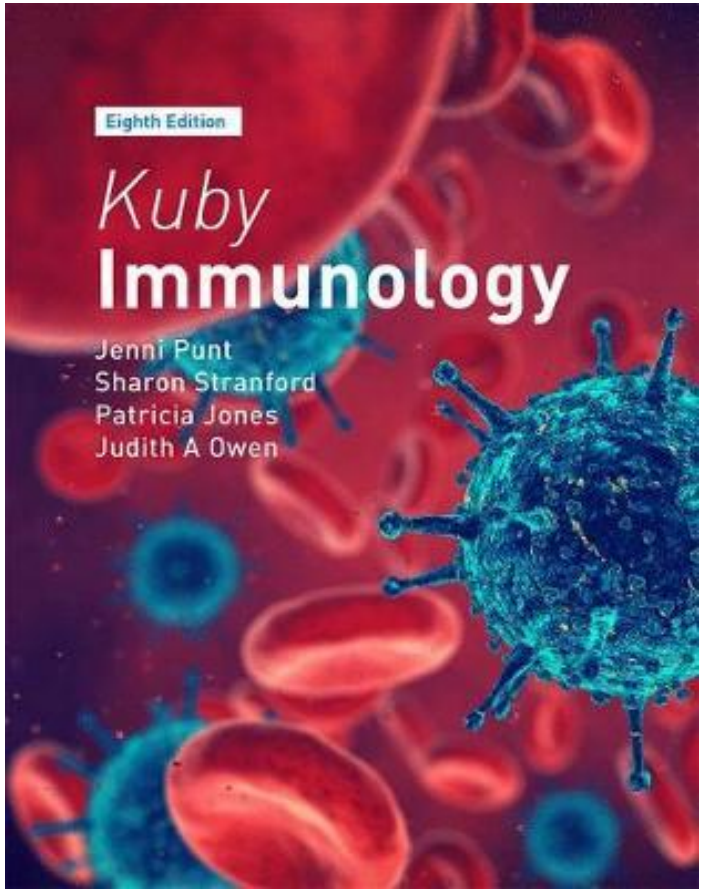
Immunologie 1: Introduction to the Immune System



Na het bestuderen van de behandelde stof kan de student:

1. De basis van vaccinatie beschrijven
2. De bloedcellen en organen van het immuunsysteem herkennen en beschrijven
3. De componenten en karakteristieken van de twee lijnen van afweer waaruit het aangeboren immuunsysteem bestaat identificeren en beschrijven
4. Het basisprincipe van PRRs en PAMPs en effect van activatie beschrijven
5. Cellen en weefsels koppelen aan de effector functies van het aangeboren immuunsysteem
6. Onderdelen van het aangeboren en verworven immuunsysteem koppelen en beschrijven hoe het aangeboren immuunsysteem helpt een effectieve adaptieve immuunrespons op te wekken voor een specifiek pathogeen
7. De drie routes van het complementsysteem en effecten van complementactivatie beschrijven en de gevolgen van een immuundeficiëntie van complement componenten inzichtelijk maken
8. Het gedrag van het aangeboren en verworven immuunsysteem voor en tijdens een immuunrespons visualiseren

Inflammatory responses

Inflammatory responses

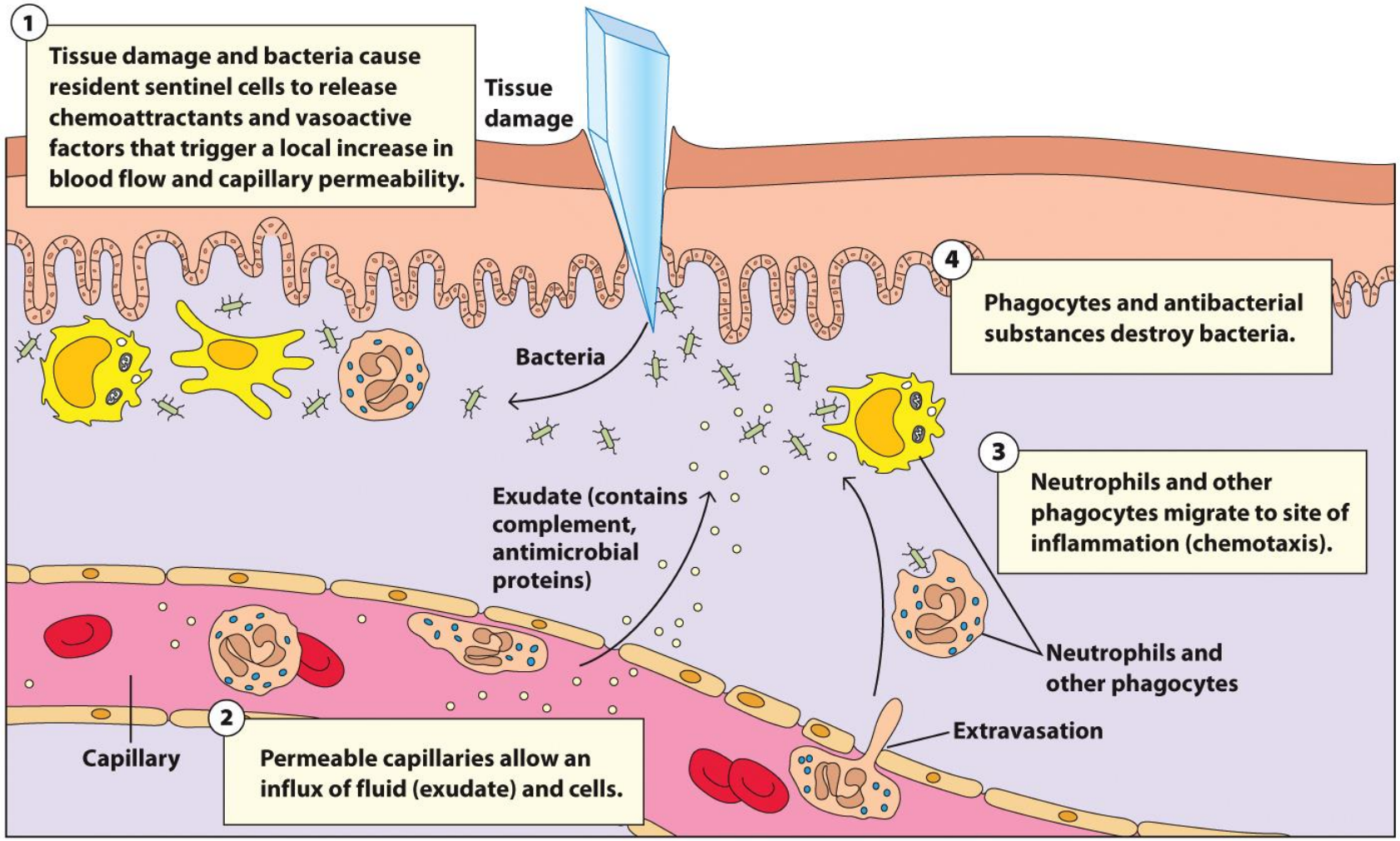


Figure 4-22
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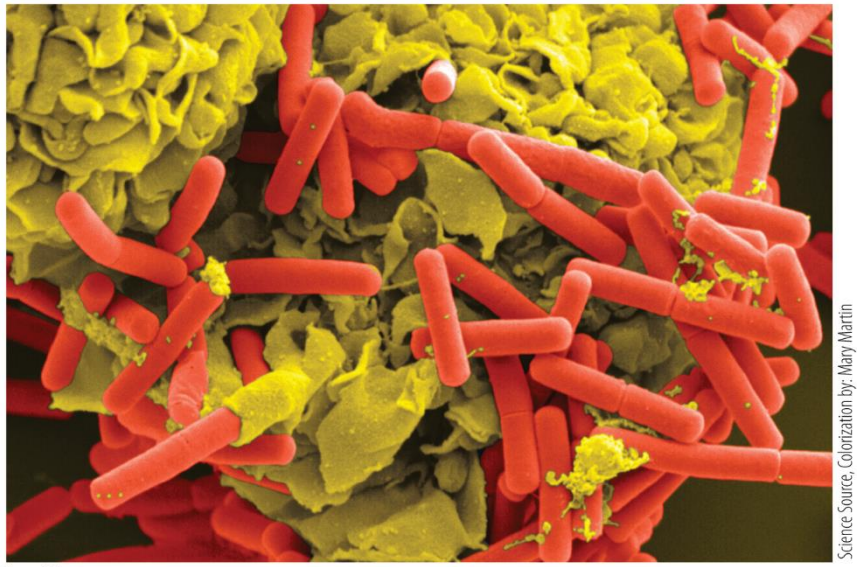
Phagocytosis

Phagocytosis

- Defined as **engulfment** and **internalization** of materials such as microbes for their clearance and destruction



Science Source, Colorization by: Mary Martin

Figure 4-18a
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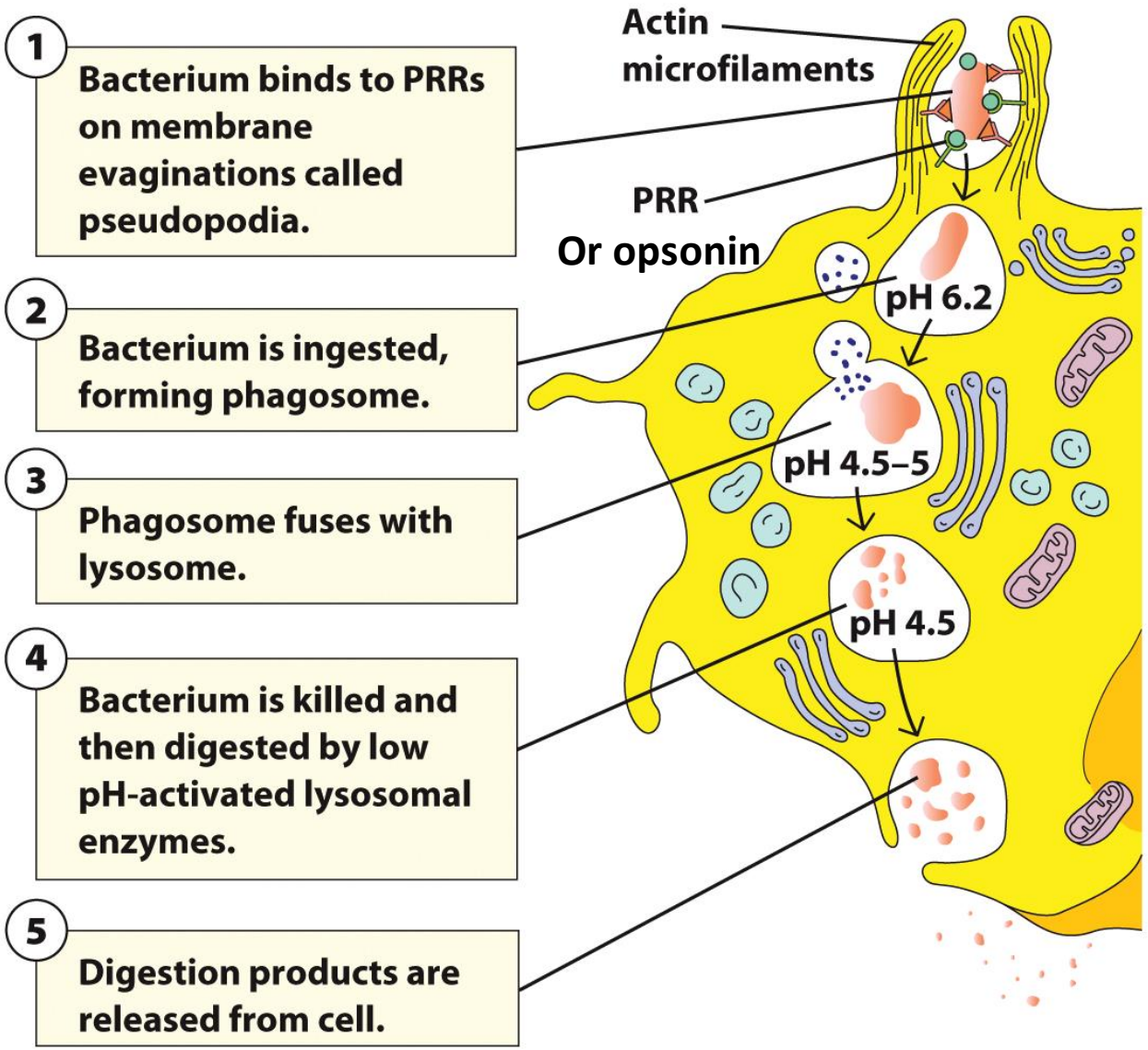

Figure 4-18b
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Phagocytosis

- Microbes are recognized by receptors on phagocytes
  - May recognize soluble **opsonin** protein bound to microbes

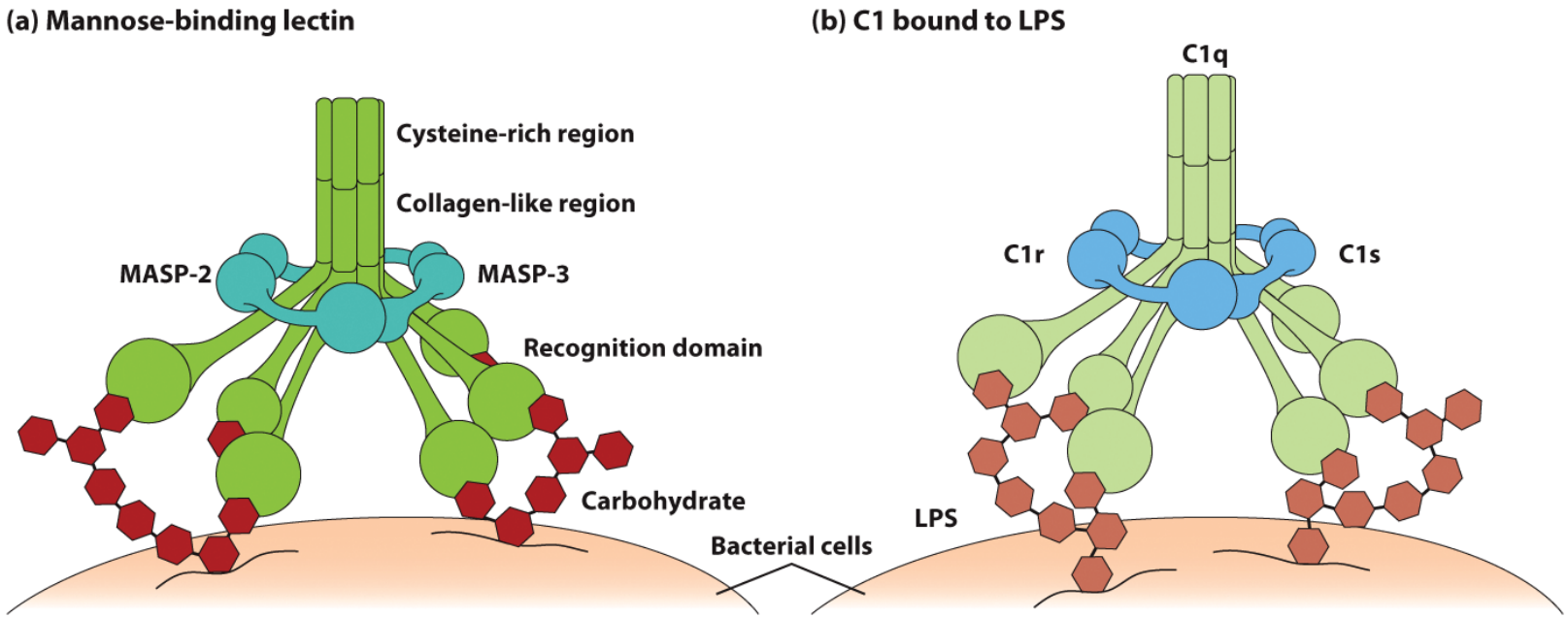

Figure 4-19
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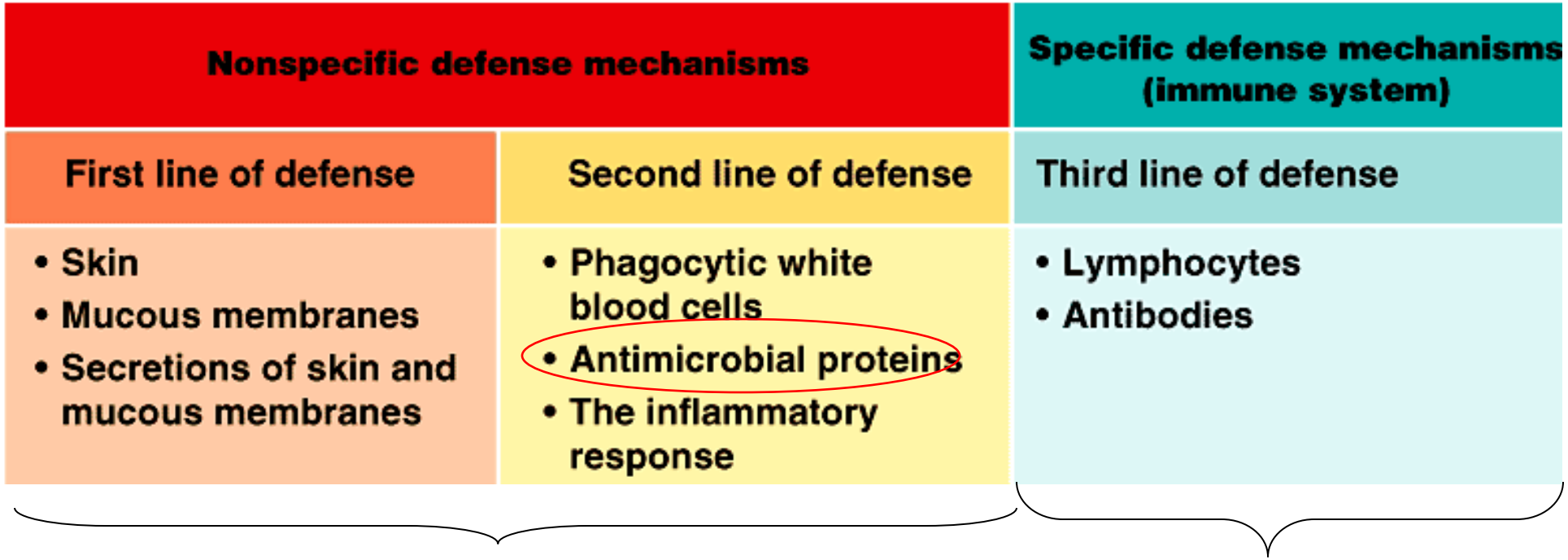
Het immuunsysteem biedt bescherming tegen infecties

Indeling immuunsysteem:



Overzicht van de immuunrespons

- https://www.youtube.com/watch?v=Nw27_jMWw10 (Complement wordt nog behandeld)
- https://www.youtube.com/watch?v=zQGOcOUBi6s

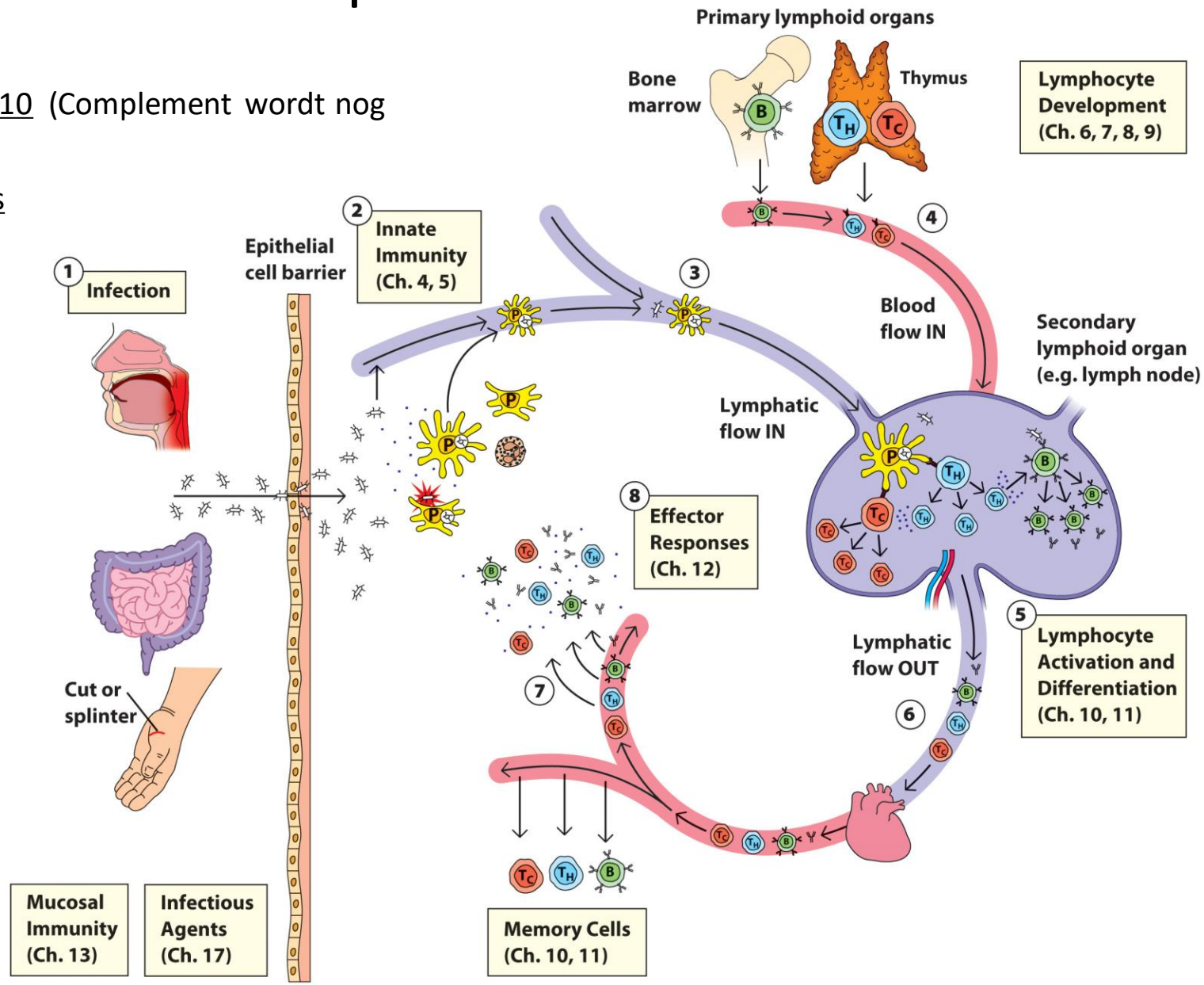


Figure 1-7
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Inleiding complement

- Ontdekt in 1894 door Jules Bordet

Jules Bordet (1870-1961)

- Schaap antiserum + *Vibrio cholerae* → lysis bact.
  Verhit schaap antiserum + *Vibrio cholerae* → geen lysis
  Verhit schaap antiserum + normaal schaap serum +*Vibrio cholerae* → lysis

- Conclusie: antilichamen alleen zijn niet genoeg voor lysis, er is iets "complementairs" nodig: **complement**! Complement is hittegevoelig (kapot na 1 uur verhitting bij 56ºC).

Punt • Stranford • Jones • Owen

Kuby Immunology

EIGHTH EDITION

Lecture PowerPoint

CHAPTER 5

The Complement System

The complement system

- Group of serum proteins circulating in inactive form
- Once activated, multiple possible outcomes
  - Target cell membrane **lysis**
  - **Chemotaxis**
  - **Opsonization** to enhance phagocytosis
  - **Inflammation**

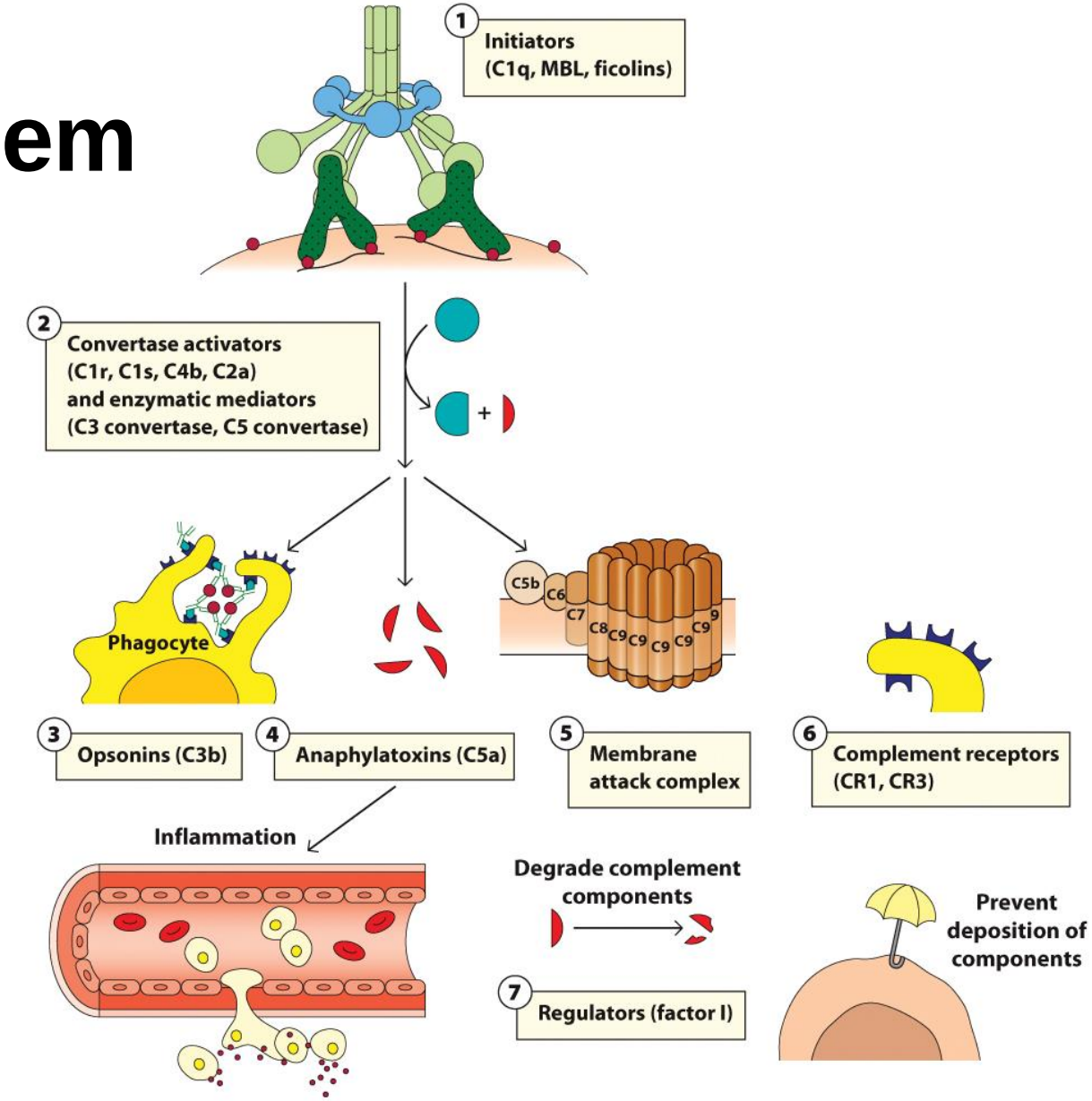

Figure 5-1
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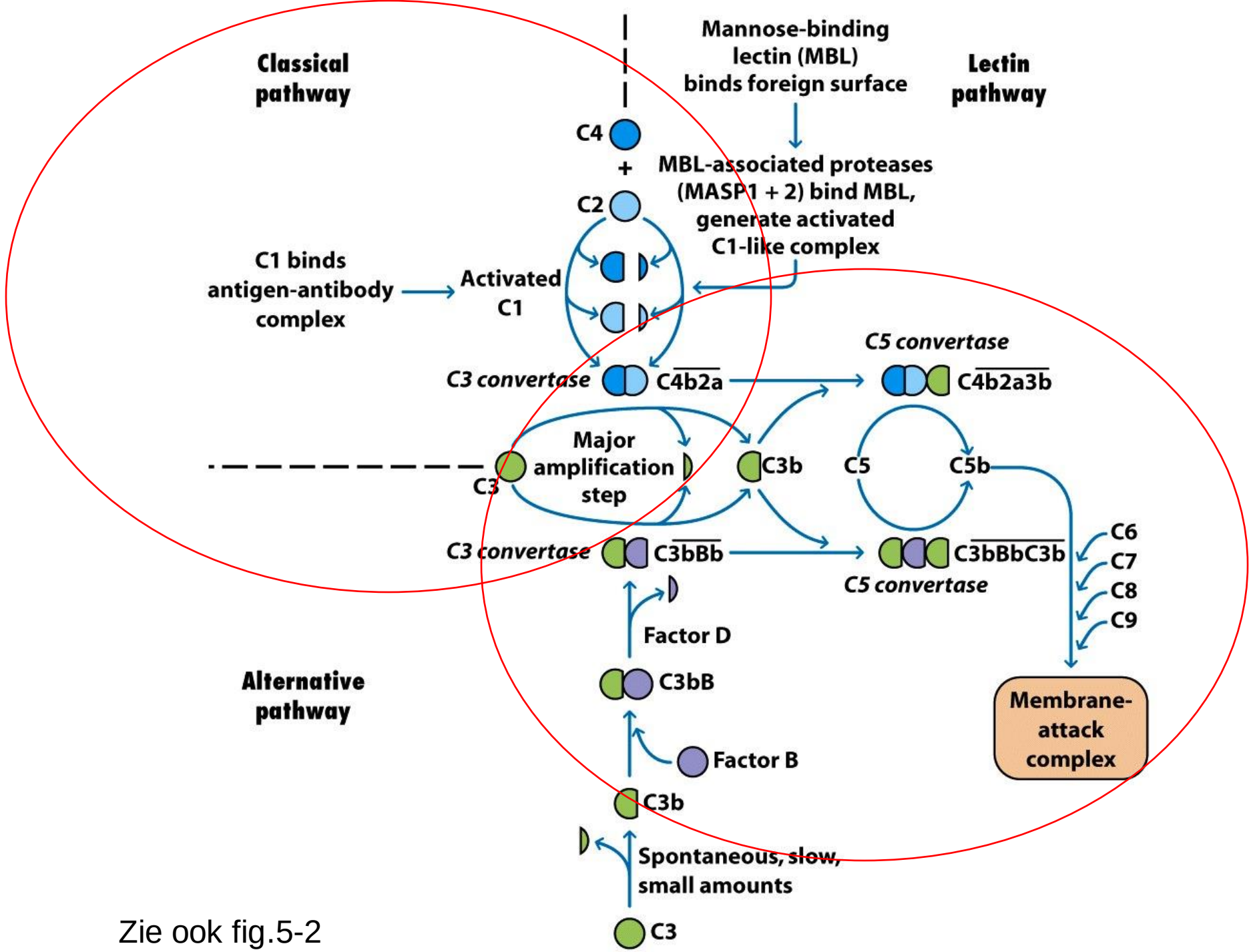
Overzicht van de 3 routes van het complement



Zie ook fig.5-2

The complement system

- Three activation pathways exist
  - **Classical**
  - **Lectin**
  - **Alternative**

- All three pathways generate **C3b**, an important, multifunctional complement protein

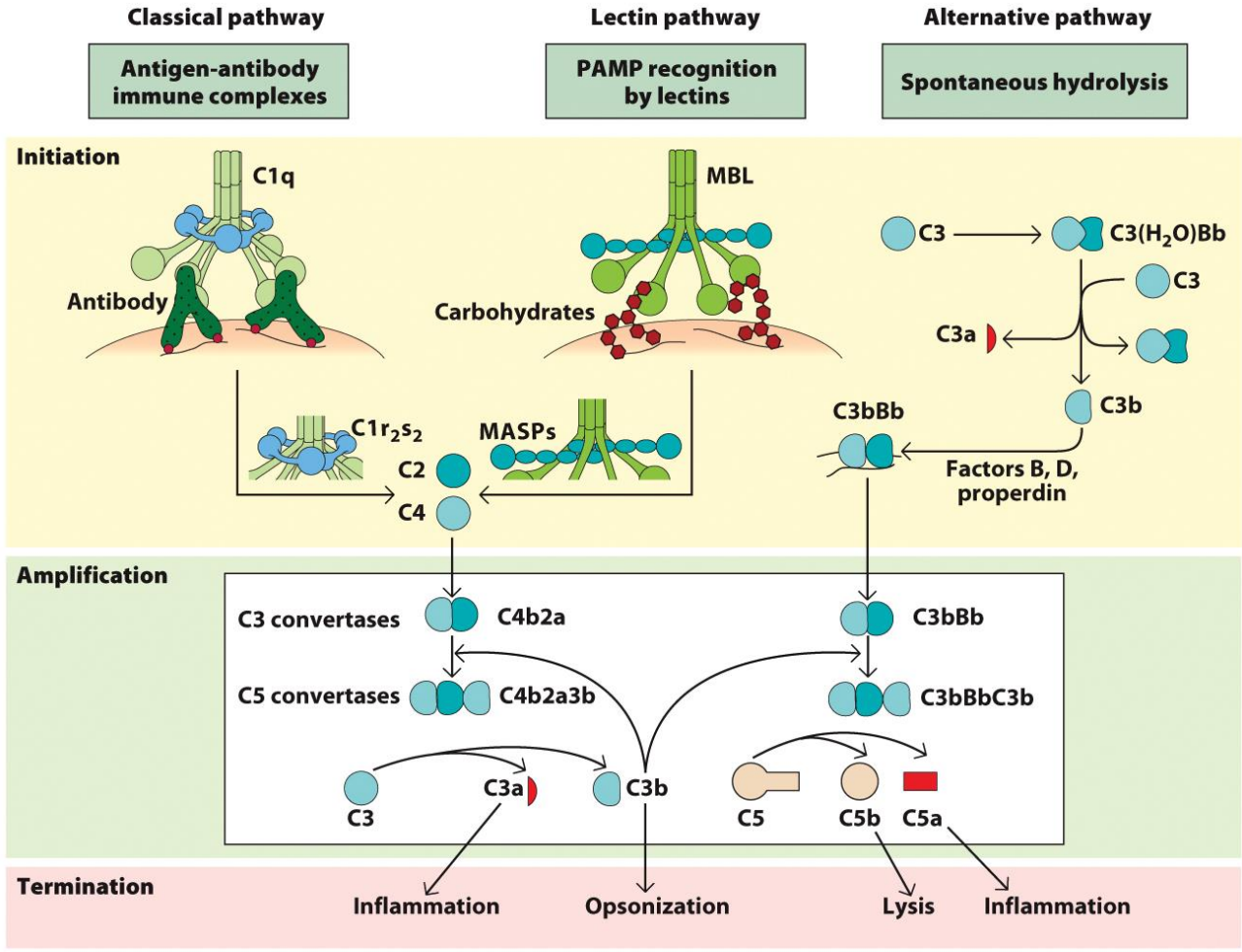


Figure 5-2
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Mannosebindend lectine (MBL)

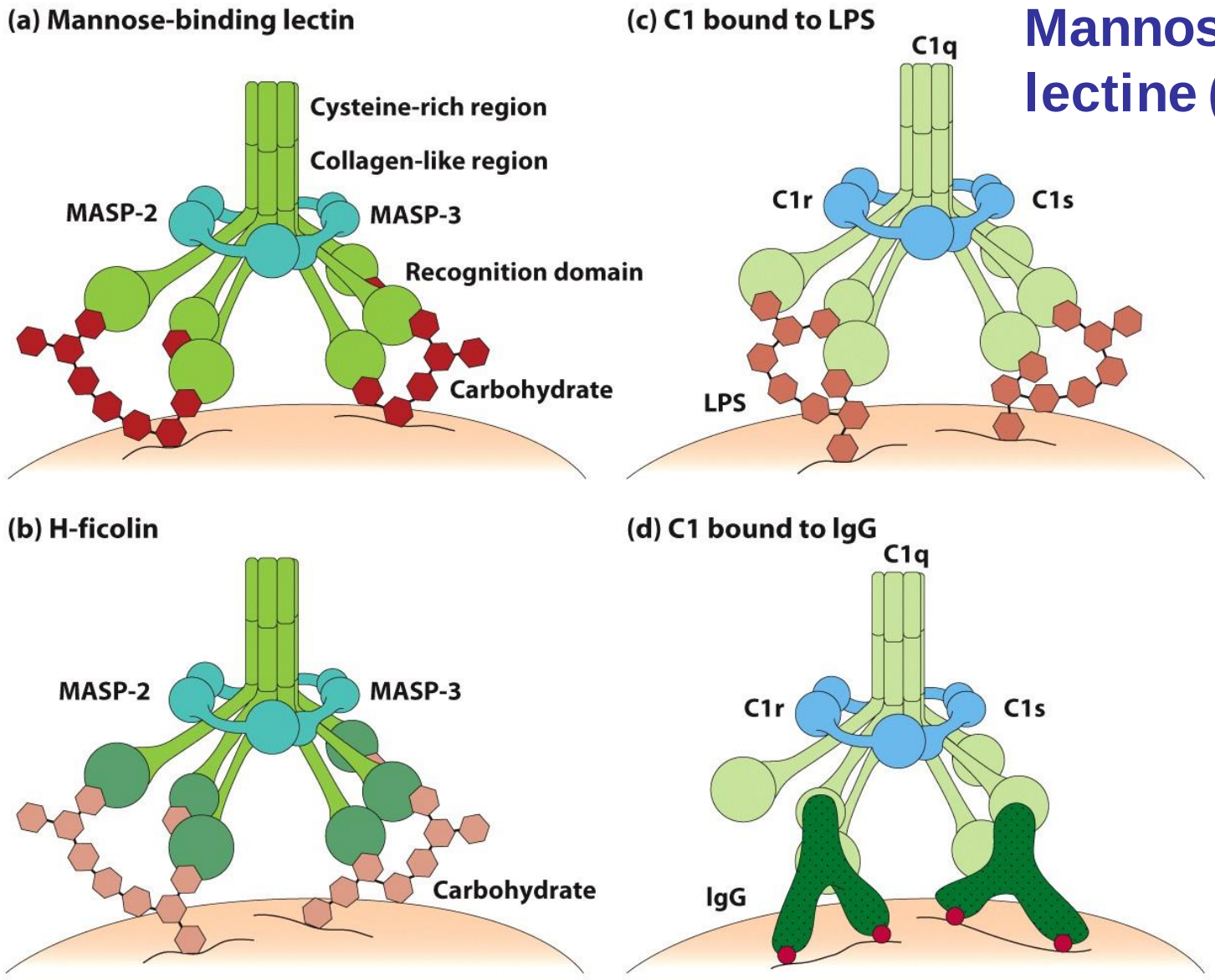

Figure 5-7
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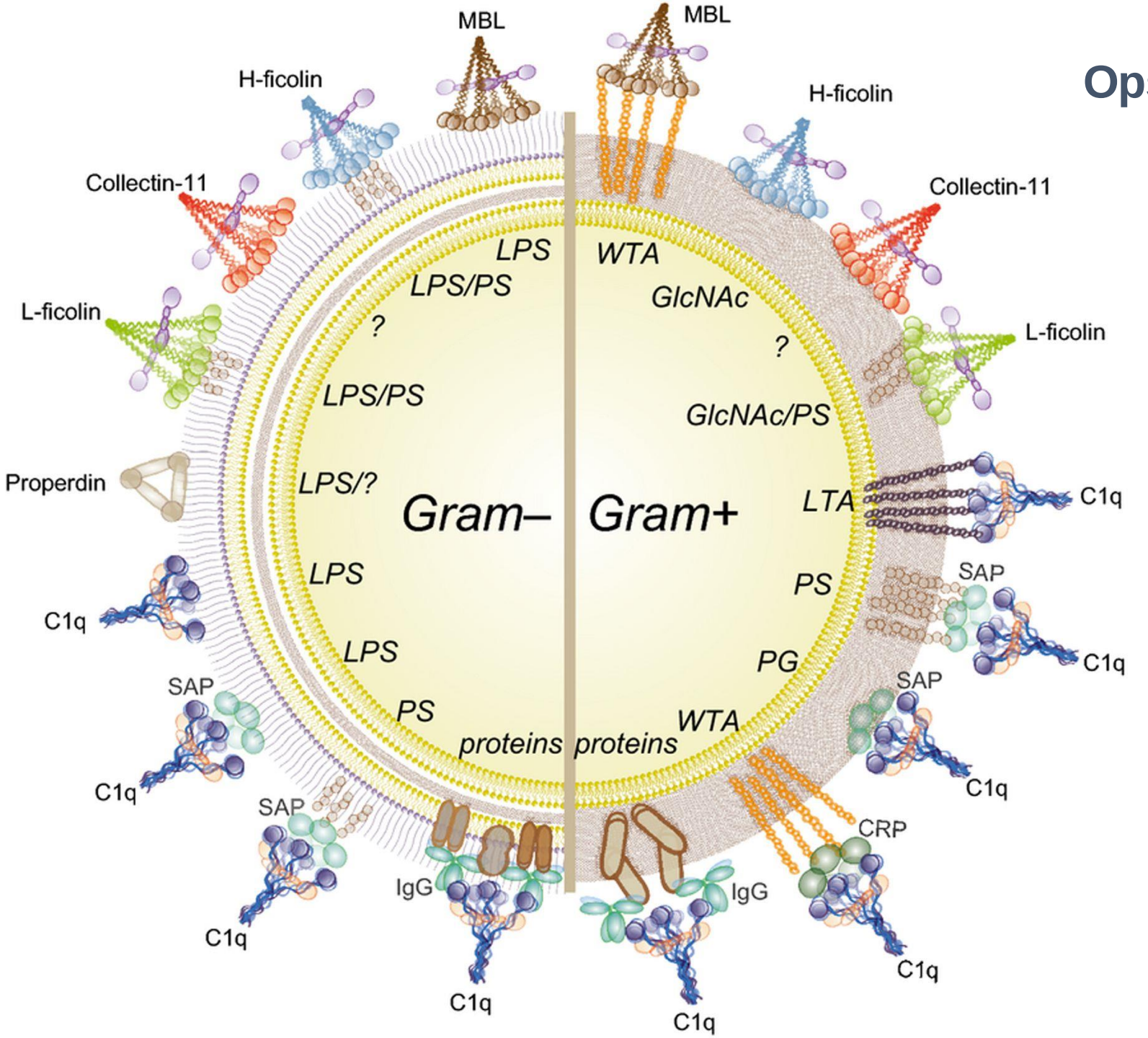
Collectinen (MBL en surfactant eiwitten), ficoline en complement factor C1q hebben een gemeenschappelijk structuur en binden aan dezelfde receptor CD91 (opsonin receptor) op fagocyterende cellen.

Opsoninen


MBL
MBL
H-ficolin
H-ficolin
Collectin-11
Collectin-11
L-ficolin
L-ficolin
Properdin
C1q
C1q
C1q
C1q
C1q
C1q
C1q
C1q
C1q
SAP
SAP
SAP
SAP
IgG
IgG
CRP
LPS
LPS/PS
?
LPS/PS
LPS/?
LPS
LPS
PS
proteins
WTA
GlcNAc
?
GlcNAc/PS
LTA
PS
PG
WTA
proteins
Gram–
Gram+

Filmpje: Centrale werking van het complement systeem

- https://www.youtube.com/watch?v=_5bj0oUrqDQ

Nog een filmpje: de klassieke en de MBL route

- https://www.youtube.com/watch?v=Nx8BFTNCi1o

The major pathways of complement activation: classical pathway

- IgM or IgG binds to a **multivalent** antigen
- This allows the binding of C1q, beginning the process of complement **deposition**
- C1 binds Fc on **adjacent IgG** molecules or on **IgM** bound to antigen

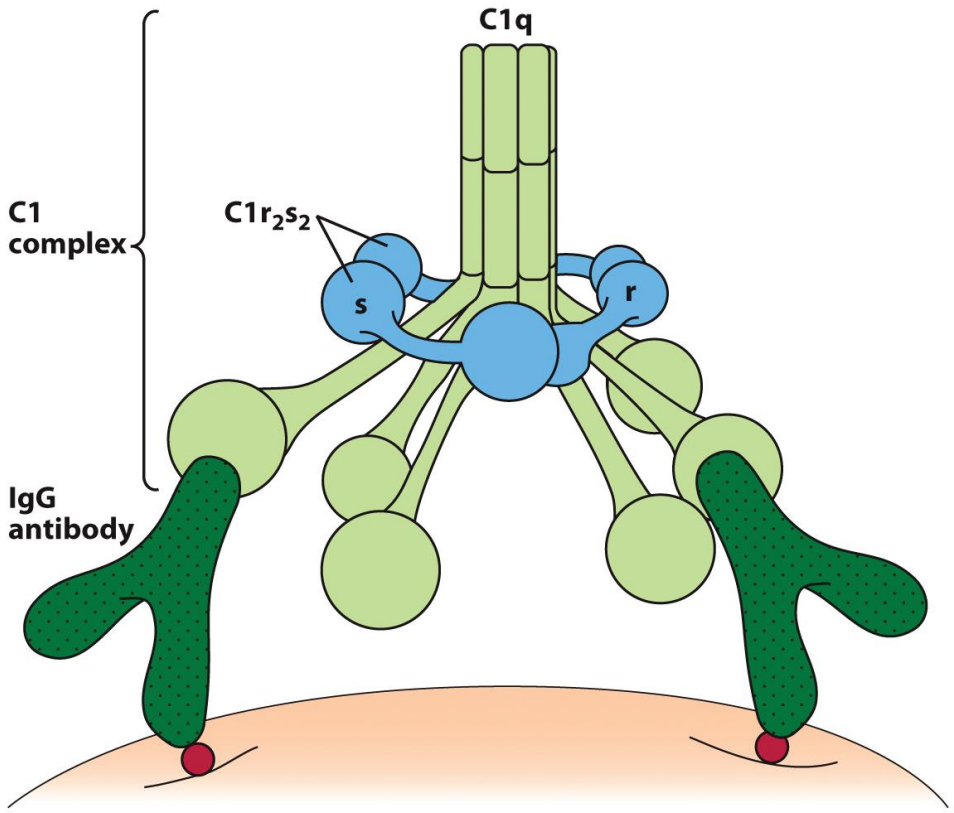


Figure 5-3
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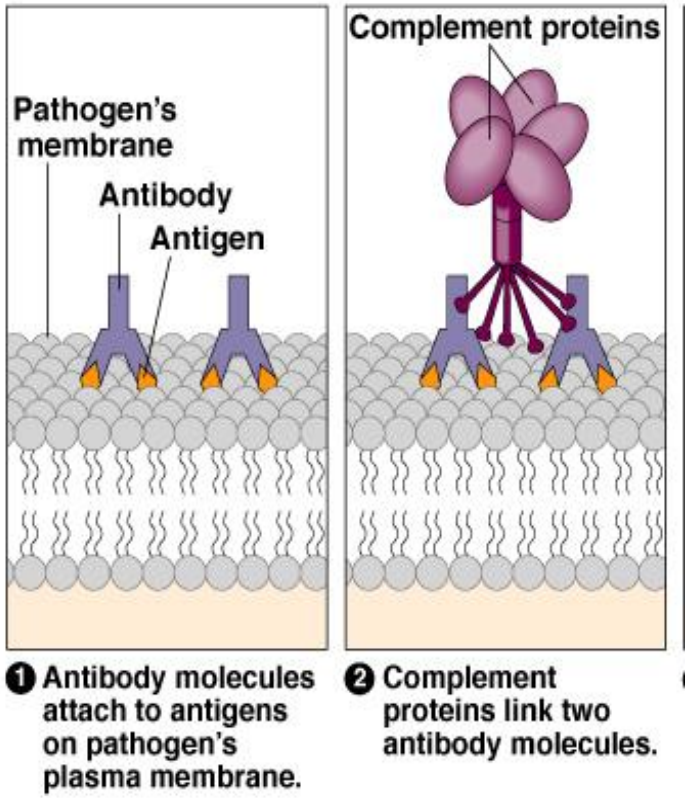
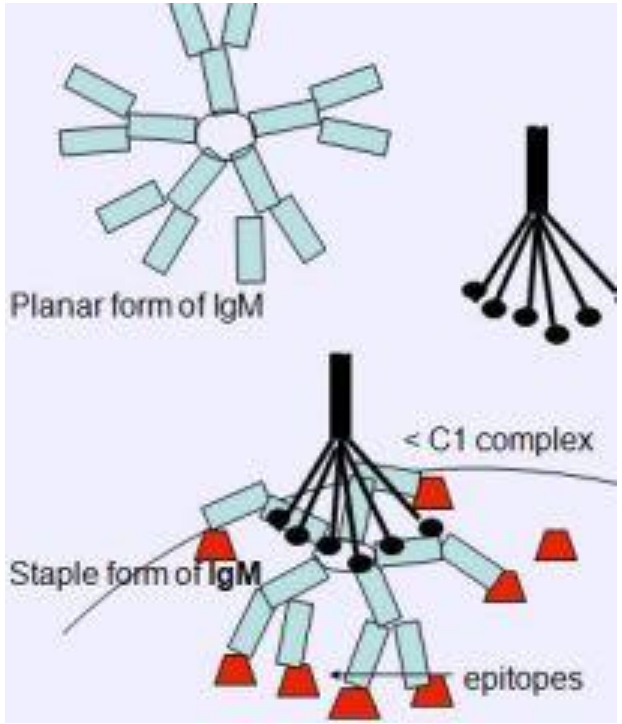
IgM en IgG binden complement

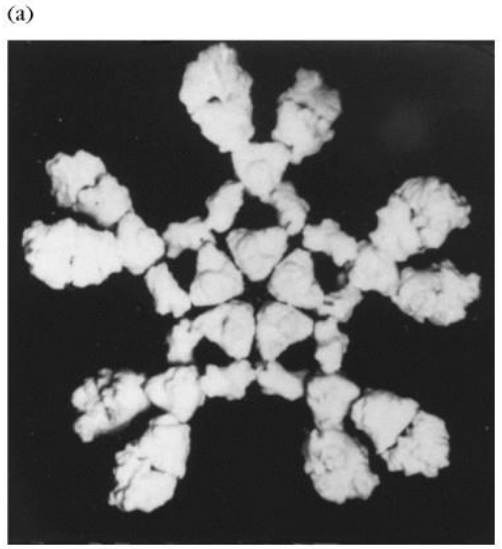


- C1q heeft 6 bindingsplaatsen, heeft 2x binding nodig voor stabiele binding
- Waarom zijn er minder IgM moleculen nodig dan IgG om complement te binden?
- Gemiddeld 1000 IgG moleculen op de membraan zijn nodig voordat complement geactiveerd wordt, terwijl minder dan 10 IgM moleculen al voldoende is!

IgM is een pentameer



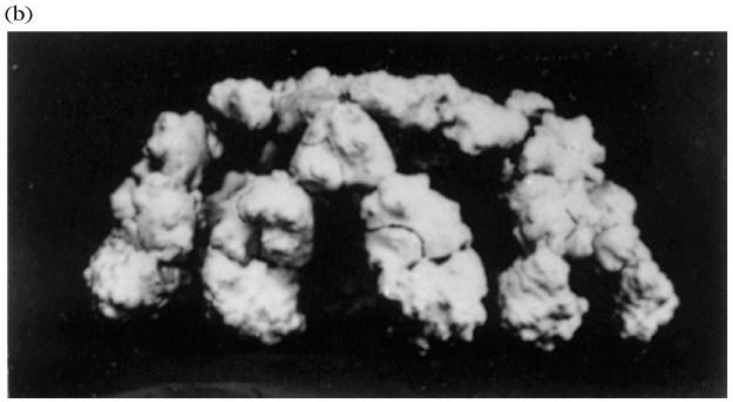
Staple = nietje



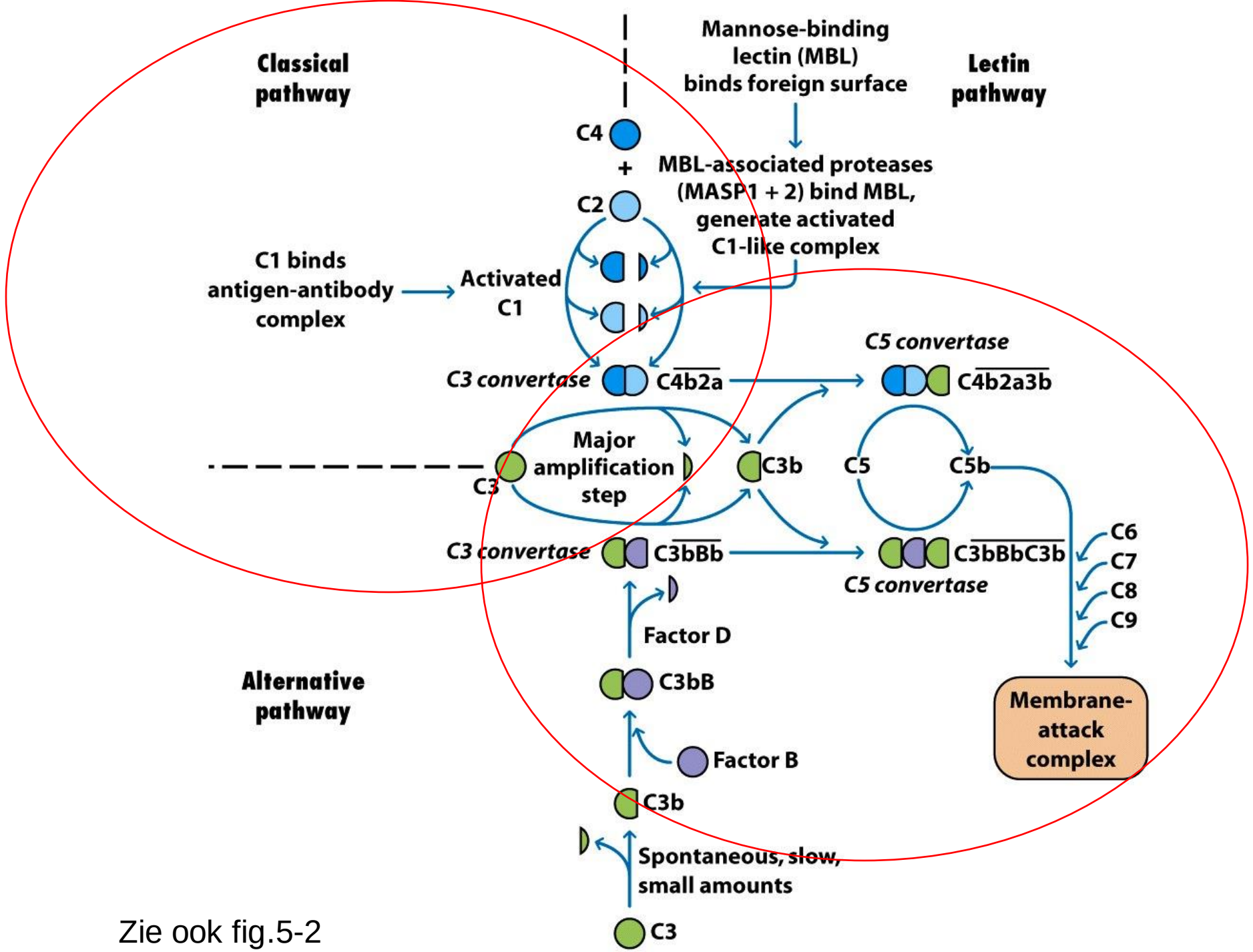
Ongebonden IgM

Fig.6-4

Gebonden IgM



Overzicht van de 3 routes van het complement

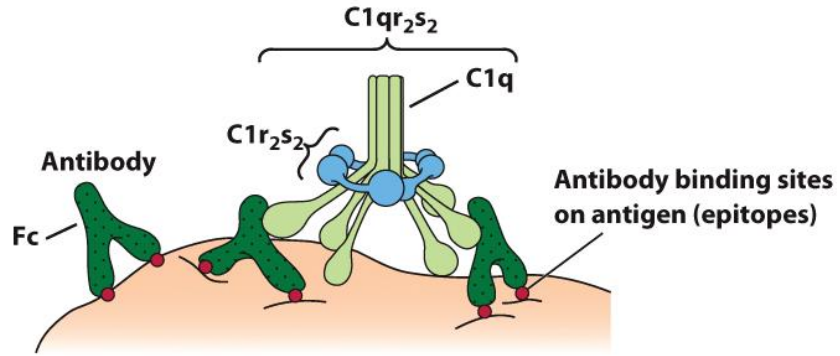


Zie ook fig.5-2

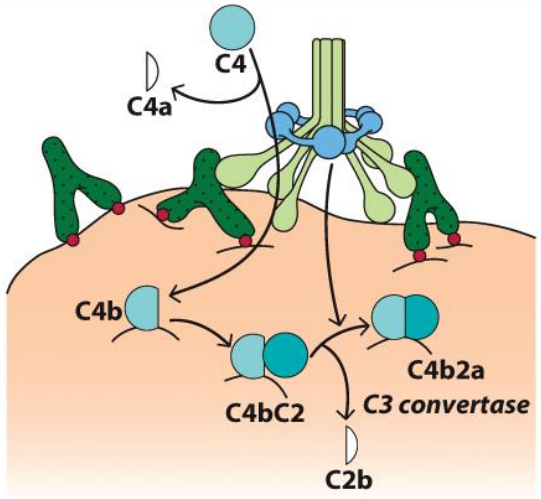
The major pathways of complement activation: classical pathway

- The classical pathway is initiated by antibody binding
  - **C1qrs** initiates a cascade of reactions enabling the next reaction in the sequence
  - C1 binding is followed by cleavage of C4, then C2
  - C4b2a bound to the cell surface is **C3 convertase**
  - C3 convertase cleaves many C3 proteins
  - Some combine with C3 convertase to form C5 convertase
  - **C5 convertase** cleaves C5 protein

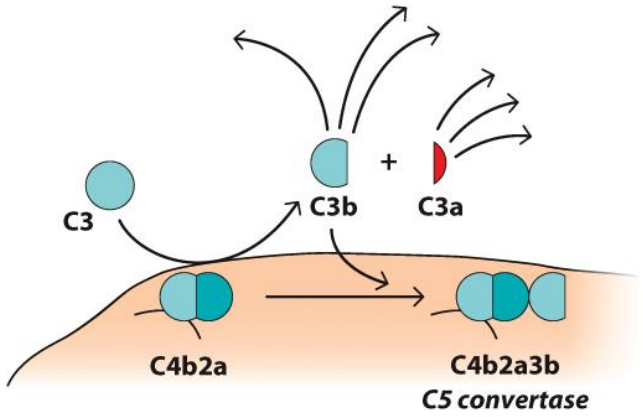
1 C1q binds antigen-bound antibody, and induces a conformational change in one C1r molecule, activating it. This C1r then activates the second C1r and the two C1s molecules.



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.

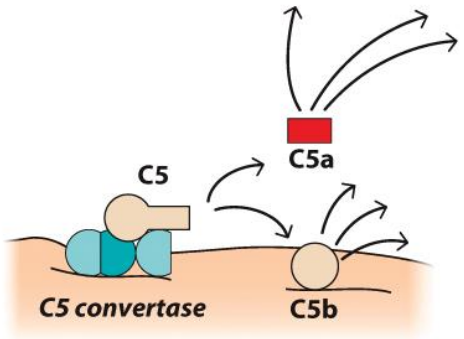


Figure 5-5
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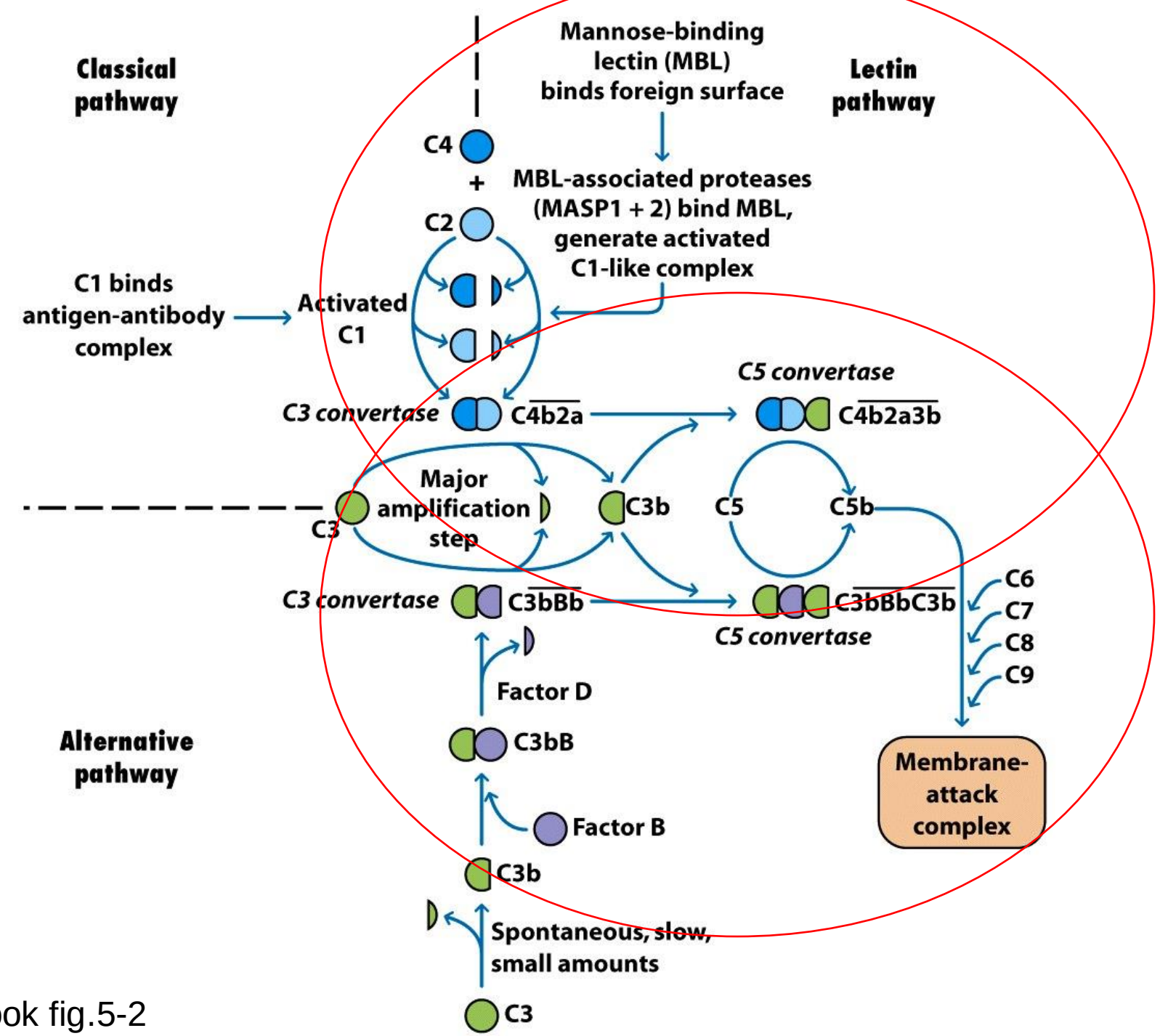
Overzicht van de 3 routes van het complement



Zie ook fig.5-2

The major pathways of complement activation: lectin pathway

- The lectin pathway is initiated when soluble proteins recognize microbial antigens
  - Lectins (e.g., **mannose-binding lectin**, or MBL) bind to microbial surfaces
  - Lectins can serve as docking sites for MBL-associated serine proteases (**MASPs**)
    - MASPs cleave C4 and C2 to form the C3 convertase
    - Subsequent steps are the same as the classical pathway

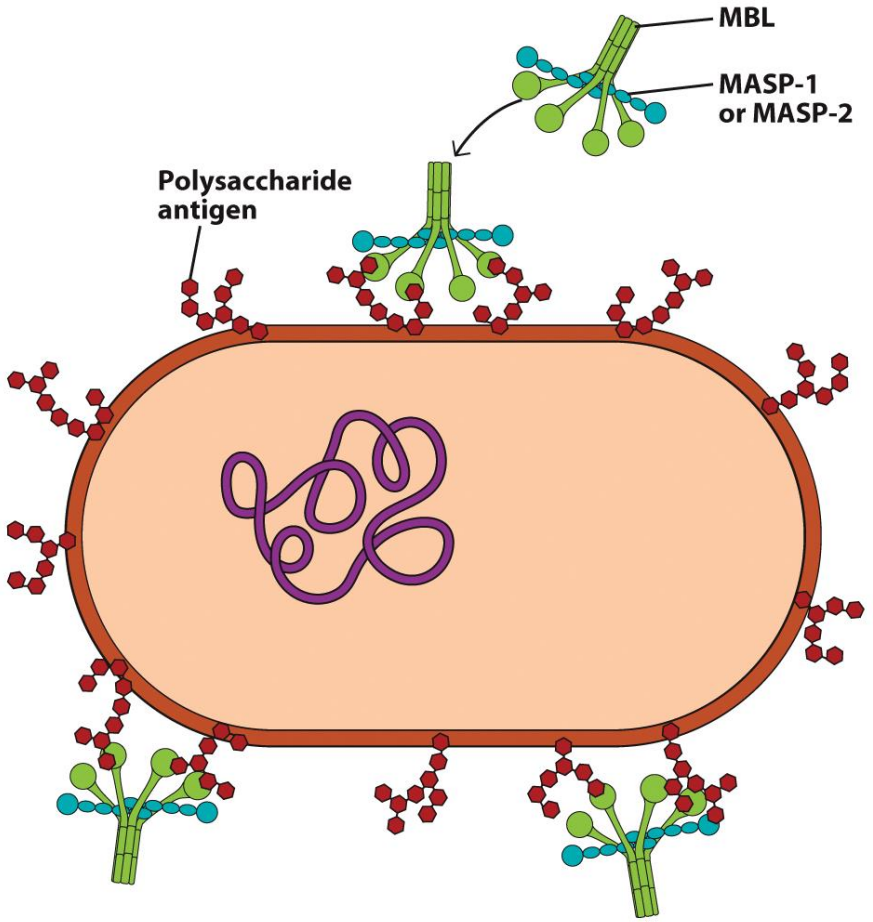


Figure 5-7
Kuby Immunology, Eighth Edition

The major pathways of complement activation: protease-activated pathway

- The alternative protease-activated pathway
  - Initiation of **clotting cascades** has also been shown to stimulate cleavage of complement proteins
    - **Thrombin** cleaves C3 and C5 in vitro
    - **Platelet activation** releases ATP, calcium ions, and serine/threonine kinases that could stabilize C3b in fluid phase
  - This indicates that strong inflammatory reactions could potentially activate complement systems

Filmpje:
De alternatieve pathway

- https://www.youtube.com/watch?v=RwJlj0OULns

Multiple choice vraag:

Welke factor(en) is/zijn (een) C3 convertase(s):

A. C4b2a

B. C3bBbC3b

C. C4b2a3b

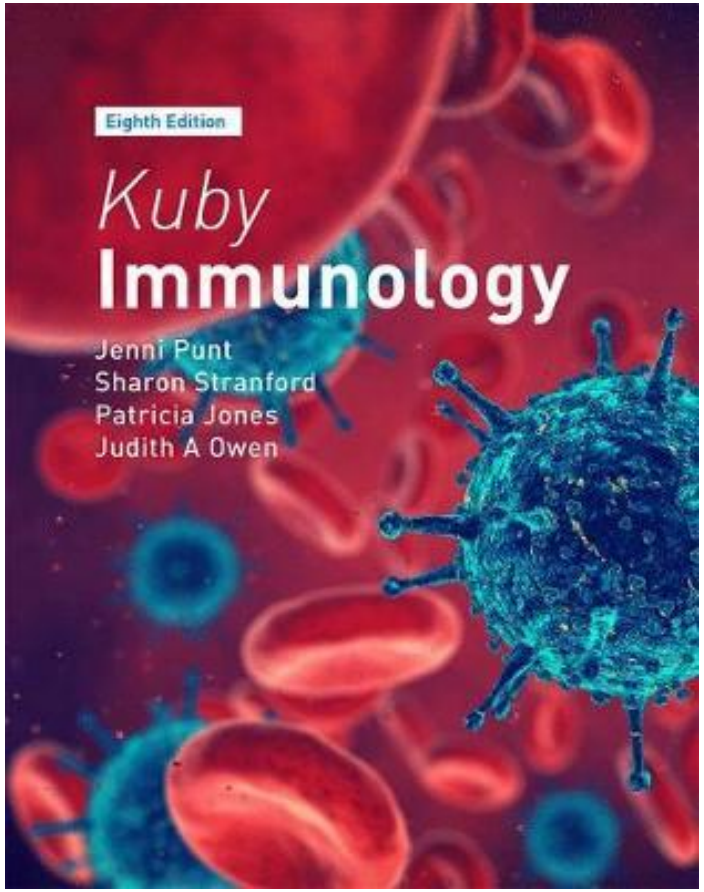
D. (A) en (B) beide

E. (B) en (C) beide

Een patiënt heeft niet werkend MBL (bij 25% van de bevolking!). Gevolg?

- De klassieke route “loopt niet” .**Waar/niet waar**
- De lectine route “loopt niet”. **Waar/niet waar**
- De alternatieve route “loopt niet”. **Waar/niet waar**
- Er is geen opsonisatie mogelijk. **Waar/niet waar**
- Er is geen C3a en C5a(chemotaxis). **Waar/niet waar**
- Er is geen lysis (via MAC) mogelijk. **Waar/niet waar**

Immunologie 1: Introduction to the Immune System



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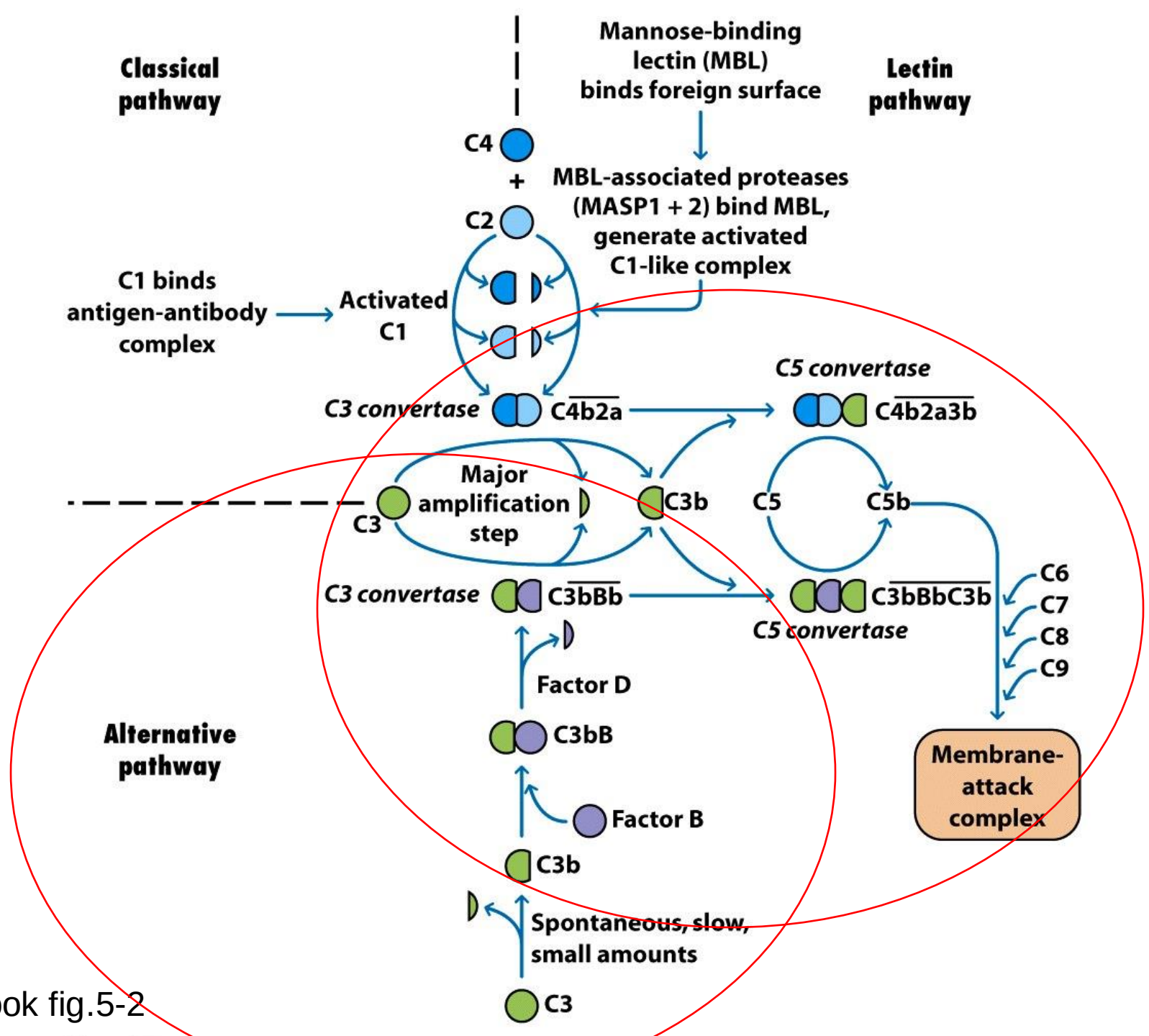
8. Het gedrag van het aangeboren en verworven immuunsysteem voor en tijdens een immuunrespons visualiseren

Waar/niet waar vragen:

1. IgG bindt complement beter dan IgM
2. MBL van de lectineroute lijkt sterk op C1q.
3. Bacteriën, die factor H maken worden minder makkelijk geopsoniseerd door complement-factor C3b.
4. C2 en C4 spelen alleen een rol in de klassieke route van het complement.

Overzicht van de 3 routes van het complement



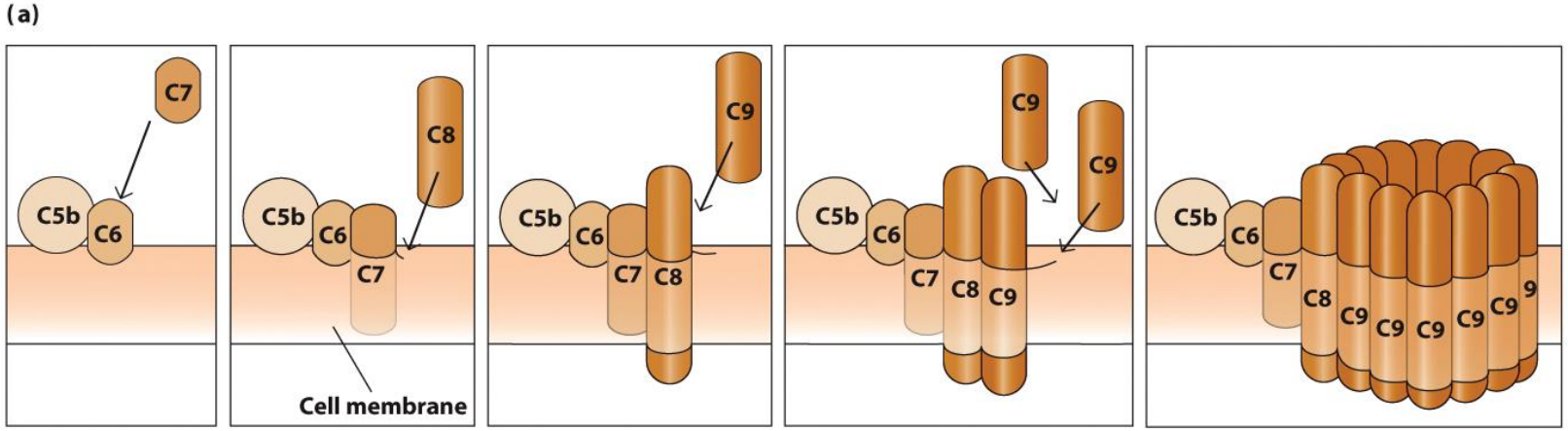
Zie ook fig.5-2

The major pathways of complement activation

- The three complement pathways converge at the formation of the **C5 convertase**
- C5 initiates the generation of the **Membrane Attack Complex (MAC)**
  - Membrane attack complex is the result of deposition of C5b, C6, C7, C8, and C9 in target cell membranes
  - This pore structure disrupts **osmotic integrity**, resulting in cell death

Filmpje:
Membrane Attack Complex

- https://www.youtube.com/watch?v=9ezkuJ08jMU



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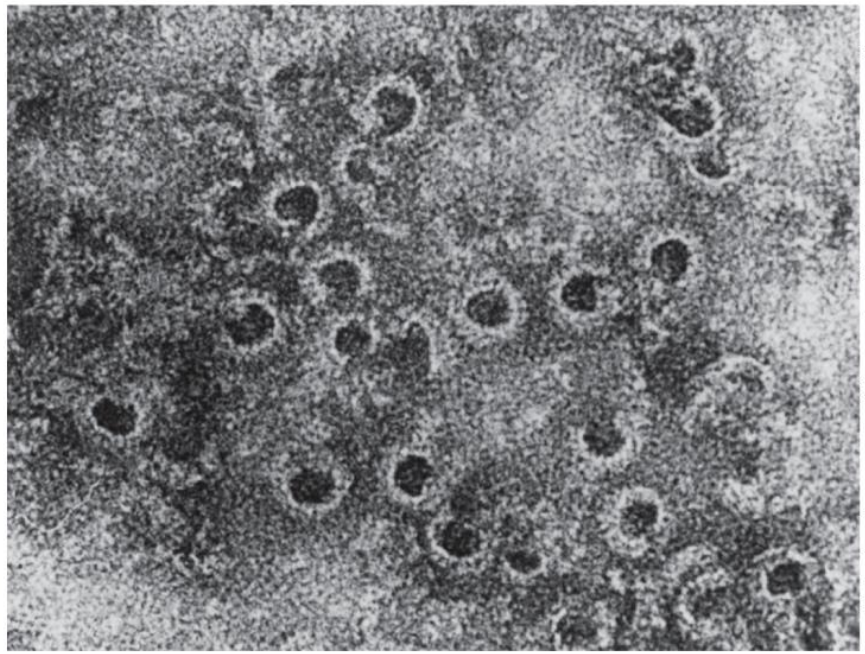

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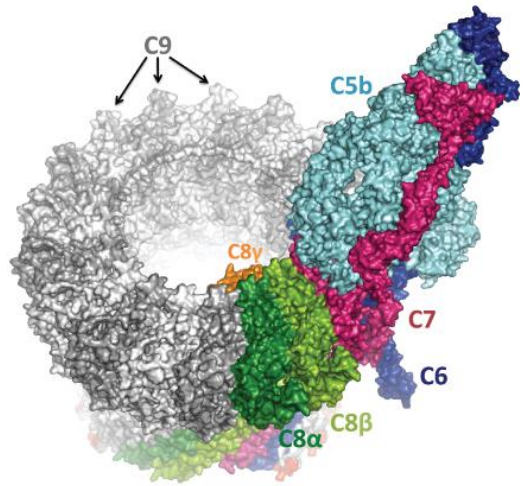

Drs. Robert Liddington and Alex Aleshin, SBP Medical Discovery Institute, La Jolla, CA.

Figure 5-10
Kuby Immunology, Eighth Edition

The diverse functions of complement

- Complement receptors connect complement-tagged pathogens to effector cells
  - Receptors on host cells allow for discrete and differentiated responses

The complement system

- Group of serum proteins circulating in inactive form
- Once activated, multiple possible outcomes
  - Target cell membrane **lysis**
  - **Chemotaxis**
  - **Opsonization** to enhance phagocytosis
  - **Inflammation**

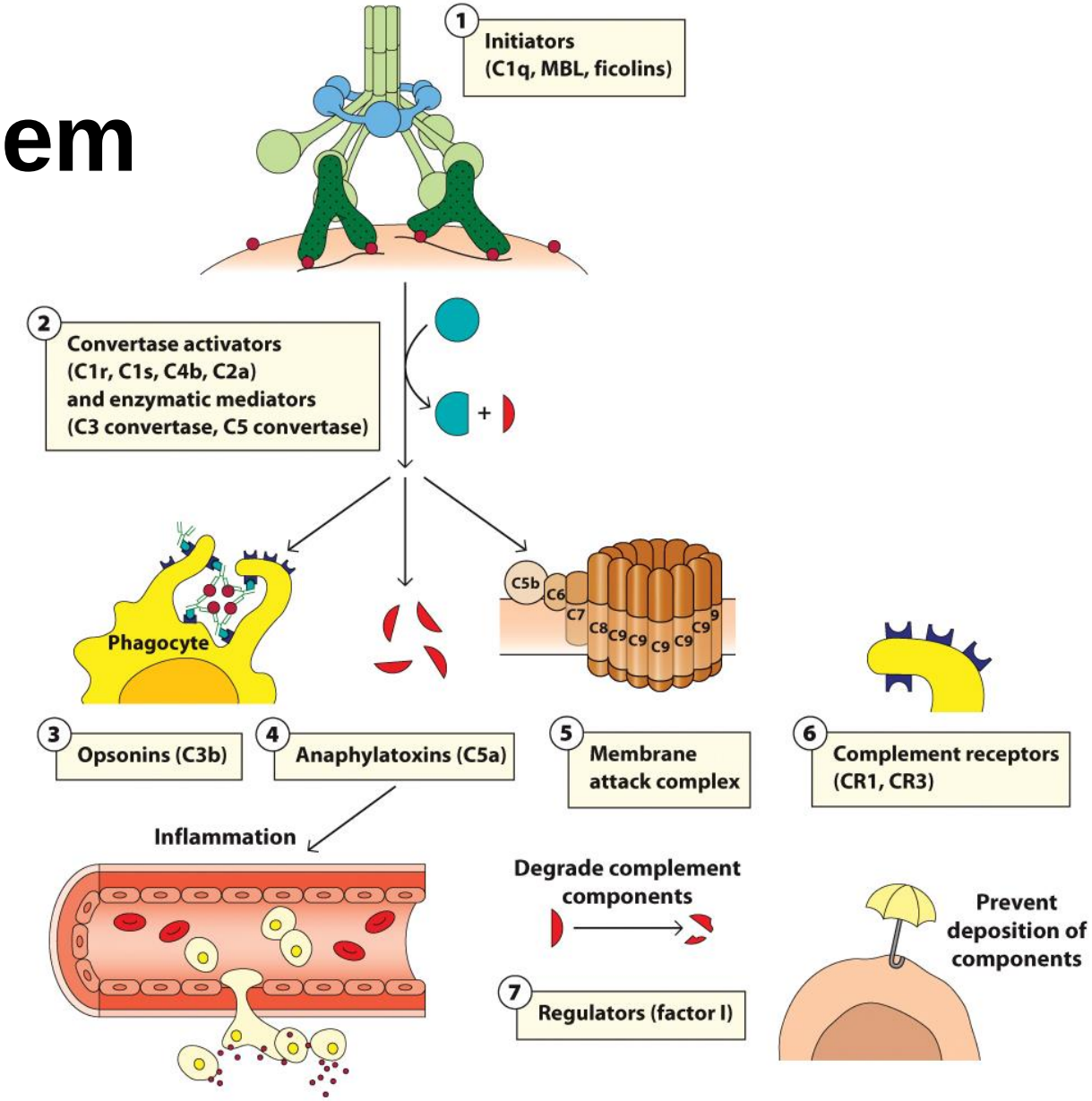

Figure 5-1
Kuby Immunology, Eighth Edition

Receptor	Other name(s)	Ligand	Cellular expression pattern	Function
CR1	CD35	C3b, C4b, C1q, iC3b	Erythrocytes, neutrophils, monocytes, macrophages, eosinophils, FDCs, B cells, some T cells	Clearance of immune complexes, enhancement of phagocytosis, regulation of C3 breakdown
CR2	CD21, Epstein Barr virus receptor	C3d, C3dg C3d, iC3b	B cells, FDCs	Enhancement of B-cell activation, B-cell coreceptor, and retention of C3d-tagged immune complexes
CR3	CD11b/CD18, Mac-1	iC3b and factor H	Monocytes, macrophages, neutrophils, NK cells, eosinophils, FDCs, T cells	Binding to adhesion molecules on leukocytes, facilitates extravasation; iC3b binding enhances opsonization of immune complexes
CR4	CD11c/CD18	iC3b	Monocytes, macrophages, neutrophils, dendritic cells, NK cells, T cells	iC3b-mediated phagocytosis
CRIg	VSIG4	C3b, iC3b, C3c	Fixed tissue macrophages	iC3b-mediated phagocytosis and inhibition of alternative pathway

Receptor	Other name(s)	Ligand	Cellular expression pattern	Function
C1qRp	CD93	C1q, MBL	Monocytes, neutrophils, endothelial cells, platelets, T cells	Induces T-cell activation; enhances phagocytosis
SIGN-R1	CD209	C1q	Marginal zone of spleen, lymph node macrophages	Enhances opsonization of bacteria by MZ macrophages
C3aR	(None)	C3a	Mast cells, basophils, granulocytes	Induces degranulation
C5aR	CD88	C5a	Mast cells, basophils, granulocytes, monocytes, macrophages, platelets, endothelial cells, T cells	Induces degranulation; chemoattraction; acts with IL-1β and/or TNF-α to induce acute-phase response; induces respiratory burst in neutrophils
C5L2	(None)	C5a	Mast cells, basophils, immature dendritic cells	Uncertain, but most probably downregulates proinflammatory effects of C5a

The diverse functions of complement

- **Complement receptors** connect complement-tagged pathogens to effector cells
  - **CR1** on leukocytes and erythrocytes
    - On erythrocytes, helps to bring immune complexes to the liver for **clearance** by phagocytes
    - On phagocytes, helps bind to complement-coated bacteria to enhance **ingestion and destruction**
    - On B cells, helps bind to complement-coated antigens, enhancing ingestion for **processing and presentation** to helper T cells

The diverse functions of complement

- Complement receptors connect complement-tagged pathogens to effector cells
  - **CR2** on B cells
    - **Binds to C3b** on opsonized bacteria/antigens
    - Helps **provide secondary signals** to B cells through BCR complex for more efficient activation

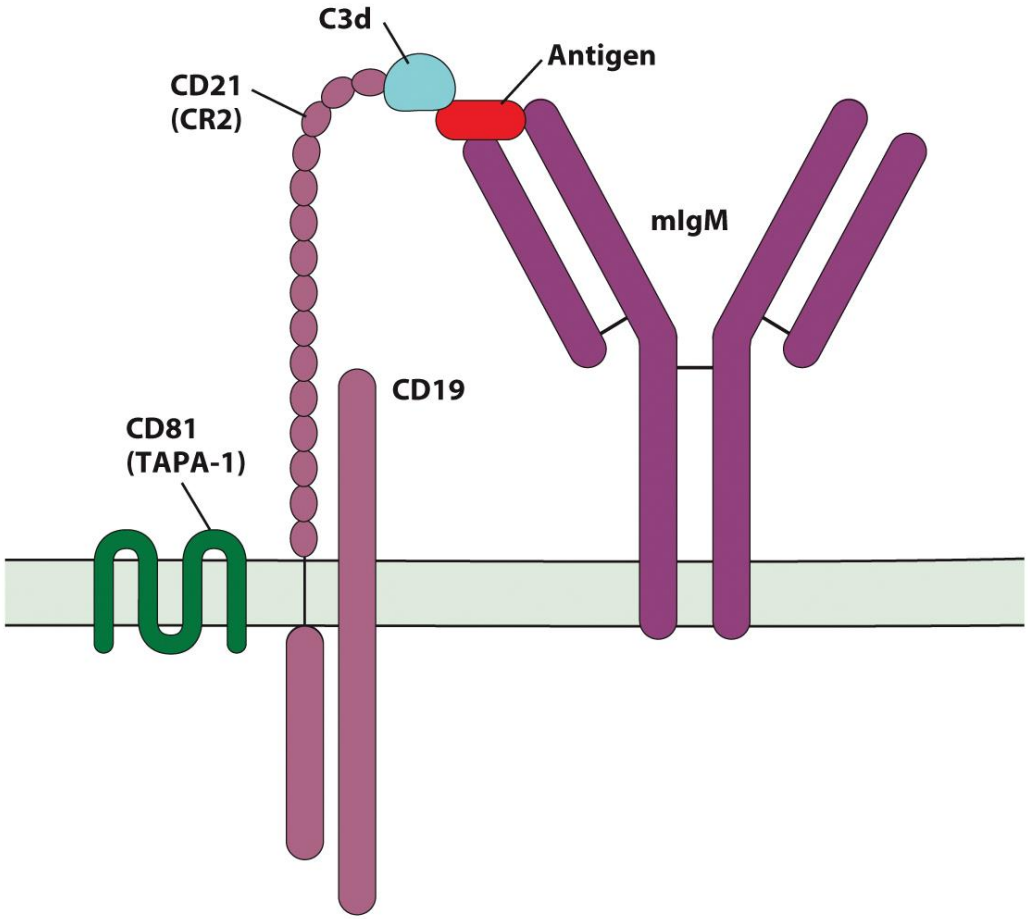

Figure 5-11
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The diverse functions of complement

- Complement receptors connect complement-tagged pathogens to effector cells
  - **C3aR/C5aR** on granulocytes
    - Stimulates release of **proinflammatory** cytokines and **granule components** from basophils, eosinophils, neutrophils

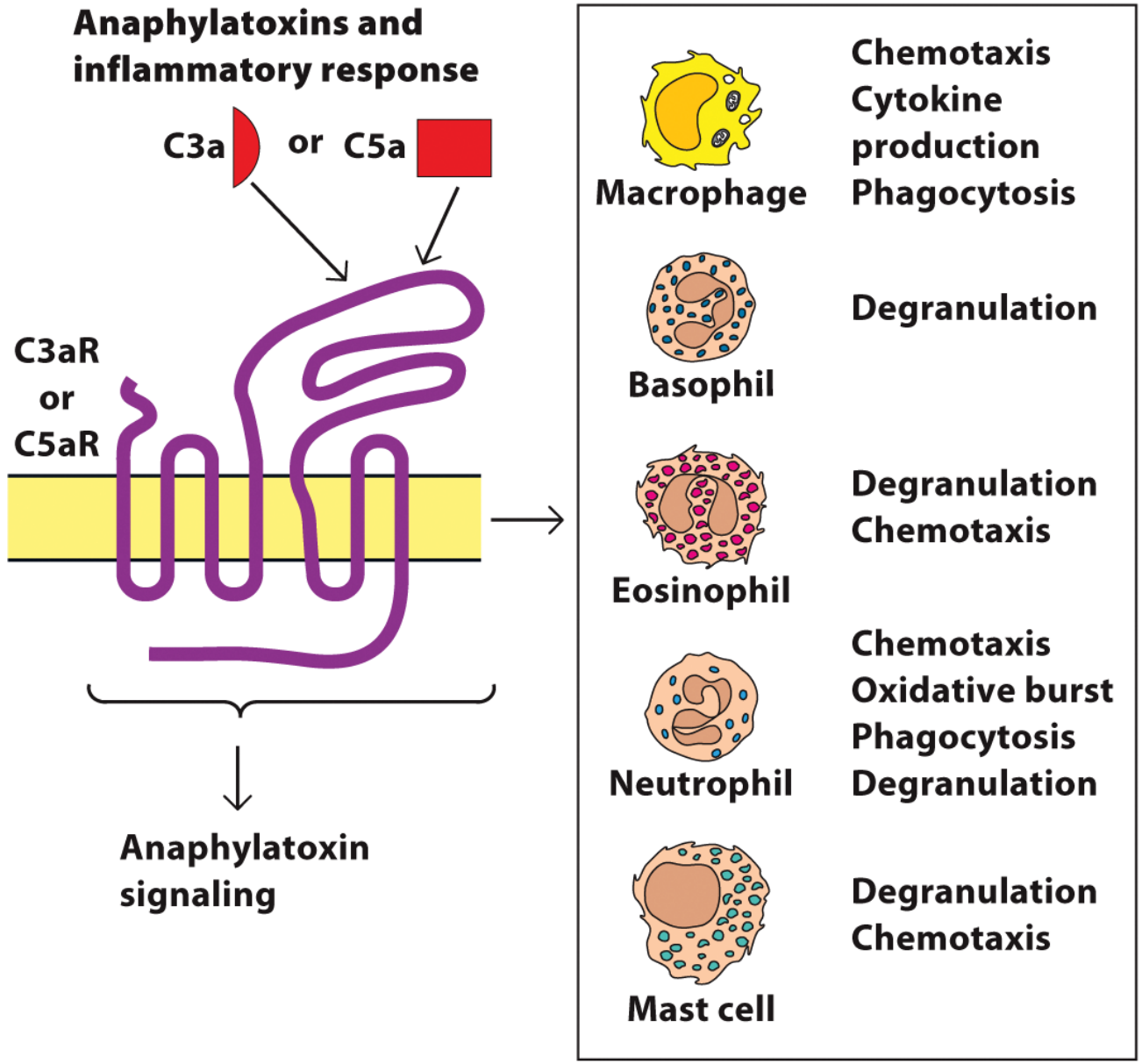

Figure 5-12
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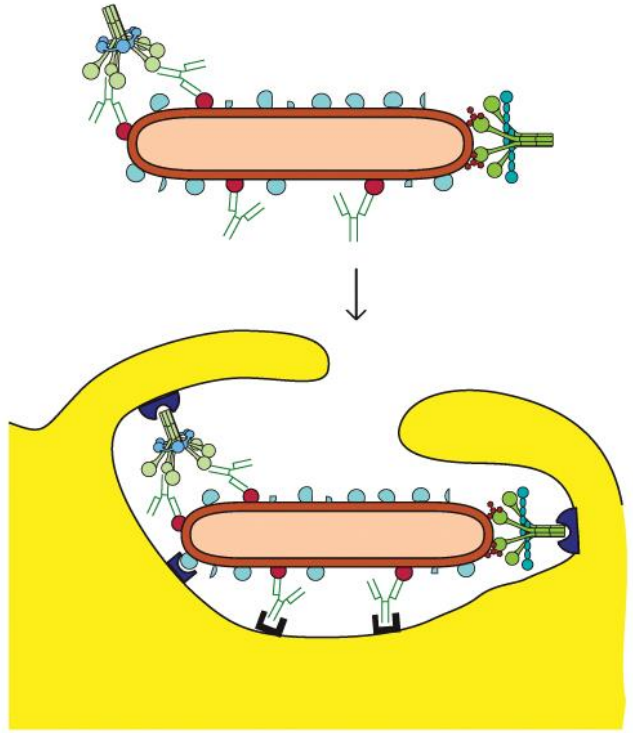
The diverse functions of complement

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



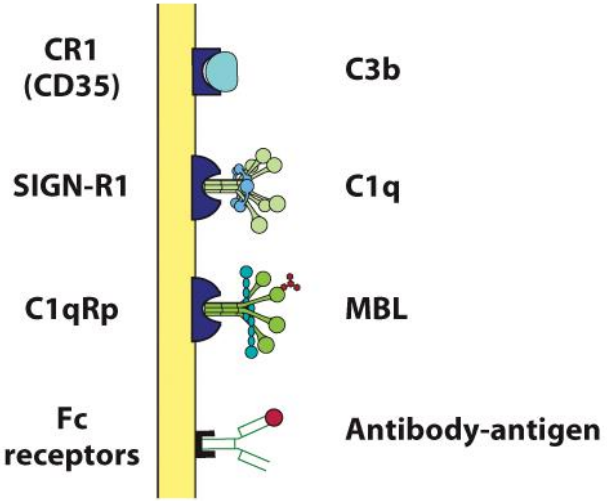


Figure 5-13
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The diverse functions of complement

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

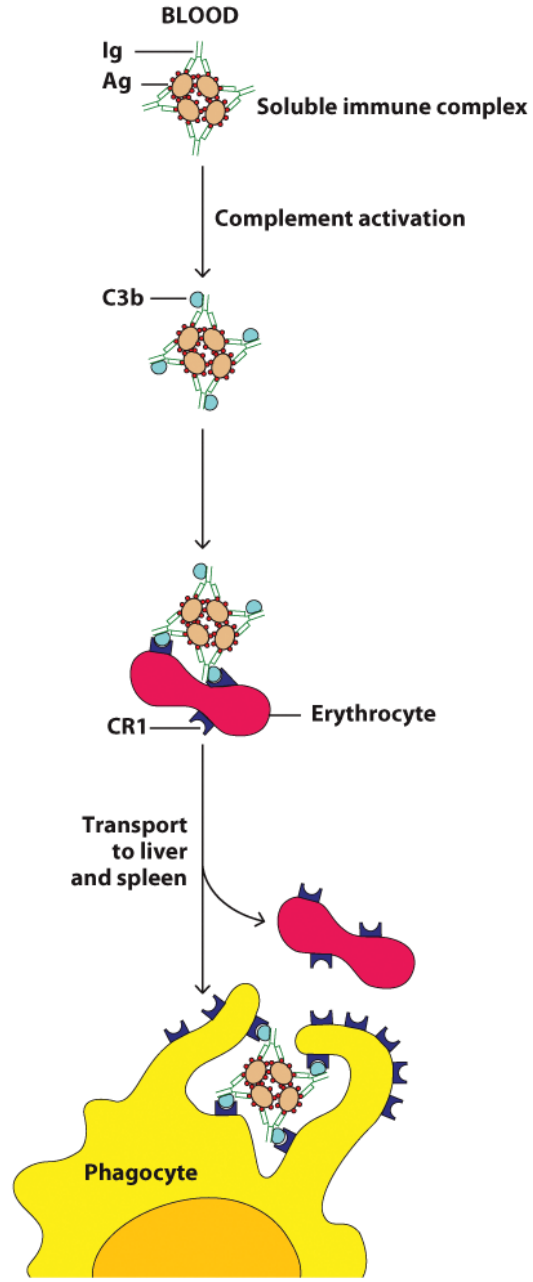

Figure 5-15
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The diverse functions of complement

- Complement mediates interface between innate and adaptive immunities
  - Enhances **antigen uptake** of antigen bound to MBL, C1q, C3b, and C4b that bind receptors on APCs
  - Enhances **B-cell response** by an increasing avidity of B-cell binding to complement-bound antigen
  - **Lyse** immature T cells with low sialic acid content, a carbohydrate that increases in concentration as a protective coating on maturing T cells
  - Binding of C3a, C5a, and C3b to their receptors on mature T cells **facilitates** their growth, differentiation, and survival

The diverse functions of complement

- Complement aids in the **contraction phase** of the immune response
  - As lymphocytes are no longer required, complement aids in disposal of **apoptotic cells and bodies**
  - Complement also aids in removal/disposal of **immune complexes** formed during responses
  - These responses avoid damaging inflammation induction in the absence of antigens following clearance of an infection

Complement deficiencies

- Genetic deficiencies have been described for each of the complement components, but outcomes vary
  - Patients with any C1q, C1r, C1s, C4, or C2 deficiency often present with immune complex disorders due to inadequate **clearance**
  - Some with MBL deficiency may exhibit greater frequency of infections by **encapsulated bacteria** due to inefficient opsonization and phagocytosis
- Animal models exist for most complement deficiencies, allowing for further study

Overzicht van de immuunrespons

- https://www.youtube.com/watch?v=Nw27_jMWw10 (Complement wordt nog behandeld)
- https://www.youtube.com/watch?v=zQGOcOUBi6s

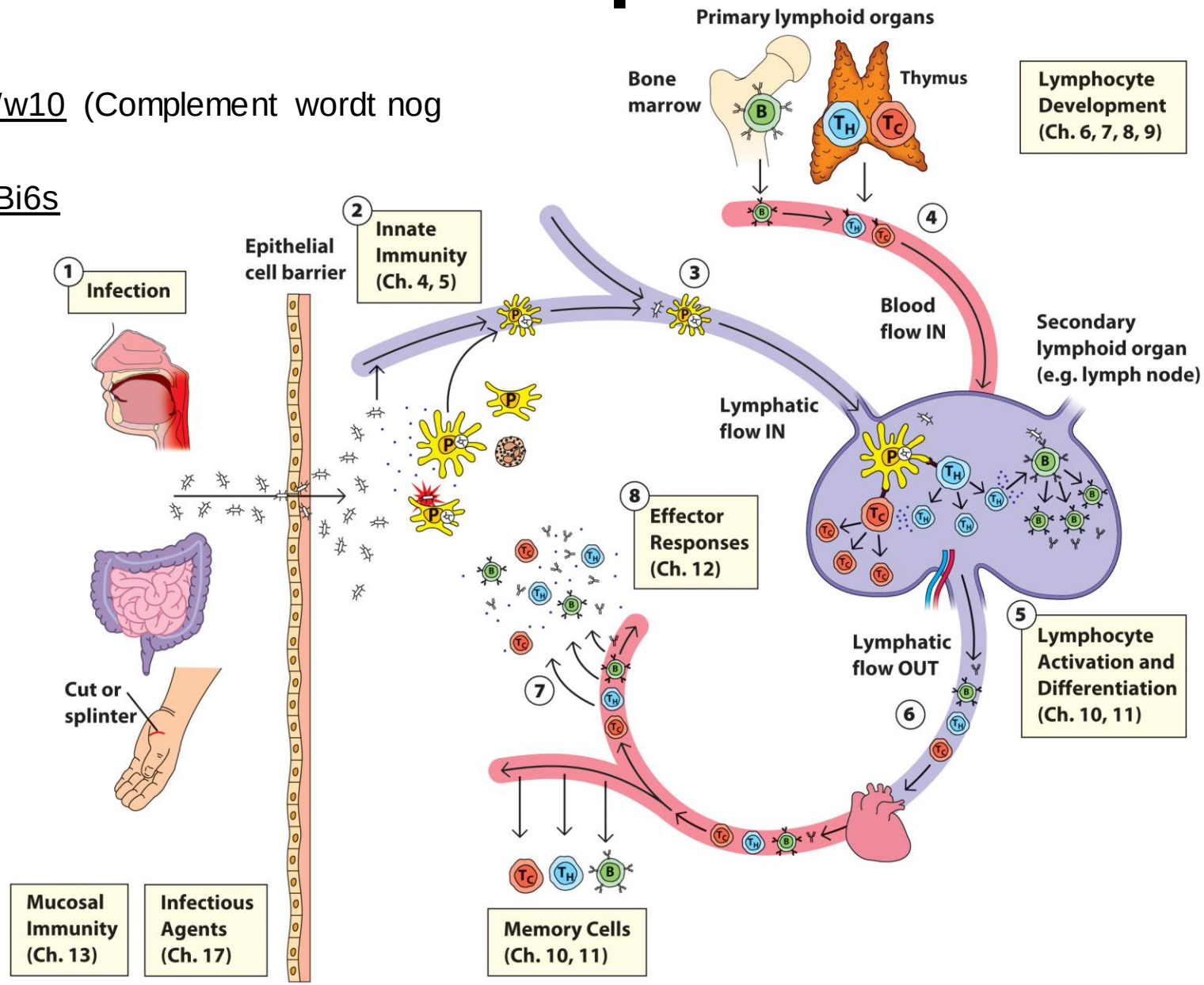

Figure 1-7
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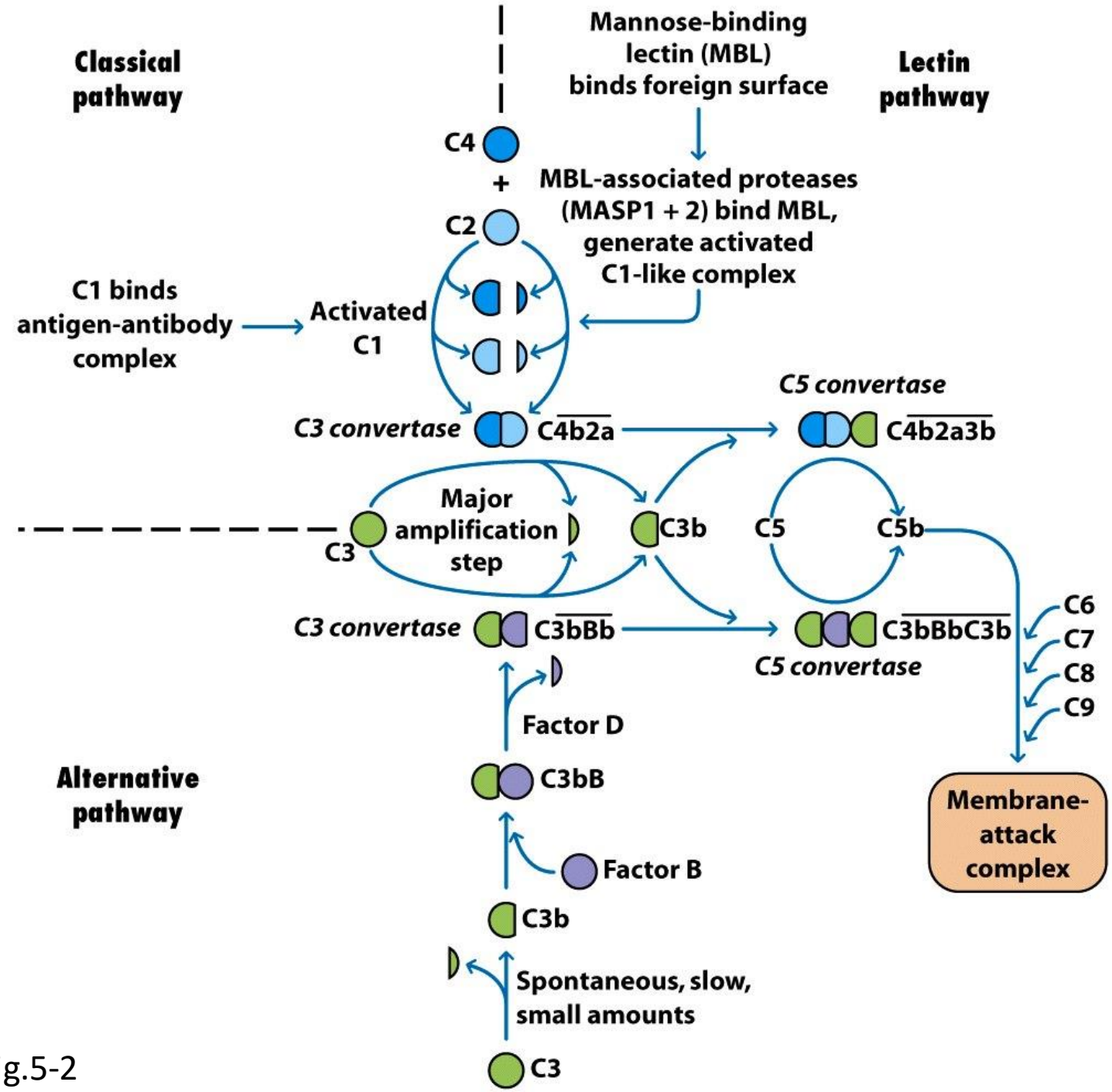
The regulation of complement activity

- Complement activity is passively regulated by protein stability and cell-surface composition
  - Short **half-life** of C3 convertase unless stabilized by properdin
  - **Self-cells** possess different carbohydrate structures that are more effectively bound by fluid-phase proteases
    - These more readily inactivate C3b through hydrolysis, protecting self-cells

The regulation of complement activity

- Numerous **regulatory proteins** help to prevent the complement system from harming self-cells

Overzicht van de 3 routes van het complement



Zie ook fig.5-2

The regulation of complement activity

- The C1 inhibitor, **C1INH**, promotes dissociation of C1 components
  - Binds in the active site of **serine proteases**
  - Causes C1r2s2 to dissociate from C1q
  - No further cleavage of C4 or C2 is possible
  - Inhibits initiation of **classical and lectin** complement pathways

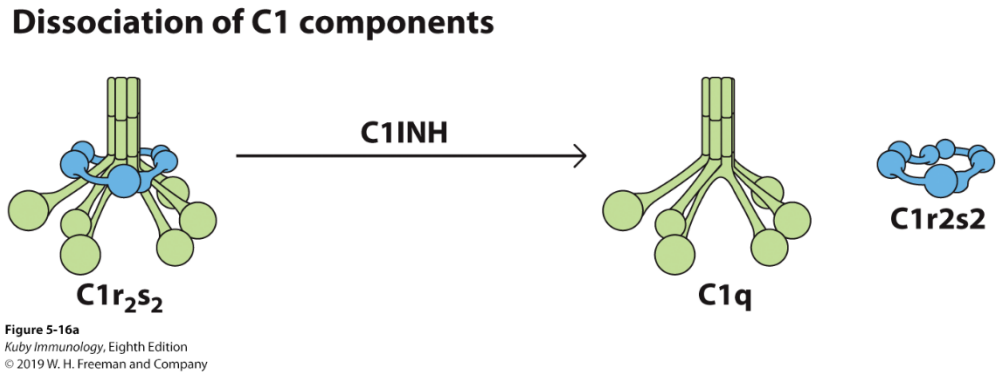


Figure 5-16a
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The regulation of complement activity

- **Decay accelerating factors** promote decay of C3 convertases
  - 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 unique to **eukaryotic** cell surfaces
- Work to accelerate the decay of C4b2a (C3 convertase) on the surface of host cells

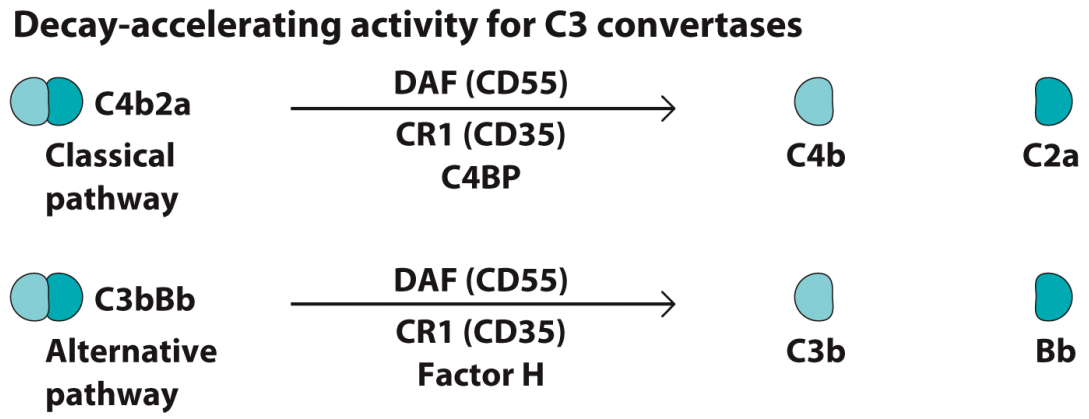

Figure 5-16b
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The regulation of complement activity

- **Factor I** degrades C3b and C4b
  - Soluble, constitutively active **serine protease**
  - Cleaves membrane-associated C3b and C4b into inactive fragments
    - Requires **MCP** (CD46) and **CR1** (found on membranes of host cells) to function

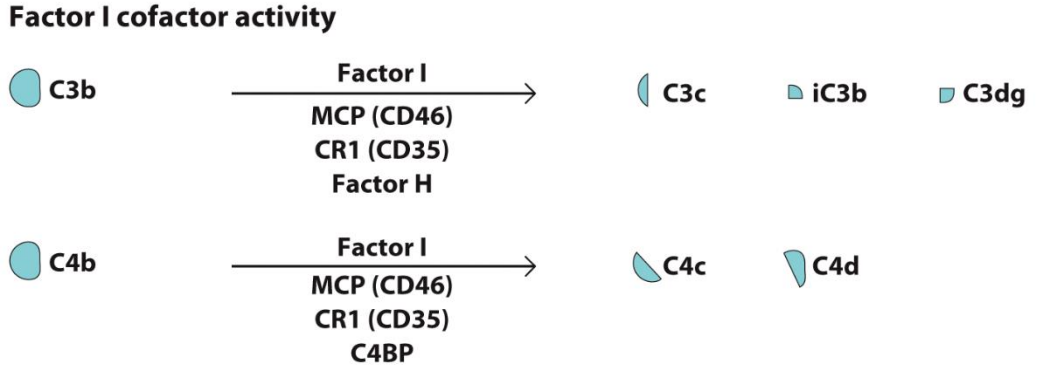

Figure 5-16c
Kuby Immunology, Eighth Edition

The regulation of complement activity

- **Protectin** (CD59) inhibits the MAC attack
  - Binds C5b678 complexes deposited on host cells
    - Prevents their insertion into the plasma membrane
    - Also blocks C9 recruitment, preventing MAC formation

  - Similarly, soluble complement S protein (**vitronectin**) binds fluid phase C5b67 to prevent insertion into host cell plasma membranes

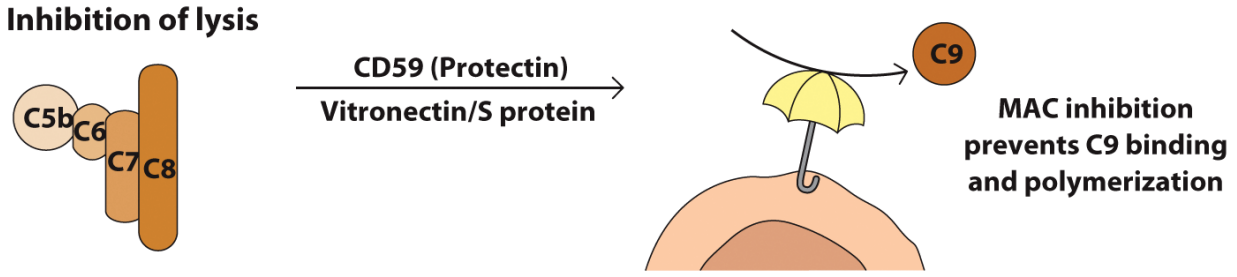

Figure 5-16d
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The regulation of complement activity

- **Carboxypeptidases** can inactivate the **anaphylatoxins** C3a and C5a
  - Remove arginine residues from the C termini of C3a and C5a
    - Creates **des-Arg** (without arginine) inactive forms
    - Helps to shut down unnecessary or dangerous chemotactic and inflammation induction

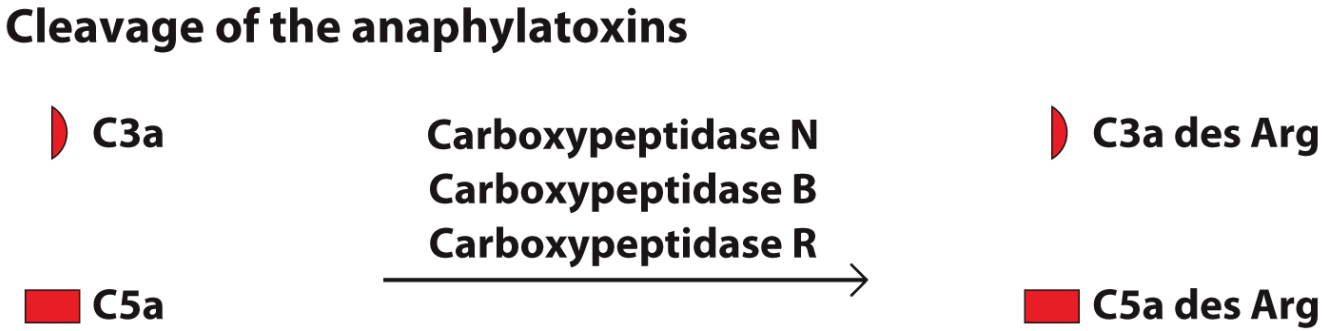

Figure 5-16e
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Microbial complement evasion strategies

- Different mechanisms exist and are highly varied
  - Some **interfere** with the first step of Ig-mediated complement activation
  - Microbial proteins may **bind and inactivate** complement proteins
  - Microbial proteases **destroy** complement proteins
  - Some microbes **mimic** or bind complement regulatory proteins

Complement evasion strategy	Example
Interference with antibody-complement interaction	Antibody depletion by staphylococcal protein A Removal of IgG by staphylokinase
Binding and inactivation of complement proteins	*S. aureus* protein SCIN binds to and inactivates the C3bBb C3 convertase Parasite protein C2 receptor trispanning protein disrupts the binding between C2 and C4
Protease-mediated destruction of complement component	Elastase and alkaline phosphatase from *Pseudomonas* degrade C1q and C3/C3b ScpA and ScpB from *Streptococcus* degrade C5a
Microbial mimicry of complement-regulatory components	*Streptococcus pyogenes* M proteins bind C4BP and factor H to the cell surface, accelerating the decay of C3 convertases bound to the bacterial surface *Variola* and *Vaccinia* viruses express proteins that act as cofactors for factor I in degrading C3b and C4b

The evolutionary origins of the complement system

- Genes for complement components belong to five families
  - Alternative pathway genes appear first in evolution
  - Terminal complement components appear last

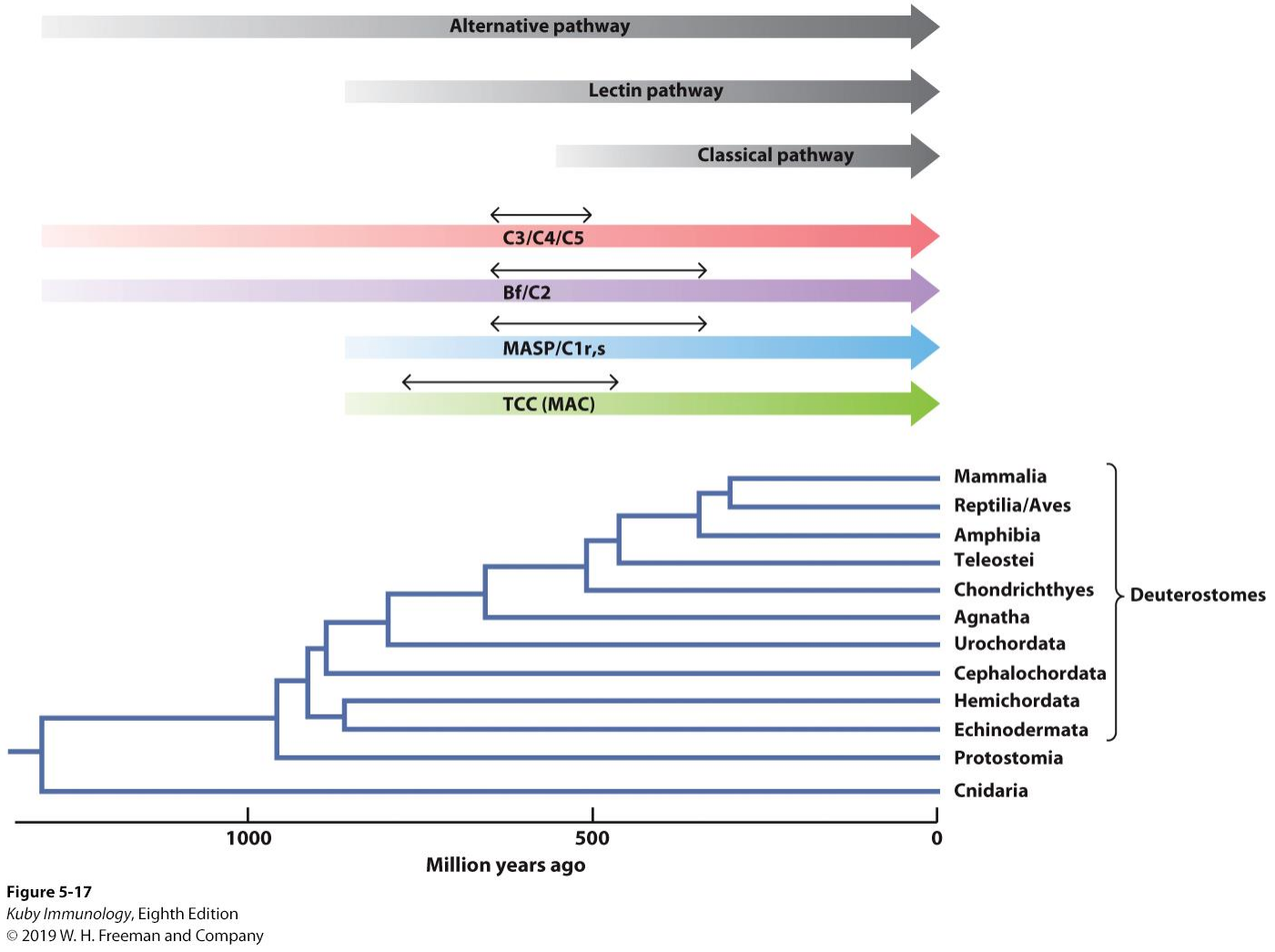

Figure 5-17
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The evolutionary origins of the complement system

- Five families of genes for complement components
  - Complement served to assist phagocytosis prior to evolution of adaptive immunity

Table 5-8, Complement system pathways in the major groups of deuterostome animals, Page 199

Animal group	Alternative pathway	Classical pathway	Lectin pathway	Membrane attack complex	Antibodies present?
Mammals	+	+	+	+	+
Birds	+	+	+	+	+
Reptiles	+	+	+	+	+
Amphibians	+	+	+	+	+
Teleost fish	+	+	+	+	+
Cartilaginous fish	+	+	+	+	+
Agnathan fish	+	−	+	?	−
Tunicates	+	−	+	?	−
Echinoderms	+	−	?	?	−

Summary

- The complement system serves many different purposes, helping to link innate and adaptive immune responses
- It is tightly controlled but enhances many other responses once activated
- It also provides a window into the evolution of immunity
- Understanding the system and its methods of activation and regulation helps us to better understand innate immunity and evolution

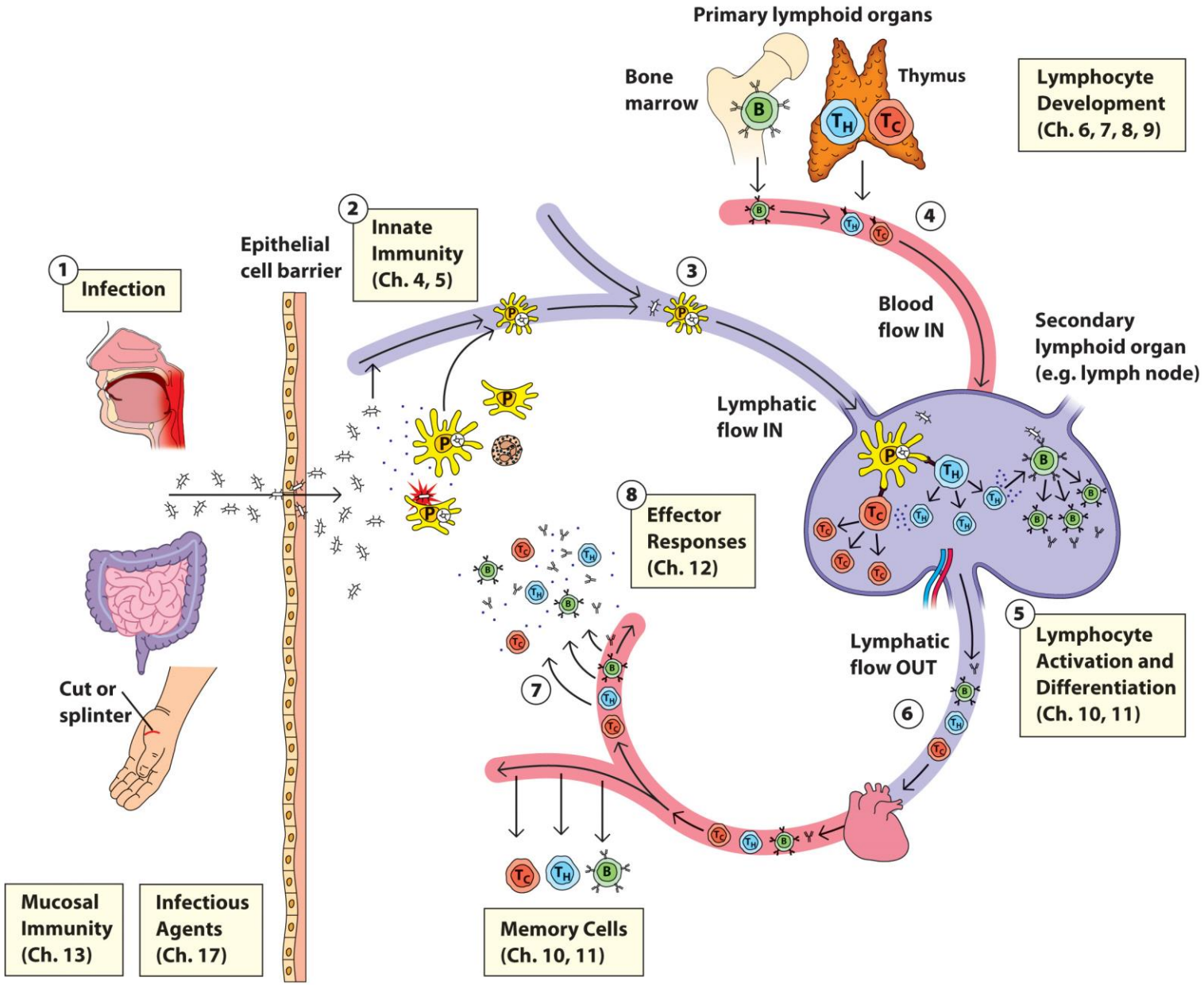

Figure 1-7
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