PLASMA DERIVED MEDIATORS OF ACUTE INFLAMMATION

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Learning objectives

- By the end of this lecture student should be able to;
- Enumerate systems of plasma derived mediators of acute inflammation.
- Discuss in detail the complement system and other systems of plasma derived mediators.

• Plasma Protein-Derived Mediators

- A main event in the generation of several circulating mediators of inflammation is activation of Hageman factor (factor XII).
- Activated Hageman factor (factor XIIa) initiates four systems involved in the inflammatory response.

1. Complement system
2. Kinin system
3. Clotting system
4. Fibrinolytic system

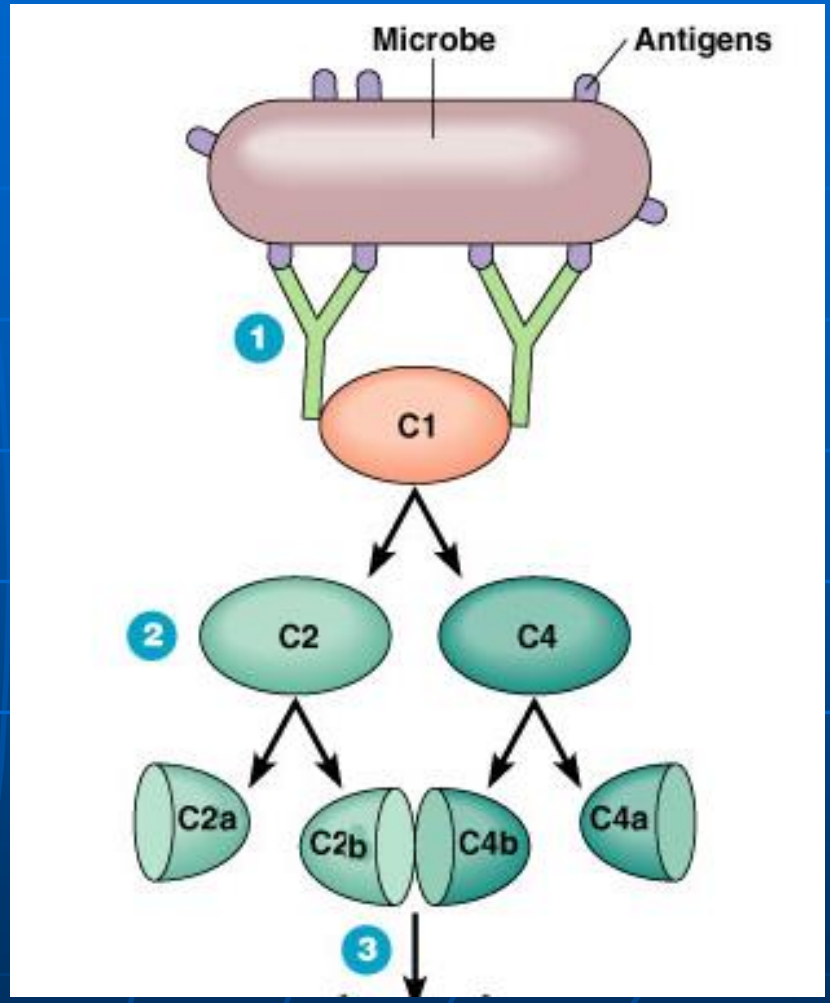
1. Complement system:

- It is a complex of 20 plasma proteins and their cleavage products.
- Its components C1-C9 are present in inactive form in plasma.
- They are activated by cleavage in a cascade pattern
- The most important step is the activation of C3 component.
- There are three pathways for the activation of C3.

1. Classical Pathway
2. Alternate Pathway.
3. Lectin Pathway

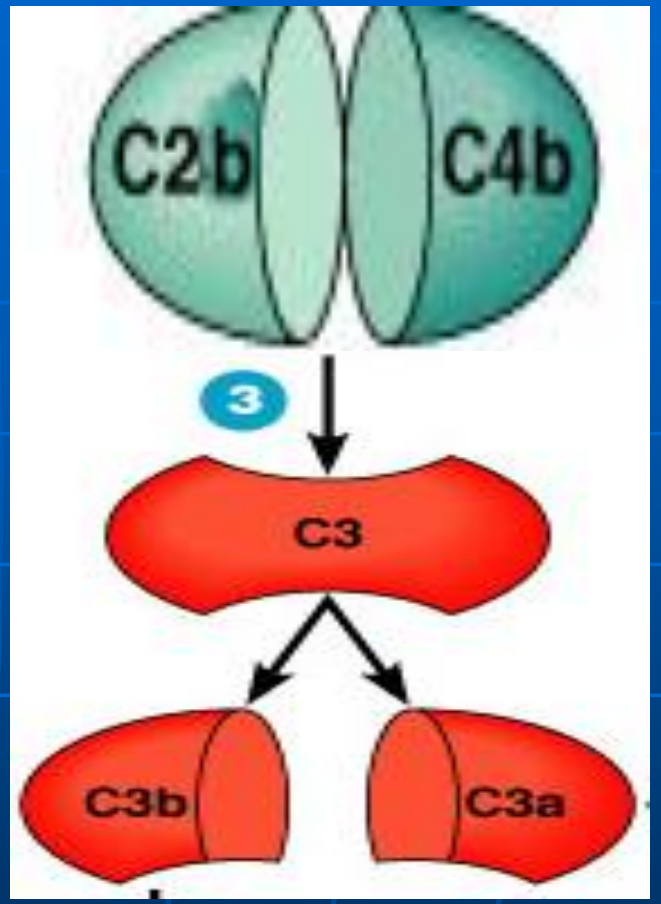
a. Classical pathway

- Commences by fixation of the first complement component C1 to antigen-antibody complexes.
- The C1 becomes activated.
- The C1 activates 2 other complement proteins, C2 and C4 by cutting each of them in half.



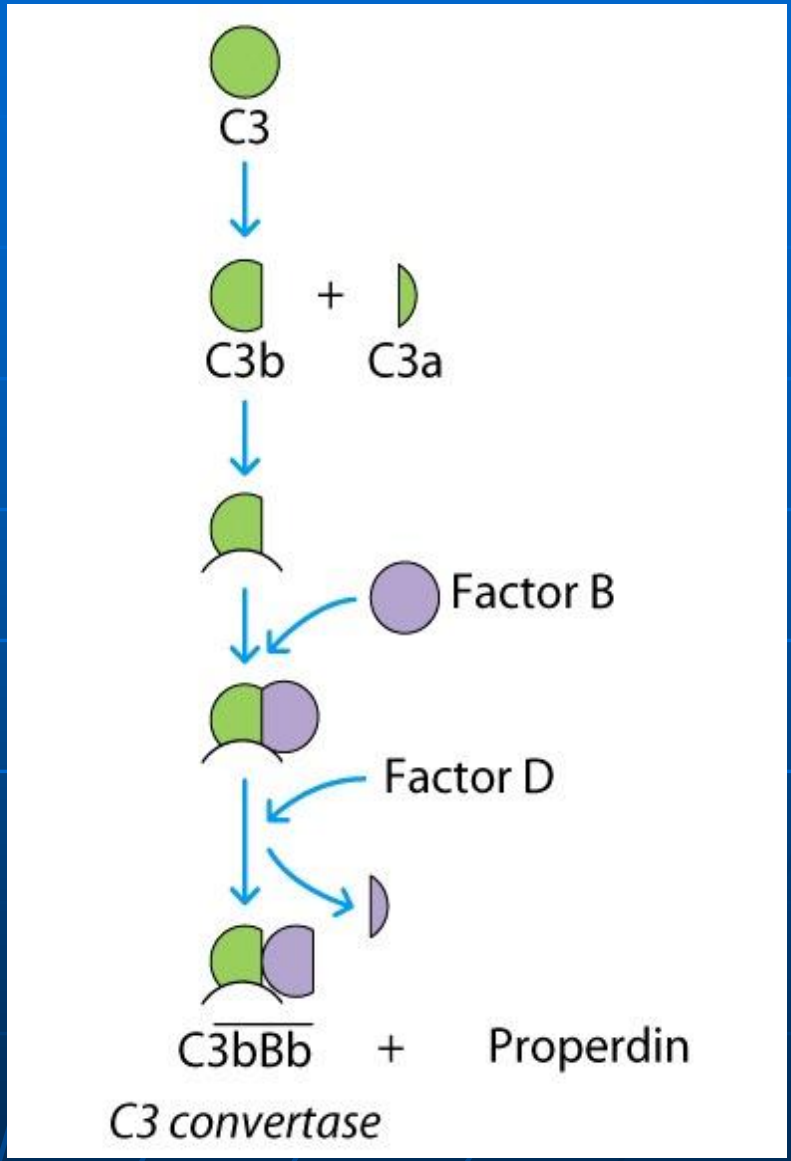
- Each component forms two components a and b.
- C2a and C4a diffuse away
- C4b and C2b bind to form C3-convertase.
- C3 convertase then acts on C3 to produce C3a and C3b.

C3 Convertase



b. The Alternate pathway

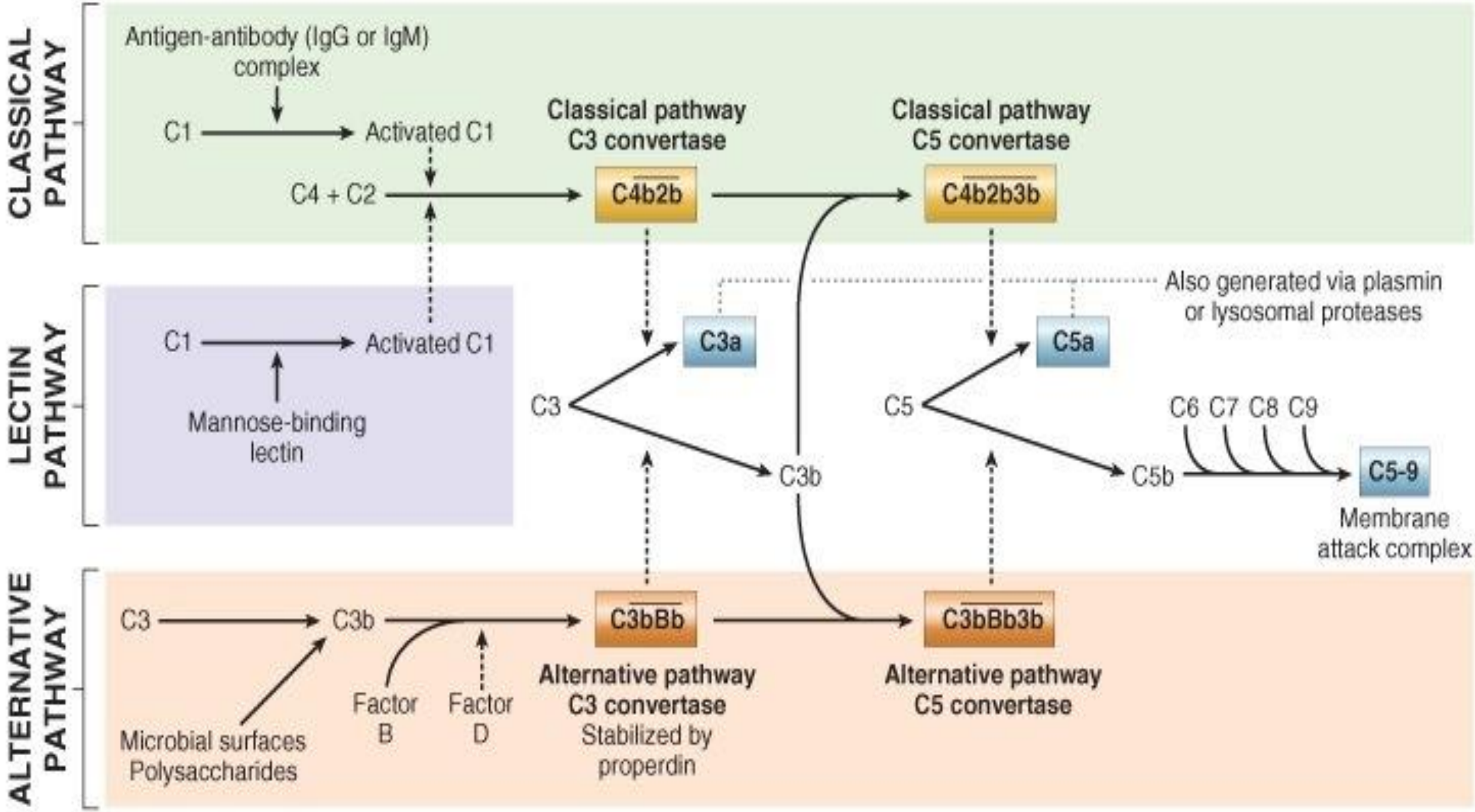
- C3 contains an unstable bond.
- This unstable bond causes slow spontaneous break down of C3 to C3b and C3a
- C3b on the surface of a pathogen binds to another plasma protein called factor B. This complex binds to Factor D resulting in the formation of C3 convertase (C3bBb) of alternate pathway stabilized by properdin.



c. Lectin pathway:

- In which a plasma Manose binding lectin (Carbohydrate-binding protein)binds to mannose residues on microbes and then activates C1, an early component of the classical pathway but in the absence of antibodies.
- From onwards the pathway joins the classical one
- All three pathways lead to the formation of C3 convertase which cleaves C3 into C3a and C3b.

- The fate of C3b is to bind to the C3 convertase complex of classical pathway (C4b2b) to form C5 convertase (C4b2b3b).
- Similarly C3b binds to C3 convertase of alternate pathway (C3bBb) to form C5 convertase (C3bBb3b)
- C5 convertase cleaves C5 to generate C5a and C5b.
- C5a plays its independent role while C5b combines with the C6, C7, C8 and C9.
- C5b-C9 together form membrane attack complex or MAC.


CLASSICAL PATHWAY
Antigen-antibody (IgG or IgM) complex
C1
Activated C1
C4 + C2
Classical pathway C3 convertase
C4b2b
Classical pathway C5 convertase
C4b2b3b
LECTIN PATHWAY
C1
Activated C1
Mannose-binding lectin
C3a
C5a
Also generated via plasmin or lysosomal proteases
C3
C5
C6 C7 C8 C9
C3b
C5b
C5-9
Membrane attack complex
ALTERNATIVE PATHWAY
C3
C3b
C3bBb
C3bBb3b
Factor B
Factor D
Microbial surfaces Polysaccharides
Alternative pathway C3 convertase
Stabilized by properdin
Alternative pathway C5 convertase

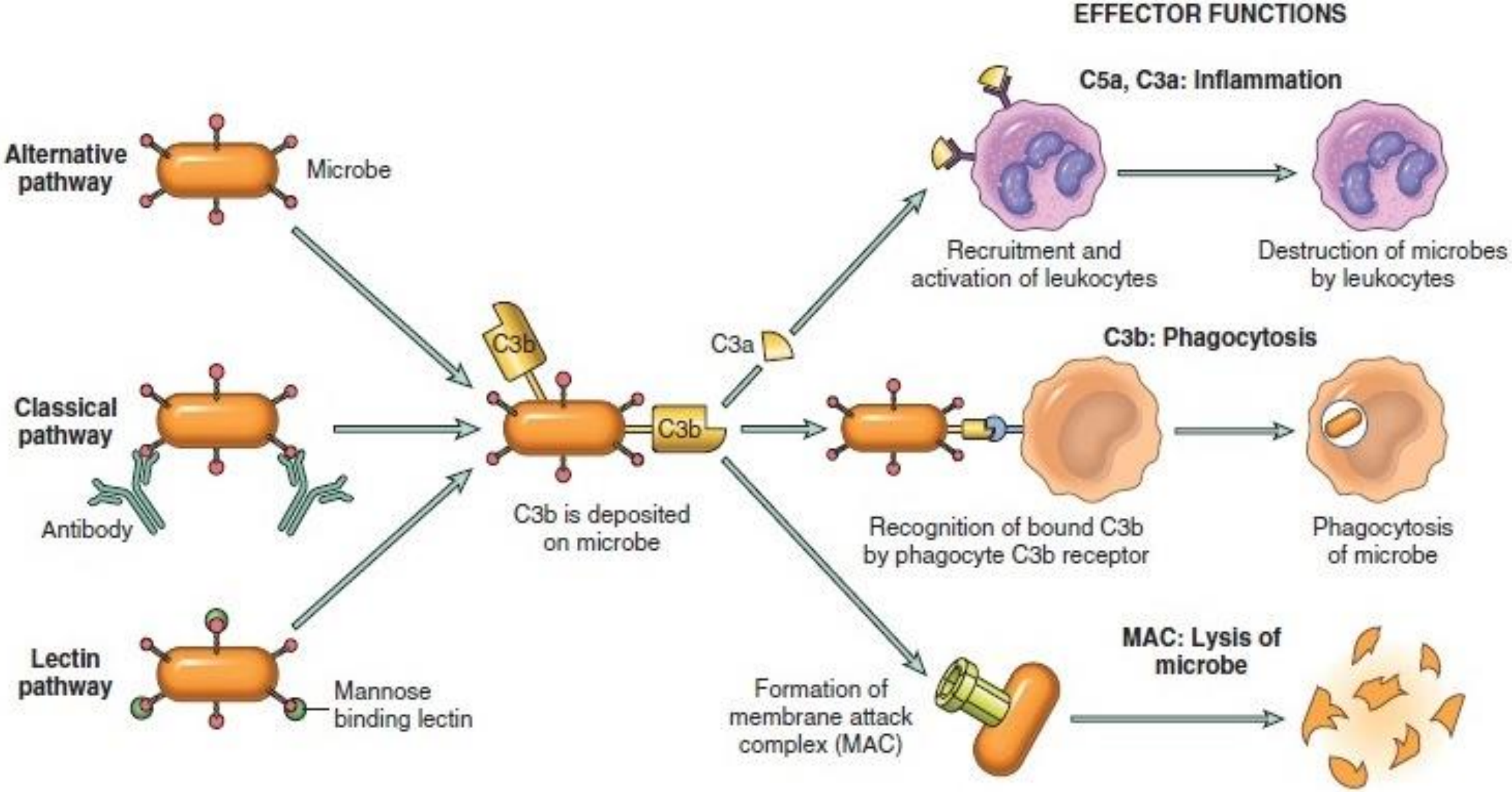


Figure 3.12 Activation and functions of the complement system. Activation of complement by different pathways leads to cleavage of C3. The functions of the complement system are mediated by breakdown products of C3 and other complement proteins and by the membrane attack complex *(MAC)*.

- Functions of complement can be discussed as

1. Membrane Attack Complex (MAC) induced lysis:

- This complex causes punch holes in the membranes of microbes.
- MAC especially kills thin walled bacteria like Neisseria species.
- Complement deficiency leads to Neisseria infections.

2. Complement fragments induced functions:

a. C3a, C5a and up to some extent C4a (anaphylatoxins) cause release of histamine from mast cells and therefore cause vasodilatation.

b. C5a acts as chemotactic substance for inflammatory cells.

c. C5a activates Lipoxygenase pathway and thus increase the production of leukotriens.

d. C3b opsonizes the microbes.

- The activation of complement is tightly controlled by cellular and circulating regulatory proteins.
- The presence of these inhibitors protects normal cells from inappropriate damage during protective reactions against microbes.

- Some important regulatory proteins are;

a. C1 inhibitor (C1 INH) blocks the activation of C1, the first protein of classical pathway.

- Hereditary deficiency of this inhibitor is the cause of hereditary angioedema.

b. Decay accelerating factor (DAF) and CD59 are two proteins that are attached to plasma membranes of the cells.

- DAF prevents formation of C3 convertases, and CD59 inhibits formation of MAC.
- An acquired deficiency of an enzyme which helps in attachment of these proteins to plasma membrane causes paroxysmal nocturnal hemoglobinuria.
- Factor H is a glycoprotein that inhibits the alternative pathway by cleaving and destroying C3b.

- Inherited defect of this factor leads to an atypical hemolytic uremic syndrome.

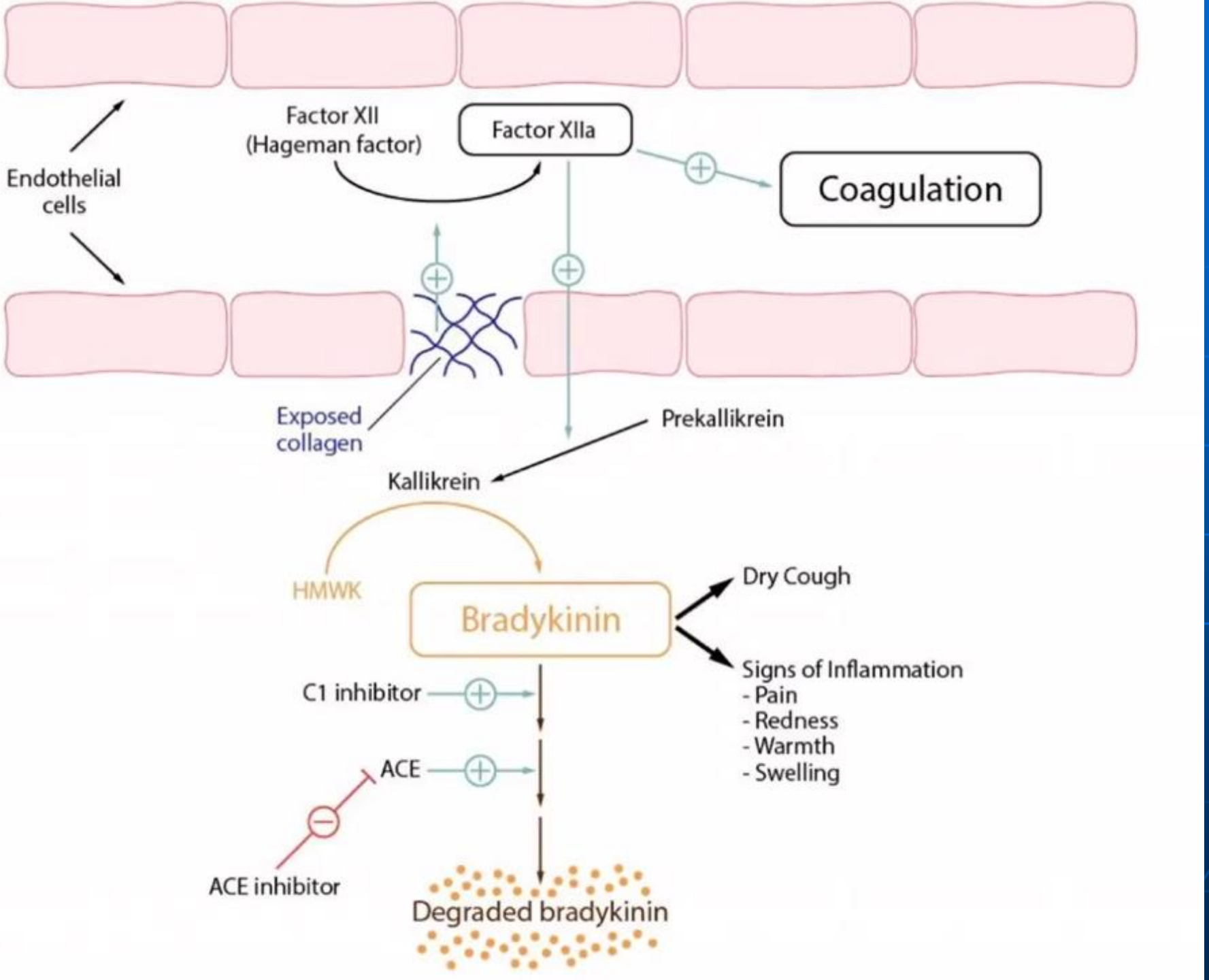
2. Kinin system:

- The liver produces two proteins in addition to Hageman factor (factor XII) that circulate freely in the blood.

1. Prekallikrein
2. High Molecular Weight Kininogen (HMWK).

- During inflammation, after endothelial damage factor XII comes in contact with sub-endothelial collagen.

- It is converted to factor XIIa.
- It then acts on already produced prekallikrein to produce kallilrein.
- Kallikrein converts HMWk into bradykinin.
- End product and main effector.


Endothelial cells
Factor XII (Hageman factor)
Factor XIIa
Coagulation
Exposed collagen
Prekallikrein
Kallikrein
HMWK
Bradykinin
Dry Cough
Signs of Inflammation
- Pain
- Redness
- Warmth
- Swelling
C1 inhibitor
ACE
ACE inhibitor
Degraded bradykinin

- Bradykinin has following actions

1. Smooth muscle contraction of bronchi
2. Vasodilation
3. Increased vascular permeability
4. Pain

- Bradykinin breakdown up-regulated by C1 inhibitor.
- In C1 inhibitor deficiency levels of bradykinin rise dangerously.

- It leads to development of hereditary angioedema.
- As there is vasodilation and increased vascular permeability.

3. Clotting system:

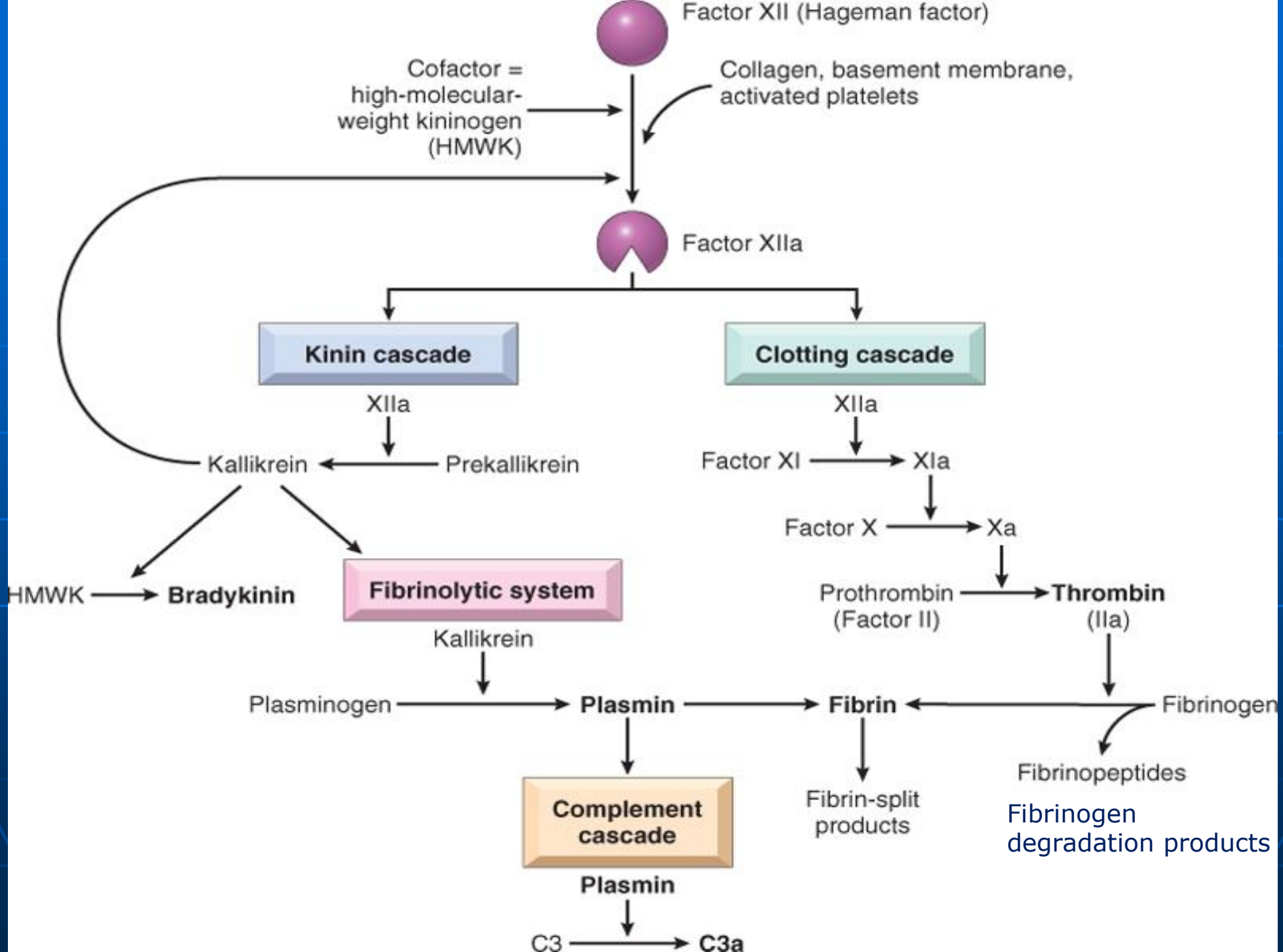
- The activated Hageman factor(Factor XIIa) leads to activation of different clotting factors and ultimately forming prothrombin activator or factor Xa.

- Factor Xa causes conversion of prothrombin to thrombin.
- Thrombin acts upon fibrinogen to produce Fibrin and fibrinopeptides (fibrinogen degradation products).
- Fibrinopeptides perform following functions

1. Increased vascular permeability
2. Chemotaxis of leukocytes
3. Anti coagulant activity

4. Fibrinolytic system:

- It involves the breakdown of plasminogen in presence of kallikrein to produce plasmin. Plasmin then
- Acts on Fibrin to yield FSPs
- Plays a role in activation of complement.
- It actually causes conversion of C3 to C3a



Fibrinogen degradation products

- **SUMMARY**
- Cell-derived Mediators of Inflammation
- Vasoactive amines:
- Histamine and serotonin:
- Main effects are vasodilation and increased vascular permeability
- Arachidonic acid metabolites
- Prostaglandins, leukotrienes and lipoxins:

- They mediate almost every step of inflammation.
- Lipoxins are antagonists to them, they inhibit inflammation.
- Chemokines
- Chemotaxis and leukocyte activation.
- Reactive oxygen species:
- Have role in microbial killing, tissue injury.

- Nitric oxide: Vasodilation, microbial killing
- Lysosomal enzymes: Role in microbial killing, tissue injury

- **Plasma Protein-Derived Mediators**
- Complement proteins:
- Activation of the complement system by microbes or antibodies leads to the generation of multiple breakdown products, which are responsible for leukocyte chemotaxis, opsonization and phagocytosis and killing of microbes and other particles.

- Coagulation proteins:
- Activated factor XII triggers the clotting, kinin and complement cascades, and activates the fibrinolytic system.