Immune Response

Primary

-Lag phase longer (differentiates into plasma & memory B. cells)

- Logarithmic phase increase in serum antibodies

Secondary

- Lag phase shorter
- Memory B cells more
- Higher affinity of memory B cells

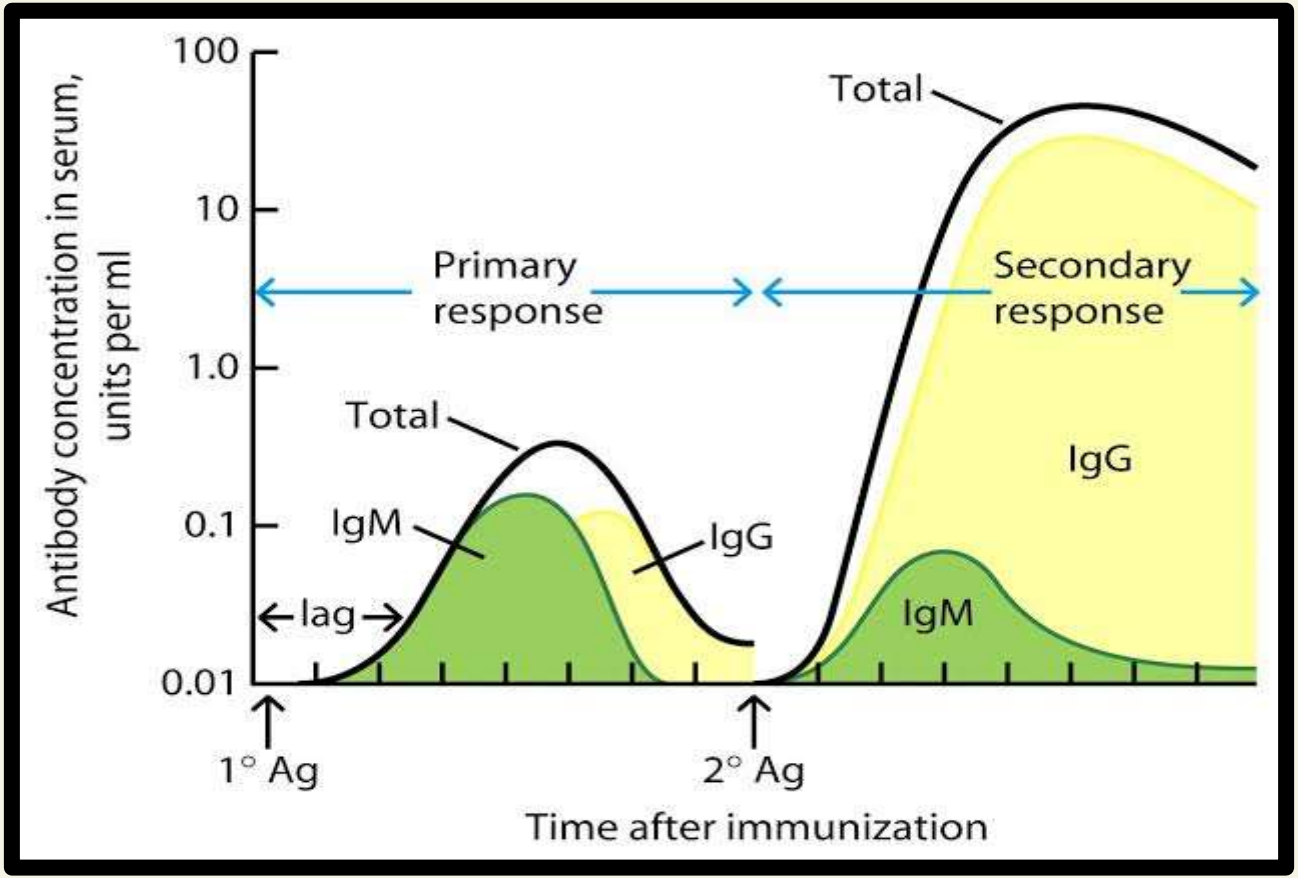

100
10
1.0
0.1
0.01
Antibody concentration in serum, units per ml
Primary response
Secondary response
Total
IgM
IgG
lag
Total
IgG
IgM
1° Ag
2° Ag
Time after immunization

TABLE 11-4 Comparison of primary and secondary antibody responses

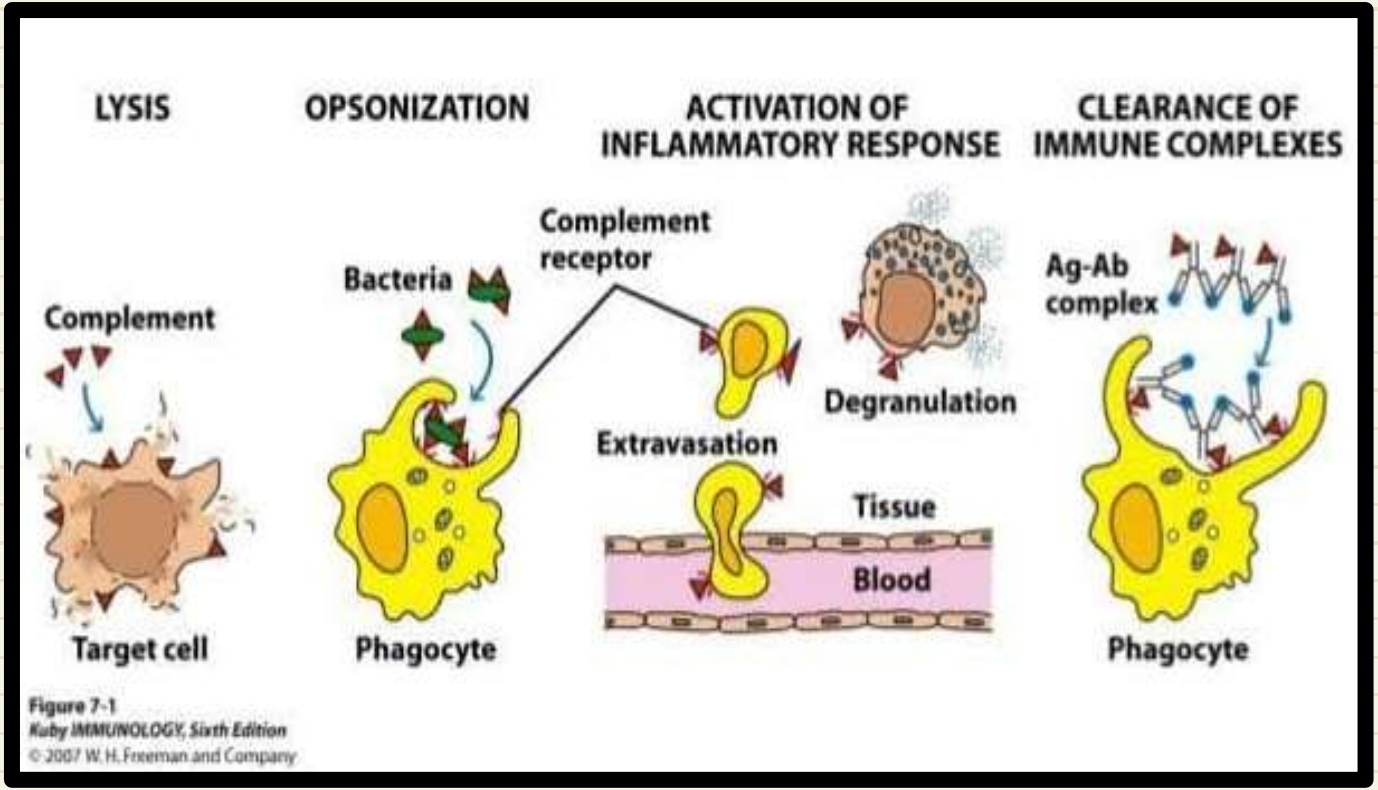
Property	Primary response	Secondary response
Responding B cell	Naive (virgin) B cell	Memory B cell
Lag period following antigen administration	Generally 4–7 days	Generally 1–3 days
Time of peak response	7–10 days	3–5 days
Magnitude of peak antibody response	Varies depending on antigen	Generally 100–1000 times higher than primary response
Isotype produced	IgM predominates early in the response	IgG predominates
Antigens	Thymus-dependent and thymus-independent	Thymus-dependent
Antibody affinity	Lower	Higher

02

The Complement System

- Complement is the name given to a complex series of some 20.proteins which, along with blood clotting, fibrinolysis and kinin formation, forms one of the triggered enzyme systems found in plasma
- Present in inactive form in serum
- Produce a rapid, highly amplified response to a trigger stimulus mediated by a cascade phenomenon
- Complement components are designated by the letter 'C‘ followed by a number.
- Most pivotal component is C3 .

- Peptide fragments formed by activation of a component are denoted by small letters like C3a, C3b etc.
- Complement fragments interact with one another to form functional complexes (C452a) which have enzymatic activity
- Functions:
- -Lysis of cells, bacteria, and viruses
- - Opsonization- Inflammation
- - Immune clearance


LYSIS
OPSONIZATION
ACTIVATION OF INFLAMMATORY RESPONSE
CLEARANCE OF IMMUNE COMPLEXES
Complement
Target cell
Bacteria
Complement receptor
Phagocyte
Extravasation
Degranulation
Tissue
Blood
Ag-Ab complex
Phagocyte
Figure 7-1
Kuby IMMUNOLOGY, Sixth Edition
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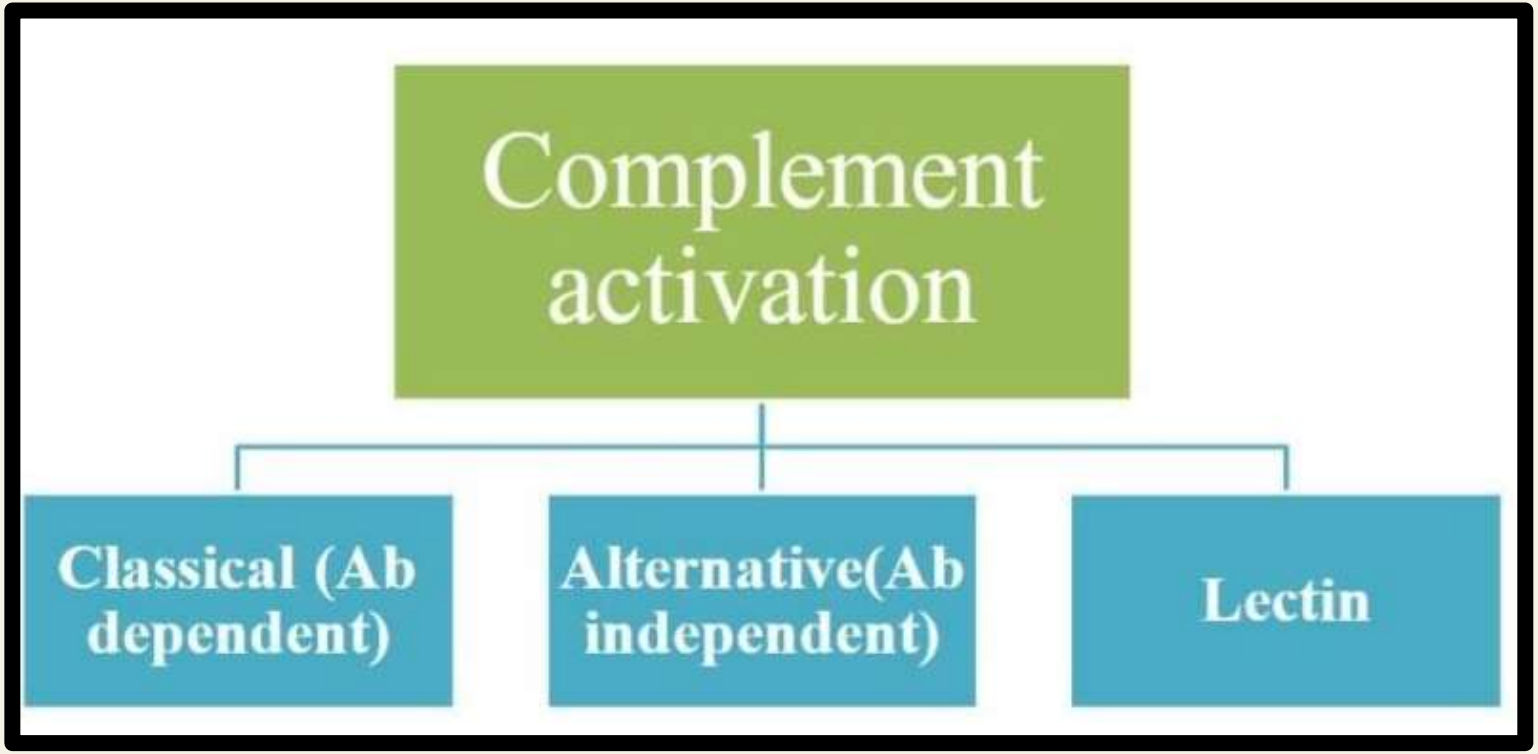
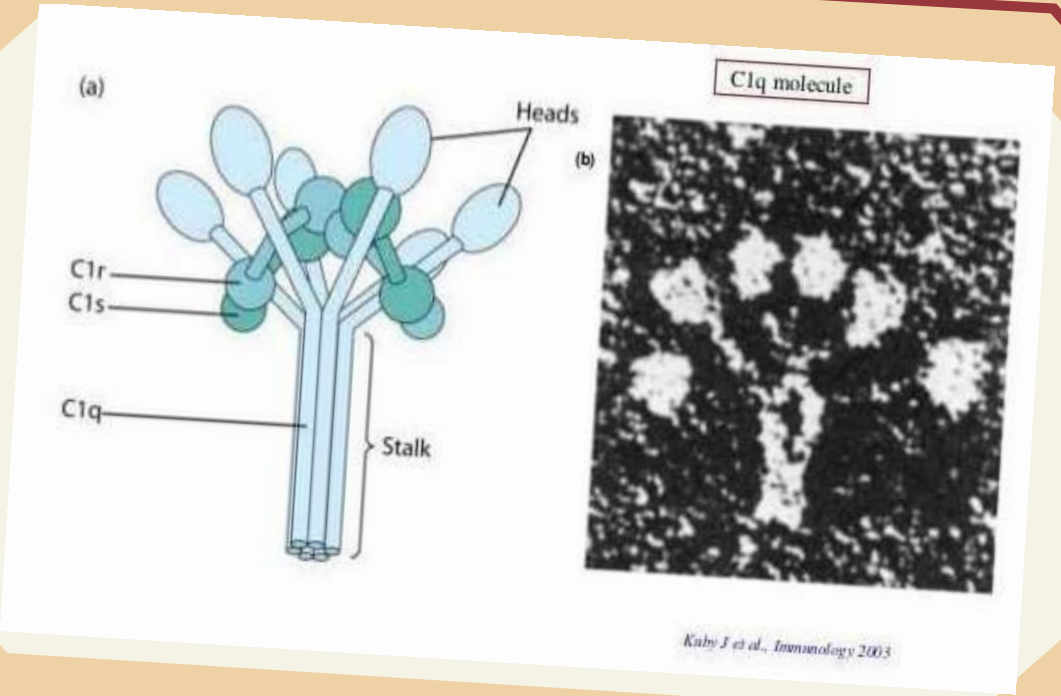
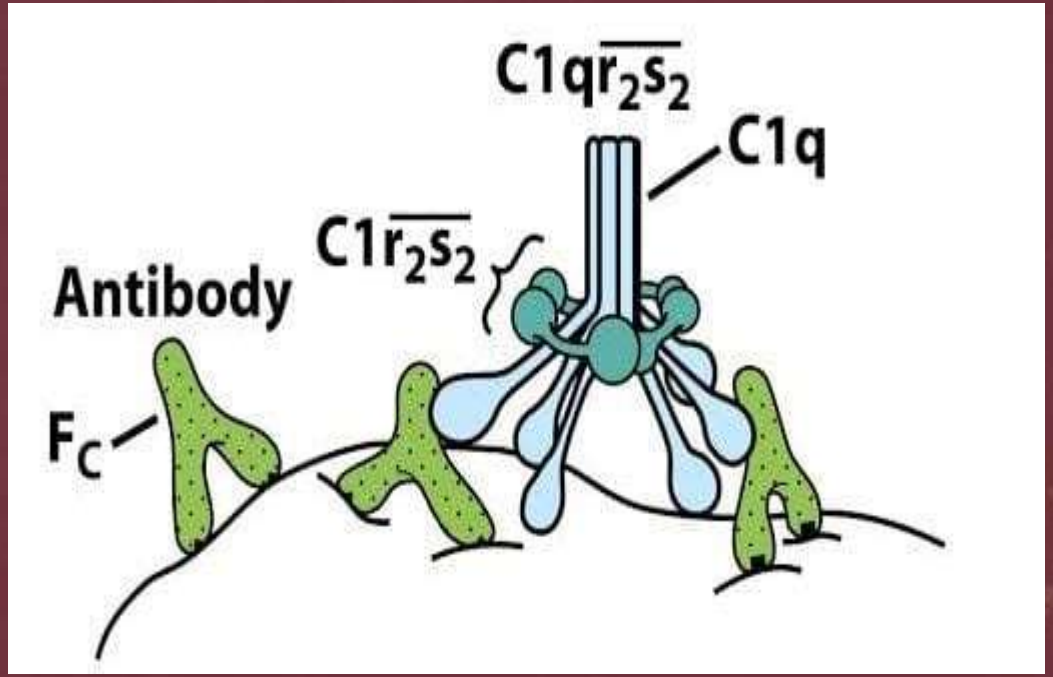

Complement activation
Classical (Ab dependent)
Alternative(Ab independent)
Lectin

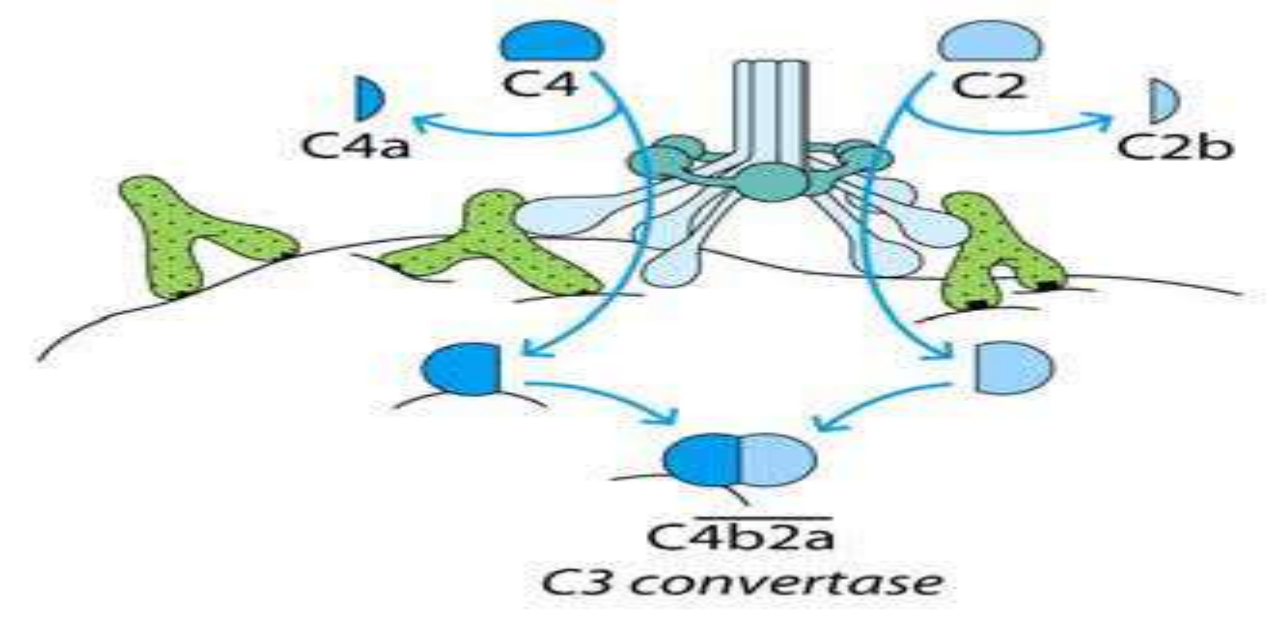
Classical Pathway

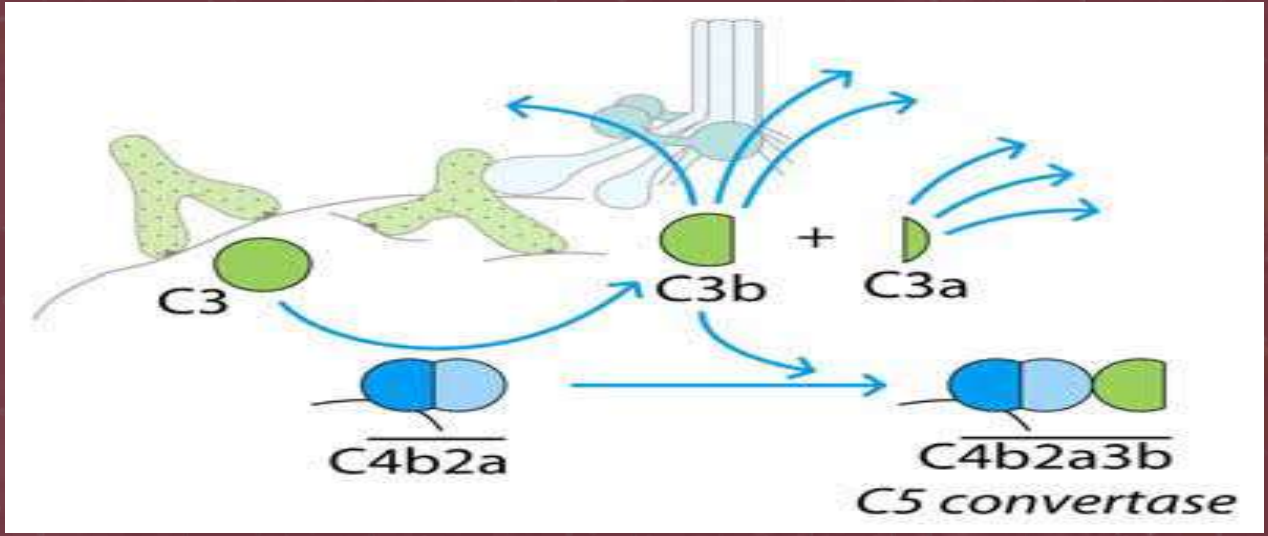
- Begins with the formation of soluble antigen-antibody complexes (immune complexes) or with the binding of antibody to antigen on a suitable target, such as a bacterial cell
- IgM and certain subclasses of IgG (human IgGI, IgG2, and IgG3) can activate the classical complement pathway
- Formation of an antigen-antibody complex induces conformational changes in the Fe portion of the IgM molecule that expose a binding site for the C1 component
- This further activates Cls component of C1 complement


(a)
Heads
C1r
C1s
C1q
Stalk
C1q molecule
(b)
Kuby J et al., Immunology 2003


C1qr2s2
C1q
C1r2s2
Antibody
FC

- C4 is activated when CTS hydrolyzes a small fragment (C4a) from the amino terminus of the chain, exposing a binding site on the larger fragment (C4b)
- C4b fragment attaches to the target surface in the vicinity of C1, and the C2 proenzyme then attaches to the exposed binding site on C4b•
- C2 is then cleaved by the neighboring CTS, forming C4b2a complex is called C3 convertase


C4
C2
C4a
C2b
C4b2a
C3 convertase



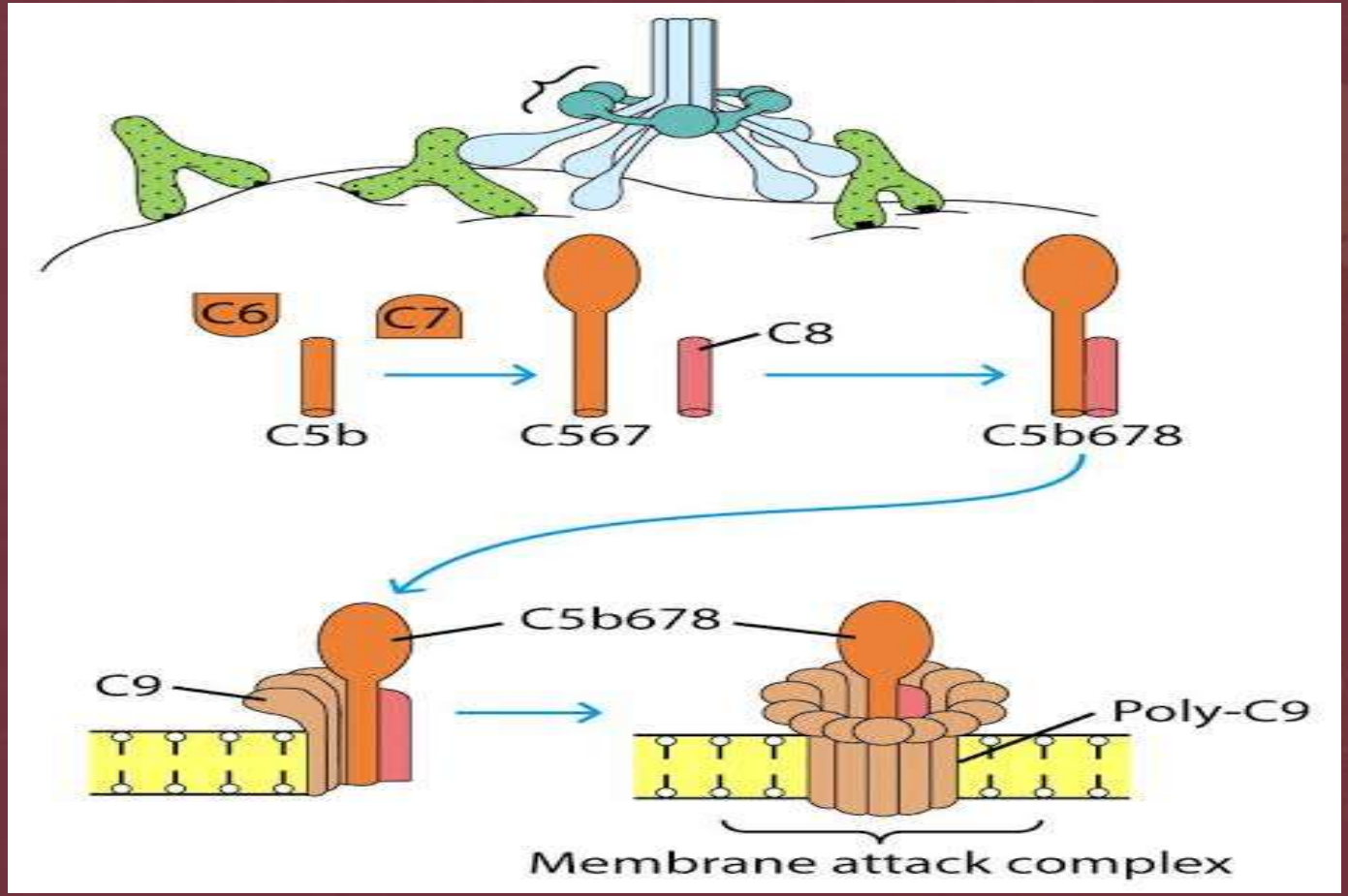
- C3 convertase molecule can generate over 200 molecules of C3b, which binds to C4b2a to form a tri molecular complex C4b2a3b, called C5 convertase

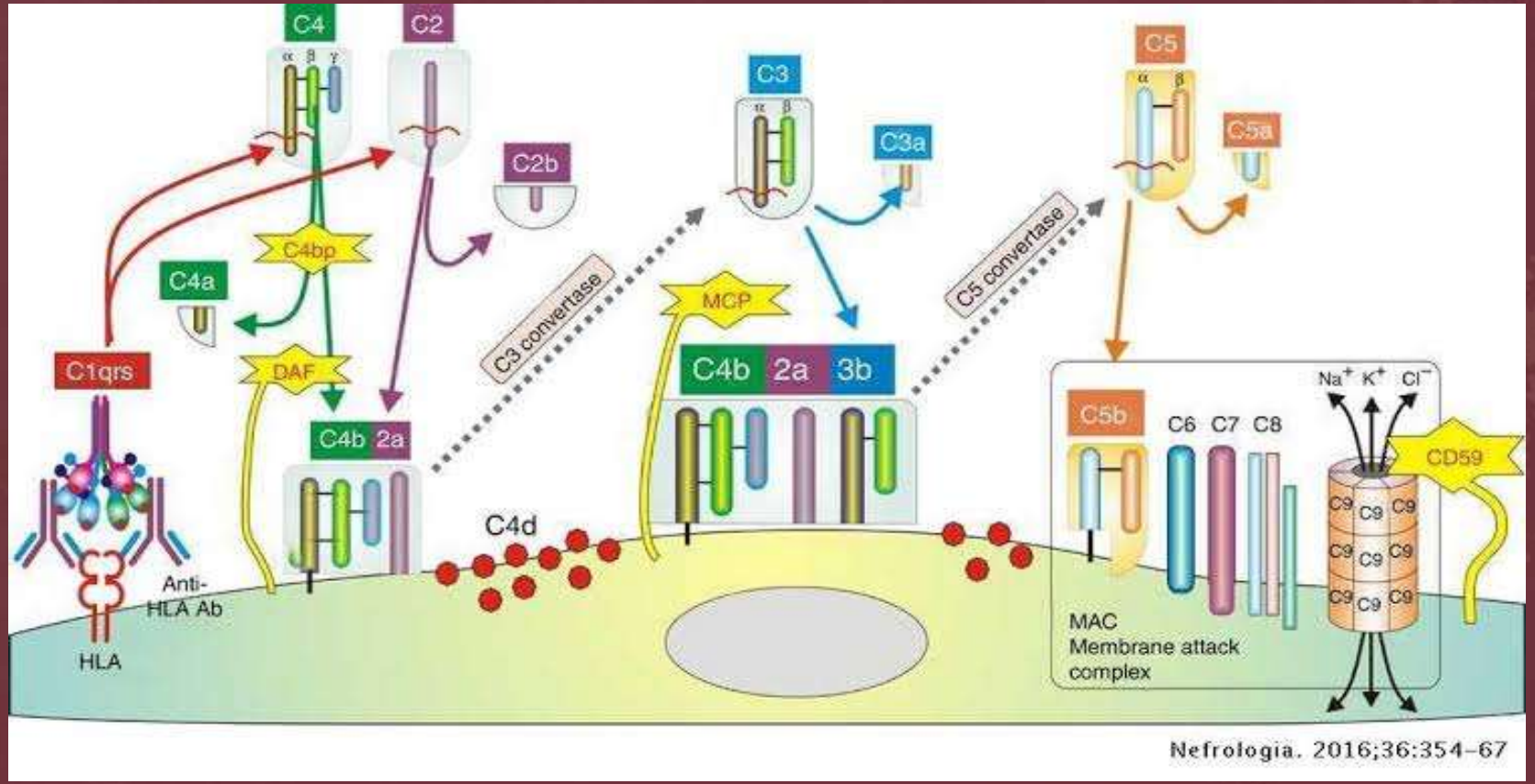
- C5 convertase breaks C5 complement, generating C5b, which attaches to the surface of the target cell and C6 and initiates formation of the membrane- attack complex

- C5b6 binds to C7,the resulting complex undergoes a hydrophilic-amphiphilic structural transition which serve as binding sites for membrane phospholipids

- Binding of CS to membrane-bound C5b67, forming C5b678 complex which creates a small pore, 10 A in diameter

- Final step involves polymerization of C9, a perforin-like molecule, to the C5b678 complex completing MAC formation(functional pore size of 70-100 A).

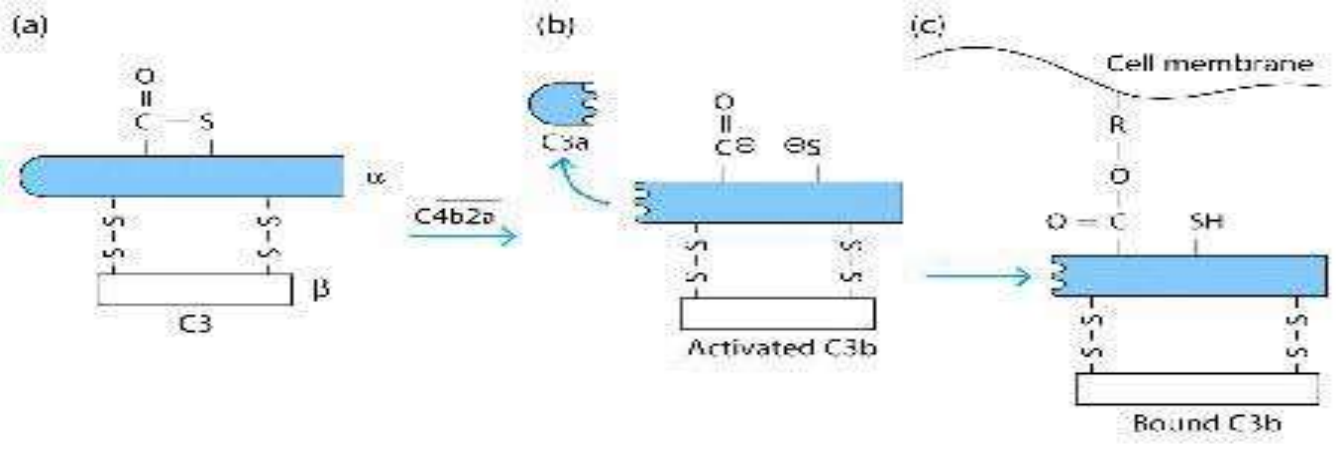

C6
C7
C8
C5b
C567
C5b678
C5b678
C9
Poly-C9
Membrane attack complex


C4
C2
C2b
C3
C3a
C5
C5a
C4bp
C4a
C1qrs
DAF
C4b 2a
C3 convertase
MCP
C4b 2a 3b
C5 convertase
C5b
C6 C7 C8
Na+ K+ Cl−
CD59
C4d
Anti-
HLA Ab
HLA
MAC
Membrane attack
complex
Nefrologia. 2016;36:354–67

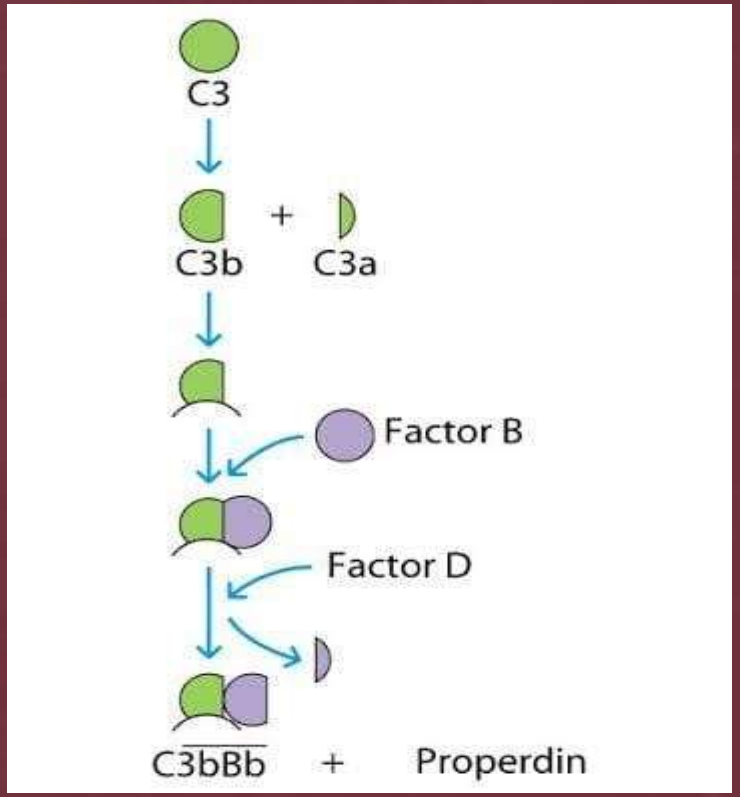
Alternate Pathway

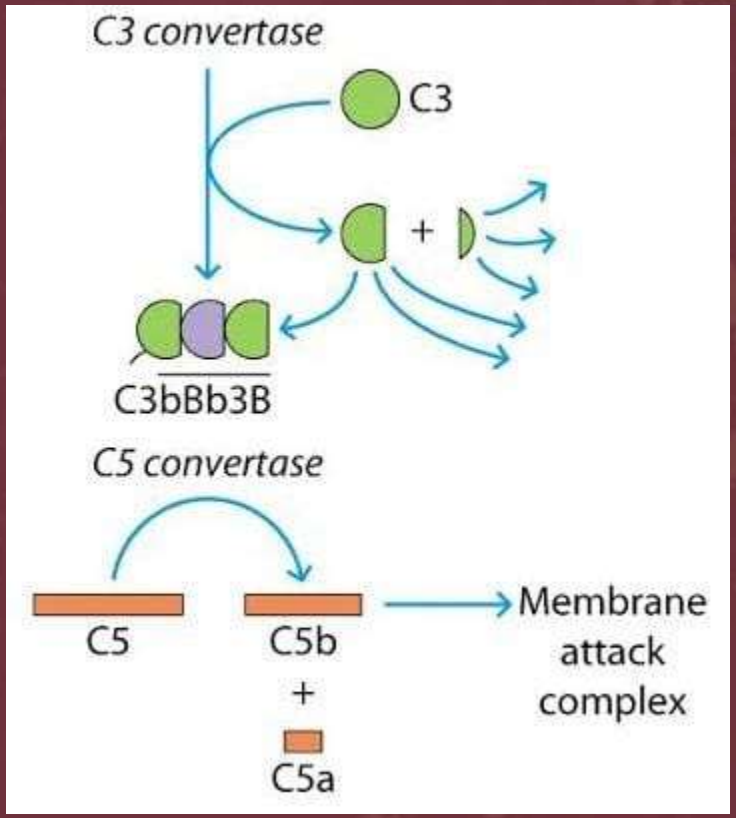
- Alternative pathway does not need for antigen-antibody complexes for initiation

- Serum C3, is subjected to slow spontaneous hydrolysis to yield C3a and C3b



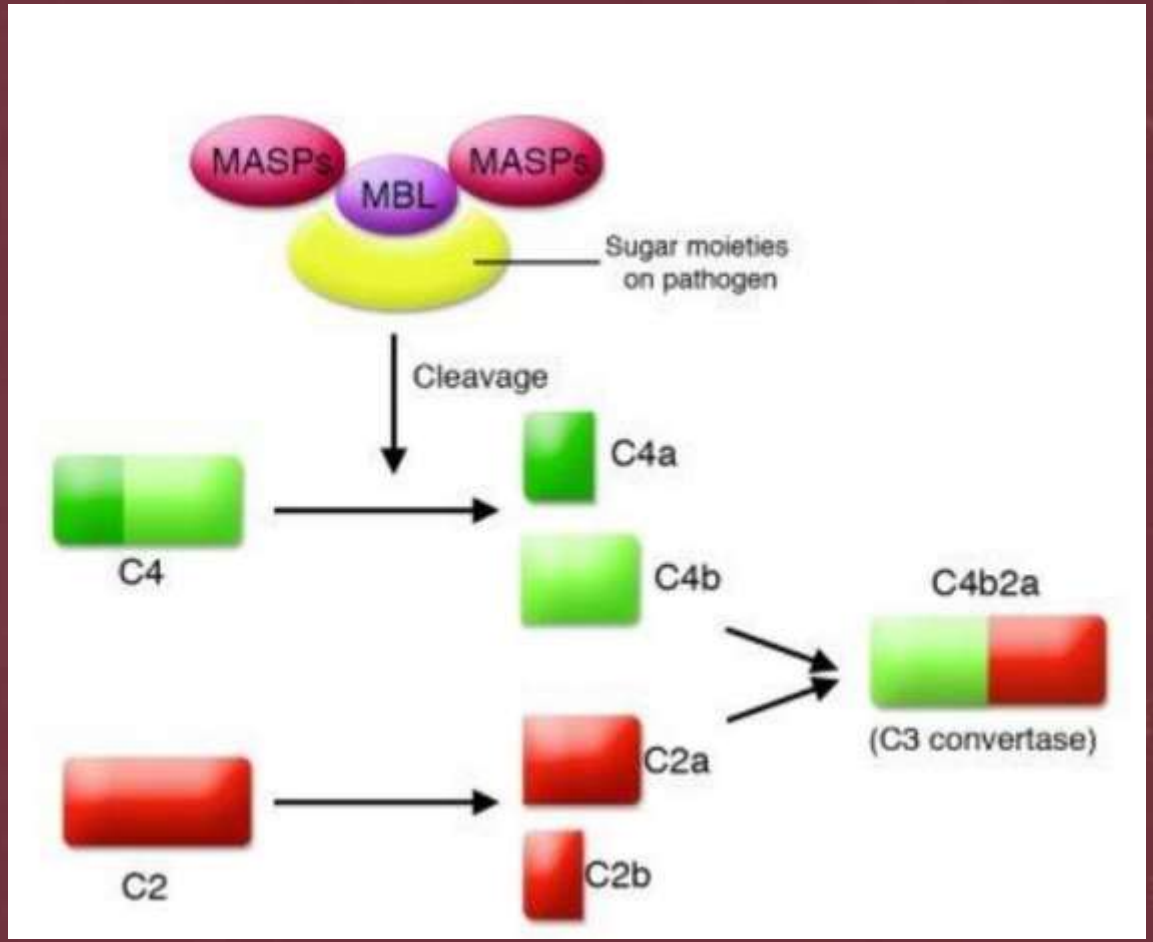
- C3b component can bind to foreign surface antigens, which can bind another serum protein called factor B
- Factor D cleaves the C3b-bound factor B, generating C3bBb -C3 convertase..
- Further serum protein properdin binds to it and stabilizes it.
- C3 convertase cleaves C3 complemet generating the C3bBb3b complex, which exhibits C5 convertase activity


C3
C3b
+
C3a
Factor B
Factor D
C3bBb
+
Properdin


C3 convertase
C3
+
C3bBb3B
C5 convertase
C5
C5b
+
C5a
Membrane attack complex

Lectin Pathway

- Lectin pathway is activated by the binding of mannose-binding lectin (MBL) to mannose residues on glycoproteins or carbohydrates on the surface of microorganisms
- Next MBL-associated serine proteases, MASP-1 and MASP 2, bind to MBL
- This association causes cleavage and activation of C4 and C2
- After this follows the classical pathway to generate C5 convertase


MASPs
MBL
MASPs
Sugar moieties on pathogen
Cleavage
C4a
C4
C4b
C4b2a
(C3 convertase)
C2a
C2
C2b

Biological Effects of Complements

Effect	Complement product mediating*
Cell lysis	C5b–9, the membrane-attack complex (MAC)
Inflammatory response	
Degranulation of mast cells and basophils†	C3a, C4a, and C5a (anaphylatoxins)
Degranulation of eosinophils	C3a, C5a
Extravasation and chemotaxis of leukocytes at inflammatory site	C3a, C5a, C5b67
Aggregation of platelets	C3a, C5a
Inhibition of monocyte/macrophage migration and induction of their spreading	Bb
Release of neutrophils from bone marrow	C3c
Release of hydrolytic enzymes from neutrophils	C5a
Increased expression of complement receptors type 1 and 3 (CR1 and CR3) on neutrophils	C5a
Opsonization of particulate antigens, increasing their phagocytosis	C3b, C4b, iC3b
Viral neutralization	C3b, C5b–9 (MAC)
Solubilization and clearance of immune complexes	C3b

Regulation Of Complement System

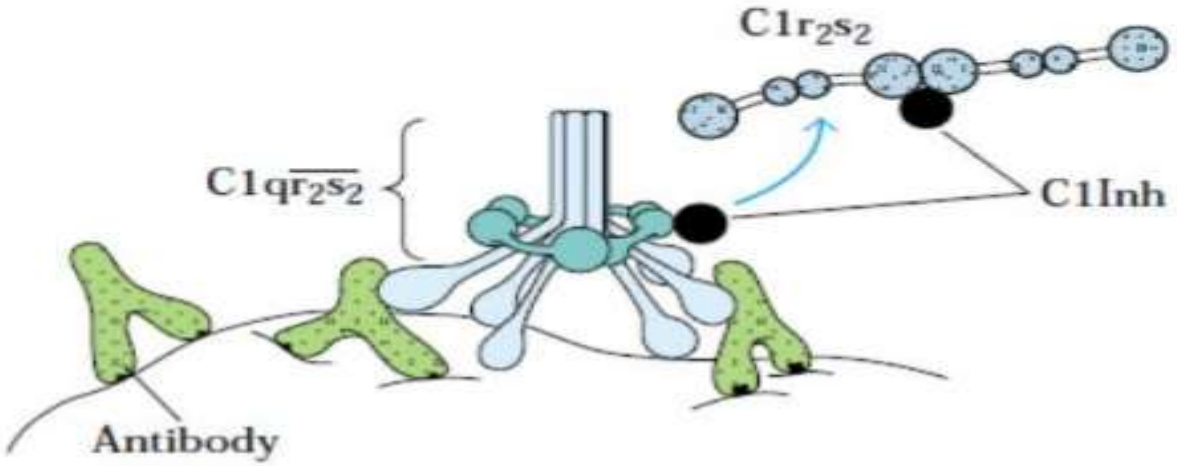
TABLE 13-2 Proteins that regulate the complement system

Protein	Type of protein	Pathway affected	Immunologic function
C1 inhibitor (C1Inh)	Soluble	Classical	Serine protease inhibitor; causes $C1r_2s_2$ to dissociate from C1q
C4b-binding protein (C4bBP)*	Soluble	Classical and lectin	Blocks formation of C3 convertase by binding C4b; cofactor for cleavage of C4b by factor I
Factor H*	Soluble	Alternative	Blocks formation of C3 convertase by binding C3b; cofactor for cleavage of C3b by factor I
Complement-receptor type 1 (CR1)*	Membrane bound	Classical, alternative, and lectin	Block formation of C3 convertase by binding C4b or C3b; cofactor for factor I-catalyzed cleavage of C4b or C3b C3bBb
Membrane-cofactor protein (MCP)*			
Decay-accelerating factor (DAF or CD55)*	Membrane bound	Classical, alternative, and lectin	Accelerates dissociation of $\overline{C4b2a}$ and C3bBb (classical and alternative C3 convertases)

*An RCA (regulator of complement activation) protein. In humans, all RCA proteins are encoded on chromosome 1 and contain short consensus repeats.

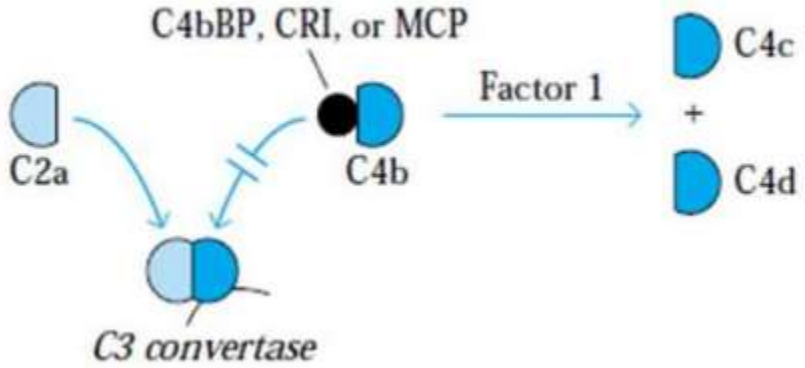
(a) Before assembly of convertase activity

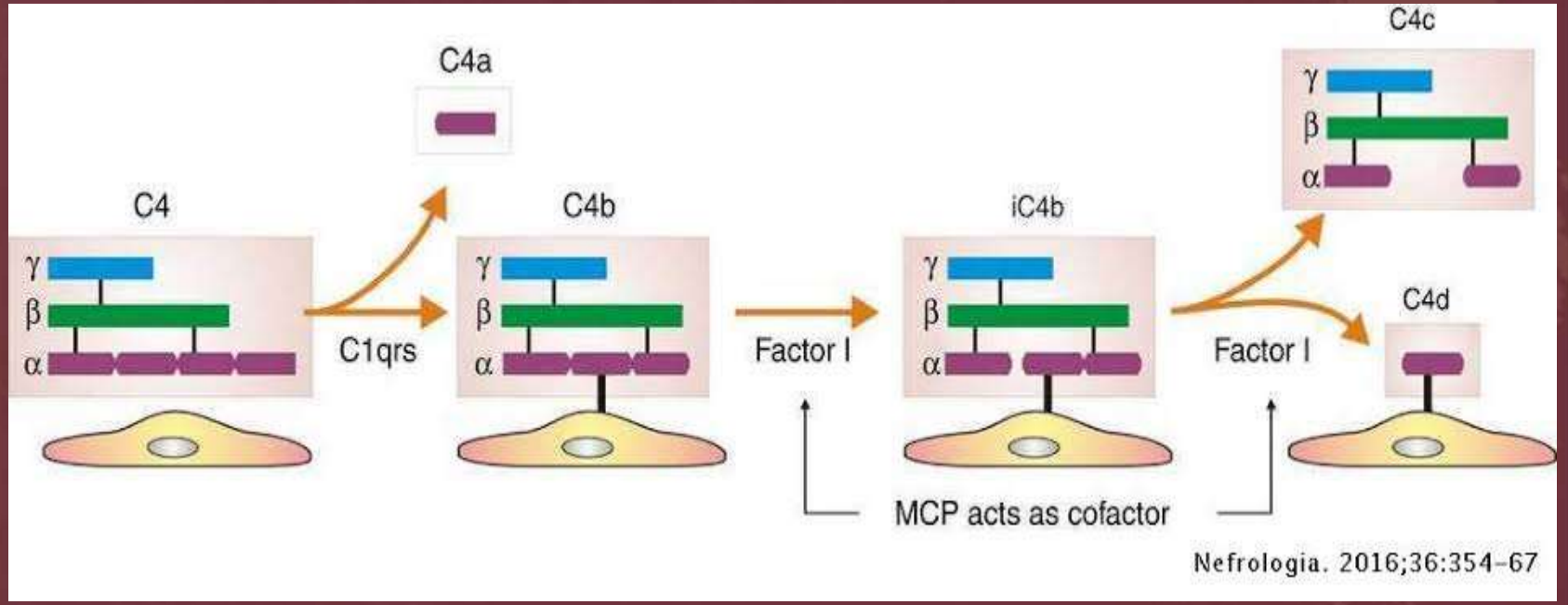
1 C1 inhibitor (C1Iab) binds $C1r_2s_2$, causing dissociation from C1q



2. Association of C4b and C2a is blocked by binding C4b-binding protein (C4bBP), complement receptor type I, or membrane cofactor protein (MCP)

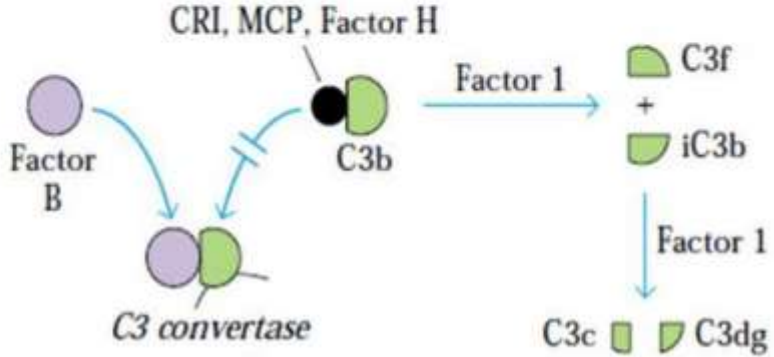
3. Inhibitor-bound C4b is cleaved by Factor 1




C4a
C4c
C4
C4b
iC4b
γ
β
α
C1qrs
Factor I
Factor I
C4d
MCP acts as cofactor
Nefrologia. 2016;36:354-67

4. In alternative pathway, CR1, MCP, or Factor H prevent binding of C3b and Factor B

5. Inhibitor-bound C3b is cleaved by Factor 1



(b) After assembly of convertase

C3 convertases are dissociated by C4bBP, CR1, Factor H, and decay-accelerating Factor (DAF)

C4bBP, CR2
Factor H, DAF

Dissociation of convertase; remaining C4b or C3b cleaved by Factor 1

Regulation at assembly of membrane-attack complex (MAC)

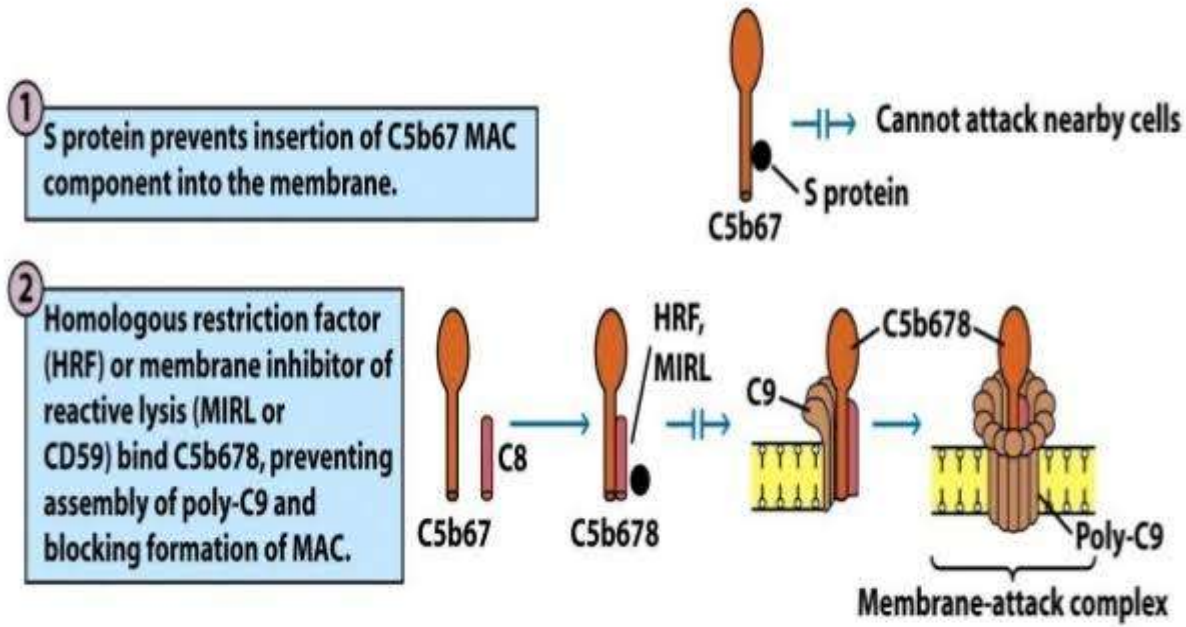


Figure 7-10c
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