

1. Complement System

2. Antigen Specific Receptors

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Complement System

Composition: proenzyme → enzyme **plasma protein cascade** system with >25 proteins (enzymes, receptors, and complement inhibitors)

Synthetic source: liver, macrophages

Function: mediates inflammation by increasing vascular permeability, attracting phagocytes, enhancing phagocytosis, and causing microbial lysis

Topic Outline

- Complement System
 - Activation pathways
 - Bioactive complement peptides & functions
 - Complement regulatory proteins
- Lymphocyte receptors for antigens
 - B cell receptor (immunoglobulin) and T cell receptor (TcR) structure

Complement Activation Pathways, their activating signals, and common immune functions

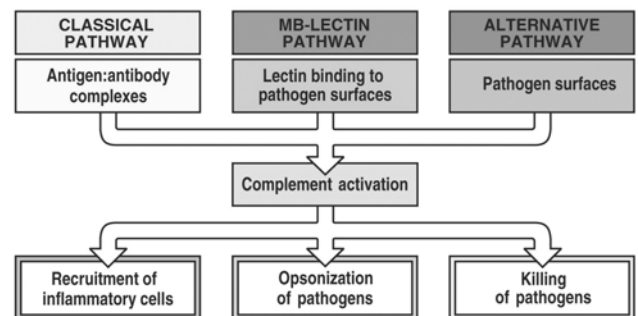
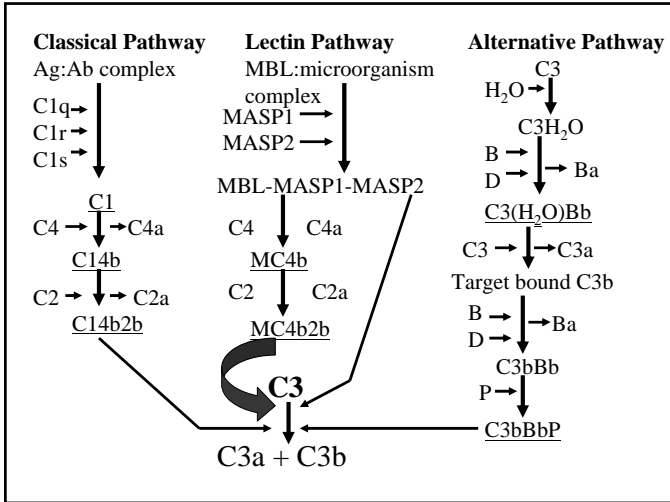
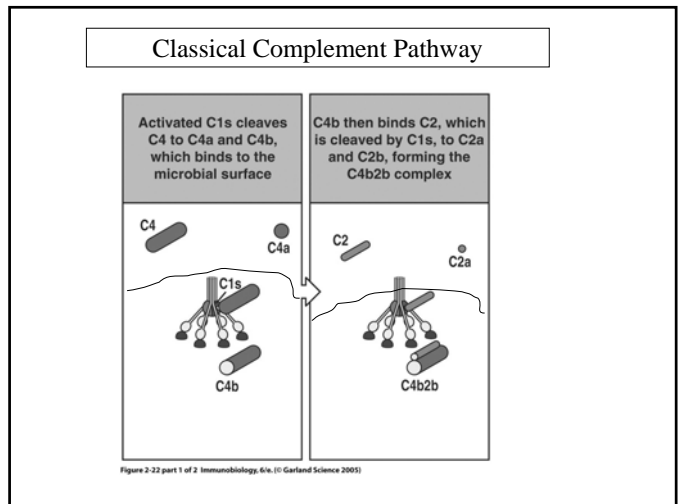
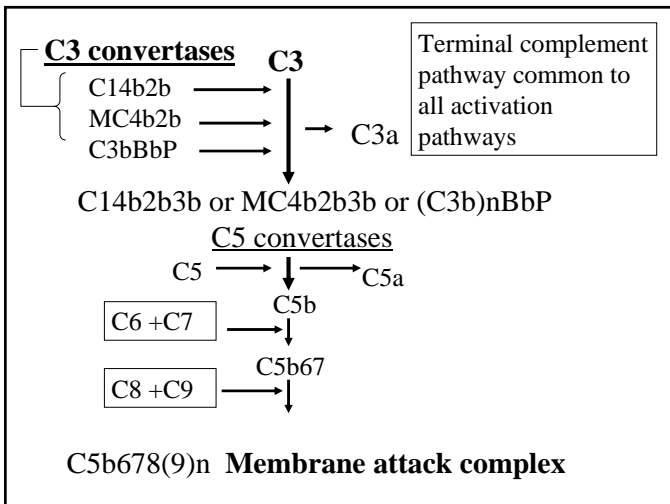


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Bioactive Complement Peptides

- Plasma protease cascade generates peptides active in inflammation and innate immunity
 - C3a & C5a **anaphylatoxins** release histamine from mast cells → ↑vascular permeability
 - C5a **chemotaxin**, recruits phagocytes
 - C3b & C3bi **opsonins** (coats microbes to enhance recognition & uptake by phagocytes)
 - C5b6789n **membrane attack complex** (lyses microbial cell membranes)



Classical Complement Pathway- continued

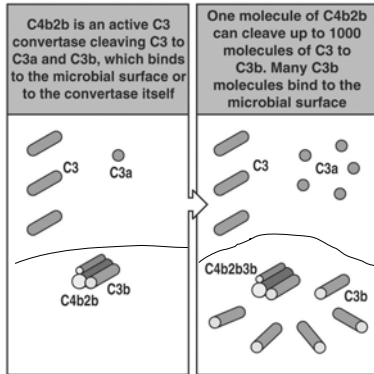


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Alternative Complement Pathway -2

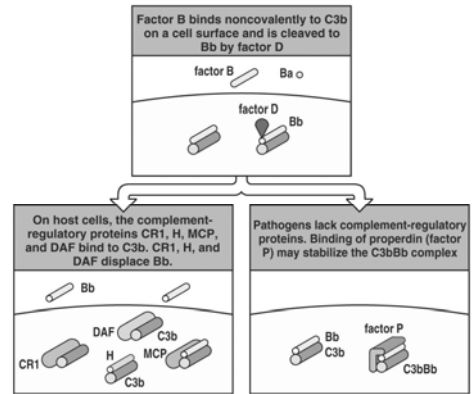
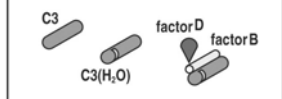


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C3 undergoes spontaneous hydrolysis to C3(H₂O), which binds factor B allowing it to be cleaved by factor D into Ba and Bb



The C3(H₂O)Bb complex is a C3 convertase, cleaving more C3 into C3a and C3b. C3b is rapidly inactivated unless it binds to cell surface

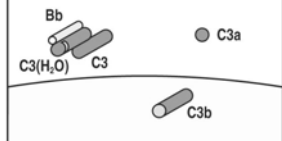


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Alternative Complement Pathway -1

Alternative Complement Pathway -3

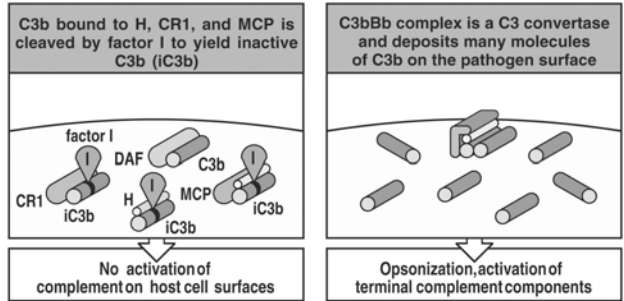
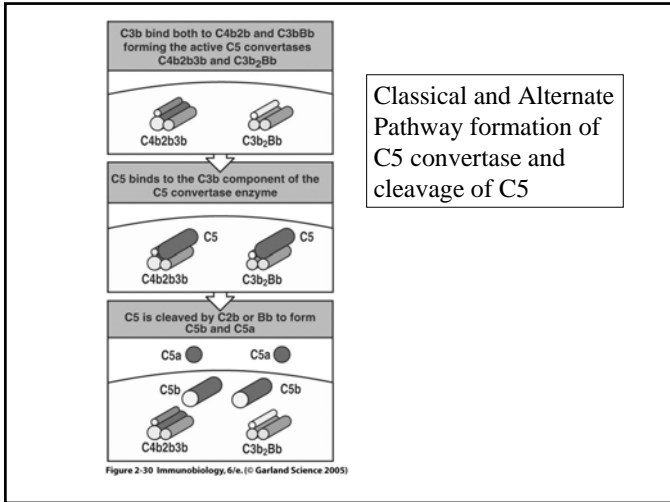


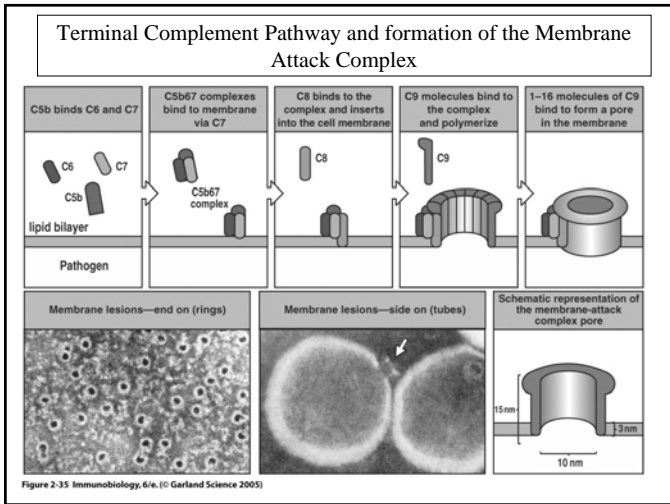
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Receptor	Specificity	Functions	Cell types
CR1 (CD35)	C3b, C4b, IC3b	Promotes C3b and C4b decay Stimulates phagocytosis Erythrocyte transport of immune complexes	Erythrocytes, macrophages, monocytes, polymorphonuclear leukocytes, B cells, FDC
CR2 (CD21)	C3d, IC3b, C3dg Epstein-Barr virus	Part of B-cell co-receptor Epstein-Barr virus receptor	B cells, FDC
CR3 (Mac-1) (CD11b/CD18)	IC3b	Stimulates phagocytosis	Macrophages, monocytes, polymorphonuclear leukocytes, FDC
CR4 (gp150,95) (CD11c/CD18)	IC3b	Stimulates phagocytosis	Macrophages, monocytes, polymorphonuclear leukocytes, dendritic cells
C5a receptor	C5a	Binding of C5a activates G protein	Endothelial cells, mast cells, phagocytes
C3a receptor	C3a	Binding of C3a activates G protein	Endothelial cells, mast cells, phagocytes

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Cells detect and respond to complement peptides via cell-membrane receptors for complement peptides.



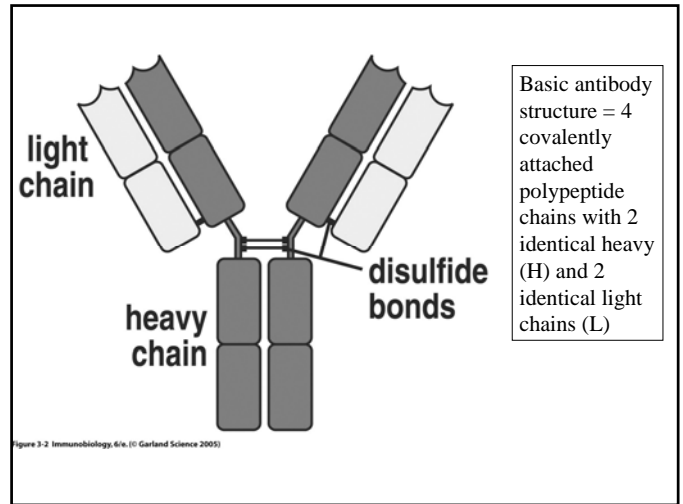
Spontaneous or chronic activation of complement is prevented by inhibitory proteins, both soluble and membrane associated.

Regulatory proteins of the classical and alternative pathways	
Name (symbol)	Role in the regulation of complement activation
C1 inhibitor (C1INH)	Binds to activated C1r, C1s, removing them from C1q
C4-binding protein (C4BP)	Binds C4b, displacing C2b; cofactor for C4b cleavage by I
Complement receptor 1 (CR1)	Binds C4b, displacing C2b, or C3b displacing Bb; cofactor for I
Factor H (H)	Binds C3b, displacing Bb; cofactor for I
Factor I (I)	Serine protease that cleaves C3b and C4b; aided by H, MCP, C4BP, or CR1
Decay-accelerating factor (DAF)	Membrane protein that displaces Bb from C3b and C2b from C4b
Membrane cofactor protein (MCP)	Membrane protein that promotes C3b and C4b inactivation by I
CD59 (protectin)	Prevents formation of membrane-attack complex on autologous or allogenic cells. Widely expressed on membranes

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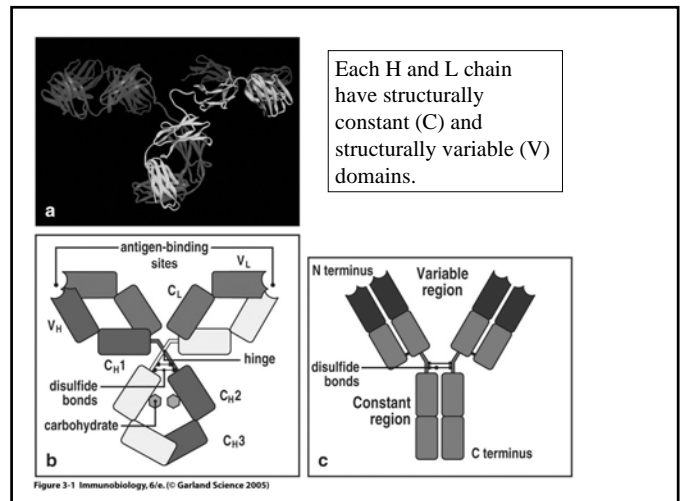
Antigen Recognition

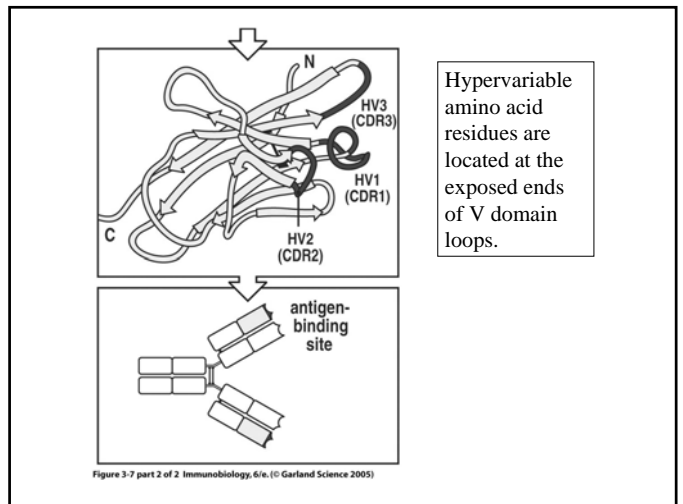
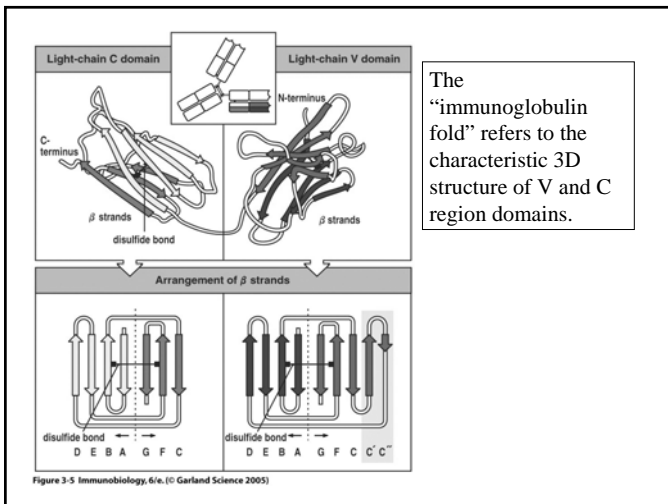
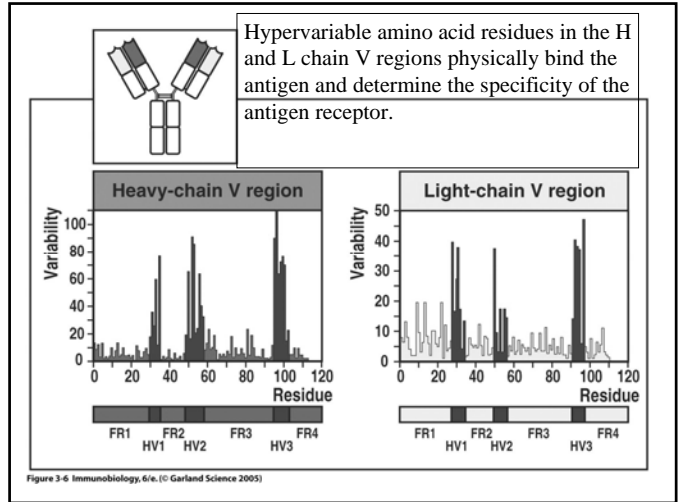
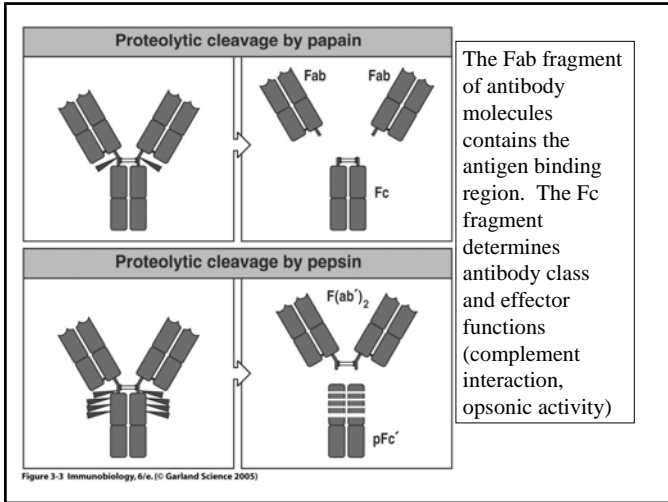
- B cells recognize antigens via *membrane associated* immunoglobulin molecules (antibodies)
 - Antigen-activated B cells synthesize and secrete a *soluble form* of this receptor (plasma antibody) which accumulates in fluids and specifically binds and eliminates the stimulating antigen.
- T cells recognize antigens via a membrane associated heterodimeric protein, the T cell receptor or TcR
 - TcR are not secreted



Antibody Activity

- Antibodies specifically recognize and bind to the inducing antigen
- Humoral immunity: antibody-mediated immunity can be transferred from an immune to a non-immune person by transfer of serum
- The gamma-globulin protein fraction of serum contains the antibody activity





V_H and V_L domains fold to form antigen binding sites that resemble pockets, grooves, open faces, or extrusions.

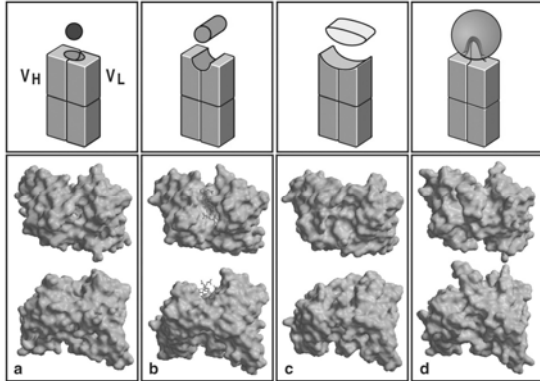


Figure 3-8 Immunobiology, 6/e. (© Garland Science 2005)

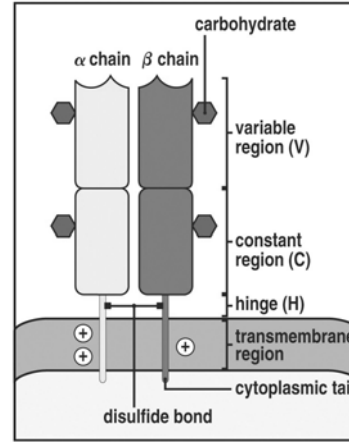


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The structure of the T cell receptor (TcR) resembles that of antibody but consists of only 2 polypeptide chains with a single binding site. Each chain has a constant and variable structural domain. An $\alpha\beta$ TcR and a $\gamma\delta$ TcR have been described.

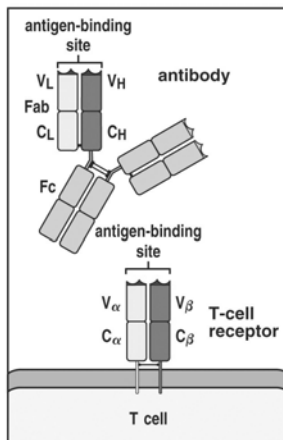


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The TcR binding site for antigen (one site per receptor) is also formed by the variable domains of an alpha and beta chain polypeptide.

Antigen interaction with receptors is noncovalent and reversible.

Noncovalent forces	Origin	
Electrostatic forces	Attraction between opposite charges	$-\text{NH}_3^+ \quad \ominus \text{OOC}-$
Hydrogen bonds	Hydrogen shared between electronegative atoms (N,O)	$\begin{array}{c} \text{N} \quad \text{H} \quad \text{O} \\ \delta^- \quad \delta^+ \quad \delta^- \\ \text{---} \quad \text{---} \quad \text{---} \\ \text{---} \quad \text{---} \quad \text{---} \end{array}$
Van der Waals forces	Fluctuations in electron clouds around molecules oppositely polarize neighboring atoms	$\begin{array}{c} \delta^+ \quad \delta^- \\ \delta^- \quad \delta^+ \end{array}$
Hydrophobic forces	Hydrophobic groups interact unfavorably with water and tend to pack together to exclude water molecules. The attraction also involves van der Waals forces	$\begin{array}{c} \text{H} \quad \text{O} \quad \text{H} \\ \text{H} > \text{O} \quad \delta^+ \quad \delta^- \quad \text{O} < \text{H} \\ \delta^- \quad \delta^+ \\ \text{H} \quad \text{H} \\ \text{O} \end{array}$

Figure 3-9 Immunobiology, 6/e. (© Garland Science 2005)

There are 5 immunoglobulin classes based on structural similarity of the H chain C domains.

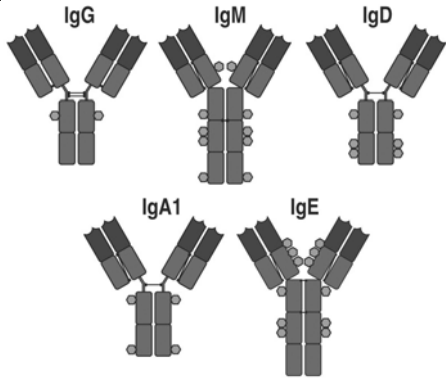


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Nomenclature for structural differences between any 2 antibodies.

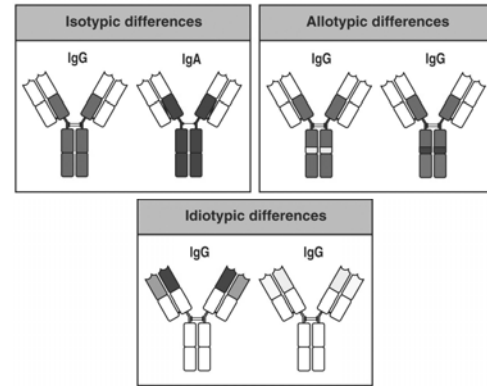


Figure 4-24 Immunobiology, 6/e. (© Garland Science 2005)

IgM and IgA are secreted as pentamers and dimers respectively. The J chain protein promotes polymerization.

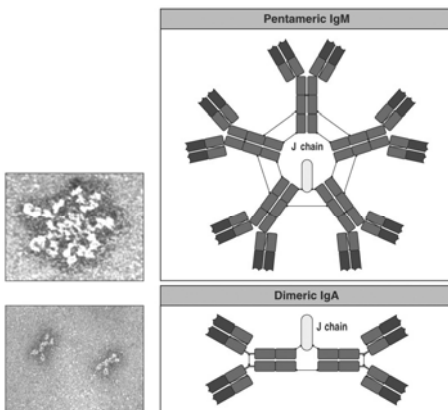


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Antigen-Antibody Reactions, Definitions and Characteristics to Know

- Size of Epitope/antigenic determinant
- specific, noncovalent, reversible binding
- affinity vs. avidity
- valency, crosslinking, agglutination, precipitation
- multideterminant antigens,
- heterogeneous antibody responses
- cross reactions

