

C3-Dominant Glomerulopathy

Complement dysregulation • glomerular morphology •
clinicopathologic diagnosis

Dense deposit disease | C3 glomerulonephritis

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Learning objectives

- Explain how alternative-pathway dysregulation produces C3-dominant glomerular deposits.
- Distinguish dense deposit disease from C3 glomerulonephritis by ultrastructure.
- Integrate light microscopy, immunofluorescence, electron microscopy and clinical context.
- Recognize key diagnostic pitfalls and implications for prognosis and transplantation.

MPGN is a pattern of injury, not one etiology

Morphologic designation

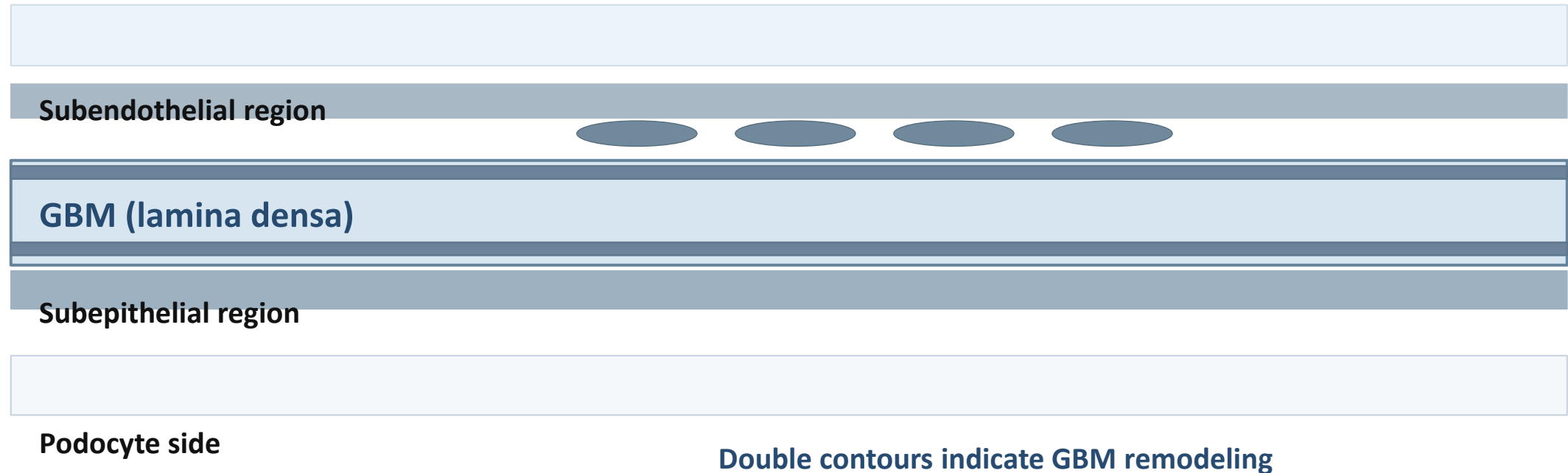
- Glomerular cell proliferation with capillary-wall remodeling.
- Basement-membrane duplication produces double contours.

Mechanistic diagnosis

- Immune complex-mediated disease and complement-mediated C3G can share this appearance.
- Deposits and pathway of injury determine classification.

The MPGN pattern remodels capillary walls

Mesangial interposition and new basement-membrane material can create double contours.



Simplified cross-section — not an electron micrograph

Two pathogenetic pathways behind MPGN

Feature	Immune complex–mediated MPGN	C3-dominant glomerulopathy
Primary driver	Immunoglobulin-containing immune complexes	Alternative complement-pathway dysregulation
Glomerular IF	IgG and C3; C1q/C4 often present	C3-dominant; IgG usually absent
Characteristic EM	Discrete subendothelial deposits	DDD ribbon or C3GN cloudy deposits

Historical types do not equal modern mechanisms

Older classification

- Type I MPGN: Often immune complex-mediated.
- Type II MPGN: Now termed dense deposit disease.

Mechanism-led classification

- C3G encompasses dense deposit disease and C3 glomerulonephritis.
- Morphologic MPGN is not obligatory in C3G.

C3G encompasses two major deposit patterns

Dense deposit disease (DDD)

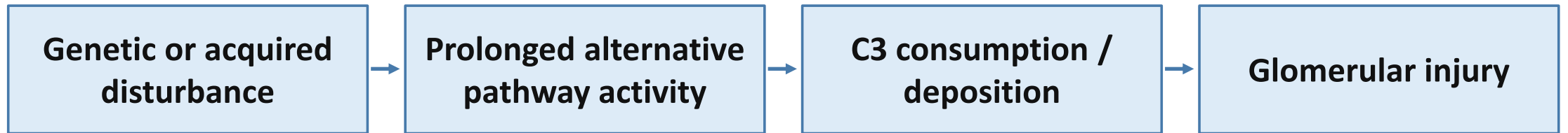
- Formerly type II MPGN.
- Extremely electron-dense intramembranous ribbonlike deposits.

C3 glomerulonephritis (C3GN)

- Ill-defined or cloudy electron-dense deposits.
- Deposits may occupy several glomerular compartments.

The unifying mechanism is alternative-pathway excess

Mechanistic / diagnostic sequence

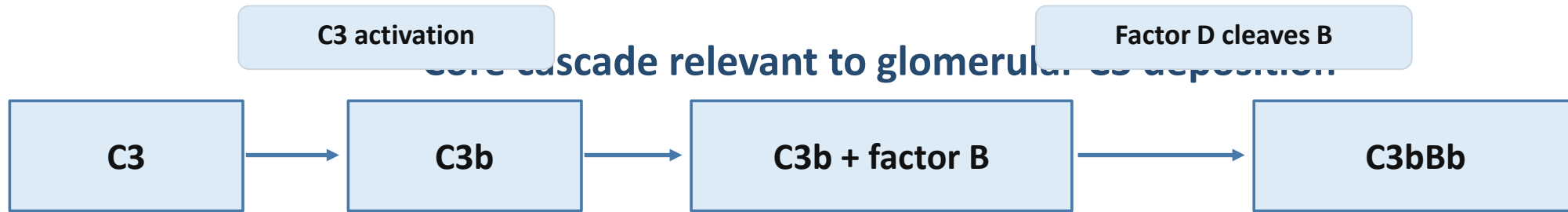


Distinct etiologies converge on the same complement-driven lesion.

Why C3 deposition can occur without IgG

- The alternative pathway can activate complement without immunoglobulin-containing immune complexes.
- C3-containing products accumulate in glomeruli.
- IgG is usually absent or much weaker than C3 on immunofluorescence.
- Predominance of C3 is therefore pathogenetically informative.

Alternative-pathway activation: The components



Convertase identity

- C3bBb is the alternative-pathway C3 convertase.
- This enzyme generates additional C3b.

Mechanistic consequence

- More active convertase amplifies C3 activation.
- Poor control promotes glomerular complement deposition.

Stimuli that initiate alternative-pathway activation

Bacterial polysaccharides

A non-antibody microbial activator named.

Endotoxin

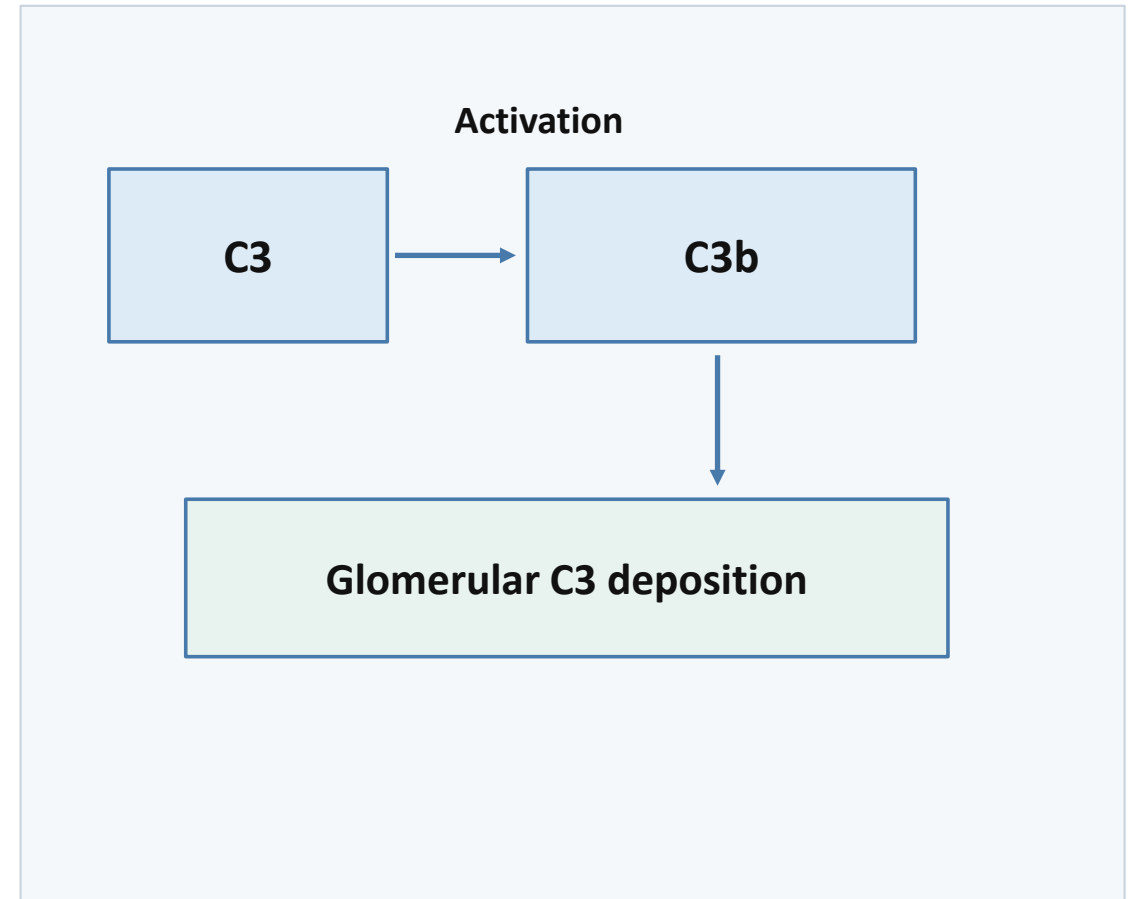
A microbial trigger of the complement cascade.

IgA aggregates

An additional triggering stimulus.

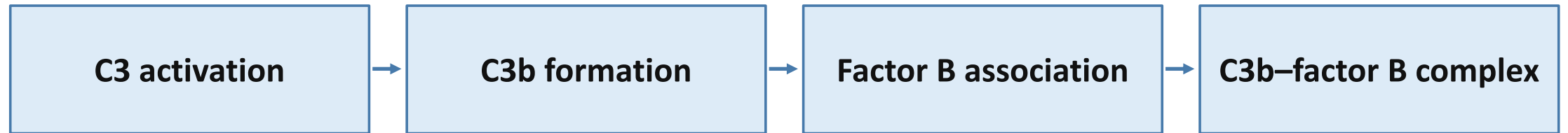
C3 activation generates C3b

- C3 is central to alternative-pathway activation.
- Activation yields C3b, which participates in convertase assembly.
- Excessive cleavage leads to increased downstream complement activity.



Factor B enters the convertase assembly pathway

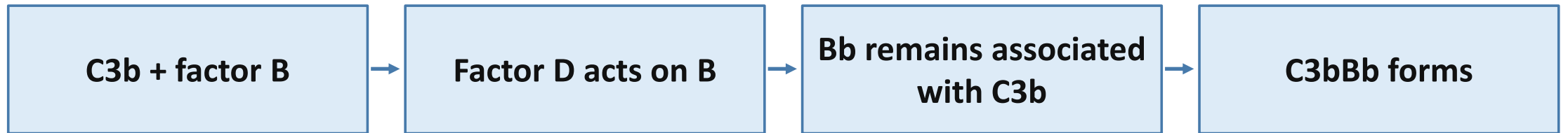
Mechanistic / diagnostic sequence



Factor B is a core alternative-pathway component.

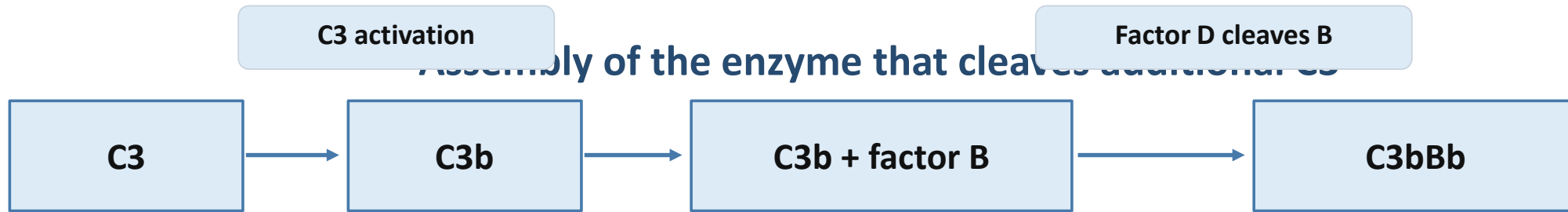
Factor D supports generation of the convertase

Mechanistic / diagnostic sequence



The active C3 convertase comprises C3bBb.

C3bBb is the alternative-pathway C3 convertase



Convertase identity

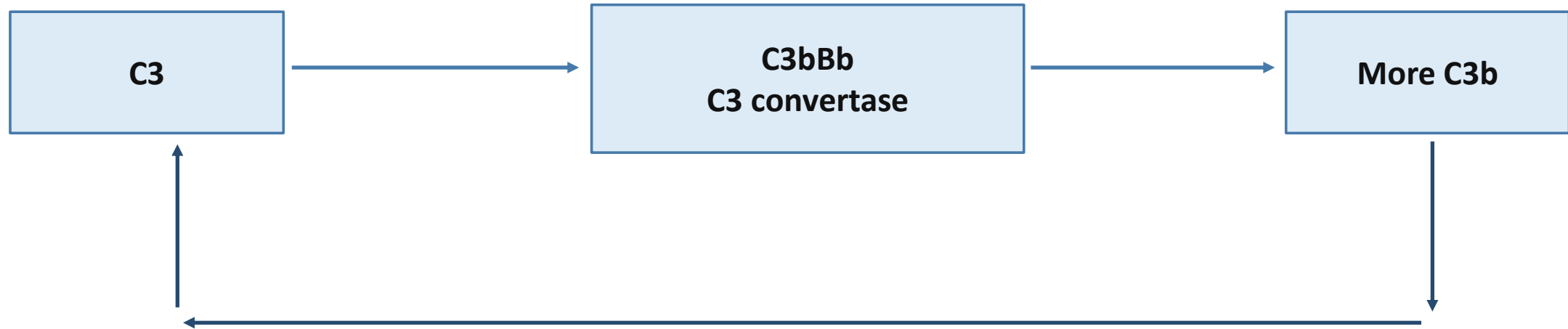
- C3bBb is the alternative-pathway C3 convertase.
- This enzyme generates additional C3b.

Mechanistic consequence

- More active convertase amplifies C3 activation.
- Poor control promotes glomerular complement deposition.

C3 amplification creates positive feedback

Persistent C3 convertase activity multiplies C3b production



Positive feedback: New C3b sustains more convertase assembly

Normal C3bBb is intrinsically labile

Normal behavior

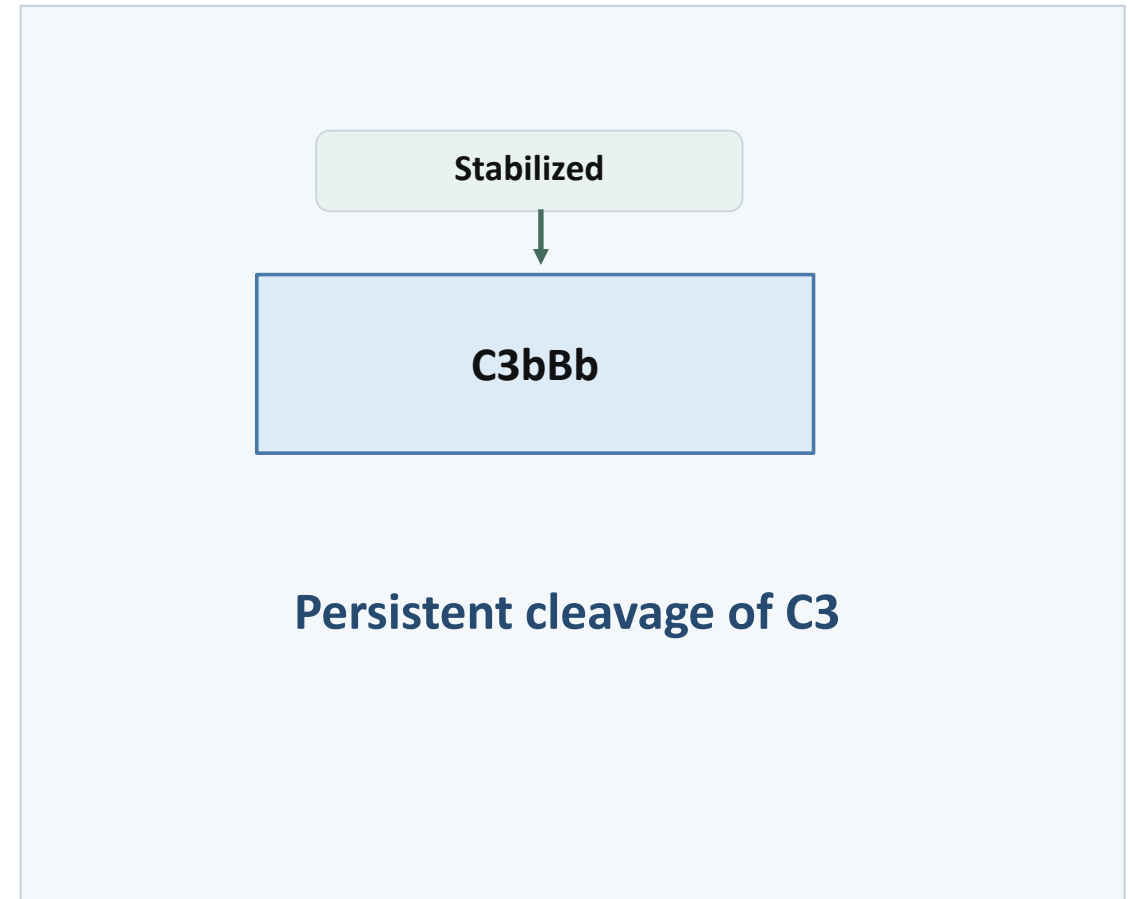
- C3bBb does not remain indefinitely active.
- Its limited stability constrains complement amplification.

Disease-state implication

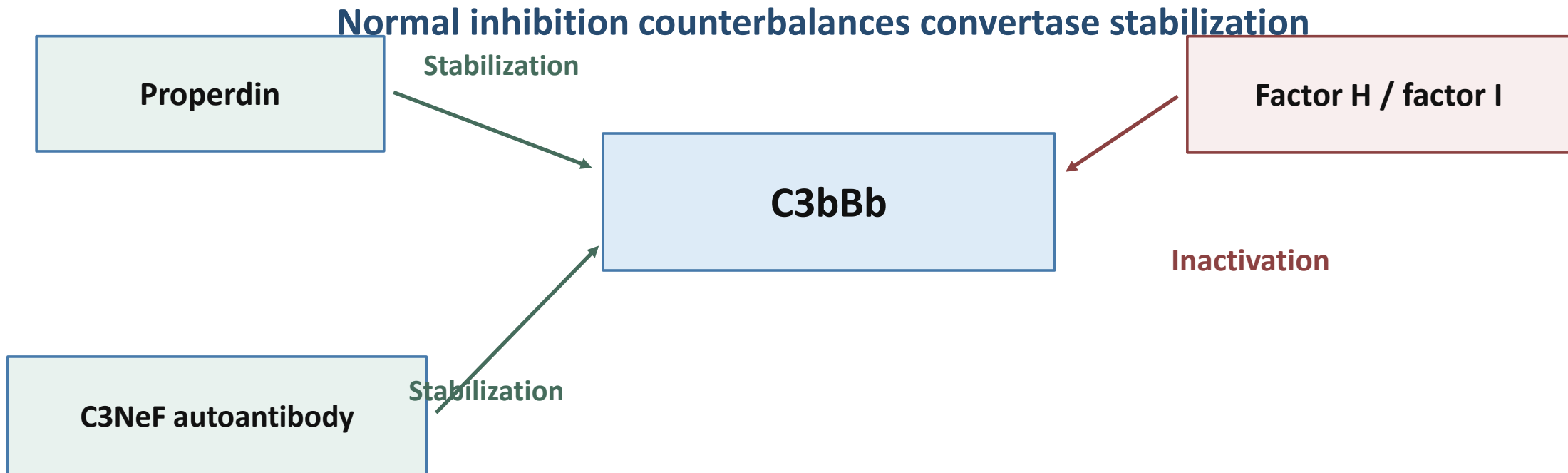
- Stabilization or impaired inactivation allows continued C3 cleavage.
- Persistent activation drives complement consumption.

Properdin stabilizes C3 convertase

- Properdin is a physiologic alternative-pathway component.
- It prolongs the activity of C3bBb.
- This positive influence contrasts with regulatory inactivation by factor H and factor I.



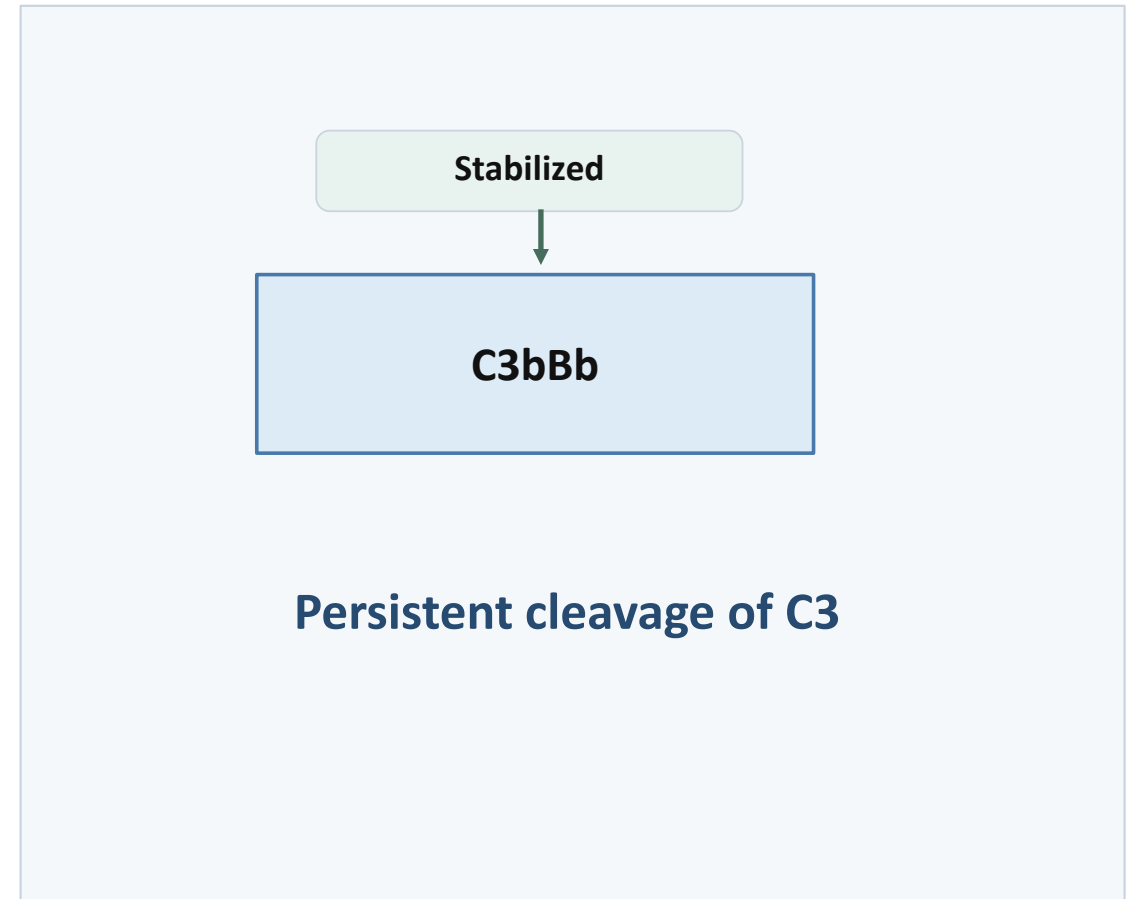
Factor H and factor I restrain complement activity



Disease results when activation persists despite normal restraining mechanisms.

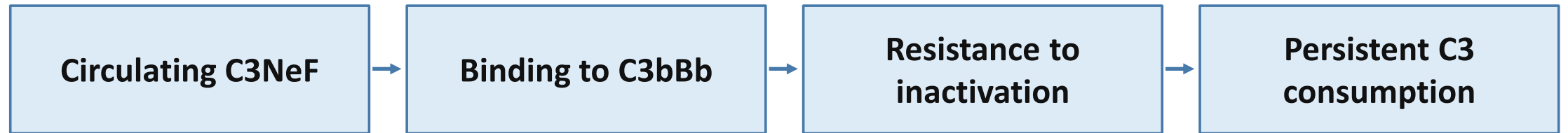
C3 nephritic factor sustains C3bBb

- C3 nephritic factor (C3NeF) is an acquired autoantibody.
- It binds and stabilizes the C3bBb convertase.
- Protection from inactivation permits persistent C3 activation and C3 depletion.



C3NeF mimics a convertase-stabilizing action

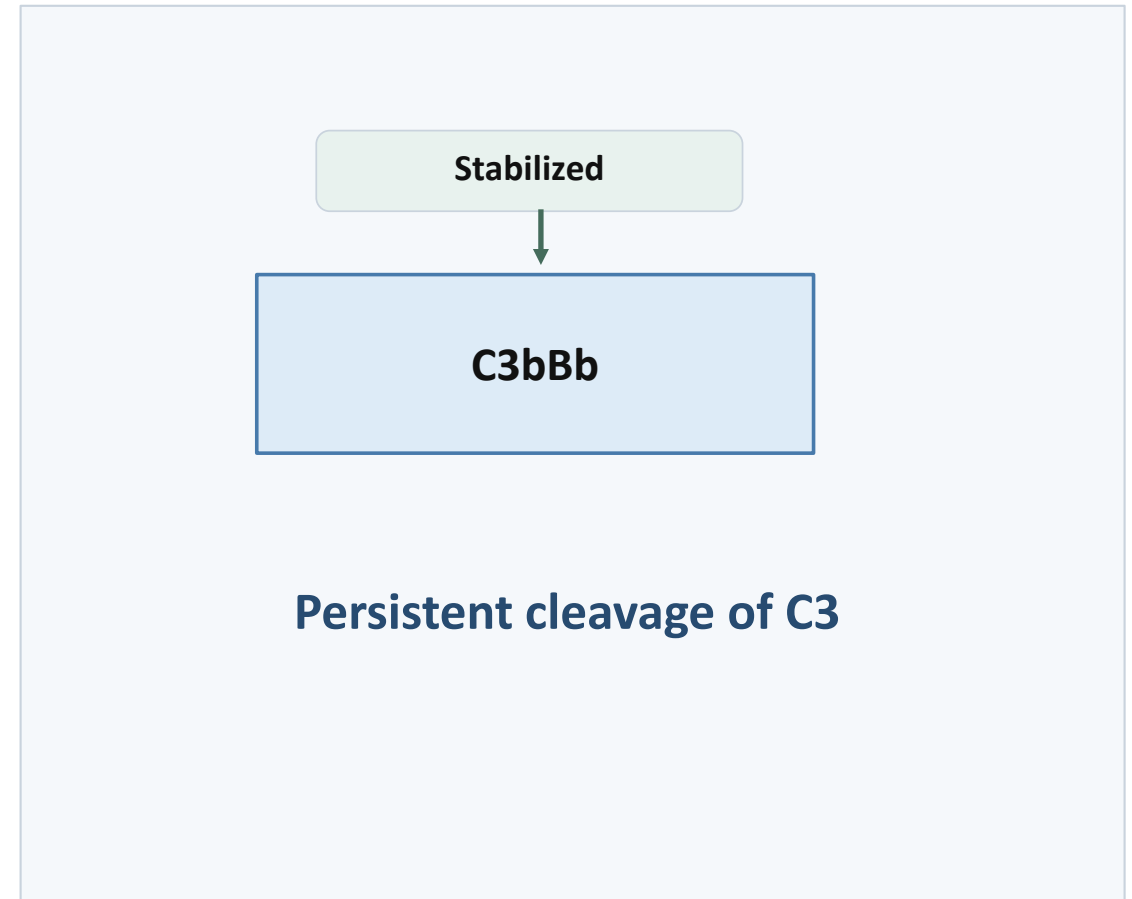
Mechanistic / diagnostic sequence



C3NeF in acquired C3GN.

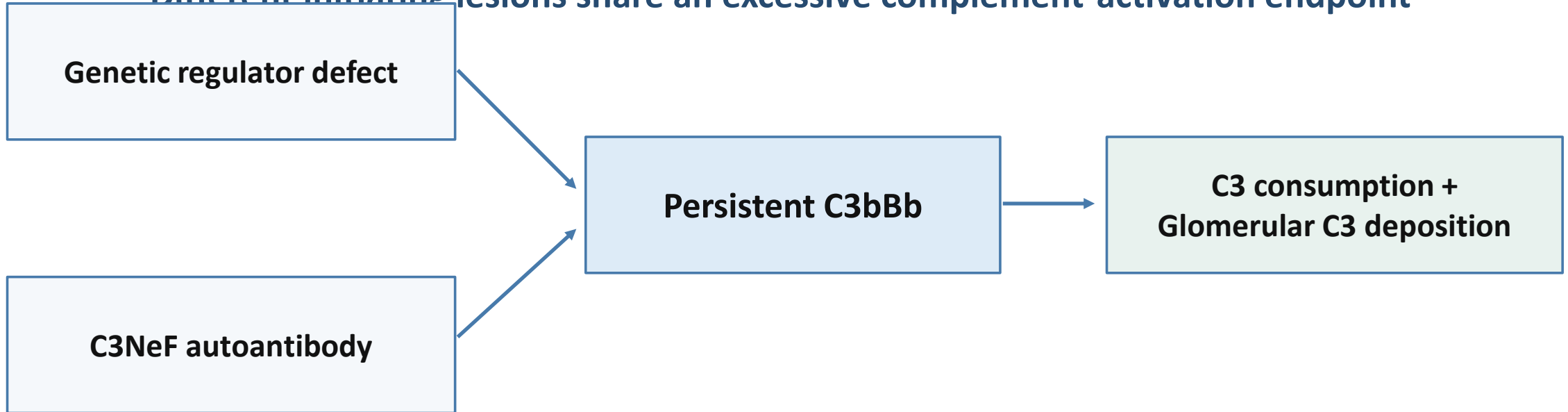
Inherited complement abnormalities also cause C3G

- Genetic variants in alternative-pathway components or regulators may produce disease.
- Factor H is one example cited.
- Genetic forms may present in children and younger adults.



Acquired and inherited routes converge

Different initiating lesions share an excessive complement-activation endpoint



Two initiating pathways converge on excessive alternative-pathway activation.

The complement profile reflects pathway consumption

Typically decreased

- Serum C3.
- Factor B and properdin may be reduced through alternative-pathway activity.

Relatively preserved

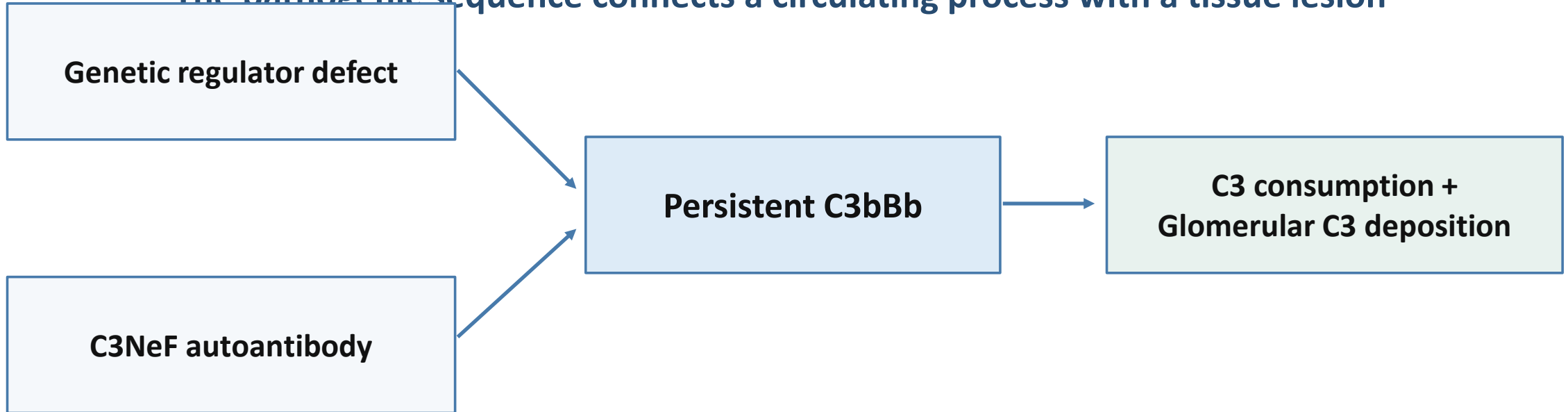
- Early classical pathway components such as C1 and C4.
- An alternative-pathway pattern is suggested by low C3 with preserved C4.

C3 and C4 help localize the activated pathway

Serologic observation	Mechanistic interpretation
Low C3	Supports complement activation / consumption
Normal C4 and early classical components	Compatible with preferential alternative-pathway involvement
Low factor B or properdin	Further supports alternative-pathway activity
A normal serum complement test	Cannot by itself exclude tissue-defined C3G

Complement dysregulation becomes glomerular injury

The pathogenic sequence connects a circulating process with a tissue lesion



Two initiating pathways converge on excessive alternative-pathway activation.

Pathologic confirmation needs three modalities

Light microscopy

Defines the glomerular injury pattern and severity.

Immunofluorescence

Establishes dominance of C3 over routine immune reactants.

Electron microscopy

Localizes and characterizes deposits; Distinguishes DDD from C3GN.

C3G displays diverse light-microscopic patterns

Mesangial proliferative

Mesangial cells and matrix predominate.

Inflammatory / endocapillary

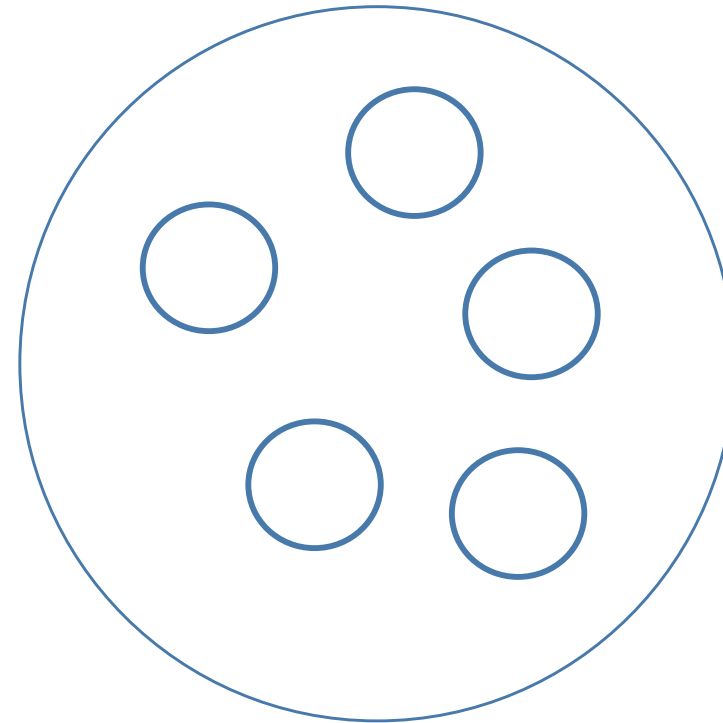
Infiltrating leukocytes and increased glomerular cellularity.

Crescentic / MPGN-like

Crescents or double-contour capillary walls may occur.

Mesangial proliferation is common in C3G

- Many C3G biopsies are predominantly mesangial proliferative.
- This differs from the assumption that every case must show classic MPGN.
- Cellular and matrix expansion are patterns of injury, not proof of a specific complement defect.

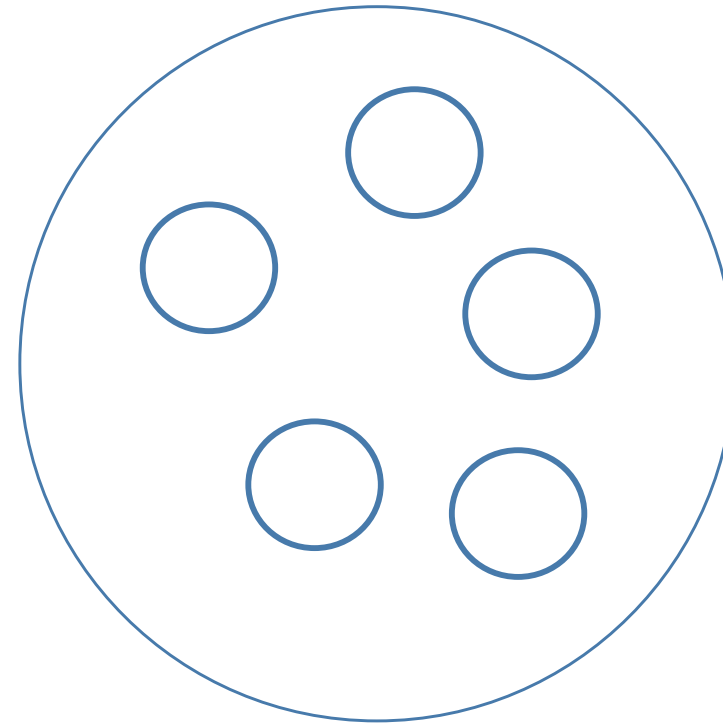


Remodeled glomerular loops

Schematic — not a clinical or histologic specimen

An inflammatory pattern can obscure the cause

- Some glomeruli are hypercellular with inflammatory leukocytes.
- Endocapillary inflammation may accompany complement deposition.
- Immunofluorescence and EM remain necessary for mechanistic classification.



Remodeled glomerular loops

Schematic — not a clinical or histologic specimen

Crescents signal a severe injury pattern

What is observed

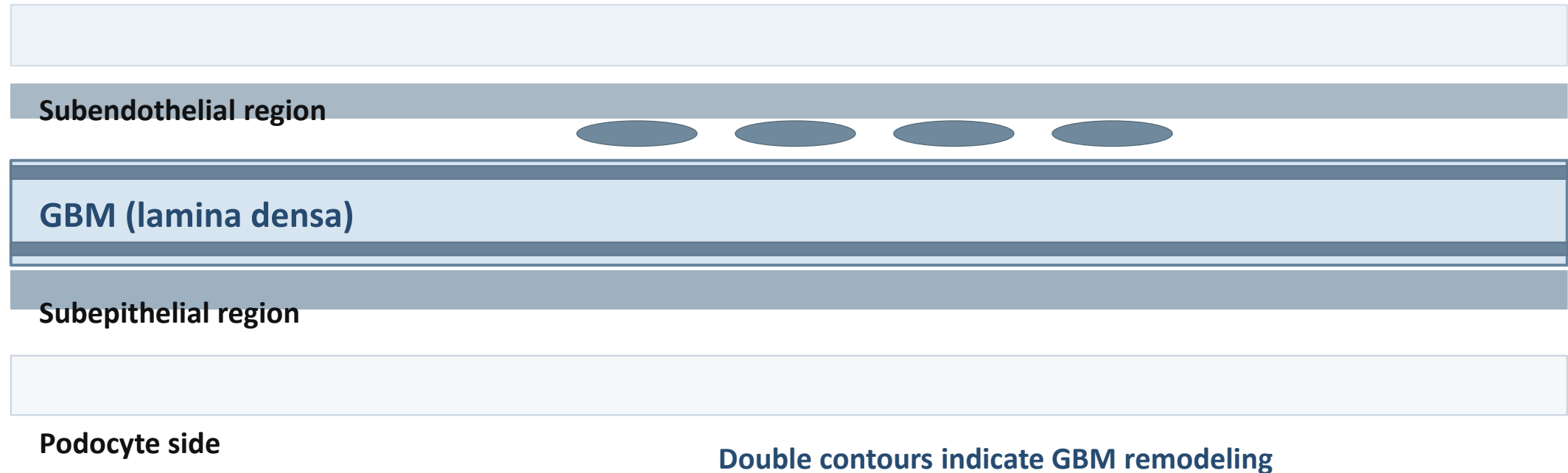
- C3G may show focally crescentic lesions.
- Crescents indicate major glomerular capillary-wall injury.

Why it matters

- A crescentic pattern raises concern for rapidly progressive clinical dysfunction.
- The presence of crescents does not specify the deposit etiology.

A classic MPGN pattern may also occur in C3G

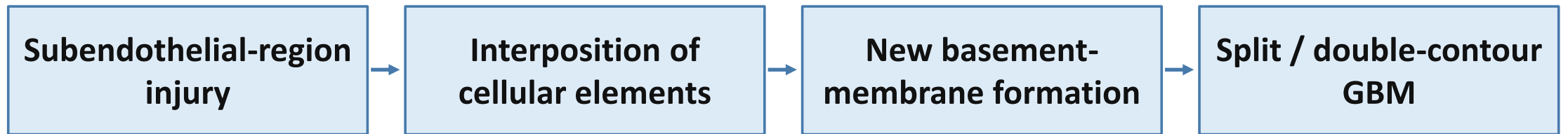
Capillary lumen / endothelium **MPGN remodeling and alternative-pathway disease are compatible.**



Simplified cross-section — not an electron micrograph

Double contours reflect GBM remodeling

Mechanistic / diagnostic sequence



These changes can occur in immune complex MPGN and complement-driven lesions.

Light microscopy cannot separate DDD from C3GN

LM can establish

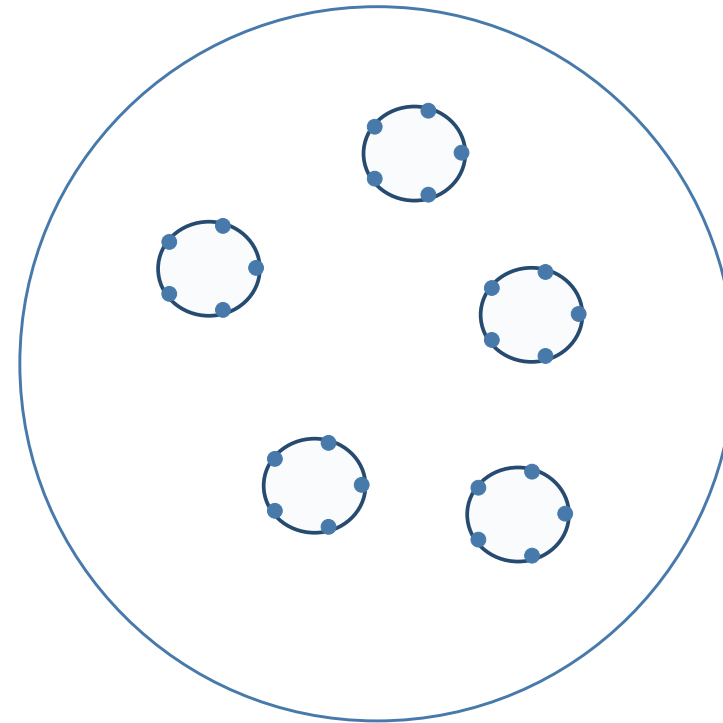
- Mesangial, endocapillary, crescentic or MPGN pattern.
- Severity of glomerular cell response.

LM cannot reliably establish

- The characteristic ultrastructural nature of deposits.
- DDD versus C3GN without electron microscopy.

Immunofluorescence identifies dominant C3

- C3 signal is stronger than routine immune reactants.
- The dominant component is complement, not deposited IgG.
- C3-dominant staining directs attention to alternative-pathway dysregulation.



C3-dominant glomerular signal

Schematic — not a clinical or histologic specimen

C3 dominance is a semiquantitative IF concept

Source / convention	Description
Robbins, 11th edition	C3 is typically much stronger than other routine reactants.
Consensus reporting convention	At least two IF intensity grades above any other immune reactant (0–3+ scale).
Interpretation	Do not equate this semiquantitative comparison with a literal biochemical concentration ratio.

Immunoglobulin staining is usually absent

Expected C3G profile

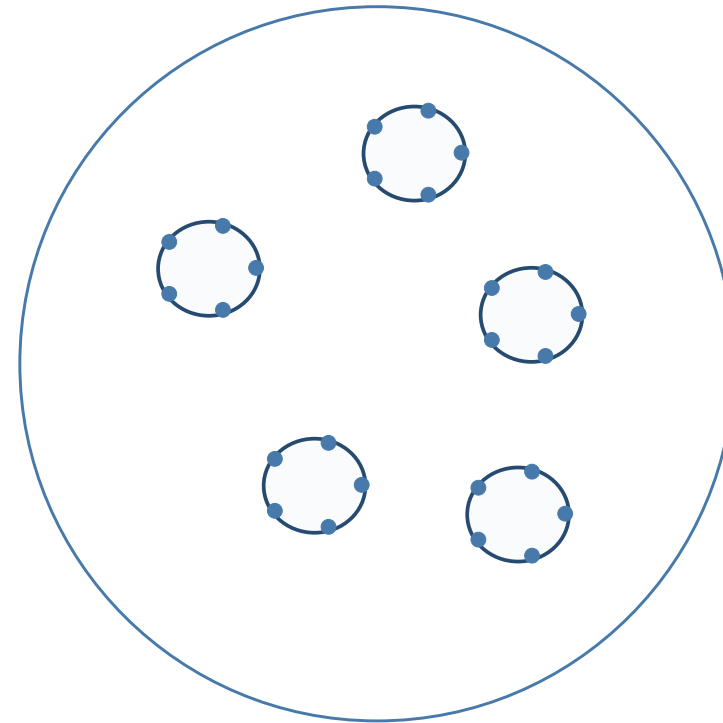
- Intense glomerular C3.
- IgG generally absent or weak description.

Interpretation caveat

- Some C3G biopsies can contain weaker immunoglobulin staining.
- Absolute Ig negativity is not the defining requirement.

Dense deposit disease has a distinctive IF distribution

- C3 may outline capillary walls in irregular granular or linear foci.
- C3 signal adjacent to, rather than within, the most electron-dense material.
- Correlate the IF compartment with EM rather than expecting exact spatial identity.

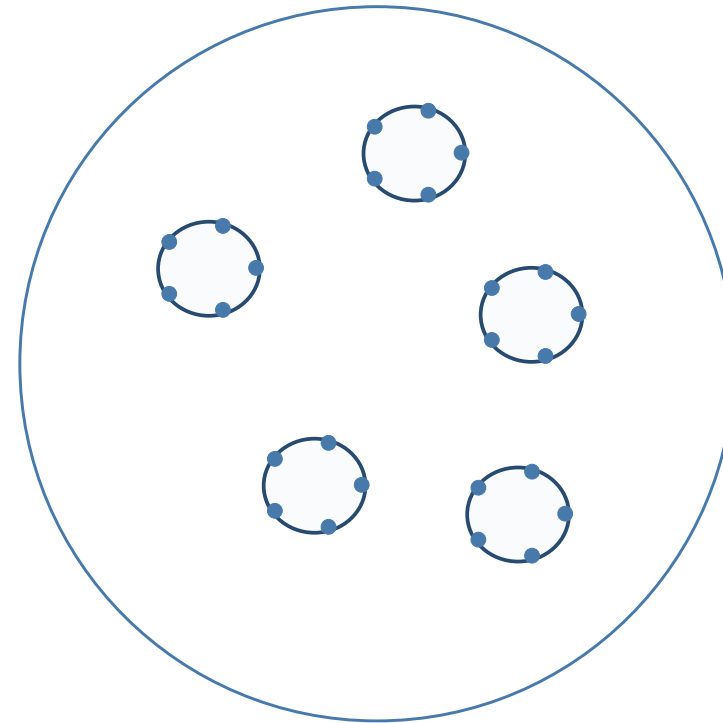


C3-dominant glomerular signal

Schematic — not a clinical or histologic specimen

C3 and properdin deposition support the mechanism

- C3 and properdin within glomeruli.
- These are products or components of the alternative pathway.
- The deposited complement pattern links pathway dysregulation to the renal lesion.



C3-dominant glomerular signal

Schematic — not a clinical or histologic specimen

Classical-pathway components are usually inconspicuous

Analyte	Typical pattern	Implication
Glomerular C3	Dominant signal	Complement-mediated injury
Glomerular IgG	Usually absent	Against conventional immune-complex dominance
C1q / C4	Generally absent in deposits	Classical-pathway activation less prominent

Masked monoclonal immunoglobulin is a pitfall

Why caution is needed

- Circulating paraproteins can accompany alternative complement activation.
- Some deposits may be hidden on routine IF techniques.

What the pathologist must exclude

- Masked monoclonal immunoglobulin deposits.
- A paraprotein-related lesion that changes the final clinicopathologic diagnosis.

EM requires precise compartment recognition

Distinguish mesangial, subendothelial, intramembranous and subepithelial locations.
Capillary lumen / endothelium

Subendothelial region

GBM (lamina densa)

Subepithelial region

Podocyte side

Simplified cross-section — not an electron micrograph

Dense deposit disease: The hallmark is a ribbon

Capillary lumen / endothelium **DDD shows homogeneous, extremely electron-dense material in the GBM.**

Subendothelial region

GBM (lamina densa)

Continuous intensely dense intramembranous ribbon

Subepithelial region

Podocyte side

Simplified cross-section — not an electron micrograph

DDD deposits are intramembranous, not merely external

Anatomic location

- The characteristic dense material lies within the lamina densa.
- On EM it appears as a continuous or ribbonlike dense band.

Differential significance

- This differs from discrete subendothelial immune-complex deposits.
- The intramembranous ribbon strongly favors DDD.

The biochemical nature of dense deposits is unresolved

Established morphology

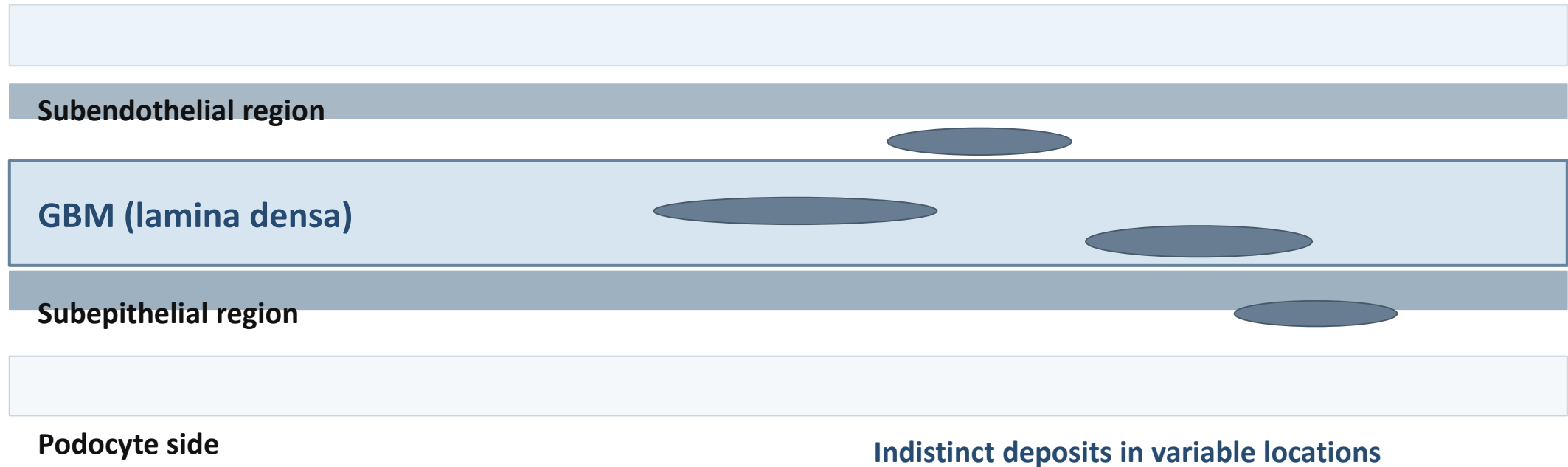
- Extremely electron-dense, homogeneous ribbonlike material.
- The hallmark remains ultrastructural rather than molecular.

Source nuance

- The precise composition as unknown.
- Apolipoprotein E enrichment has been reported in dense deposits; This is not a substitute for EM diagnosis.

C3GN shows less defined electron-dense deposits

Capillary lumen / endothelium **Cloudy, ill-defined deposits contrast with the dense ribbons of DDD.**



Simplified cross-section — not an electron micrograph

C3GN deposits occupy multiple compartments

Mesangium

Glomerular mesangial deposits may be present.

Capillary wall

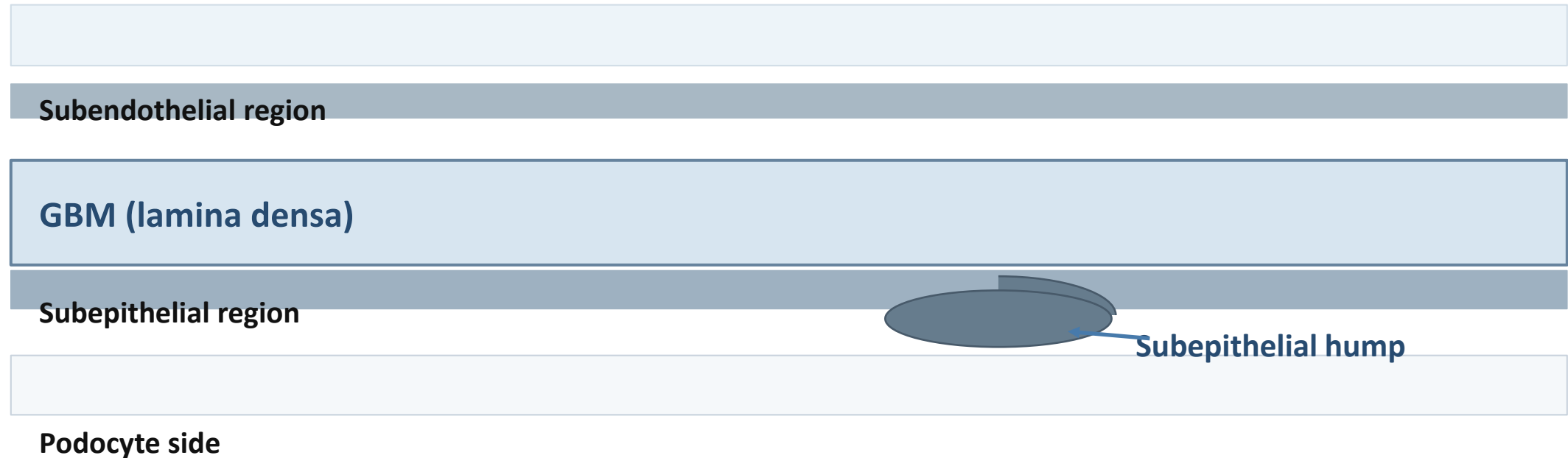
Subendothelial and intramembranous deposits can occur.

Variable pattern

No defining continuous, extremely dense lamina-densa ribbon.

Subepithelial humps occur in both C3G forms

Both DDD and C3GN may show subepithelial hump-shaped deposits.



Simplified cross-section — not an electron micrograph

DDD versus C3GN: The decisive EM features

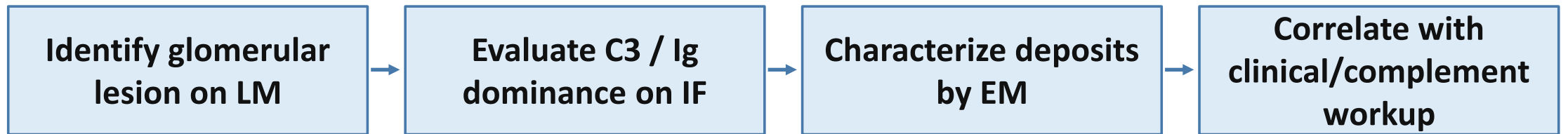
Feature	Dense deposit disease	C3 glomerulonephritis
Deposit texture	Homogeneous, exceptionally dense	Ill-defined, cloudy
Dominant location	Intramembranous lamina densa	Mesangial / intramembranous / subendothelial
Subepithelial humps	May occur	May occur
Light microscopy	Several proliferative patterns	Several proliferative patterns

Immune-complex MPGN differs on IF and EM

Diagnostic axis	Immune complex MPGN	C3G
Mechanism	Immune complexes activate complement	Alternative-pathway dysregulation
IF	IgG + C3; C1q/C4 may be seen	Dominant C3; IgG usually weak/absent
EM	Discrete subendothelial deposits	DDD ribbon / cloudy C3GN deposits
LM	Can show GBM duplication	Can also show GBM duplication

A practical biopsy interpretation pathway

Mechanistic / diagnostic sequence



Exclude masked monoclonal immunoglobulin when the phenotype suggests paraprotein-associated disease.

Clinically, C3G bridges nephritic and nephrotic syndromes

Nephritic features

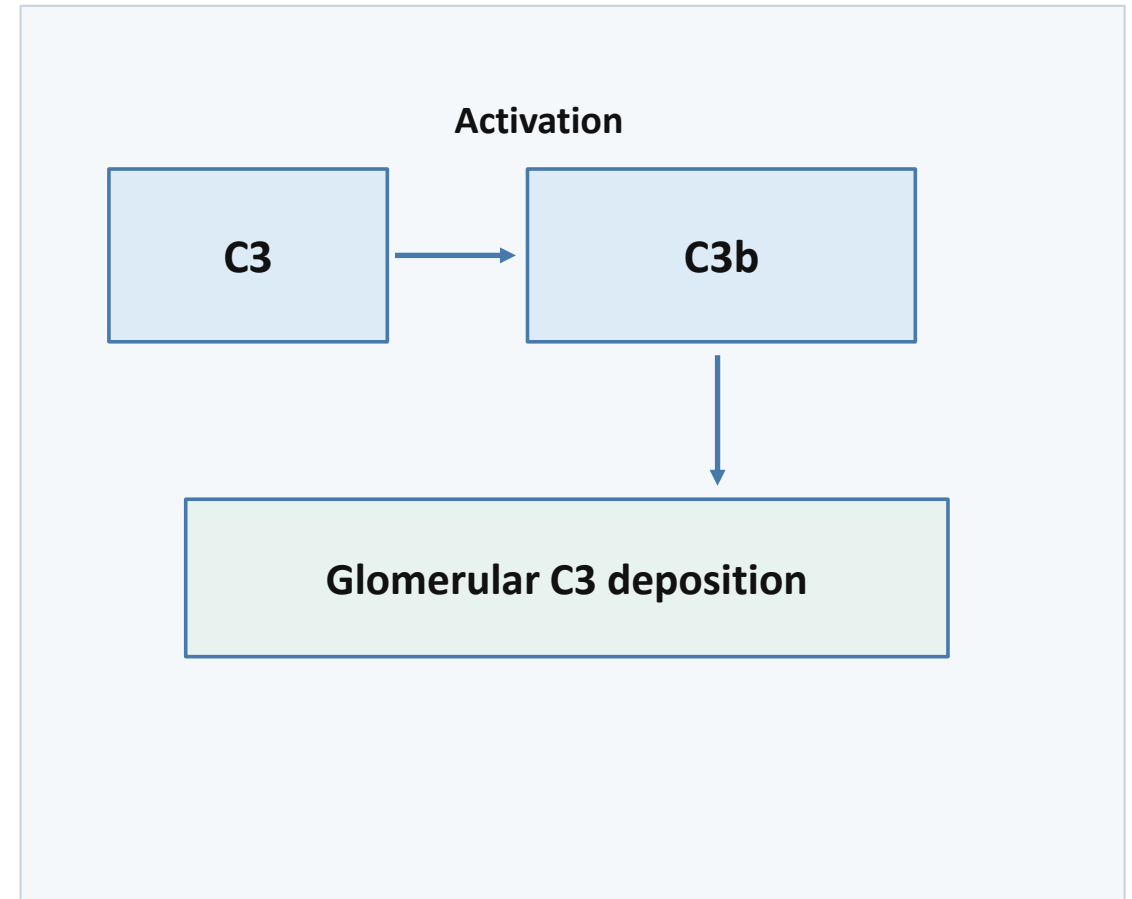
- Hematuria and inflammatory glomerular injury.
- Can coexist with substantial proteinuria.

Nephrotic features

- Heavy proteinuria from filtration-barrier damage.
- Patients may have a mixed nephritic–nephrotic phenotype.

Dense deposit disease tends to present earlier

- Children and young adults.
- Clinical presentation may be nephritic, nephrotic, or mixed.
- Age is a useful clue but is not itself diagnostic.



C3GN occurs across a broader age range

Early-onset / genetic forms

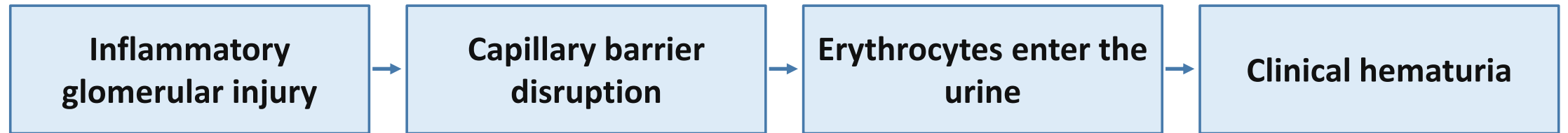
- Genetic complement-regulator abnormalities may present in children or younger adults.
- Factor H-related mechanisms are a textbook example.

Acquired forms

- Age may reflect an associated disease.
- Lymphoproliferative disorders are particularly relevant in older adults.

Hematuria represents the nephritic dimension

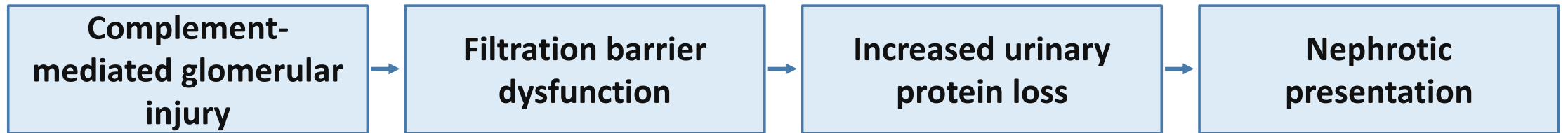
Mechanistic / diagnostic sequence



Nephritic features arise from glomerular inflammation and capillary-wall injury.

Proteinuria represents the nephrotic dimension

Mechanistic / diagnostic sequence



Marked proteinuria may coexist with active inflammatory changes.

A single biopsy can show mixed injury

Cell proliferation

Mesangial or endocapillary hypercellularity.

Capillary-wall remodeling

GBM double contours when MPGN-like.

Complement deposits

C3 dominance on IF with EM-defined dense material.

The prognosis can be unfavorable

Natural history

- Substantial progression to end-stage kidney disease.
- More than one-half progress to ESRD in the cited textbook overview.

Meaning for assessment

- Morphologic activity and chronic damage are clinically consequential.
- The patient needs longitudinal renal evaluation beyond the initial biopsy.

Dense deposit disease frequently recurs after grafting

Textbook observation

- Transplant recurrence in DDD at rates up to 90%.
- The systemic complement abnormality can persist after renal replacement.

Pathogenetic lesson

- Replacing the kidney does not automatically correct an upstream alternative-pathway defect.
- Allograft pathology must be interpreted in clinical context.

Teaching case: C3-dominant nephritis in a child

A child has hematuria, proteinuria, depressed serum C3, preserved C4, and a biopsy with dominant glomerular C3 staining.

Which pathway is implicated most directly?

A. Classical pathway only

B. Alternative complement pathway

C. A podocyte-only lesion

D. A primary IgG immune-complex process

Teaching case: Interpret the complement findings

Best interpretation

- Alternative-pathway dysregulation is strongly supported.
- Low C3 with preserved C4 fits pathway consumption.

What biopsy data complete the workup?

- LM identifies the injury pattern.
- EM separates DDD from C3GN and assesses deposit distribution.

Teaching case: An older adult with paraprotein

An older adult has an MPGN-like lesion, strongly dominant C3 staining and a circulating monoclonal protein.

Which issue requires particular exclusion?

A. Masked monoclonal immunoglobulin deposits

B. Foot-process effacement alone

C. An isolated podocyte structural mutation

D. A primary inherited collagen IV lesion

Teaching case: A diagnostic pitfall resolved

Why this matters

- Paraproteins may alter complement regulation.
- Masked monoclonal deposits can change mechanistic classification.

The correct interpretation

- Do not stop at a C3-dominant IF pattern alone.
- Investigate paraprotein-related renal pathology with appropriate laboratory and pathology correlation.

Morphology plus mechanism determines the diagnosis

Domain	The finding that matters
Pathogenesis	Abnormal alternative complement-pathway activity
LM	Variable injury pattern: Mesangial / inflammatory / crescentic / MPGN
IF	Dominant C3 staining; Assess immunoglobulins and C1q
EM	DDD ribbon vs C3GN cloudy deposits
Clinical	Hematuria, proteinuria, complement profile and associated conditions

Test yourself: Classify the ultrastructure

Biopsy A

- Intensely electron-dense homogeneous ribbon transforming lamina densa.
- C3 is dominant on IF.

Biopsy B

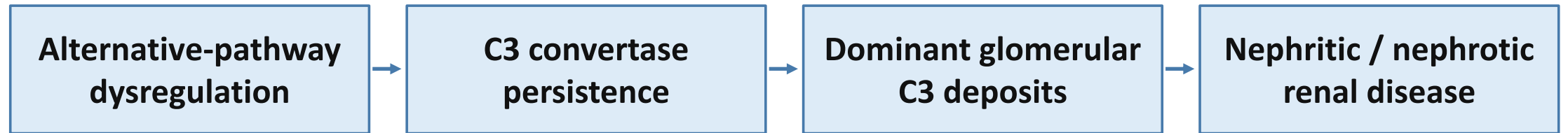
- Ill-defined mesangial and subendothelial deposits.
- C3 is dominant on IF.

EM classification: A is DDD, B is C3GN

Teaching biopsy	Subclassification	Decisive evidence
Biopsy A	Dense deposit disease	Ribbonlike extremely dense intramembranous deposits
Biopsy B	C3 glomerulonephritis	Cloudy, ill-defined mesangial / capillary-wall deposits

C3G: Mechanism, tissue, clinic

Mechanistic / diagnostic sequence



EM morphology separates dense deposit disease from C3 glomerulonephritis.

References and source distinctions

Primary textbook

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026). Chapter 20: The Kidney.

Supplementary diagnostic convention

Pickering MC, et al. C3 glomerulopathy: consensus report. Kidney International (2013).

All glomerular wall / immunofluorescence illustrations are original editable schematics, not patient images.