Cihan University/ Sulaymaniyah

College of Health Science

Medical Laboratory Analysis

4^{th} Stage- 1^{st} Semester

Pr. Clinical Immunology

Lecture- 4: Specific Immunity

Third line of defense: An Overview of Specific Immunity (Part-2)

Antibodies and Cytokines

2023- 2024

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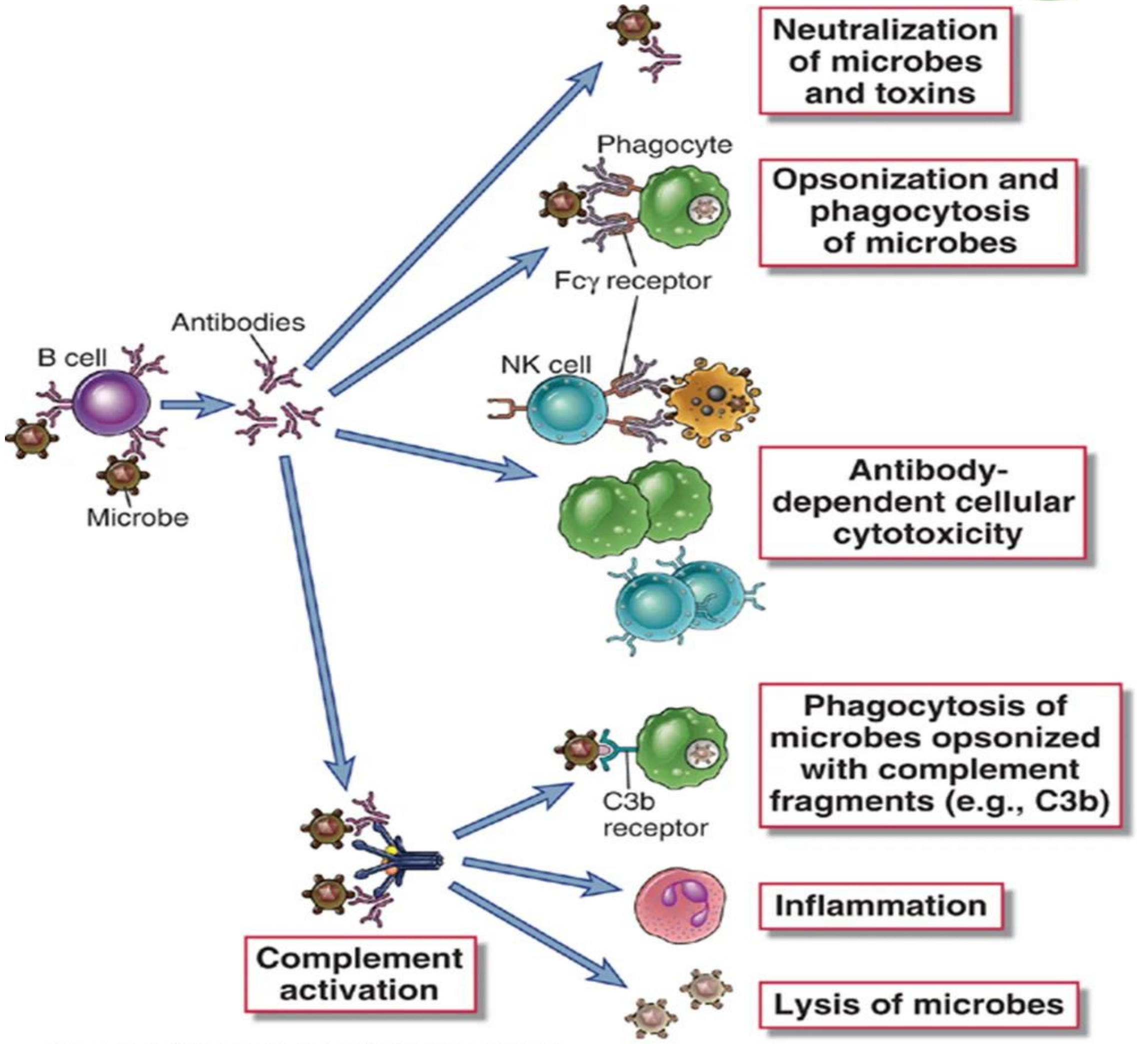
Antibodies or Immunoglobulins

- They are **globular proteins** present in the **serum** and **tissue fluids**.
- They are produced by the **plasma cells** (B-cells) and are used in the **immune system** of the body to neutralize pathogenic microbes or other toxic foreign components.
- **Antibodies** are the antigen binding proteins found on the **B-cell membrane** and **Body secretions which are secreted by the plasma cells** of the immune system.
- Antibodies are commonly called as '**IMMUNOGLOBULINS**' = IG.

Function of Antibody

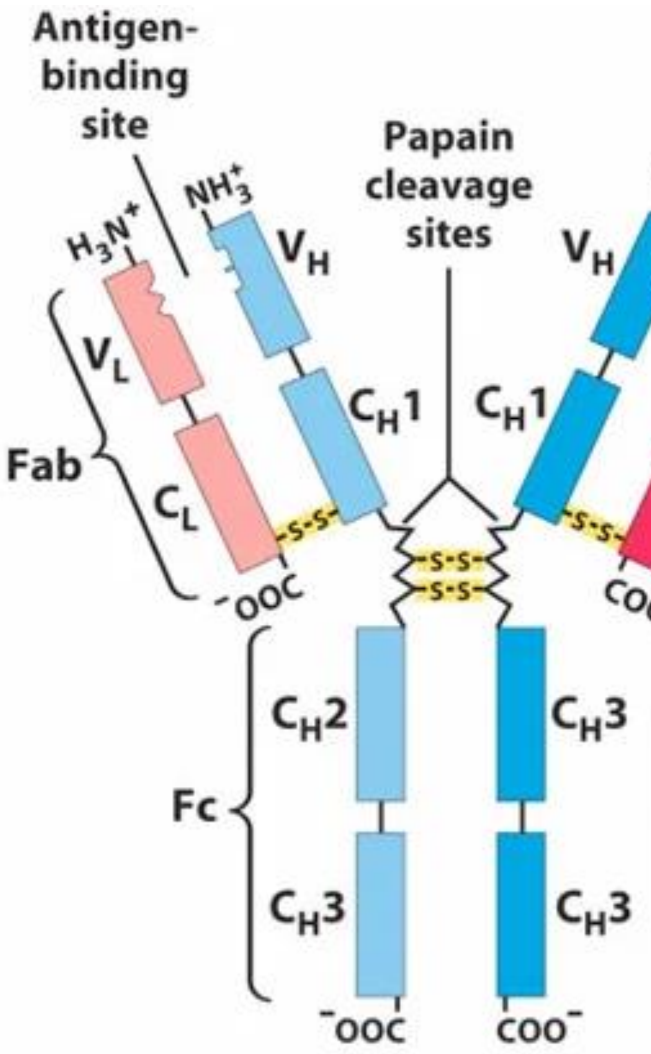
1. They can **prevent the attachment of microbes** to the **mucosal surface of the host**.
2. They **reduce the virulence of the pathogen** by neutralizing the toxins and viruses.
3. They **facilitate phagocytosis** by opsonization of microbes.
4. They can **activate the complement system**.



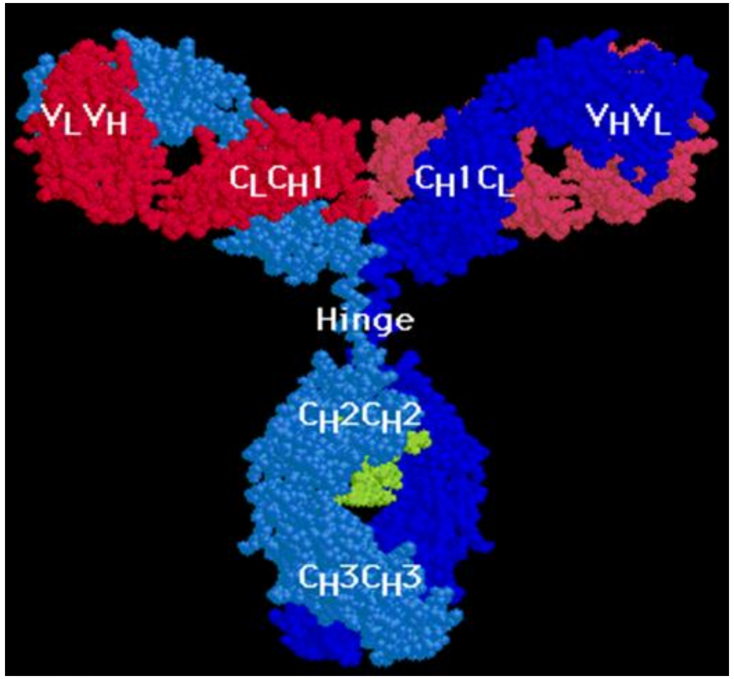
Structure of Immunoglobulins

- The basic unit of a single immunoglobulin consists of **four linear** polypeptide chains.
- These peptide chains are named as two identical **Heavy Chains** and two identical **Light Chains**.
- The heavy chains are long and heavy with a molecular weight of 50 –70 kDa.
- The light chains are smaller and lighter in weight with a molecular weight of 25 kDa.
- The heavy chains are designated as '**H**' and the light chains are designated as '**L**'
- Since an immunoglobulin contain **two** heavy (H) chains and **two** light (L) chains, they are together represented as **H_2L_2.**
- H_2L_2 is the basic structural unit of any class (isotypes) of immunoglobulins.
- Both H chains and L chains are connected through **disulfide bonds**.
- Some antibodies are very complex as in **Immunoglobulin M (IgM) which is a pentamer**. In such case, the basic structural units will be **H_2L_2** and they are multiplied in 'n' times **$(H_2L_2)n$**

Typical Antibodies Structure

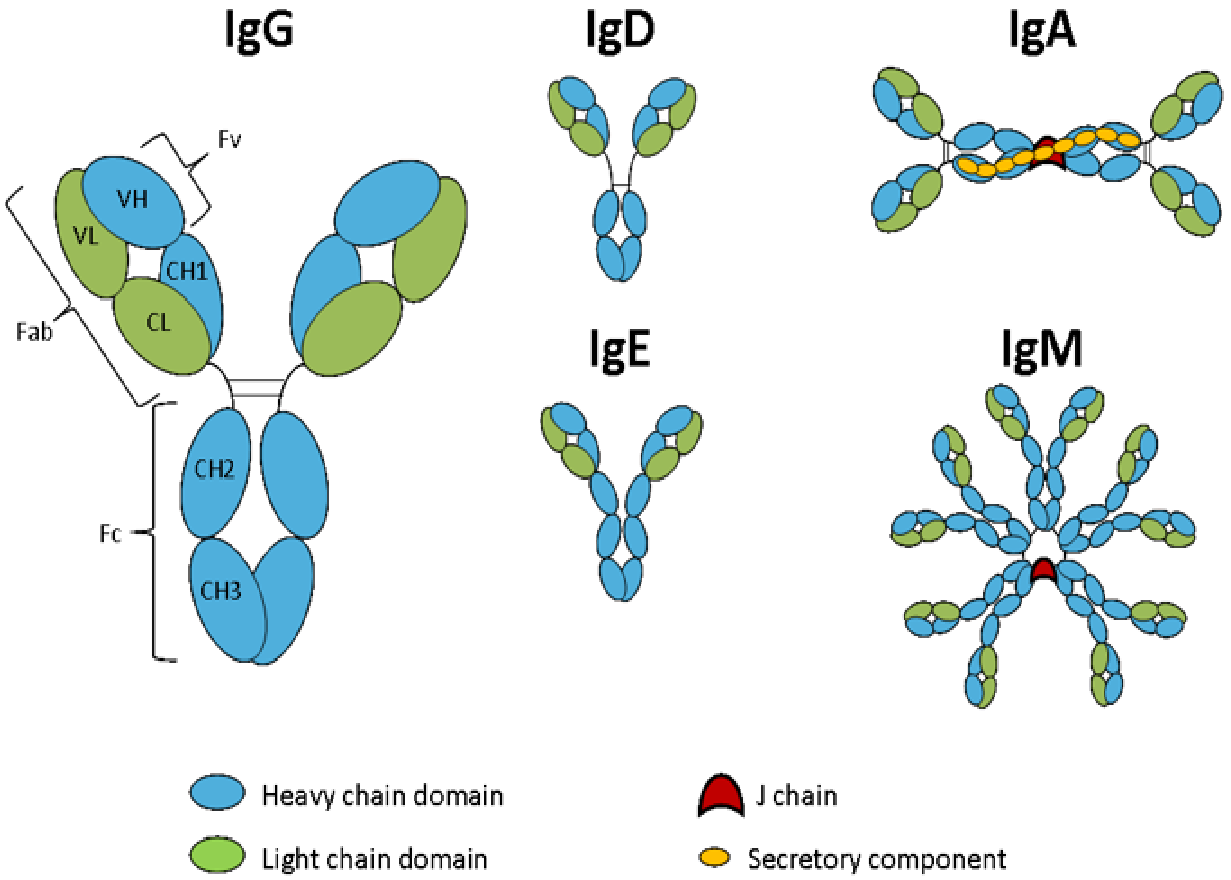


C = constant domain
V = variable domain
H, L = heavy, light chains



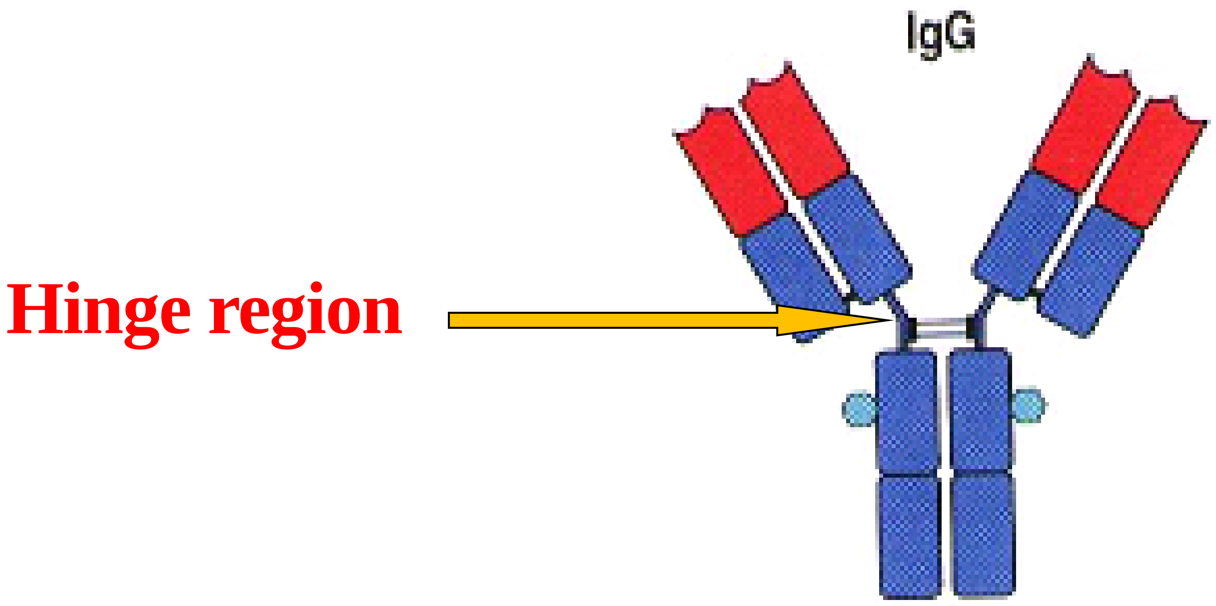
Classes and types of Ig

- According to the differences of H chains (amino acid composition , sequence, H chains) can be divided into five classes of H Chain: γ α μ δ ε (IgG IgA IgM IgD IgE).
- The heavy chains of Immunoglobulin M (IgM) contains mu (μ), IgG contains gamma (γ), IgA contains alpha (α), IgE contains epsilon (ε) and IgD contains delta (δ) chains.



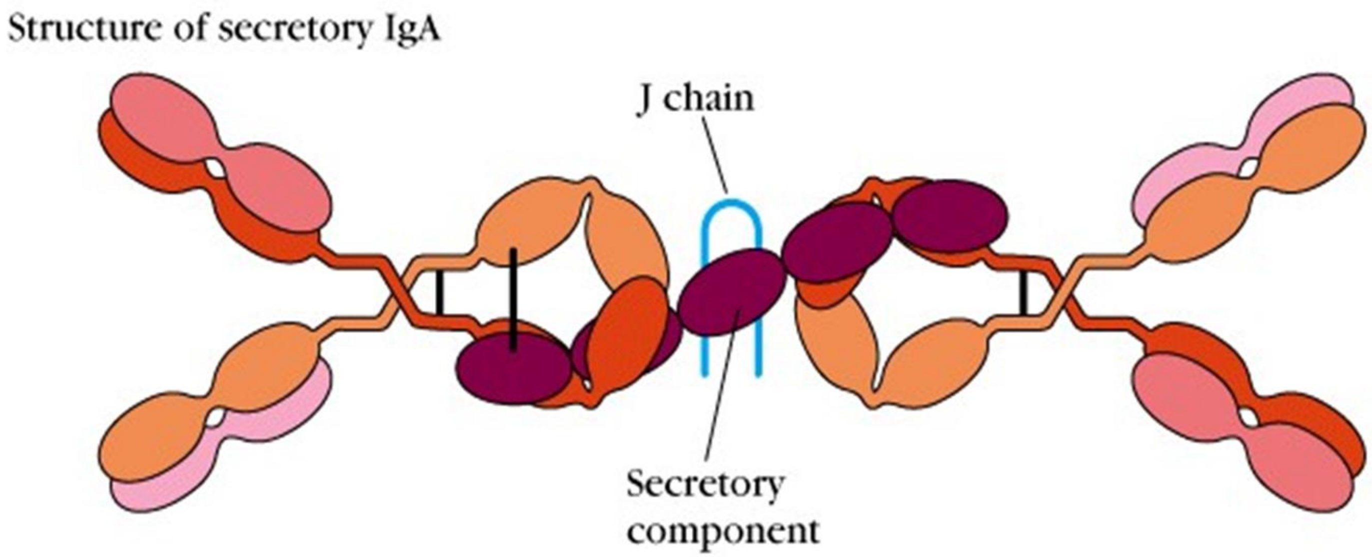
Hinge region

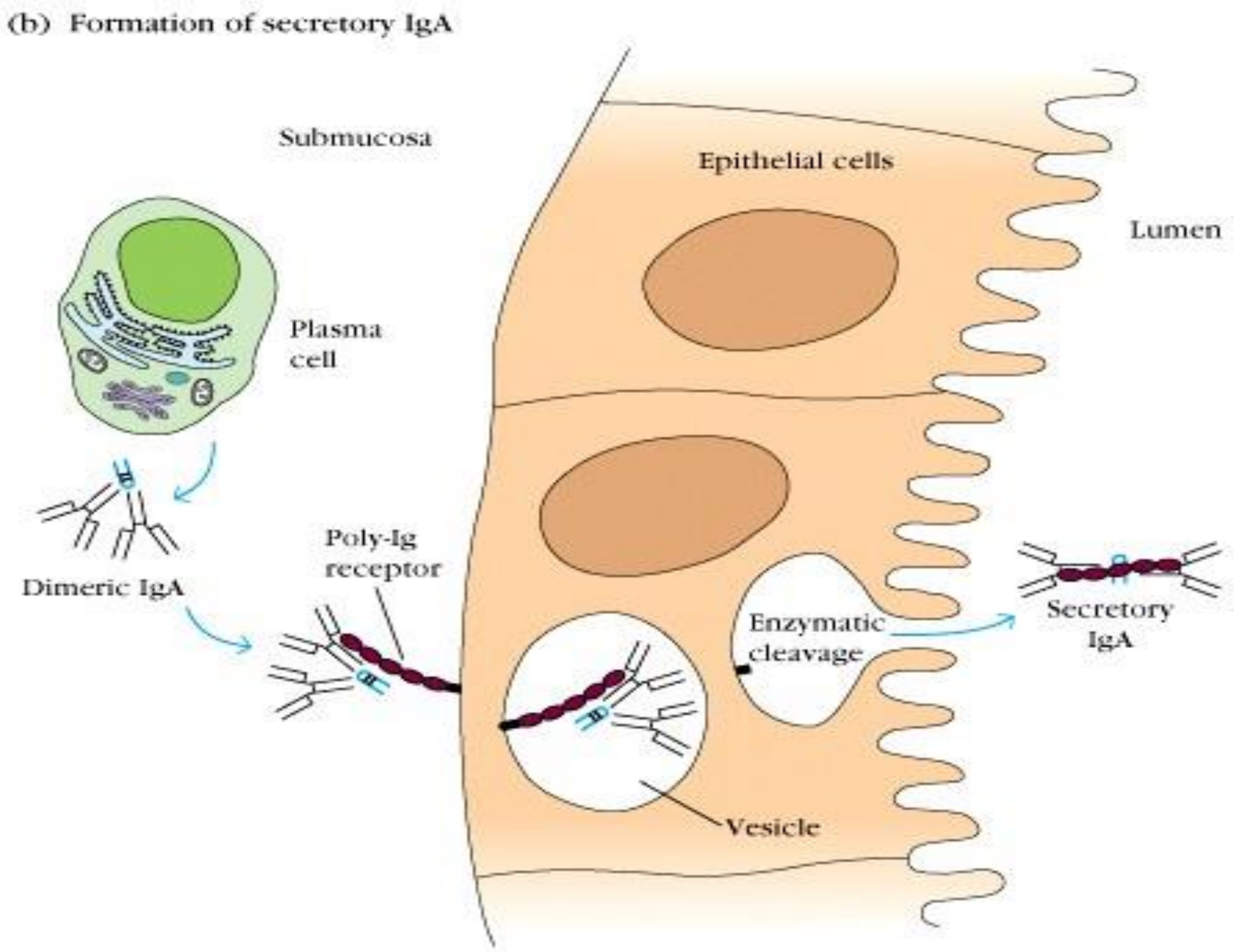
- The **hinge region** is segment of heavy chain between the CH1 and CH2 domains.
- **Flexibility** in this area permits the **two antigen-binding sites** to **operate independently**.



Other components of Ig

- **Joining chain(J): Produced by plasma cells.**
  - ✓ **Functions: linker: Join monomer of Ig to form dimer (Ig A, IgM).**
- **Secretory piece (SP):** Produced by mucosa epithelial cells.
  - ✓Bind to dimer of IgA to form secretory IgA (SIg A)
  - ✓Functions: protect SIgA against proteolysis in secretory liquid.



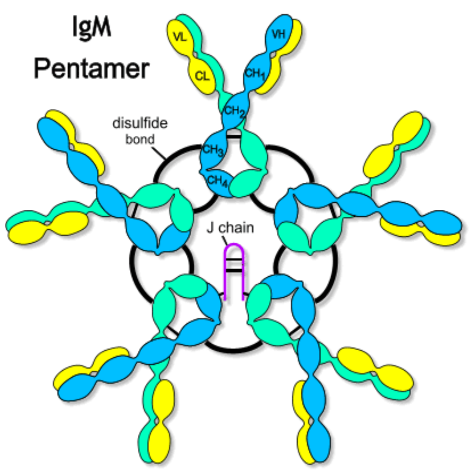


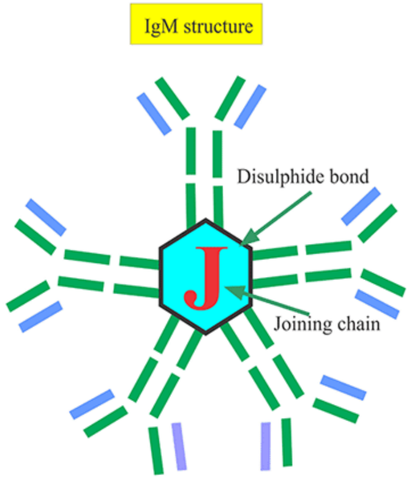
- **Secretory component** is an epithelial-derived glycoprotein that facilitates transfer of Igs from subepithelial sites into epithelial-lined lumina by transepithelial transport and secretion.

Types of Antibody (Immunoglobulin)

1. IgM

- Largest of all the antibody molecules, consists of five of the basic units (**pentamer**) mu heavy chains joined together by a structure known as **J-chain**.
- Expressed on **membrane of mature B cells** as monomer
- **MW is highest： pentamer（90KD）**
- **life is shorter (4~5 days)**
- **IgM is more efficient in anti-infection and anti-bacterium**
- Restricted almost entirely to the intravascular space due to its large size.
- 5-10% of serum immunoglobulin
- Membrane (mIgM) expressed on B-cells as BCR
- First Ig of primary immune response
- More efficient than IgG in **complement activation**
- ***Does not cross the placenta.***



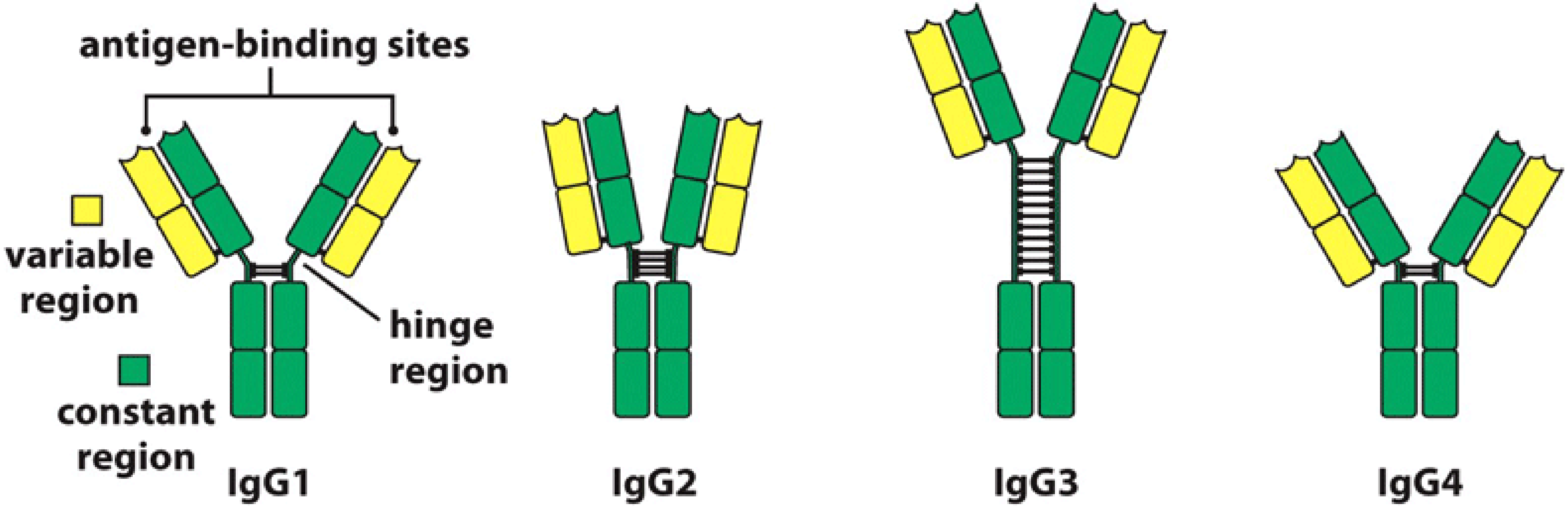


2. IgG

- Most abundant immunoglobin 80% of serum Ig
- ~10 mg/mL
- One basic structural unit, i.e. Y-shaped molecule having 2 light chains and 2 Gamma heavy chains.
- Produced in response to a wide variety of antigens, including bacteria, viruses,
- Coats organisms to enhance phagocytosis by neutrophils and macrophages.
- Through its **ability to cross the placenta**, maternal IgG provides the **major line of defense against infection for the first few weeks of a baby's life.**
- Four subclasses which differ in their heavy chain composition and in some of their characteristics such as biologic activities. IgG1, IgG2, IgG3 and IgG4.
- Partial activator of the Complement System

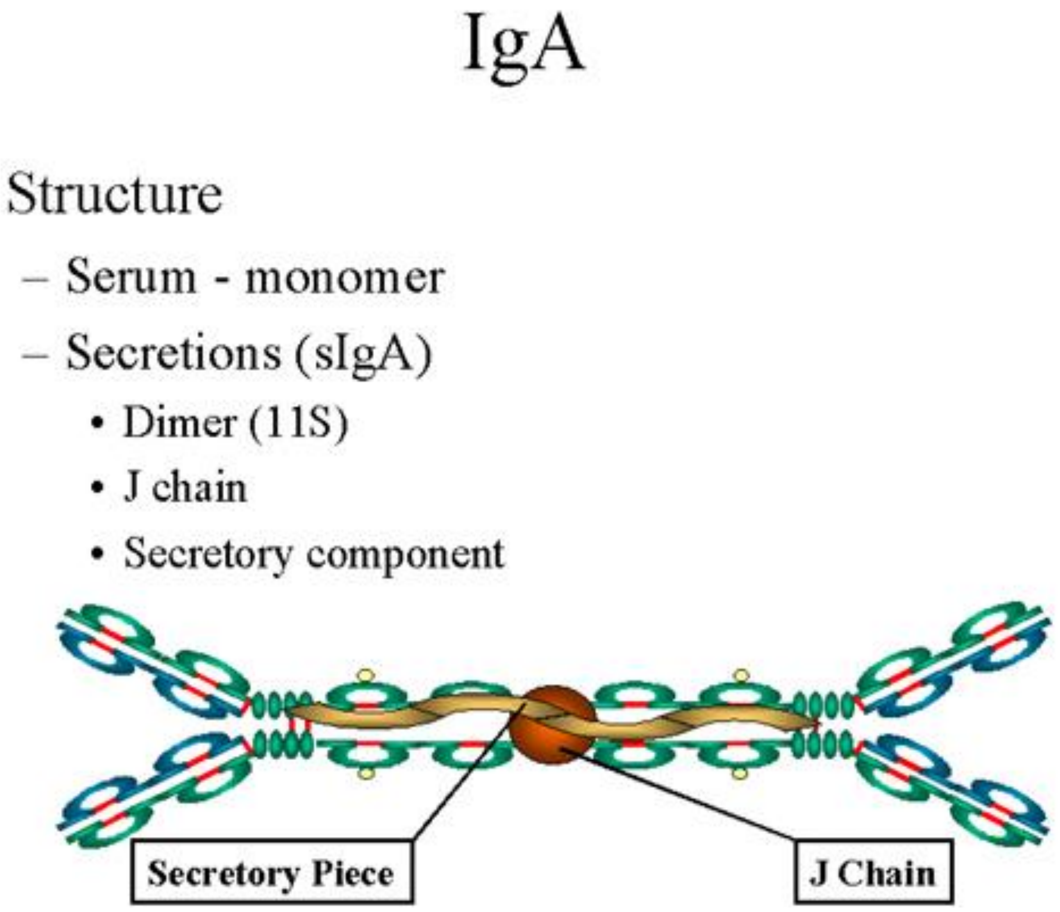
Immunoglobulin G (IgG)

- Structure, Subclasses and Functions



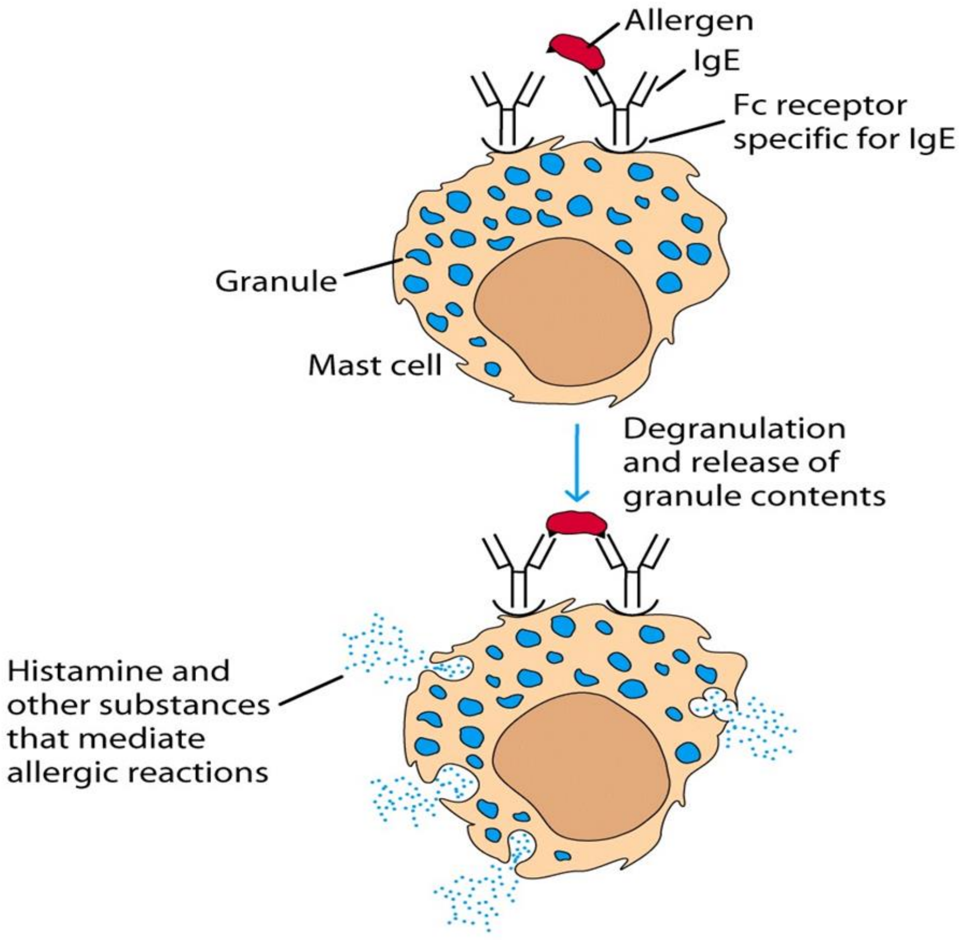
3. IgA

- 10-15% of serum IgG
- Predominant Ig in secretions
  - ✓ Milk, saliva, tears, mucus and in nasal, bronchial and intestinal secretions.
- Secretions, as dimer or tetramer+J-chain polyptetide + secretory component (Poly IgR)
- The IgA present in secretions exists as two basic units (a dimer) attached to another molecule know as secretory component.
- **<u>IgA does not cross the placenta and does not bind complement.</u>**



4. IgE

- **Clinical effects** of IgE mediated reactions include increased vascular permeability, skin rashes, respiratory tract constriction (wheezing), and increased secretions from epithelium (watery eyes, runny nose).
- Not much else is known about its biologic role.
  - ✓ Very low serum concentration, 0.3μg/mL
  - ✓ Participate in immediate hypersensitivities reactions. Ex. Asthma, anaphylaxis,
  - ✓ *responsible for an individual's immunity to invading parasites.*
- Fc regions bind very well to high affinity IgE receptors on Mast Cells (tissue) and basophils (blood) through FcεR
- Binding causes degranulation (Histamine Release)
- ***IgE does not fix complement and does not cross the placenta.***



5. IgD

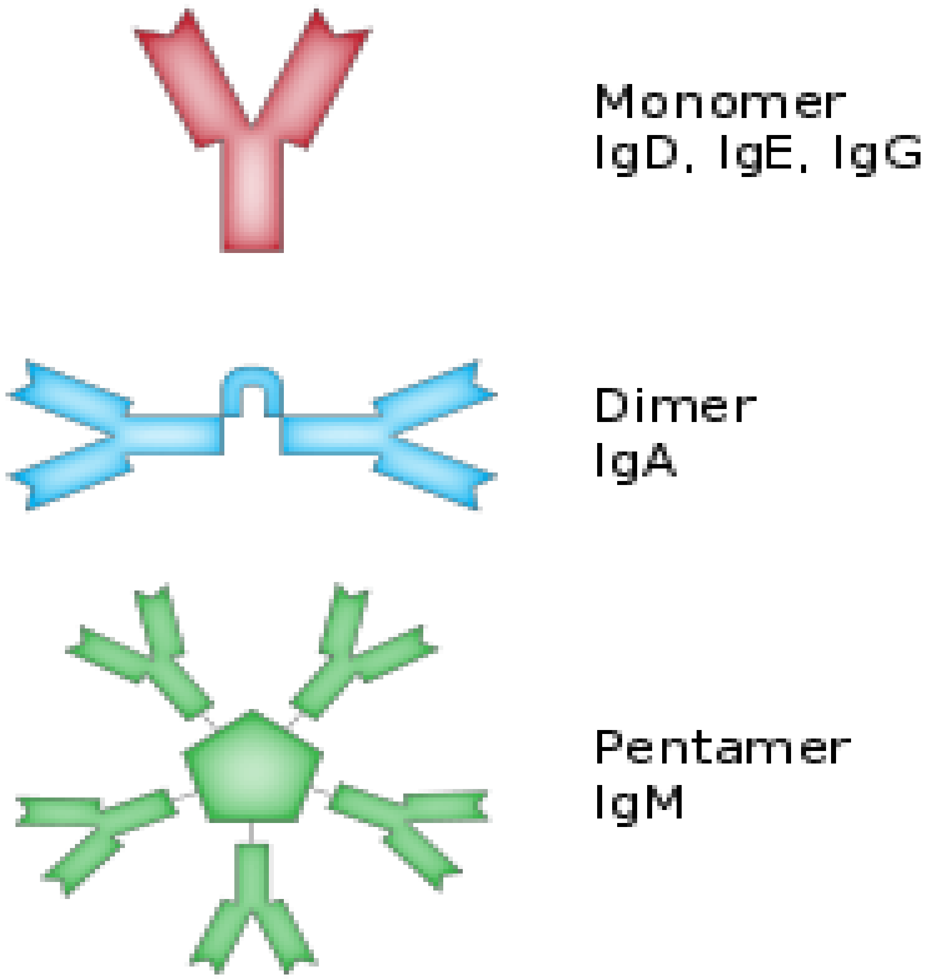
- Accounts for less than 1% of the total immunoglobulin pool.
- This is primarily a **cell membrane** immunoglobulin found on the surface of B lymphocytes.
- ***IgD does not fix complement and does not cross the placenta.***
- Little is known about the function of this class of antibody.

Structural differences among Ig isotypes

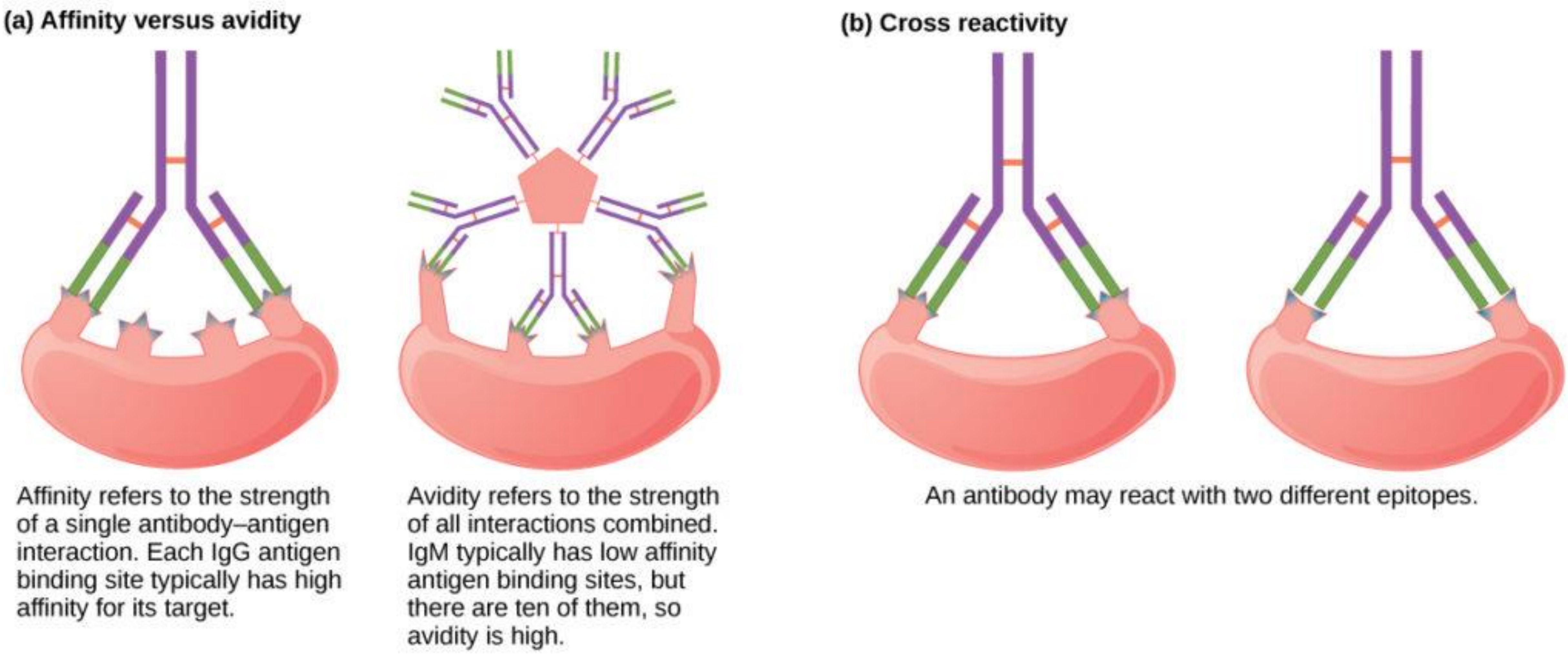
1. Monomer

2. Dimer

3. Pentamer



Affinity, Avidity and Cross Reactivity



Isotypes, Allotypes, and Idiotypes of Immunoglobulins

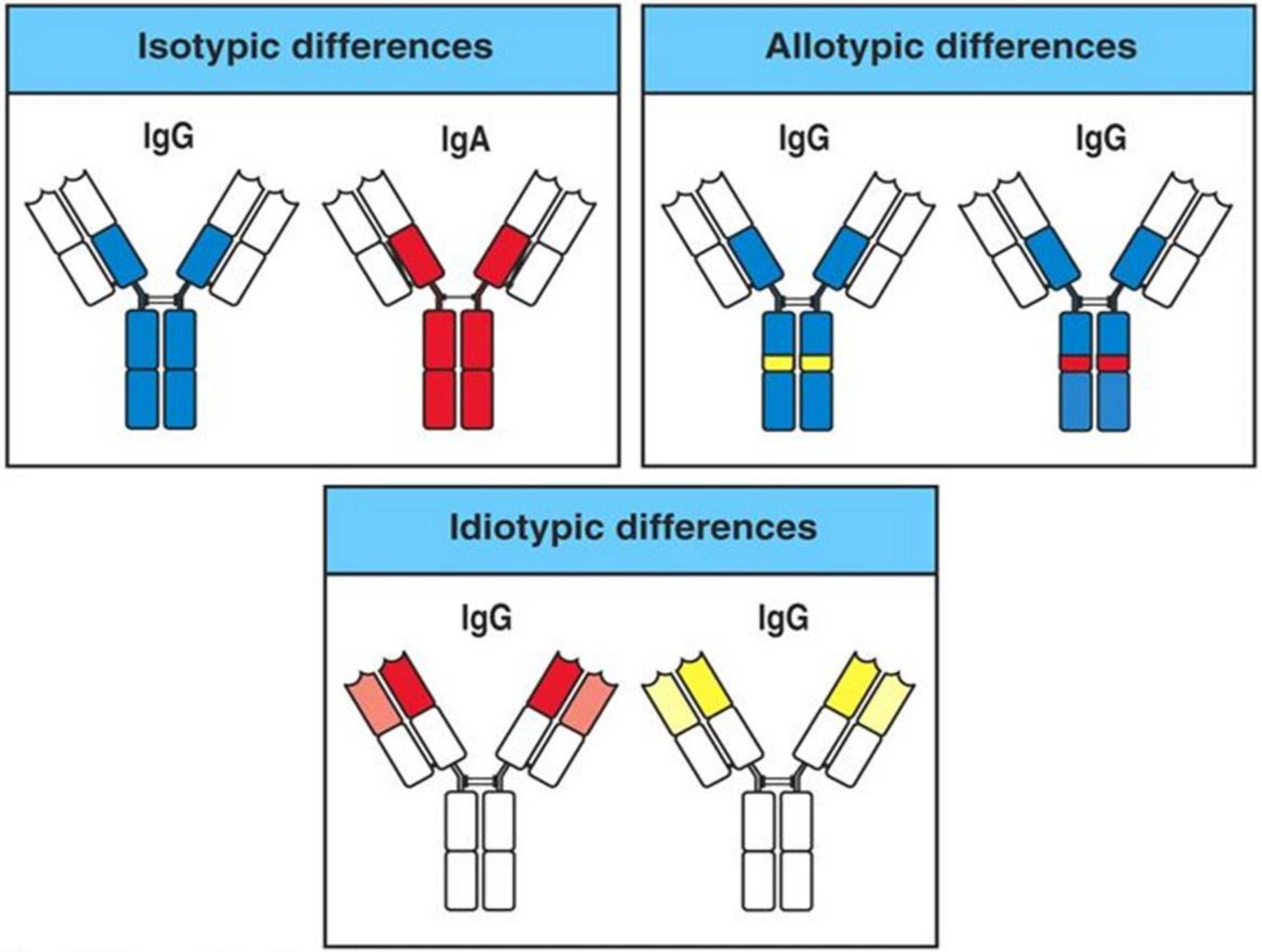


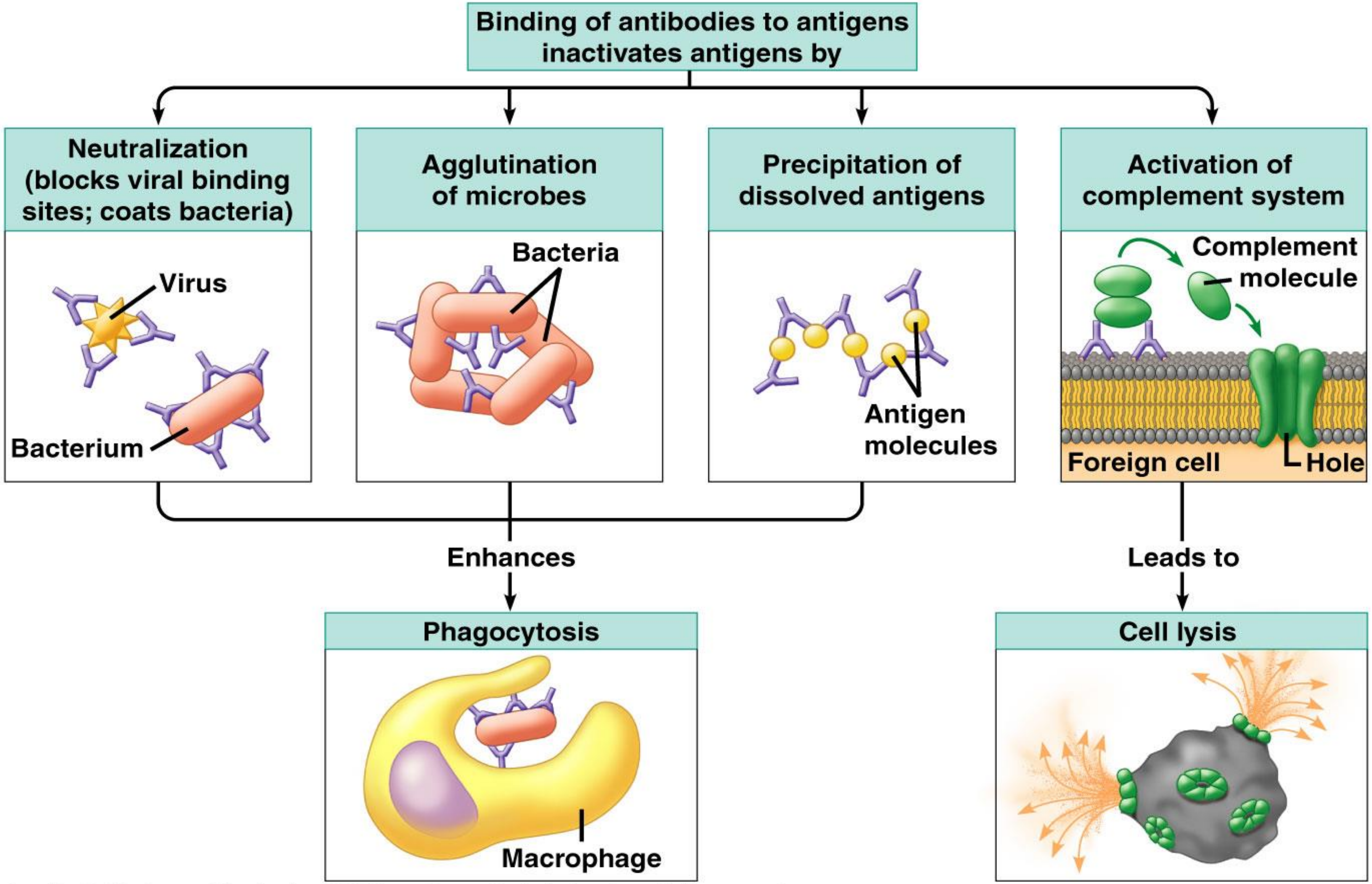
Figure 4-24 Immunobiology, 6/e. (© Garland Science 2005)

Definitions:

Isotype:
- Different Fc
- Different type of Ab
- IgG, IgA, IgM, IgE, IgD

Allotype:
- Difference between species
- Most differences in Fc region.

Idiotypes
- Different specificities of the antibody molecules.
- Eg: each idioptye recognizes a different part of or different antigen



Binding of antibodies to antigens inactivates antigens by
Neutralization (blocks viral binding sites; coats bacteria)
Virus
Bacterium
Agglutination of microbes
Bacteria
Precipitation of dissolved antigens
Antigen molecules
Activation of complement system
Complement molecule
Foreign cell
Hole
Enhances
Leads to
Phagocytosis
Macrophage
Cell lysis

Cytokines

- **Cytokines**, in general, **are secreted molecules** involved in **cell-to-cell signaling**.
- **All cytokines** are **proteins/ glycoproteins**.
- They are usually **secreted by cells of the immune system**. **Some cytokines (e.g., type I interferons [IFNs] and tumor necrosis factor [TNF]) can be secreted by nonimmune cells (e.g., epithelial cells).**
- **Most cytokines** are only secreted when cells become **activated as part of the response** to **infection**.
- **Cells of the immune system** use cytokines to **communicate** and **coordinate action**.

Chemokines

- **Chemokines** are **chemo-attractants**: They are approximately 50 different chemokines and approximately 20 different chemokine receptors.
- **Chemoattractants** = **molecules that attract cells** by **influencing cellular structure** and **cell surface adhesion molecules**.
- **Chemokines** = **mobilize immune cells from one location to another**.
- They can **attract cells into inflamed tissues** and play a role in leukocyte homing.
- Chemokines in the peripheral tissues **recruit cells of the innate and adaptive immune response** to **fight off an infection**.

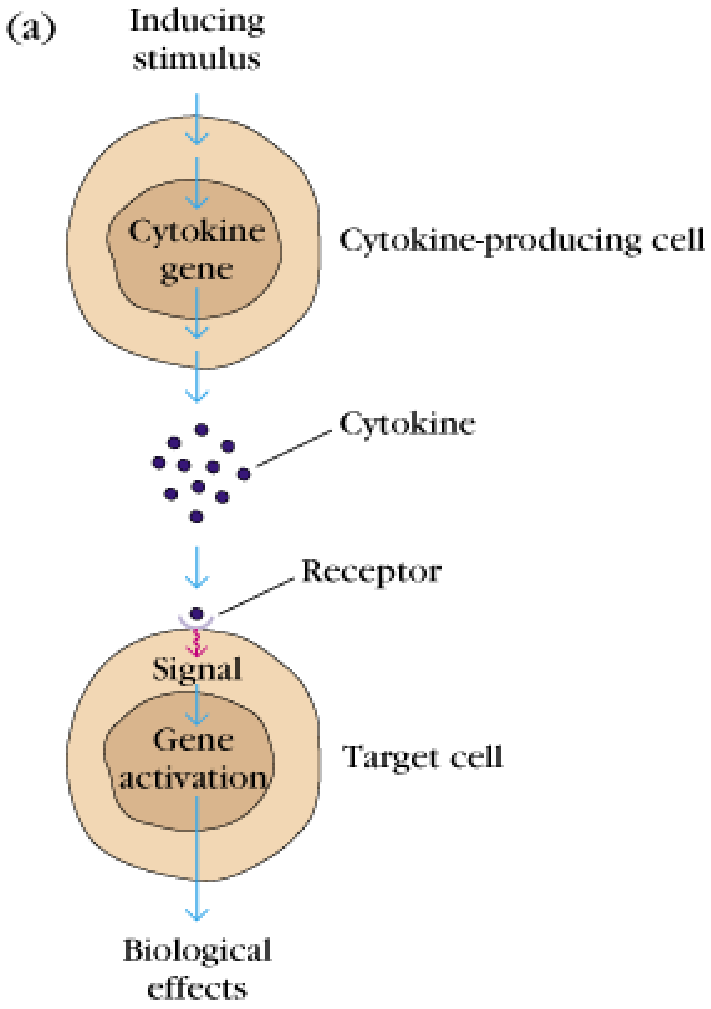
Functional Features

1. **Potent:**
   - ✓ Some function at 10^{-15} molar
2. **Local:**
   - ✓ Autocrine
   - ✓ Paracrine
   - ✓ (Sometimes) endocrine
3. **Highly interactive:**
   - ✓ Pleiotropic
   - ✓ Redundant
   - ✓ Synergistic / antagonistic

Functional Features

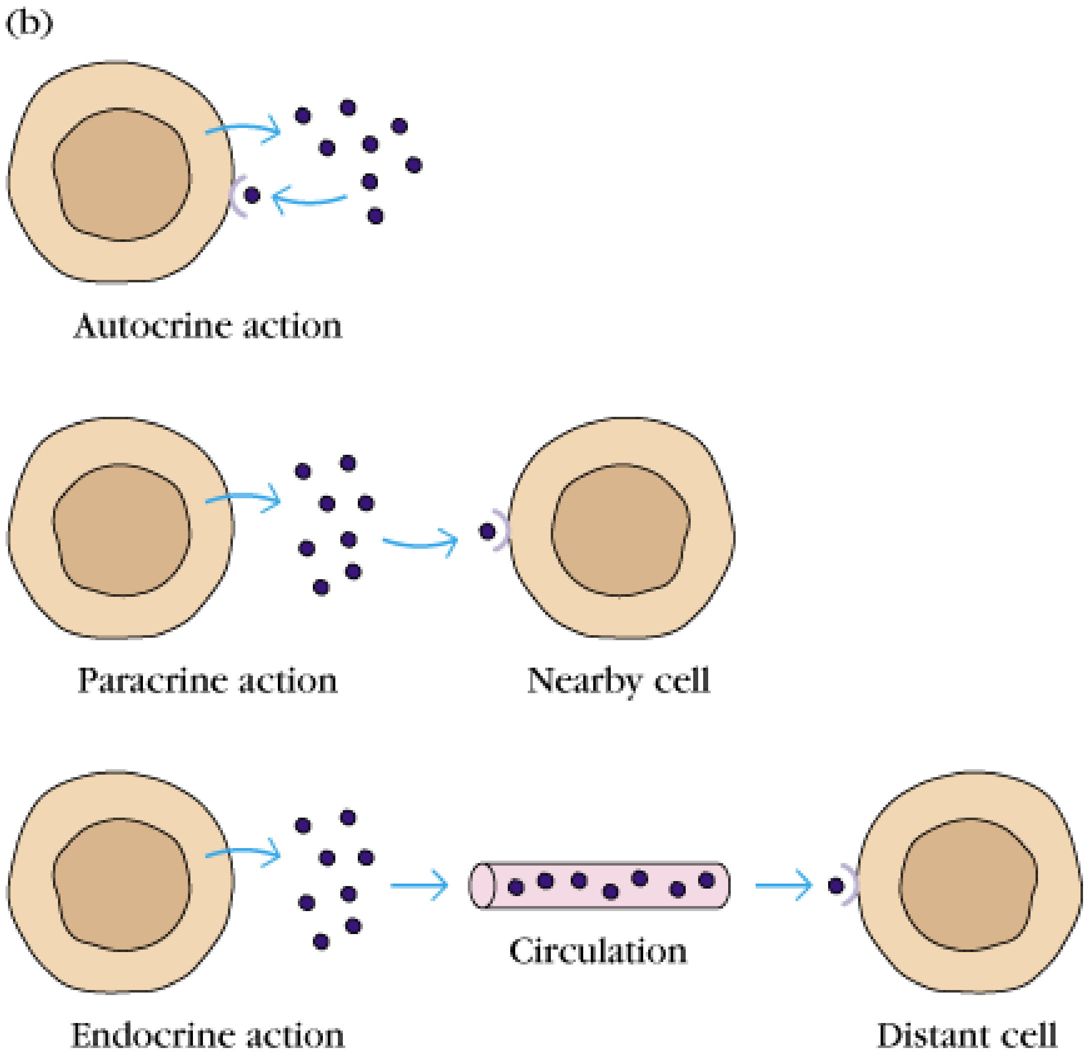
- Potent: Cytokines Mediate the Activation, Proliferation, and Differentiation of **Target Cells**:

  ✓Some function at10^{-15} Molar.



Functional Features

- Local:
  1. Autocrine
  2. Paracrine
  3. (Sometimes) Endocrine



Functional Features

- **Highly Interactive:**

a.**Pleiotropic** = induces different biological effects depending on the nature of the target cell type.

b.**Redundant**= two or more cytokines that mediate similar functions.

c.**Synergy** = combined effect of two cytokines on cellular activity is greater than the additive effects of the two cytokines.

d.**Antagonize** = the effect of one cytokine cancels out the effect of another cytokine.

e.**Cascade induction** = the effect of one cytokine on a target cell leads to the production of one or more additional cytokines from that target cell.

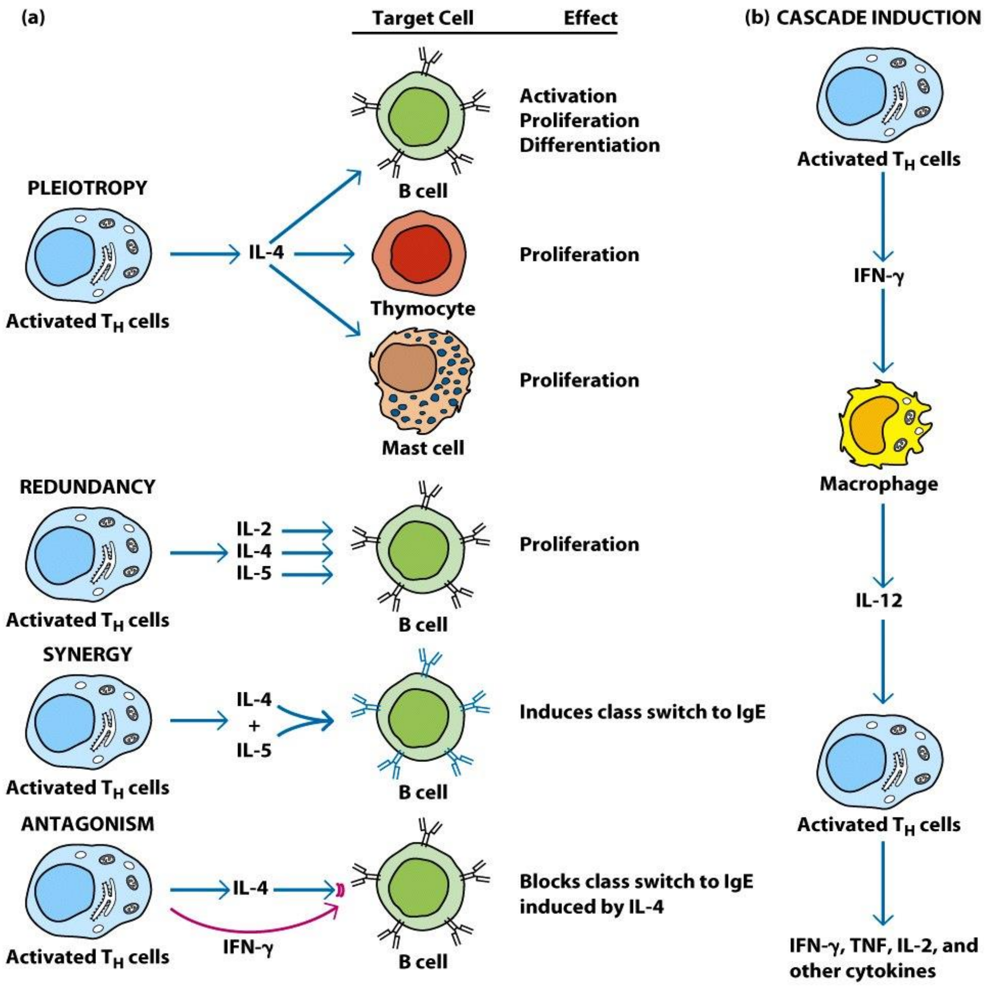


Figure 12-2
Kuby IMMUNOLOGY, Sixth Edition

Cytokine Families

I. Hematopoietic family

II. Interferon family

III. Tumor necrosis factor family

IV. Chemokine family

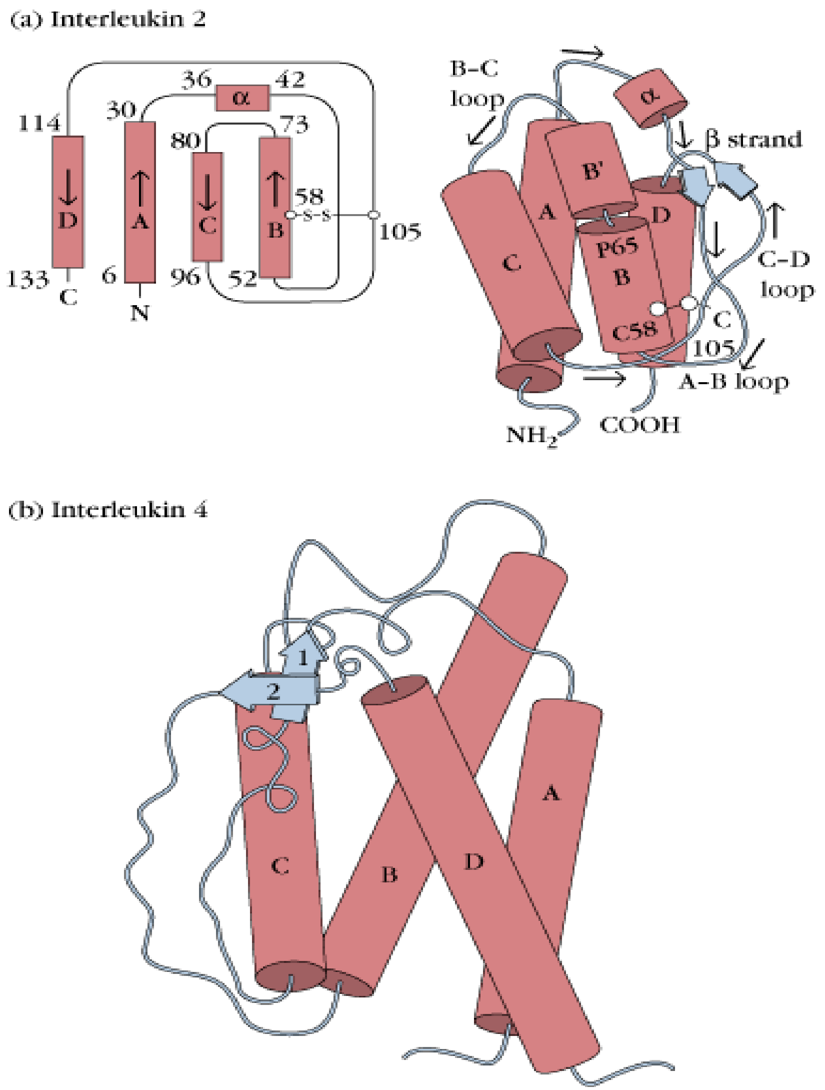
V. Interleukin 1 (IL-1)

VI. Interleukin 17 (IL-17)

- I, II, and III elicit physiological responses.
- IV serves as a chemoattractant.

Hematopoietic family

- Large family of small cytokine molecules with functional diversity.
- Not all involved in hematopoietic functions.



Interferon (Class II) First cytokines to be discovered

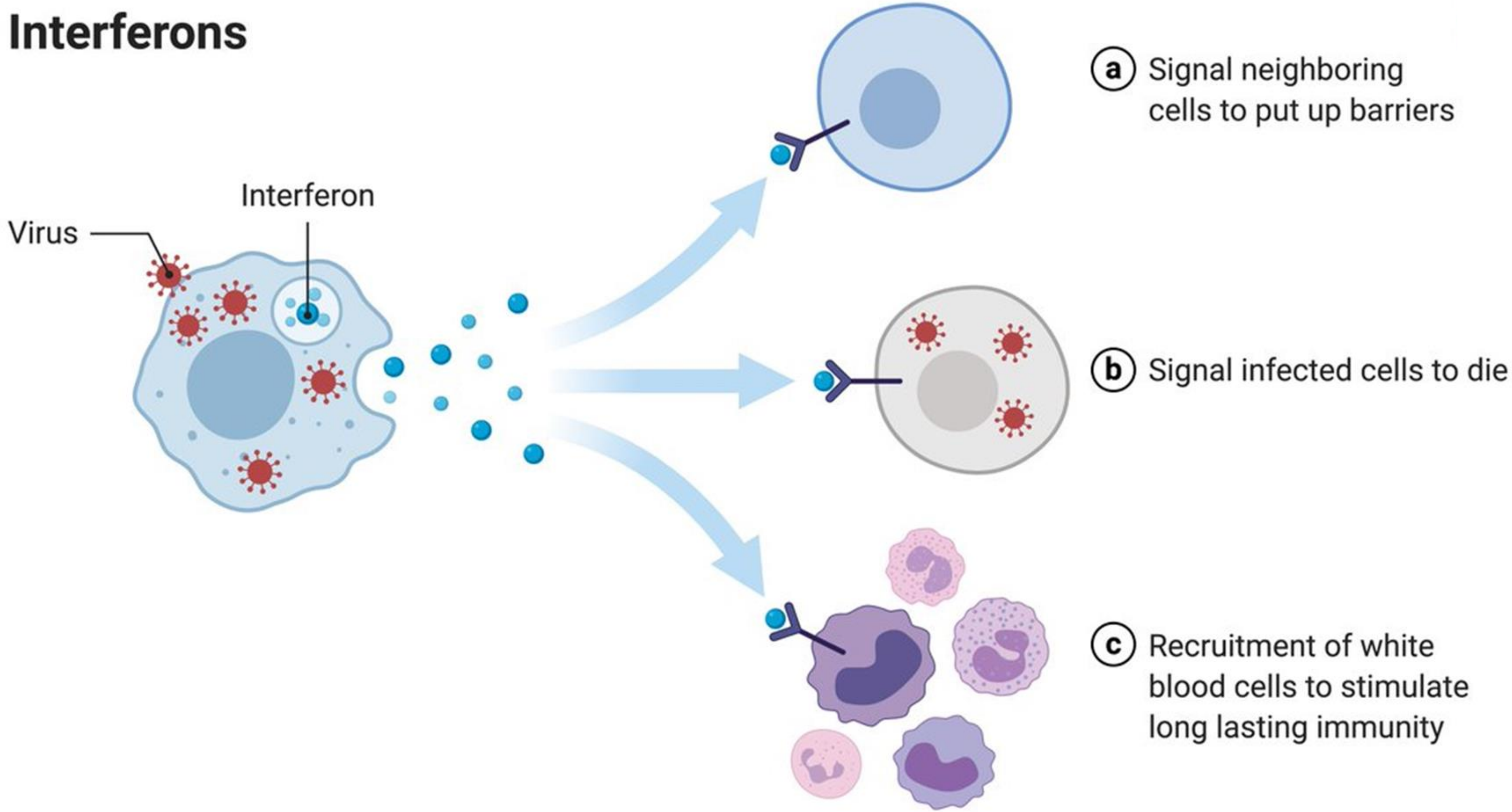
Type I - Secreted by not only macrophages and dendritic cells but also by virus infected cells:

Interferons α, and **interferon-β,**

Type II – produced by activate T and NK cells **, known as interferon-γ & cytokines include IL-10.**

- Interferon-γ is used medically to bias the adaptive immune system toward a cytotoxic response in diseases such as leprosy (Hansen's disease) and toxoplasmosis (intracellular pathogens), in which antibody responses are less effective.

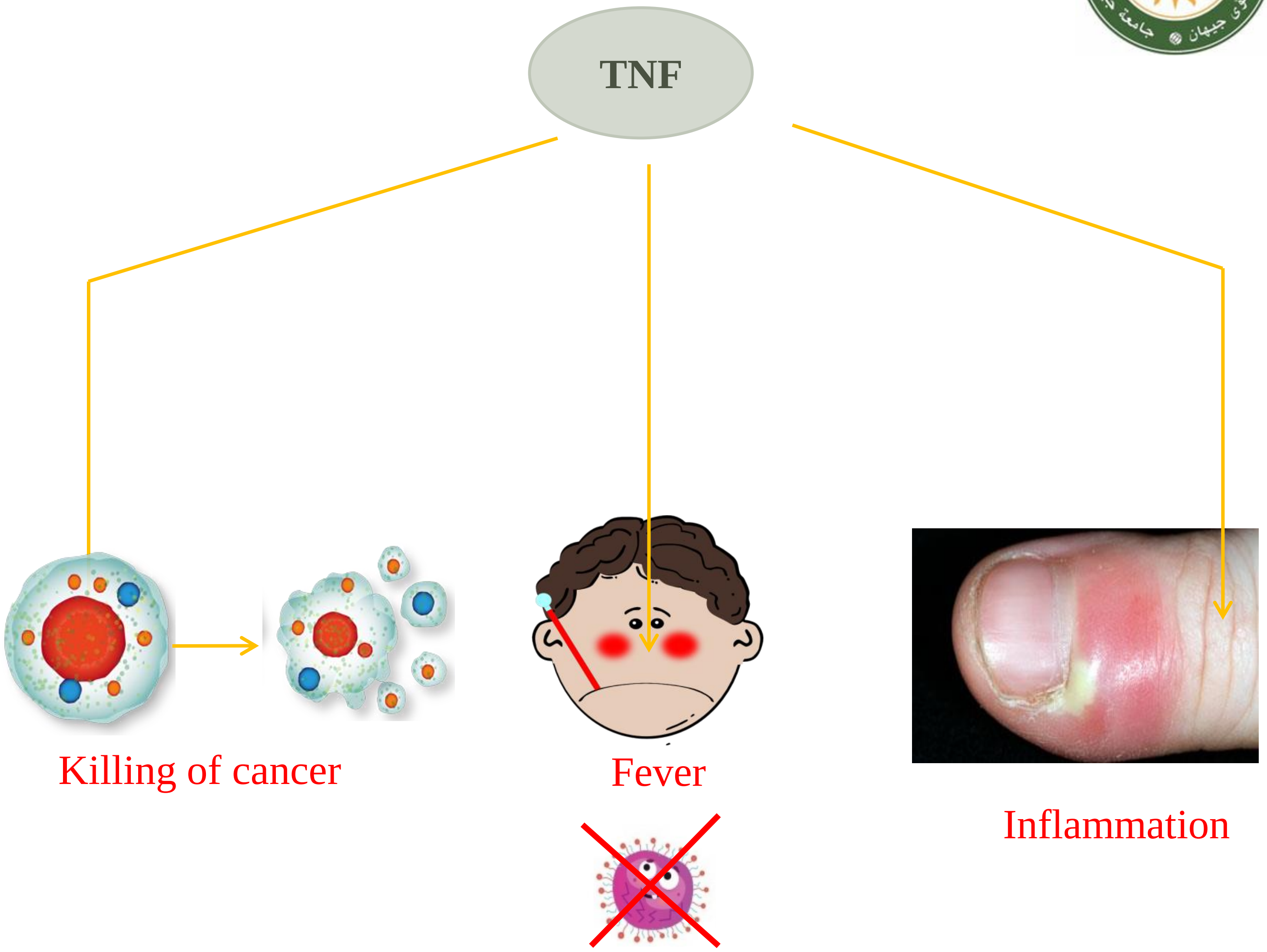
Interferons



Tumour Necrosis Factor (TNF)

- **TNF:** can signal development, activation, or death of certain cells (homeostasis) Which induce apoptosis**,**

❖ **Programmed cell death**, is a mechanism of cell death in which the cell dies from within and is fragmented into membrane-bound vesicles that can be rapidly phagocytosed by neighboring macrophages.



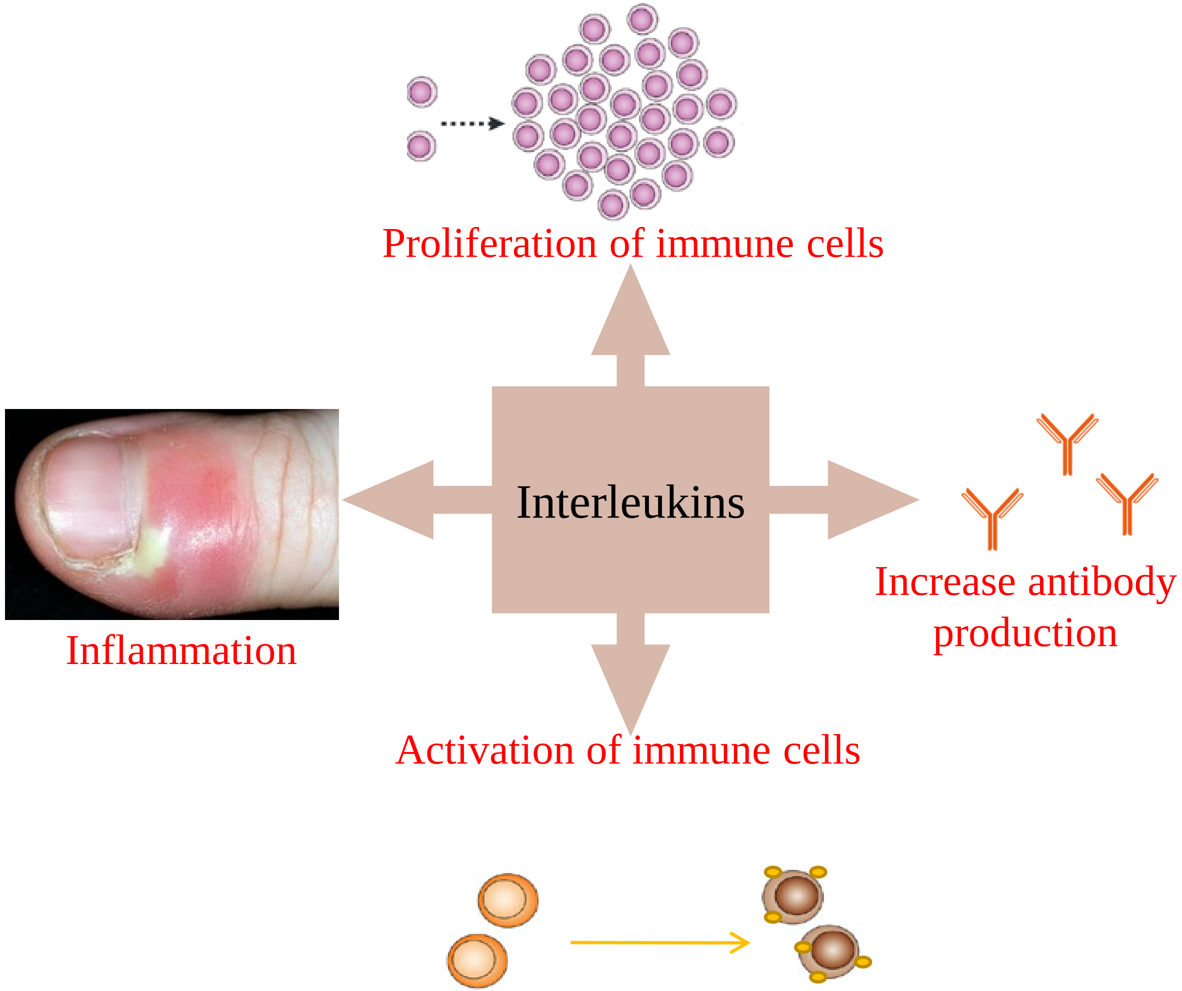
Tumour Necrosis Factor Family

- **There are two members of the TNF family**:
- **TNF-α** and **TNF-β**. Both of these are **secreted as soluble proteins**.
  - ✓ **TNF-α** is a **proinflammatory cytokine**, **produced** primarily by activated macrophages, and lymphocytes, in response to infection, or inflammation.
  - ✓ **TNF-β** is **produced** by activated lymphocytes and **can deliver a variety of signals**.
  - ✓ On binding to neutrophils, endothelial cells lead to increased expression of MHC and of adhesion molecules.
  - ✓ **Fas-ligand (FasL)**, induces apoptosis.

Interleukins

- Interleukins – 1-37
- Not stored inside cells.
- Quickly synthesized and secreted in response to infection.
- Key modulators of behaviour of immune cells
- Mostly secreted by T-lymphocytes & macrophages

What interleukins do ?



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