: lysozyme

d. Biological barriers: commensal microbes or flora inhibit growth of pathogenic bacteria

Innate Immunity

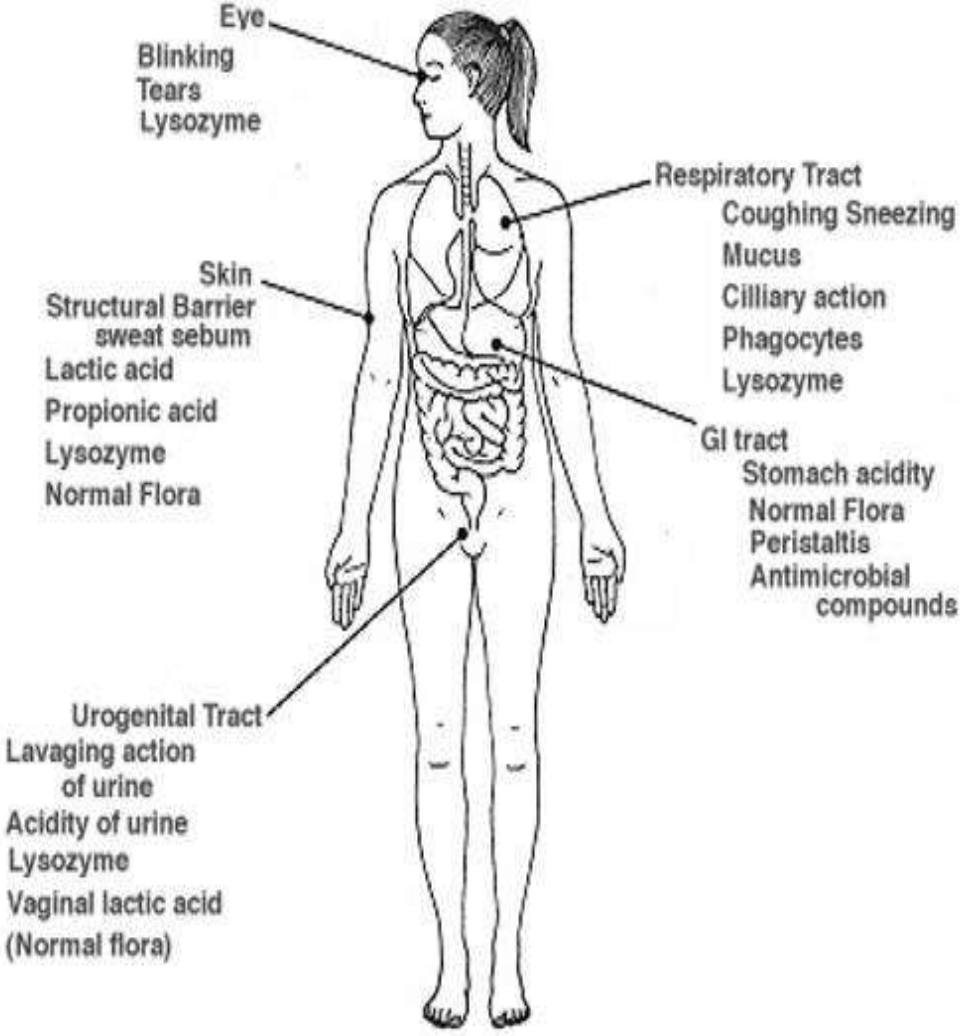
2. Innate immune cells: phagocytes (Macrophage & neutrophil)& NK cells
3. Cytokines: TNF &IL1& IL12& IFNγ & chemokines
4. Complement: Alternative pathway & lectin pathway
5. Other plasma proteins (acute phase response):

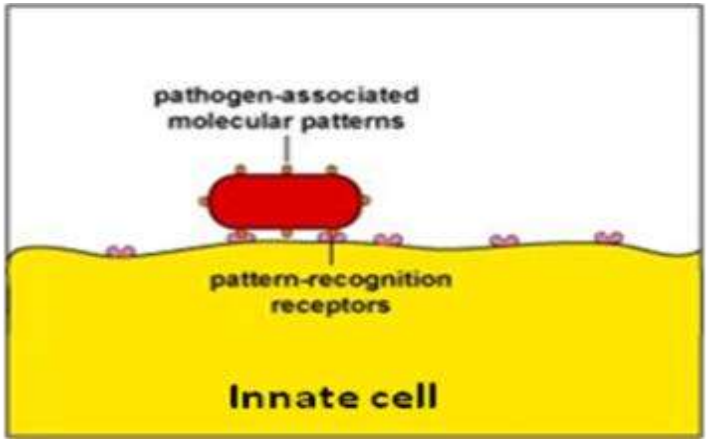
↑ Mannose Binding Lectin : participate in lectin pathway of complement

↑ C Reactive Protein: coat microbes and help in phagocytosis

NB: Recognition of microbes by the innate system: the receptors of innate cells (pathogen-recognition receptors) recognize structures called pathogen- associated molecular patterns (PAMPs) shared by different microbes

Innate Immunity





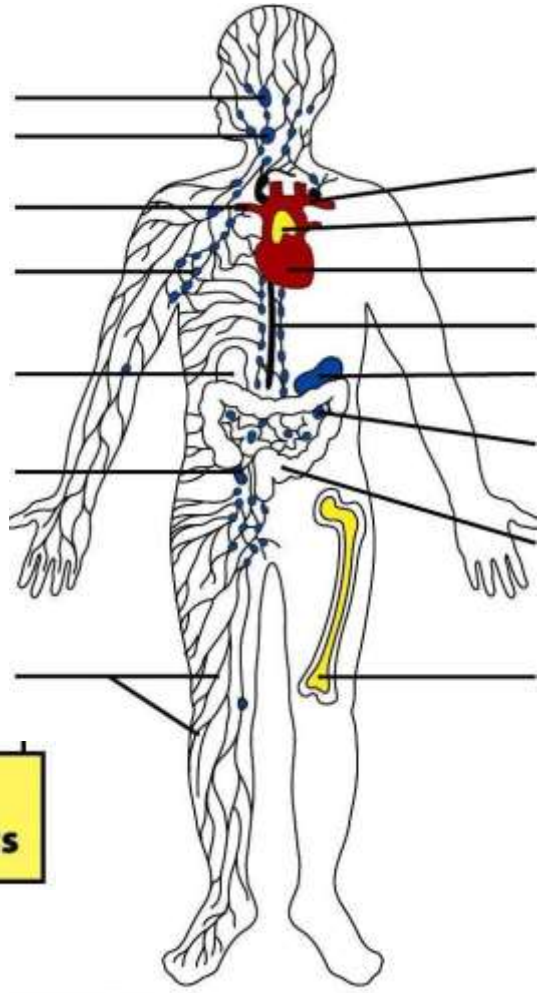
Lymphoid organs

- Primary lymphoid organs
  - Bone marrow
  - Thymus
- Secondary lymphoid organs
  - Lymph nodes
  - Spleen
  - MALT (mucosa-associated lymphoid tissues)
    - GALT (e.g., Peyer patches)
    - BALT (e.g., tonsils, appendix)

  These sites are where B and Tcells reside and respond to antigenic challenge.

Primary and Secondary Lymphoid Organs

Lymph Nodes collect lymph and antigen from peripheral sites



nd Science 2008)

The Spleen collects antigens from circulating blood

Antigens from sites of infection reach lymph nodes via lymphatics

Adaptive immunity

- **Characters**

1. 2nd line of defense
2. Delayed as response to infection
3. Specific for microbes & Antigen (can differentiate Antigen)
4. Has memory cell which remember microbes and give strong immune response on re-exposure

Adaptive immunity

components (sequential phases)

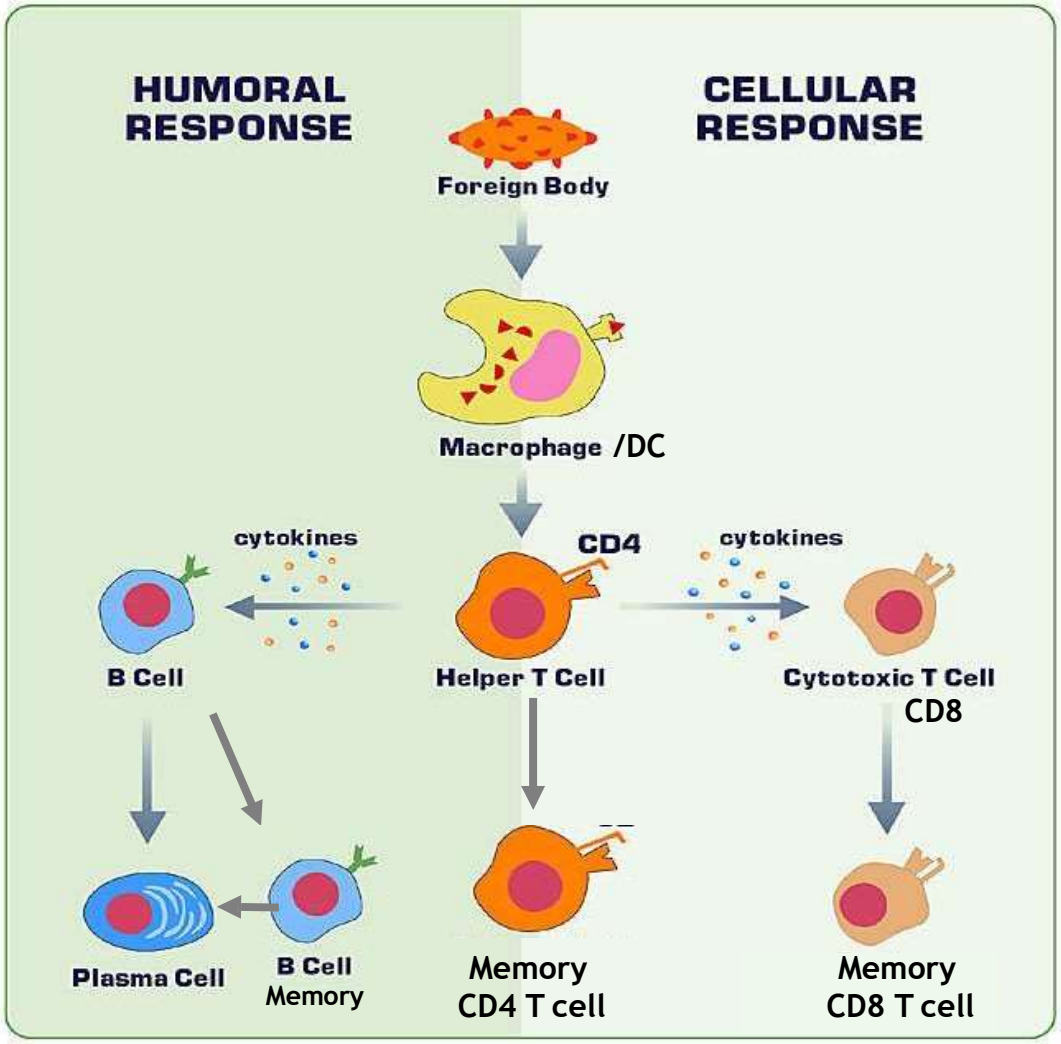
1. Ag recognition by lymphocyte through specific receptor to Ag
2. Activation of lymphocyte → proliferation → differentiation into memory cell & effector cell
3. Elimination of microbes
4. Decline & Termination of immune response
5. Long lived memory cell

Cells of adaptive immunity

1. **B lymphocyte : produce antibodies that neutralize and eliminate extracellular microbes and toxins(humoral immunity)**
2. **T lymphocyte: eradicate intracellular microbes (cell mediated immunity**

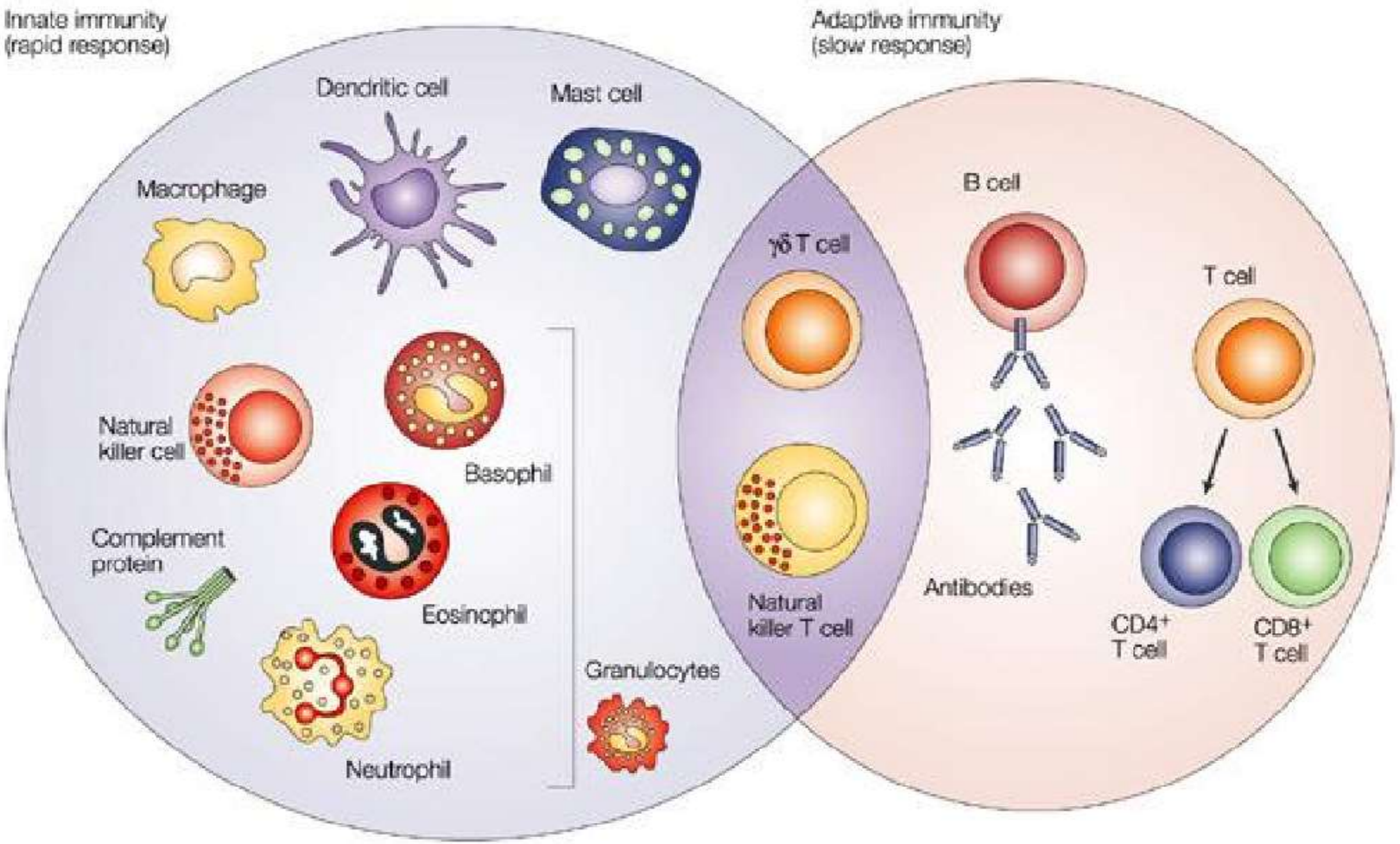
Adaptive Immune Responses

Antibodies present in blood allow immunity to be transferred via proteins



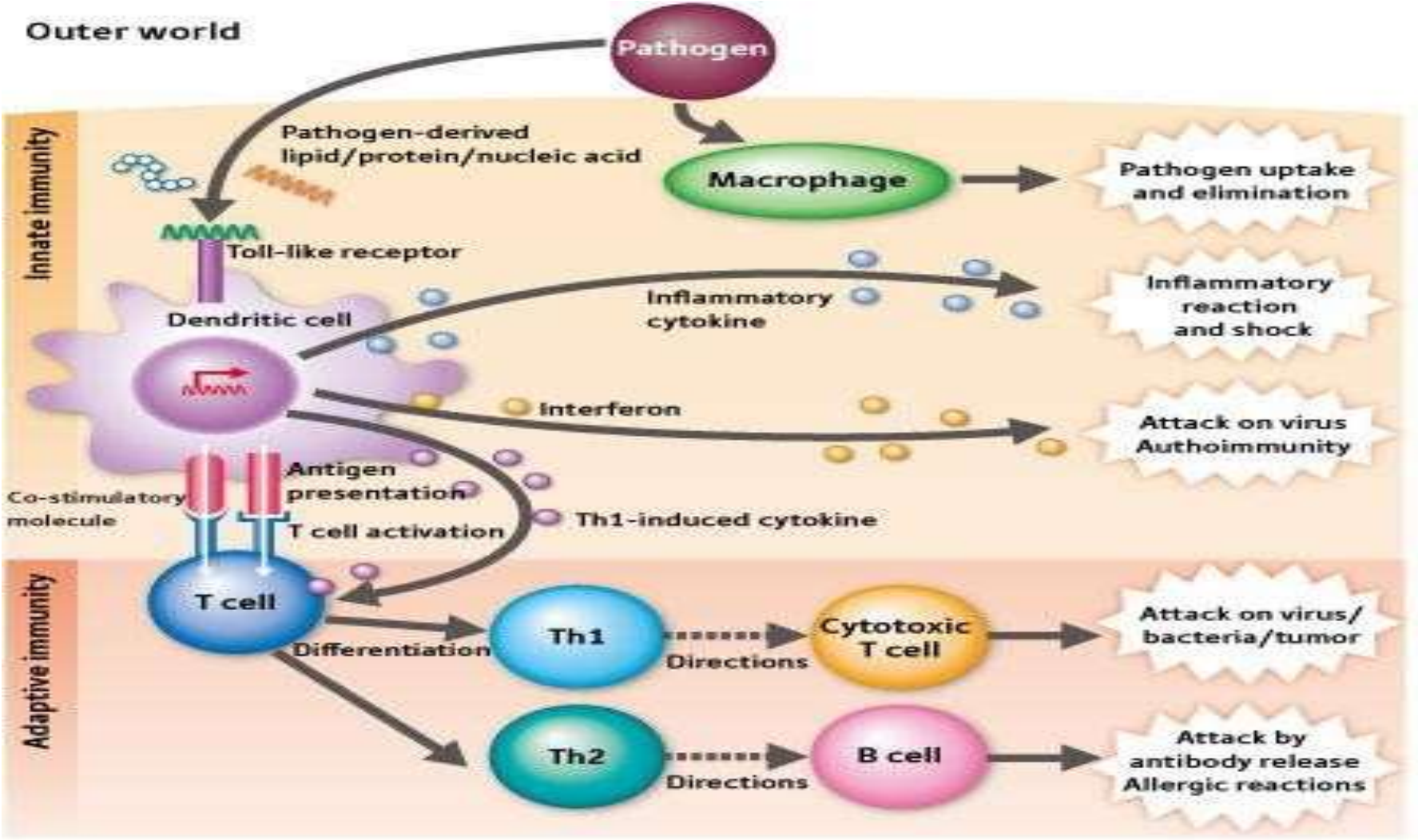
Immunity is mediated by cells

Innate & Adaptive Immunity- Components and cross talk



Nature Reviews | Cancer

Innate & Adaptive Immunity- Components and cross talk



Immune response

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

Cells of the Immune System

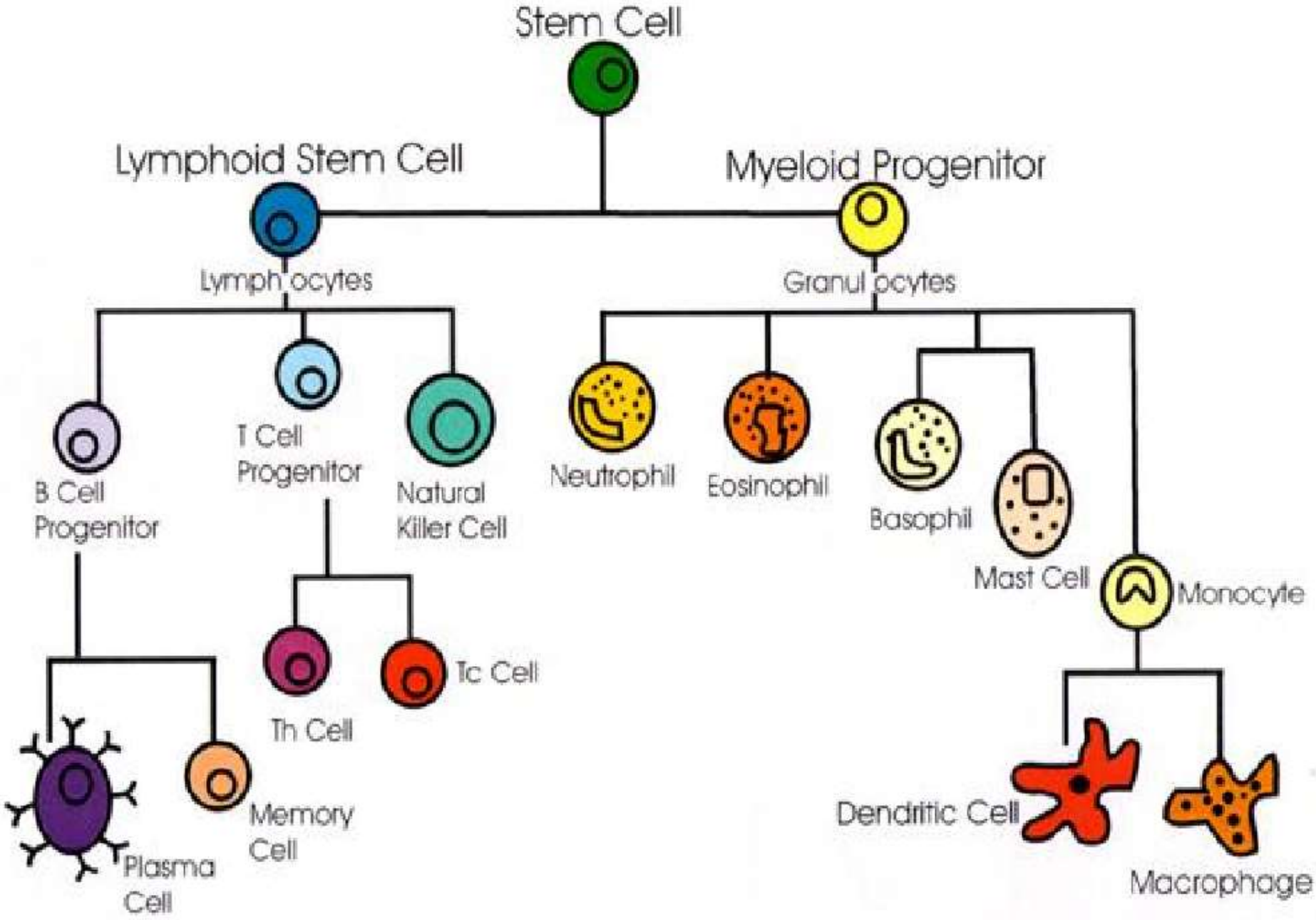
Hematopoitic stem cell in the bone marrow give

a. **Lymphoid progenitor: give** T lymphocyte
B lymphocyte
NK cell

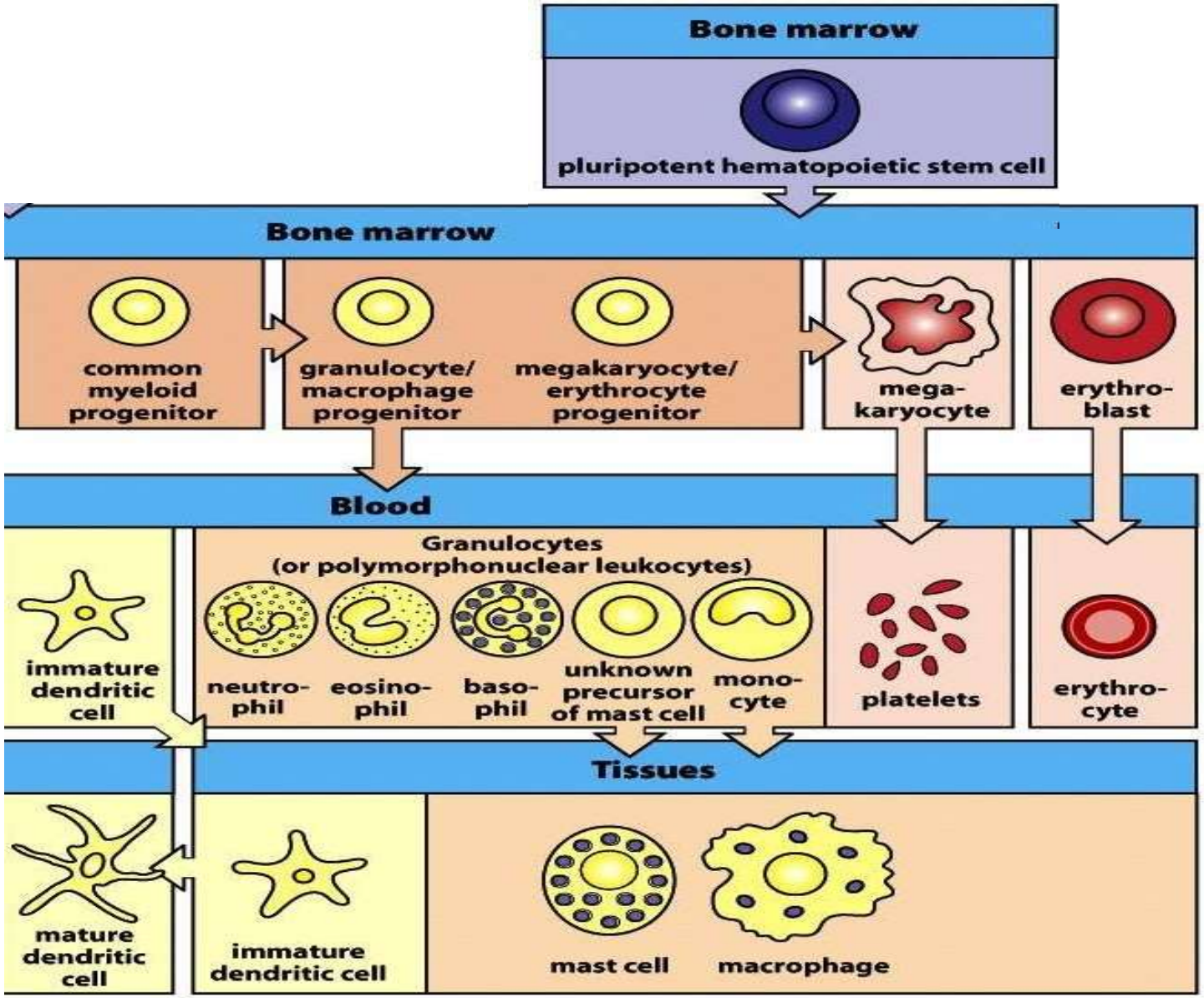
b. Myeloid progenitor: give

Leucocytes (neutrophils & eosinophils & basophils & mast cells & monocytes)

Cells of the Immune System



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

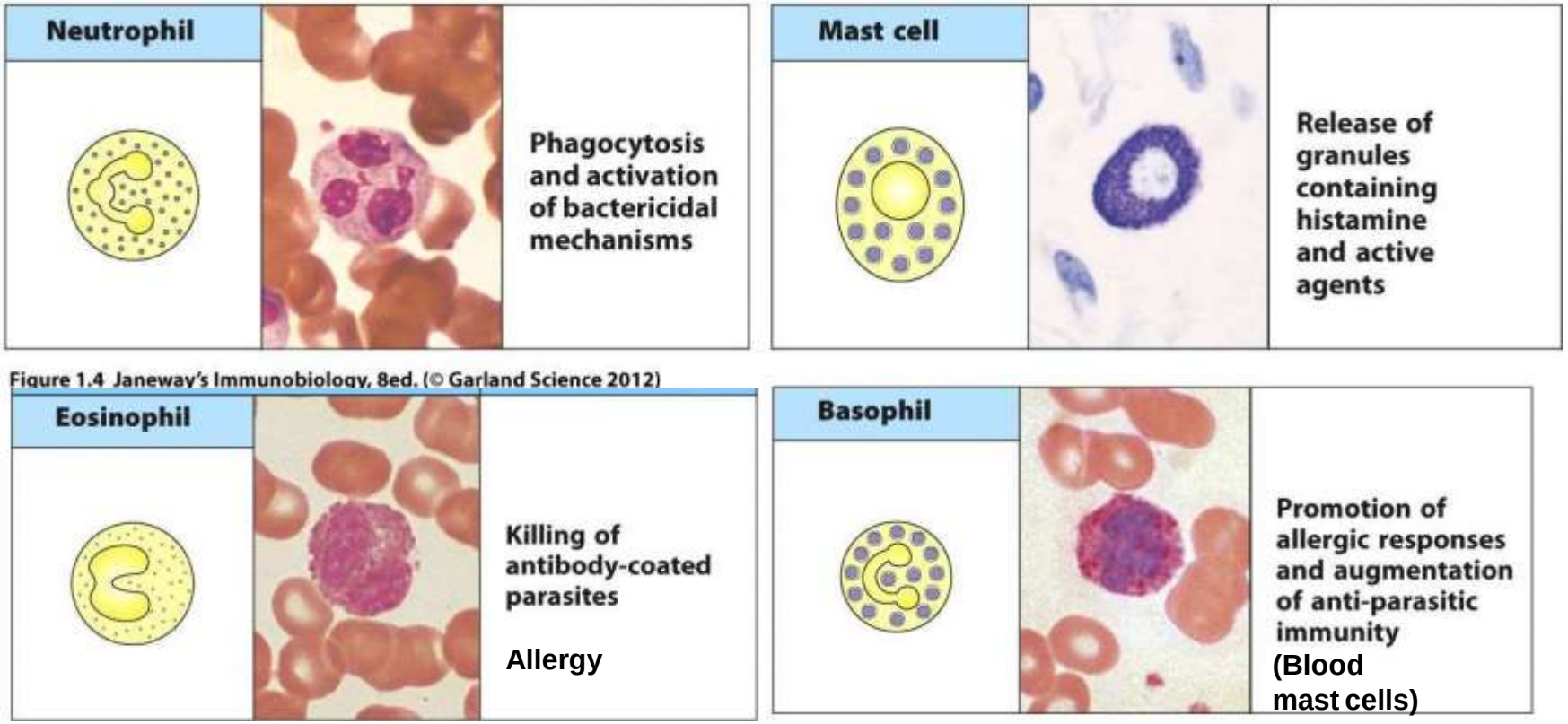


Figure 1.4 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

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

Phagocytes

Neutrophils, Macrophages, and Dendritic Cells

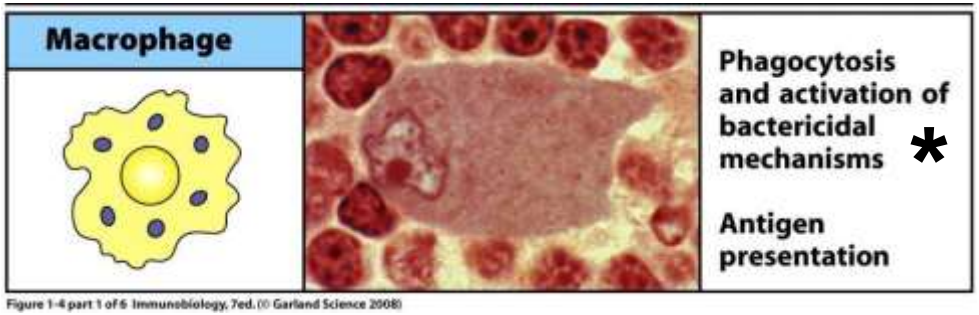


Figure 1-4 part 1 of 6 Immunobiology, 7ed. (© Garland Science 2008)

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

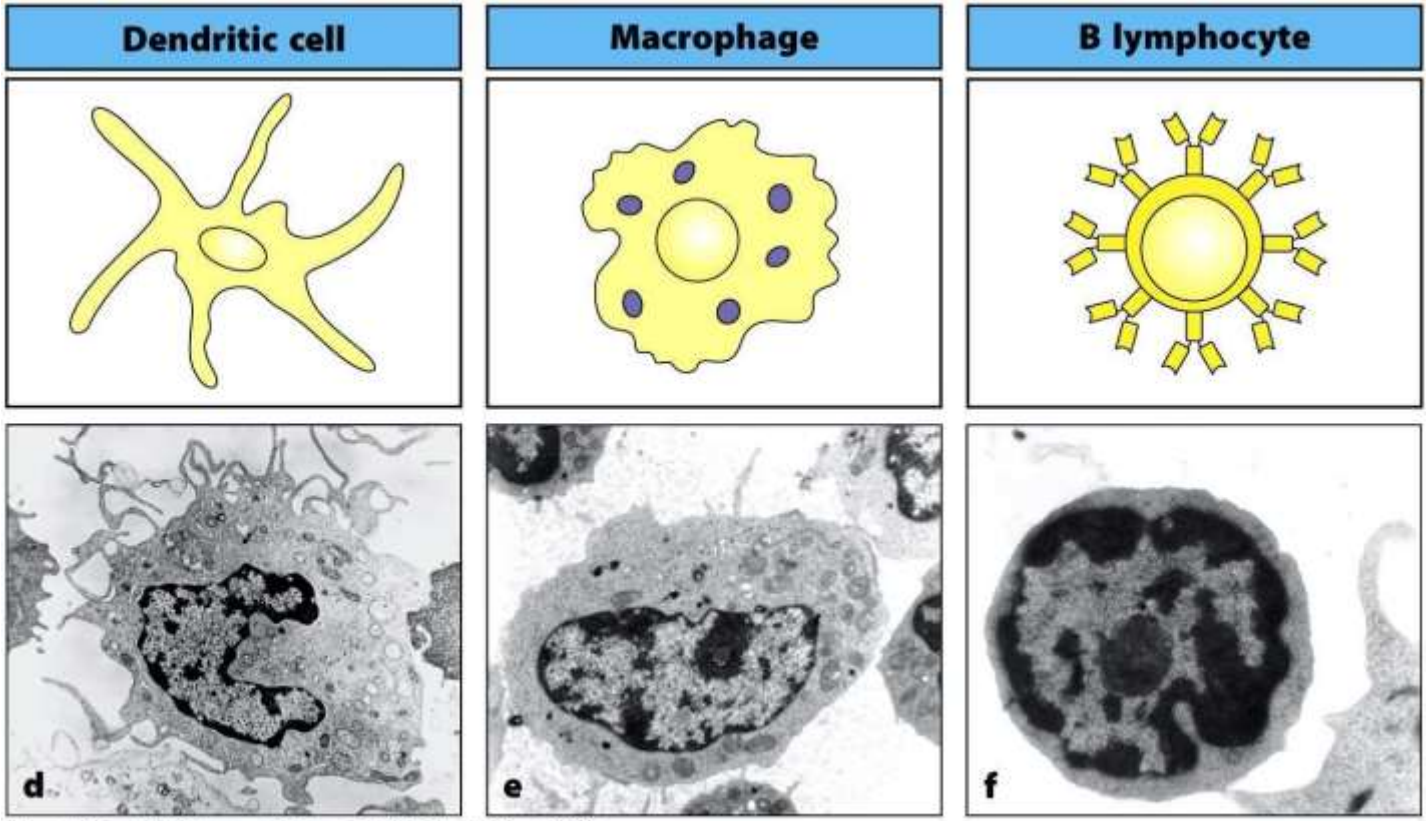


Figure 1-22 part 2 of 3 Immunobiology, 7ed. (© Garland Science 2008)

Immature DCs
very efficient at
Ag processing (in tissues)

→

Mature DCs
very efficient at
Ag presentation (in LNs)

Lymphocytes

Generally: small inactive cells

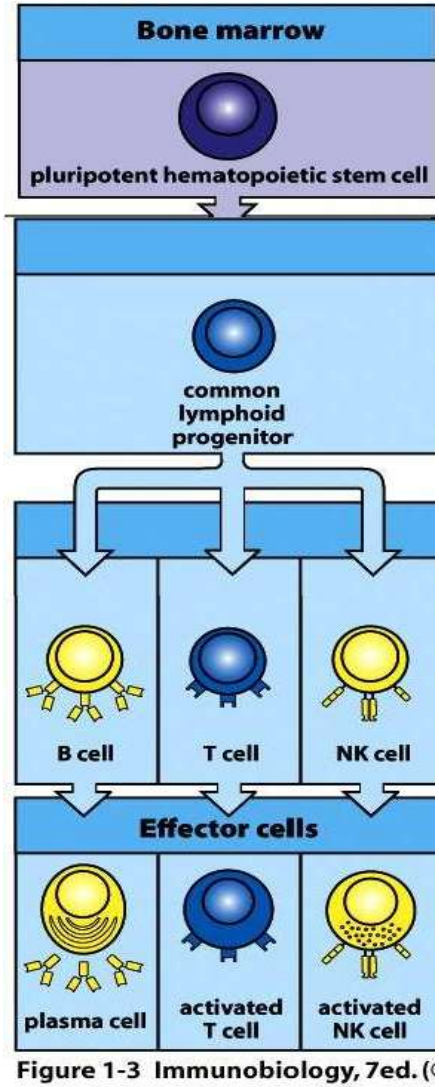


Figure 1-3 Immunobiology, 7ed. (

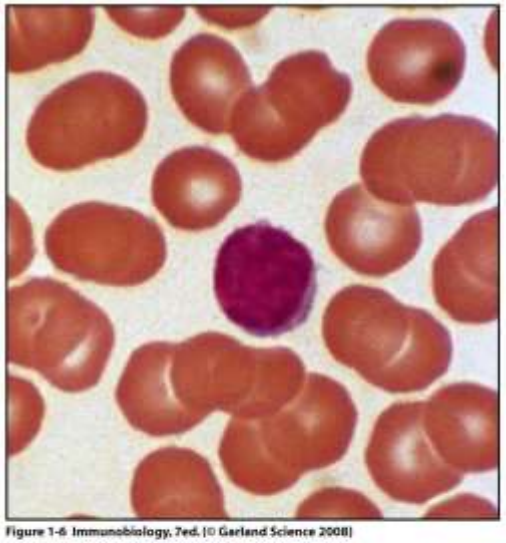
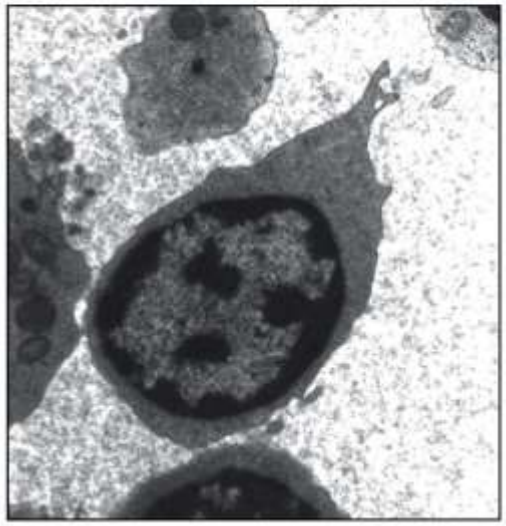


Figure 1-6 Immunobiology, 7ed. (© Garland Science 2008)



<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)

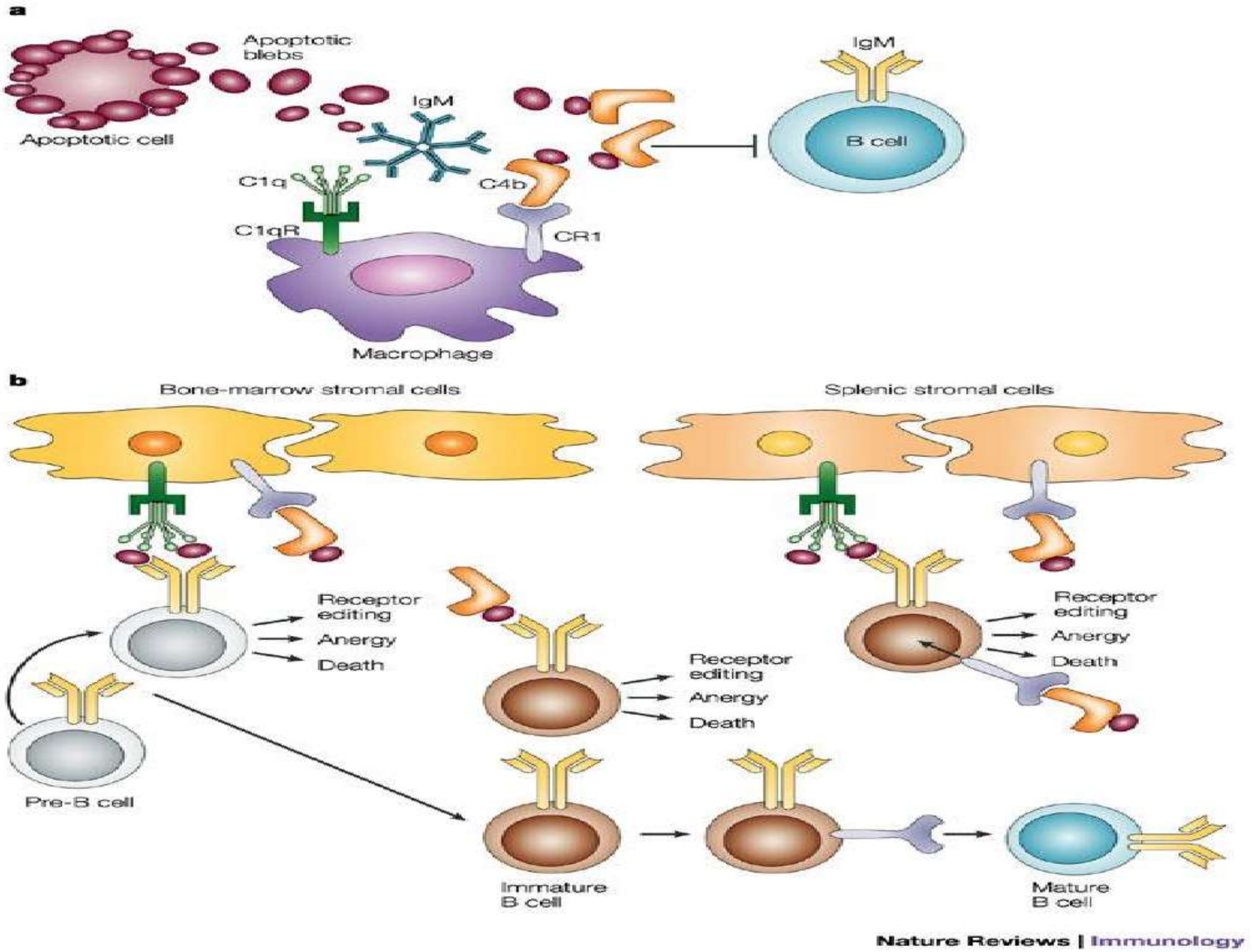
Lymphocytes

- ❖ Lymphocytes are the only cells with specific receptors for antigens and are the key mediators of adaptive immunity.

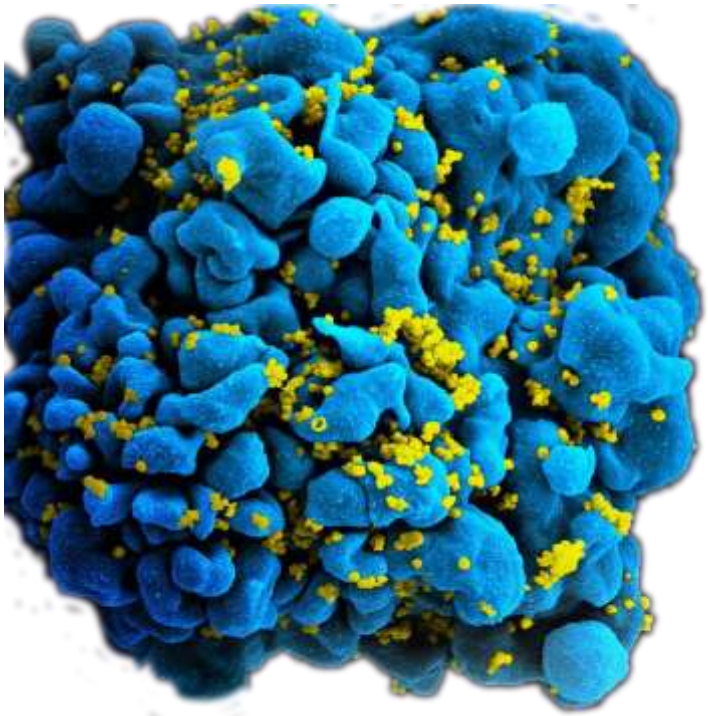
- ❖ They can be distinguished by surface proteins identified by monoclonal antibodies, the standard nomenclature for these proteins is the “CD” (cluster of differentiation) and a number; for example CD1, CD2 etc.

- **Lymphocytes include:**
  - B lymphocytes: mediators of humoral immunity
  - T lymphocytes: mediators of cell-mediated immunity.
  - Natural killer cells: cells of innate immunity

	B lymphocyte	T lymphocyte
arise from	Bone marrow	
mature in	Bone marrow	Thymus
Name	Bone marrow lymphocytes	Thymus derived lymphocytes
% of total blood lymphocyte	10 – 15 %	Majority
Steps in maturation	Stem cell → lymphoid progenitor → pre B cell → immature B cell → mature/naïve B cell → leave bone marrow to meet antigen in the 2nd lymphoid organs	Stem cell → lymphoid progenitor → immature T cell → leave bone marrow to thymus gland → maturation & selection → mature/naïve T cells T helper (CD4) T cytotoxic (CD8) → leave thymus to meet antigen in the 2nd lymphoid organs
phenotypic markers	1. CD 19 & CD 21 2. Fc receptor 3. class II MHC molecule	1. CD 3 2. CD 4 or CD 8 3. T cell receptor (TCR)
Function	Antibody production (humoral immunity)	Cell mediated immunity
Antigen recognized	Protein , polysaccharide, lipid, nucleic acid and small chemicals (free & soluble)	Protein only - CD4 cell recognize → peptide + MHC II molecule - CD8 cell recognize → peptide + MHC I molecule
Antigen recognition receptor	**B cell receptor (BCR)**: membrane Immunoglobulin (Ig M & Ig D)	**TCR**: 2 types α/β TCR & γ/δ TCR **α/β TCR:** common type → 2 poly peptide chain α & β
Stimulation by Ag	B cell proliferation → differentiation into → memory cell & plasma cell which produce antibodies to eliminate Ag	**TCR complex**: - Ag presented on MHC, bind with variable domain of α & β of **TCR** - **CD3 & zeta protein** (signal transduction) → activate T cell
Signaling molecules	2 polypeptide chains → Ig α & β transmit signal inside B cell → B cell proliferation & differentiation into plasma cell	TCR & CD3 & zeta protein
Types	1. naïve B cell 2. plasma cell 3. memory cell	**1. T helper (CD4)** → produce cytokines which help other cells eg **2. Th1** help B cell to produce antibodies **3. Th2** help macrophage to destroy ingested microbes **4. T cytotoxic (CD8)** Also called cytolytic as lyse virus infected cell & kill tumor cells & graft rejection **1. T regulatory (Treg)** Suppress the immune response


a
Apoptotic blebs
Apoptotic cell
IgM
C1q
C4b
C1qR
CR1
Macrophage
IgM
B cell
b
Bone-marrow stromal cells
Splenic stromal cells
Receptor editing
Anergy
Death
Receptor editing
Anergy
Death
Receptor editing
Anergy
Death
Pre-B cell
Immature B cell
Mature B cell

T cells

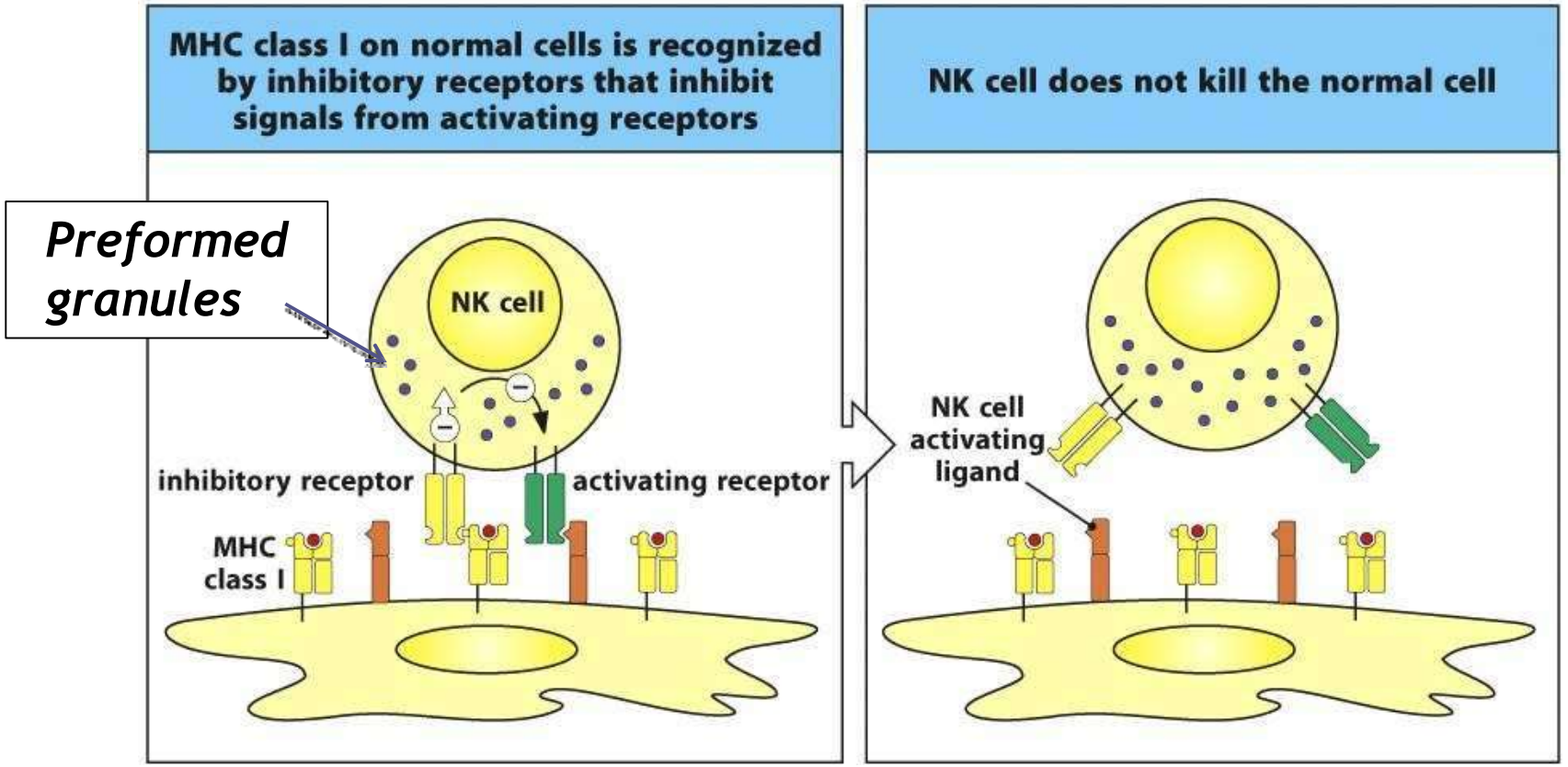


Cells infected with virus

- Cytotoxic T cells
  - Kill infected cells, cancer cells
- Helper T cells
  - drive specific B-cell responses and antibody class
- Memory T-cells remain to fight the same infection another day

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

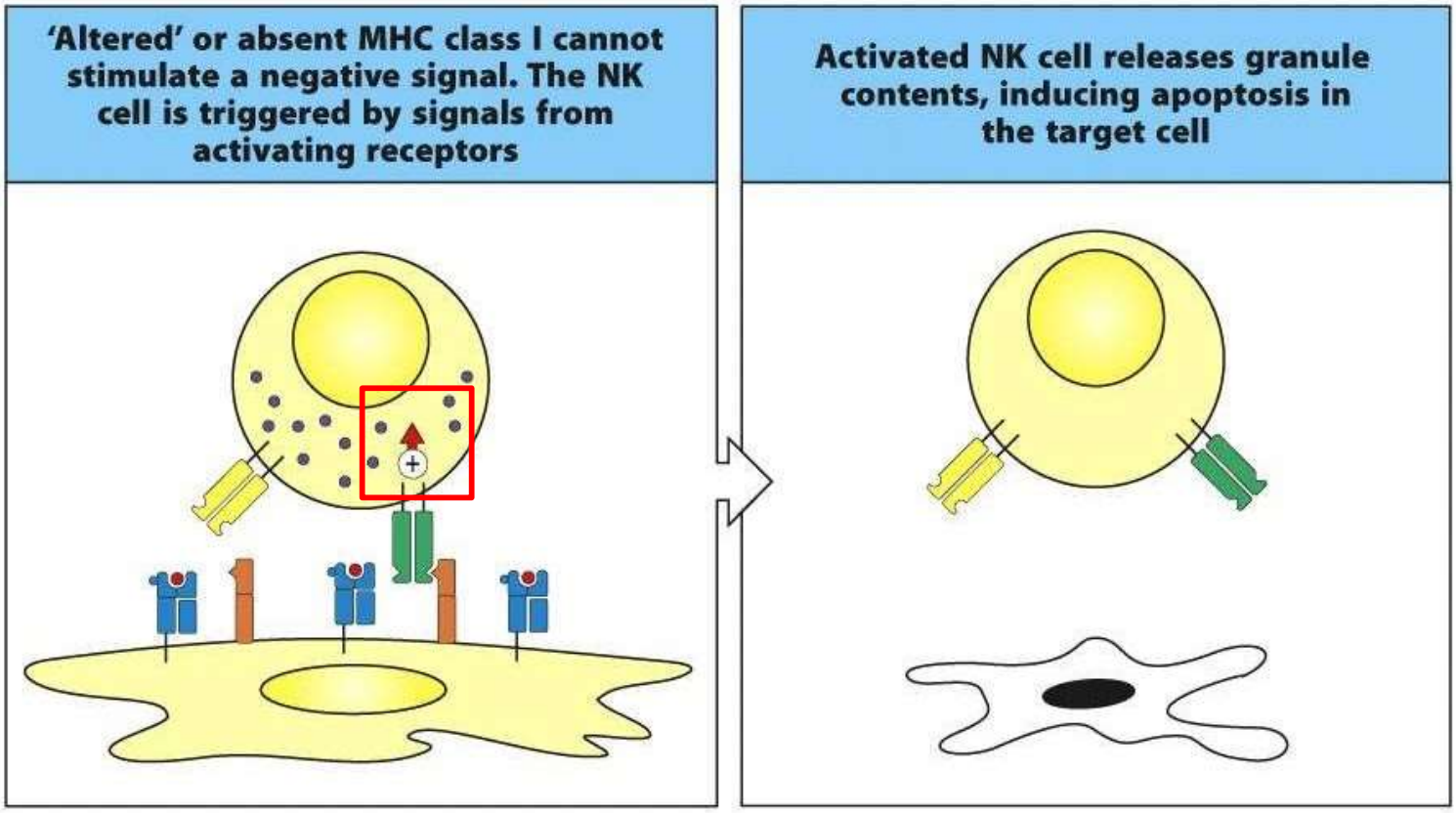
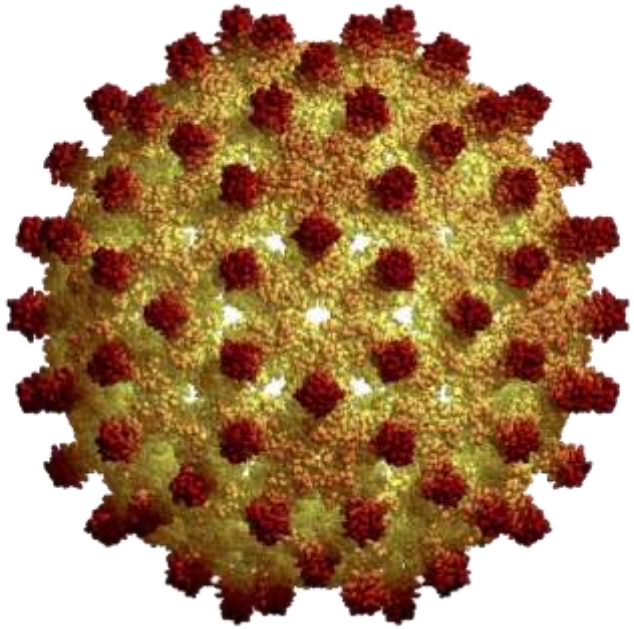


Figure 3.31 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

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

Antigens - molecular shapes

- Drive the immune response
- Include proteins, sugars or nucleic acids
- Vaccines often contain purified antigen



Immunogens, Antigens and Epitopes

- Almost all of the proteins and carbohydrates associated with an infectious agent (bacterium, fungus, virus or parasite) are considered foreign to the human host and

- have the potential to induce an immune response

- Immunogen: a substance (protein or carbohydrate) that challenges the immune system and can initiate an immune response; may contain more than one antigen (e.g., bacteria).

- Antigen: is a molecule recognized by specific antibody or T cells

- Epitope (antigenic determinant): the molecular structure that interacts with a single antibody molecule

- Not all molecules are immunogens. Proteins are the best immunogens, carbohydrates are weaker immunogens and lipids are poor immunogens.

- Hapten (incomplete immunogen) are often too small to immunize (initiate a response) an individual but can be recognized by antibody.

  Haptens can be made immunogenic by attachment to a carrier molecule, such as a protein.

- Adjuvant: substance that usually prolong the presence of antigen in the tissue and activate or promote uptake of the immunogen by dendritic cells, macrophages and lymphocytes.

  During artificial immunization (e.g.,vaccines), an adjuvant is used to enhance the response to antigen.

Antigen Receptors

Antibody (Ab)

T cell Receptor (TCR)

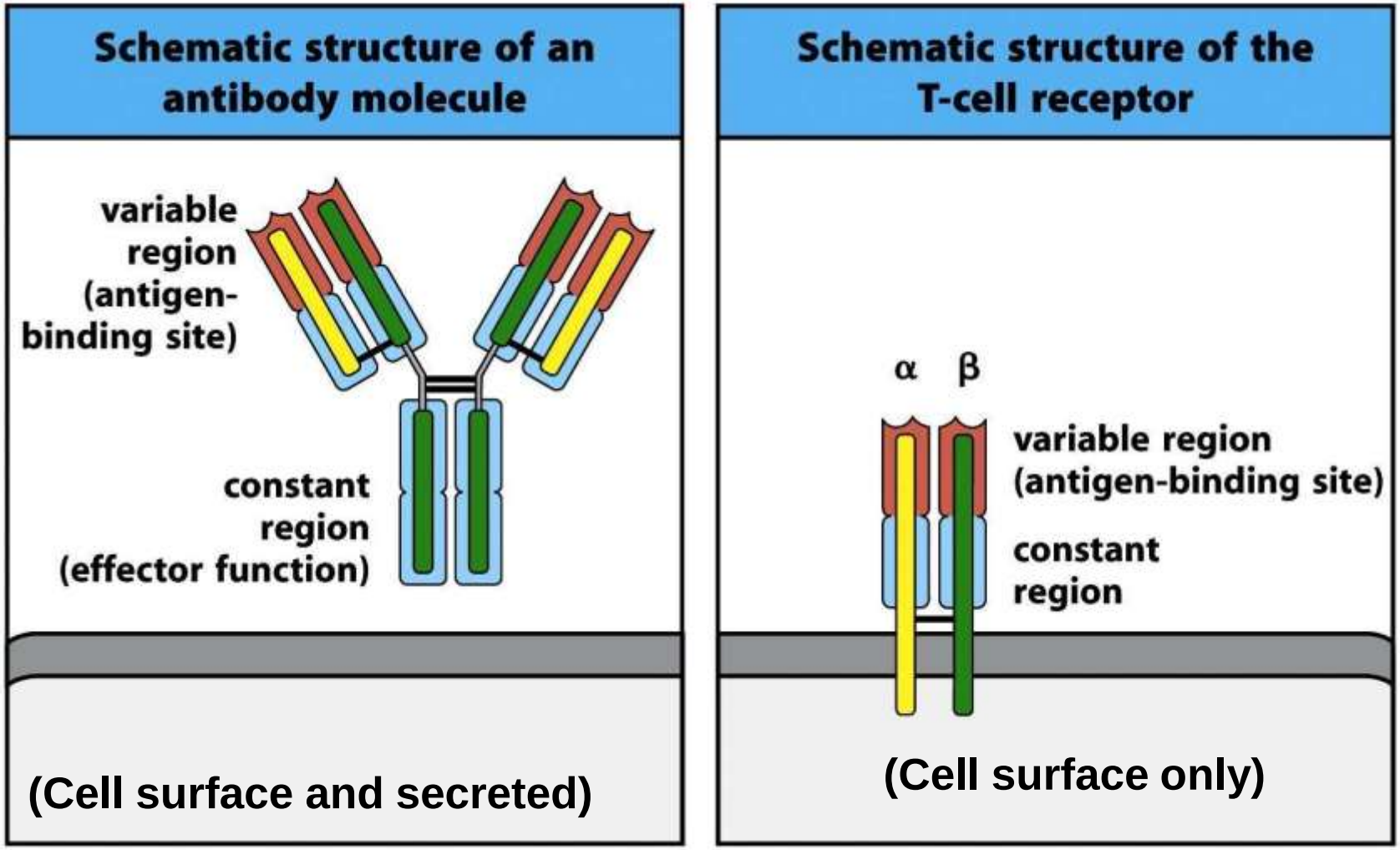


Figure 1-13 Immunobiology, 7ed. (© Garland Science 2008)

Antigen Recognition by Antibodies

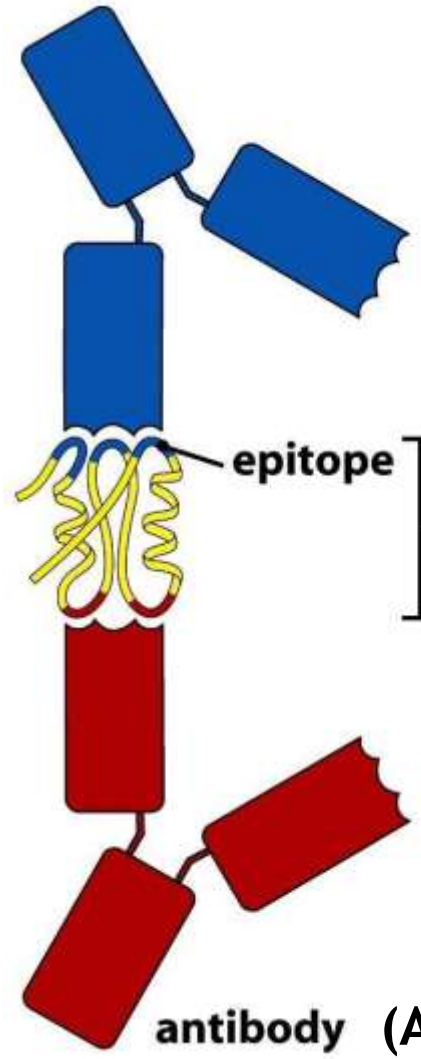


Figure 1-15 Immunobiology, 7ed. (© Garland Science 2008)

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

Inflammation

Swelling, redness, heat

Damage → danger signal

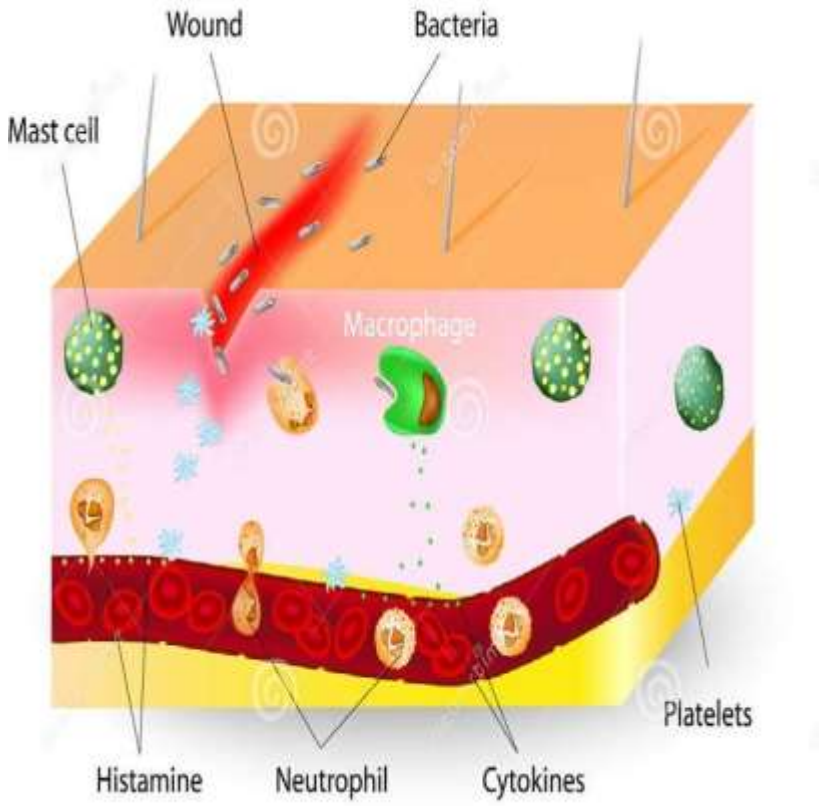
Inflammatory mediators

- Increased blood flow
- Increased capillary permeability

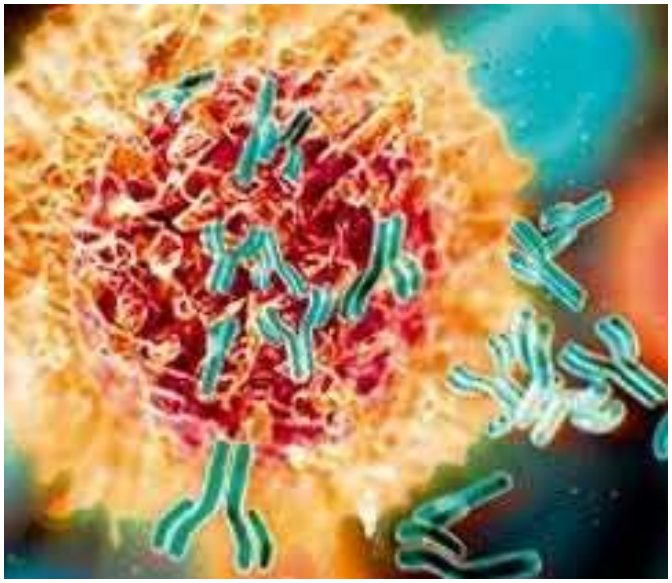
Attracts cells

Alerts immune system

Clotting

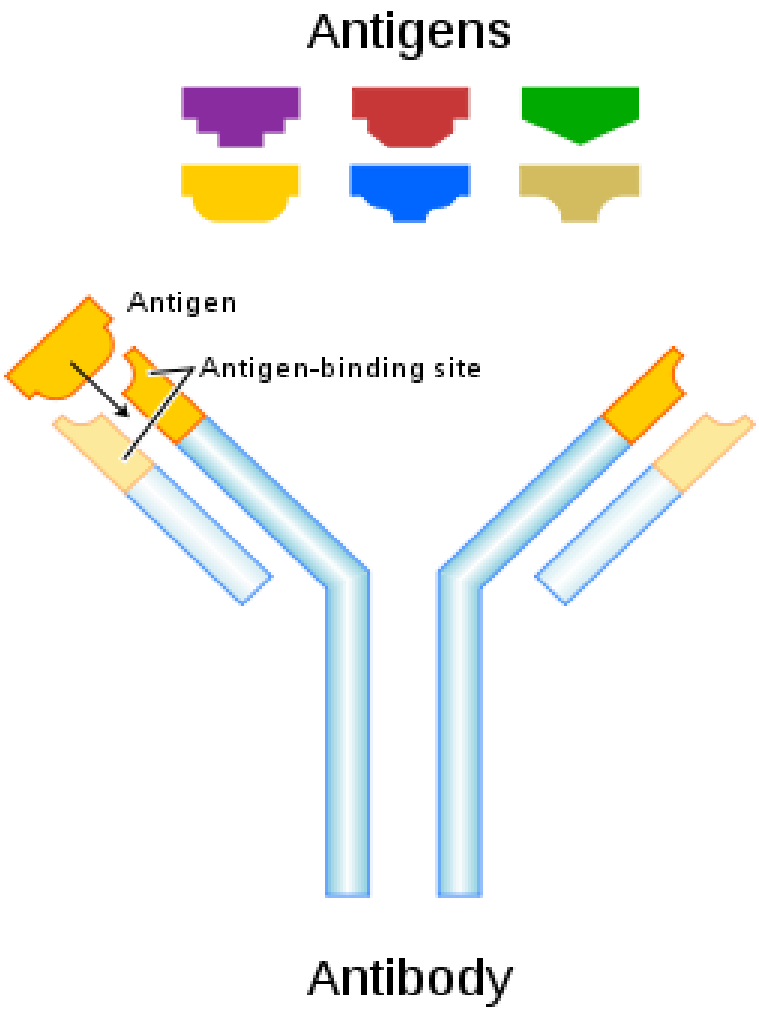


Specific – B cells and antibody



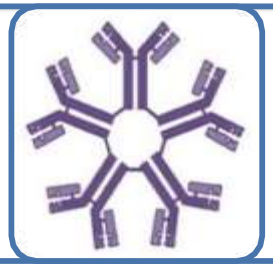
- Plasma cells
  - activated B-cells
  - secrete antigen-specific antibodies
- T cell dependent or independent responses
- Memory B-cells and antibody

Antibody – humoral immunity



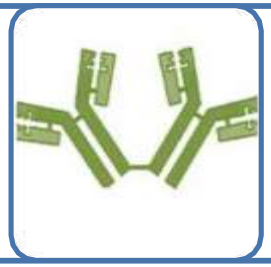
- Immunoglobulins
- Secreted by plasma cells
- Bind to specific antigen
  - Neutralise
  - Block attachment
  - Label
  - Activate complement
  - Trigger cytokine release
  - Present antigen to T cells

Key classes of antibody

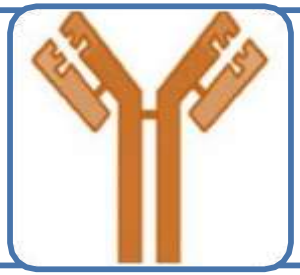


IgM – low affinity, in primary immune responses; complement activation; largest Ab, does not cross placenta

IgG – high affinity, most important class of Ab in secondary immune responses, crosses the placenta

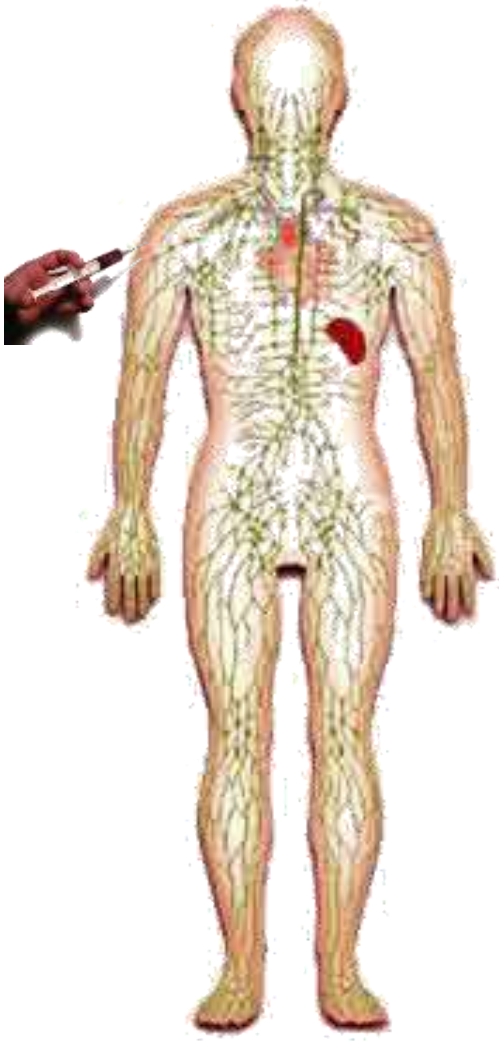


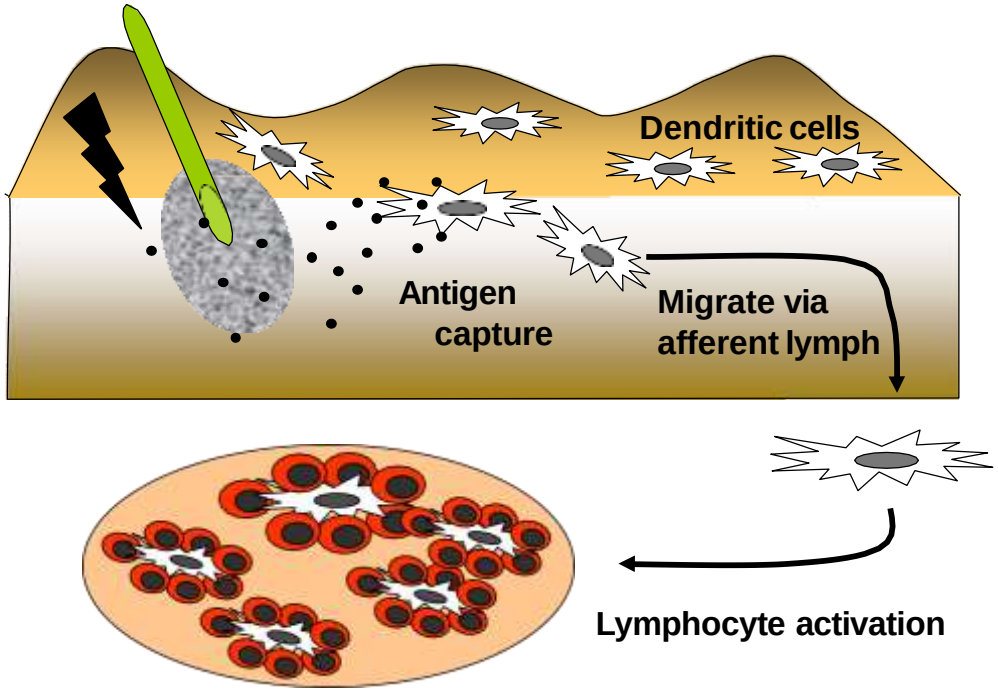
IgA - found primarily in secretions such as breast milk, tears, saliva and mucosal membranes



IgE - Evolved to provide protection for parasitic infections; associated with allergic diseases e.g. asthma & hay fever; histamine release

What happens to the injected vaccine?





- Antigen carried to lymph node where specific response takes place
- Other ingredients excreted via blood, kidneys, urine.

Development of specific immunity

Primary immune response

- Activation of T and B cells
- Antibody produced by short-lived plasma cells
- Low affinity antibody appears in serum - IgM
- Takes 2 weeks, peaks around 30 days

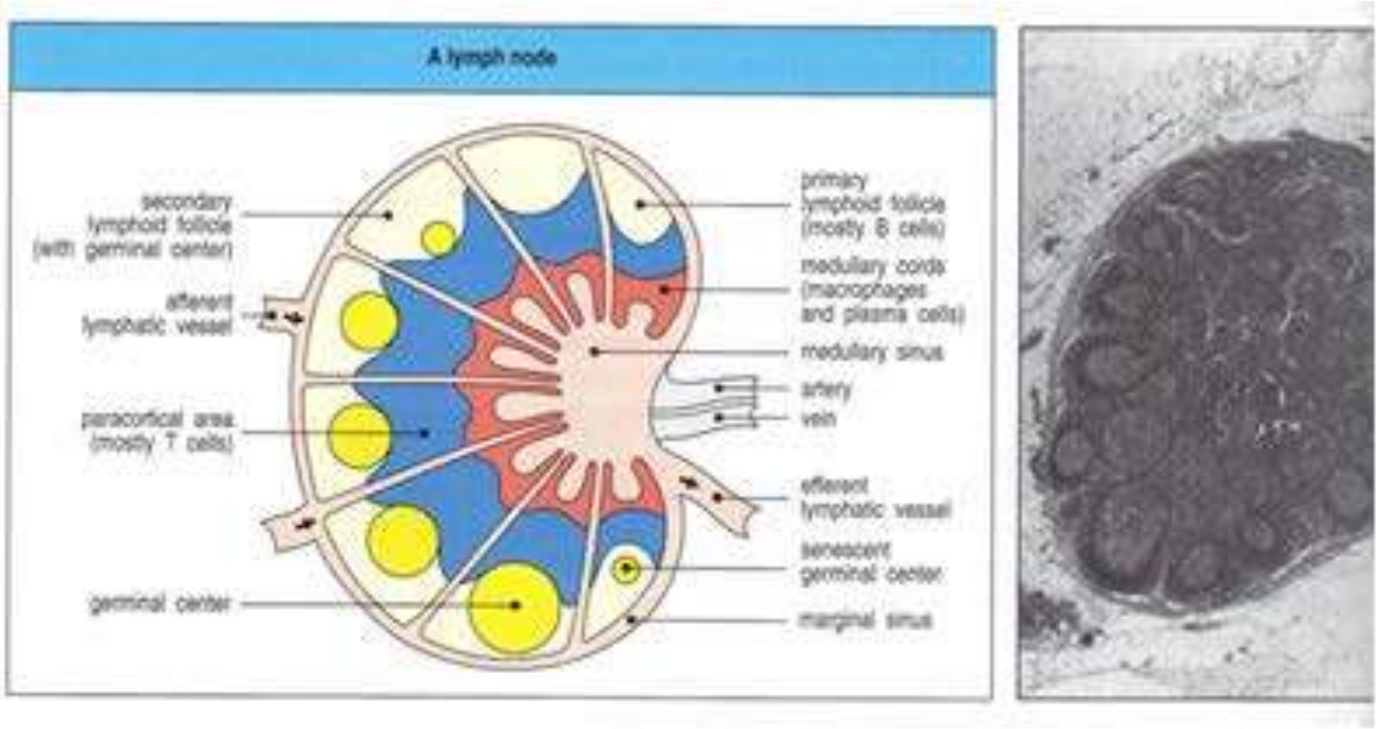
Immune memory

- Immune memory is slow - at least four months
- T cell dependent
- High affinity IgG
- Only immune memory can be 'boosted'

Secondary response

- rapid (4 days)

Lymph node

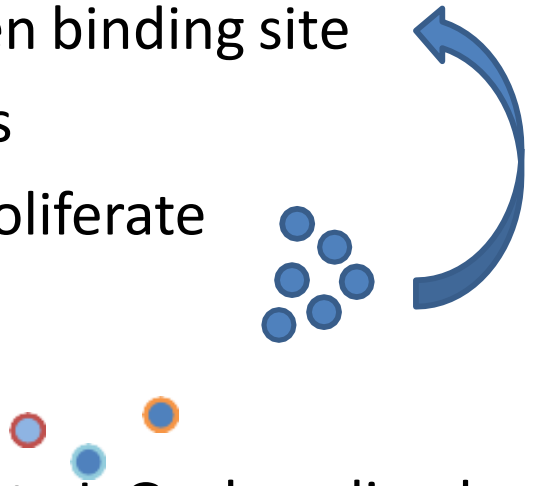


- **Cortex** – containing dividing B cells and T cells
- **Medulla** – macrophages and antibody producing plasma cells
- **Sinuses** – net of reticular fibres spanning lymphatic capillaries

Specific immunity – generation of high affinity antibodies

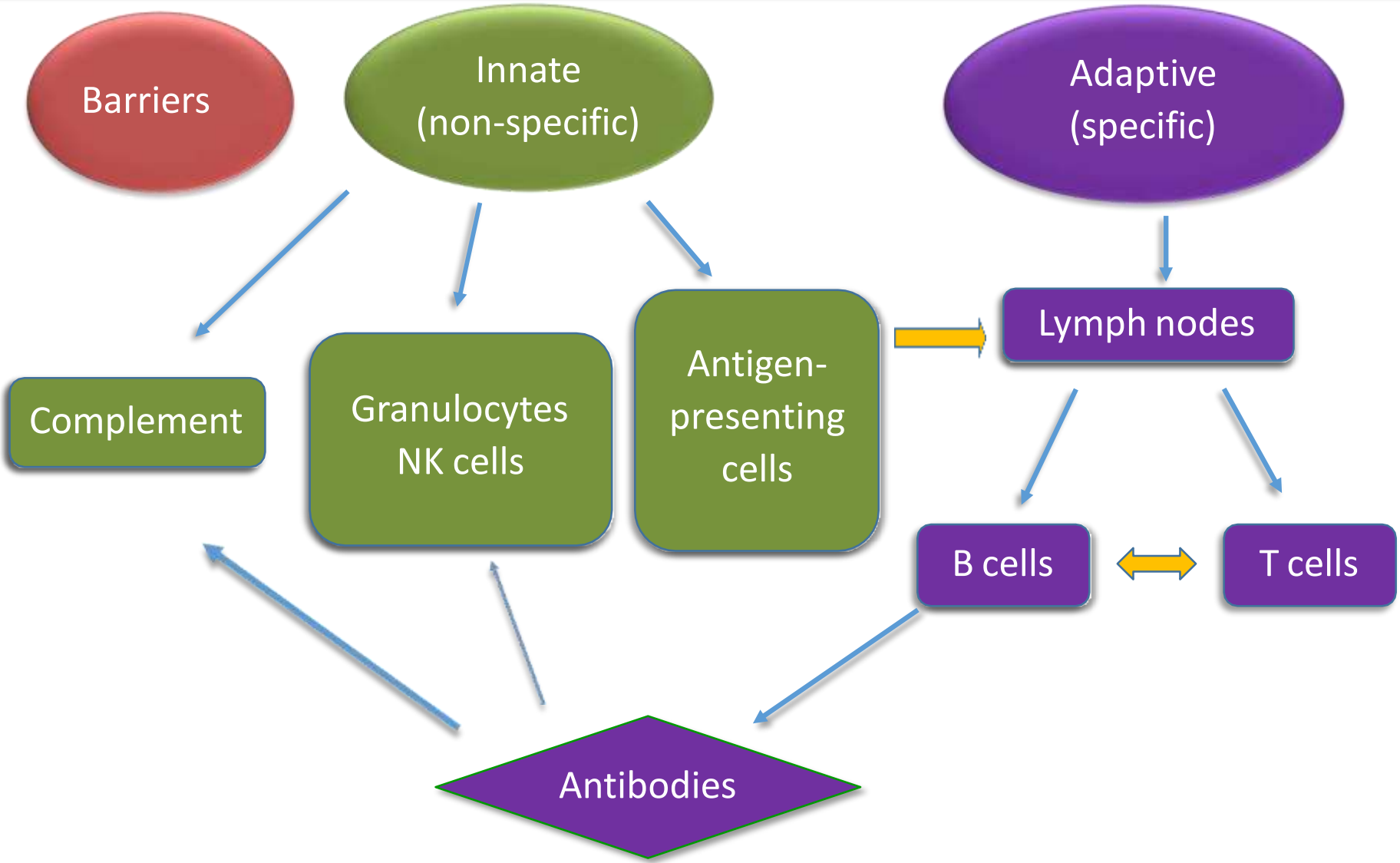
Affinity maturation – in germinal centres

1. Activated B cells proliferate
2. Mutations in DNA coding for antigen binding site
3. Presented antigen by DC and T cells
4. Positive – high affinity => clones proliferate
5. Negative – low affinity => death †



- Differentiation and class switching - IgM to IgG – long lived memory

Innate works with adaptive immunity



Immune memory

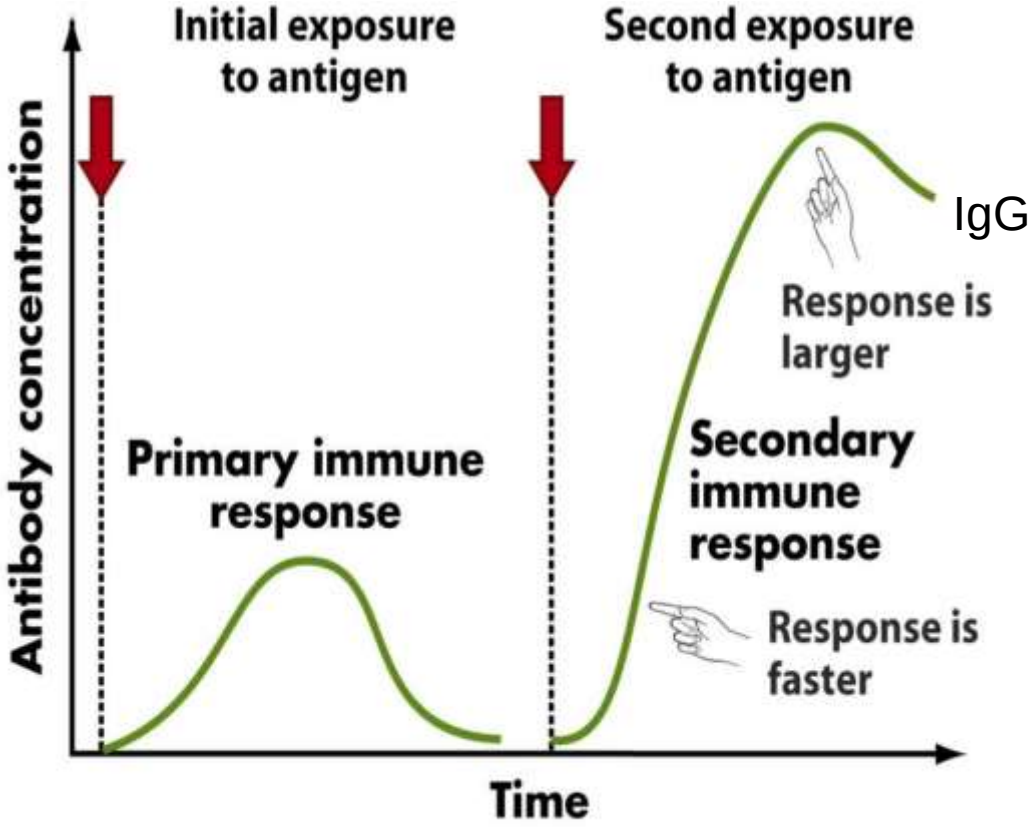


Figure 49-16 Biological Science, 2/e
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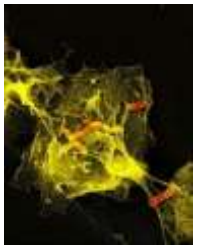
- Specific, adaptive immunity
- Long lived protection from reinfection

Communication enhances immunity



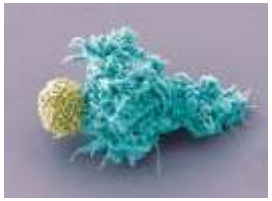
Specific antibodies label targets

Innate

IL-5
IL-4
IL-2
IFN-γ

IL-1
IL-6
IL-12

Antigen presented by DC



Adaptive

- Instruct B cells
- Enhance innate response
- New cell production

Antigen-specific T and B cells activated

Cytokines

- Proteins produced by lymphoid and other cells
- Stimulate and regulate the immune response

Interferons

- Low-molecular-weight proteins
- produced in response to viral infections
  - Interferon-α and interferon-β
- on activation of the immune response Interferon-γ
- promote antiviral and antitumor immune responses