Immunology

I M.Sc., Biotechnology

COMPLEMENT PATHWAYS

Mnemonics-Easy to understand

Complement is a cascade of chemicals similar to the clotting cascade.

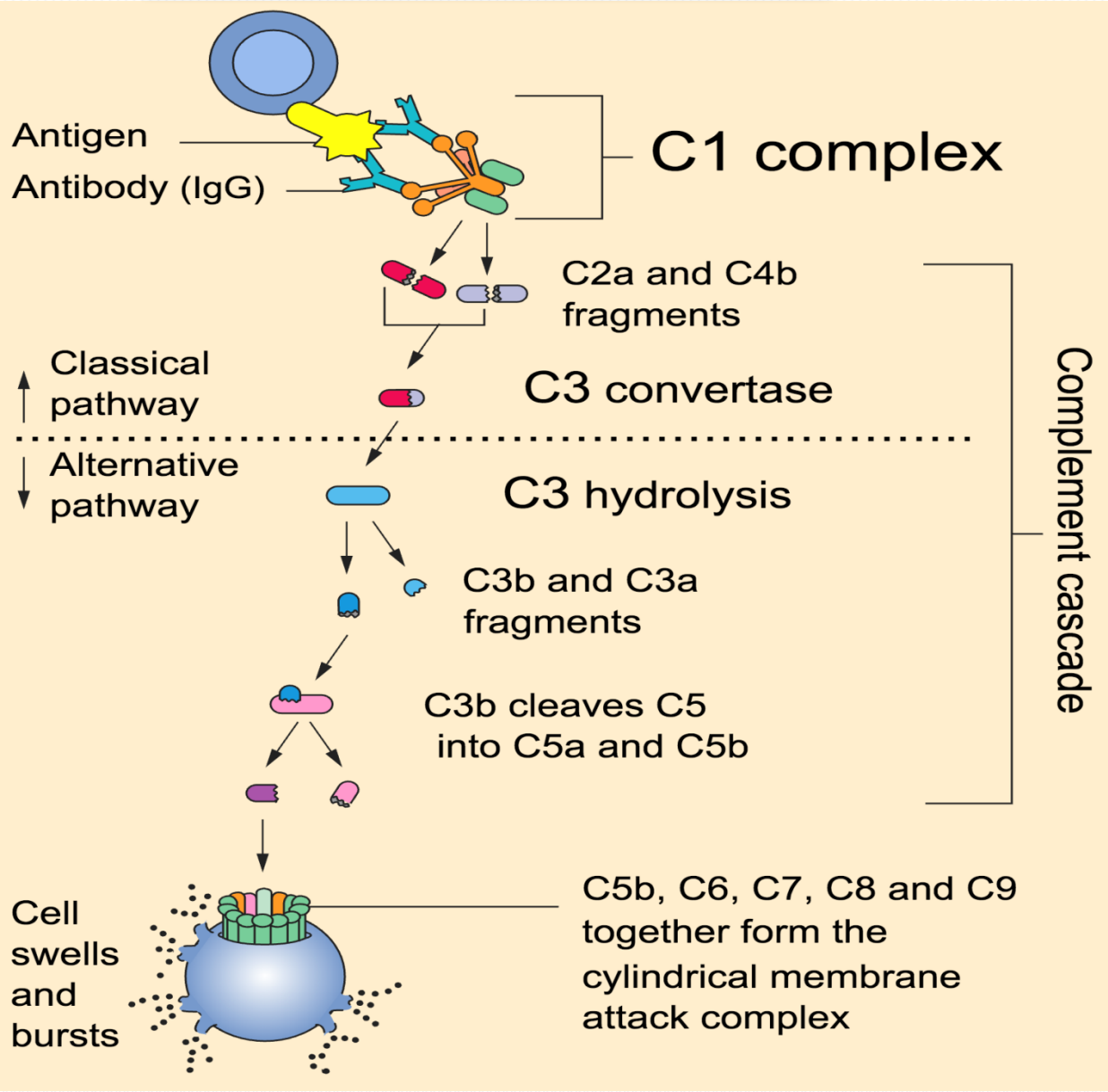
There are three separate pathways which activate the complement system:

classical pathway: activated by antibody-antigen complexes (a.k.a immune complexes) on pathogen surfaces

mannose-binding lectin pathway: activated when mannose-binding lectin binds to the carbohydrate molecule mannose on pathogen surfaces

alternative pathway: C3 reacts directly with pathogen surfaces

Complement pathway

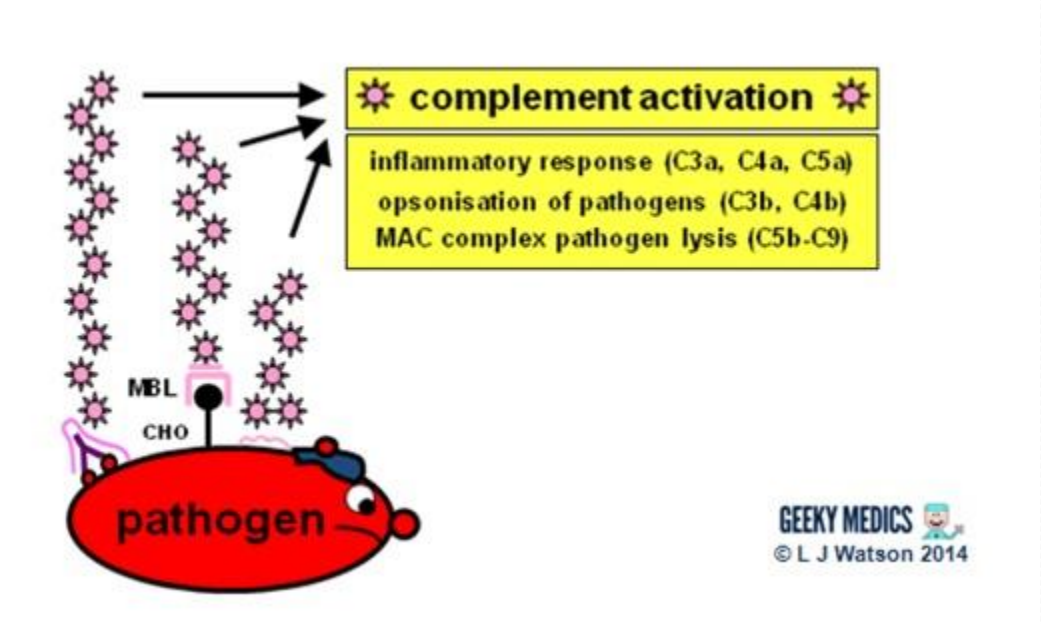


All three of these pathways act to generate the enzyme **C3 convertase**. This cleaves C3 into two parts (**C3a and C3b**) and activates the rest of the cascade.

C3a, along with **C4a** and **C5a**, is a mediator of inflammation which augments the **inflammatory response**. These molecules are also **anaphylotoxins** which trigger mast cell degranulation, histamine release and further inflammation.

C3b binds to and coats pathogens, making them easier for phagocytes to identify and ingest. This process is called **opsonisation**. It also binds to **immune complexes** to facilitate their removal by the spleen and triggers the production of terminal components including C5b.

- **C5b** initiates the membrane attack pathway or "terminal lytic sequence". This triggers the formation of a **membrane attack complex (MAC)** made from C5b, C6, C7, C8 and C9. MACs are ring-shaped and essentially punch a hole in the pathogen cell membrane, resulting in **osmotic lysis**.
- complement mainly provides **bacterial immunity**. In viral infections, interferons play a similar role.



Mnemonics for Classical Pathway

Summary

The Classical Complement Pathway is one of three initiating pathways of the complement system. Specifically, the classical pathway requires antibodies like IgM or IgG to be bound to the target. C1 recognizes this bound antibody, and fixes (binds) to the hinge region in the Fc portion. Activated C1 then cleaves C2 and C4, causing them to activate in turn. Finally, active C2 and C4 combine to form C3 convertase, the final step in the Classical Complement Pathway, and the starting point of the Common Complement Pathway.

Key Points

- **Classical Complement Activation**
  - One of three initiating pathways of complement
  - End goal is to **kill cells with bound antibody**
  - Requires bound **Immunoglobulin G (IgG)** or **Immunoglobulin M (IgM)** on surface
    - **C1** binds near **hinge portion** within Fc region of antibody
      - Actually formed by complex of C1q, C1r, and C1s
      - Regulated/Inhibited by C1 esterase inhibitor
        - Defective in hereditary angioedema or with ACE inhibitors
    - Activated C1 cleaves **C4** and **C2**
      - Cleavage of C4 produces C4a and C4b
      - Cleavage of C2 forms C2a and C2b
    - Cleaved C4 and C2 combine to form **C3 Convertase** (C4bC2b)
      - Leads to **Common Complement Pathway**

Mnemonics for Lectin Pathway

Summary

The Lectin Complement Pathway is one of three initiating pathways of the complement system. The pathway is initiated by Mannose-binding Lectins (MBLs) that bind mannose, a sugar found on the surface of many pathogens. Lectin binding to mannose creates a complex that cleaves C2 and C4. Cleaved C2 and C4 then combine to form a C3 convertase. This C3 convertase then continues onwards as part of the common pathway of complement activation. The primary purpose of the lectin complement pathway is to kill microbes expressing mannose.

Key Points

- **Lectin Complement Pathway**
  - One of three initiating pathways of the complement system
  - Goal is to **kill microbes expressing mannose**
  - Mannose-binding **Lectin** (MBL) binds **mannose** on pathogen surfaces
    - Mannose is expressed on many microbial surfaces
  - Forms a complex that cleaves **C4** and **C2**
    - MASPs (mannose-associated serine proteases) cleave C4 and C2
  - Cleaved C4 and C2 combine to form **C3 Convertase**
    - C4b and C2b combine to form C4bC2b, a C3 convertase
    - Leads to **Common Complement Pathway**

Mnemonics for Alternative Pathway

Summary

The Alternative Complement Pathway is one of three initiating pathways of the complement system. In this pathway, circulating C3 is spontaneously cleaved to form C3b, which is stabilized by microbial surfaces. C3b bound to a surface recruits Factor B, which is then cleaved by Factor D. Together, this forms a C3bBb complex, which is a C3 convertase. Formation of the C3 Convertase kicks off the Common Complement Pathway, which ultimately results in the death of the microbe.

Key Points

- **Alternative Complement Activation**
  - One of three initiating pathways of the complement system
  - End goal is to **kill foreign cells** without alternative complement inhibitors
  - Begins with **spontaneous cleavage of C3**
    - C3 is inherently unstable
  - C3b **stabilized by microbial surfaces**
    - Normal cell surfaces express inhibitors Factors H and I
      - Prevent excess complement activation on normal cells
  - C3b cleaves **Factor D** and **Factor B** in turn
  - Cleaved Factor B combines with C3b → **C3 convertase**
    - This C3 convertase is actually C3bBb
    - Leads to **Common Complement Pathway**

Proinflammatory cytokines are the second key component of the innate chemical immune response. They are small messenger proteins released by immune cells in response to evidence of infection, which interact to mediate the **acute inflammatory response** . There are a huge number of different cytokine molecules, including whole families of **interleukins**, **tumour necrosis factors** and **chemokines**.

Some important examples include:

IL-1 – causes fever and activates lymphocytes

IL-6 – causes fever, stimulates the liver to produce acute-phase proteins such as CRP, activates lymphocytes and promotes antibody production

IL-8 (a.k.a CXCL8) – causes neutrophil chemotaxis

IL-12 – activates NK cells and TH1 cells (important for intracellular infections)

TNF-alpha – increases vascular permeability to allow immune cells to reach tissues

IL-4, IL-5 + IL-13 – promote IgE production and eosinophilic reactions in patients with allergies

Interferon gamma (IFNγ) – essential in activating cell-mediated immunity in viral infections

IL-10 – has an anti-inflammatory effect


Thank
you