

## Complement/ Acquired Immunity

- Functions of Complement
- Components and Activation
- Regulatory Proteins
- Complement Diseases
- Acquired Immunity

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## Complement

- The complement system is a series of serum proteins (9 factors) which, through sequential proteolysis, non-specifically increase immunity to infectious organisms and proteins.
- The initial, inactive complement components are named C1 - C9

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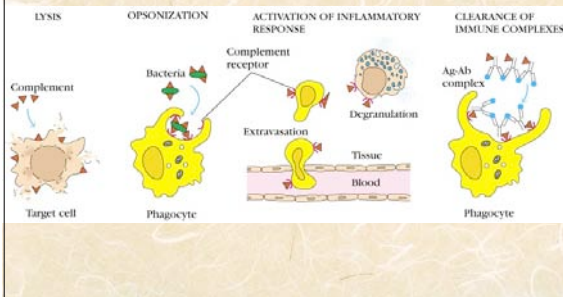
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## Functions of Complement



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## Complement Nomenclature

- Each complement component is synthesized in an "inactive" form. Once initial activation occurs, the inactive complement component (named C1-C9) is split into fragments, designated by letters (e.g. C1q, C3a, C53b, etc.)

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## Complement Activation

- The complement system may be activated in 3 distinct ways, named:
  - **The Classical Pathway** - activated by antigen/antibody complexes
  - **The Alternative Pathway** - activated by microbial cell walls
  - **(The Lectin Pathway** - activated by bacterial lectins).
- The end result of this activation is always the same. Only the initial steps differ.

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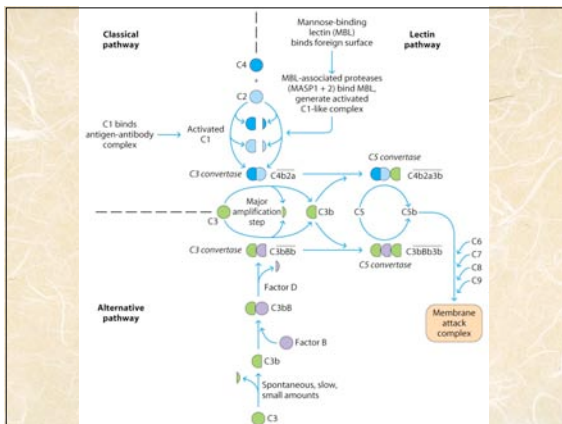
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## Complement Protein Functions

- The ultimate end-result of complement activation is the formation of the Membrane Attack Complex, formed by components C5 through C9, which literally punches holes in membranes
- In addition, intermediate products such as C3a, C5a, and C3b may play a role in upregulating the immune response through chemotaxis or opsonization.

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## Classical Pathway

- The classical pathway of complement activation begins when C1 is cleaved due to interactions with Fc regions of IgM or IgG complexed with antigen.
- The cascade continues as C2 and C4 are cleaved, yielding a new protease complex with cleaves C3 to yield C5 convertase.

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## Alternative Pathway

- C1 is not involved
- Microbial surfaces directly activate the conversion of C3, which is completed through the interaction of **Factor D with its substrate Factor B.**
- Once the C3 convertase is formed (as C3bBb) the addition of an additional C3b molecule will result in formation of the C5 convertase. This will result in conversion of the C5-9 MAC.

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**TABLE 13.2 ALTERNATIVE COMPLEMENT PATHWAY: PROTEINS THAT PARTICIPATE IN FORMATION OF C3 CONVERTASE**

Component	Active protein/split product	Immunologic function
C3	C3a C3b	Peptide mediator of inflammation (anaphylatoxin) Binds factor B, forming complex that is cleaved by factor D to yield C3bBb
Factor B	Ba Bb	Opsonin function Serine protease. C3bBb acts as C3 convertase, which generates C3bBb (C3 convertase)
Factor D	D	Serine protease cleaves factor B that is bound to C3b to form C3 convertase
Properdin		Binds to and stabilizes C3bBb

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**Formation of the Membrane Attack Complex**

**TABLE 13.5 TERMINAL COMPLEMENT PATHWAY: PROTEINS INVOLVED IN THE FORMATION OF THE MEMBRANE-ATTACK COMPLEX (MAC)**

Component	Active protein/split product	Immunologic function
C5	C5a C5b	Peptide mediator of chemotaxis and inflammation (anaphylatoxin) Binds C6 to initiate formation of MAC
C6	C6	C5b6 binds C7
C7	C7	After an amphiphilic transition of C5b67, the resulting complex inserts into the lipid bilayer
C8	C8	C5b678 binds multiple C9 molecules, initiating their polymerization
C9	C9	Polymerizes to complete formation of MAC pore

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**Complement Regulation**

- Because the complement system is a cascade, which is capable of self-initiation, a number of proteins exist which regulate the process. These include C1 inhibitor, Factor H, Factor I, or DAF (Decay Accelerating Factor)

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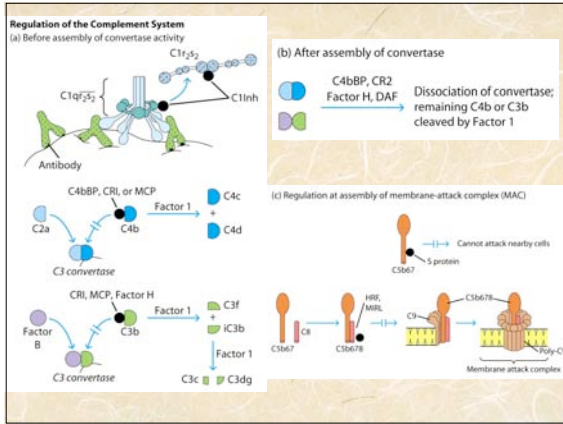
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## Complement Opsonization

- Complement interacts with the immune cells through specific cell surface receptors, functionally similar to Fc Receptors on B cells. Interaction of complement with these receptors increases phagocytosis and may increase immune reactivity (through C3b/CD21 and the membrane Ig receptor)

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**TABLE 13-4 Complement-binding receptors**

Receptor	Major ligands	Activity	Cellular distribution
CR1 (CD35)	C3b, C4b	Blocks formation of C3 convertase; binds immune complexes to cells	Erythrocytes, neutrophils, monocytes, macrophages, eosinophils, follicular dendritic cells, B cells, some T cells
CR2 (CD21)	C3d, C3dg,* iC3b	Part of B cell coreceptor; binds Epstein-Barr virus	B cells, follicular dendritic cells, some T cells
CR3 (CD11b/18)	iC3b	Bind cell-adhesion molecules on neutrophils, facilitating their extravasation; bind immune complexes, enhancing their phagocytosis	Monocytes, macrophages, neutrophils, natural killer cells, some T cells
CR4 (CD11c/18)			
C3a/C4a receptor	C3a, C4a	Induces degranulation of mast cells and basophils	Mast cells, basophils, granulocytes
C5a receptor	C5a	Induces degranulation of mast cells and basophils	Mast cells, basophils, granulocytes, monocytes, macrophages, platelets, endothelial cells

\*Cleavage of C3d by serum proteases generates C3d and C3g.

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## Complement and Disease

- Complement deficiencies have been associated with a disability to clear immune complexes (SLE), resulting in physical blockage of fine vascular beds (e.g. kidney).
- There is also an association of complement deficiency with development of chronic infections (inability to clear microbial infections).
- The precise symptoms depend upon which factor is deficient (how far along the pathway that the cascade is interrupted).

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## Cobra venom factor

- A biological activity of cobra venom is to systemically activate the complement cascade. This is due to a homology between CVF and human C3b
- Complement can be experimentally depleted using cobra venom factor. Depletion of complement prior to a primary immunization eliminates the development of a strong memory response.

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## Adaptive Immune System

- Unlike the **Innate** immune system, the adaptive/acquired Immune system exhibits 2 specific characteristics:

**SPECIFICITY - Antigenic Specificity**  
**Diversity**  
**Self/Non-Self Recognition**

**MEMORY**

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## Specificity:

- The exquisite specificity of the immune system allows it to selectively recognize billions of different foreign antigens, while maintaining tolerance to an equally diverse panel of self antigens
- Failure of this system results in increased susceptibility to disease, or autoimmune disorders.

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## Memory

- This is the basis of vaccination. The Acquired/Specific/Adaptive Immune system will respond more effectively, and more vigorously to a secondary exposure of any given antigen. Normally, this results in a protective response.

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The adaptive immune system can be subdivided into antibody-based (**humoral**) and cell based (**cellular**) immunity.

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## Humoral Immunity

- Humoral immunity is generated by **ANTIBODY RESPONSES**. Antibodies bind to foreign antigens and assist in their destruction/elimination by the innate immune system
- Humoral immunity targets **extracellular** antigens, including viruses, bacteria, protozoa, parasites.

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## Cellular Immunity

- Cellular Immunity serves 2(3) basic purposes:
  - *To assist the humoral response by secretion of cytokines*
  - *To kill foreign eukaryotic cells, or altered self cells.*
    - Virally infected cells
    - Organ grafts
    - Cancer
  - *(To suppress specific immune responses)*

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## Cellular Immunity 2

- Cellular Immunity targets **intracellular antigens**, through the interaction of specific cell surface molecules on T cells with complementary molecules on target or antigen-presenting cells (MHC molecules).

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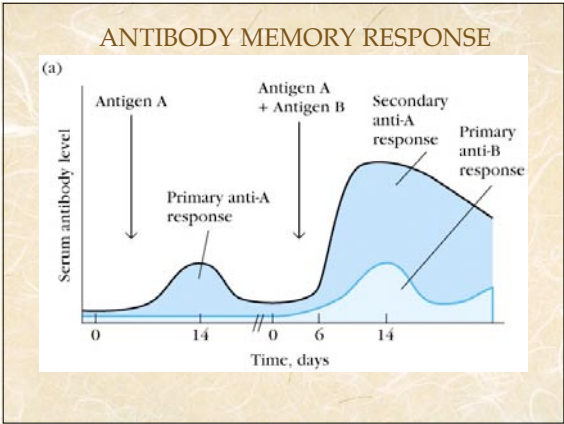
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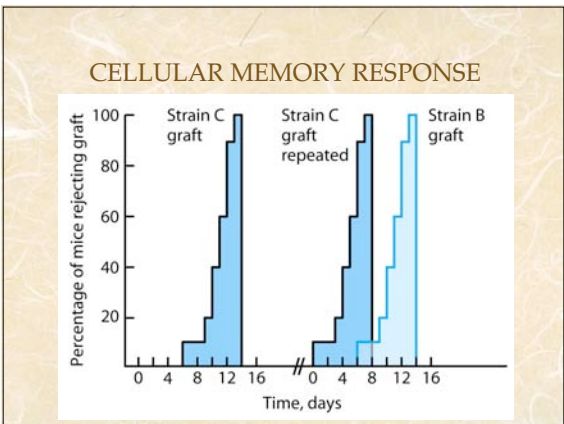
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### Cells of the Immune System

- The cells which give the immune system its specificity are the lymphocytes (a subset of leukocytes).
- Lymphocytes are assisted in their function by specialized accessory cells called **Antigen Presenting Cells (APCs)**

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## Next Lecture

- Acquired Immune System
- Lymphocytes
  - B cells
  - T cells
- Lymphoid Organs.

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