
Complement System

Activation pathways · effector functions · regulation · disease

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Learning objectives

By the end of this lecture, students should be able to:

- Differentiate the classical, alternative, and lectin pathways by the initiating signal.
- Trace C3 and C5 cleavage to their biologically distinct products.
- Explain complement-driven inflammation, opsonization, and microbial lysis.
- Predict clinical phenotypes from defective complement components or regulators.

Complement is a plasma-protein defense network

What the term “complement” encompasses

- More than 20 proteins circulate or interact with cells as a coordinated system.
- Many proteins are present as inactive precursors until an activation trigger appears.
- The system participates in host defense and can mediate inflammatory tissue injury.

Innate and adaptive immunity converge in complement

Innate contribution

- Alternative pathway can respond directly to microbial surface molecules.
- Lectin pathway detects carbohydrate structures on microbes.
- Activation can proceed before a specific antibody response.

Adaptive contribution

- Classical pathway recognizes antigen-bound IgM or IgG through C1.
- Antibody-directed complement activation focuses effector activity on a target.
- The same downstream complement machinery generates inflammatory and antimicrobial effects.

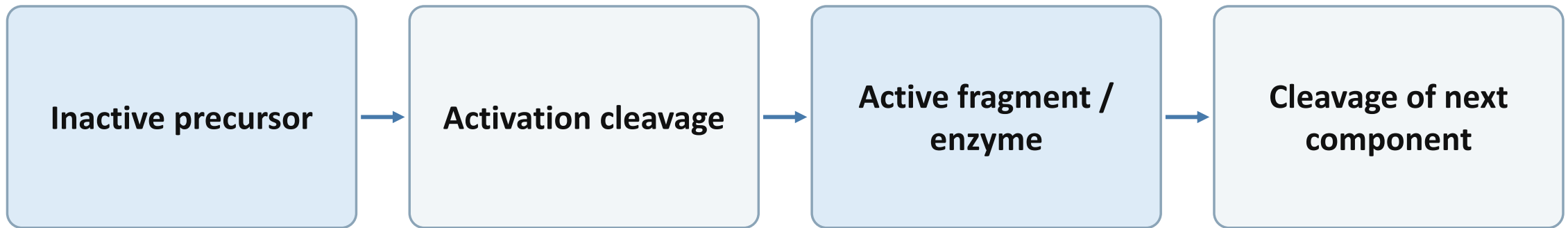
Complement proteins form a coordinated cascade

Principal components and products

- Several components are designated C1 through C9; Additional proteins mediate regulation and pathway initiation.
- Proteolytic activation converts selected components into enzymes or biologically active fragments.
- Surface-associated fragments and soluble fragments have different destinations and actions.

Proteolysis drives complement activation

Successive cleavage reactions transmit and amplify the initiating signal.



An enzymatic cascade converts a recognition event into a larger effector response.

Cascade amplification explains biological potency

Why a small initiating event matters

- Activated complement enzymes cleave additional complement proteins.
- Repeated proteolysis generates multiple active fragments from an initial trigger.
- Regulatory proteins are therefore essential to confine activation to appropriate sites.

C3 is the central complement component

The critical convergence point

- C3 is the most abundant complement component described in the source.
- Classical, alternative, and lectin pathways all culminate in its cleavage.
- C3-derived fragments connect pathway activation to inflammation and opsonization.

Complement activation converges on C3

CLASSICAL

Antigen–antibody + C1

ALTERNATIVE

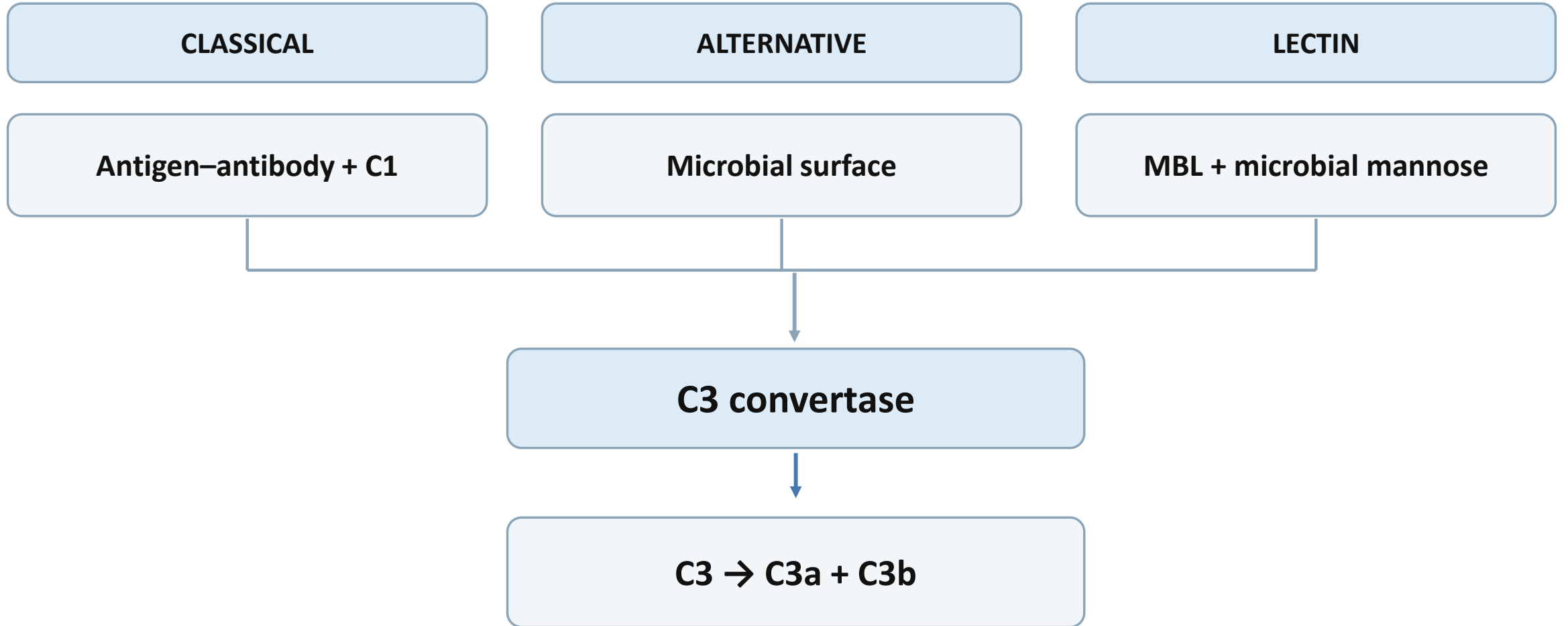
Microbial surface

LECTIN

MBL + microbial mannose

C3 convertase

C3 → C3a + C3b



Classical pathway: Antigen-bound antibody is the trigger

Recognition of an immune target

- IgM or IgG first binds its cognate antigen.
- C1 subsequently binds the antigen–antibody complex.
- Recognition couples adaptive antibody specificity to complement activation.

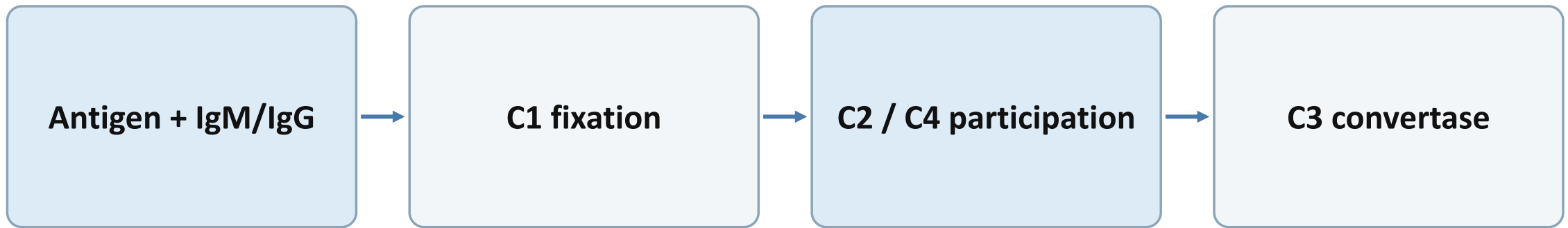
Classical activation requires target-bound antibody

Binding context determines activation

- The Robbins description emphasizes IgM or IgG combined with antigen, not antibody alone.
- The classical pathway begins with fixation of the C1 complex.
- Downstream proteolysis ultimately generates a C3-cleaving enzyme.

Classical pathway: Sequential activation

The sequence is simplified to the component-level description.



The classical route uses antibody-dependent recognition to reach C3.

C1 is the initiating component of the classical pathway

A selective entry point for regulation

- C1 engagement follows recognition of antigen-bound IgM or IgG.
- Subsequent classical-pathway activation involves C2 and C4.
- C1 inhibitor restrains initiation of this pathway.

C2 and C4 act upstream of C3

Early classical-pathway function

- C2 and C4 participate in the sequence that produces a C3-cleaving enzyme.
- Deficiency of either component can reduce classical-pathway activity.
- The alternative pathway can still control many infections in some affected individuals.

Mechanistic example: Antibody-coated host cell

CLINICAL PATTERN

IgM or IgG binds a surface antigen on a host cell.

Mechanistic interpretation

Classical complement activation can deposit C3-derived opsonins on the cell and promote its recognition by phagocytes; The terminal pathway may also damage the cell membrane.

Alternative pathway: Microbial surfaces activate complement

Antibody-independent defense

- Endotoxin (LPS), complex polysaccharides, and other activating substrates may trigger the pathway.
- Classical antigen–antibody binding is not required.
- This permits a direct innate response to microbial surface chemistry.

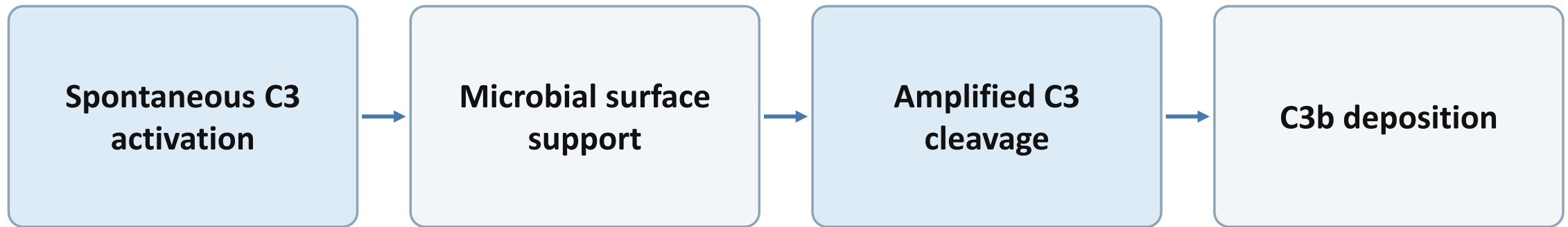
Alternative pathway uses spontaneous C3 cleavage

Activation begins without an antibody trigger

- Spontaneous activation of C3 provides a starting point.
- Activation is amplified and stabilized on microbes or other permissive surfaces.
- The pathway thereby enriches complement activity where activation can persist.

Alternative-pathway amplification on microbial surfaces

The scheme shows the conceptual sequence; Detailed factor names are not required here.



Local amplification is the defining feature of the alternative route.

Alternative activation is not restricted to bacteria

Activating surfaces and substrates

- Microbial lipopolysaccharide is one trigger.
- Complex polysaccharides and other activating substances can initiate or sustain this route.
- Cobra venom is listed as a nonmicrobial activator.

Classical and alternative pathways differ at initiation

Classical recognition

- Requires antigen-associated IgM or IgG for its characteristic trigger.
- C1 is recruited to the antigen–antibody complex.
- C2 and C4 contribute to the classical C3 convertase.

Alternative recognition

- No antigen-bound antibody required.
- Spontaneous C3 activation becomes stabilized on permissive substrates.
- The route is particularly suited to microbial surface recognition.

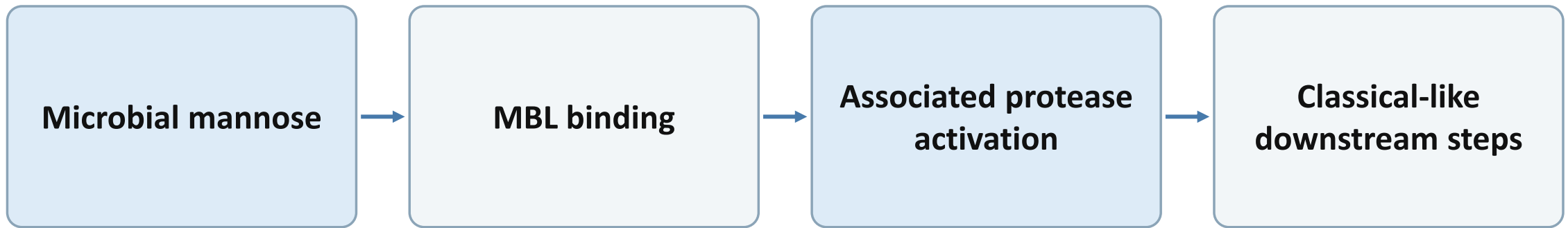
Lectin pathway recognizes microbial carbohydrates

A carbohydrate-dependent trigger

- Circulating mannose-binding lectin (MBL) recognizes mannose-containing microbial surface structures.
- The recognition event occurs without relying on specific antibody.
- Lectin binding activates a protease with homology to C1-associated activation machinery.

Lectin pathway: Recognition to C3 cleavage

After the initial recognition step, the pathway follows the classical route toward C3.



Its recognition event is distinct; Its downstream activation sequence converges.

MBL links microbial pattern recognition to complement

Mechanistic interpretation

- The lectin pathway detects carbohydrate patterns on a microbial surface.
- It does not require antigen-specific IgM or IgG.
- MBL defects may increase susceptibility to infection.

Initiation pathways: A functional comparison

Pathway	Primary trigger	Antibody required?
Classical	Antigen-bound IgM or IgG; C1 fixation	Yes, for the characteristic trigger
Alternative	Microbial surface molecules and other substrates	No
Lectin	MBL recognition of microbial carbohydrate	No

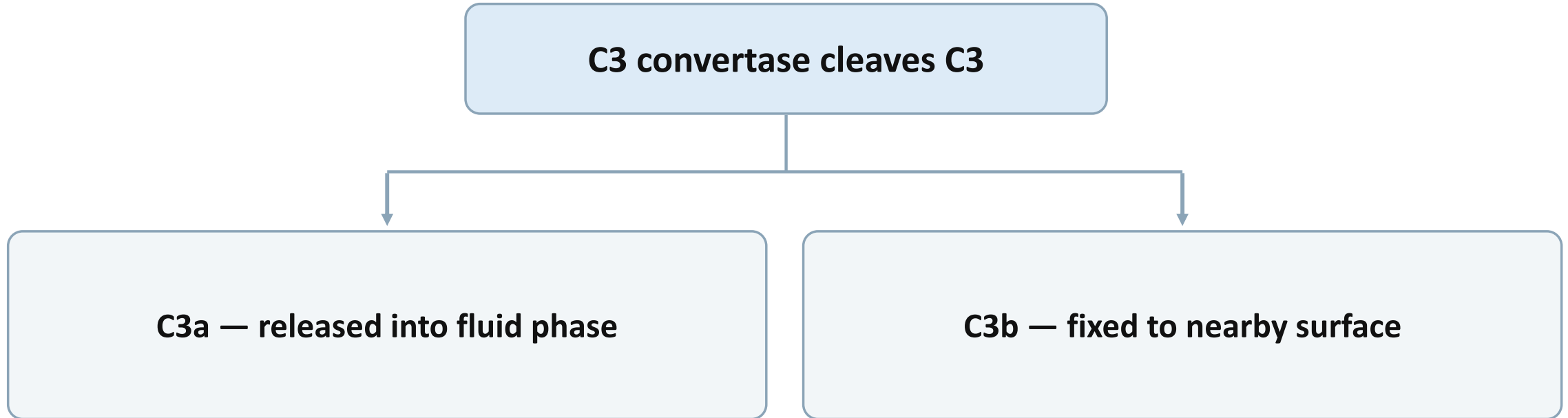
All three converge on generation of C3-cleaving activity.

C3 convertase is the shared enzymatic checkpoint

Convergence despite distinct initiating signals

- All three pathways form an active enzyme termed C3 convertase.
- The enzyme splits C3 into C3a and C3b.
- Different upstream recognition routes therefore produce overlapping downstream biological effects.

C3 cleavage creates two functionally different products



C3a promotes inflammation; C3b supports opsonization and further complement activation.

C3a is a soluble inflammatory mediator

Consequence of C3 cleavage

- C3a is released during proteolytic cleavage of C3.
- It belongs to the anaphylatoxin family of complement fragments.
- Its downstream vascular effects are mediated partly through mast-cell histamine release.

C3b becomes fixed at the activation site

Complement is spatially organized

- C3b becomes covalently attached to a nearby cell or molecular surface.
- Surface attachment facilitates its function as an opsonin.
- Additional deposited C3b participates in formation of C5-cleaving activity.

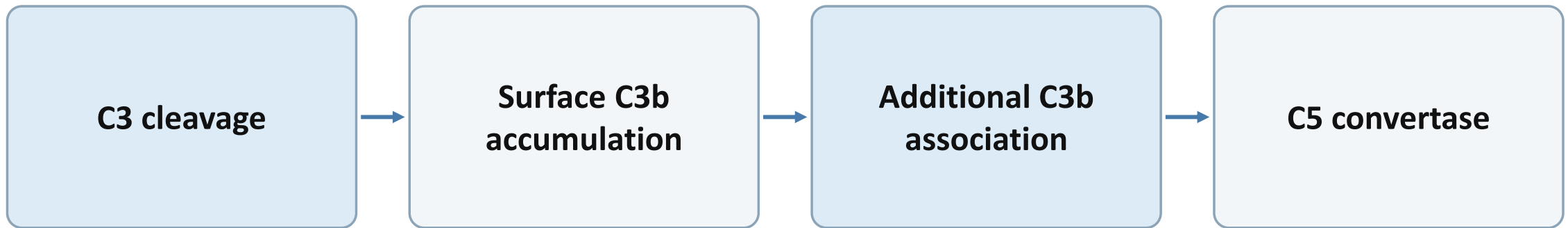
Surface-bound C3b links recognition and effector action

One fragment contributes to two tasks

- It marks a microbial surface for complement-receptor-bearing phagocytes.
- It contributes to assembly of the downstream C5 convertase.
- These actions connect microbial recognition to clearance and terminal activation.

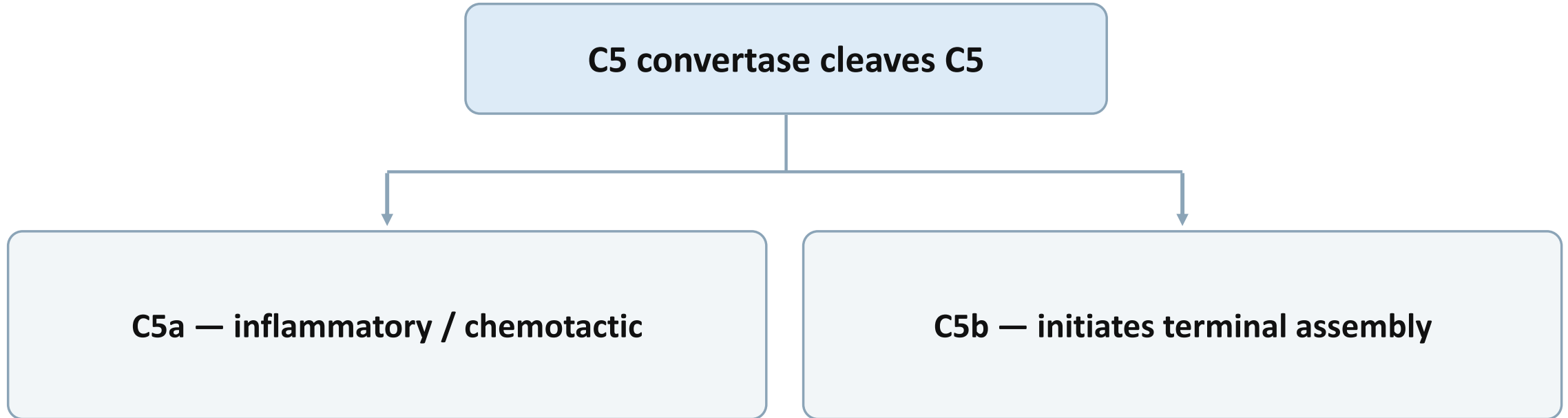
C5 convertase forms after additional C3b deposition

The shared downstream route builds upon prior C3 activation.



C5 activation depends on successful upstream complement activity.

C5 cleavage generates an inflammatory and a terminal fragment



C5a is released; C5b remains associated with the target surface.

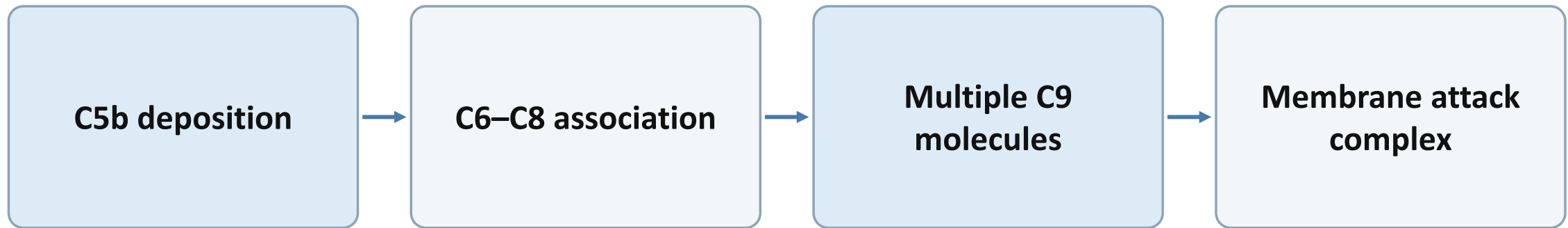
C5a is a potent inflammatory output

The C5 cleavage product acts on leukocytes and vessels

- C5a is one of the complement anaphylatoxins.
- It recruits neutrophils and several other leukocyte populations.
- It also enhances the lipoxygenase pathway of arachidonic acid metabolism in neutrophils and monocytes.

Terminal complement assembly builds the membrane attack complex

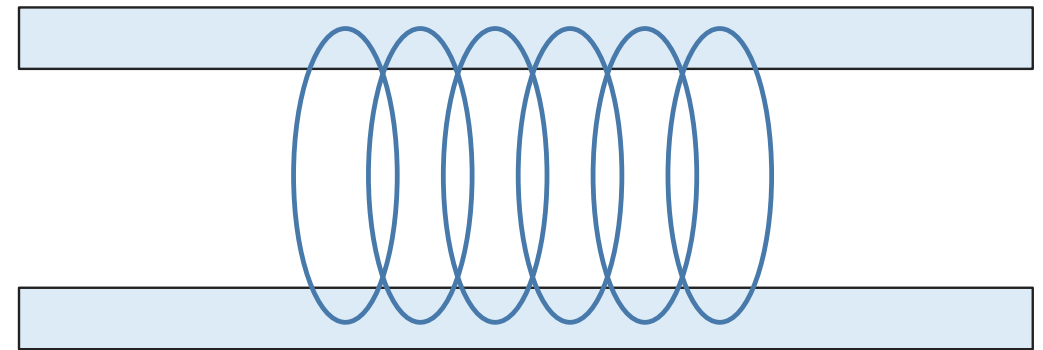
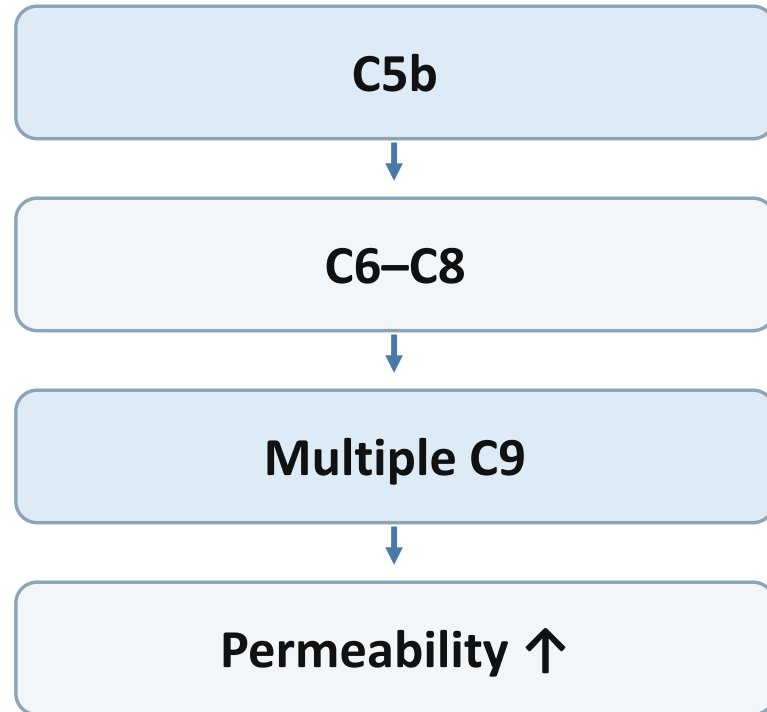
Late complement components assemble after cleavage of C5.



The membrane attack complex (MAC) is the principal direct lytic effector.

Membrane attack complex: Disruption of membrane integrity

Terminal assembly



C5b–C9 pore (schematic)

Water / ion entry → osmotic lysis

Membrane attack results in osmotic cell injury

Physical consequence of terminal complement activation

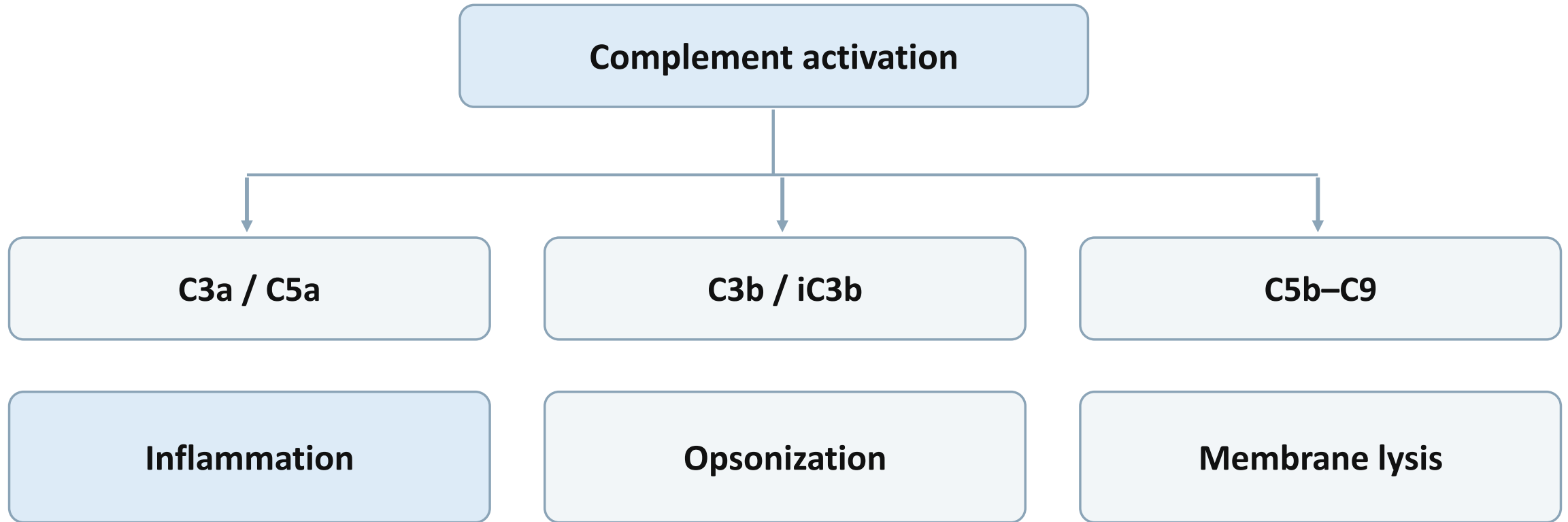
- The MAC renders target membranes permeable to water and ions.
- Loss of membrane integrity disturbs osmotic balance.
- The resulting osmotic injury may lyse susceptible target cells.

Terminal complement is especially important against Neisseria

Microbial susceptibility differs by cell-envelope properties

- Killing bacteria with relatively thin cell walls, particularly Neisseria.
- Deficiency of terminal components impairs membrane attack complex assembly.
- The clinical consequence is susceptibility to recurrent meningococcal or gonococcal infection.

One cascade, three distinct effector functions



Distinct cleavage products mediate different biological outcomes.

Inflammation is a major complement function

Generation of inflammatory cleavage products

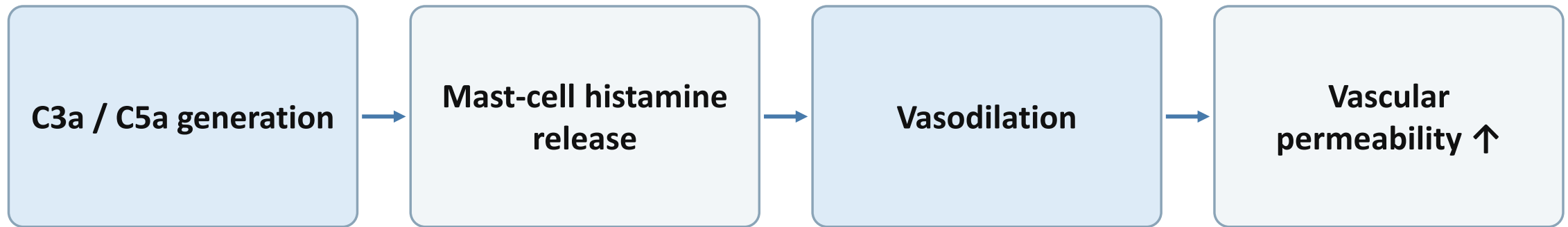
- C5a, C3a, and to a lesser extent C4a act as anaphylatoxins.
- These fragments promote mast-cell mediator release.
- Complement links innate recognition to vascular and cellular inflammation.

Anaphylatoxins: Relative functions

Fragment	Principal teaching function	Additional note
C5a	Inflammation and leukocyte chemotaxis	Enhances lipoxygenase pathway
C3a	Inflammatory vascular effects	Acts as an anaphylatoxin
C4a	Weaker anaphylatoxin effect	Less prominent than C3a/C5a

Anaphylatoxins alter microvascular function

The vascular response helps plasma proteins and leukocytes reach an inflamed site.



Inflammatory fragments act through mediator release; They are not simply pores.

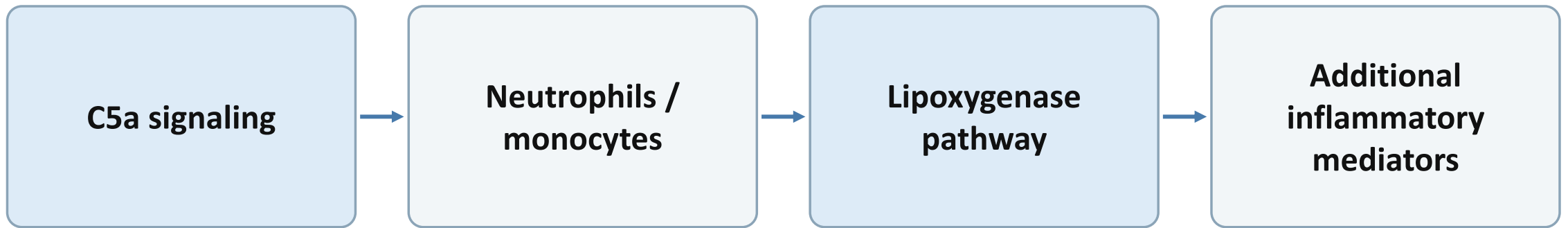
C5a is a leukocyte chemoattractant

Cell types explicitly named by Robbins

- Neutrophils are recruited toward an inflammatory focus.
- Monocytes, eosinophils, and basophils also respond to C5a.
- The chemotactic effect complements C5a-mediated changes in vascular permeability.

C5a amplifies mediator production in leukocytes

The source links C5a to arachidonic-acid-derived mediator production.



Complement can amplify inflammation beyond its initial cleavage products.

Complement-driven inflammation has a cost

Host defense and tissue injury share pathways

- Greater vascular permeability and leukocyte recruitment are advantageous during microbial defense.
- The same mechanisms can cause injury when activation occurs on host cells or in host tissues.
- Complement regulation must protect cells without abolishing microbial defense.

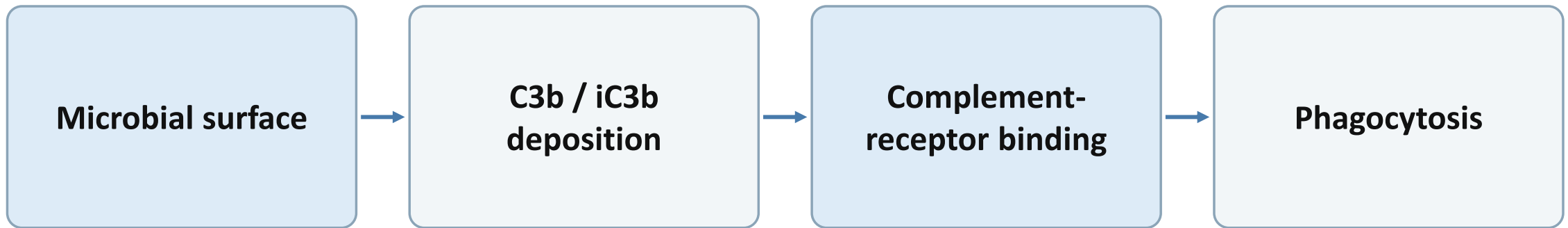
Opsonization is the second major complement function

Surface fragments help phagocytes recognize targets

- C3b deposits on microbial surfaces.
- Inactive C3b (iC3b), a cleavage product of C3b, also functions as an opsonin.
- Neutrophils and macrophages express receptors for complement fragments.

Complement opsonization leads to ingestion of microbes

The surface tag recruits the phagocytic machinery without itself causing lysis.



Opsonization improves recognition; Ingestion and destruction occur in phagocytes.

IC3b retains an opsonic role after C3b cleavage

Inactivation does not mean loss of all function

- C3b can be cleaved to inactive C3b (iC3b).
- Both C3b and iC3b as opsonins.
- Complement-fragment receptors allow phagocytes to recognize coated microbes.

Complement opsonization differs from antibody Fc recognition

Complement recognition

- C3-derived fragments decorate target surfaces.
- Neutrophils and macrophages bind complement fragments through their receptors.
- Surface coating increases phagocytic recognition.

Antibody recognition

- IgG-coated cells can bind Fc receptors on phagocytes.
- Antigen-bound IgM or IgG can trigger classical complement activation.
- Fc-receptor and complement-receptor pathways can act together.

Opsonization and lysis are different complement outcomes

Opsonization

- C3b and iC3b tag a surface.
- Requires contact with a complement-receptor-bearing phagocyte.
- Promotes cellular uptake and intracellular destruction.

Direct lysis

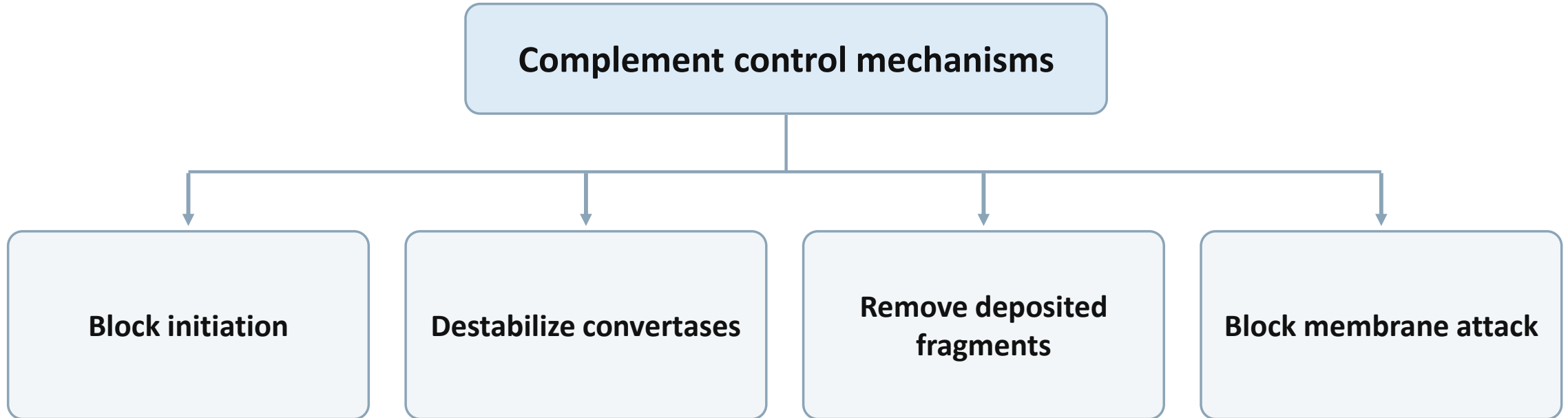
- C5b–C9 forms a membrane attack complex.
- Changes target-membrane permeability.
- Can induce osmotic rupture without phagocytic ingestion.

Host cells require protection from complement

Regulation prevents self-injury

- Complement can deposit activated fragments on healthy as well as microbial surfaces.
- Host cells express regulators that limit formation or persistence of active fragments.
- Circulating regulators provide additional restraint of complement activation.

Regulatory proteins interrupt complement at different stages



Distinct checkpoints protect normal cells against excessive complement injury.

C1 inhibitor controls classical-pathway initiation

Early control point

- C1 inhibitor (C1 INH) blocks activation of the classical pathway's first component.
- It prevents unrestricted activation at the initiation stage.
- An inherited deficiency is associated with hereditary angioedema.

Hereditary angioedema illustrates loss of protease control

Mechanism of tissue swelling

- C1 INH also regulates factor XII and the kallikrein system, not only complement.
- Deficiency permits unregulated kallikrein activity and production of vasoactive peptides, including bradykinin.
- The clinical phenotype is episodic edema involving skin and mucosal surfaces.

Clinical correlation: Hereditary angioedema

CLINICAL PATTERN

An individual experiences recurrent episodes of swelling of the skin and mucosal surfaces; Some episodes affect the larynx or gastrointestinal tract.

Mechanistic interpretation

Loss of C1 inhibitor permits dysregulated protease activity involving the kallikrein pathway. The important risk is potentially life-threatening laryngeal edema.

CD55 prevents formation of C3 convertases

Decay-accelerating factor (DAF)

- CD55 is also known as decay-accelerating factor.
- It is attached to the cell membrane by a glycosylphosphatidylinositol (GPI) anchor.
- Its protective action reduces persistence or formation of C3-cleaving activity on host surfaces.

CD59 prevents membrane attack complex assembly

Terminal protection of host cells

- CD59 is a GPI-anchored complement regulatory protein.
- Its main action is to inhibit formation of the membrane attack complex.
- Together, CD55 and CD59 act at distinct levels of the cascade.

Complement regulation: Site and mechanism

Regulator	Primary control point	Consequence of loss
C1 INH	Initiation / regulated proteases	Hereditary angioedema
CD55 (DAF)	C3 convertases	Excess C3 activation on affected cells
CD59	Membrane attack complex	Complement-mediated cell lysis
Factor H	Alternative pathway C3b and convertases	Complement-associated vascular injury

GPI anchoring localizes CD55 and CD59 to cell membranes

Why one biosynthetic defect affects two inhibitors

- Both CD55 and CD59 are attached to the plasma membrane by GPI anchors.
- An acquired defect in GPI-anchor synthesis can remove multiple surface protective proteins.
- The resulting loss of restraint makes vulnerable cells susceptible to complement-mediated injury.

Clinical correlation: Paroxysmal nocturnal hemoglobinuria

CLINICAL PATTERN

An acquired cellular defect eliminates normal GPI-anchored protective proteins, including CD55 and CD59, from affected erythrocytes.

Mechanistic interpretation

The red cell loses convertase and terminal-pathway protection and becomes susceptible to complement-mediated hemolysis.

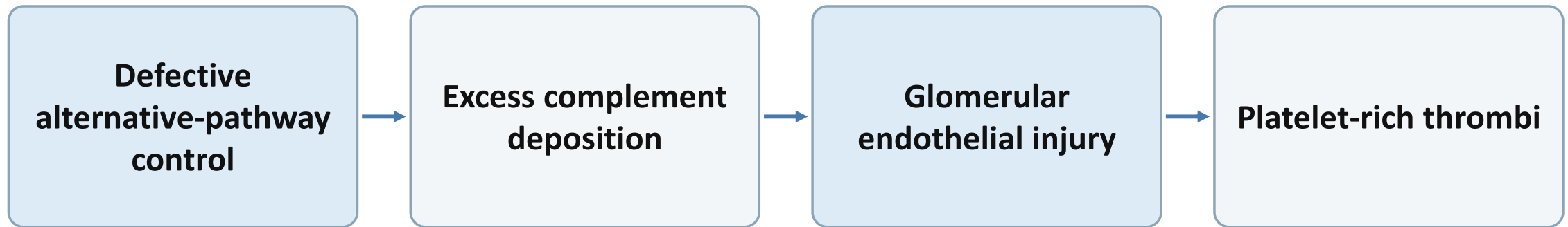
Factor H restrains the alternative pathway

Circulating control of deposited complement

- Factor H is a circulating glycoprotein that limits the alternative complement pathway.
- It promotes cleavage and inactivation of C3b.
- It also promotes turnover of C3 convertases, thereby reducing amplification.

Factor H deficiency can damage glomerular endothelium

A mechanistic sequence described for atypical hemolytic uremic syndrome.



Regulatory failure may produce thrombotic microangiopathic injury.

Clinical correlation: Atypical hemolytic uremic syndrome

CLINICAL PATTERN

Inherited abnormalities of Factor H or interacting complement regulatory proteins impair control of alternative-pathway activation.

Mechanistic interpretation

Uncontrolled complement deposition in glomerular vessels can injure endothelium and favor platelet-rich thrombus formation.

Factor H variants are also linked to retinal degeneration

A distinct consequence of complement dysregulation

- An association between Factor H gene polymorphisms and age-related macular degeneration.
- The association implicates complement regulation in a disease outside acute infection.
- The source describes a genetic association; It does not provide a quantitative individual risk estimate.

Complement activation can injure host tissue

Immune complexes and surface-reactive antibodies

- Antibodies or antigen–antibody complexes may accumulate on host cells and tissues.
- Complement activated at those sites contributes to inflammation, opsonization, and tissue injury.
- The protective cascade becomes pathogenic when its effector mechanisms target self.

Early classical-component deficiency may associate with autoimmunity

Deficiencies of C1q, C2, and C4

- C2 deficiency is described as the most common complement-protein deficiency.
- Early classical-pathway deficiencies can predispose to infection, but some individuals have no symptoms.
- Deficiency of C1q, C2, or C4 may present prominently with systemic lupus erythematosus.

C3 deficiency compromises multiple complement effects

A shared-pathway failure

- C3 is required for the convergent downstream responses of all three pathways.
- Deficiency may cause serious, recurrent pyogenic infection.
- Robbins also describes increased immune complex–mediated glomerulonephritis.

Alternative-pathway deficiencies increase infection risk

Properdin and factor D

- Deficiencies affecting properdin or factor D are described as rare.
- Loss of alternative-pathway function is associated with recurrent pyogenic infections.
- The phenotype reflects weakened antibody-independent complement defense.

MBL deficiency weakens lectin-pathway initiation

A recognition defect rather than terminal lysis defect

- Inherited deficiency or defective MBL impairs the lectin pathway's recognition event.
- The textbook associates this abnormality with increased susceptibility to infection.
- This differs mechanistically from deficiency of terminal C5–C9 components.

Terminal-component deficiency preferentially predisposes to Neisseria

Loss of membrane attack

- C5, C6, C7, C8, and C9 are required for MAC formation.
- Deficiency is associated with recurrent Neisseria infections.
- Classical and alternative upstream activation may remain possible despite ineffective terminal lysis.

Complement defects predict characteristic clinical patterns

Affected component	Primary mechanism	Illustrative clinical phenotype
C1q / C2 / C4	Impaired early classical pathway	Infection ± SLE
C3	Loss of major shared effector functions	Recurrent severe pyogenic infection
Factor D / properdin	Alternative-pathway defect	Recurrent pyogenic infection
C5–C9	Deficient membrane attack complex	Recurrent Neisseria infection
C1 INH / CD55 / CD59 / Factor H	Loss of complement regulation	Angioedema / PNH / complement-associated vascular injury

Complement inhibition targets the cascade itself

A therapeutic principle stated in the source

- Inhibitors of complement C5 activation are approved for several complement-mediated disorders.
- Inhibitors of C3 activation have also entered approved clinical use.
- The clinical rationale is to block pathological complement effects while recognizing its host-defense function.

Clinical reasoning: Recurrent Neisseria infections

CLINICAL PATTERN

A patient has repeated meningococcal or gonococcal infections without an explanation based on leukocyte dysfunction.

Mechanistic interpretation

Consider deficiency of late complement components: C5–C9-dependent membrane attack is particularly important against Neisseria.

Clinical reasoning: Severe recurrent pyogenic infection

CLINICAL PATTERN

A patient has recurrent serious pyogenic bacterial infections together with evidence of immune complex–related glomerular injury.

Mechanistic interpretation

A shared complement-component defect such as C3 deficiency can impair opsonization and multiple complement functions.

Pathogenic complement: Too little versus too much

SOLUBLE / INFLAMMATORY

Complement component deficiency



Inadequate opsonization / lysis



Susceptibility to infection

MEMBRANE / CELL-ASSOCIATED

Regulator deficiency



Excess activation on host structures



Tissue or vascular injury

Clinical phenotypes depend on where the cascade is impaired.

Synthesis: Four mechanistic checkpoints

Follow the biological logic rather than memorizing isolated proteins

- Recognition: Classical, alternative, or lectin trigger.
- Amplification: Generation of C3 convertase and C3 cleavage.
- Effector action: Inflammation, C3b/iC3b opsonization, or C5b–C9 lysis.
- Regulation: Initiation, convertase, and terminal controls prevent host injury.

Mechanism-based revision questions

Question	Mechanism-based answer
Why do three pathways produce overlapping effects?	All form C3 convertase.
Which C3 product marks target surfaces?	C3b; iC3b retains opsonic activity.
Which complement product recruits leukocytes?	C5a (especially important).
What causes osmotic membrane injury?	C5b–C9 membrane attack complex.
Why does GPI-anchor loss favor hemolysis?	Affected red cells lose CD55 and CD59 protection.

References and source boundaries

Primary textbook

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. 2026.

Chapter 3: Inflammation and Repair — “Complement System,” pp. 81–82.

Chapter 6: Diseases of the Immune System — complement deficiencies; antibody-mediated cellular injury.

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