Complement System

Learning Outcomes

1. List the stages of complement activation
2. Describe the various steps and three pathways involved in activation of complement
3. Describe and compare the formation of the C3 convertase and C5 convertase complexes in the three pathways of complement activation
4. Illustrate the role of antibodies (IgM, IgG) in activation of C1 complex
5. Apply knowledge of the role of complement proteins in complement action to explain how a deficiency in complement protein(s) may lead to increased susceptibility to infection

Overview of Innate Immunity

Innate immunity is an ancient defense mechanism present in higher order animals and plants for over 400 million years. It is the first line of defense against infectious microorganisms and diseases, functioning from birth. Unlike adaptive immunity, which is acquired and developed over time, innate immunity is always available to protect against pathogens.

Components of Innate Immunity

The first encounter of pathogens is with barrier tissues, which include:

- Skin
- Mucosa
- Respiratory epithelia
- Intestinal lining

These barriers serve as physical or anatomical defenses. If these barriers fail, the body employs pre-formed chemical mediators, including:

- Antimicrobial peptides
- Enzymes that break down bacterial cell walls
- Complement proteins: soluble factors that become activated upon encountering foreign substances, initiating a cascade of immune responses.

Role of Cytokines and Effector Cells

If initial defenses fail, cytokines are produced to recruit effector cells, which include various immune cells that can engulf pathogens, kill infected cells, or activate further protective responses. If these mechanisms are insufficient, the adaptive immune response is activated.

Introduction to the Complement System

The complement system was discovered in the early 1900s by Jules Border, who identified heat-labile factors in serum that enhanced the antimicrobial function of antibodies. The complement system consists of approximately 30 proteins, primarily produced by the liver (+macrophages and monocytes), that exist as inactive pro-enzymes or zymogens until activated in a cascade. They are widely distributed in tissues and bodily fluids.

Functions of Complement Proteins

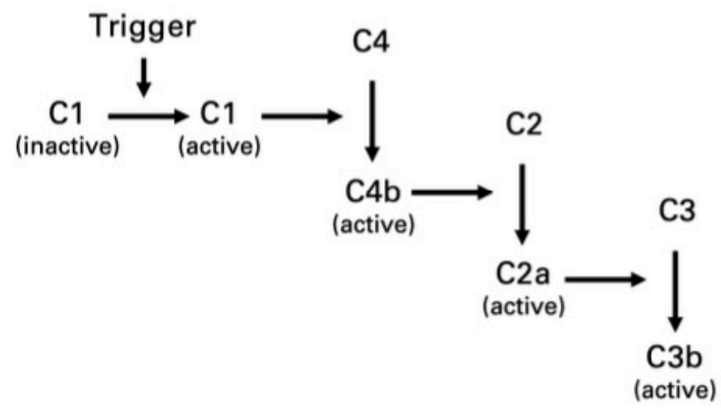
Activation of the complement system leads to several outcomes:

- Lysis of bacteria and infected cells
- Facilitation of phagocytosis through opsonization
- Promotion of inflammation and recruitment of immune cells

Complement proteins make up about 10% of the globulin fraction in plasma and are crucial for both innate and adaptive immune responses.

Activation of the Complement Cascade

The complement cascade is activated in a sequential manner, starting with an initial trigger that activates the first protein, leading to a series of amplifications. The proteins are cleaved into smaller (a) and larger fragments (b),, respectively, with the exception of C2, where the larger fragment is called C2a.



Activation and Cell Attachment

Complement activation typically occurs on the surface of pathogens or other cells. Some products of complement activation can bind to the surfaces of:

- Bacteria
- Parasites
- Infected cells
- Foreign (transplant) cells

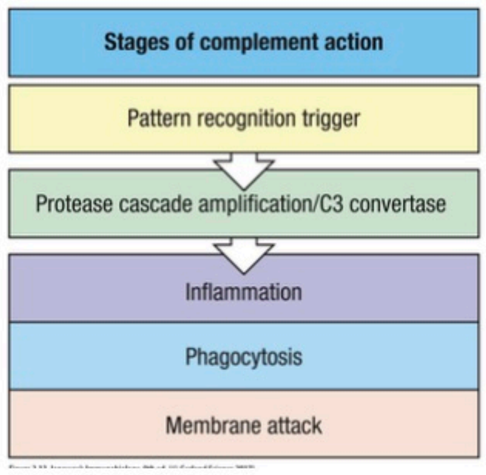
Either alone, or bound to antibody

Regulation of Complement Activation

Complement activation is tightly regulated to prevent damage to host cells. Host cells express regulatory proteins that inhibit complement binding, ensuring that complement proteins primarily target microbial surfaces. Any activated complement components that do not bind to microbial surfaces are quickly deactivated.

Stages of Complement Action

1. Pattern recognition trigger
2. Protease cascade amplification/C3 convertase
3. Inflammation + Phagocytosis + Membrane attack complex



Complement Activation Pathways

There are three main pathways for complement activation:

- **Classical Pathway:** Involves antigen-antibody complexes (IgM and IgG) and is an effector mechanism of humoral immunity.
- **Alternative Pathway:** Involves direct binding of spontaneously activated complement proteins to microbial surfaces, independent of antibodies.
- **Lectin Pathway:** Initiated by the binding of lectins to sugar residues on microbial surfaces.

All pathways converge to generate a complex known as C3 convertase, which cleaves C3 and initiates further complement activation. C3b is critical for opsonization.