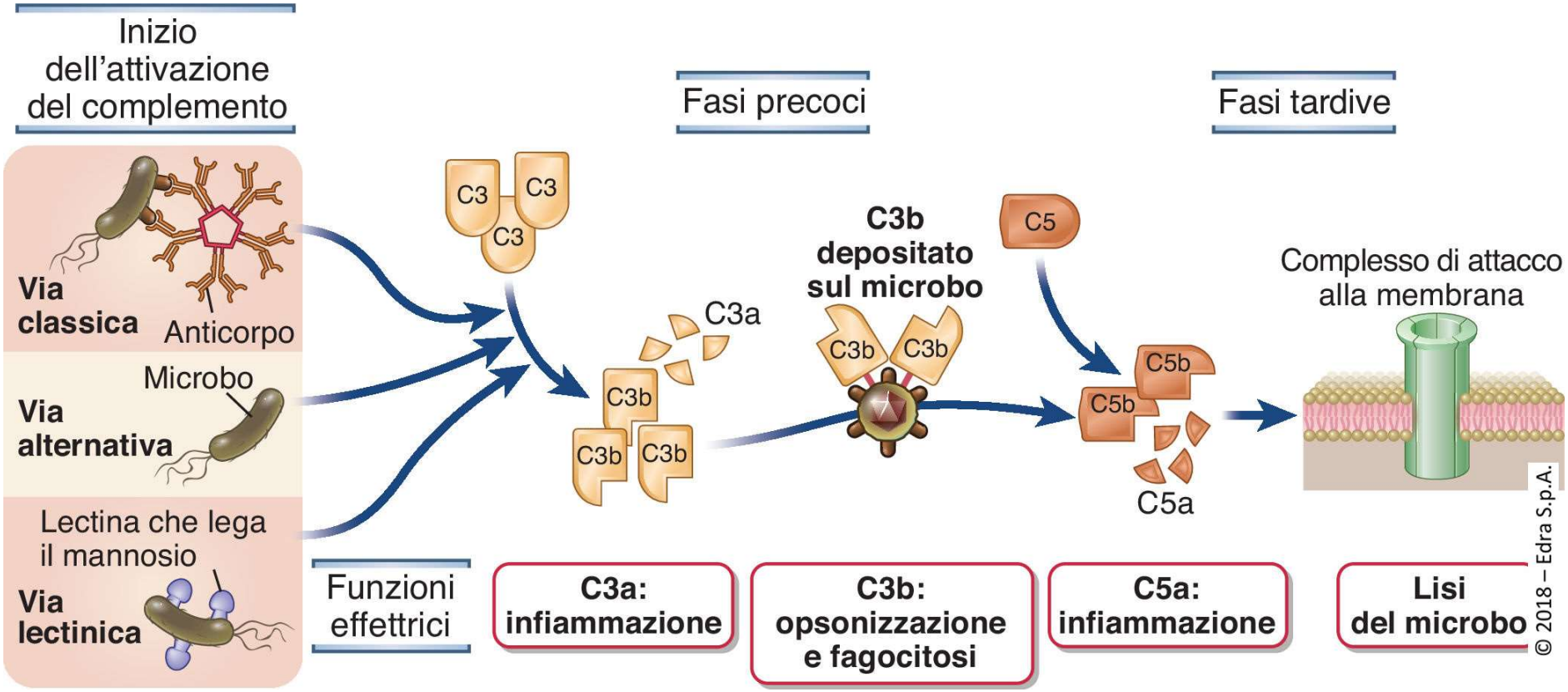
Complement system and the immune response

Prof. Giovanni Bernardini 26 Novembre 2024

Why do we study the complement system?



The complement system

The complement system is made up of several plasma and membrane proteins that activate sequentially, leading to **amplification** of a defensive response.

The function of some key molecules in the cascade is activated following a **proteolytic cleavage**

Complement activation in response to microorganisms leads to:

- **Citolysis** (**bactericidal function**)

invasive microorganisms are recognized and eliminated

- **Opsonization** (**immunoregulatory function**)

promotes the elimination of the pathogen but also of apoptotic cells and debris by phagocytosis

- **Cell activation** (**immunoregulatory function**)

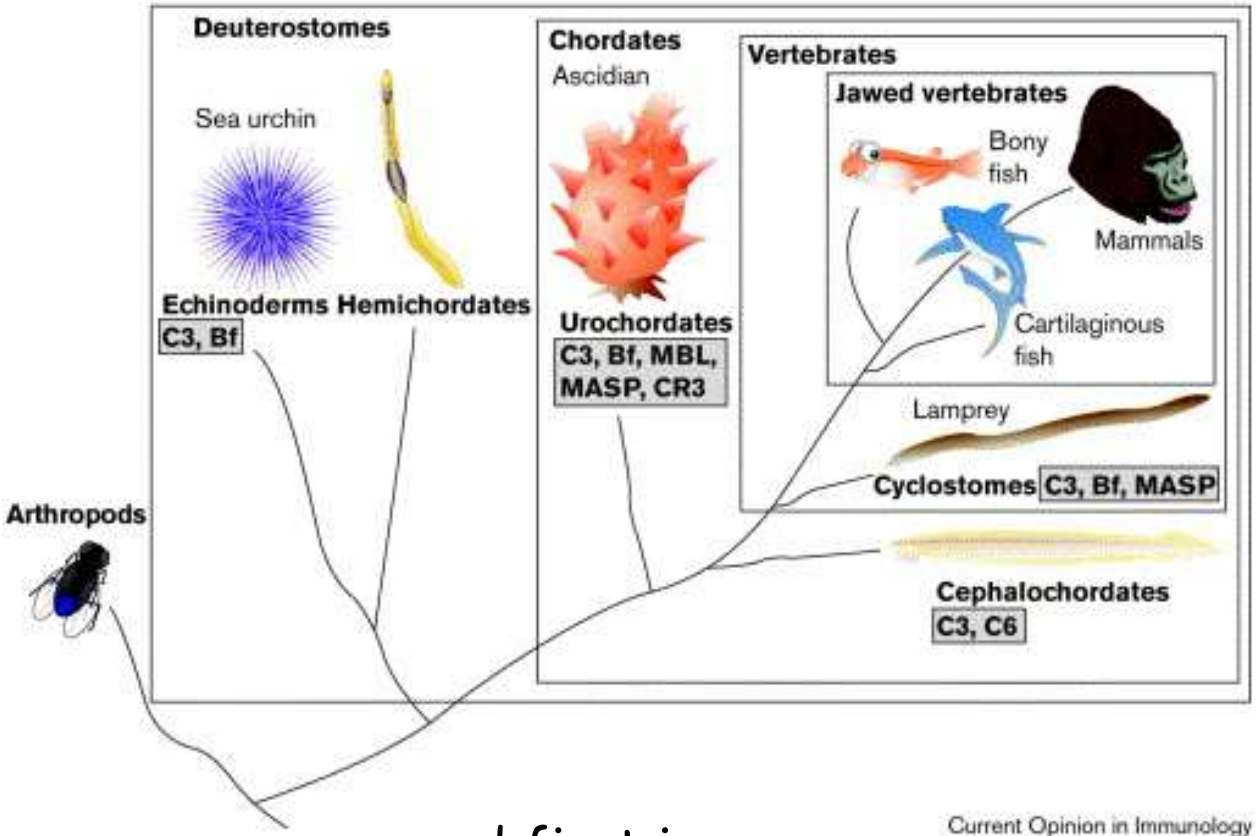
some products of the cascade promote the migration/activation of leucocytes (inflammation) and the activation of B lymphocytes

The complement system

It is a primitive form of defense against infections that has been preserved across evolution and which can be activated both by humoral immunity (adaptive response) and by innate immunity.

A primitive form of the complement system can be found in ancient animal forms

Complement genes that have been identified to date from animals are shown in bold in shaded boxes



- Alternative pathway genes appeared first in evolution.
- Terminal complement components appeared last.
- Complement served to assist phagocytosis prior to the evolution of adaptive immunity.

HISTORY

- Research in complement started in 1890s when Jules Bordet at the Institut Pasteur of Paris conducted experiment using sheep antiserum.
- He named those substances as Alexins.
- Paul Ehrlich coined the term complement.

•Nobel Prize in Physiology or Medicine, 1919

How was it discovered?

The term complement derives from the observations of Jules Bordet at the end of the 19th century, which showed that the anti-bacterial activity of immune serum required two components:

- An antigen specific, relatively heat-stable component (which we now know consists of antibodies)
- and a non-antigen specific and thermolabile component that "complemented" the action of antibodies.

Thus, the complement "completes" the task of the antibody whose function is to recognize the antigen and bind to it and start the cascade of the complement to facilitate its elimination.

But immunoregulation aimed at microbe elimination is a major complement task…..

Complement functions

Beneficial for the host

- lysis of bacteria and infected cells
-opsonization and phagocytosis
-regulation of the activation of B lymphocytes
  antibody response
- Removal of immune complexes
- Removal of apoptotic cells

Harmful to the host:

-inflammation
-anaphylaxis

Division of labor of complement proteins

(around 30 soluble and surface proteins)

in blood, inactive, activated sequentially

in blood, inactive, activated sequentially

Binding to antigen:antibody complexes and pathogen surfaces	C1q
Binding to mannose on bacteria	MBL
Activating enzymes	C1r C1s C2b Bb D MASP-1 MASP-2
Membrane-binding proteins and opsonins	C4b C3b
Peptide mediators of inflammation	C5a C3a C4a

Figure 2-20 Immunobiology, 6/e. (© Garland Science 2005)

Membrane-attack proteins	C5b C6 C7 C8 C9
Complement receptors	CR1 CR2 CR3 CR4 C1qR
Complement-regulatory proteins	C1INH C4bp CR1 MCP DAF H I P CD59

Both fluid phase and on cell surface

The cleavage of the complement cascade components gives rise to two types of factors:

- one continues and amplifies the cascade or perform functions **on the cell membrane**

- The other goes **into the circulation** (some of them are called anaphylatoxins)

Complement cascade

Some rules

Proteolysis leads to the formation of a larger fragment which is usually identified by the letter **b** after the component name and a smaller one identified by the letter **a** (only C2a is an exception**).**

The activated component is sometimes indicated with a line above the activated fraction, eg $C1\overline{qrs}$

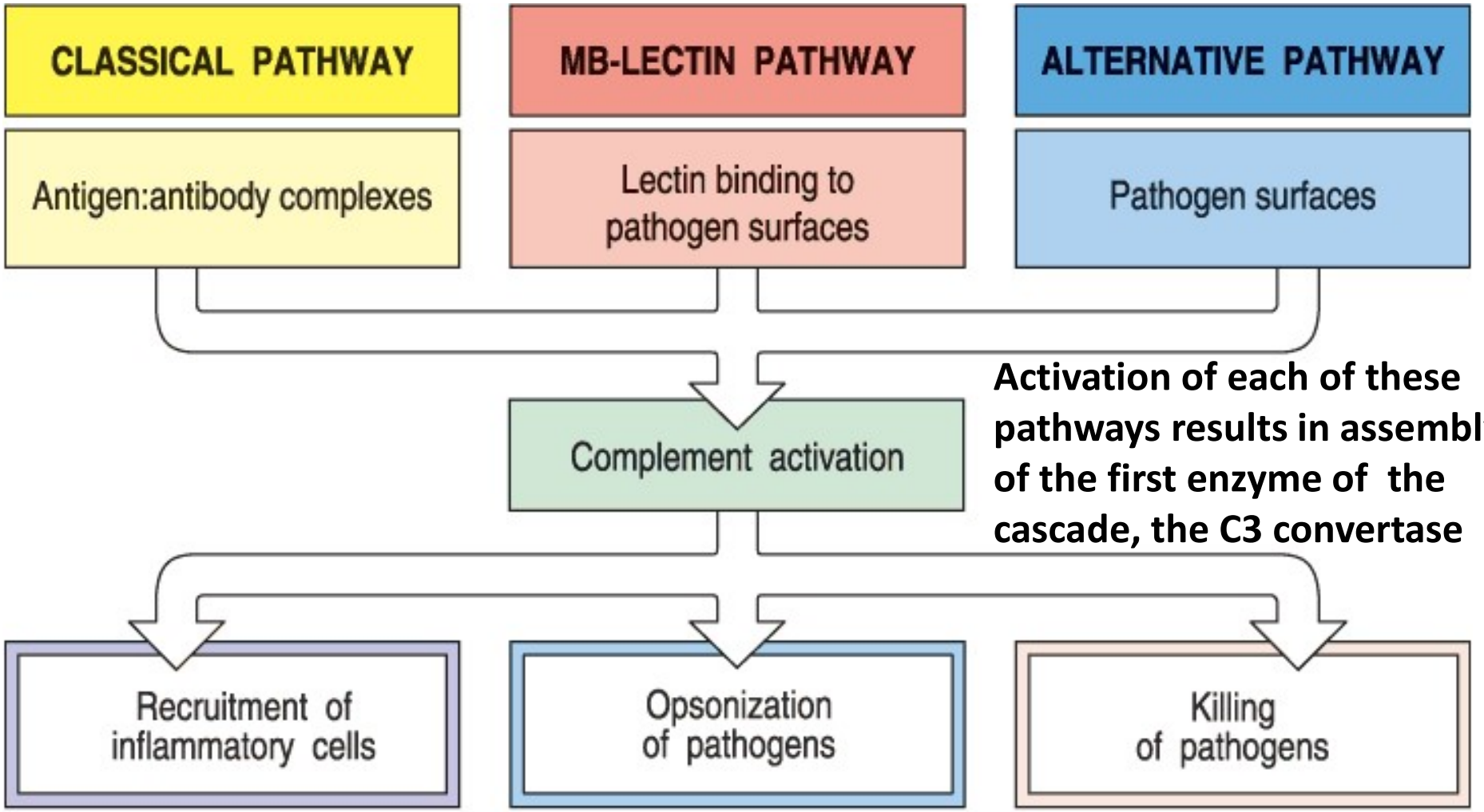
The component factors are normally classified with a number (eg C1-9) or with letters (eg Factor D)

Multiple control systems

The components of the complement are inactive in the blood, or they are **activated temporarily**.
Activation of key components **occurs** or is **stabilized only after their covalent link** to microbes or antibodies

Complement regulatory proteins present only on the host cell diminish the harmful effects of its unwanted activation.

Complement is activated by three major pathways



Activation of each of these pathways results in assembly of the first enzyme of the cascade, the C3 convertase

Component C3 activation

A key event in complement activation is the **generation of the C3 convertase** and **the covalent bond of C3b** with microbial surfaces, which allows the innate recognition of microbes to be translated into effector responses.
Covalent bond formation is due to a highly reactive **thioester bond** that is hidden inside the folded C3 protein and cannot react until C3 is cleaved.

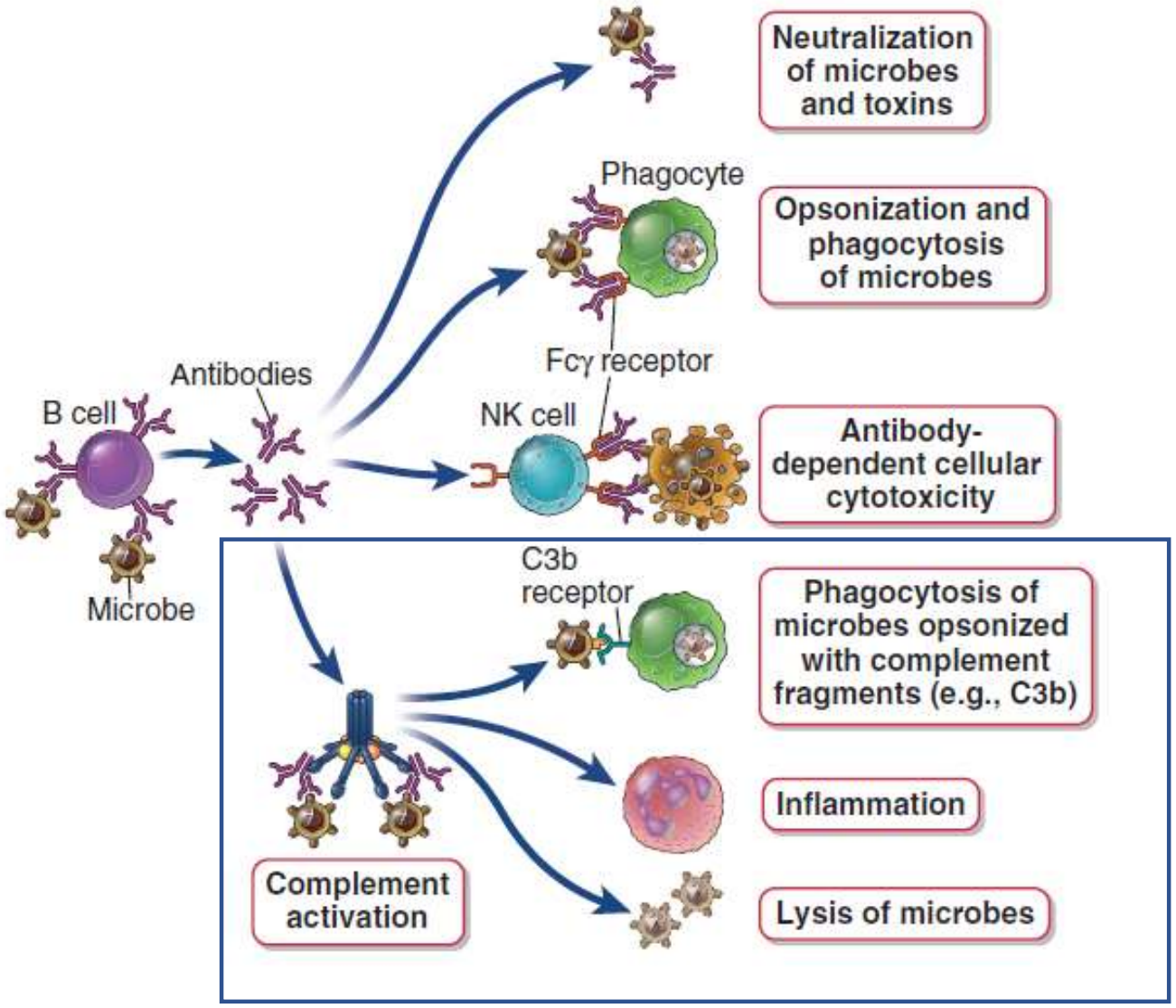
When C3 convertase cleaves C3 and releases the C3a fragment, large conformational changes occur in C3b that allow the thioester bond to react with a hydroxyl or amino group on the nearby microbial surface

This allows to proceed with the complement cascade or activate immune cells.

Match each complement pathway to the correct description

A: classical pathway	1: initiated by proteins that recognize specific carbohydrate components found on microbial cell surfaces
B: lectin pathway	2: C3 is constantly being made and then spontaneously inactivated in “tick over”
C: alternative pathway	3: considered to be part of the adaptive immune response due to involvement of an antigen-antibody complex

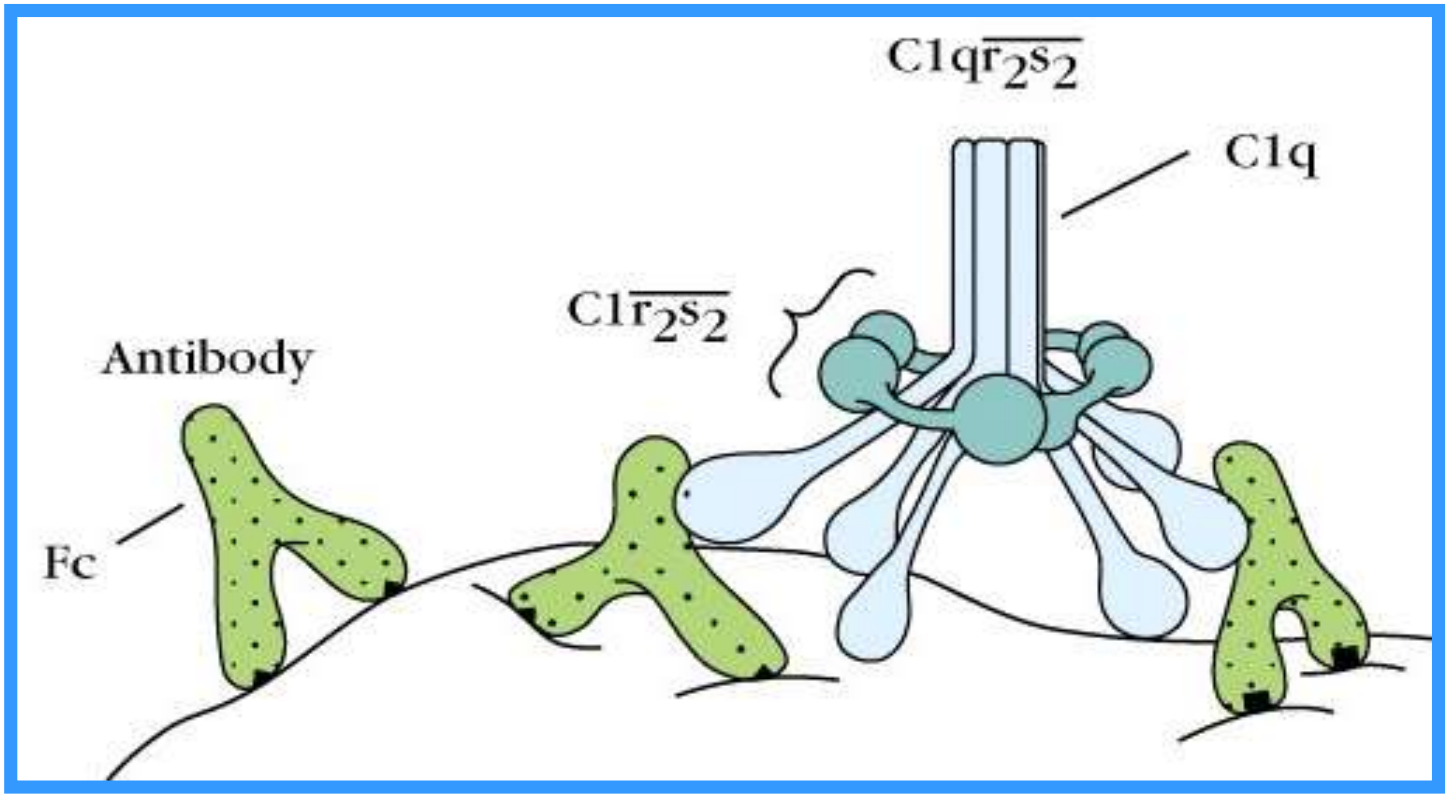
The complement system is part of the antibody-mediated responses



The classical pathway

Activation of the classical pathway

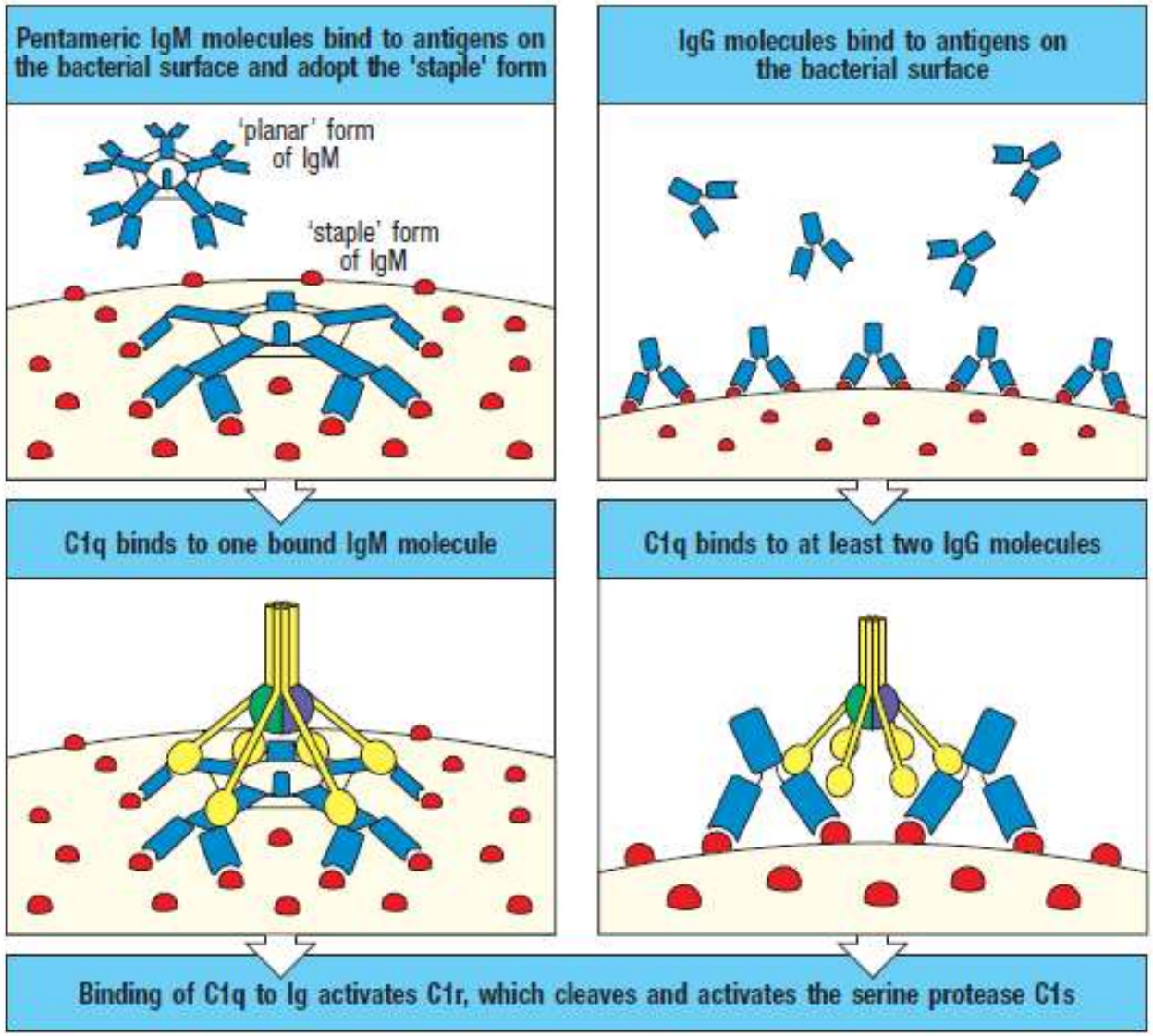
Classical pathway



IgM is about a thousand times more efficient than IgG to activate the complement.

The complement system: activation by antibodies

The classical pathway

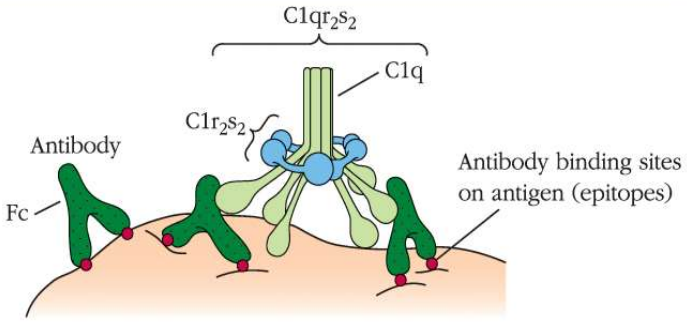


Only IgG and IgM classes bound to microbes activate the complement cascade

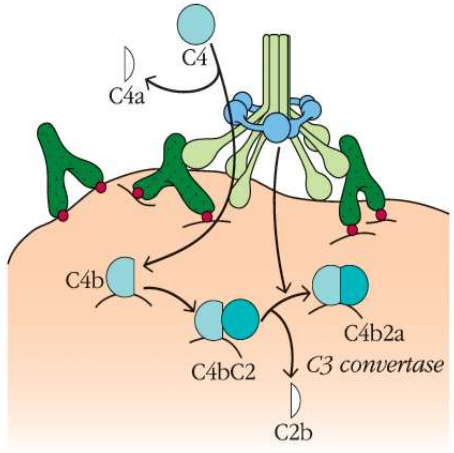
Fig. 10.35 **The classical pathway of complement activation is initiated by the binding of C1q to antibody on a pathogen surface.** When a molecule of IgM binds several identical epitopes on a pathogen surface, it is bent into the 'staple' conformation, which allows the globular heads of C1q to bind to the Fc regions of IgM (left panels). Multiple molecules of IgG bound on the surface of a pathogen allow the binding of a single molecule of C1q to two or more Fc regions (right panels). In both cases, the binding of C1q to the Fc regions induces a conformational change that activates the associated C1r, which becomes an active enzyme that cleaves the pro-enzyme C1s, generating a serine protease that initiates the classical complement cascade (see Chapter 2).

Classical Pathway Activation

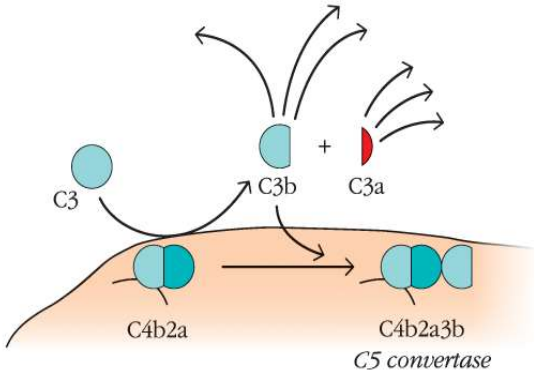
1 C1q binds antigen-bound antibody, and induces a conformational change in one C1r molecule, activating it. This C1r then activates the second C1r and the two C1s molecules.



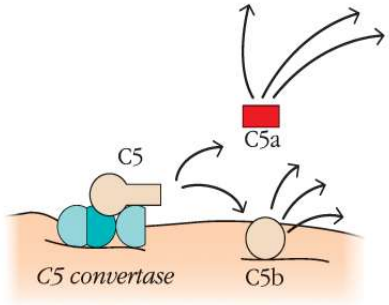
2 C1s cleaves C4 and C2. C4 is cleaved first and C4b binds to the membrane close to C1. C4b binds C2 and exposes it to the action of C1s. C1s cleaves C2, creating the C3 convertase, C4b2a.



3 C3 convertase hydrolyzes many C3 molecules. Some combine with C3 convertase to form C5 convertase.



4 The C3b component of C5 convertase binds C5, permitting C4b2a to cleave C5.



C4b Binds to the Membrane

- A thioester bond is exposed when C4 is cleaved.
- This bond is reactive, binding to amino groups on the target surface.
- If no target is present, the bond is hydrolyzed and rendered inert.

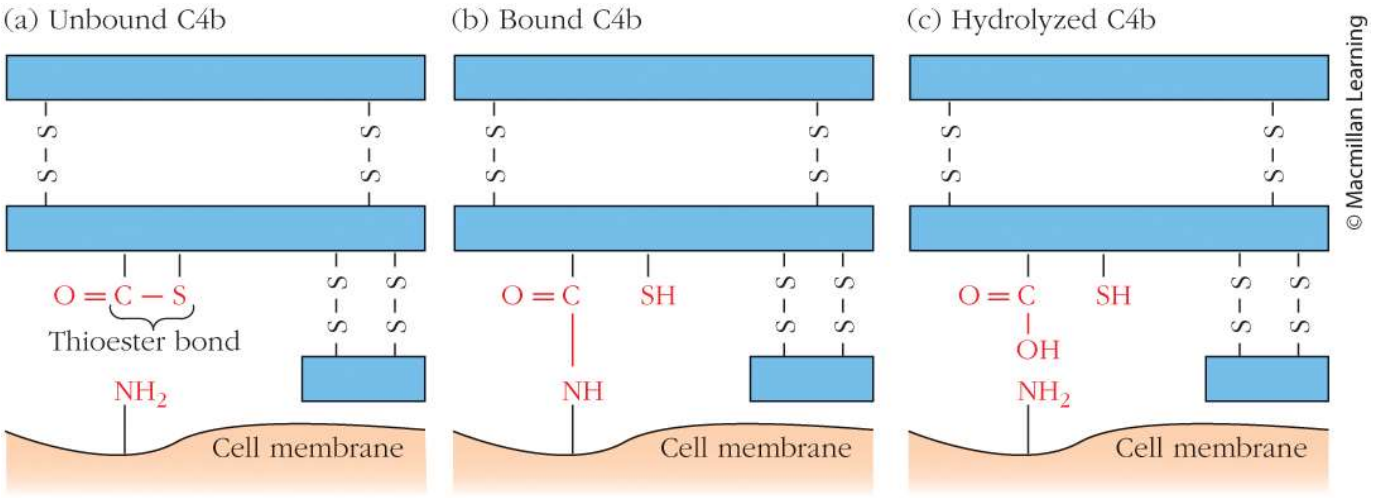
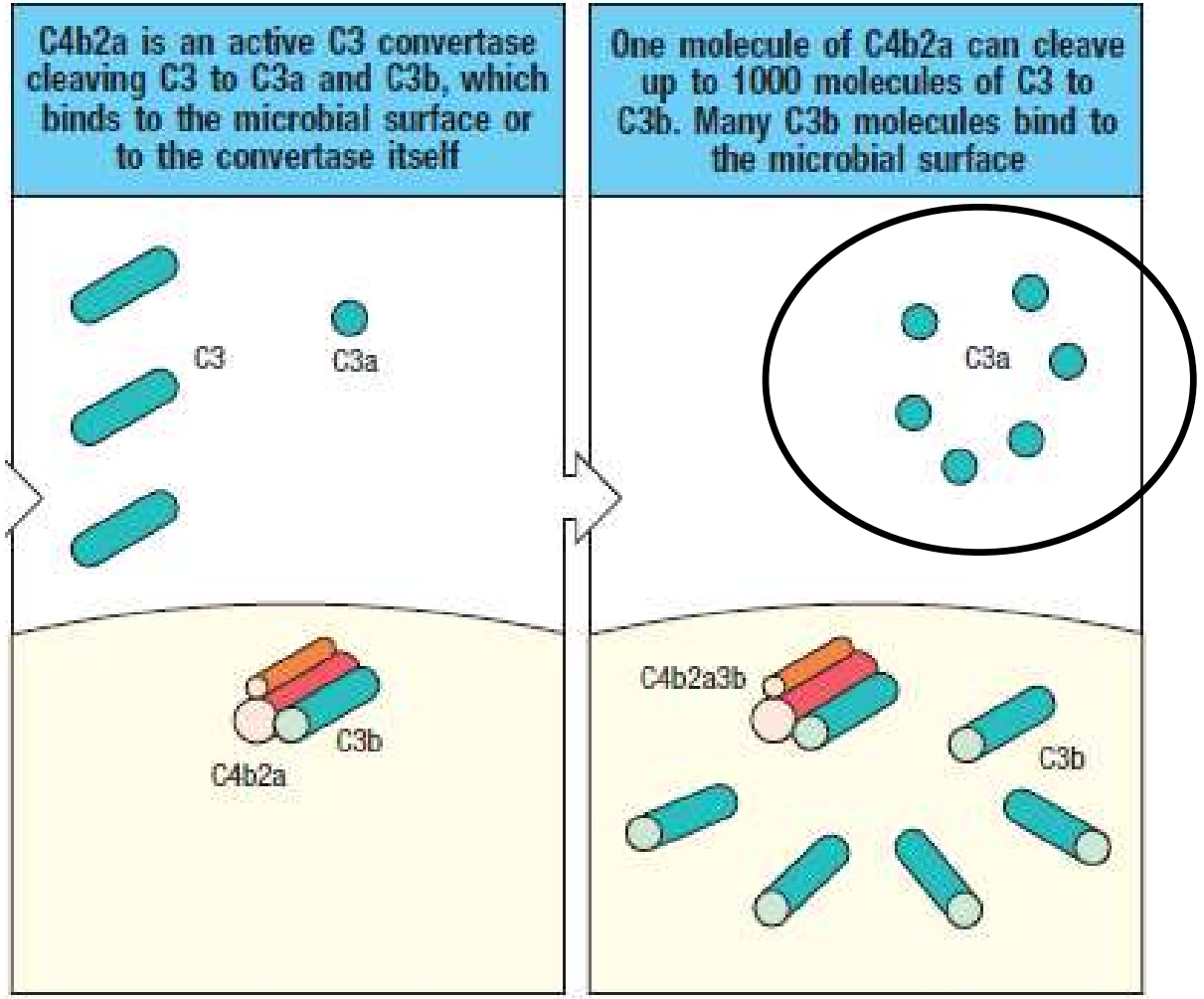


Fig. 5-6

EXPOSURE OF THE THIOESTER ON C4 or C3 ALLOWS THEM TO REACT WITH AMINIC OR HYDROXYLIC GROUPS OF PROTEINS OR CARBOHYDRATES ON TARGET CELL FORMING COVALENT BONDS

Classical pathway

The C3 convertase



Role of C3b:
Binds to pathogen surface and acts as opsonin.
Initiates **amplification** via the alternative pathway.
Binds C5 for cleavage by C2a

Activation of the alternative pathway

The Alternative Tickover Pathway

- Small amounts of C3 are always being cleaved.
- Factor B binds and is then cleaved by Factor D forming a C3 convertase in solution that can cleave C3
- Cleaved C3 is usually quickly inactivated if nothing is around for it to bind.
- Activated C3b binds to membrane of target cell.
- C3bBb at the membrane is the **C3 convertase**.
- **Properdin** stabilizes the C3 convertase, which can then cleave many more C3 proteins.

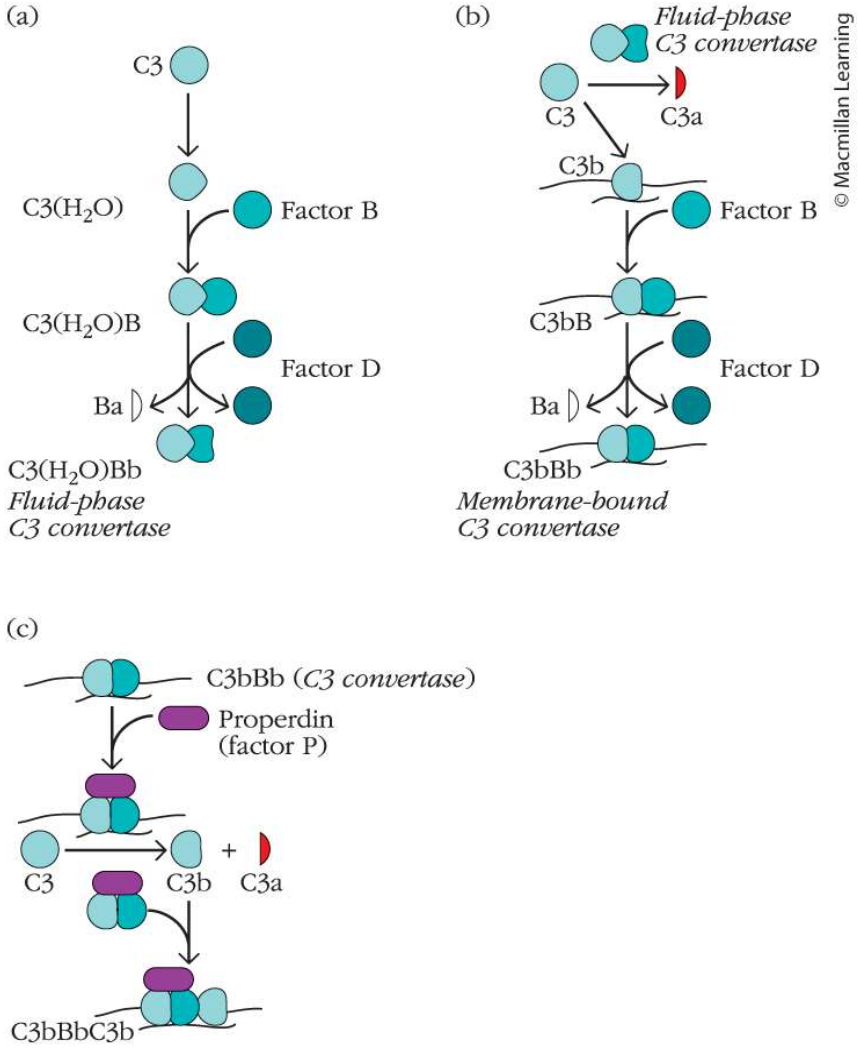


Fig. 5-8

Fluid-Phase and Membrane-Bound C3 Convertases

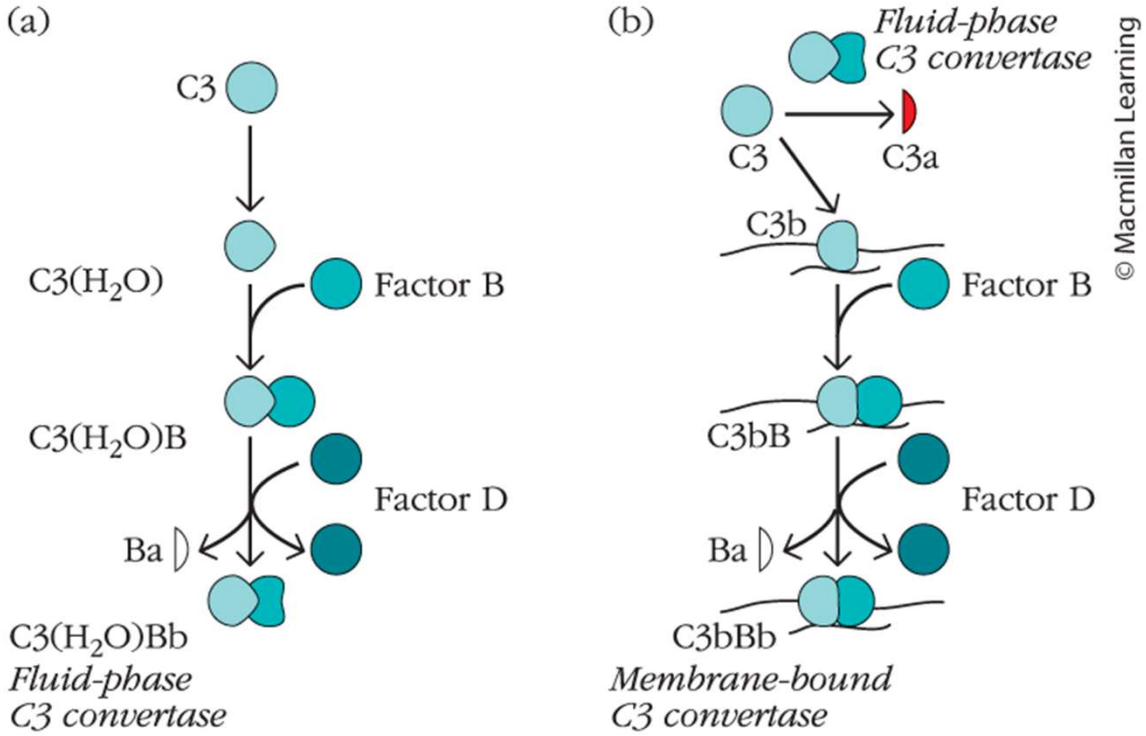


Fig. 5-8

Alternative activation of complement: proteins involved

Native component	Active fragments
C3	C3b
Factor B (B)	Ba
	Bb
Factor D (D)	D
Properdin (P)	P

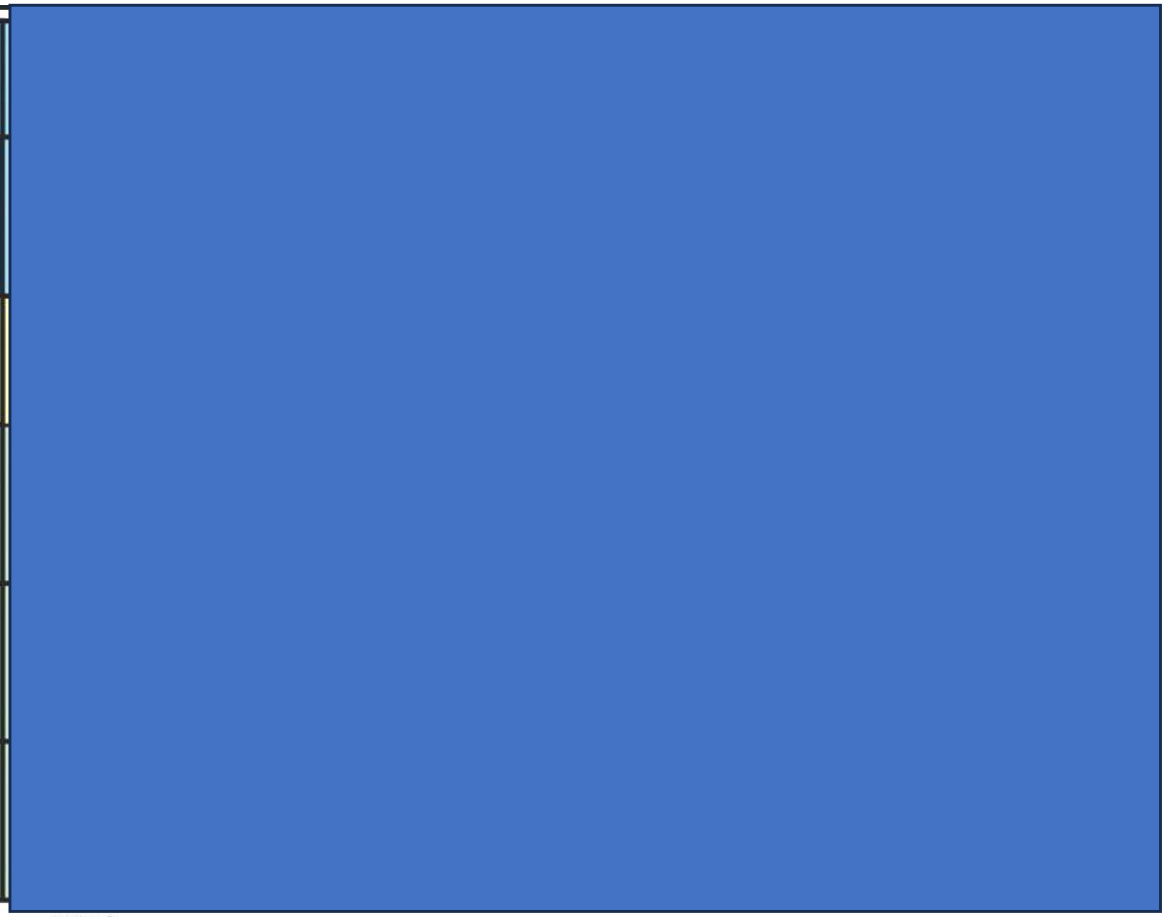
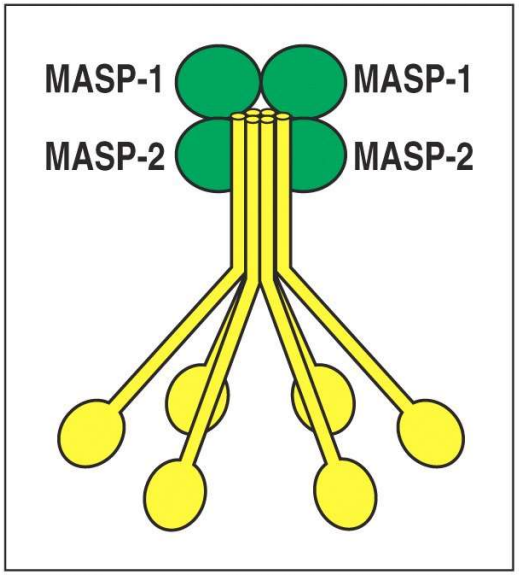


Figure 2-27 Immunobiology, 6/e. (© Garland Science 2005)

Activation of the lectin pathway

LECTIN-dependent activation



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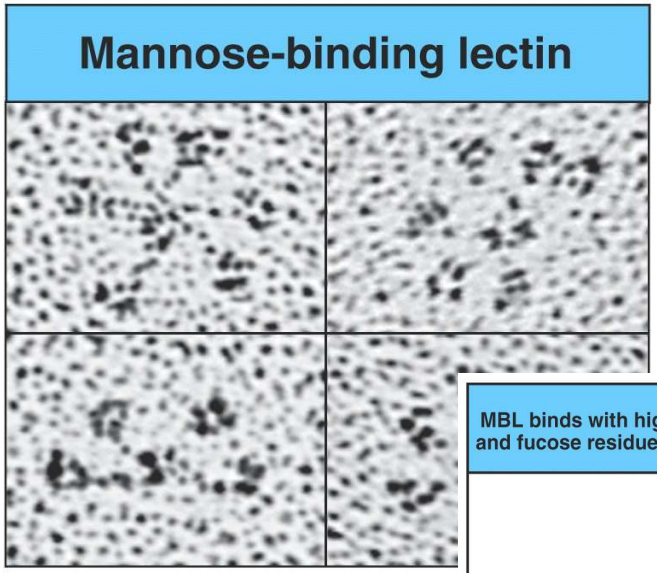


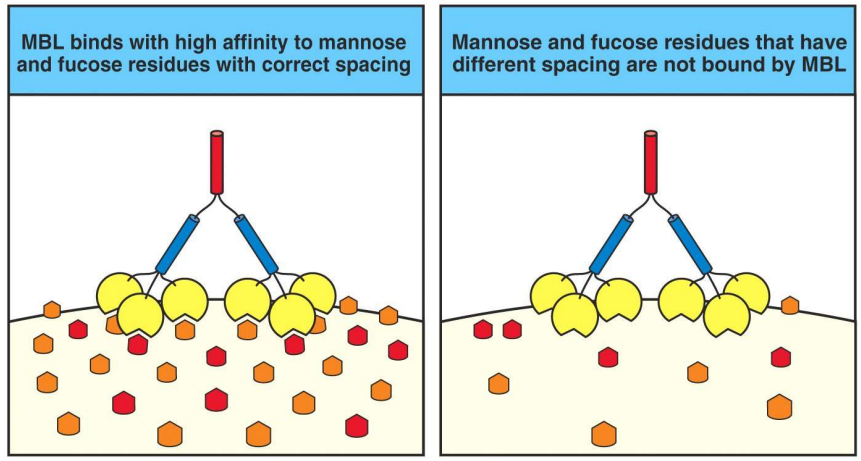


Figure 2-11 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)

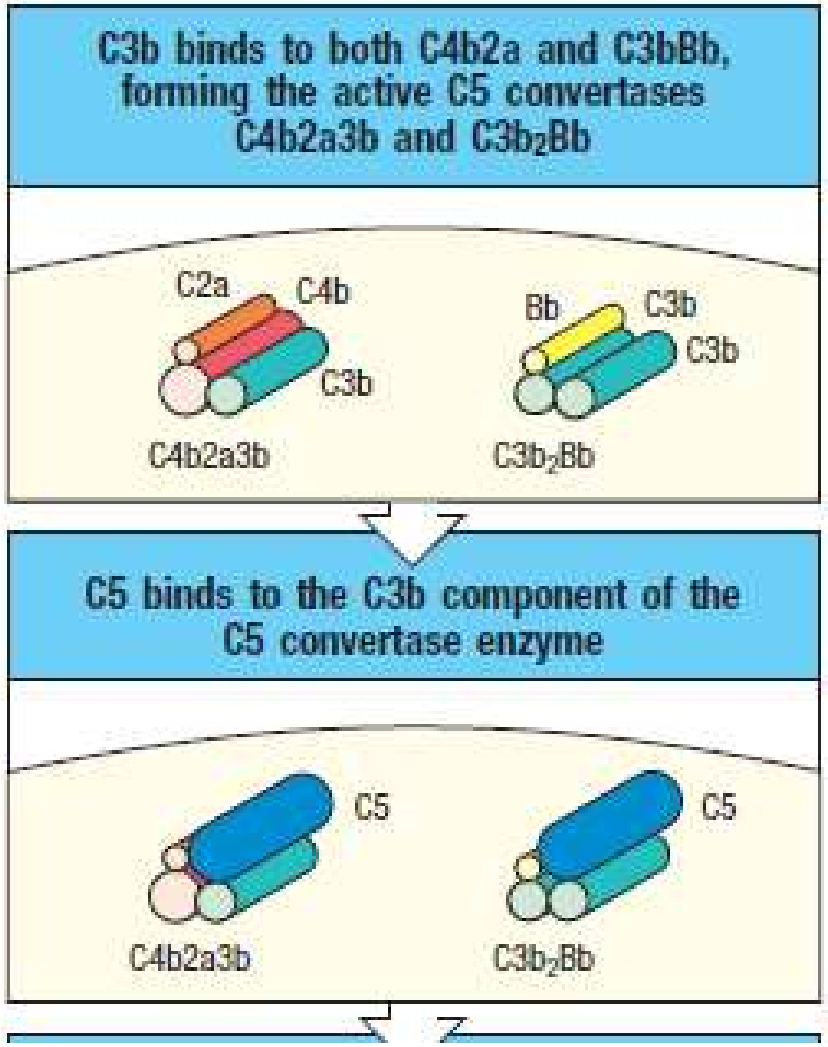
MBL associated serine protease (MASP)

- Mannose Binding Lectin (MBL) is a collectin (containing a collagen like and a lectin-like domain) present in serum, homologous to C1q.

- It binds to groups of Mannose and Fucose present on bacterial surfaces

- Interacts with MASP1 and MASP2 which are serine proteases homologous to C1r and C1s, which activate C4

C5 convertase assembly



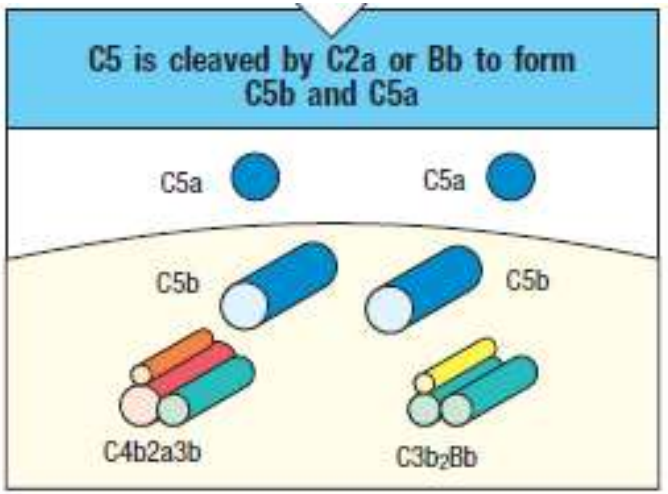
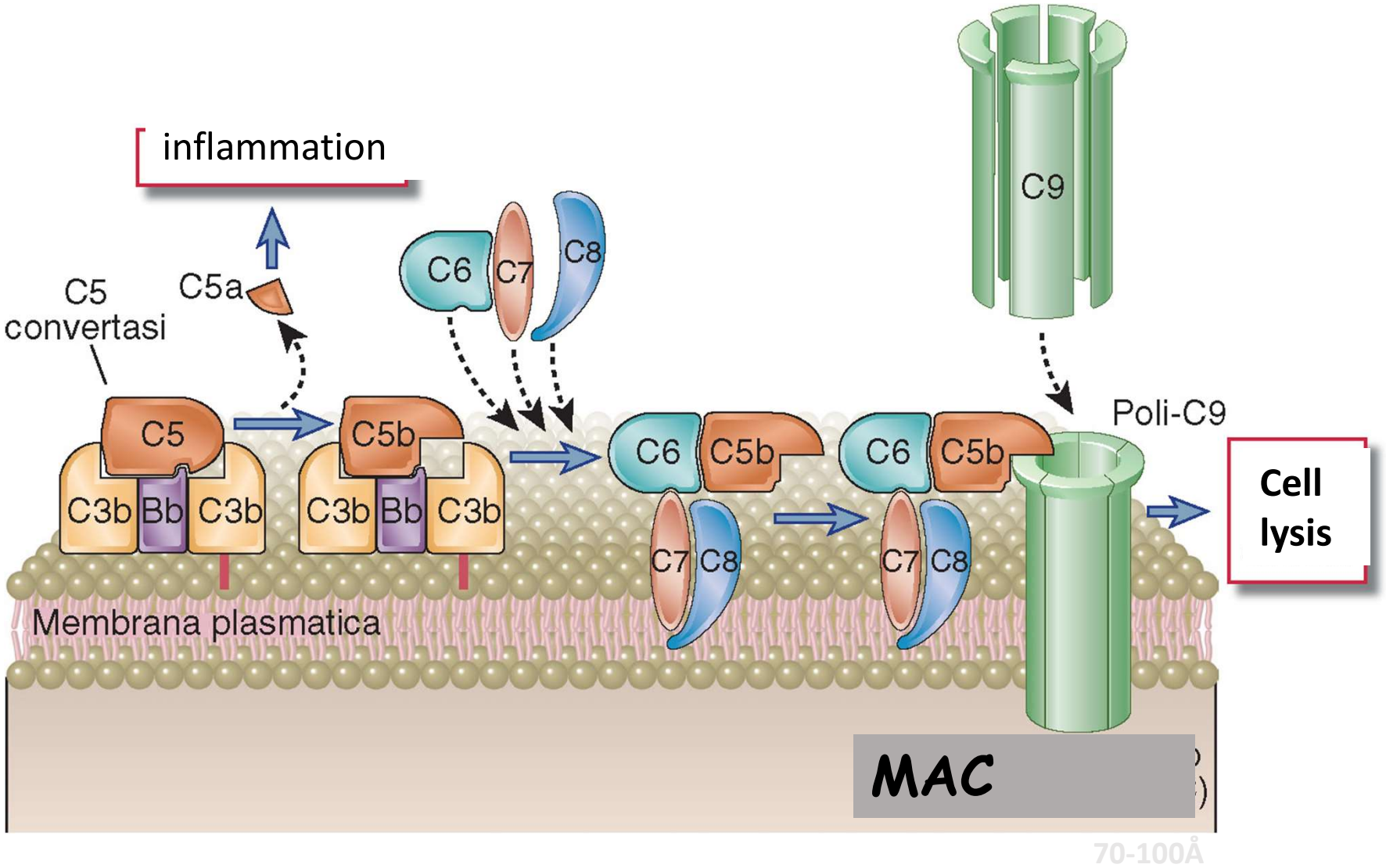
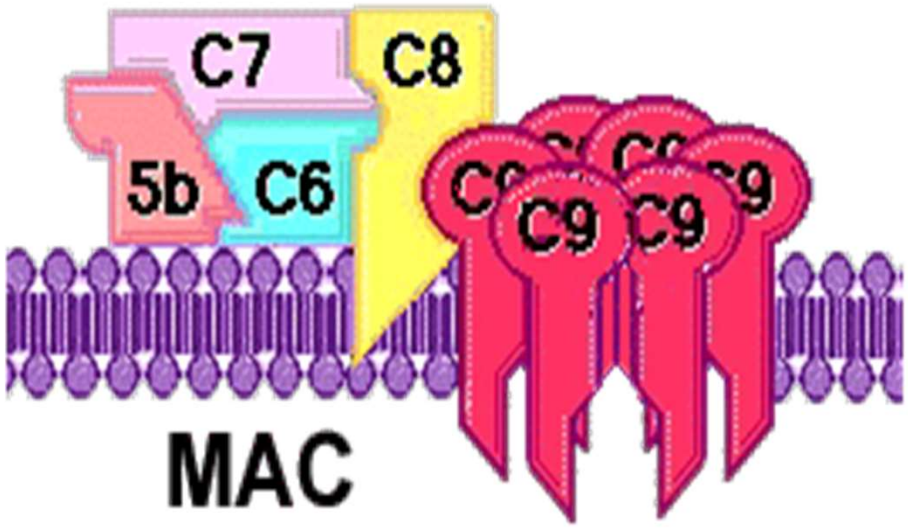


Fig. 2.29 **Complement component C5 is cleaved when captured by a C3b molecule that is part of a C5 convertase complex.** As shown in the top panel, C5 convertases are formed when C3b binds either the classical or lectin pathway C3 convertase C4b2a to form C4b2a3b, or the alternative pathway C3 convertase C3bBb to form $C3b_2Bb$. C5 binds to C3b in these complexes (center panel). The bottom panel shows that C5 is cleaved by the active enzyme C2a or Bb to form C5b and the inflammatory mediator C5a. Unlike C3b and C4b, C5b is not covalently bound to the cell surface. The production of C5b initiates the assembly of the terminal complement components.

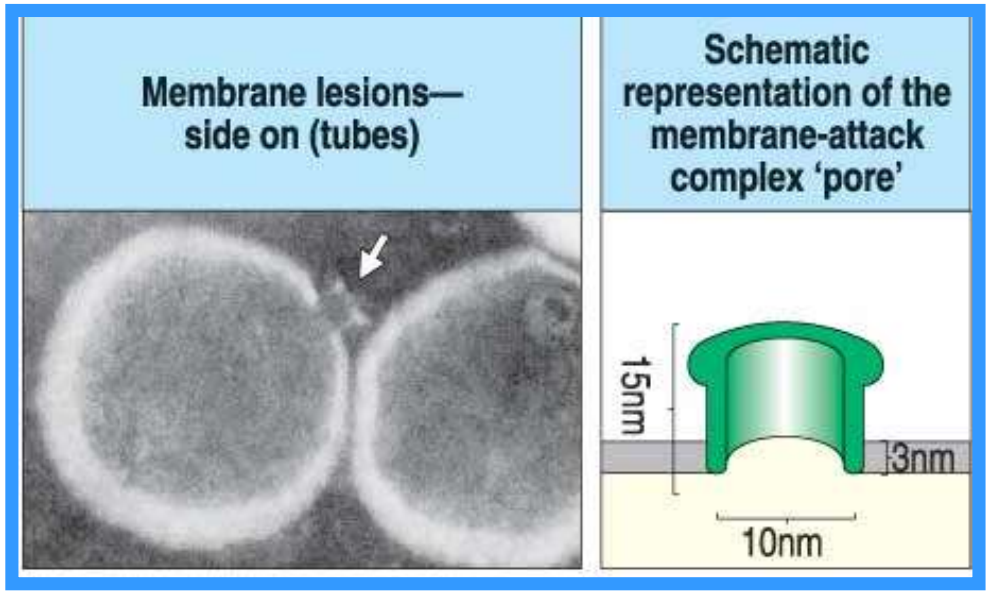
Assembly of the Membrane Attack Complex (MAC)



Assembly of the Membrane Attack Complex (MAC)



The pores formed by the MAC lead to cell lysis



Which statement about the complement activation pathways is false?

A. All three pathways form a C3 convertase.
B. All three pathways form a C5 convertase.
C. All three pathways generate C3b.
D. All three pathways generate C4b and C2a.
E. All three pathways lead to formation of the *m*embrane *a*ttack *c*omplex (MAC).

Rilevamento OPIS

			Corso di Studi	Modulo	Insegnamento
6Y7IJARZ	2025	0	BIOTECNOLOGIE (29887)	IMMUNOLOGIA I (1051487_2)	IMMUNOLOGIA (1051487)

1. **Prima del log-in è utile disattivare il blocco "pop up" del browser**
2. **Dalla *home page* di uniroma1 https://www.uniroma1.it selezionare:** STUDENTI
3. **Cliccare sul pulsante «Mobile» (procedura più rapida)**

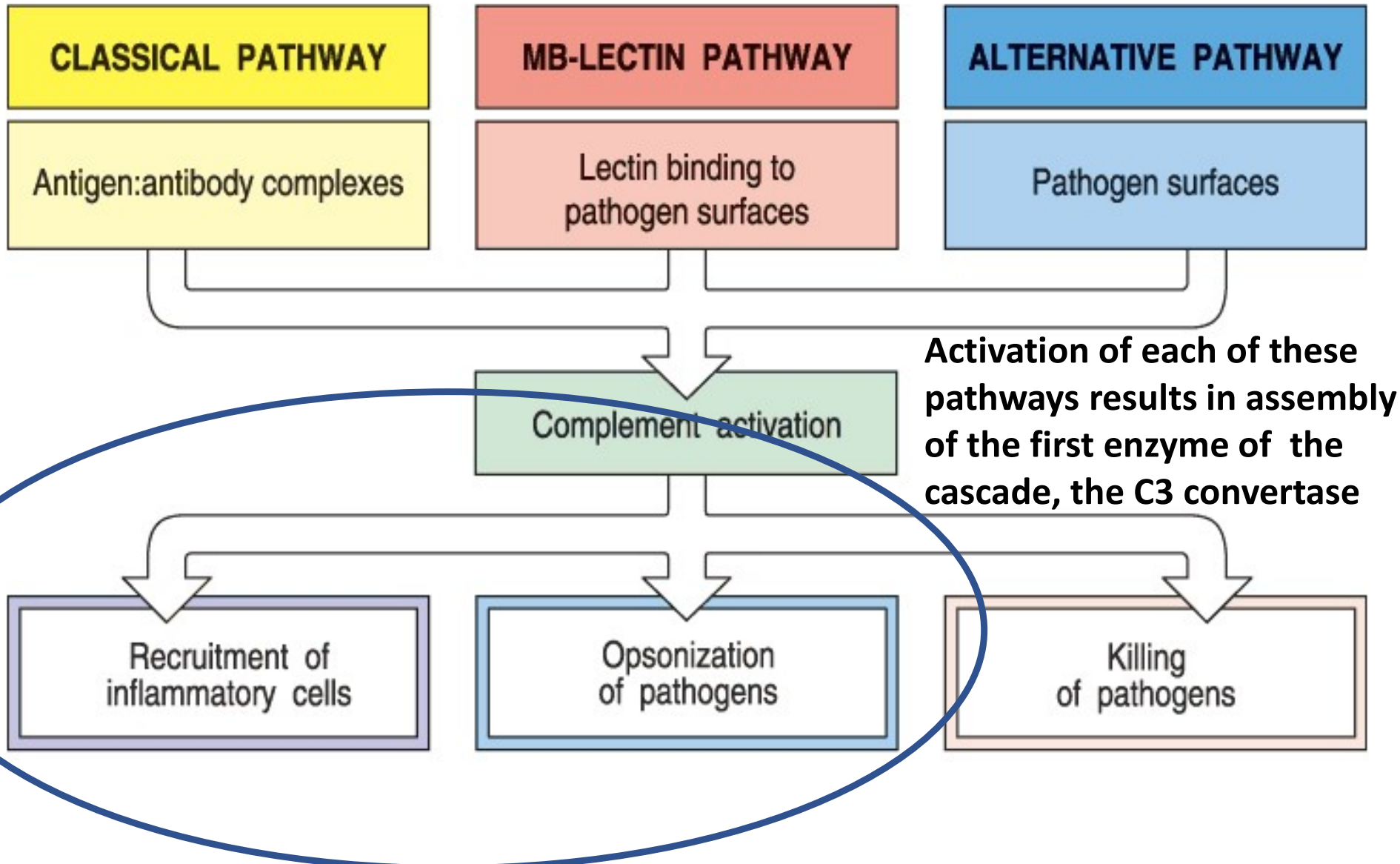
Log-in **2/2**

Inserire codice OPIS → Questionario

1. **Inserire il codice OPIS fornito dal docente**
2. **Una volta inserito il codice selezionare** vai al questionario
3. **Quindi si sarà indirizzati al questionario da compilare**

4. **Per accedere all'area riservata agli studenti di InfoStud è necessario autenticarsi tramite SPID/CIE**

Complement is activated by three major pathways



Activation of each of these pathways results in assembly of the first enzyme of the cascade, the C3 convertase

RECETTORI PER LE PROTEINE DEL COMPLEMENTO

	Receptor	Specificity	Functions	Cell types
	CR1 (CD35)	C3b, C4b iC3b	Promotes C3b and C4b decay Stimulates phagocytosis Erythrocyte transport of immune complexes	Erythrocytes, macrophages, monocytes, polymorphonuclear leukocytes, B cells, FDC
	CR2 (CD21)	C3d, iC3b, C3dg Epstein–Barr virus	Part of B-cell co-receptor Epstein–Barrvirus receptor	B cells, FDC
Integrins	CR3 (Mac-1) (CD11b/ CD18)	iC3b	Stimulates phagocytosis	Macrophages, monocytes, polymorphonuclear leukocytes, FDC
Integrins	CR4 (gp150,95) (CD11c/ CD18)	iC3b	Stimulates phagocytosis	Macrophages, monocytes, polymorphonuclear leukocytes, dendritic cells
GPCR	C5a receptor	C5a	Binding of C5a activates G protein	Endothelial cells, mast cells, phagocytes
GPCR	C3a receptor	C3a	Binding of C3a activates G protein	Endothelial cells, mast cells, phagocytes

Figure 2-31 Immunobiology, 6/e. (© Garland Science 2005)

CR1

- **CR1 on leukocytes and erythrocytes**
  - On erythrocytes, it helps to bring immune complexes to the liver for clearance by phagocytes.
  - On phagocytes, it helps bind to complement-coated bacteria to enhance ingestion and destruction.

Opsonization

- Complement enhances host defense against infection via:
  - MAC-induced cell death,
  - promotion of inflammation, and
  - promotion of opsonization.
    - **Opsonized microbes are easier to ingest/destroy.**
    - Opsonized immune complexes are easier to clear.

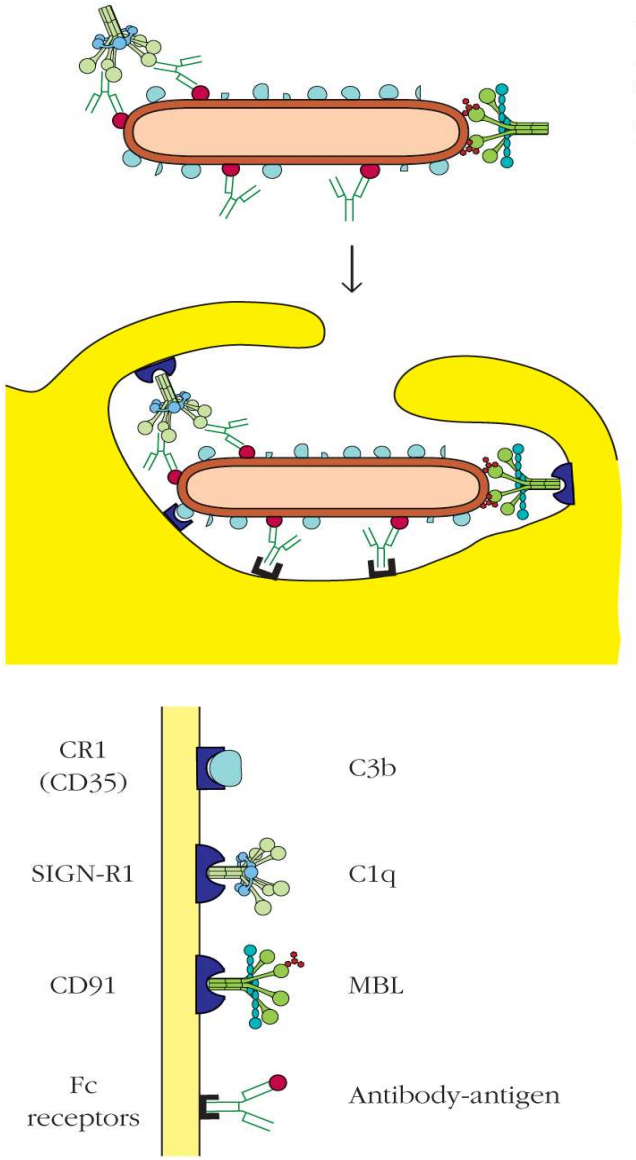


Fig. 5-13

Opsonization, Continued

- Complement enhances host defense against infection via:
  - MAC-induced cell death
  - promotion of inflammation
  - promotion of opsonization
    - Opsonized microbes are easier to ingest/destroy.
    - **Opsonized immune complexes are easier to clear.**

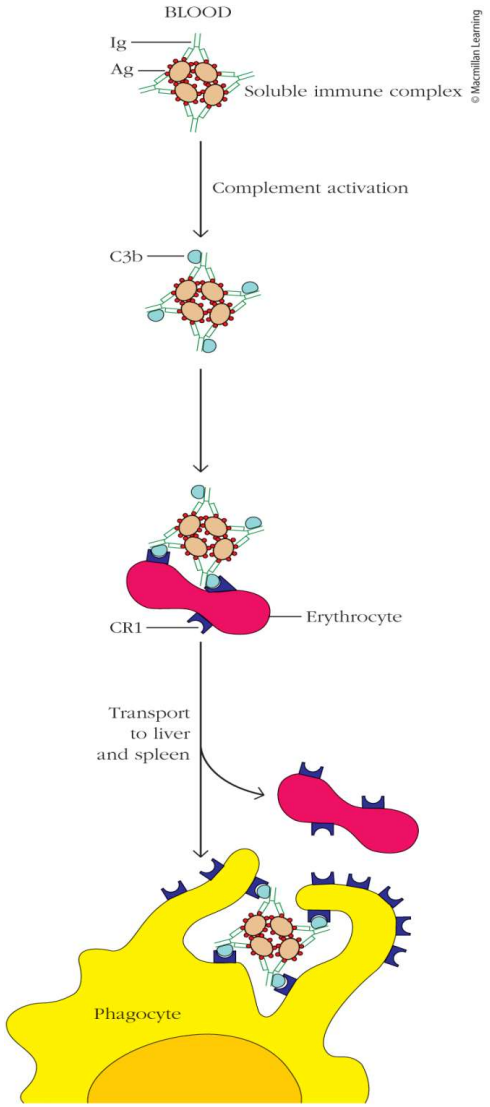
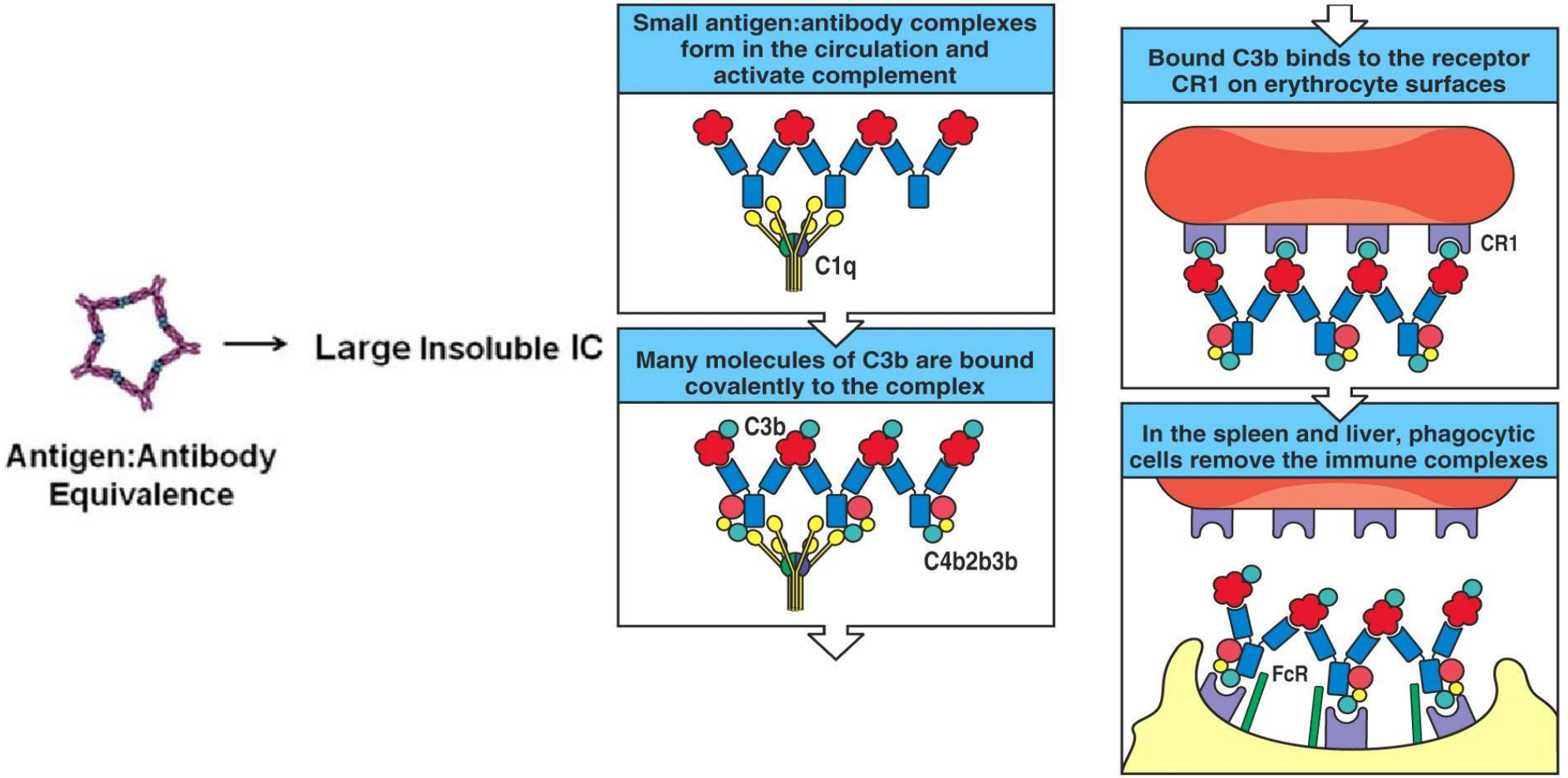


Fig. 5-15

RIMOZIONE DEI COMPLESSI IMMUNI MEDIATA DA CR1



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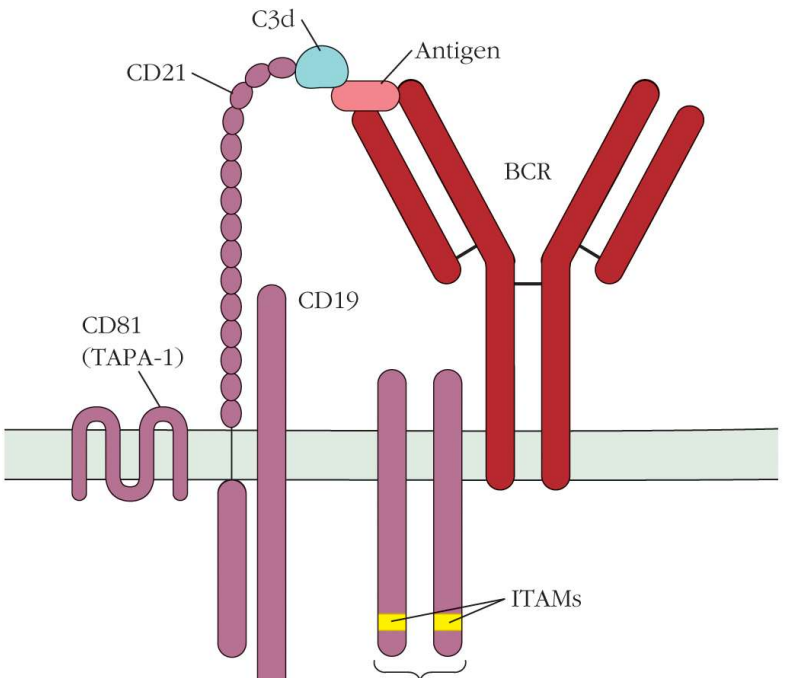
CR2

- **CR2 on B cells:**
  - binds to C3d on opsonized bacteria/antigens.
  - helps provide secondary signals to B cells through BCR complex for more efficient activation.
  - **Selection process during affinity maturation (also CR3)**



C3d si lega al recettore CR2 (CD21) espresso da linfociti B stimolando la risposta B

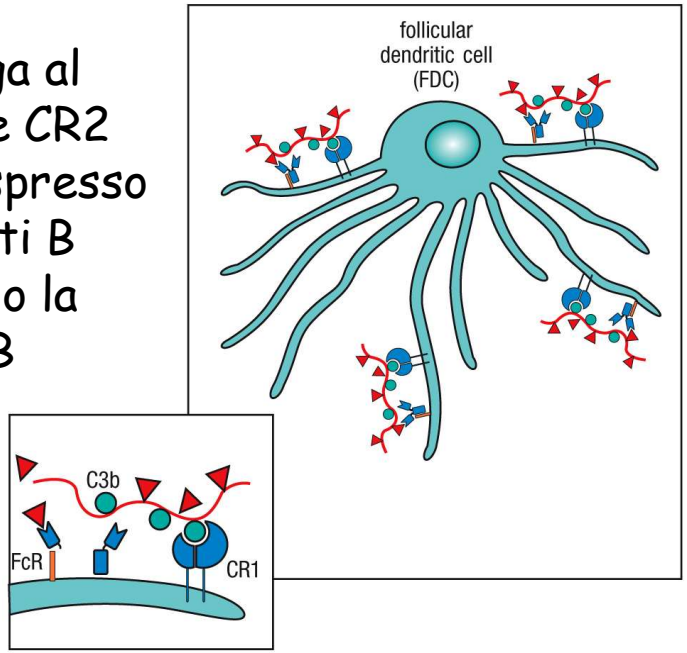


Fig. 5-11

Figure 10.16 (part 3 of 3) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

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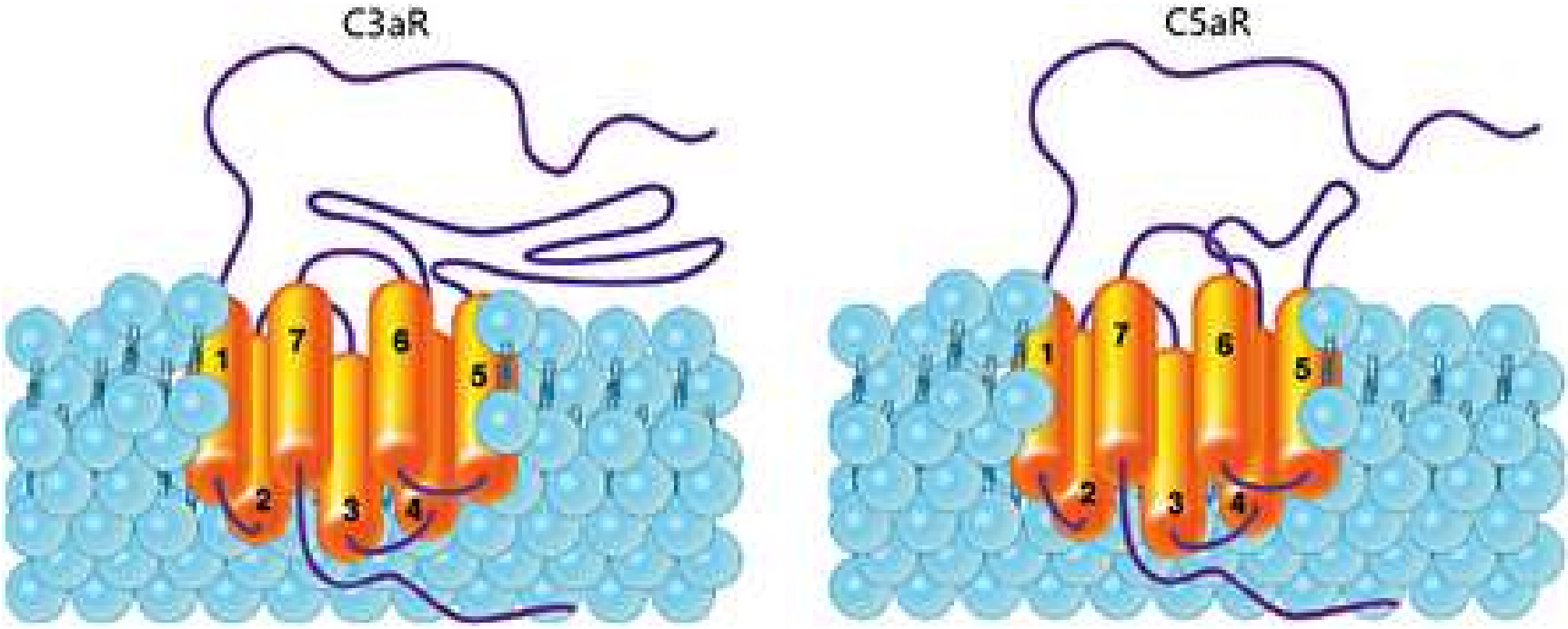
	C3a receptor	C3a	Binding of C3a activates G protein	Endothelial cells, mast cells, phagocytes

Figure 2-31 Immunobiology, 6/e. (© Garland Science 2005)

I recettori per C5a e C3a sono recettori a sette domini transmembrana accoppiati a proteine G



C3aR/C5aR

- C3aR/C5aR on granulocytes
  - stimulates release of proinflammatory cytokines and granule components from basophils, eosinophils, neutrophils

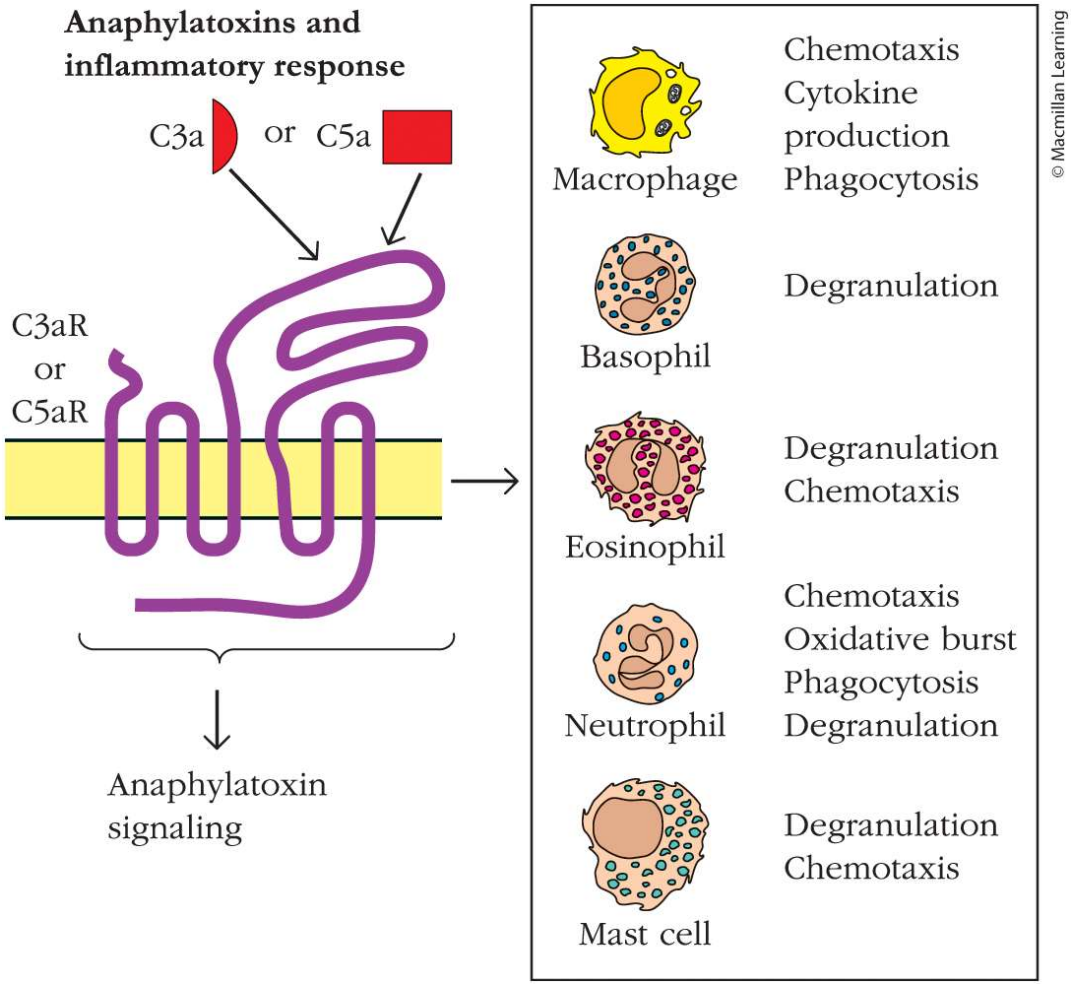
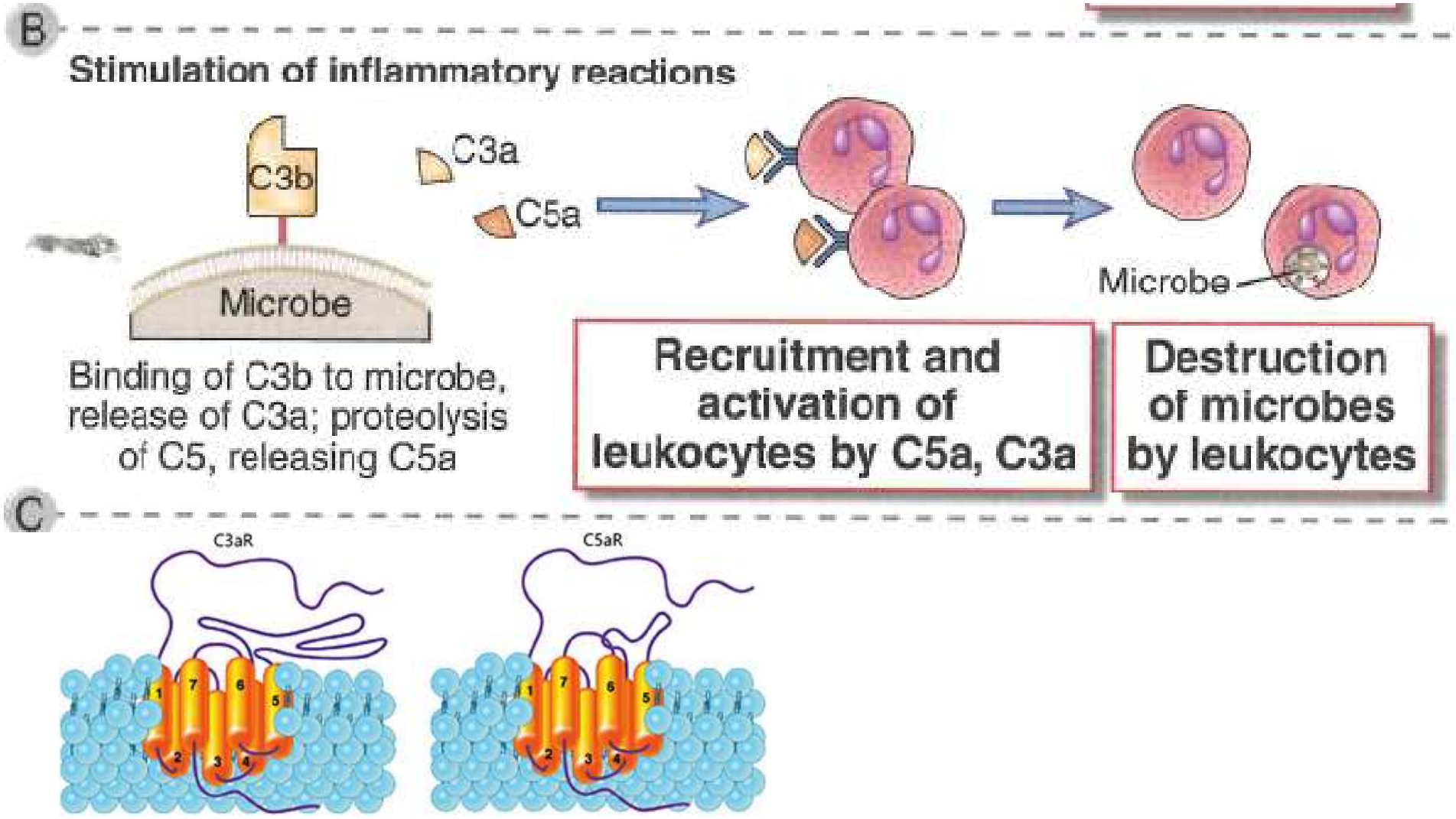


Fig. 5-12

Induction of leukocyte recruitment and activation by complement factors



Fc and complement receptors on phagocytes trigger uptake of opsonized bacteria

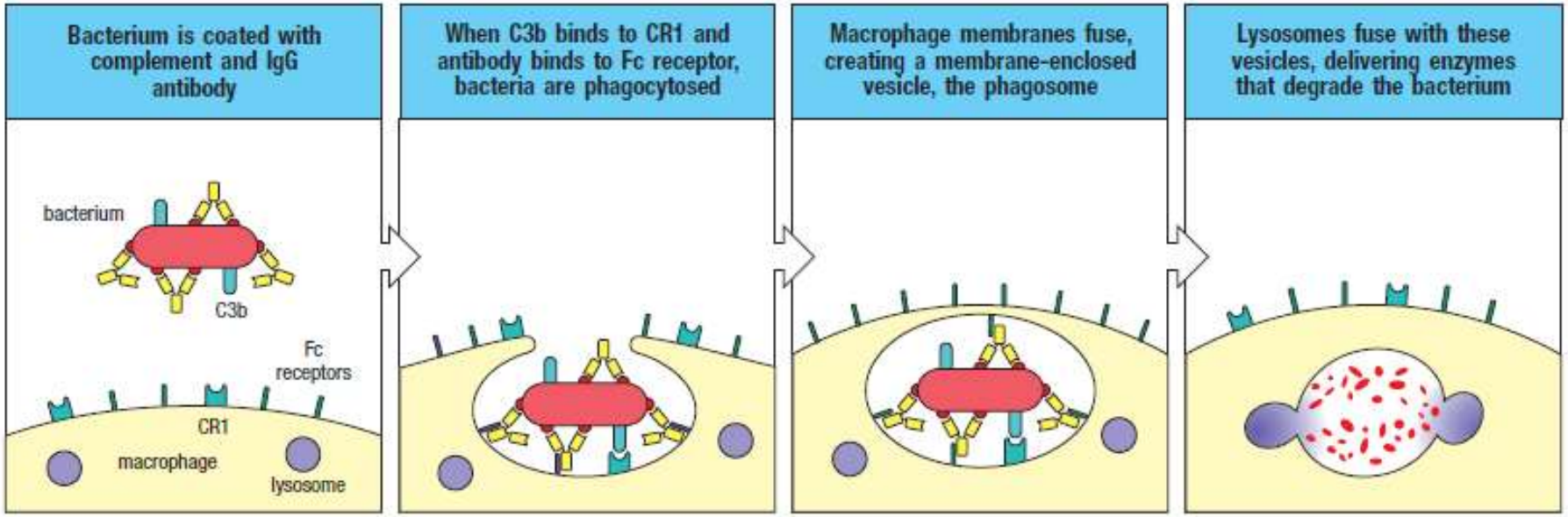


Fig. 10.39 Fc and complement receptors on phagocytes trigger the uptake and degradation of antibody-coated bacteria. Many bacteria resist phagocytosis by macrophages and neutrophils. Antibodies bound to these bacteria, however, enable the bacteria to be ingested and degraded through the interaction of the multiple Fc domains arrayed on the bacterial surface with Fc receptors on the phagocyte surface. Antibody coating also induces activation of the complement system and the binding of complement components to the bacterial surface. These can interact with complement receptors (for example, CR1) on the phagocyte. Fc receptors and complement receptors synergize in inducing phagocytosis. Bacteria coated with IgG antibody and complement are therefore more readily ingested than those coated with IgG alone. Binding of Fc and complement receptors signals the phagocyte to increase the rate of phagocytosis, to fuse lysosomes with phagosomes, and to increase its bactericidal activity.

Cell-surface complement receptor type 1 (**CR1**)

WHY OPSONIZATION?

Gram - bacteria will be destroyed by complement (they have an outer membrane)

Gram + bacteria possessing a thick wall instead of the external membrane will not be directly lysed but the release of active fragments of the complement cascade.
In this case complement facilitates the FAGOCYTOSIS and therefore the destruction

Complement participates to phagocyte regulated immune response

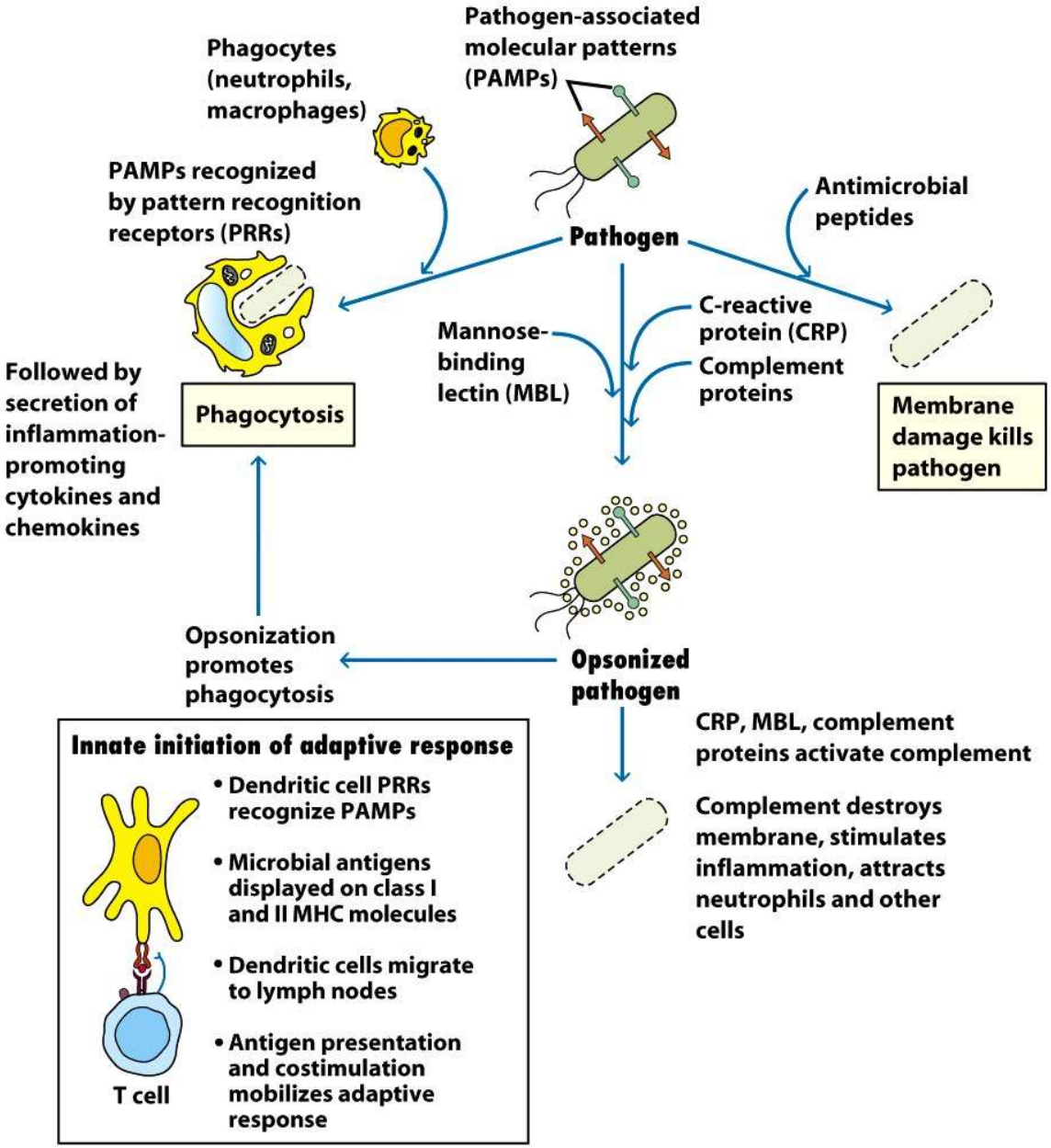
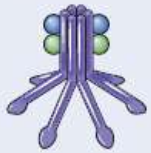
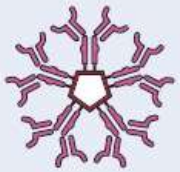


Figure 3-4
Kuby IMMUNOLOGY, Sixth Edition

Ci sono altri modi per attivare il complemento?

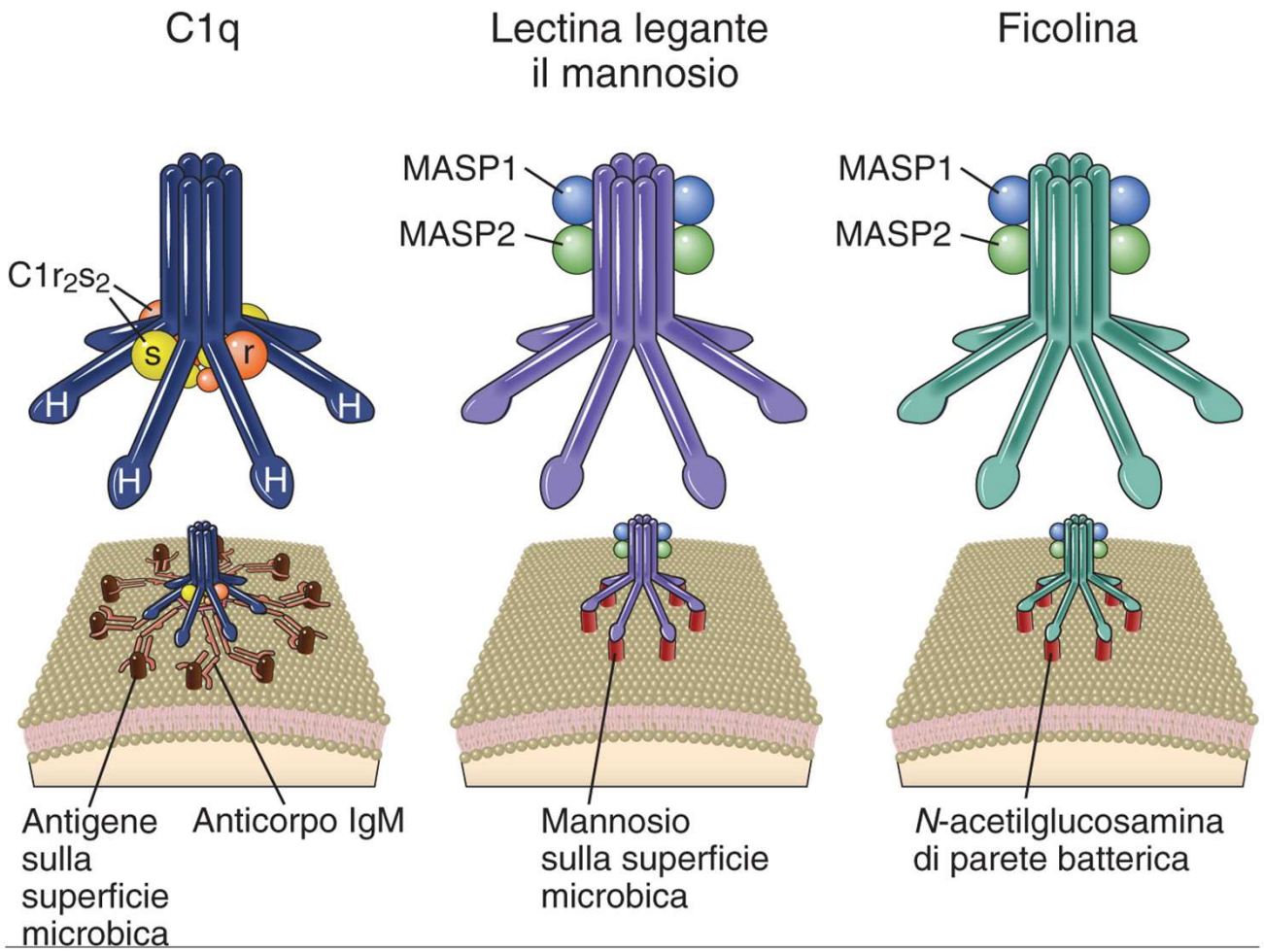
Soluble Patogen Recognition Receptor

Riconoscimento dei patogeni o del self danneggiato

PRR solubili	Localizzazione	Esempi specifici	Ligandi
Pentrassine 	Plasma	Proteina C reattiva	Fosforilcolina e fosfatidiletanolamina microbiche
Collectine 	Plasma Alveoli	Lectina che lega il mannosio Proteine del surfattante SP-A e SP-D	Carboidrati con residui di mannosio e fruttosio Varie strutture microbiche
Ficoline 	Plasma	Ficolina	*N*-acetilglucosamina e acido lipoteicoico, componenti della parete cellulare dei batteri Gram-positivi
Complemento 	Plasma	C3	Superfici microbiche
Anticorpi naturali 	Plasma	IgM	Fosforilcolina delle membrane batteriche e membrane delle cellule apoptotiche

PRR: Patogen Recognition Receptor SOLUBILI

Lectina legante il mannosio e FICOLINA



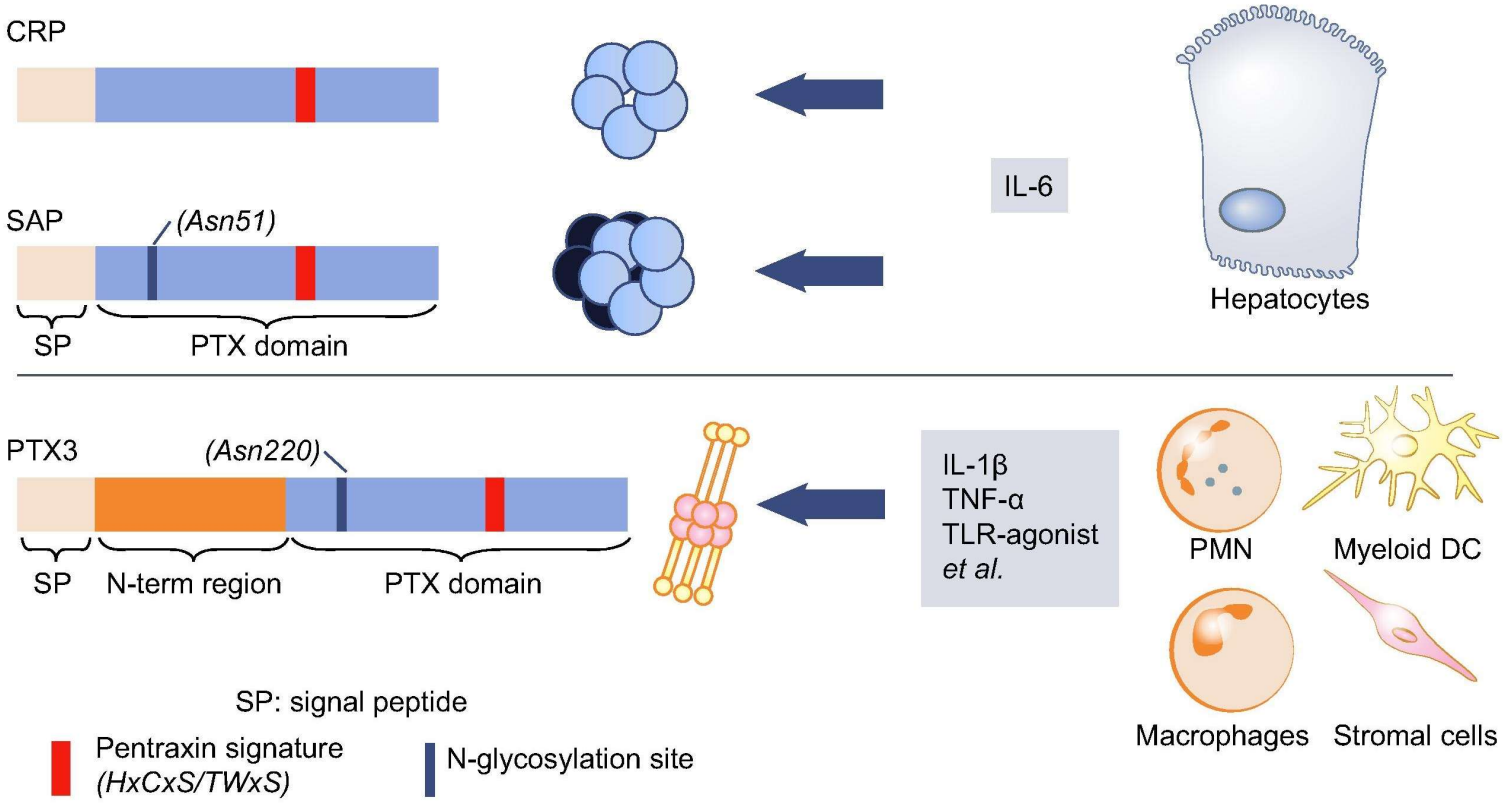
OLTRE ALLA MBL ALTRE COLLETTINE SONO:
Sufactant protein A e D
Sono proteine presenti negli alveoli
coinvolte nella protezione da infezioni polmonari

LE PENTRASSINE

Le pentrassine sono una famiglia di PRR conservate nell'evoluzione e partecipano alla difesa dell'ospite associata a componenti del sistema dell' immunità innata

Si dividono in pentrassine **corte**

pentrassine **lunghe** sulla base della lunghezza della loro struttura primaria



La Proteina C Reattiva (C-Reactive Protein, CRP) è la proteina di fase acuta più caratterizzata essendo stata scoperta nel 1929

Le pentrassine corte sono **Proteine di fase acuta** sono proteine presenti nel plasma sanguigno la cui concentrazione aumenta in presenza di **infiammazione**.

PTX domain

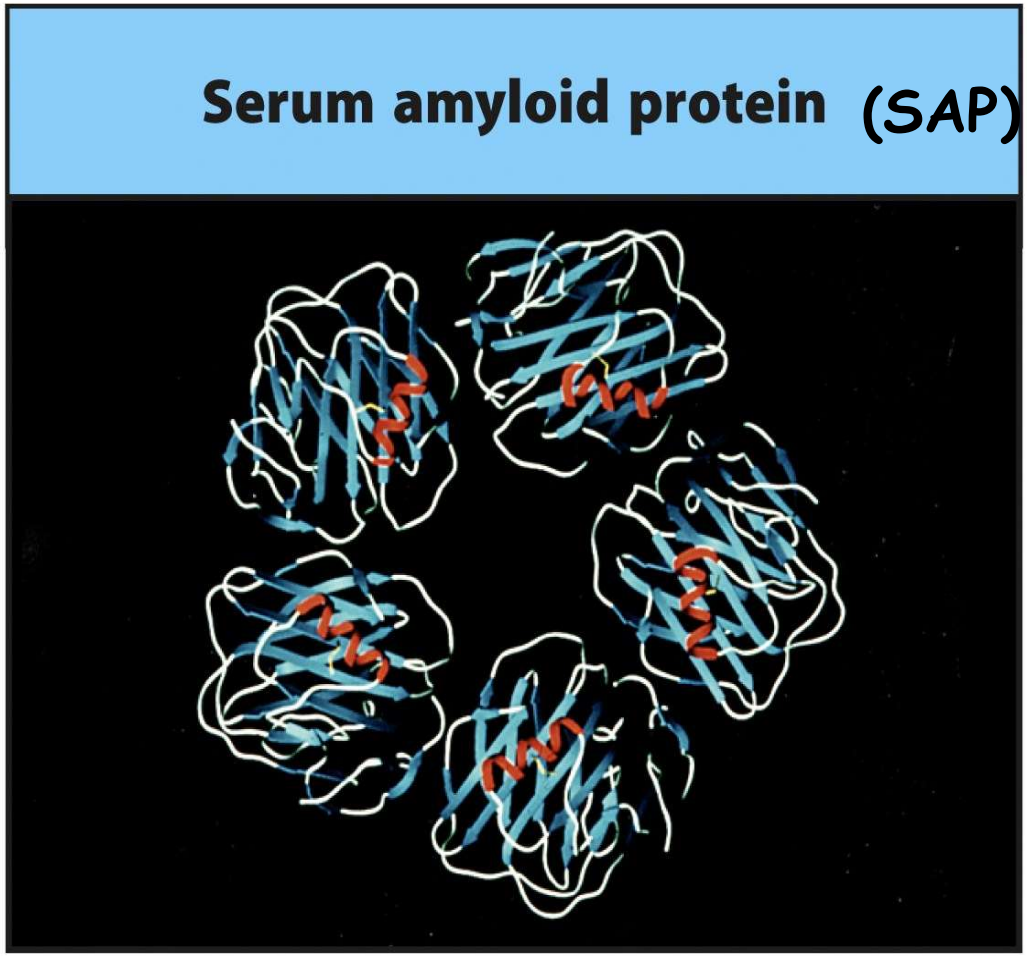
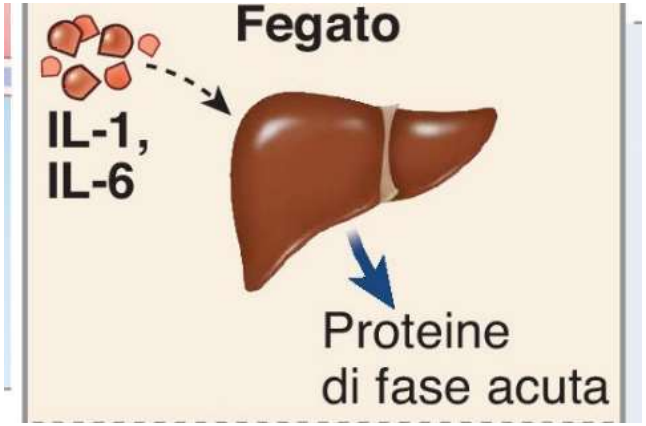


Figure 3.28 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)



CRP e SAP hanno cinque subuntà identiche di 206 aminoacidi, unite non covalentemente a formare una struttura pentamerica

La poteina C reactiva interagisce con polisaccaridi della parete di una serie di patogeni tra cui il **C-**POLISACCARIDE dello *Streptococcus Pneumoniae*

La proteina amiloide serica interagisce con una serie di batteri via LPS e protegge l'organismo dalla tossicità relata a LPS

La regolazione dell'attivazione del complemento è critica per il mantenimento dell'omeostasi

La cascata del complemento viene indotta localmente durante l'infezione, ma la persistenza del patogeno può causare il coinvolgimento di cellule dell'ospite limitrofe. Queste cellule quindi richiedono un efficace sistema di protezione che ne consenta la sopravvivenza.

Controllo dell'attivazione del complemento

I tessuti dell'ospite sono protetti dalla deposizione del complemento dalla presenza di regolatori sulla membrana cellulare o in fase fluida

I FATTORI DI REGOLAZIONE SOLUBILI O DI MEMBRANA AGISCONO A QUATTRO LIVELLI

1 Inibiscono la formazione del C1

2 Inibiscono la formazione o dissociano la C3 convertasi

3 Clivano i componenti del C presenti sulla superficie cellulare

4 Fungono da cofattori del clivaggio

La principale regolazione negativa e' comunque dovuta alla estrema instabilita' in soluzione dei componenti C4b e C3b

Host cells are protected by complement regulatory proteins

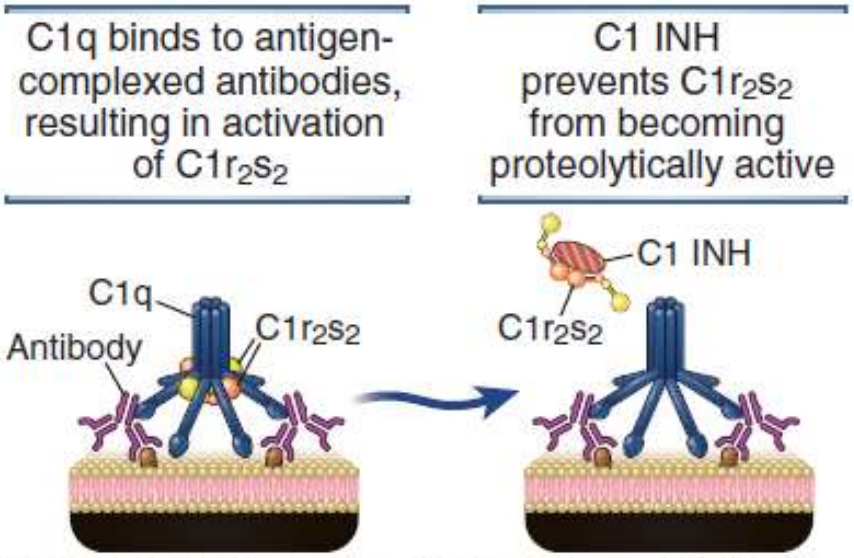
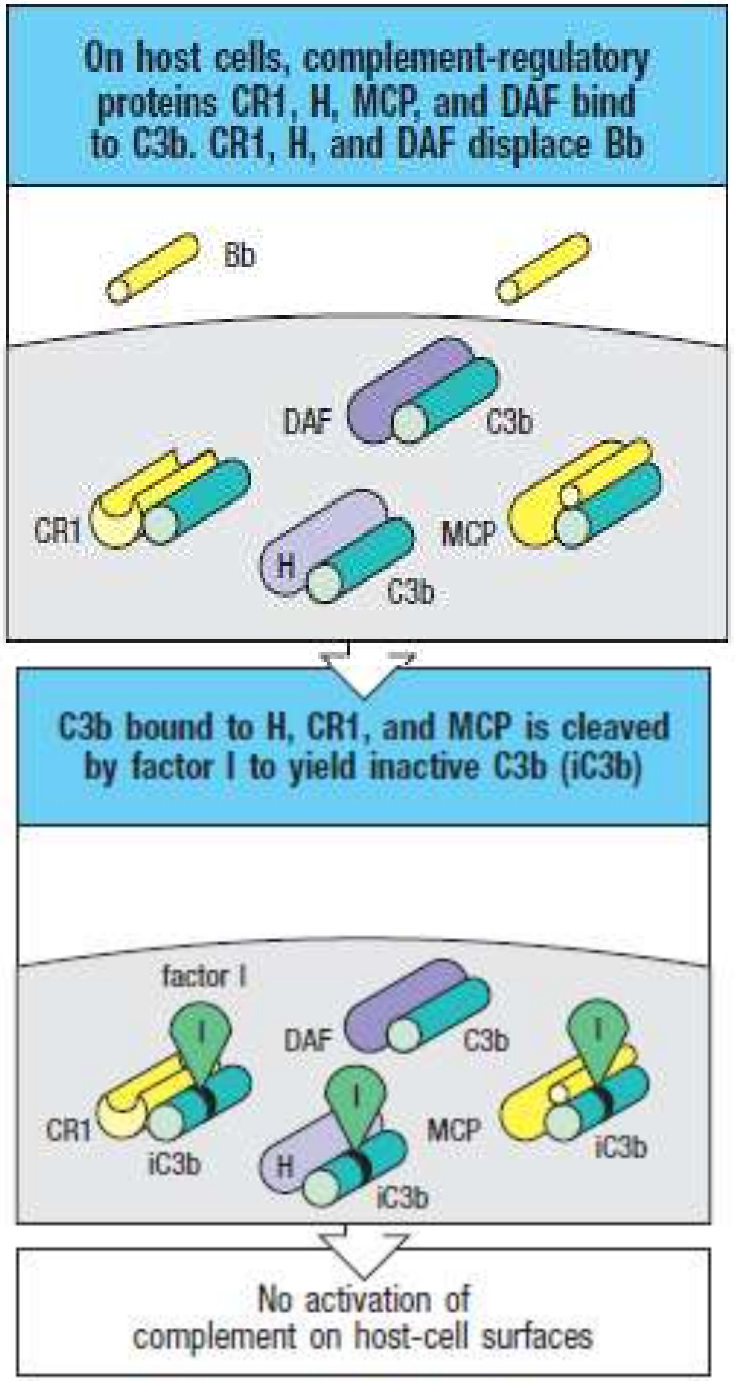


FIGURE 13.13 Regulation of C1 activity by C1 inhibitor.
C1 inhibitor displaces C1r2s2 from C1q and terminates classical pathway activation.



Decay-accelerating factor (DAF or CD55)
Cell-surface complement receptor type 1 (CR1)
Factor H
Membrane cofactor of proteolysis (MCP or CD46)

Regolazione dell'attivazione del complemento (C4bp e fattore H)

Proteine che impediscono il legame tra i componenti della cascata….. e ne promuovono in seguito il riconoscimento da parte dell'enzima **Fattore I**

Il **C4BP (C4 binding protein)** è strutturalmente e funzionalmente correlato al **fattore H** e svolge la stessa funzione che il **fattore H** opera nella via alternativa.

Il **C4BP** blocca sul C4b il sito del legame per il C2a e il **fattore H** blocca sul C3b il sito di legame al Bb prevenendo in questo modo la formazione della C3 convertasi della **via classica** o della **via alternativa.**

Inoltre, quando il C4b è associato al **C4BP**, o il C3b è associato al **fattore H**, questi divengono suscettibili alla degradazione operata dal fattore I

C1INH

- The C1 inhibitor, **C1INH**, promotes dissociation of C1 components.
  - binds in the active site of serine proteases
  - causes $C1r_2s_2$ to dissociate from C1q
  - no further cleavage of C4 or C2 is possible
  - inhibits initiation of classical and lectin complement pathways

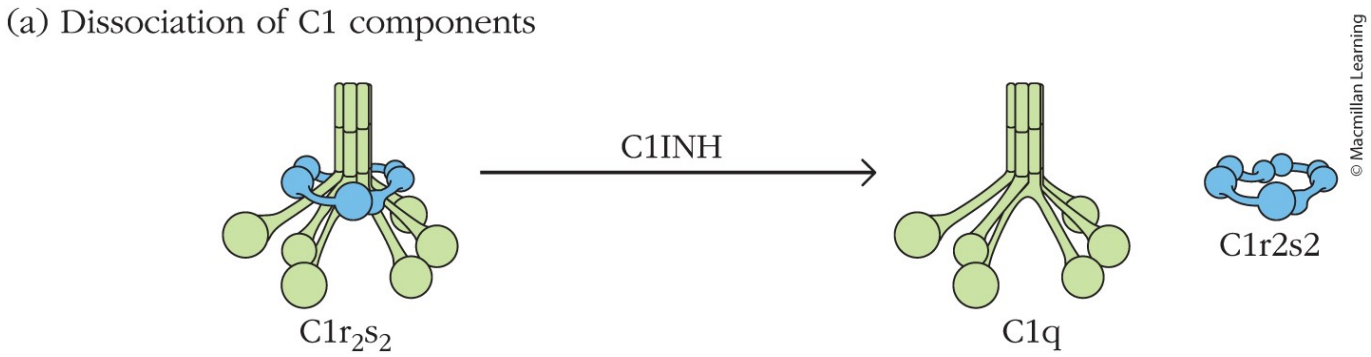


Fig. 5-16 (a)

Regulation of C3 Convertases

- Decay accelerating factors promote decay of C3 convertases.
  - There are several different proteins with similar activities:
    - **DAF (CD55), CR1, C4BP (C4-binding protein)**
    - **Factor H** binds negatively charged cell surface sialic acid and heparin, molecules that are unique to eukaryotic cell surfaces.
- They work to accelerate the decay of C3 convertase on the surface of host cells.

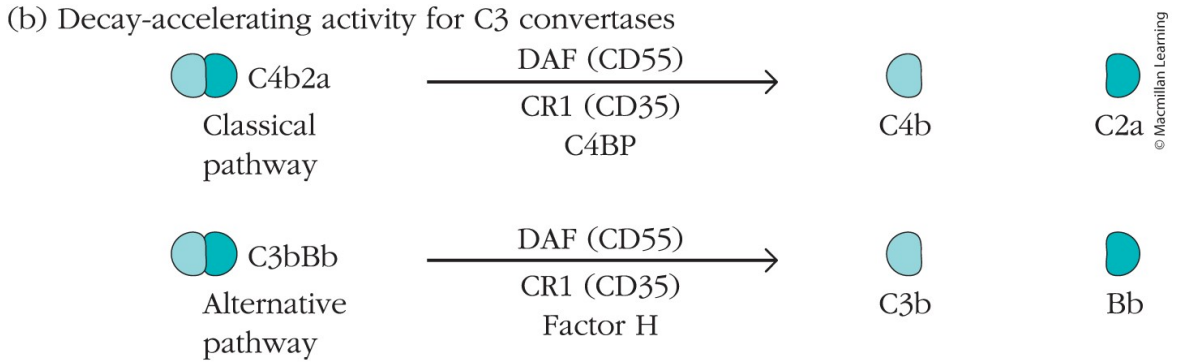


Fig. 5-16 (b)

Factor I

- **Factor I** degrades C3b and C4b. It:
  - is a soluble, constitutively active serine protease,
  - cleaves membrane-associated C3b and C4b into inactive fragments, and
  - requires MCP (CD46) and CR1 (found on membranes of host cells) to function.

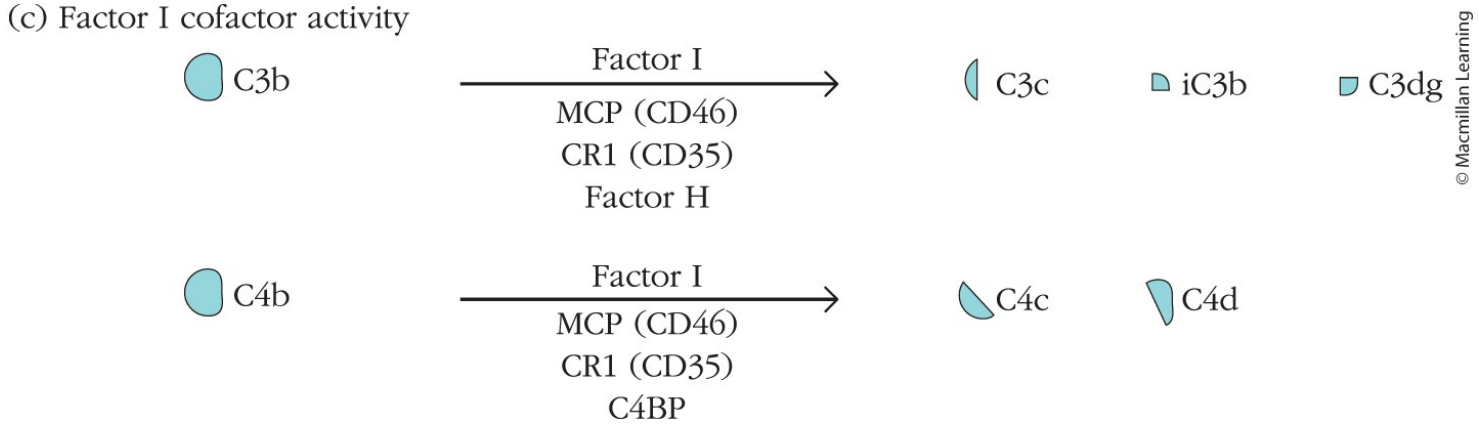


Fig. 5-16 (c)

Proteine regolatorie della via classica e alternativa

Name (symbol)	Role in the regulation of complement activation
C1 inhibitor (C1INH)	Binds to activated C1r, C1s, removing them from C1q
C4-binding protein (C4BP)	Binds C4b, displacing C2b; cofactor for C4b cleavage by I
Complement receptor 1 (CR1)	Binds C4b, displacing C2b, or C3b displacing Bb; cofactor for I
Factor H (H)	Binds C3b, displacing Bb; cofactor for I
Factor I (I)	Serine protease that cleaves C3b and C4b; aided by H, MCP, C4BP, or CR1
Decay-accelerating factor (DAF)	Membrane protein that displaces Bb from C3b and C2b from C4b
Membrane cofactor protein (MCP)	Membrane protein that promotes C3b and C4b inactivation by I
CD59 (protectin)	Prevents formation of membrane-attack complex on autologous or allogenic cells. Widely expressed on membranes

Figure 2-36 Immunobiology, 6/e. (© Garland Science 2005)

Relevant functions mediated by complement components

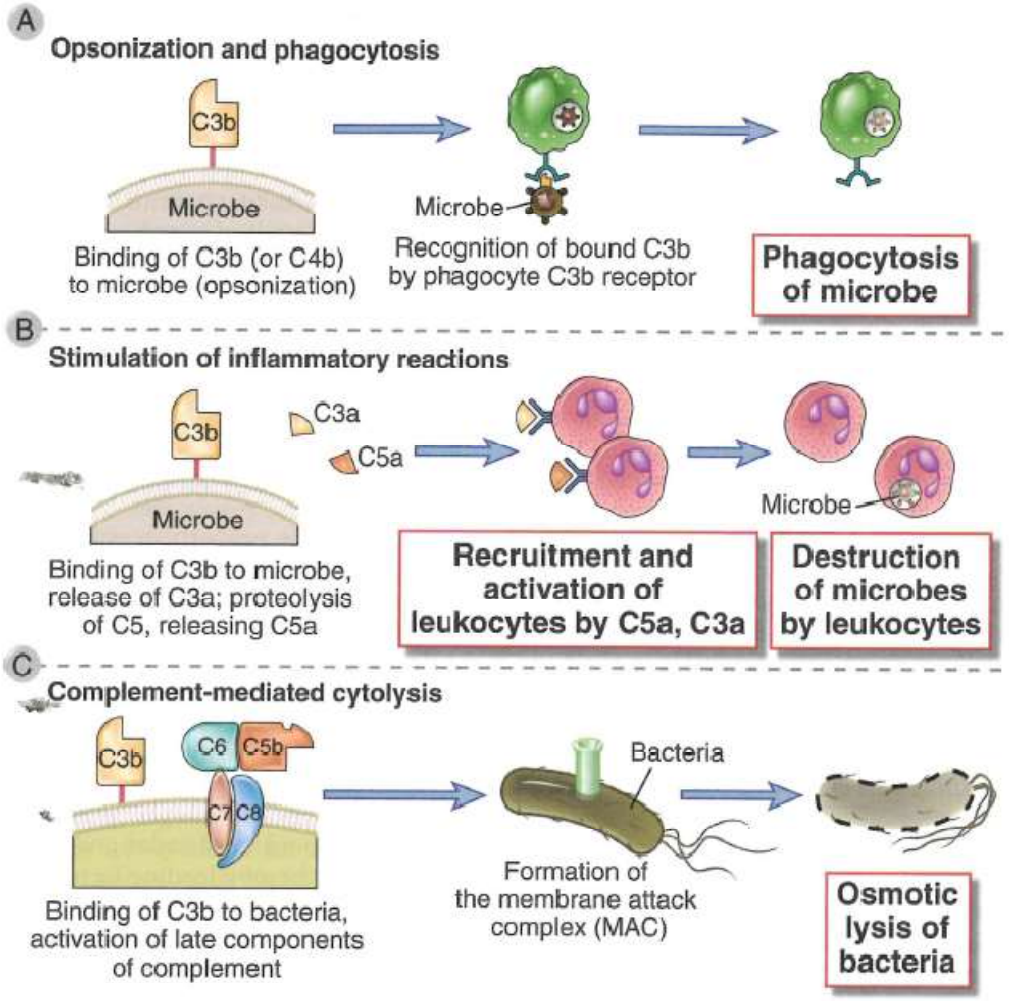
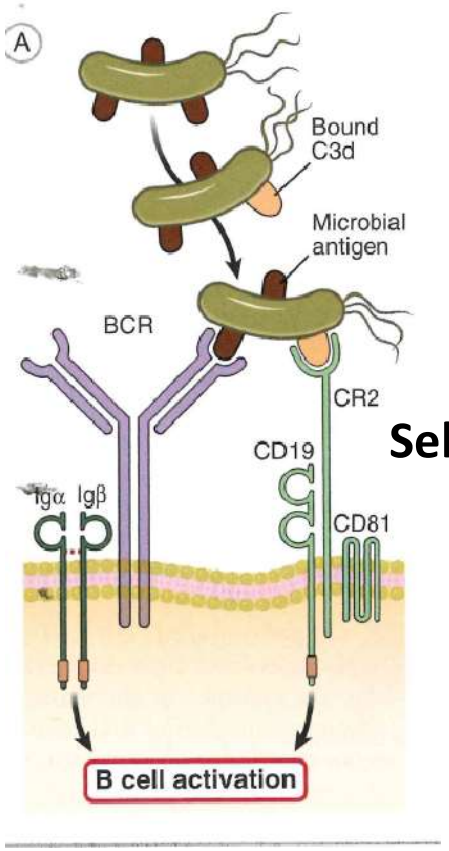
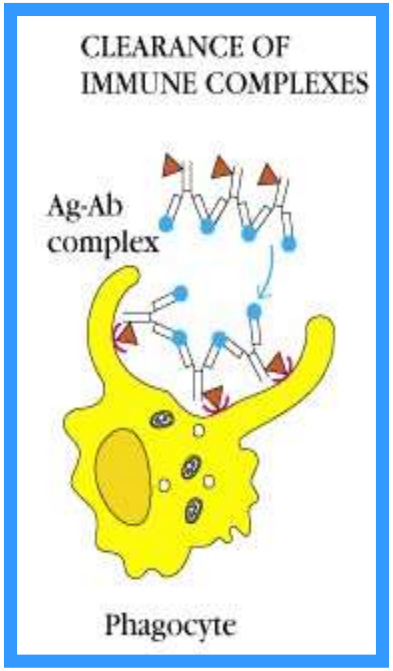


FIGURE 13-17 Functions of complement. The major functions of the complement system in host defense are shown. Cell-bound C3b is an opsonin that promotes phagocytosis of coated cells **(A)**; the proteolytic products C5a, C3a, and (to a lesser extent) C4a stimulate leukocyte recruitment and inflammation **(B)**; and the MAC lyses cells **(C)**.

B cell activation





Selection process during affinity maturation

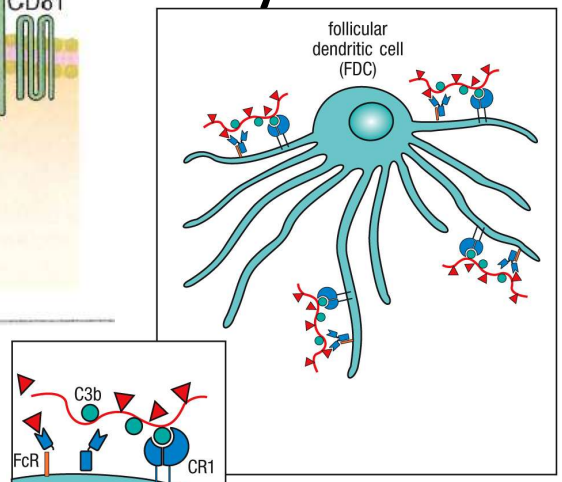
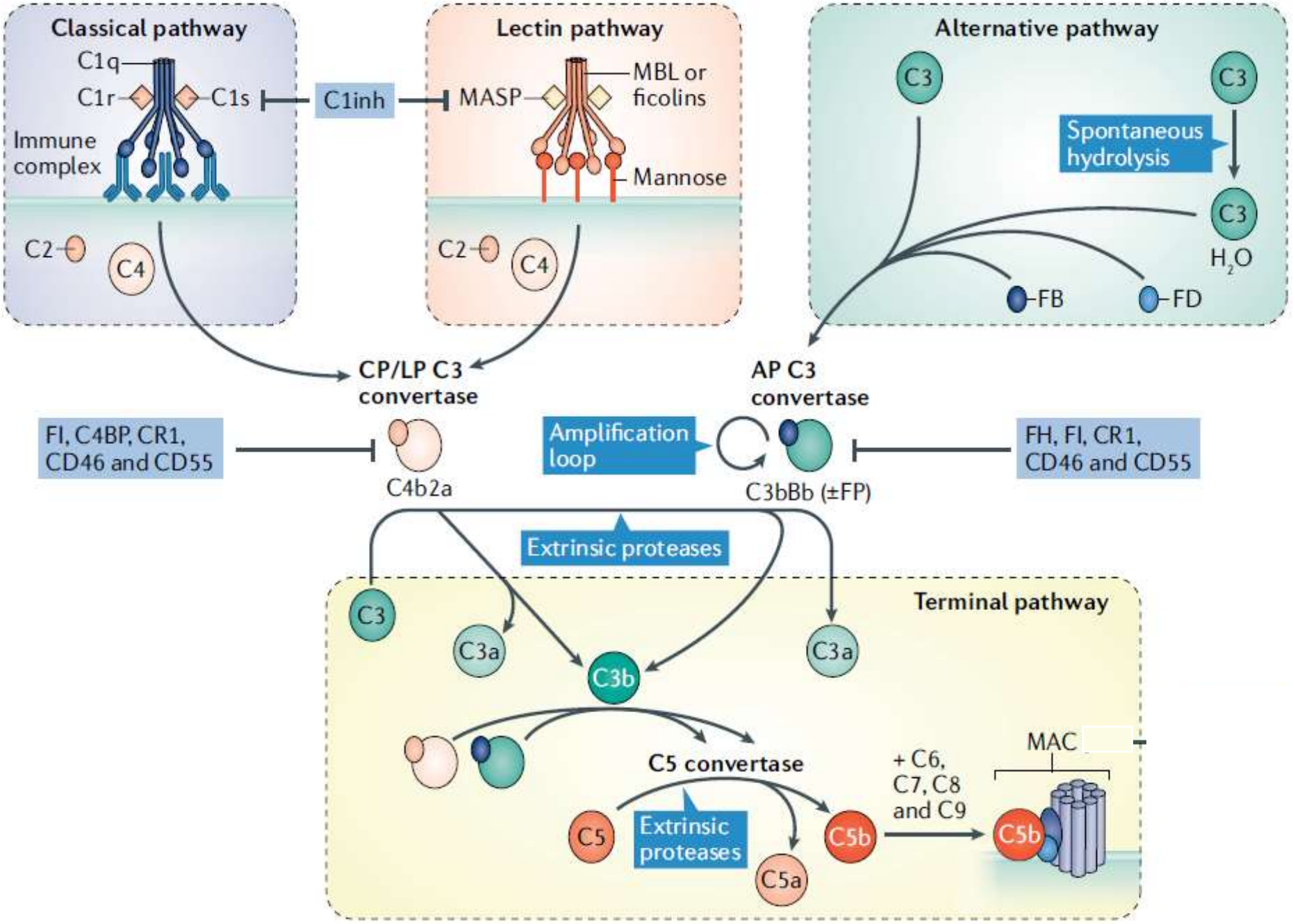
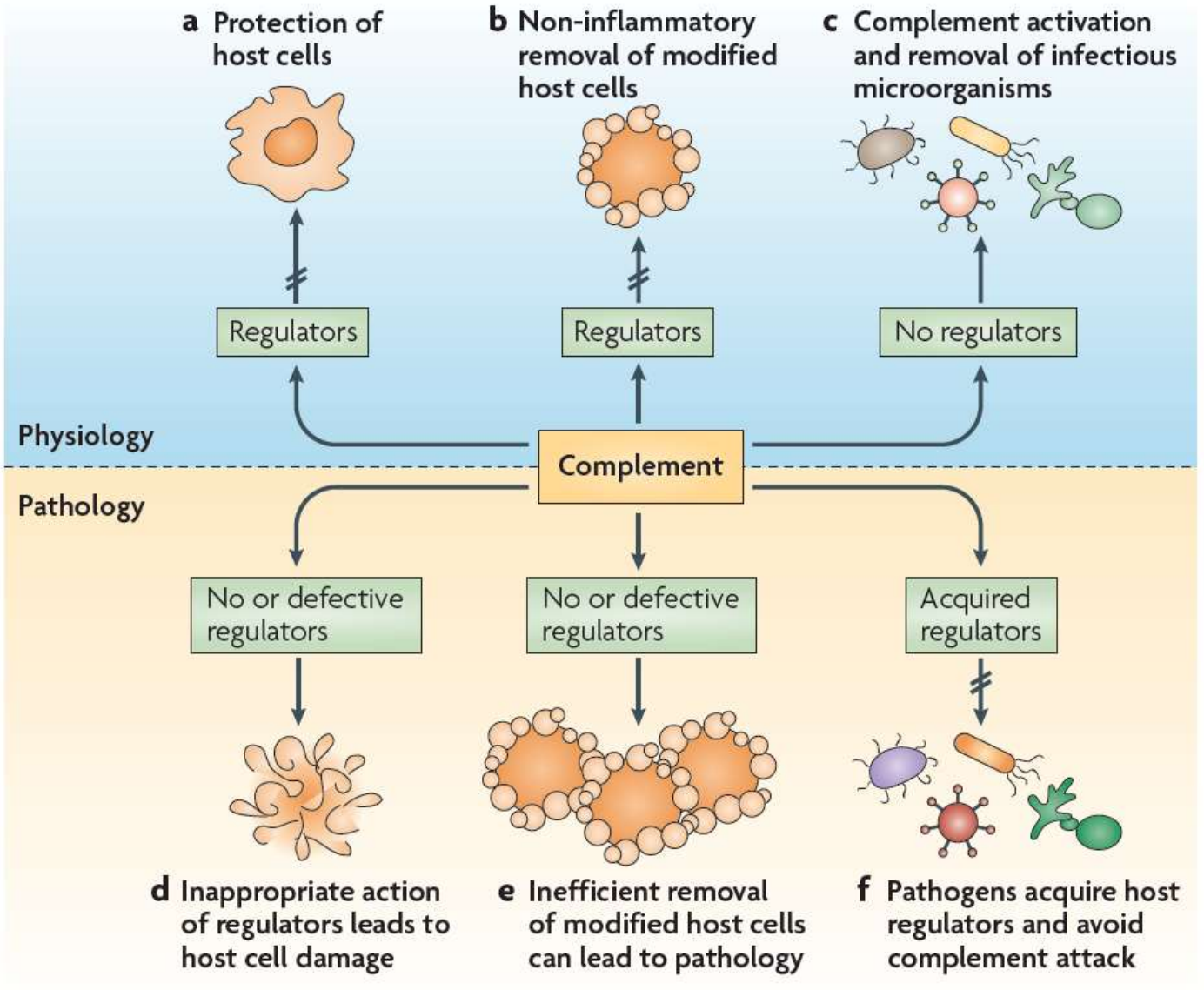


Figure 10.16 (part 3 of 3) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Meccanismi di attivazione e regolazione della cascata del complemento

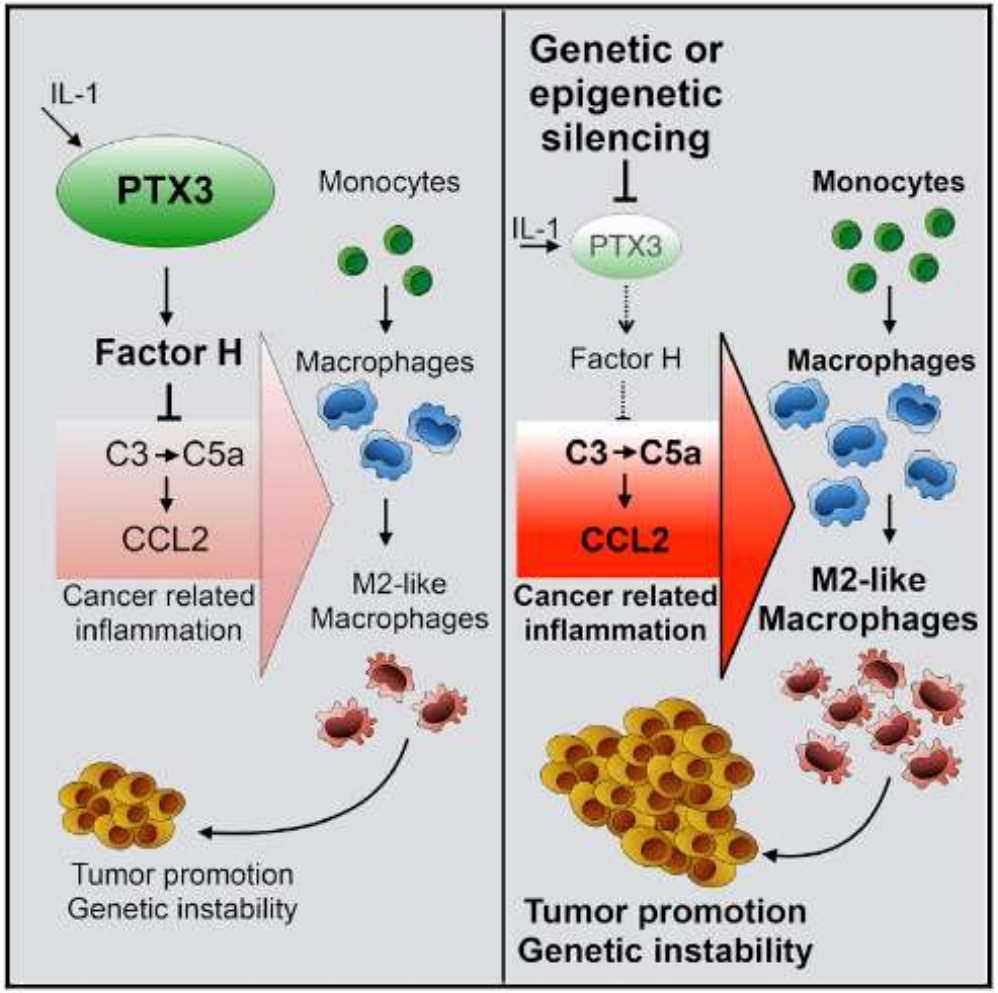


Benefici e rischi del complemento



PTX3 Is an Extrinsic Oncosuppressor Regulating Complement-Dependent Inflammation in Cancer

Graphical Abstract



Authors

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In Brief

PTX3 deficiency triggers Complement-dependent tumor-promoting inflammation, with enhanced tumor burden, macrophage infiltration, cytokine production, angiogenesis, and genetic instability, revealing the role of this innate immunity mediator as an extrinsic oncosuppressor.

The authors suggest that PTX3 deficiency unleashes Complement-dependent, C5a-mediated tumor-promoting inflammation, because of defective recruitment of the negative regulator Factor H

C1, C2, C4, C3, Factor P, MAC complex deficiencies

- No Complement activation and no elimination of Immunocomplexes: Vasculitis, Glomerulonefritis, LES
- No membrane attack complex formed: Susceptibility to Neisserial infection

Riassunto degli effetti biologici mediati dal complemento

- Il Complesso di attacco alla membrana (MAC, C5b-9) promuove la lisi cellulare.

- C5a e in minor misura C3a e C4a, promuovono la risposta infiammatoria inducendo

- *degranulazione di mastociti, basofili ed eosinofili*
- *richiamo e attivazione di leucociti nella sede dell'infiammazione*

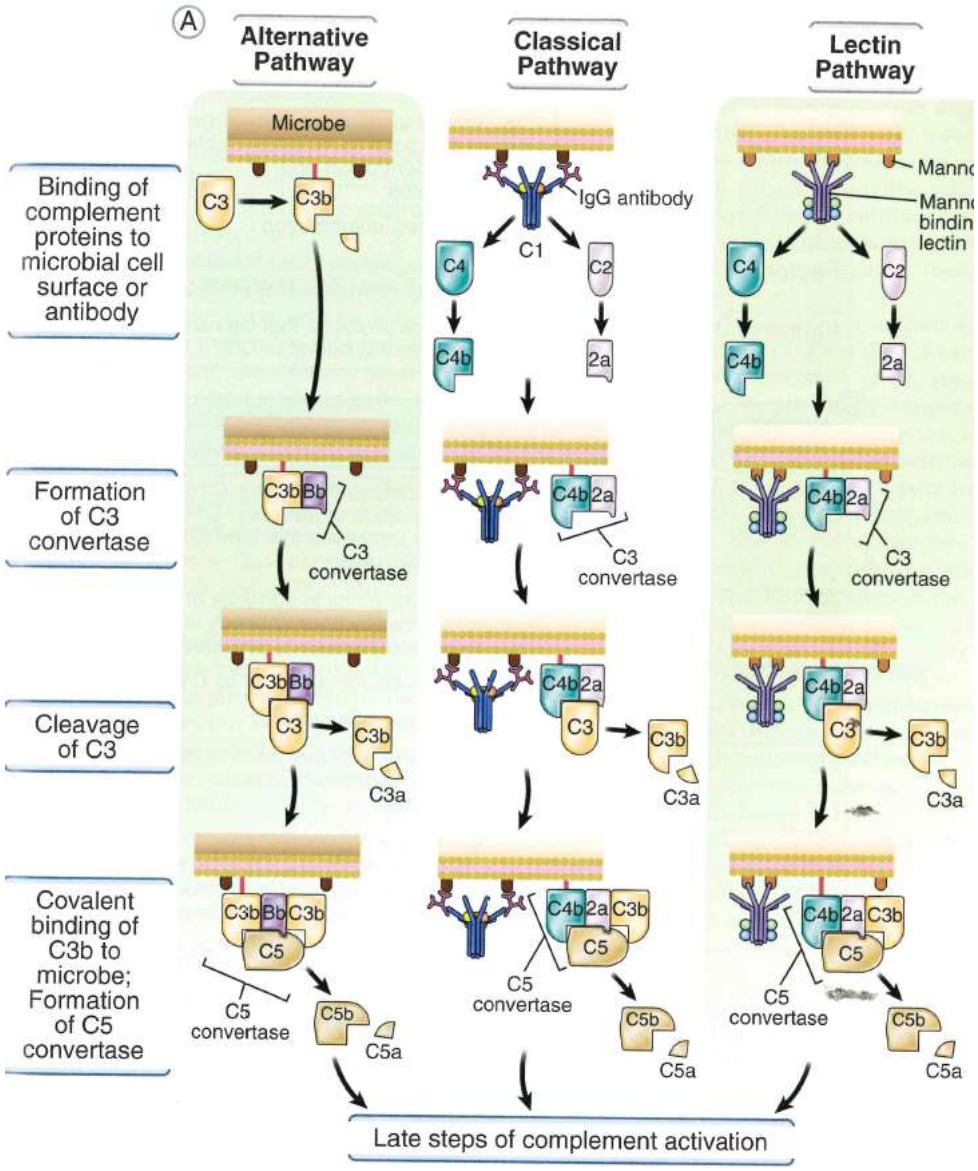
- C3b,C4b e iC3b opzonizzano antigeni corpuscolati potenziando la loro fagocitosi tramite il recettore per il complemento di tipo 1 (CR1) e CR3 e CR4

- C3d si lega al recettore CR2 espresso da linfociti B stimolando la risposta B

-Immunocomplessi rivestiti da iC3b e C3dg vengono intrappolati da cellule follicolari dendritiche (FDC)

- C3b media la solubilizzazione e rimozione degli immunocomplessi

Complement is activated by three major pathways



C1qrs binds Fc portion of IgG and IgM

BOUND TO ANTIGEN

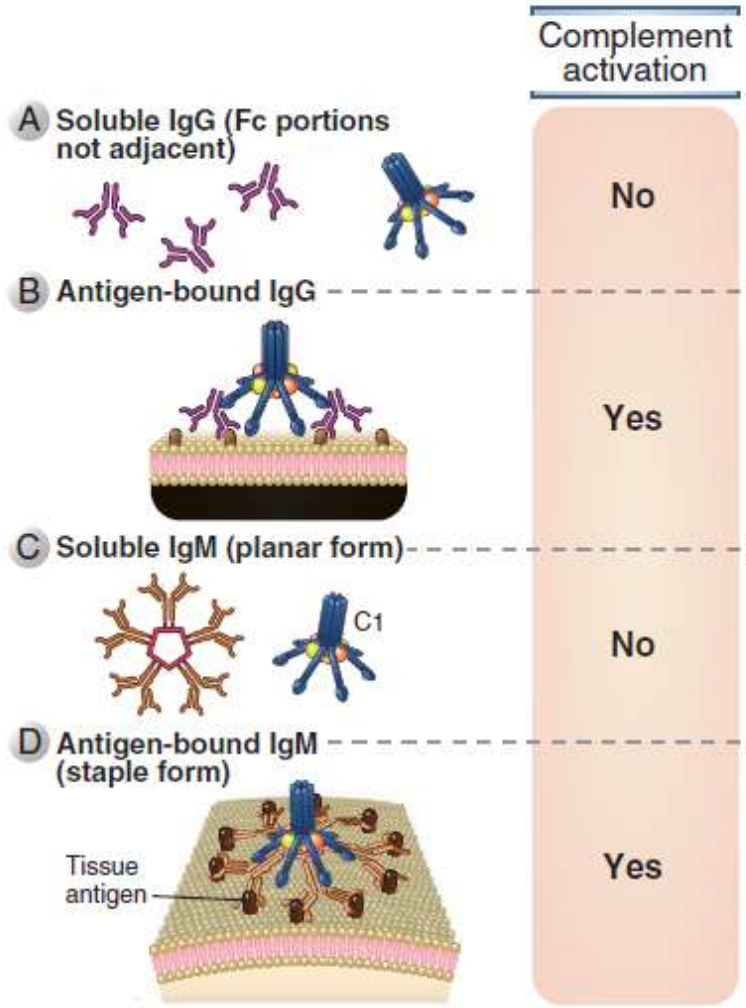


FIGURE 13.11 C1 binding to the Fc portions of IgM and IgG. C1 must bind to two or more Fc portions to initiate the complement cascade. Soluble IgG molecules will not activate C1 because each IgG has only one Fc region **(A)**, but after binding to cell surface antigens, adjacent IgG Fc portions can bind and activate C1 **(B)**. The Fc portions of soluble pentameric IgM are not accessible to C1 **(C)**. After IgM binds to surface-bound antigens, it undergoes a shape change that permits C1 binding and activation **(D)**.

The Alternative Properdin-Activated Pathway

- **Properdin** can directly bind to a surface.
- Then, C3b and Factor B are recruited.
- Factor D is recruited and cleaves Factor B into Bb.
- The resultant C3bBb is an active C3 convertase.
- Subsequent steps are identical to alternative tickover pathway.

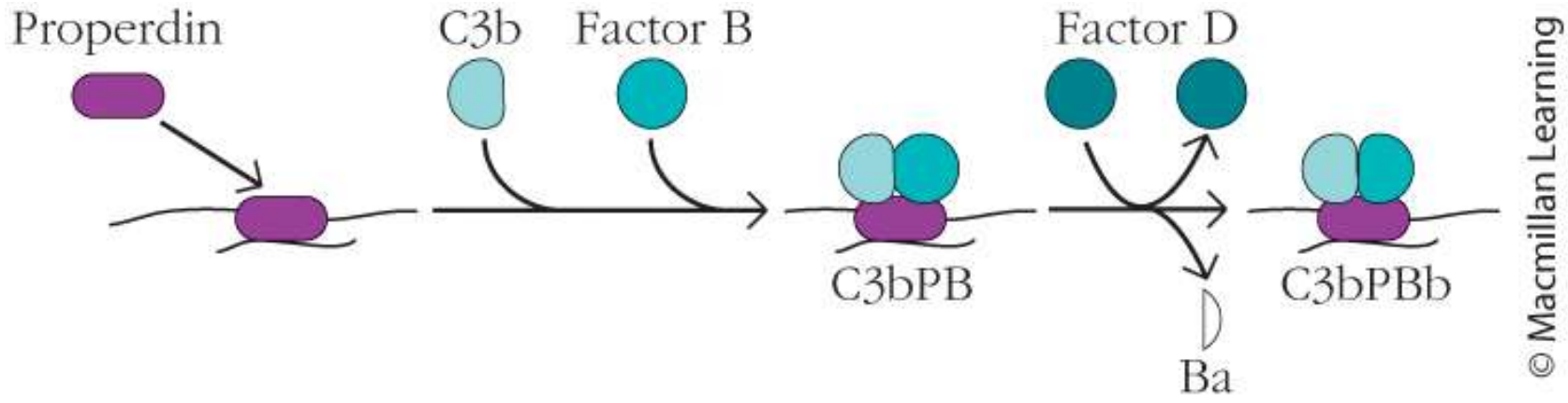
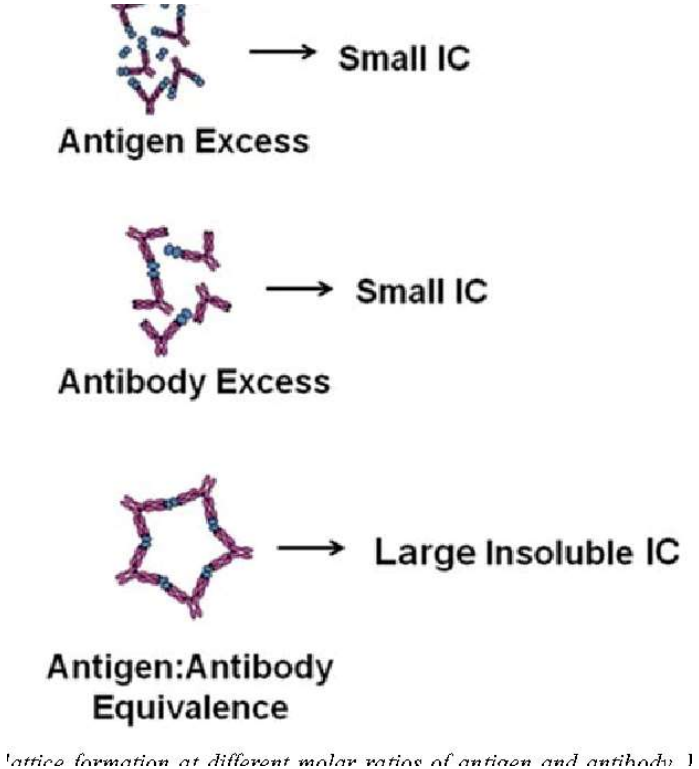


Fig. 5-9

RIMOZIONE DEI COMPLESSI IMMUNI MEDIATA DA CR1



lattice formation at different molar ratios of antigen and antibody.]

•In Ab excess or in Ag excess, low lattice formation occurs and more soluble complexes are formed.

•However, when there is both sufficient Ag and sufficient Ab (equivalence), the combination of Ag and Ab proceeds until large aggregates called immunocomplexes (IC) are formed, which are insoluble and precipitate.