

Mechanisms of Glomerular Injury Following Immune Complex Formation

From immune-reactant localization to inflammatory injury and morphology

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Mechanism determines the lesion

- Glomerular antigen–antibody complexes can provoke local inflammation.
- The site of deposition is a major determinant of cellular access and injury.
- Complement, Fc receptor engagement, and resident glomerular cells translate deposition into damage.

Formation or deposition of antigen–antibody complexes



Localization in a glomerular compartment



Effector-cell and soluble-mediator responses



Distinctive glomerular injury pattern

Four questions organize immune-complex injury

- Where do antigen–antibody complexes originate?
- Where do they localize within the glomerulus?
- Which cells and soluble mediators respond?
- Does antigen exposure resolve or persist?

Origin: Local formation or circulation



Site: Mesangial, subendothelial, subepithelial



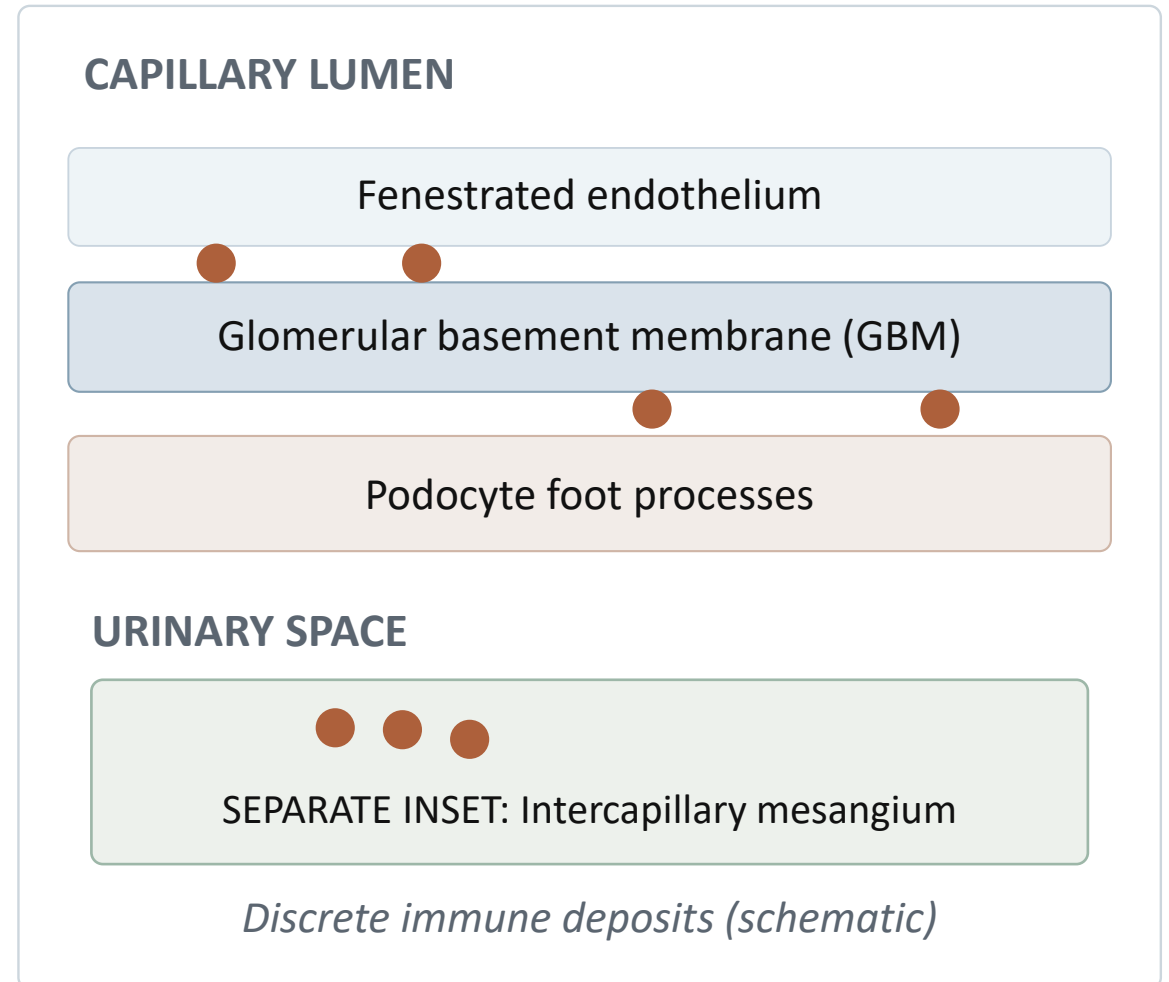
Effector system: Complement, cells, coagulation



Duration: Resolution or remodeling

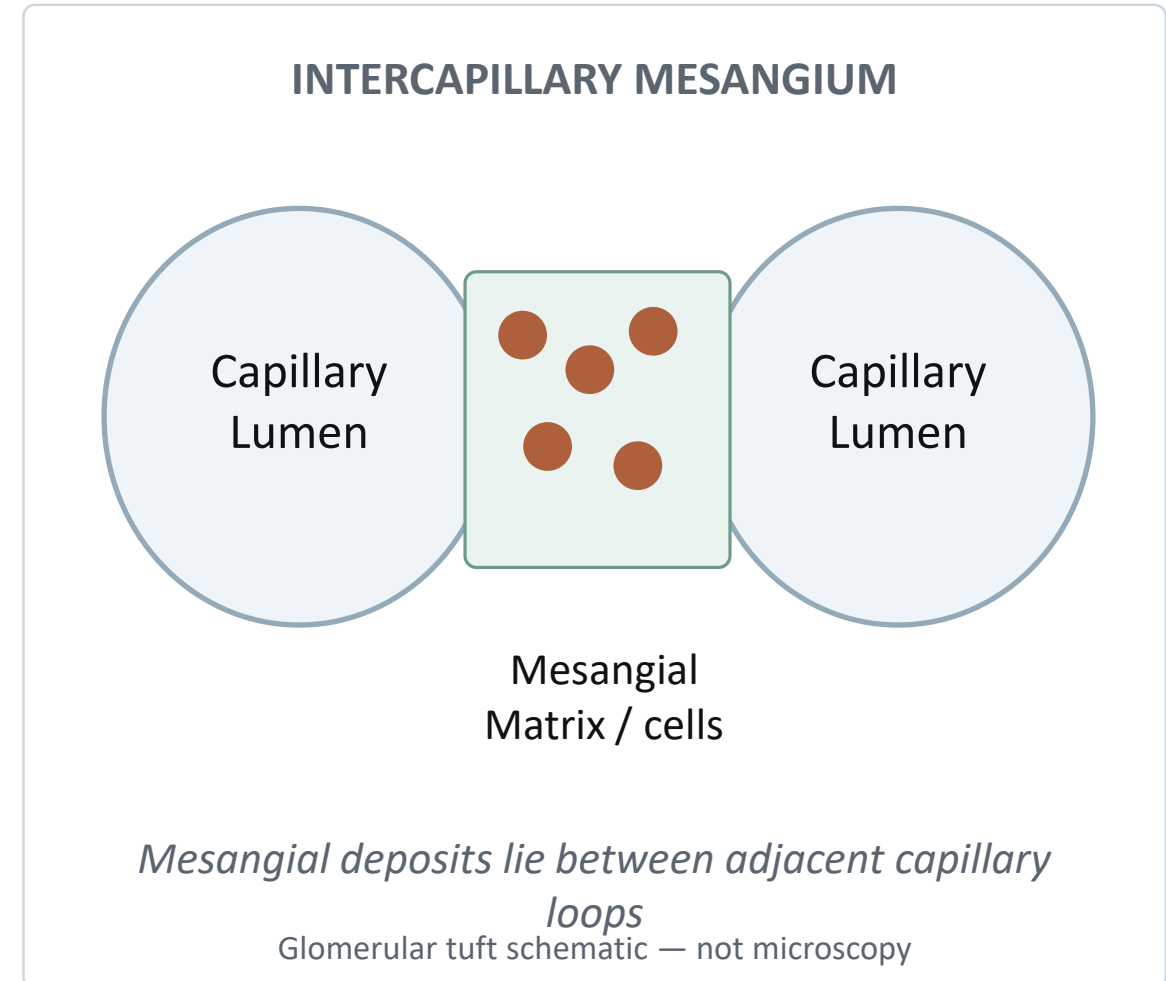
The filtration barrier defines exposure

- Capillary blood contacts fenestrated endothelium first.
- The glomerular basement membrane (GBM) separates endothelial from podocyte compartments.
- Podocyte foot processes face Bowman urinary space on the outer GBM surface.



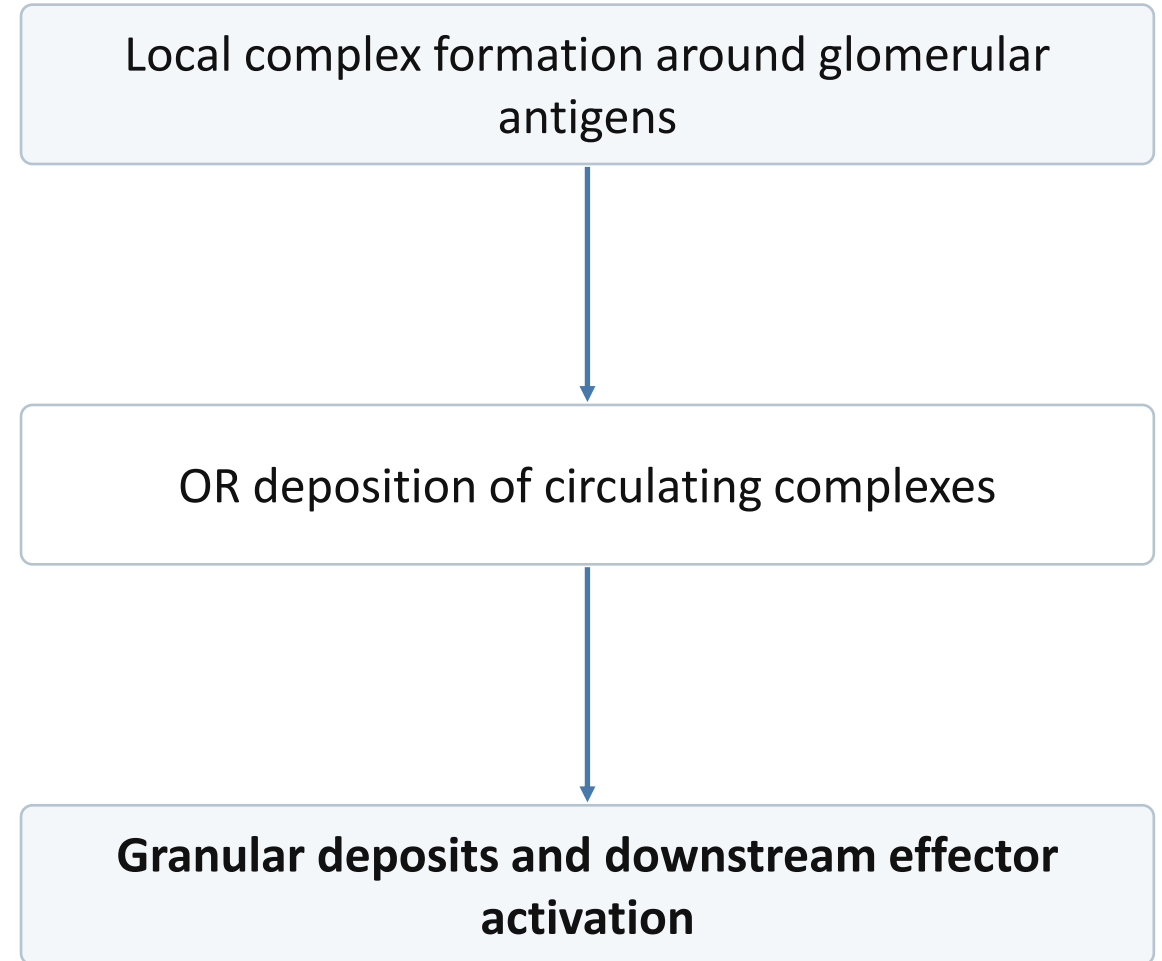
Mesangium is not behind the GBM

- The mesangial compartment lies between capillary loops.
- Unlike subepithelial sites, it is not shielded from the vascular lumen by the GBM.
- This proximity helps explain mesangial inflammatory responses to immune deposits.



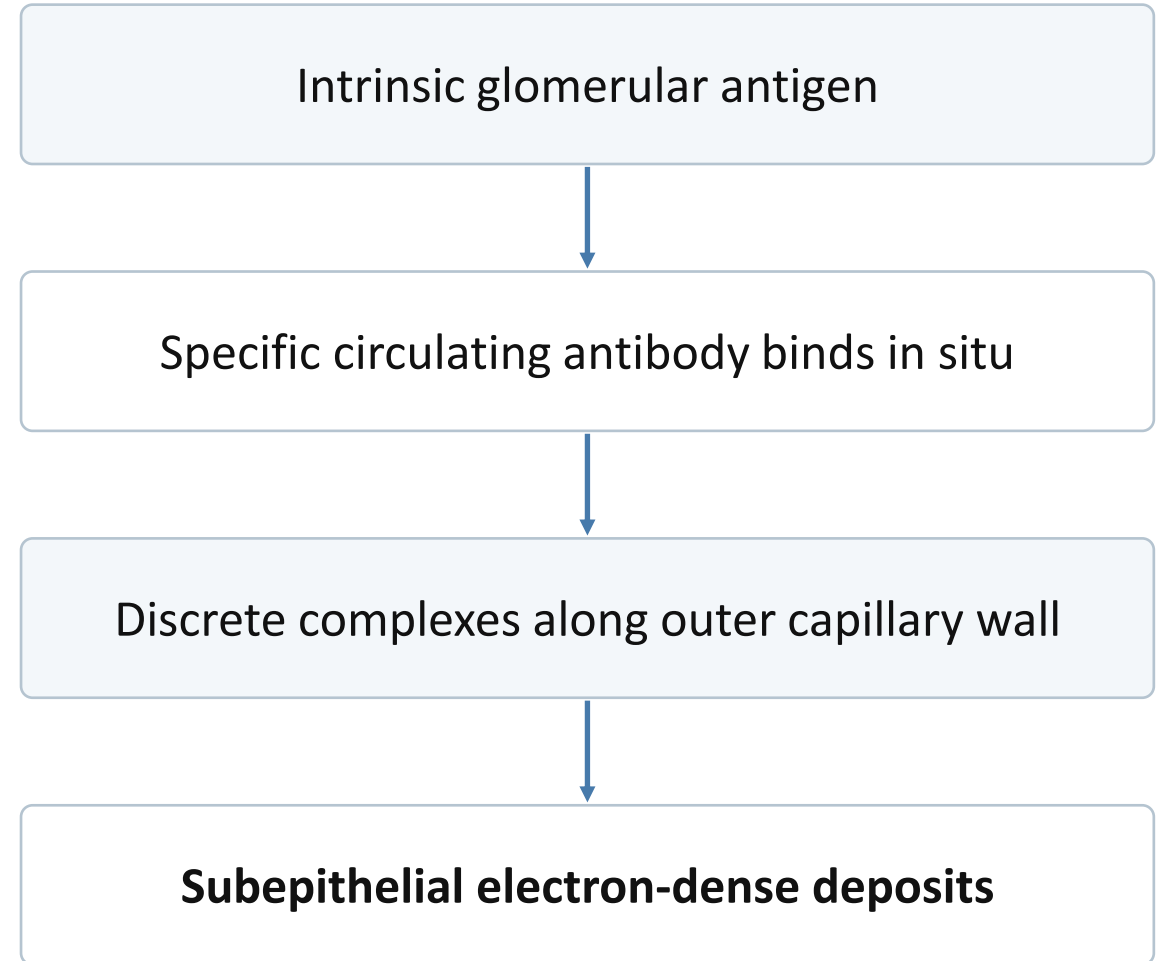
Antibodies initiate two major routes of injury

- Antibodies can bind antigen in situ within glomeruli.
- Circulating preformed antigen–antibody complexes may become trapped in the glomerulus.
- Both routes can produce discrete immune deposits with granular immunofluorescence.



In situ complexes: Intrinsic tissue antigens

- Antibodies recognize antigen molecules that are natural components of the glomerulus.
- Antigen location controls where individual immune complexes assemble.
- Membranous nephropathy exemplifies locally formed subepithelial complexes.



Planted antigens enable local assembly

- Non-glomerular antigens can lodge or bind within glomerular structures.
- Examples include nuclear proteins, bacterial products, and aggregated immunoglobulins.
- Antibody subsequently reacts at the planted antigen site.

Non-glomerular antigen localizes in glomerulus



Antigen remains accessible to antibody



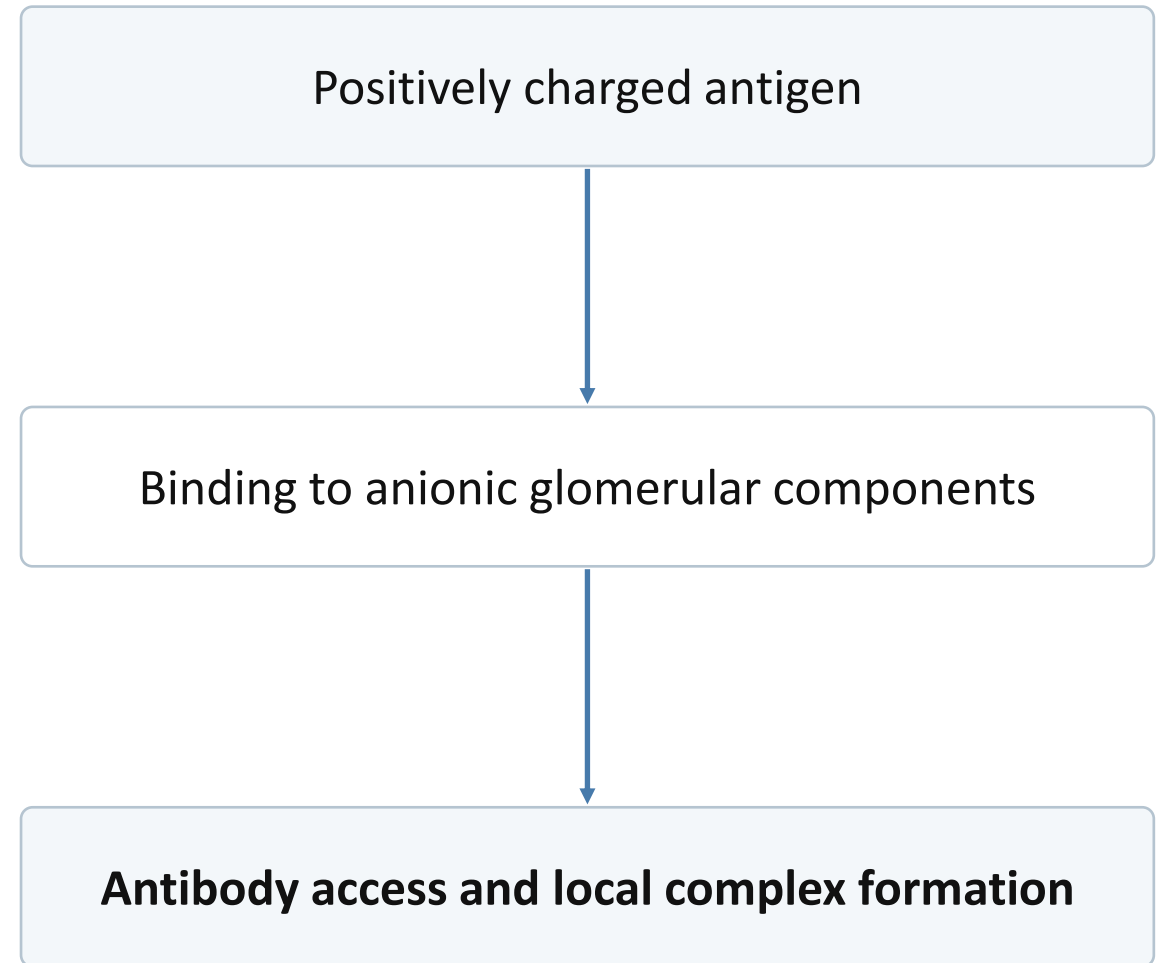
Local antigen–antibody assembly



Immune deposit and possible inflammation

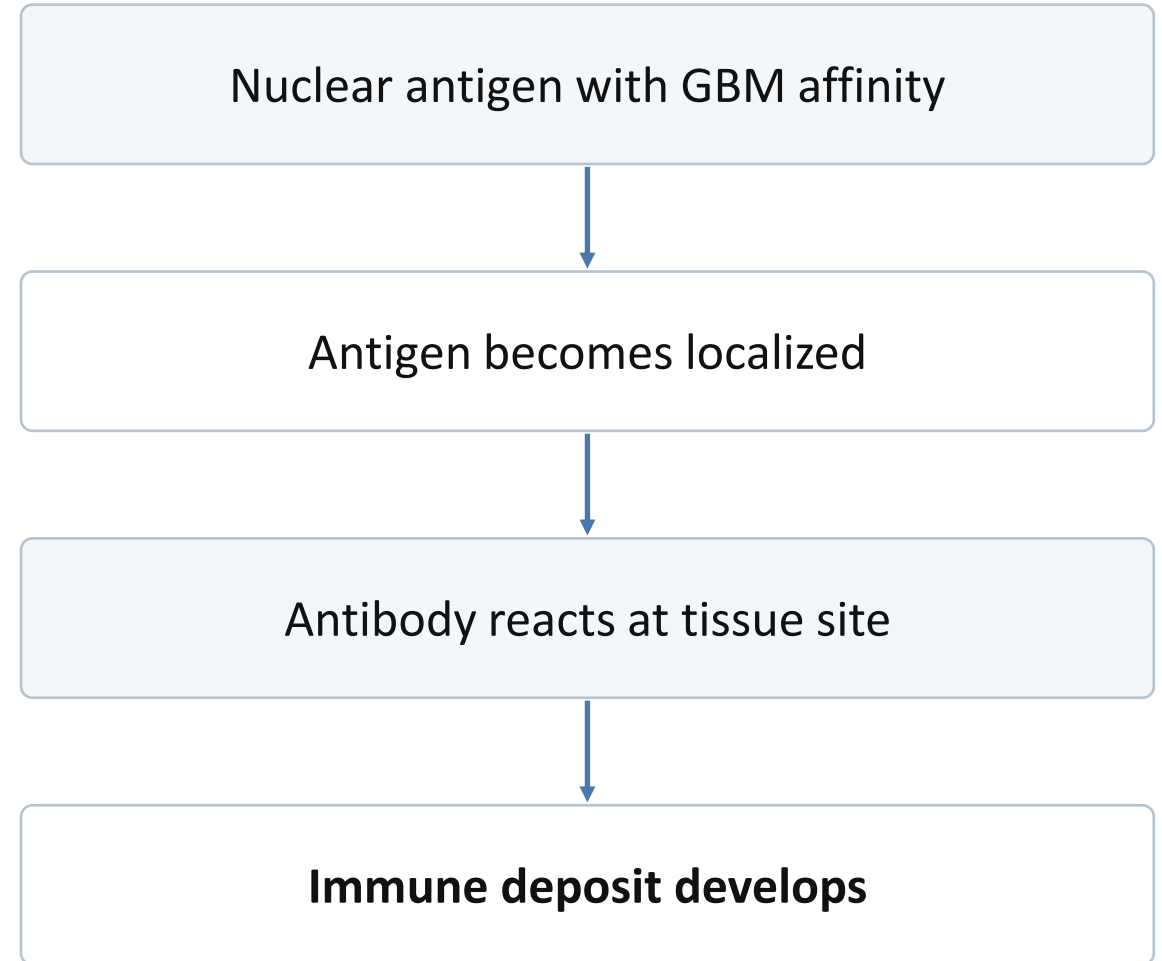
Cationic planted molecules exploit charge

- Cationic molecules may adhere to anionic glomerular components.
- Electrostatic interactions help determine where antigen becomes planted.
- The subsequent immune reaction occurs at that localization site.



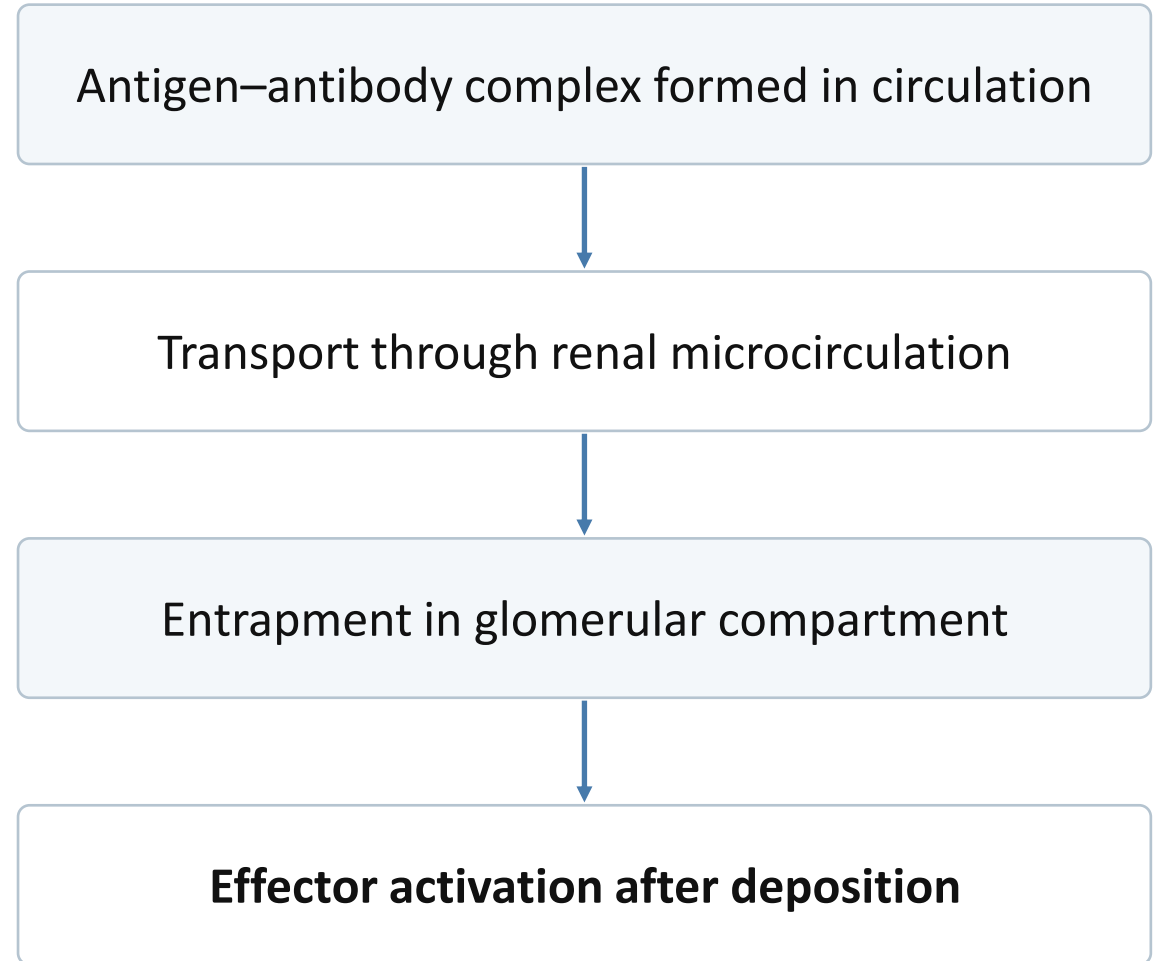
Nuclear antigens can be planted

- DNA, nucleosomes, and other nuclear proteins may bind GBM components.
- Such antigen localization permits antibody binding within the glomerulus.
- Presence of a circulating autoantibody does not, by itself, reveal the deposition route.



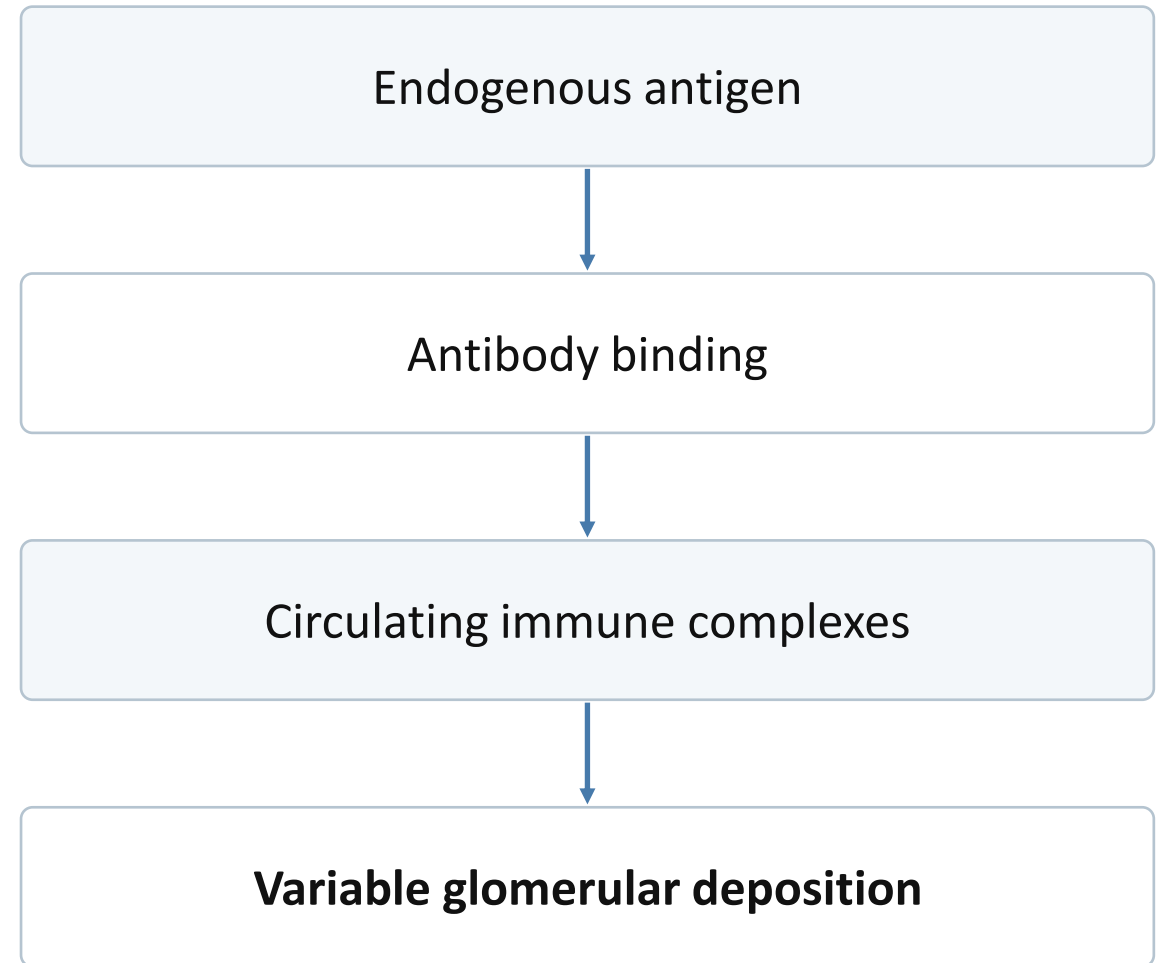
Circulating complexes do not require GBM specificity

- Antigen and antibody react outside the glomerulus.
- The antibody need not recognize an intrinsic renal structure.
- Complexes localize through physicochemical properties and glomerular hemodynamics.



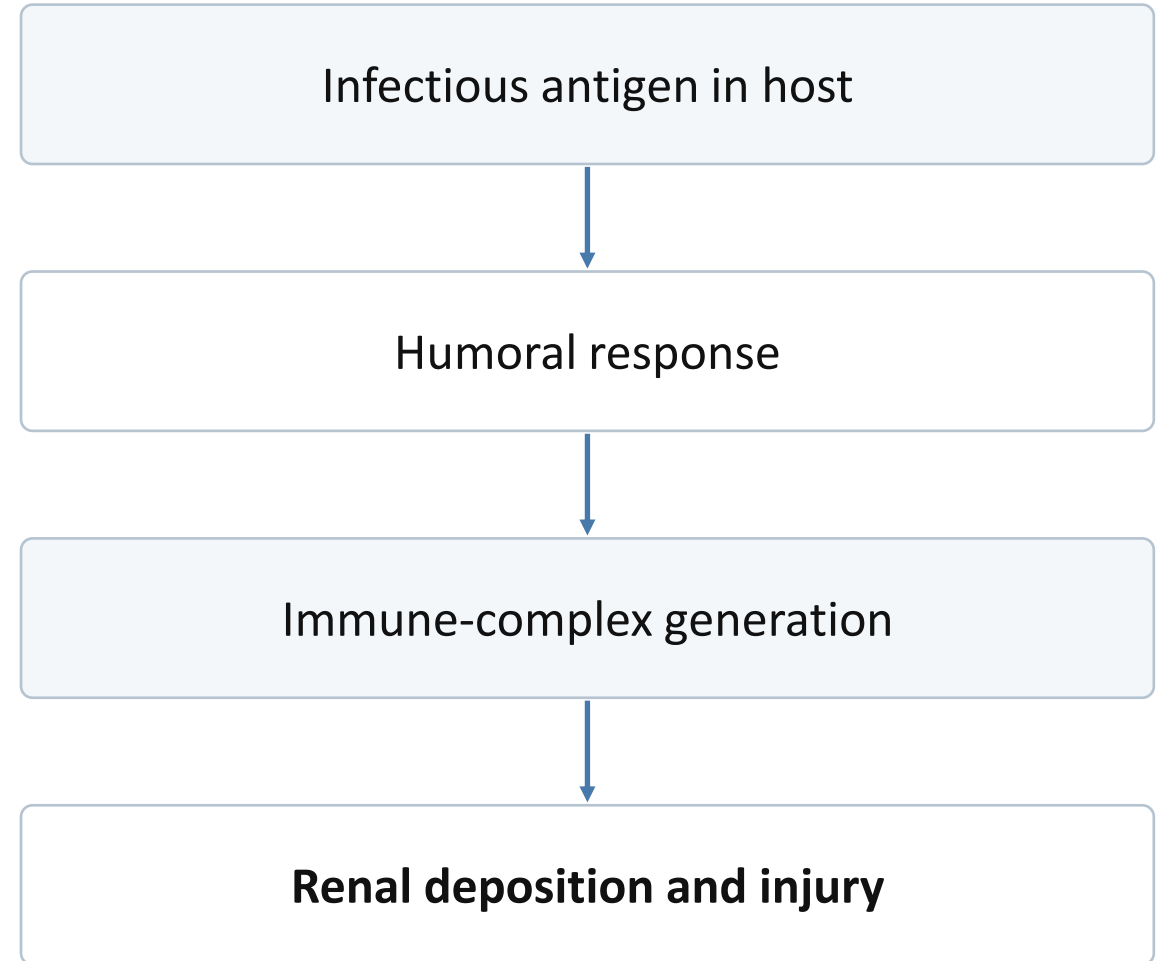
Endogenous sources of immune complexes

- Endogenous antigens are implicated in systemic lupus erythematosus (SLE).
- IgA nephropathy is included among examples of endogenous antigen-associated disease.
- Tumor antigens are also proposed contributors to some immune-complex nephritides.



Exogenous antigen sources

- Microbial antigen examples include streptococcal products.
- Hepatitis B surface antigen and hepatitis C viral antigens may be implicated.
- The textbook also lists *Treponema pallidum* and *Plasmodium falciparum* antigens.



Many triggering antigens remain unknown

- An immune-complex pattern can be established without identifying the inciting antigen.
- Do not infer a specific infection or autoimmune cause from granular staining alone.
- Etiologic interpretation requires clinical and laboratory context beyond the deposit pattern.

Granular immune-reactant deposition



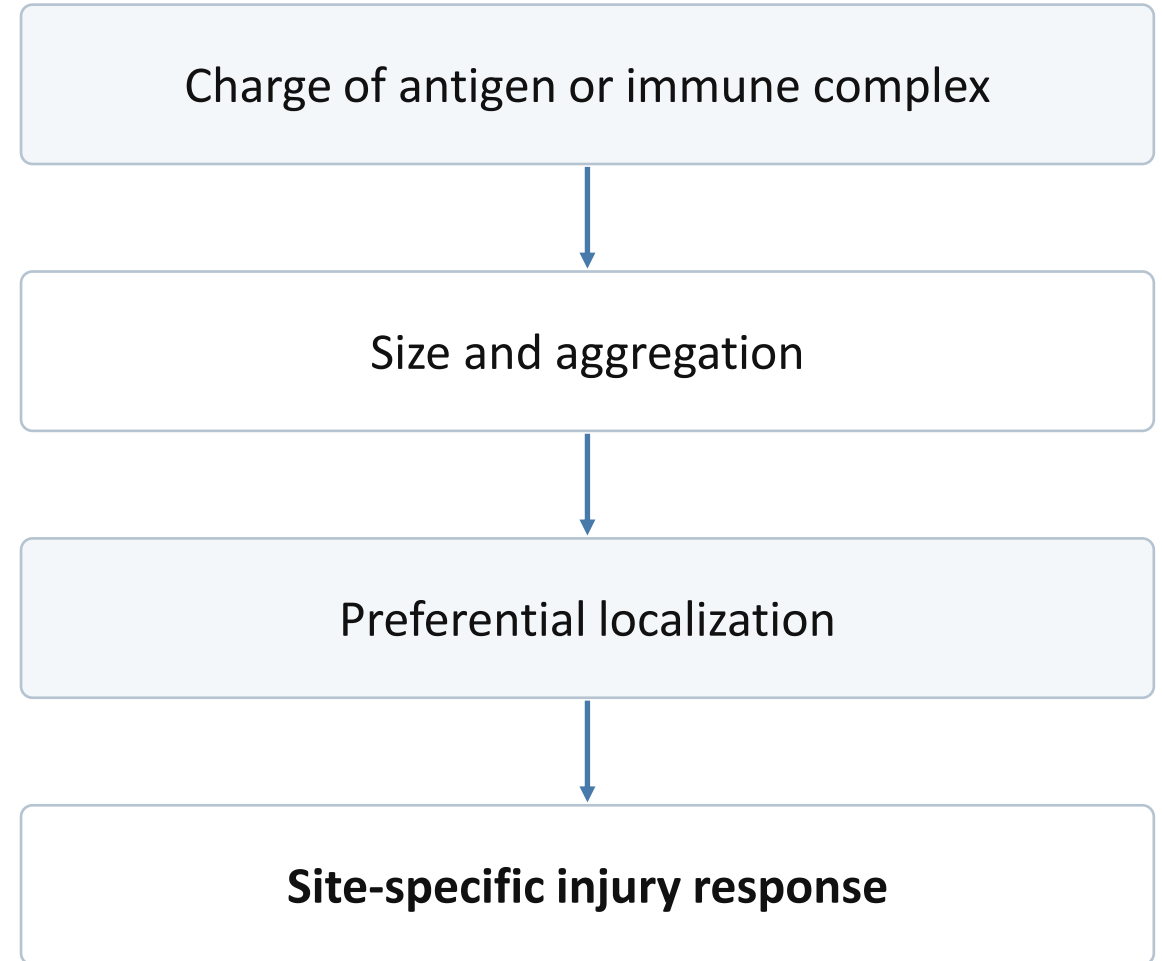
Mechanism recognized



Inciting antigen may still be uncharacterized

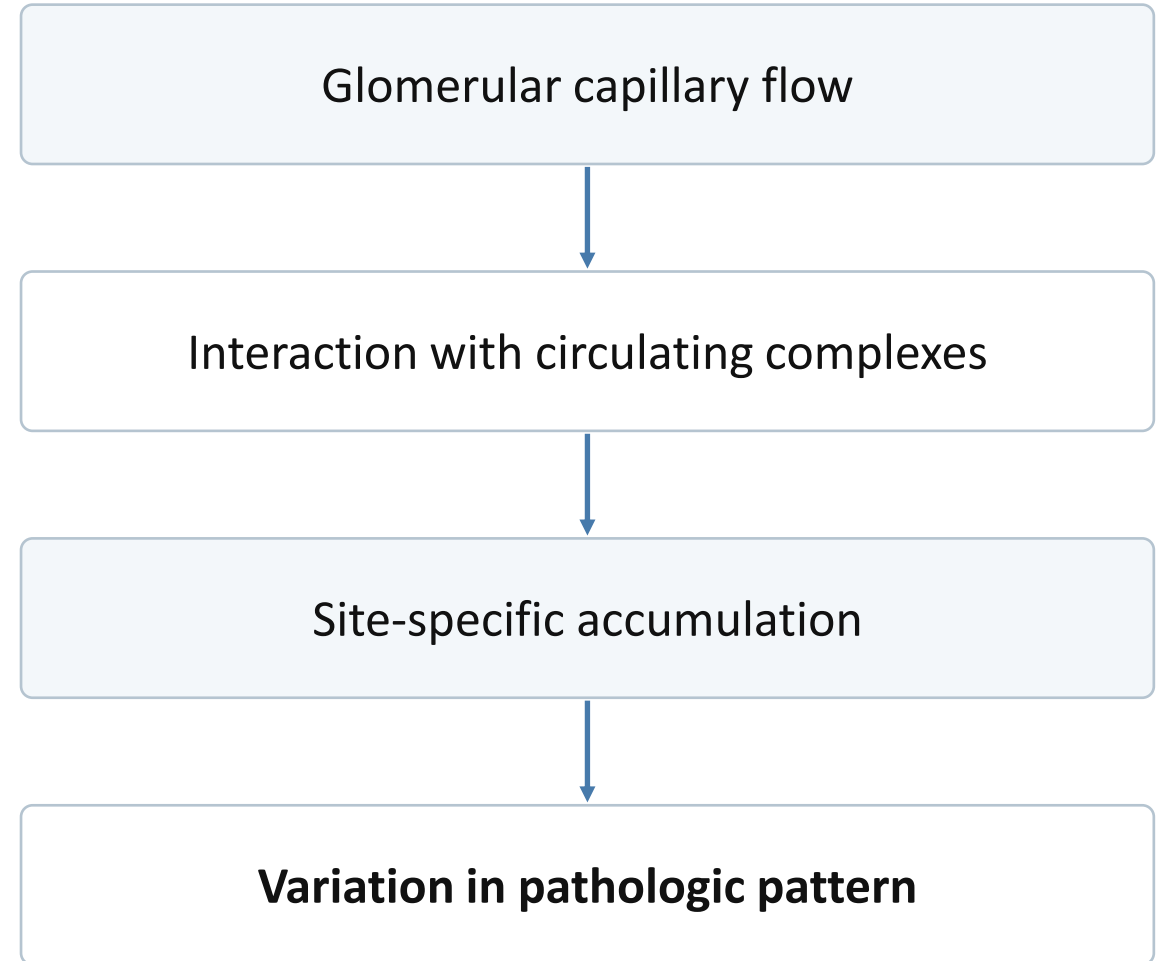
Size and charge affect localization

- Charge and size of immune reactants influence glomerular localization.
- Large aggregated proteins may accumulate within the mesangium.
- The physicochemical properties of complexes contribute to lesion heterogeneity.



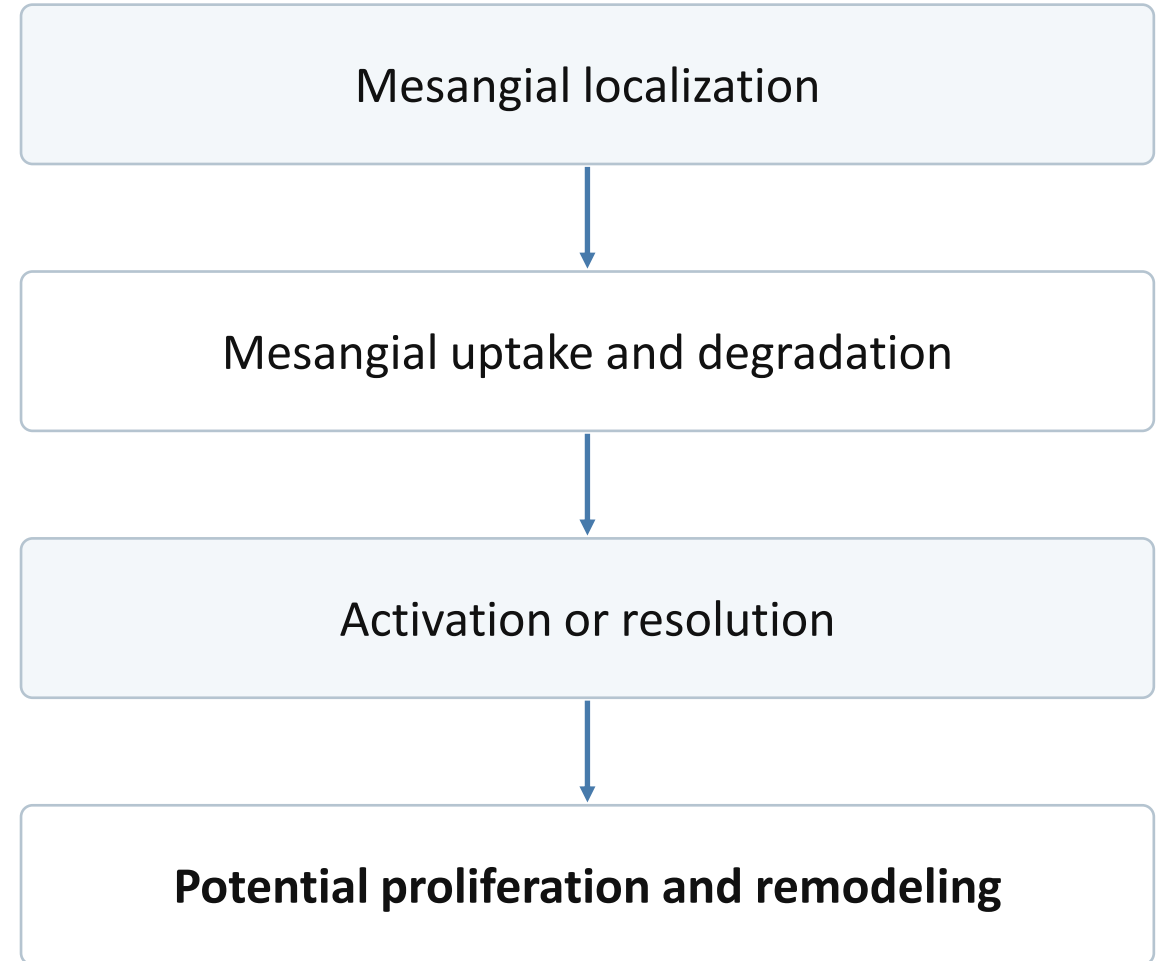
Glomerular hemodynamics alter deposition

- Flow through the glomerular microcirculation affects immune-complex trapping.
- Hemodynamic conditions act alongside antigen properties.
- A single antigen source need not result in a single structural lesion.



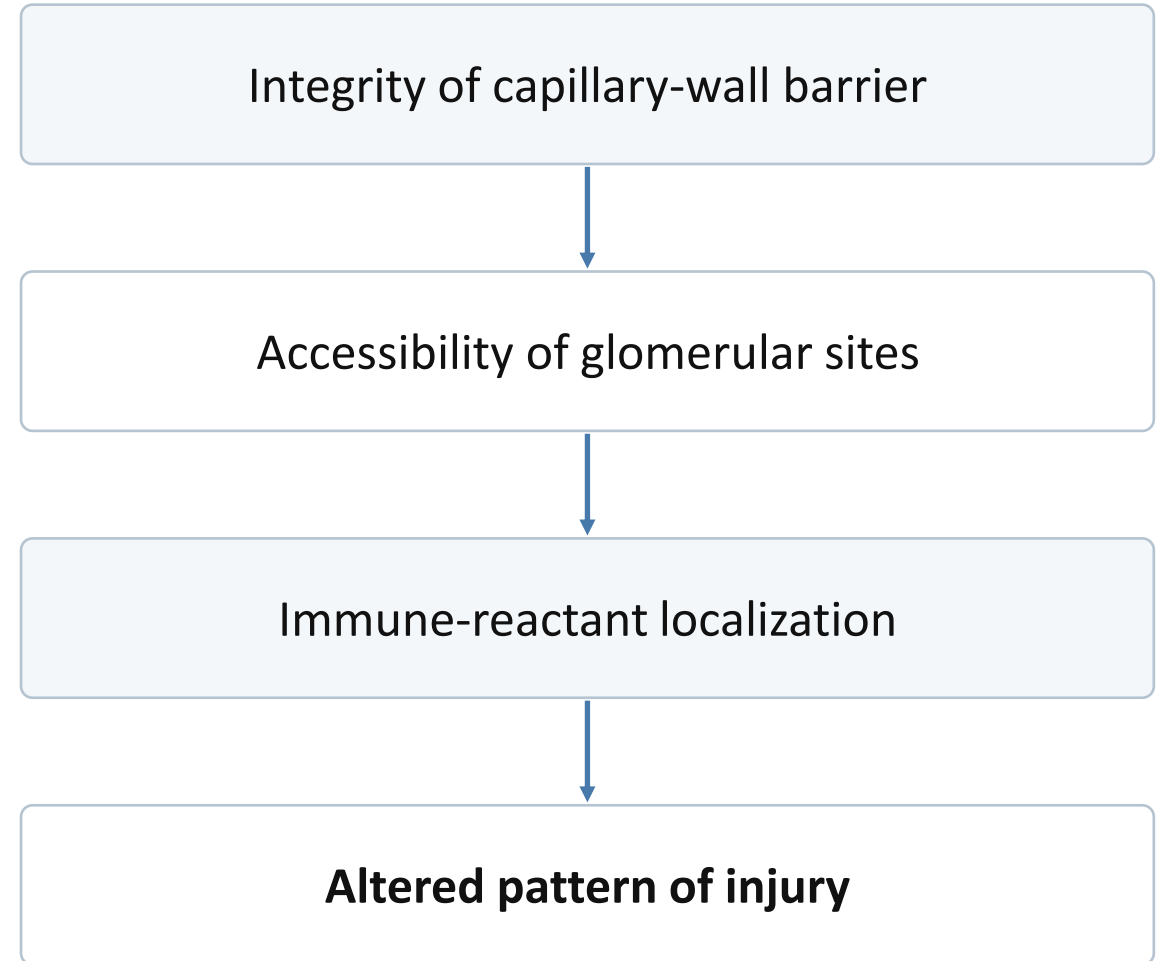
Mesangial handling affects immune deposition

- Mesangial function is one determinant of immune-reactant localization.
- Mesangial cells can participate in clearance of deposited material.
- They can also be activated to release inflammatory and growth mediators.



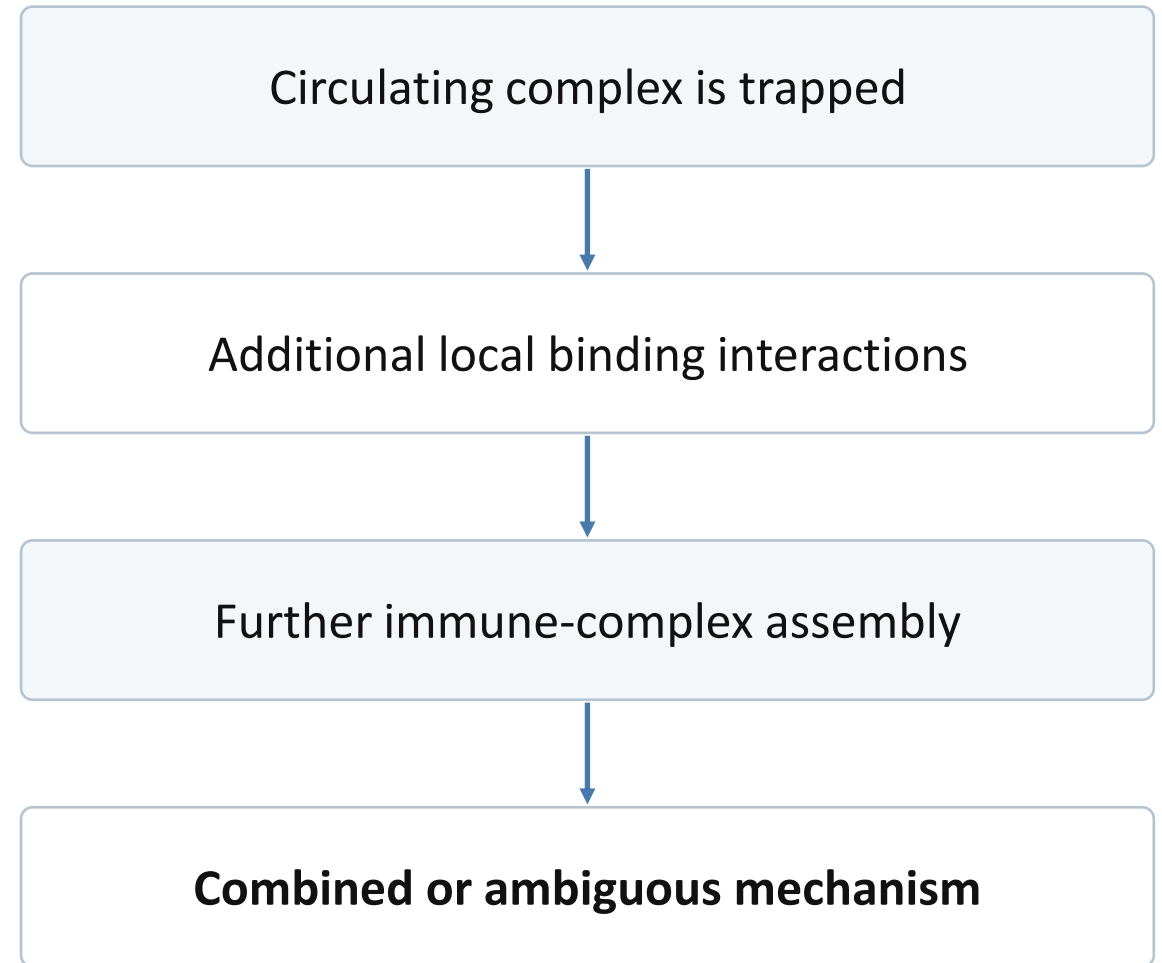
Barrier integrity modifies localization

- The charge-selective filtration barrier helps influence deposition sites.
- A change in capillary wall integrity may alter access to glomerular compartments.
- Localization and injury should be interpreted as interacting processes.



Circulating and in situ routes may coexist

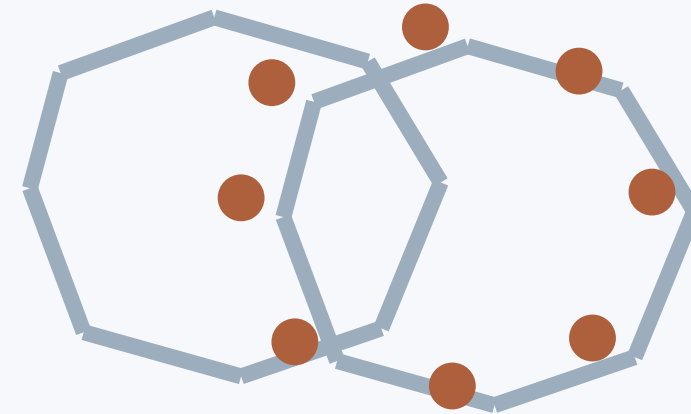
- A trapped circulating complex may retain free binding sites.
- Additional antigen, antibody, or complement can interact locally.
- Therefore, routine morphology may not prove one exclusive route of formation.



Granular IF reflects discrete complexes

- Immune-reactant deposits form discontinuous foci.
- Immunofluorescence shows a granular pattern along capillary walls or in mesangium.
- Granularity is characteristic of immune-complex localization, not one specific cause.

IMMUNOFLUORESCENCE PATTERN



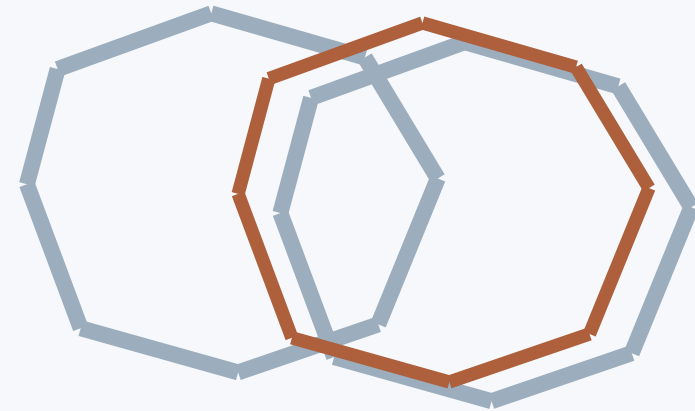
Interrupted, coarse granular signal

Stylized IF pattern — not microscopy

Linear IF points to a different mechanism

- Anti-GBM antibodies recognize antigens distributed along the length of the GBM.
- Bound antibody produces a diffuse linear immunofluorescence pattern.
- Linear anti-GBM binding must be distinguished from granular immune-complex deposition.

IMMUNOFLUORESCENCE PATTERN



Continuous linear capillary-wall signal

Stylized IF pattern — not microscopy

Immunofluorescence and electron microscopy differ

Immunofluorescence

Pattern: Granular or linear

Distribution: Capillary wall, mesangium, or both

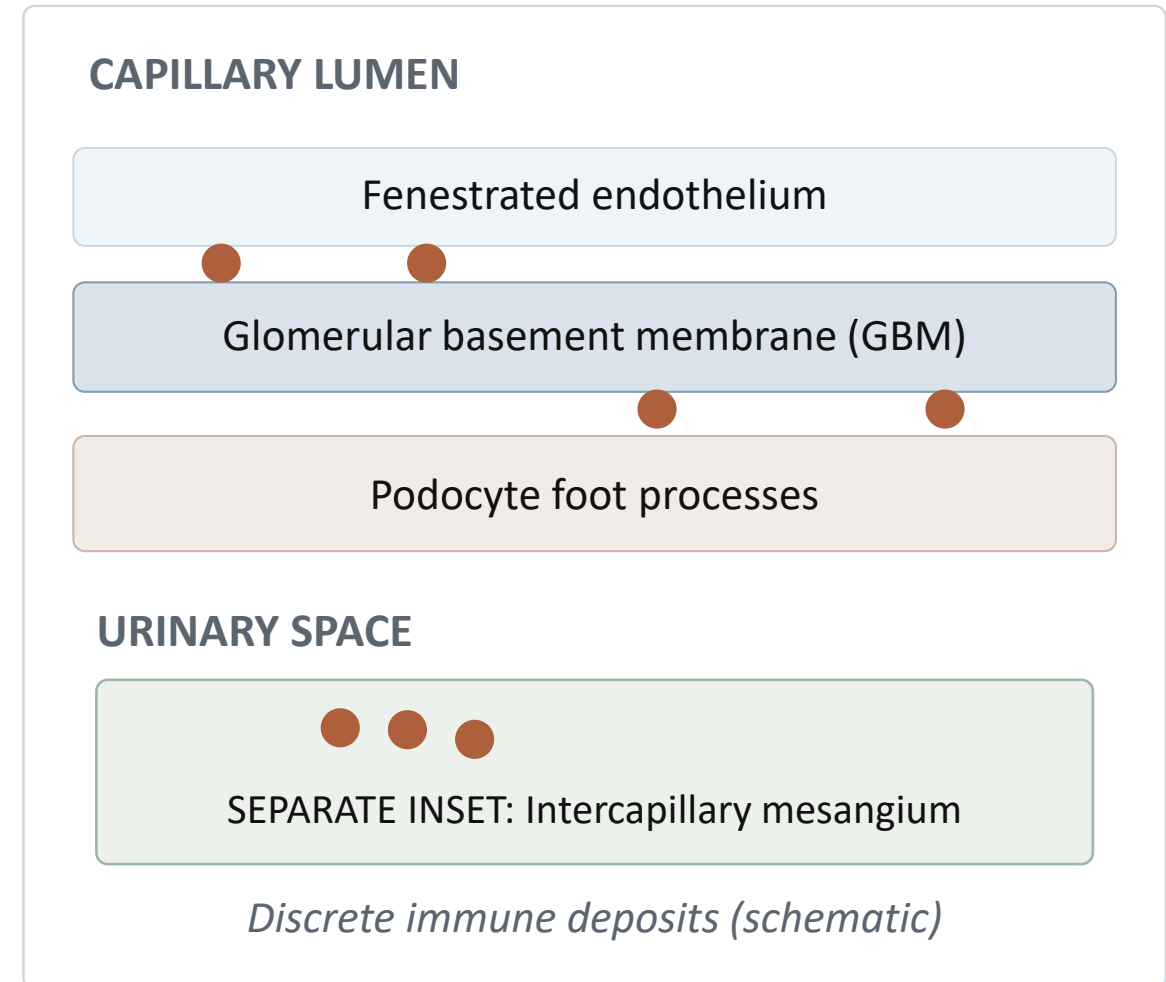
Electron microscopy

Dense deposits: Position relative to GBM

Subendothelial, subepithelial, mesangial, or multiple

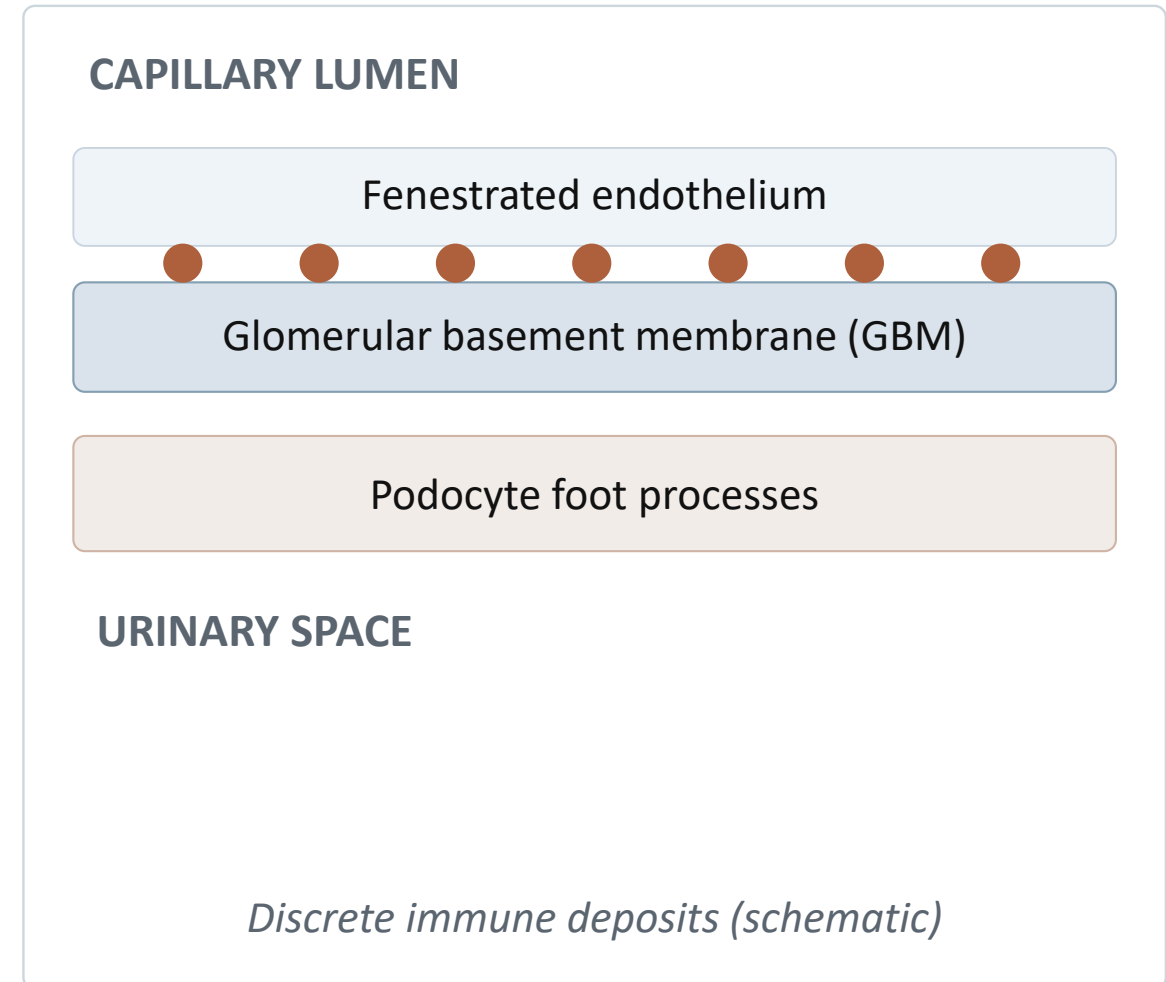
Three main immune-deposit compartments

- Subendothelial: Between endothelial cells and GBM.
- Subepithelial: Between outer GBM surface and podocytes.
- Mesangial: Within the mesangial compartment between capillary loops.



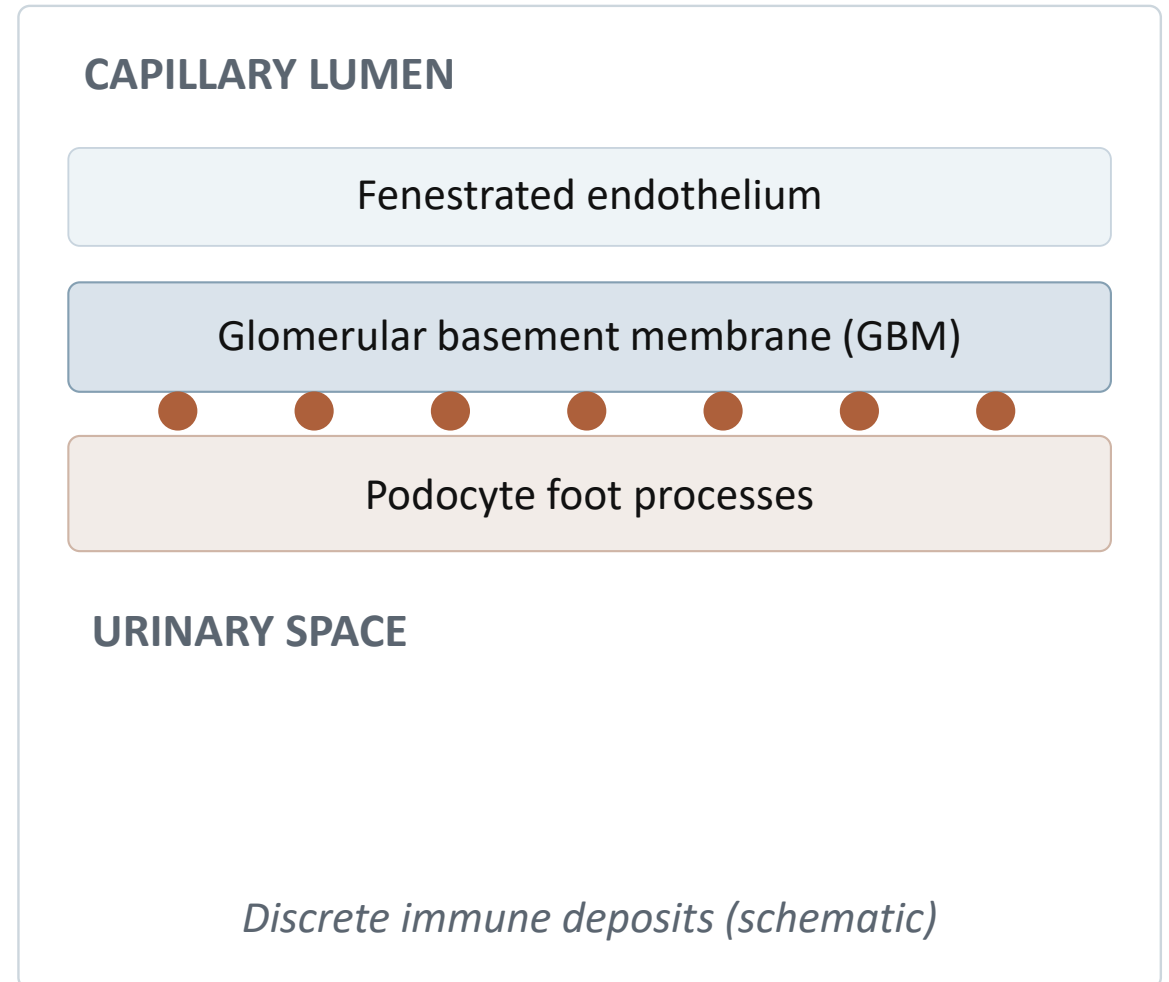
Subendothelial deposits remain blood-facing

- Deposits lie beneath endothelium, on the luminal side of the GBM.
- They readily provoke leukocyte infiltration and may be associated with crescents.
- Subendothelial immune complexes are linked to membranoproliferative patterns.



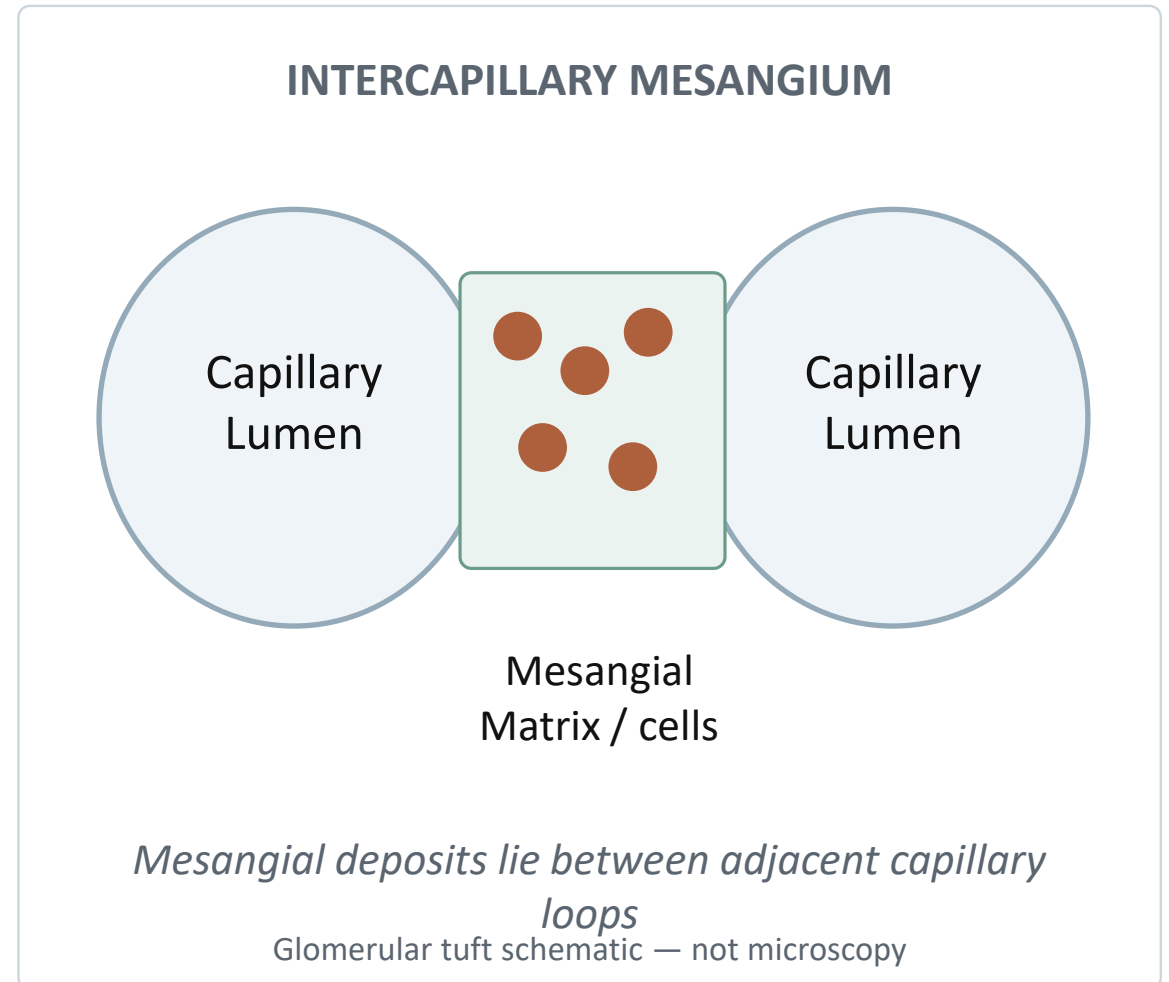
Subepithelial deposits are relatively shielded

- Deposits sit outside the GBM beneath podocytes.
- The GBM separates them from circulating leukocytes.
- They generally do not trigger the same inflammatory leukocyte response as subendothelial deposits.



Mesangial deposits have inflammatory access

- Mesangial deposits are not separated from the capillary lumen by the GBM.
- Leukocytic infiltration may occur.
- Mesangial and endothelial cells may proliferate in the resulting lesion.

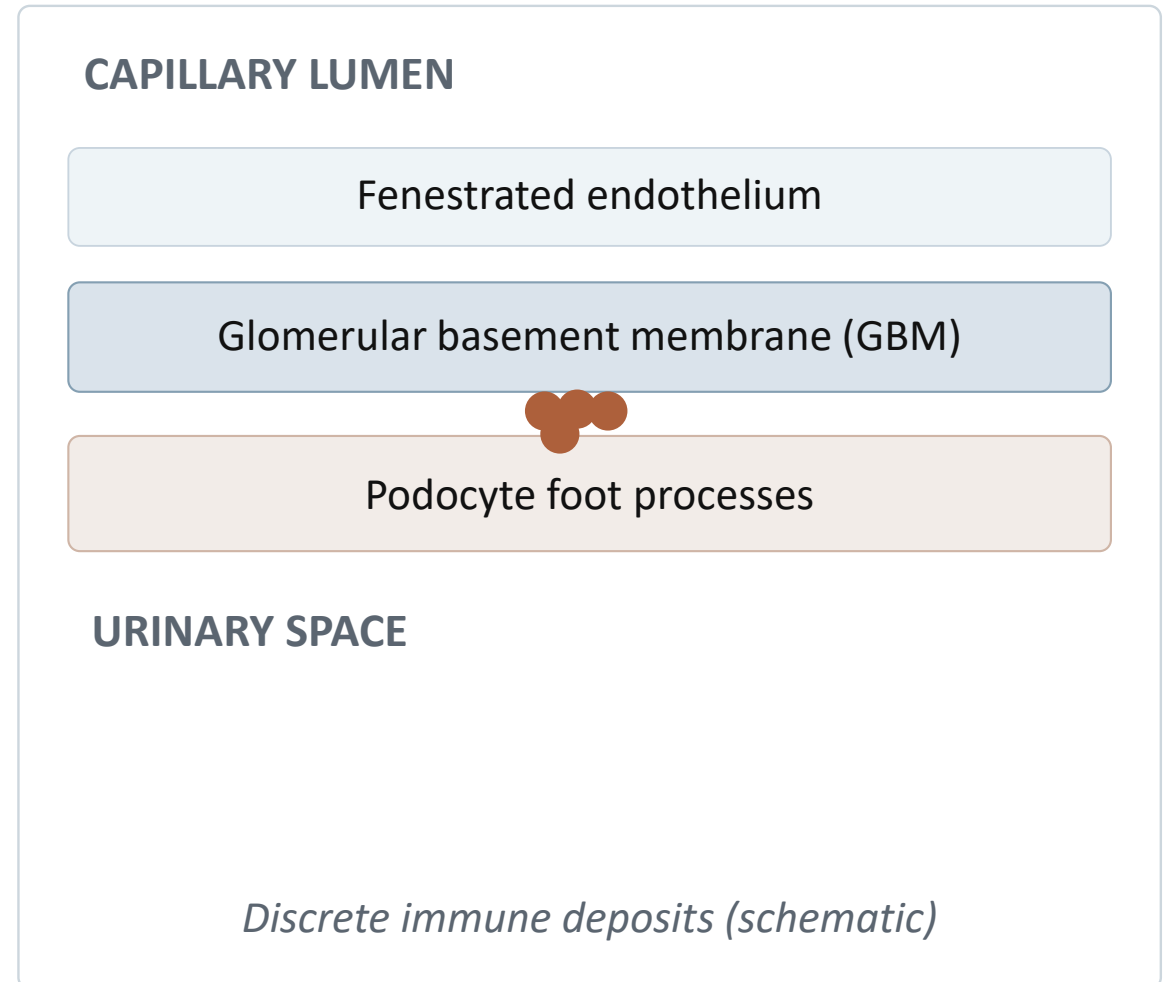


Localization predicts the response

Location	Relationship to blood	Typical response
Subendothelial	Luminal side of GBM	Leukocyte influx; Potentially crescents
Mesangial	Mesangium accessible from capillary lumen	Leukocytes; Mesangial/endothelial proliferation
Subepithelial	Separated from capillary lumen by GBM	Less leukocyte-rich inflammation; Podocyte injury

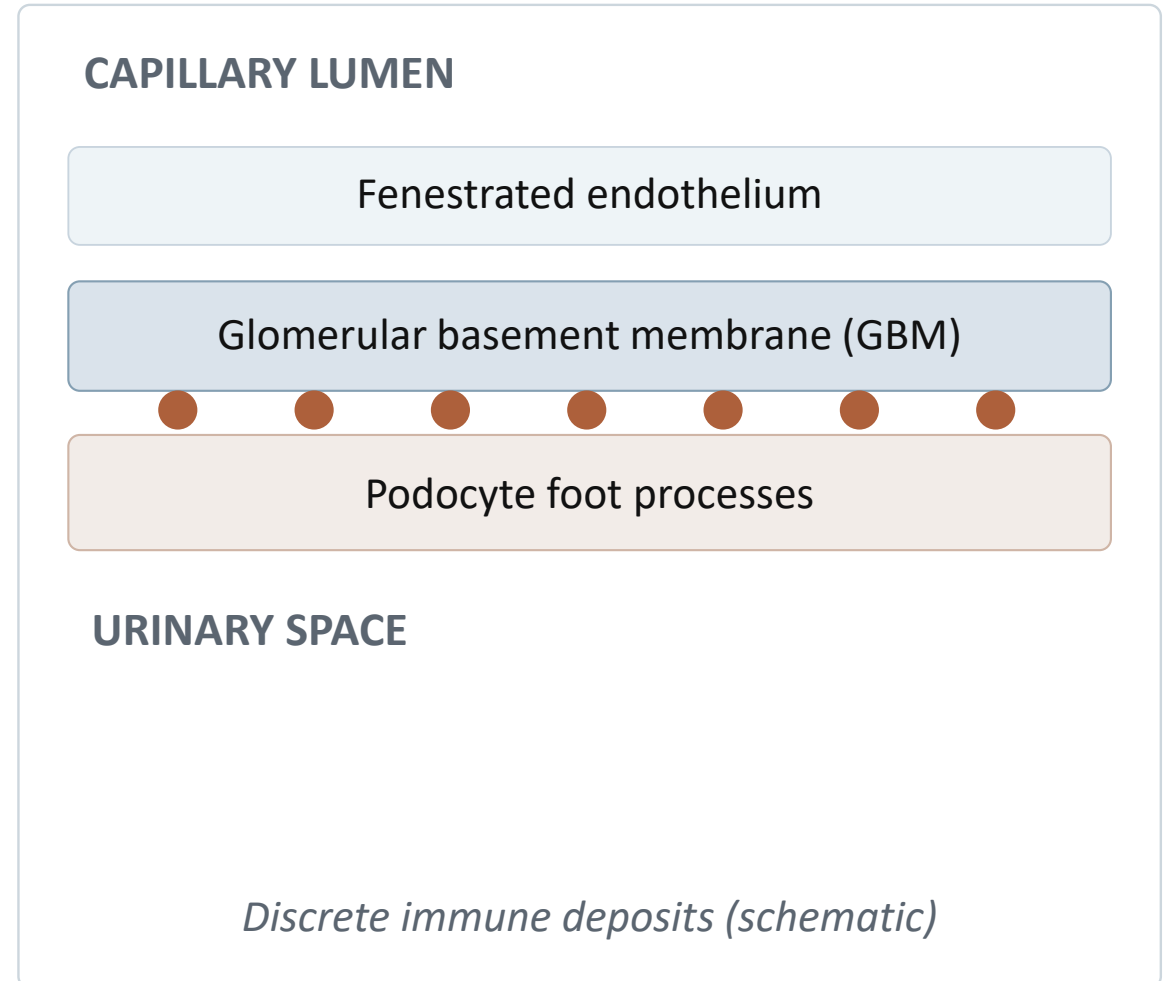
Postinfectious humps are subepithelial

- Postinfectious glomerulonephritis may show isolated dome-like subepithelial deposits.
- The term “hump” describes deposit configuration on electron microscopy.
- The isolated hump pattern differs from regularly distributed membranous deposits.



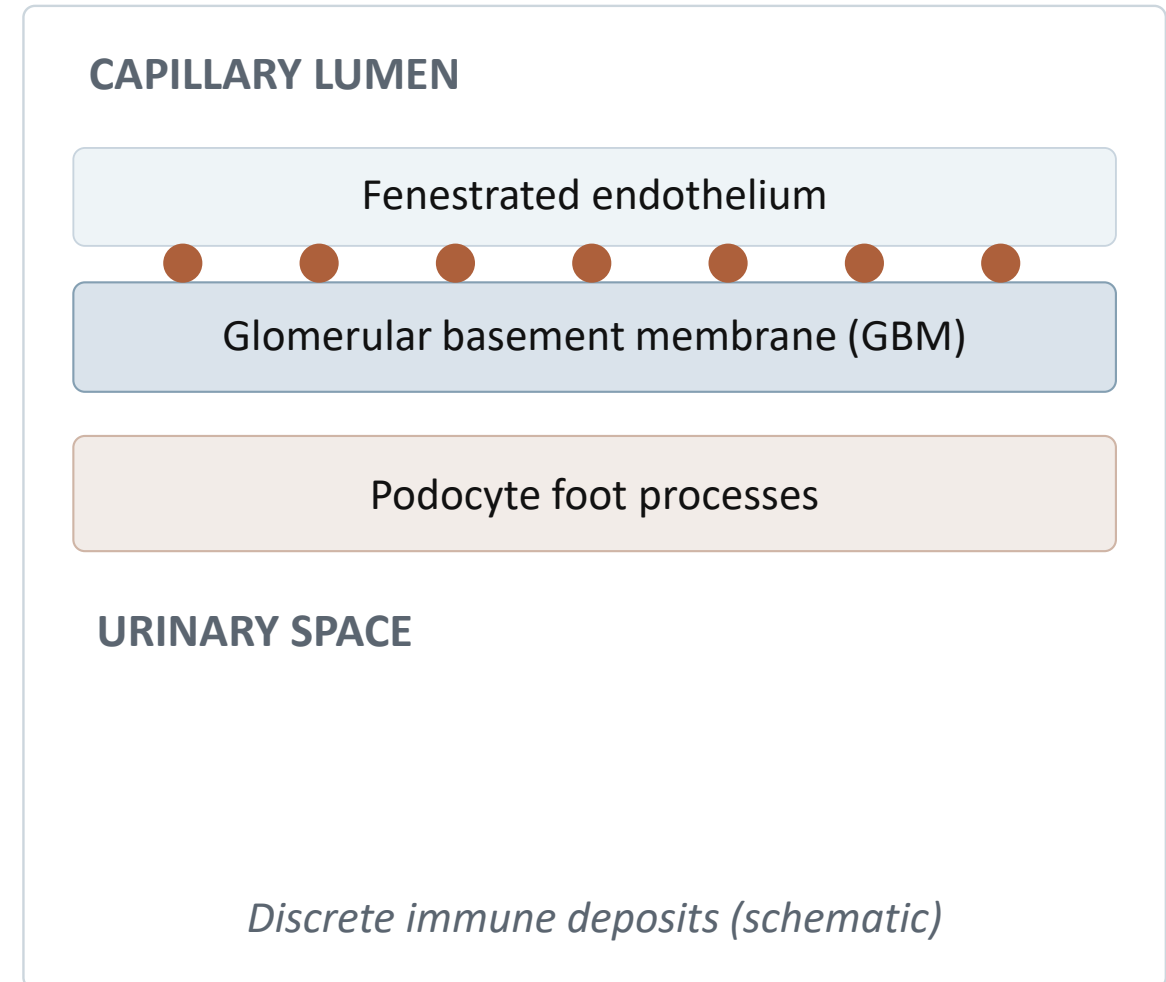
Membranous pattern: Repeated subepithelial deposits

- Membranous nephropathy classically has multiple discrete subepithelial deposits.
- Host responses around deposits produce an apparent thickened GBM by light microscopy.
- This pattern can occur without a leukocyte-rich capillary-lumen inflammatory response.



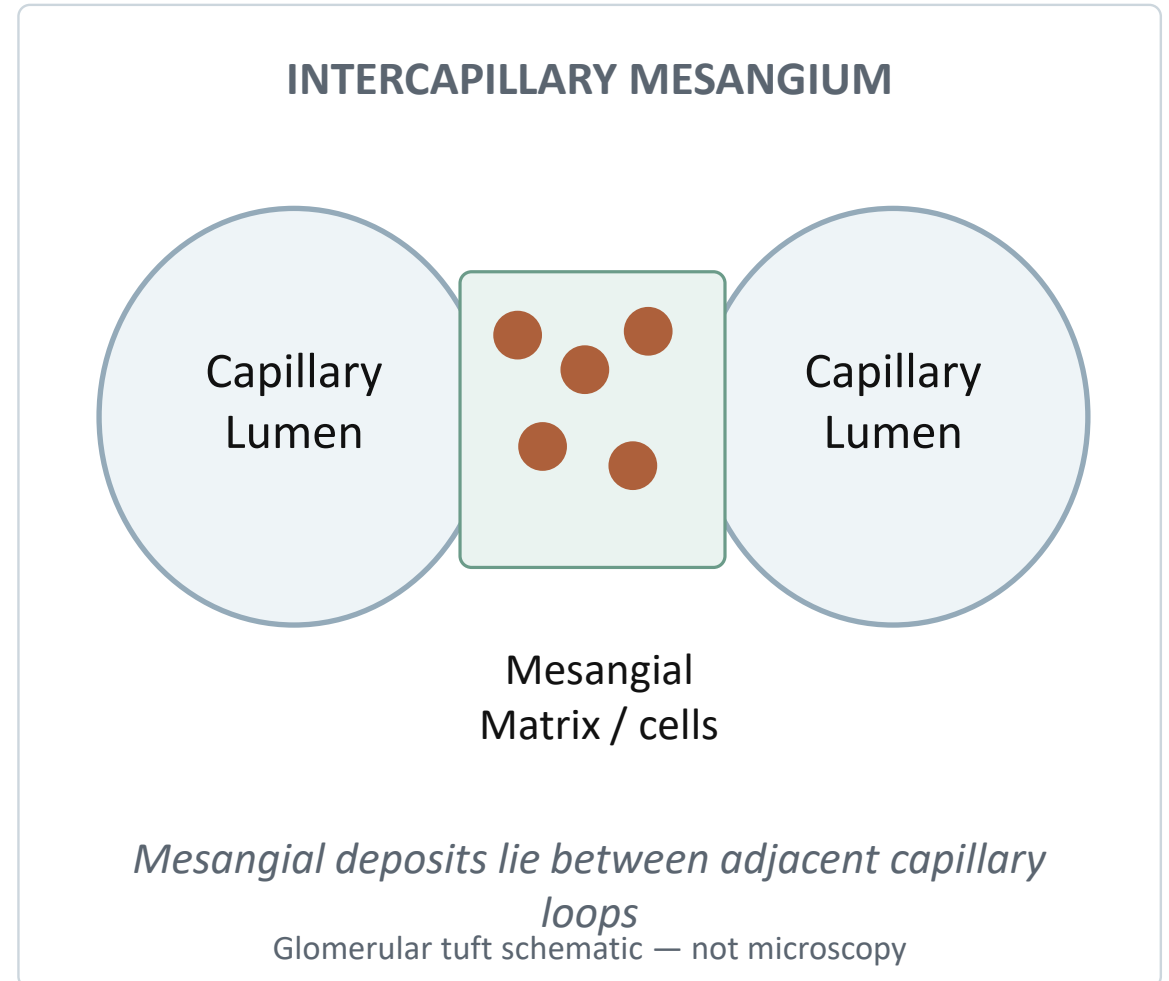
Membranoproliferative pattern: Subendothelial injury

- Subendothelial immune complexes may cause recurrent endothelial injury.
- Repeated injury and repair can produce basement membrane double contours.
- Membranoproliferative morphology is a reaction pattern rather than proof of one antigen.



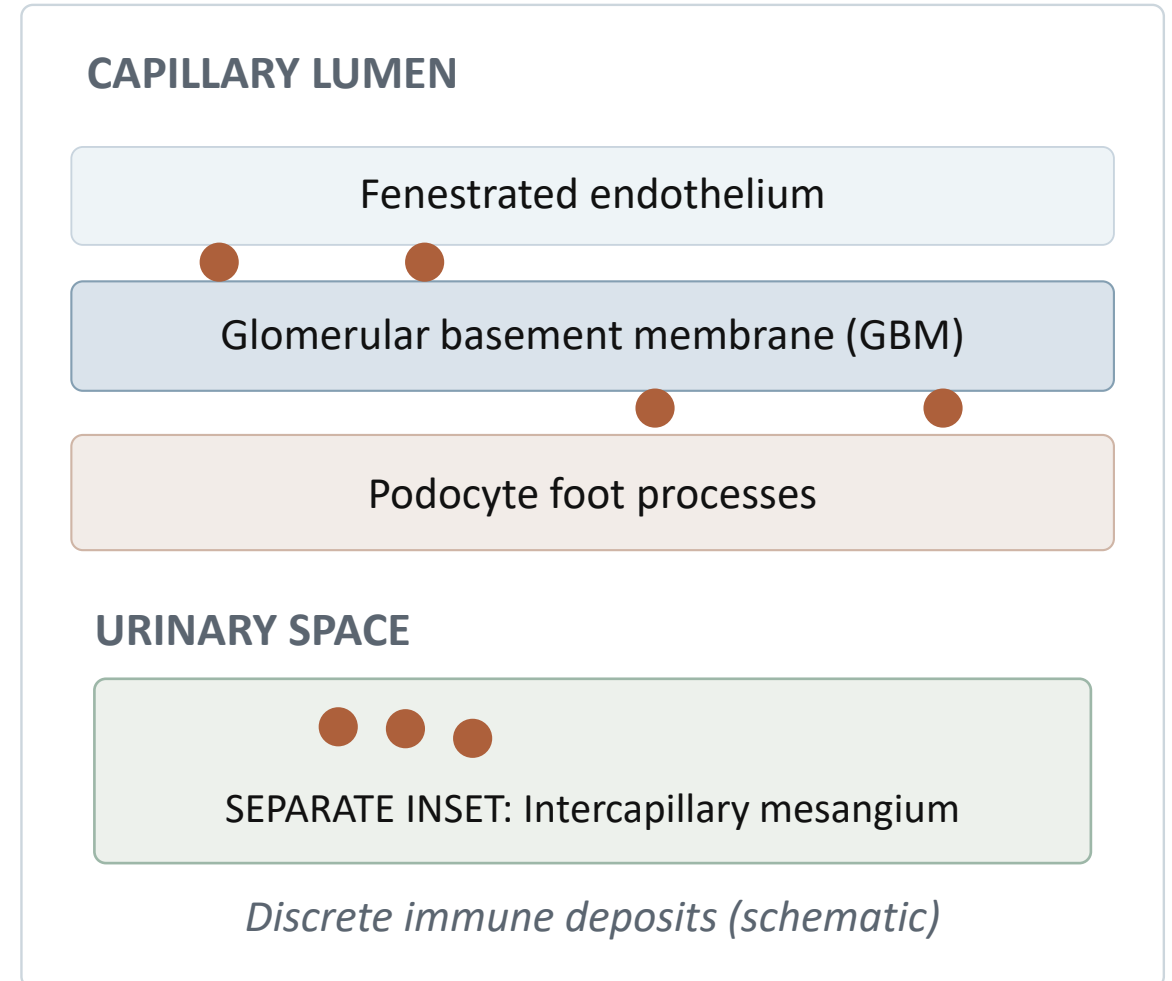
IgA nephropathy: Mesangial emphasis

- Mesangial immune deposits as typical of IgA nephropathy.
- Mesangial localization explains potential mesangial proliferation and inflammation.
- Localization describes the injury site but does not alone establish the entire etiology.



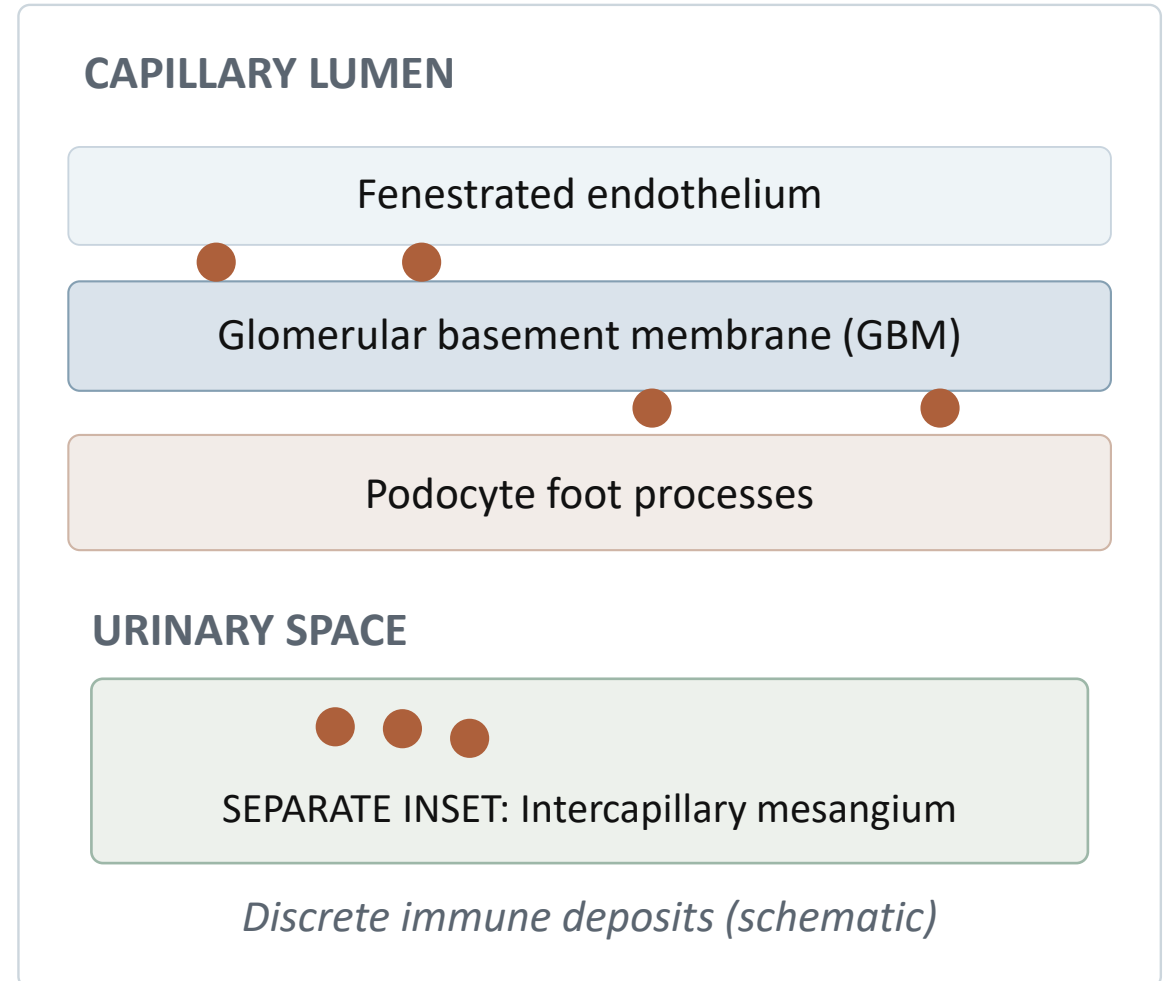
Lupus may involve several compartments

- Lupus-associated immune-complex injury may show subendothelial deposits.
- Mesangial deposits may occur, including in early lupus nephritis.
- Multiple sites can be involved within the same glomerular disease.



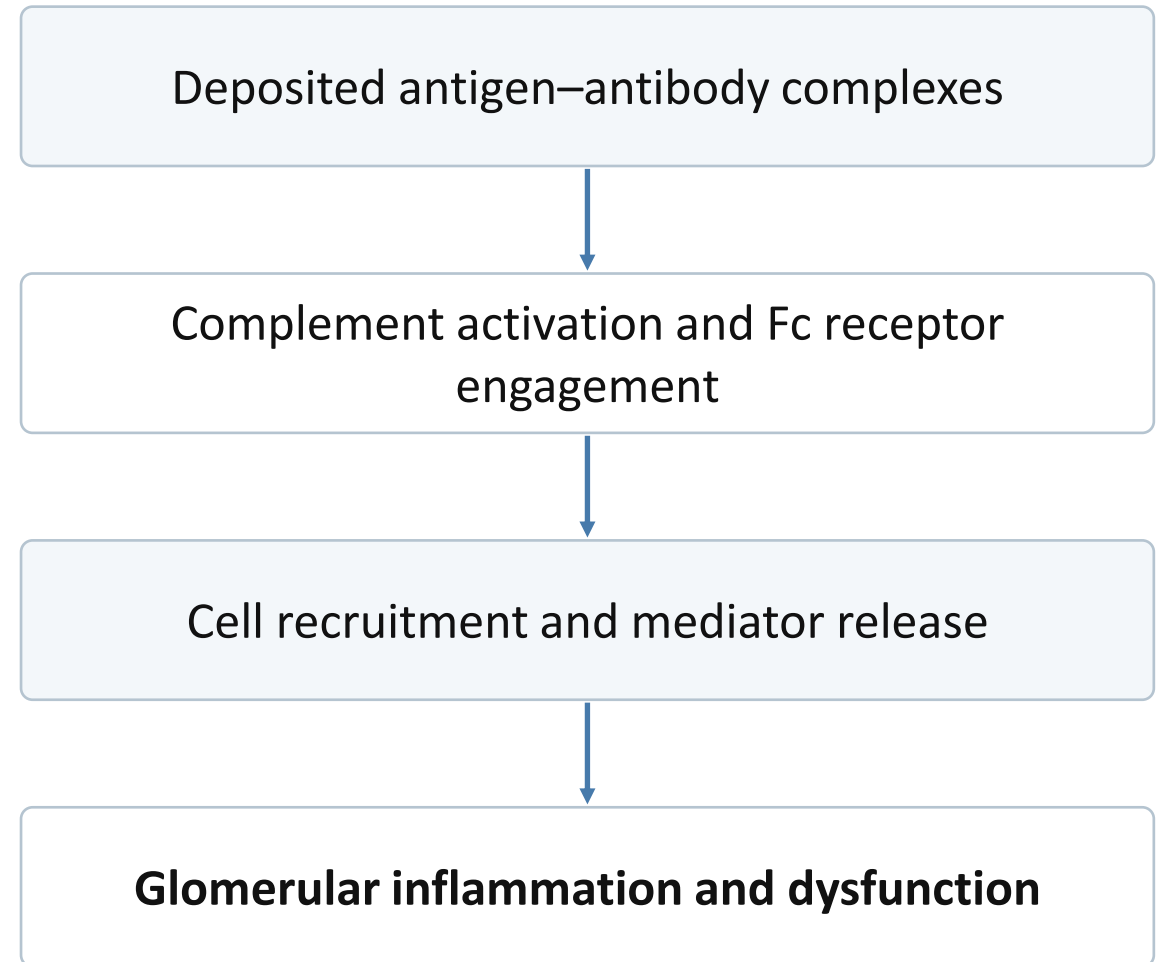
The same glomerulus may harbor multiple deposits

- Electron-dense deposits may occur at more than one ultrastructural location.
- No single simple compartment diagram fully describes every biopsy.
- Pathologic interpretation must account for the complete distribution.



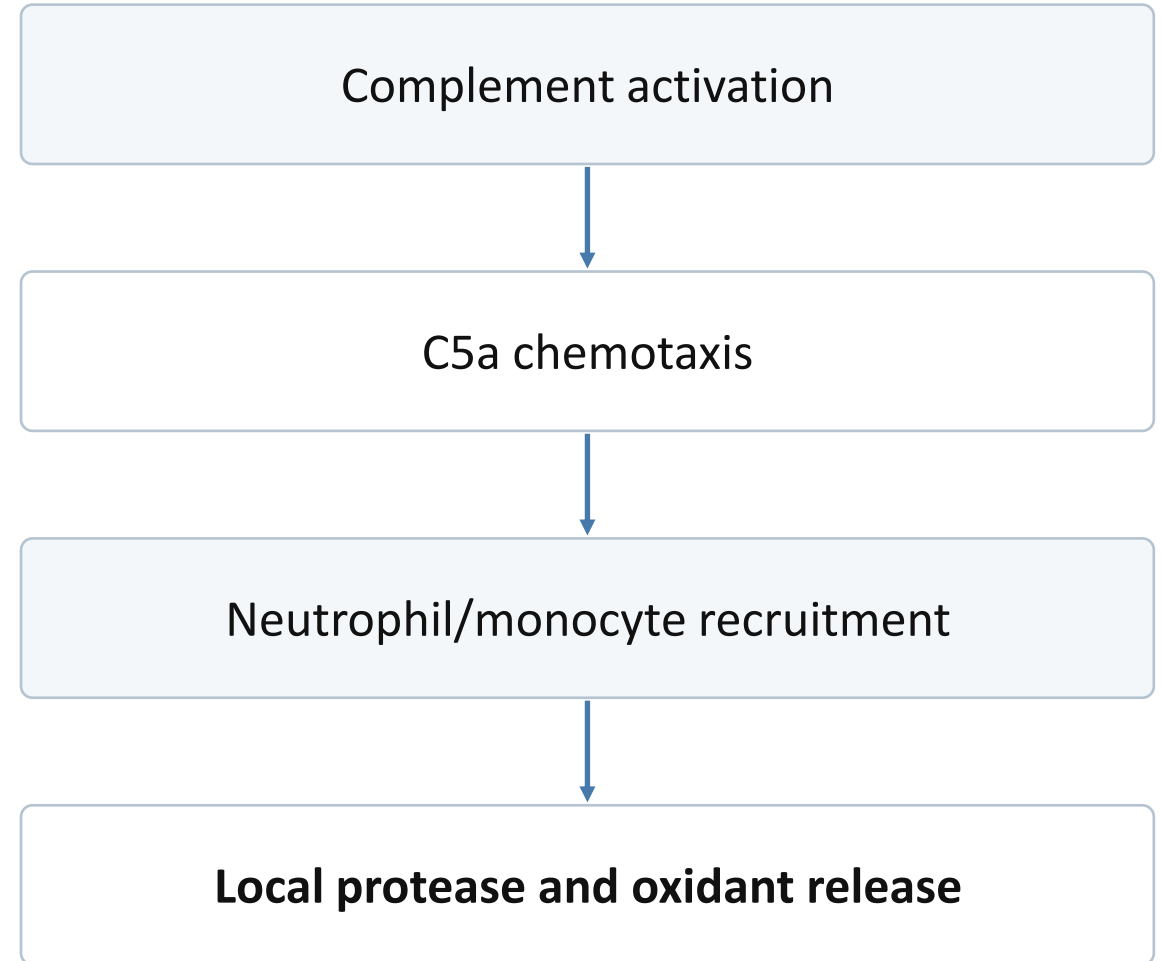
Immune deposits trigger inflammatory amplification

- Deposited antibody can activate complement.
- Antibodies may engage Fc receptors on circulating leukocytes.
- These two routes recruit and activate effectors that injure glomerular tissue.



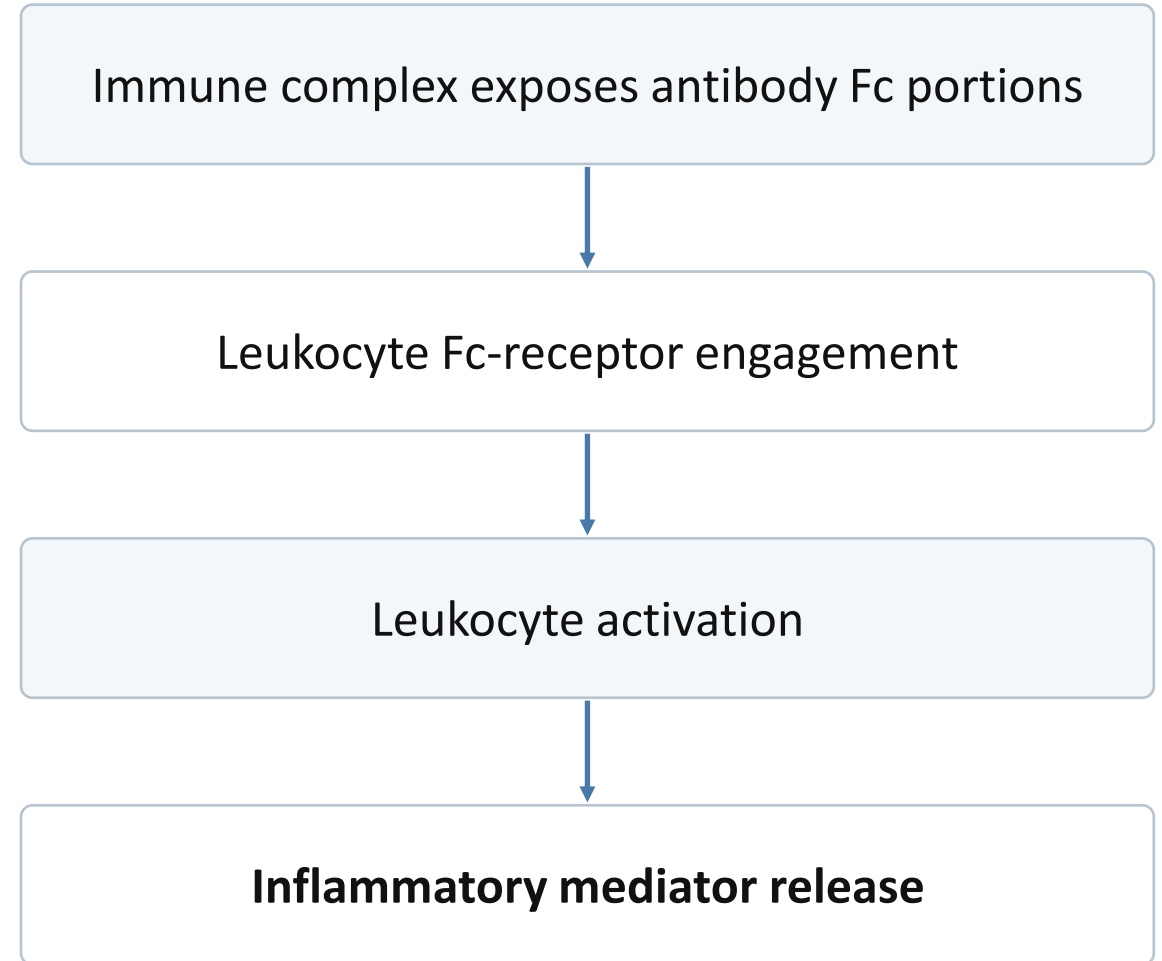
C5a links complement to leukocyte influx

- Complement activation generates chemoattractants, especially C5a.
- Neutrophils and monocytes enter susceptible glomeruli.
- The recruited cells can then damage GBM and resident cells.



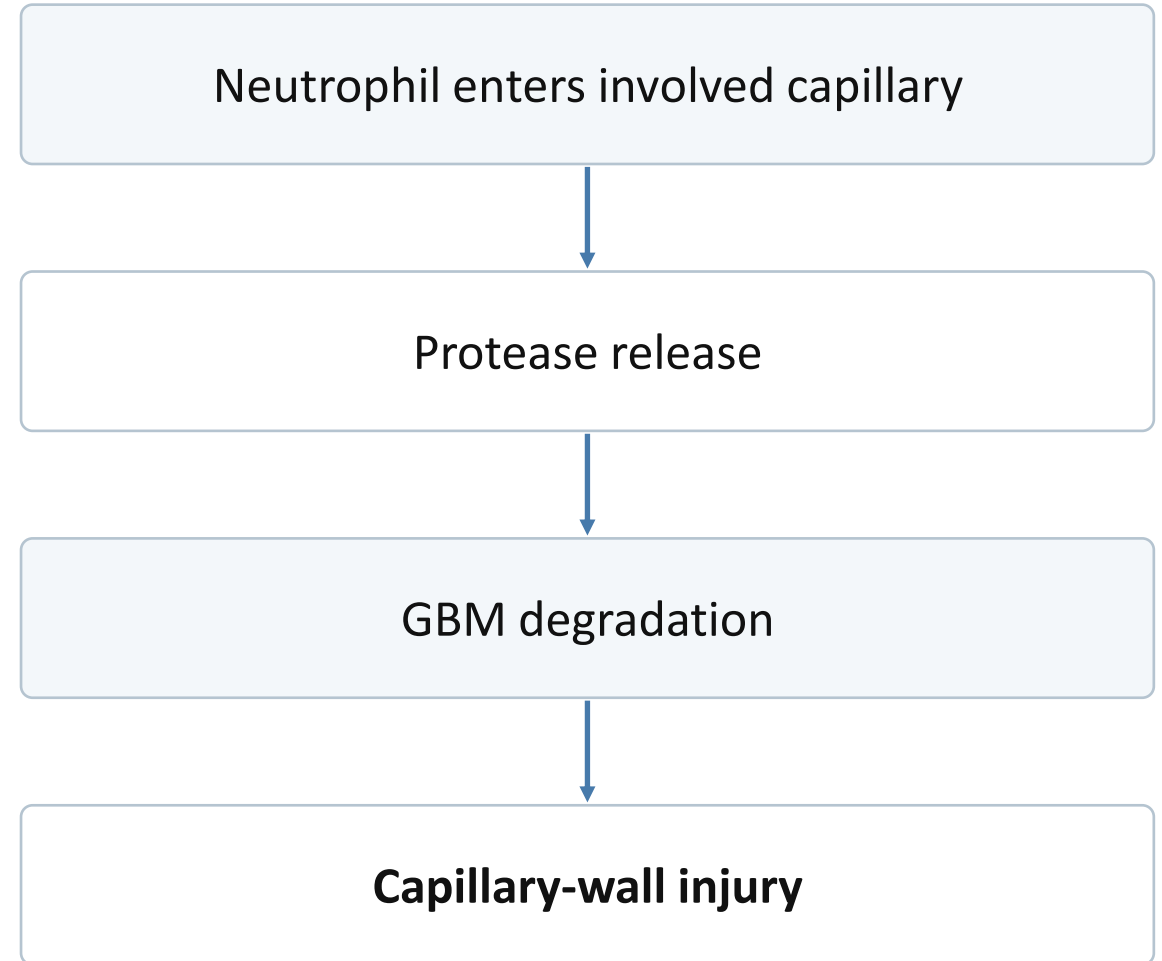
Fc receptors contribute independent activation

- Leukocyte Fc receptors recognize antibody-containing deposits.
- Fc receptor engagement promotes leukocyte activation.
- Inflammation may therefore reflect antibody–cell interactions as well as complement.



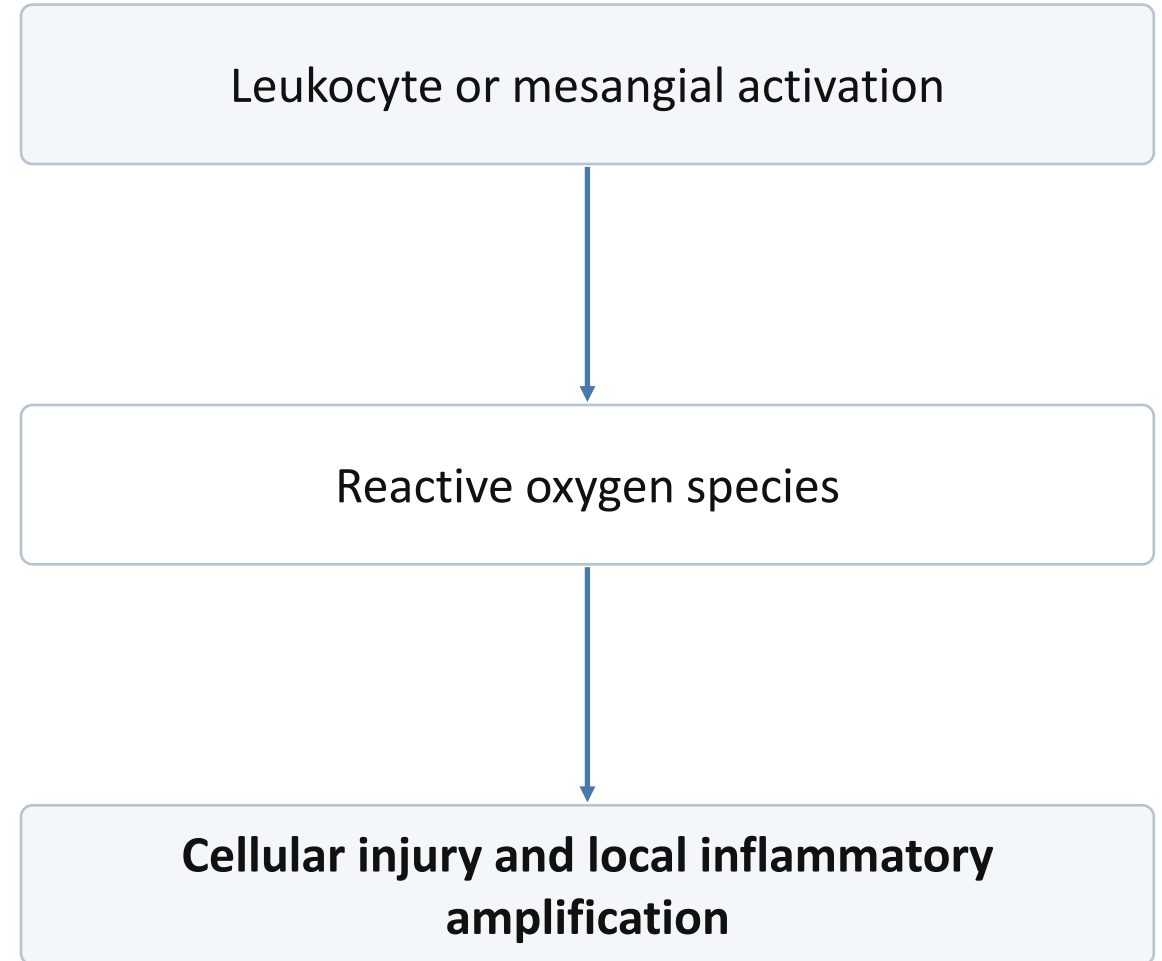
Neutrophil proteases damage the GBM

- Recruited neutrophils release proteolytic enzymes.
- Protease activity can degrade GBM matrix.
- Loss of capillary-wall integrity facilitates severe glomerular injury.



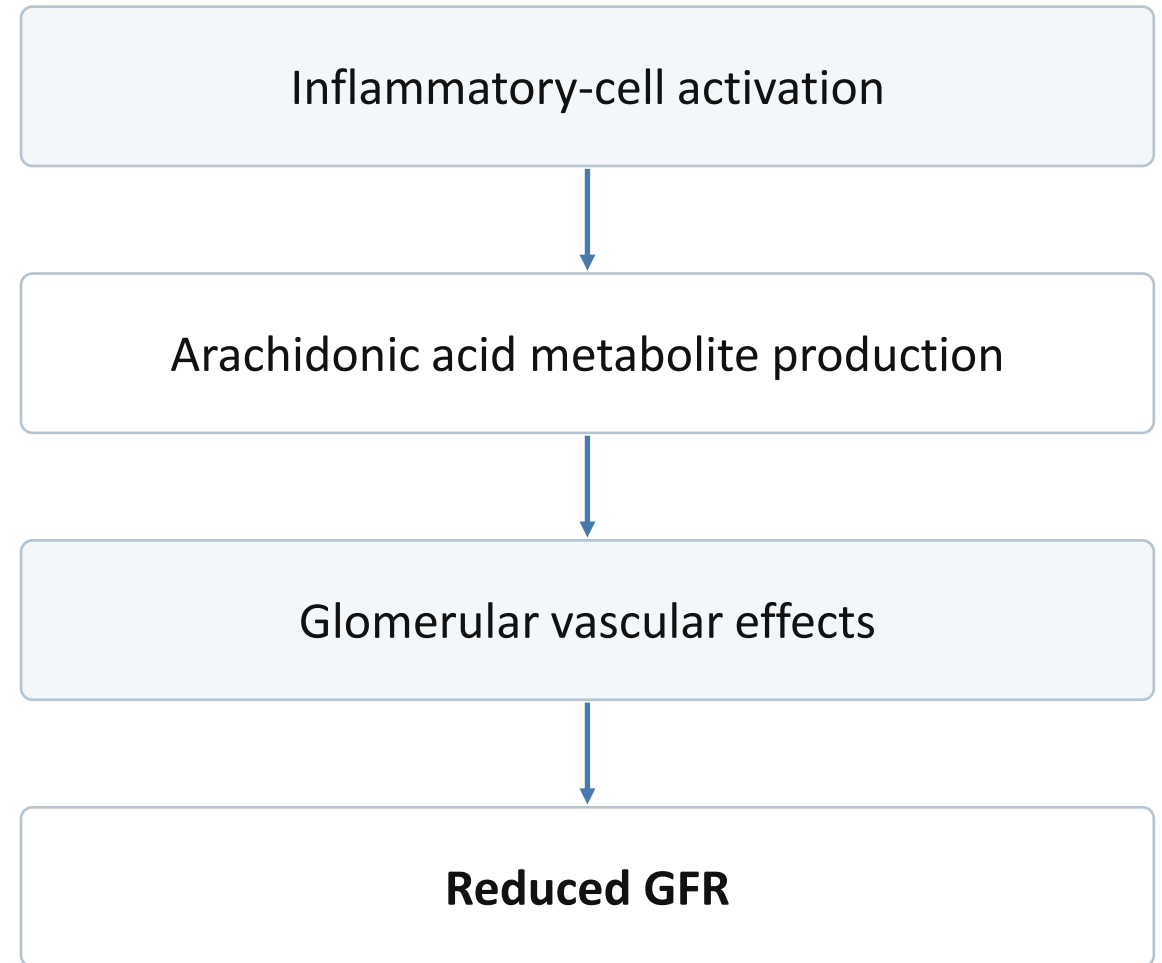
Reactive oxygen species injure glomerular cells

- Activated neutrophils release oxygen-derived free radicals.
- Reactive oxidants damage glomerular cells.
- Resident mesangial cells can also generate reactive oxygen species.



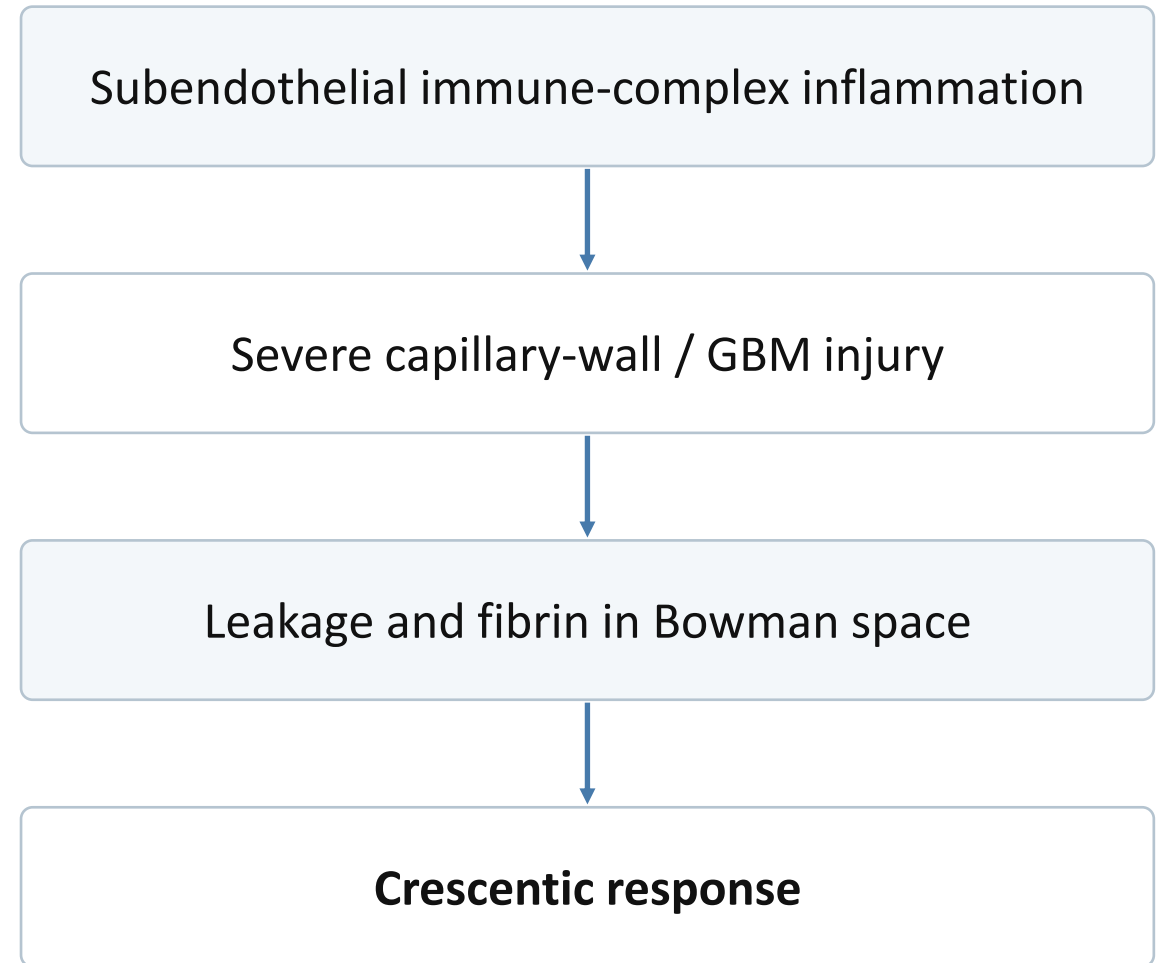
Arachidonic acid metabolites alter filtration

- Neutrophil-derived arachidonic acid metabolites influence vascular tone.
- These vascular changes contribute to reduced glomerular filtration rate (GFR).
- Functional impairment may reflect mediators in addition to structural damage.



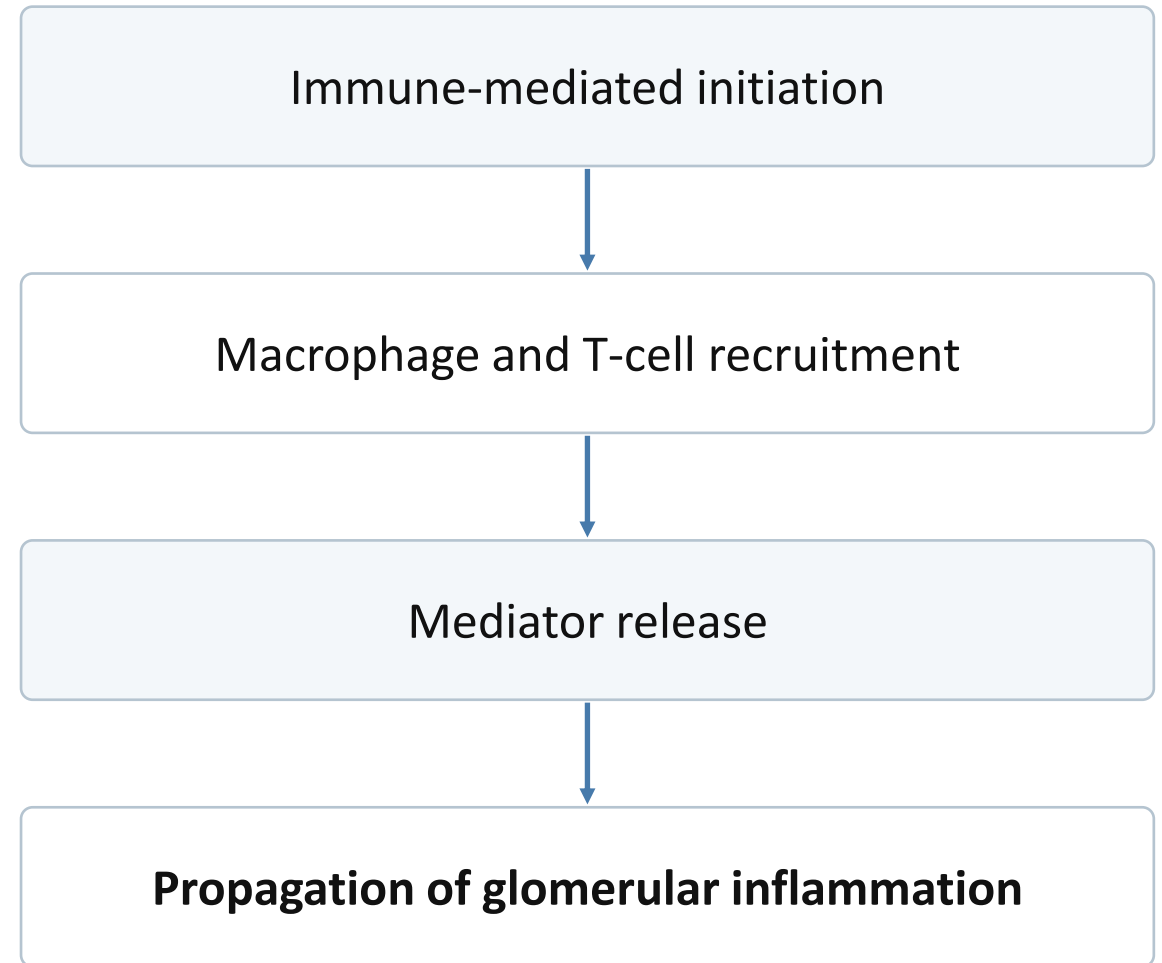
Subendothelial inflammation can produce crescents

- Subendothelial deposits commonly elicit leukocyte-rich injury.
- Severe injury may disrupt the GBM and leak plasma proteins into Bowman space.
- Fibrin and coagulation mediators contribute to crescent formation.



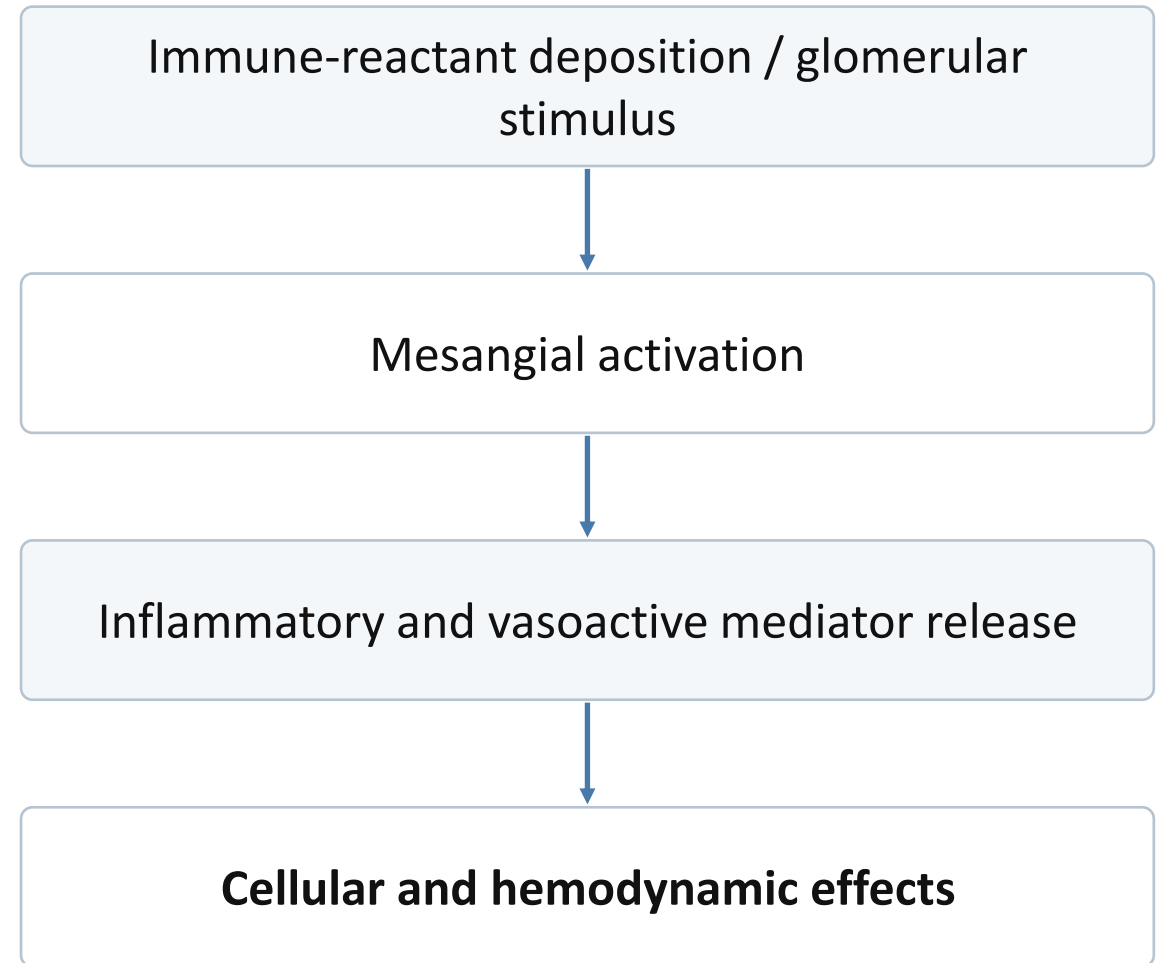
Macrophages and T cells sustain inflammation

- Infiltrating macrophages and activated T lymphocytes release multiple mediators.
- These cells may contribute to injury initiated by immune complexes.
- Experimental evidence for T-cell amplification is strongest in selected crescentic models.



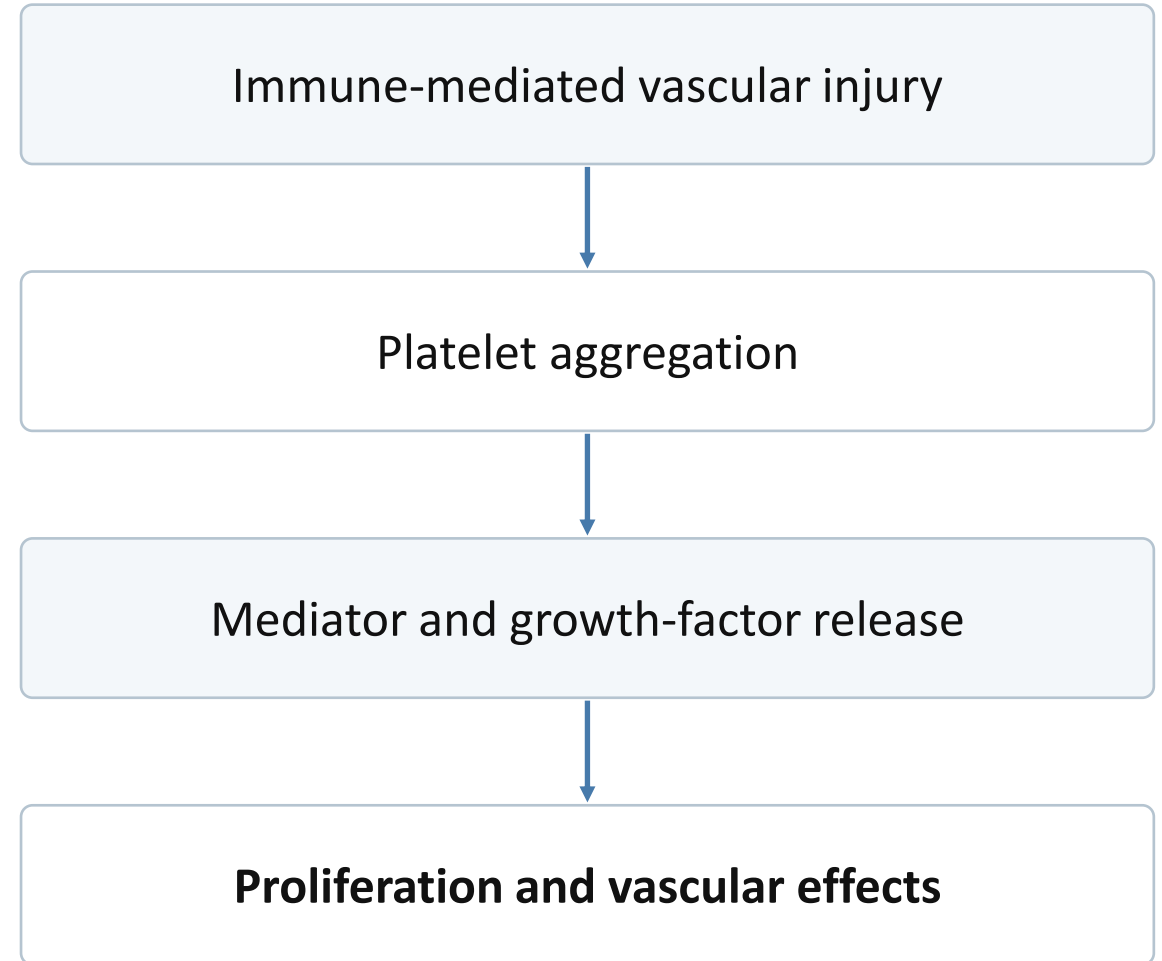
Activated mesangial cells are effector cells

- Mesangial cells may produce cytokines, chemokines, oxidants, and growth factors.
- They also release eicosanoids, nitric oxide, and endothelin.
- Intrinsic-cell responses can occur without major leukocyte infiltration.



Platelets can amplify glomerular injury

- Platelets may aggregate within inflamed glomeruli.
- They release eicosanoids, growth factors, and other mediators.
- These products may support vascular injury and glomerular cell proliferation.



Complement has two major effector modes

C5a-driven pathway

Chemotaxis

Neutrophils and monocytes

Leukocyte-dependent injury

C5b–C9 pathway

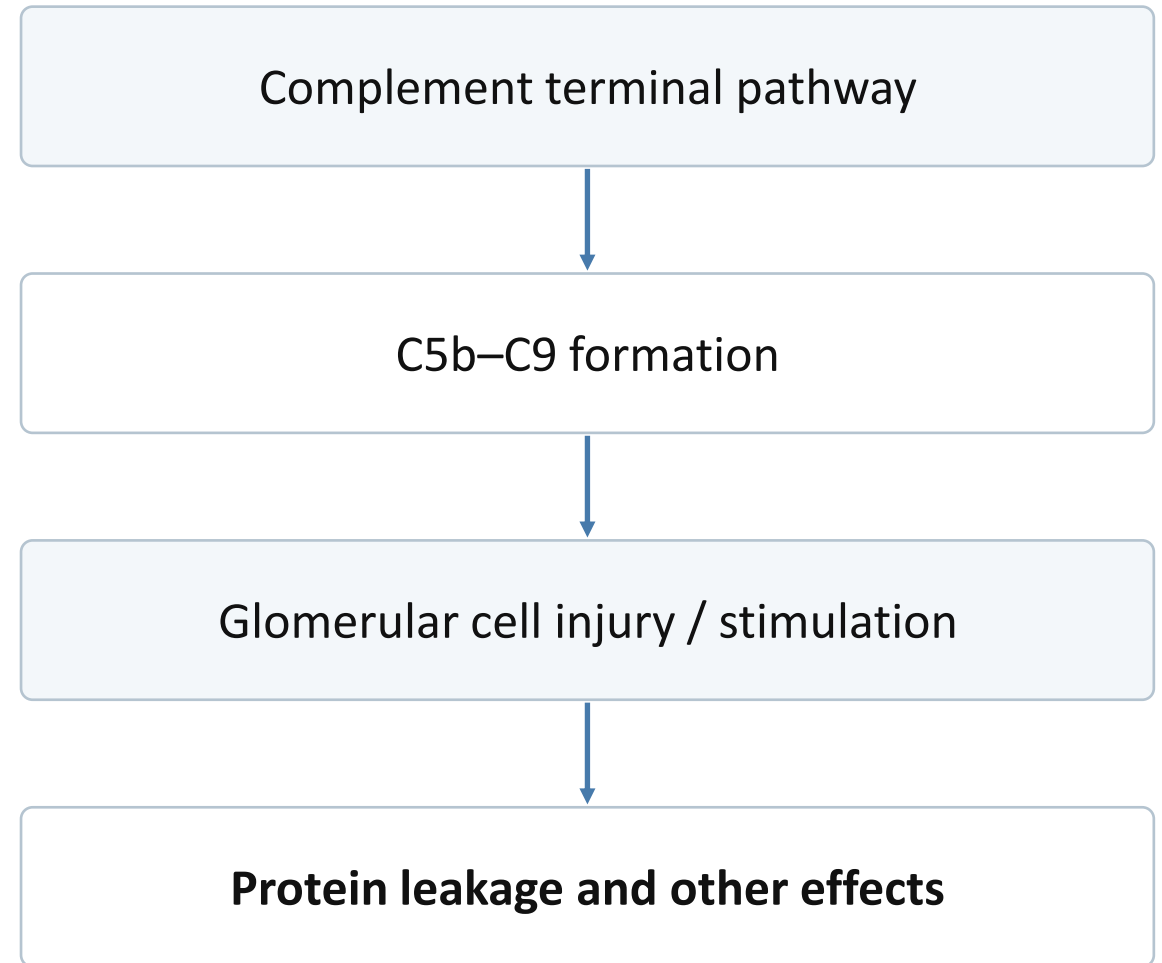
Membrane attack complex

Cell injury or activation

Can operate without neutrophils

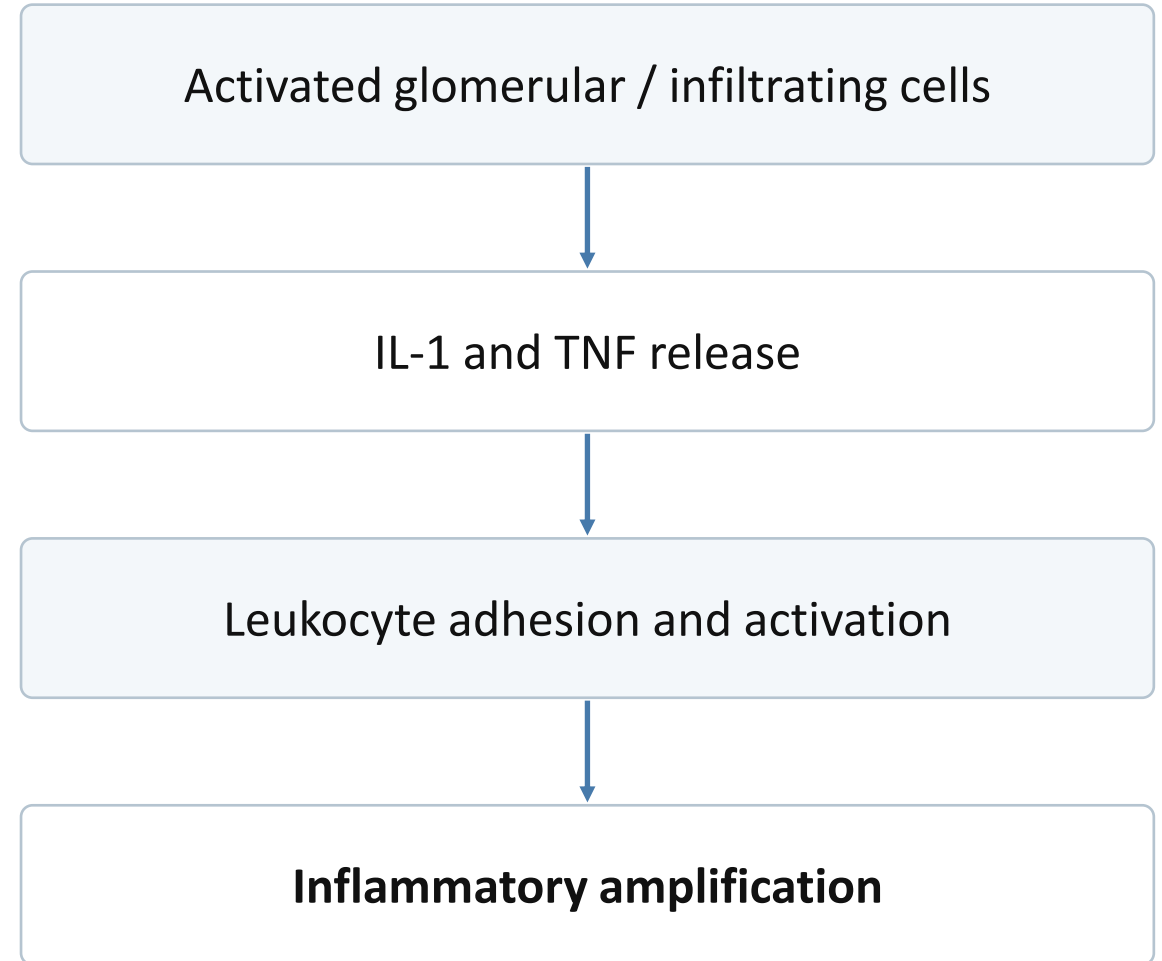
C5b–C9 can injure cells without neutrophils

- The C5b–C9 membrane attack complex can cause cell lysis.
- It may stimulate mesangial cells to release oxidants and proteases.
- Experimental membranous glomerulopathy demonstrates MAC-associated proteinuria without neutrophils.



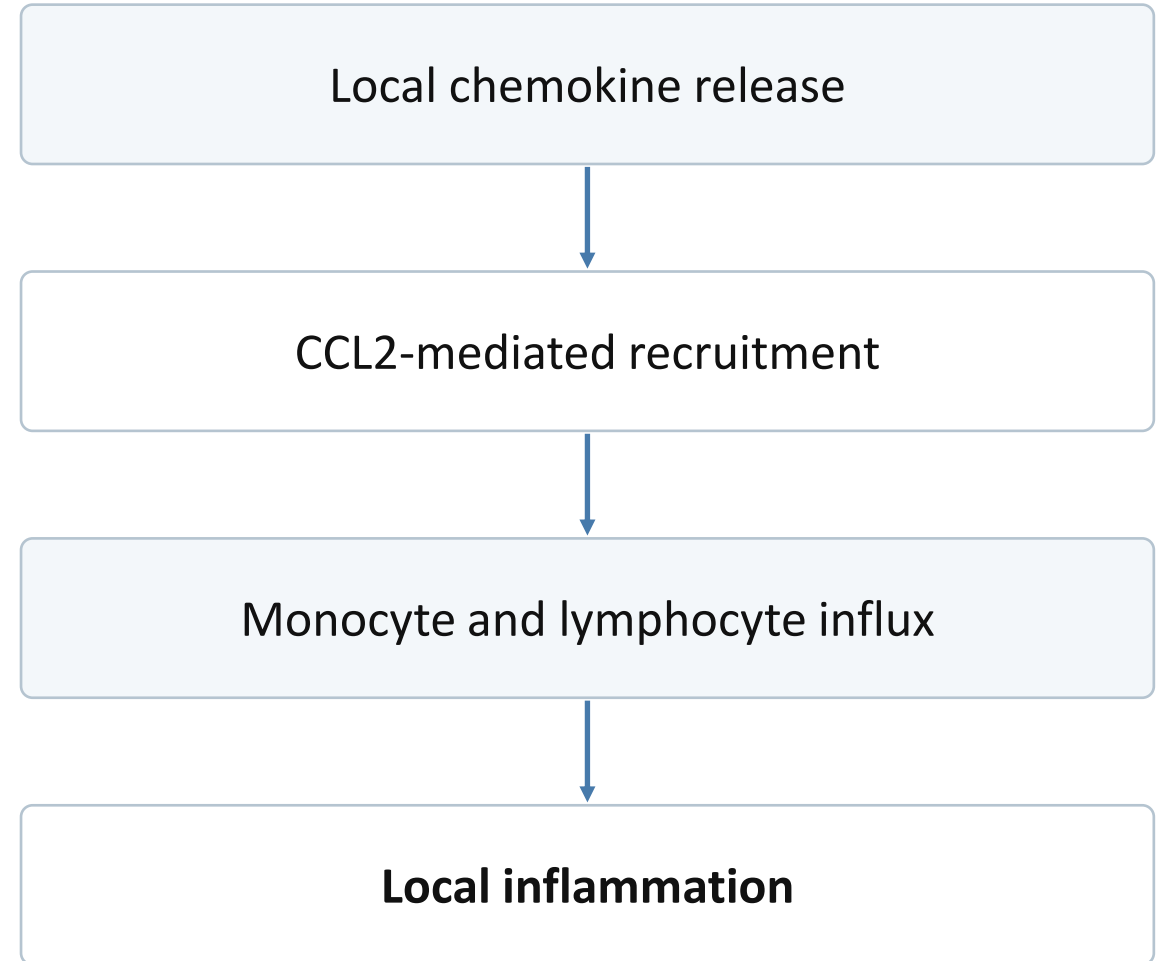
Cytokines support leukocyte adhesion

- Interleukin-1 and tumor necrosis factor are identified glomerular injury mediators.
- Both infiltrating leukocytes and resident cells can produce cytokines.
- They promote adhesion and other inflammatory responses.



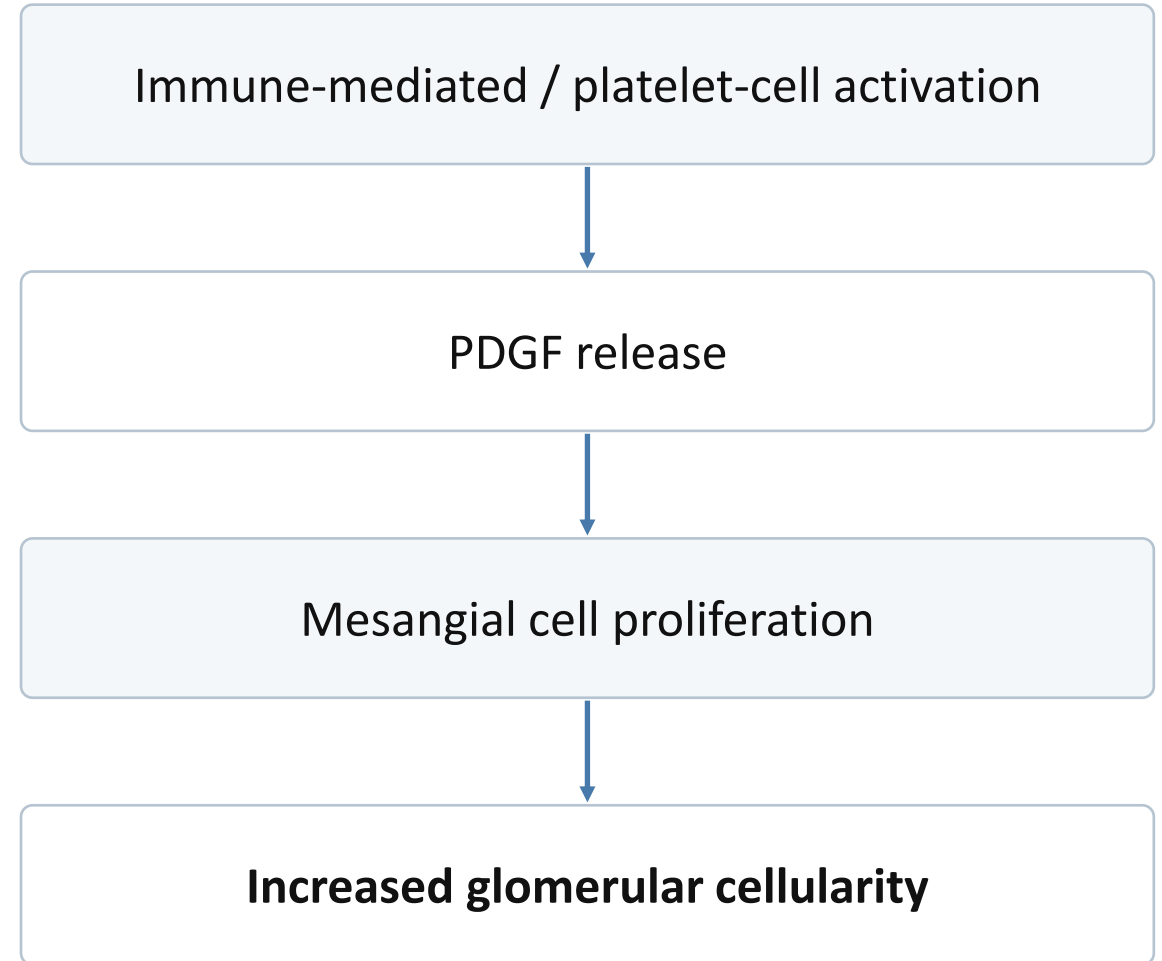
CCL2 recruits mononuclear cells

- Monocyte chemoattractant protein-1 is also termed CCL2.
- This chemokine promotes entry of monocytes and lymphocytes.
- Cell recruitment can sustain glomerular inflammatory activity.



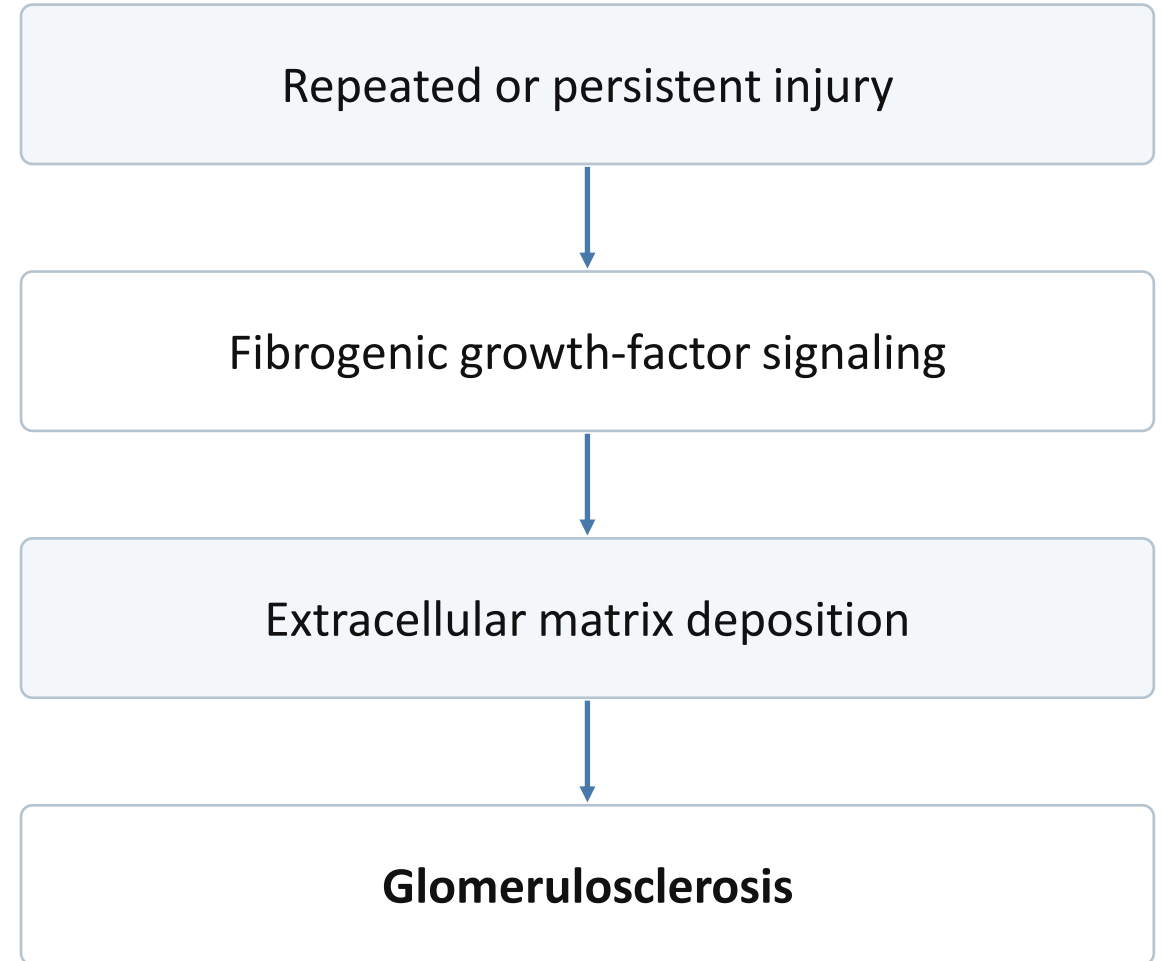
PDGF promotes mesangial proliferation

- Platelet-derived growth factor (PDGF) contributes to mesangial cell proliferation.
- Growth responses may accompany mesangial immune-complex inflammation.
- Cellularity is therefore both an inflammatory and proliferative manifestation.



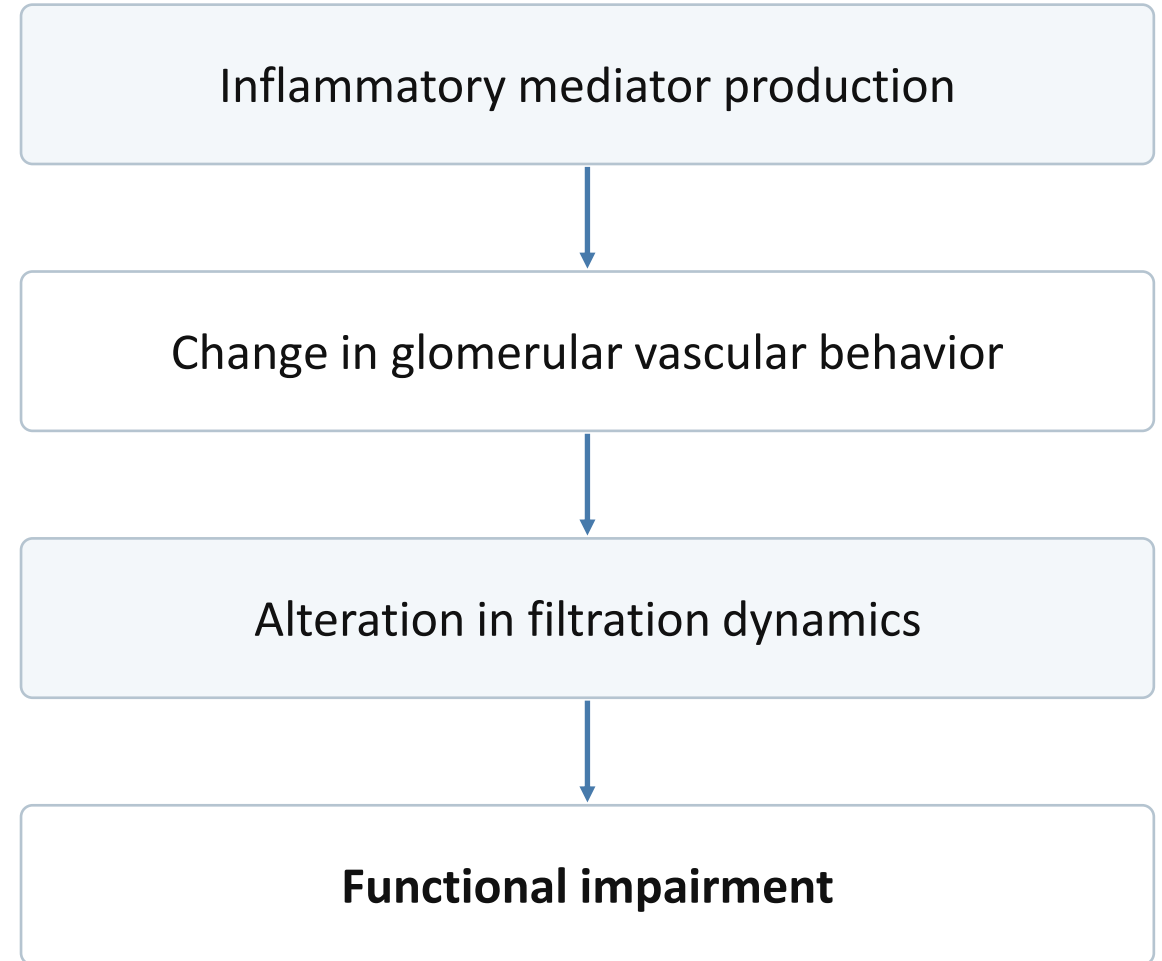
Fibrogenic growth factors drive remodeling

- Transforming growth factor- β , connective tissue growth factor, and fibroblast growth factor favor matrix accumulation.
- Extracellular matrix deposition and hyalinization contribute to sclerosis.
- This links persistent immune injury to structural chronic damage.



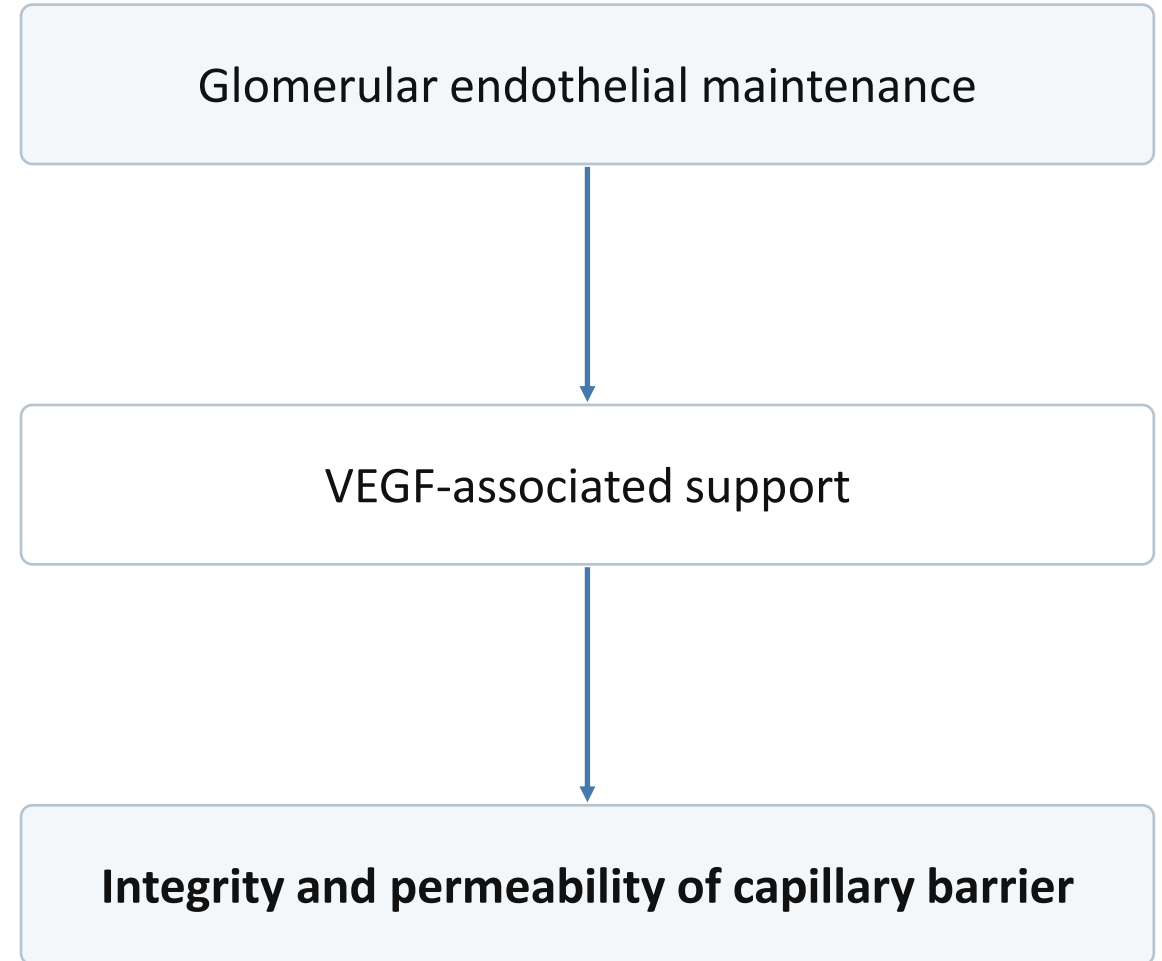
Hemodynamic mediators change renal function

- Eicosanoids, nitric oxide, angiotensin, and endothelin influence glomerular hemodynamics.
- Vascular responses can change filtration before extensive sclerosis appears.
- Resident cells and infiltrating leukocytes contribute to mediator production.



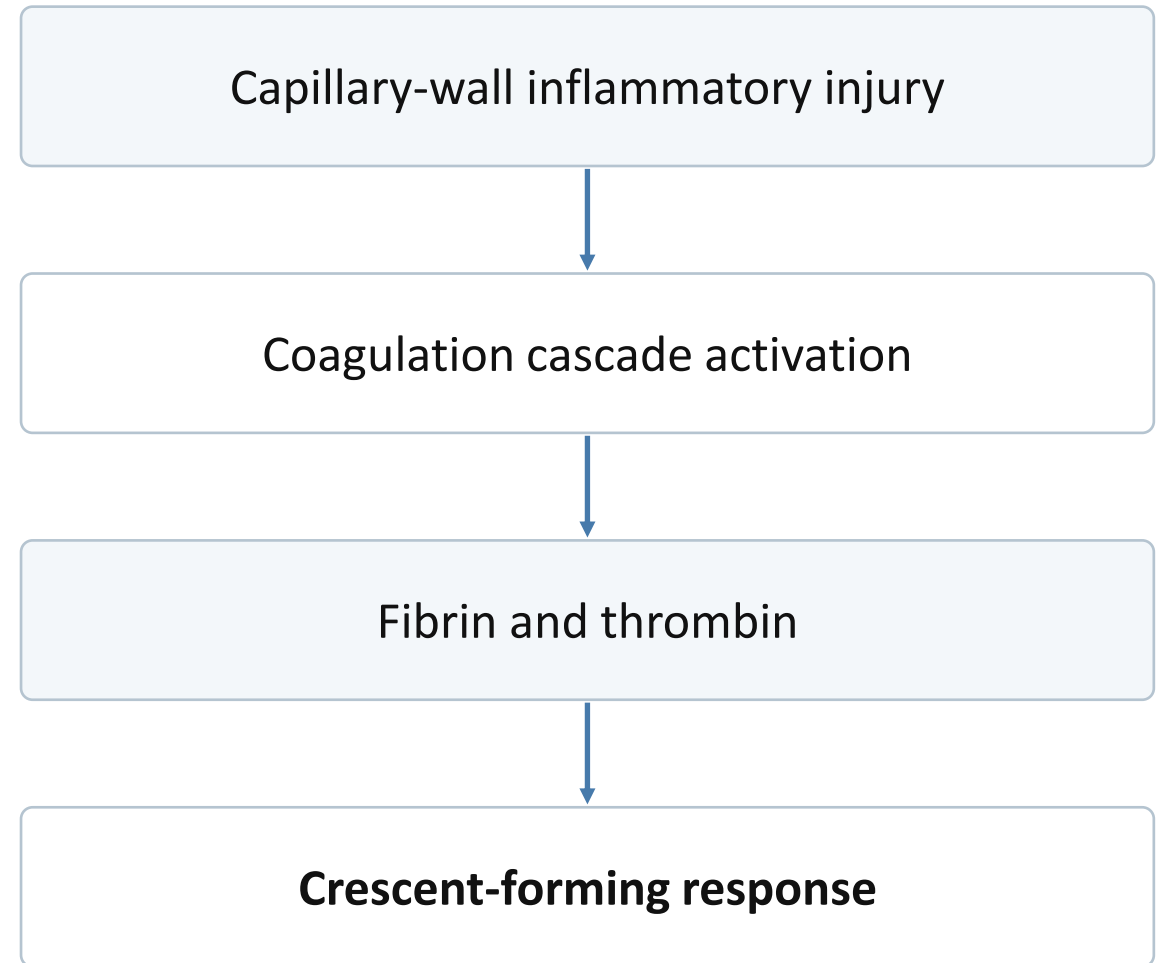
VEGF helps maintain endothelial integrity

- Vascular endothelial growth factor supports glomerular endothelial integrity.
- It may participate in regulation of capillary permeability.
- Barrier function reflects interactions among intrinsic glomerular cells.



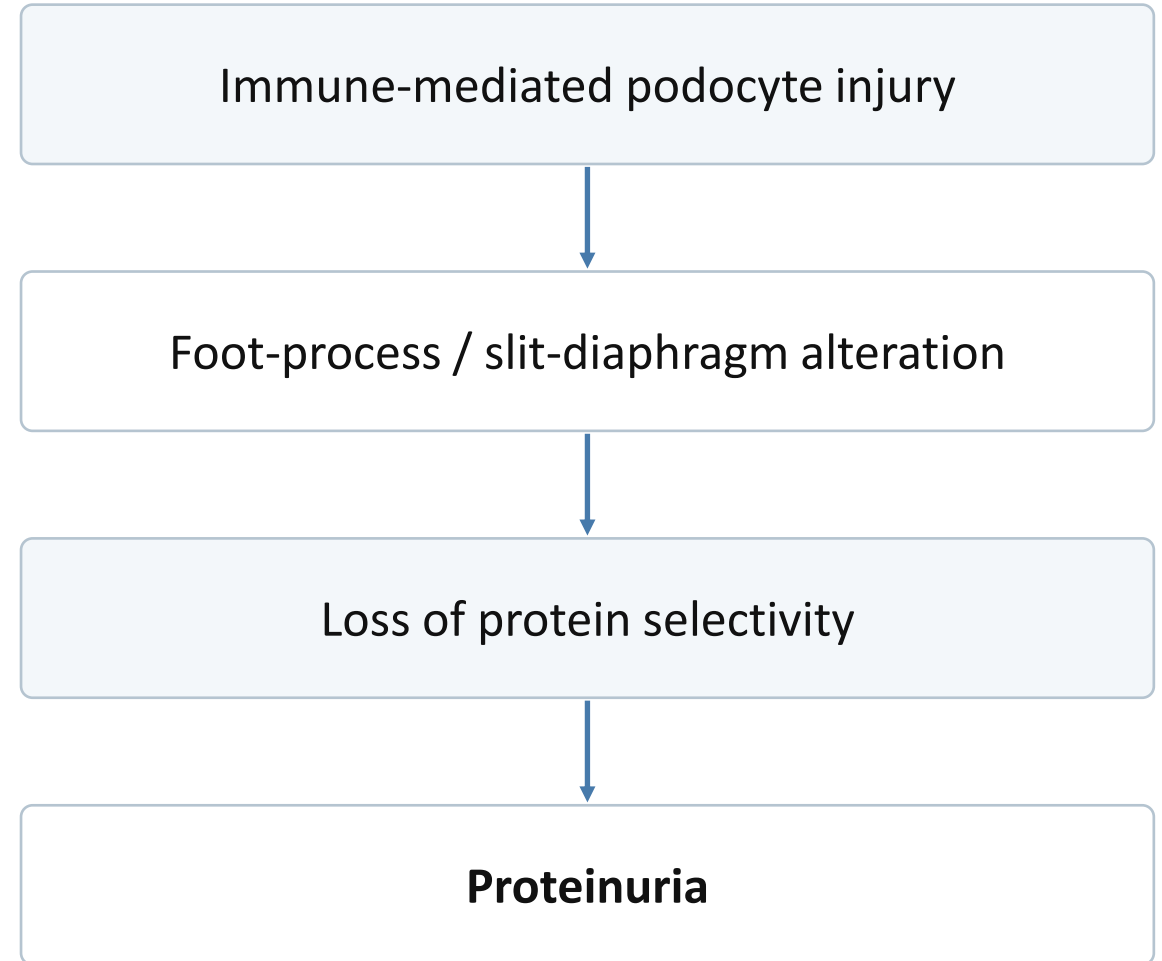
Coagulation links vascular injury to crescents

- Fibrin can accumulate within glomeruli and Bowman space.
- This indicates local coagulation cascade activation.
- Activated coagulation factors, particularly thrombin, may stimulate crescent formation.



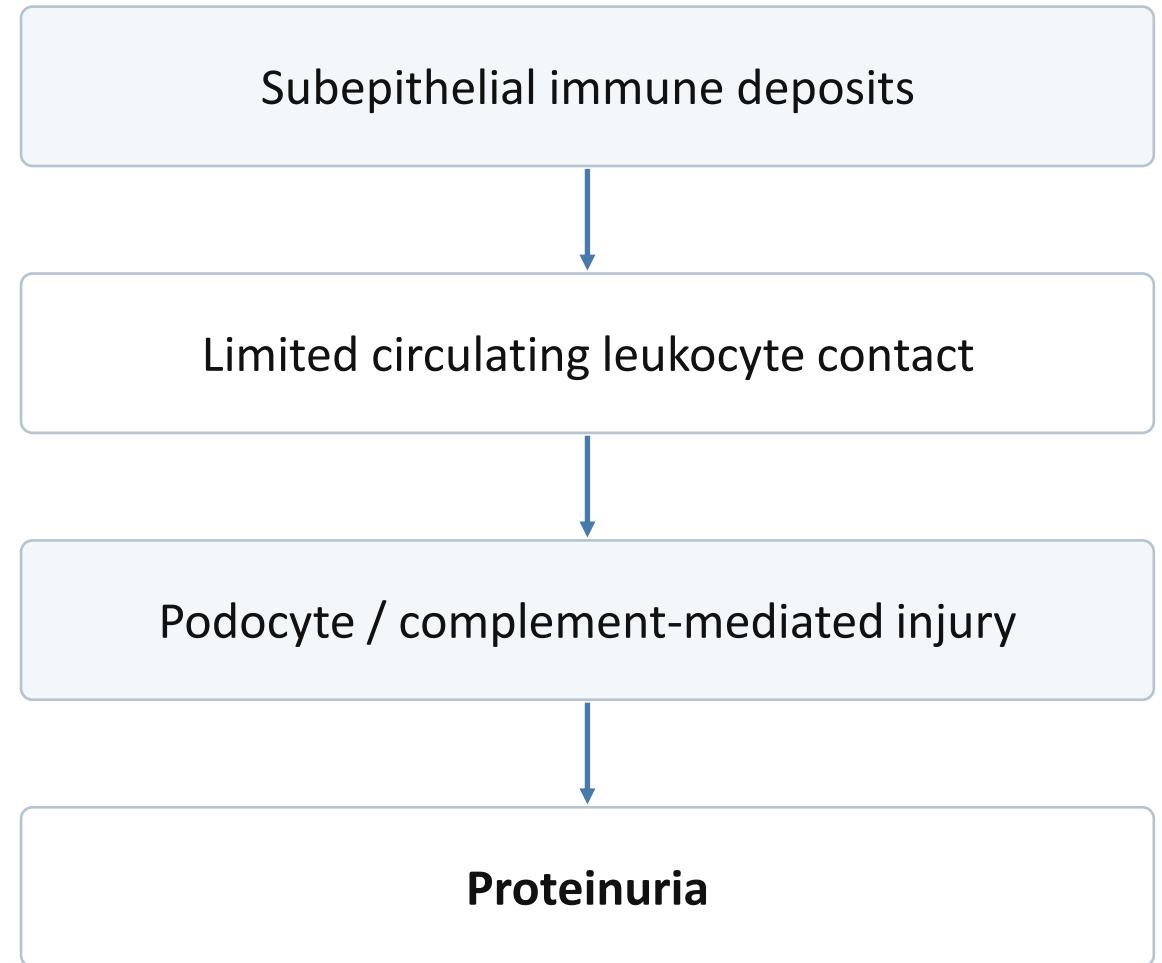
Podocyte injury is a distinct consequence

- Immune mechanisms can injure podocytes, including antibodies to podocyte antigens.
- Foot-process effacement and slit diaphragm disruption compromise filtration selectivity.
- Proteinuria results when the barrier no longer retains plasma proteins.



Subepithelial deposits can cause proteinuria

- GBM shielding limits leukocyte access to subepithelial deposits.
- Nevertheless, local complement-mediated epithelial injury may impair the filtration barrier.
- Lack of a leukocyte-rich lesion does not imply absence of clinically relevant damage.



Two pathways produce protein leakage

Inflammatory capillary-wall injury

Subendothelial / mesangial access

Leukocytes and capillary damage

Barrier disruption

Podocyte-dominant injury

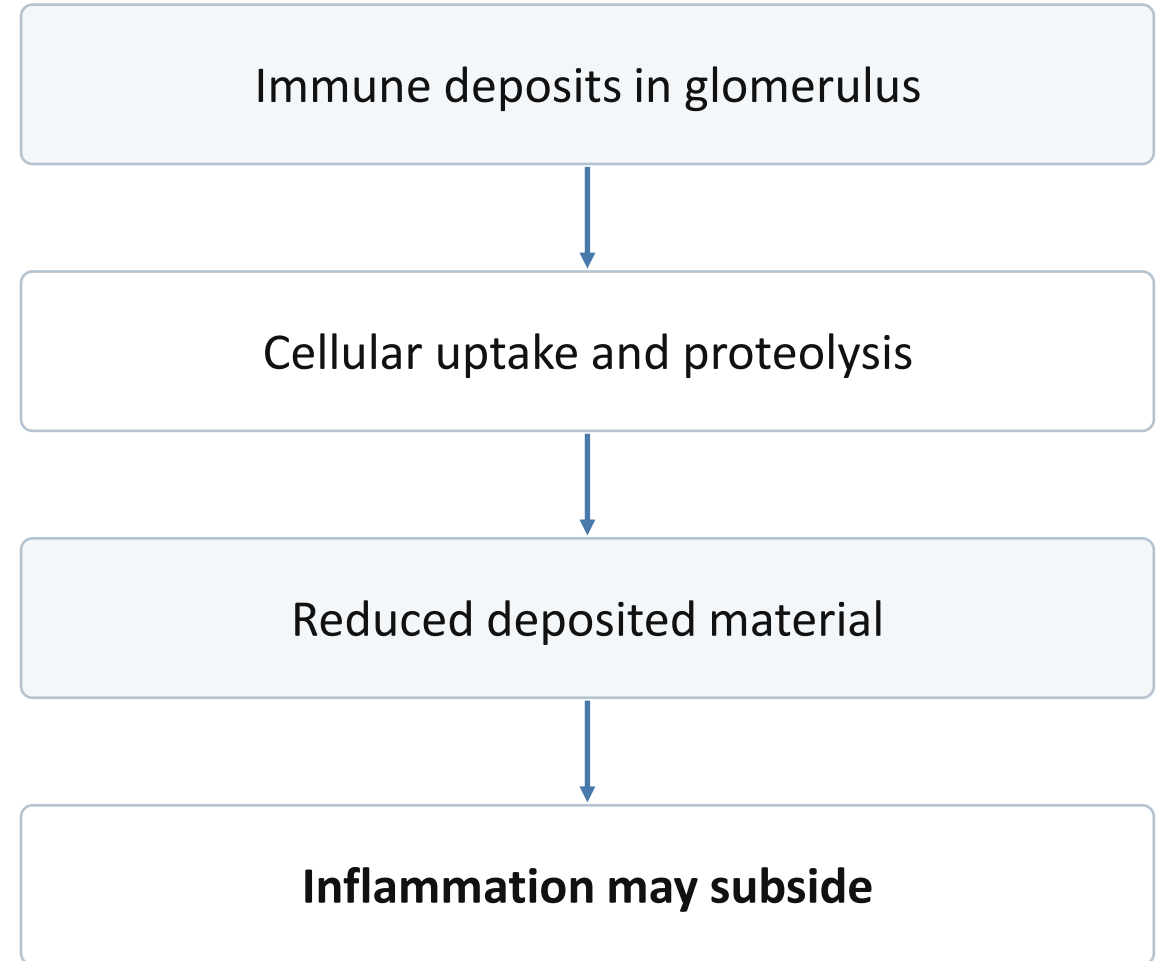
Subepithelial or podocyte-directed events

Foot process / slit diaphragm damage

Albumin leakage

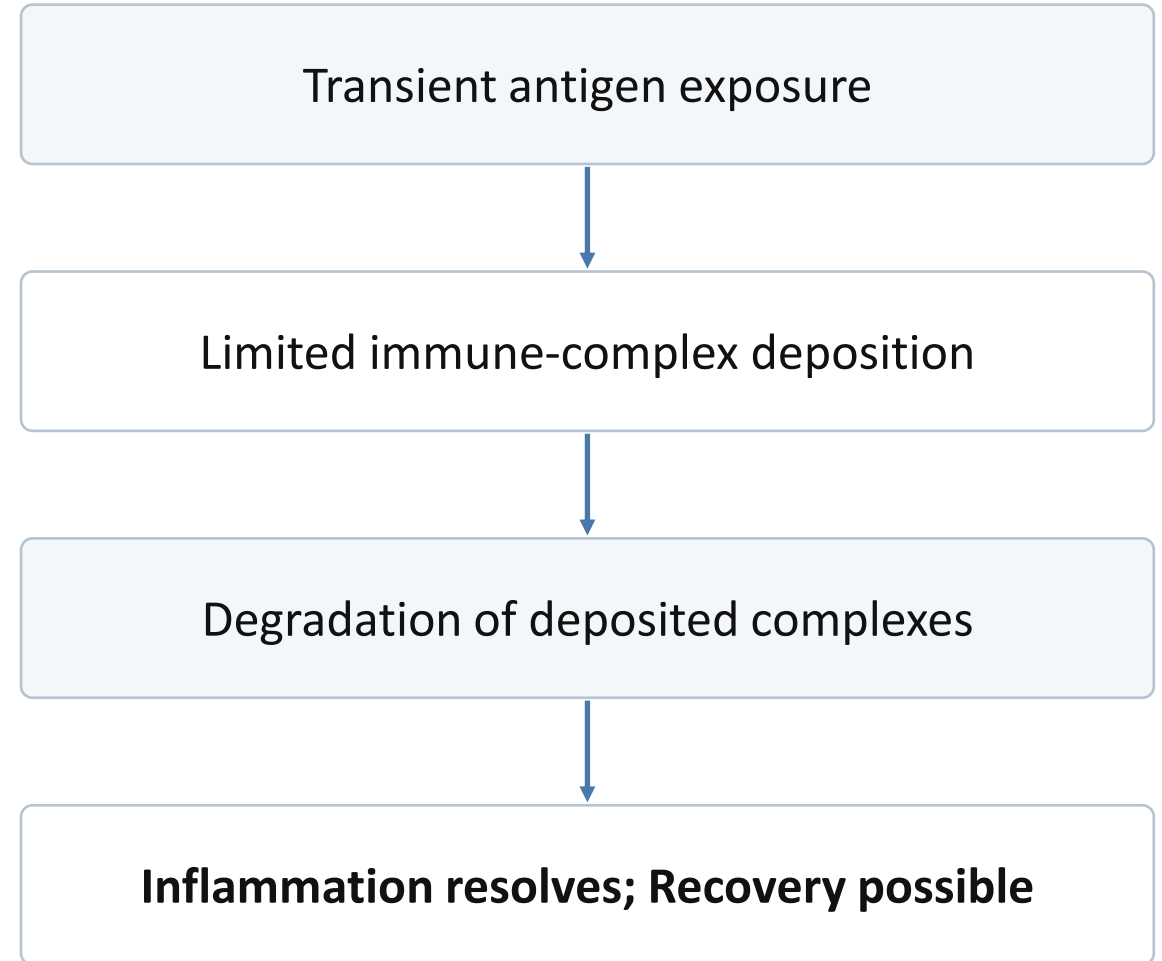
Deposits can eventually be degraded

- Neutrophils and macrophages can remove deposited immune complexes.
- Mesangial cells also participate in degradation and clearance.
- Endogenous proteases contribute to removal of deposited material.



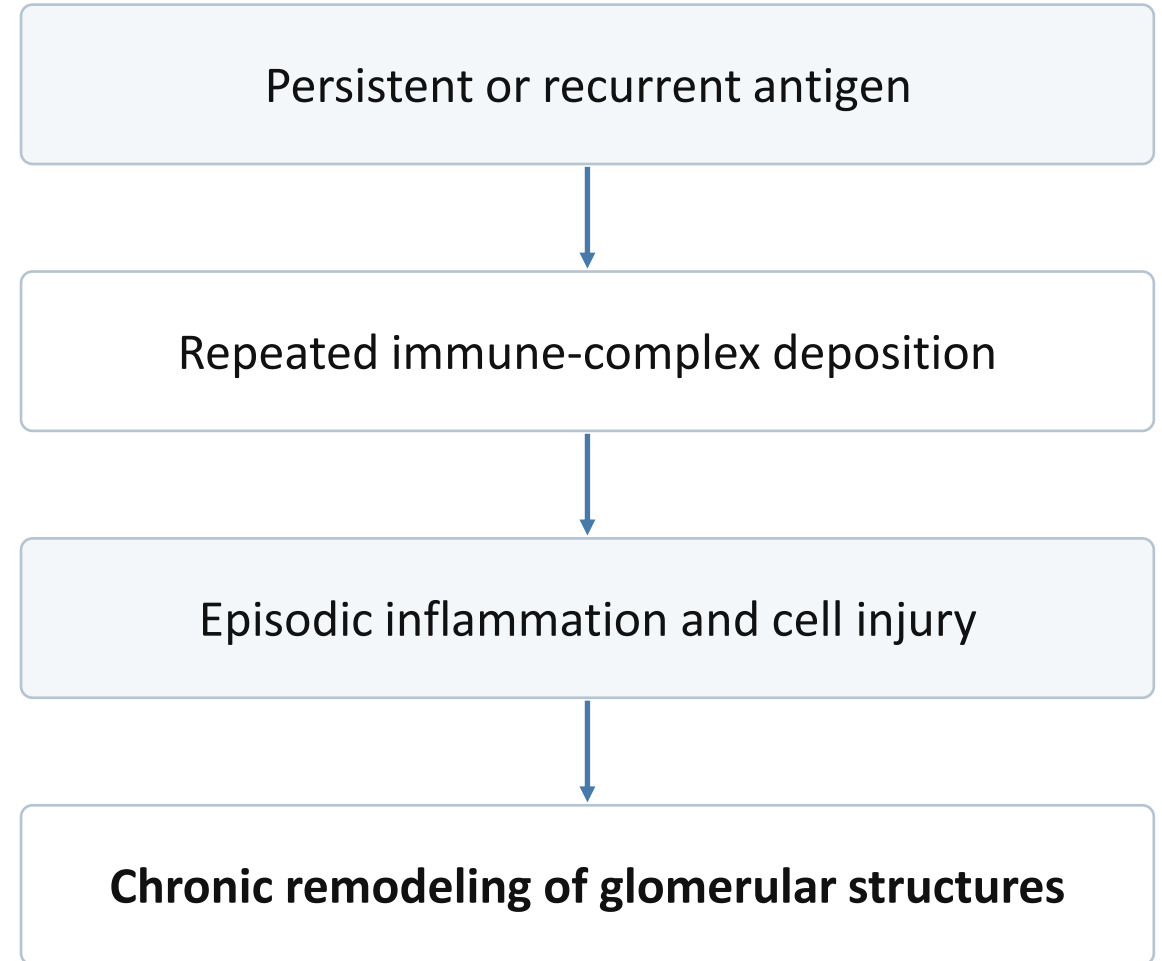
Limited antigen exposure permits recovery

- When antigen exposure is short-lived or limited, deposit clearance can outpace new deposition.
- The inflammatory reaction may subside completely.
- Most poststreptococcal glomerulonephritis cases illustrate this potentially reversible course.



Persistent exposure drives recurrent remodeling

- Prolonged antigen exposure can generate repeated immune-complex deposition.
- Each episode can cause cellular injury and subsequent tissue remodeling.
- SLE and viral hepatitis are textbook examples of prolonged or recurrent exposure.

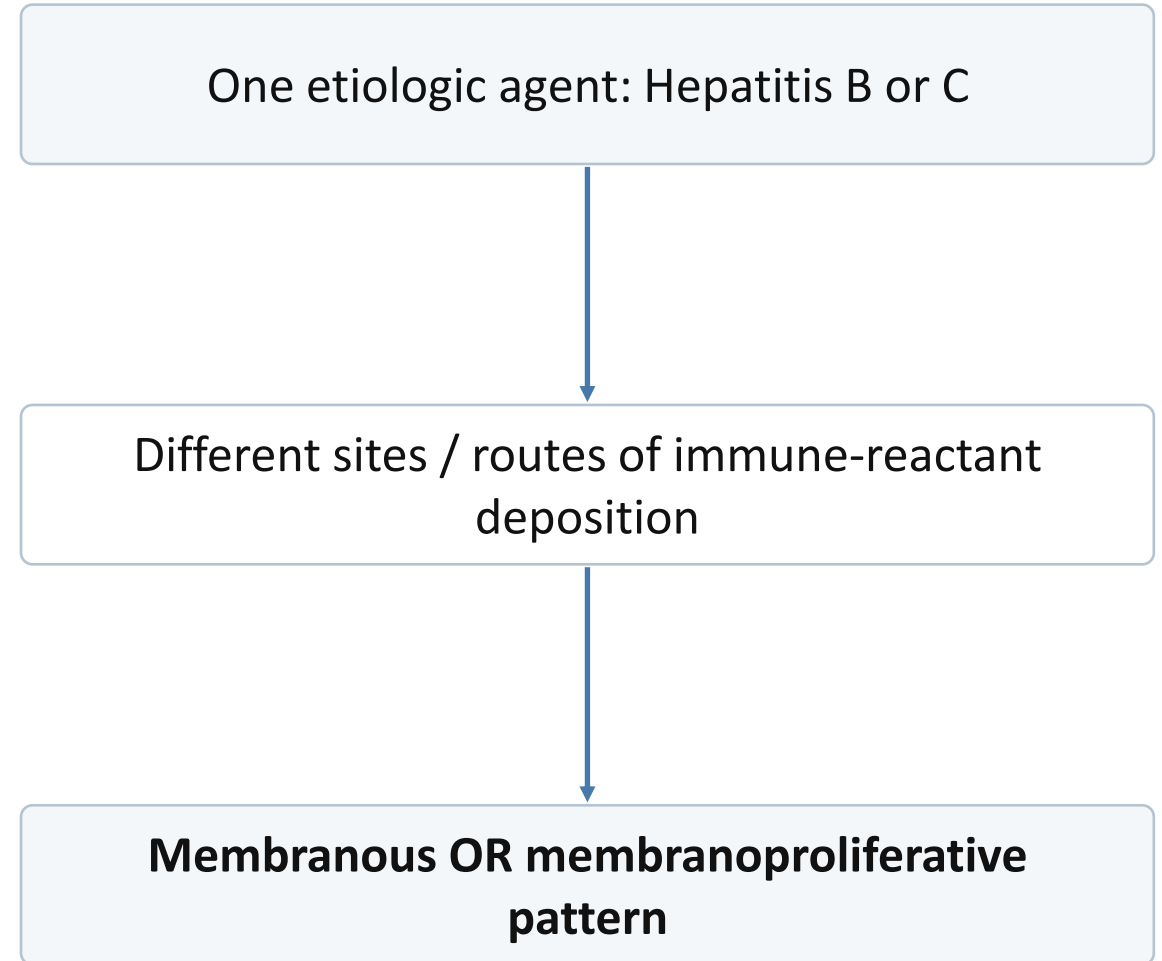


Location influences chronic morphologic pattern

Dominant deposit	Potential chronic pattern	Mechanistic rationale
Subepithelial	Membranous	Persistent outer capillary-wall deposition and GBM response
Subendothelial	Membranoproliferative	Recurring endothelial injury; Repair and matrix remodeling
Mesangial	Mesangial proliferative features	Mesangial exposure and growth response

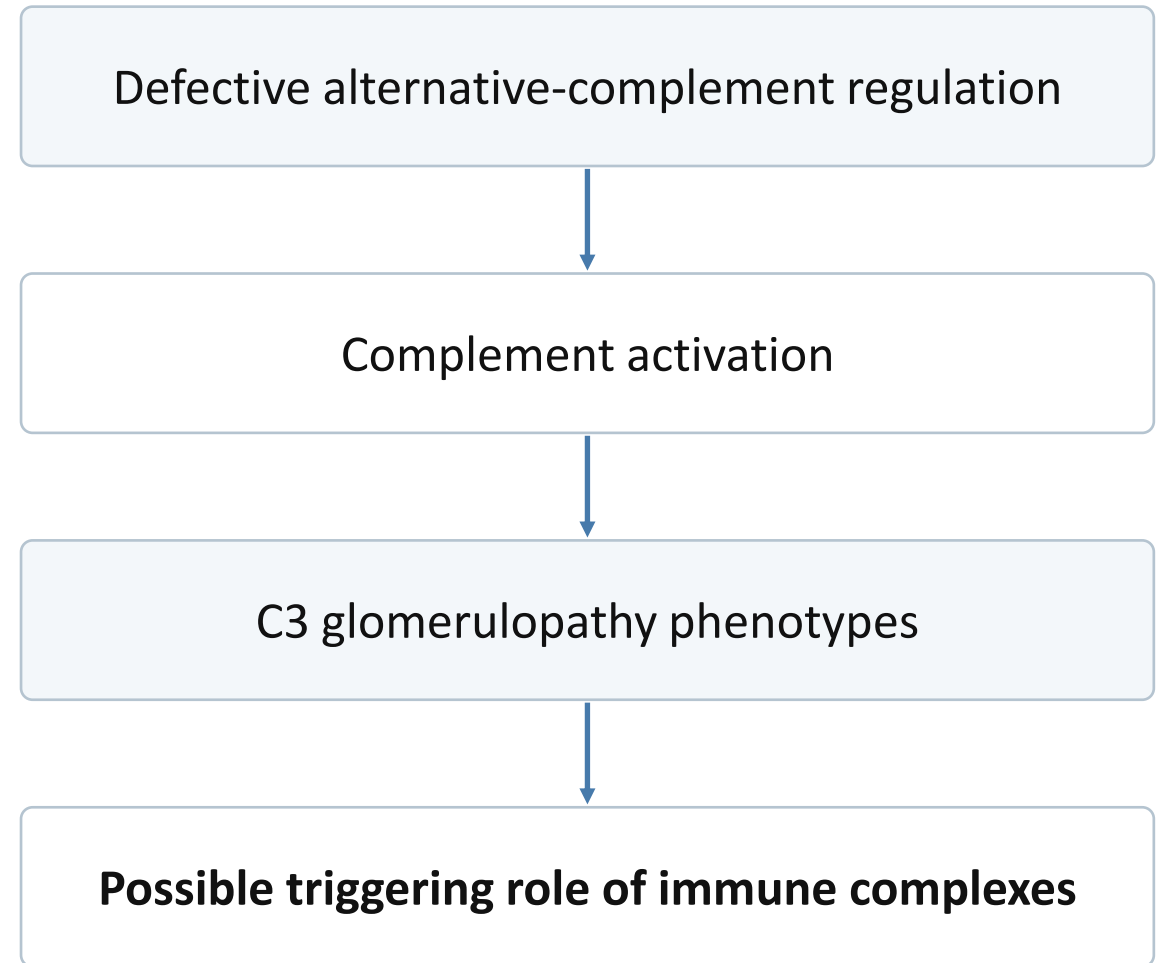
One viral antigen can produce different patterns

- Hepatitis B or C antigens are associated with more than one immune-complex injury pattern.
- Subepithelial in situ localization may yield membranous morphology.
- Subendothelial antigen deposition or circulating complexes may yield membranoproliferative morphology.



C3 glomerulopathy is a related but distinct pathway

- Alternative complement dysregulation characterizes C3 glomerulopathy.
- Dense deposit disease and C3 glomerulonephritis are included under this category.
- Immune complexes or monoclonal immunoglobulins may trigger or exacerbate dysregulation.



The role of T cells requires careful qualification

- Activated T cells and macrophages occur in some human and experimental glomerulonephritides.
- Experimental depletion and transfer studies support cellular contributions to injury.
- The source explicitly notes no proof that human glomerulonephritis arises primarily from T-cell activation.

Antibody-mediated initiation in many diseases



T-cell / macrophage inflammatory contribution



Disease propagation in selected experimental systems



Primary T-cell etiology in humans unproven

Inflammatory, membranous, and mesangial responses differ

Predominant setting	Cellular response	Pathologic emphasis
Subendothelial	Leukocyte-rich; Possible crescents	Proliferative and severe inflammatory lesions
Mesangial	Mesangial/endothelial proliferation	Mesangial inflammation and cellularity
Subepithelial	Typically less leukocyte-rich	GBM remodeling and podocyte dysfunction

Clinically relevant functional consequences

- Damage to the capillary wall can permit hematuria and impair GFR.
- Podocyte and slit-diaphragm injury allow albumin leakage and proteinuria.
- The combination and severity of lesions determine the clinical presentation.

Endothelial / GBM injury → hematuria and GFR decline



Podocyte filtration-barrier injury → proteinuria



Histologic lesion + functional phenotype

A biopsy answers different mechanistic questions

Technique	What is evaluated	Interpretive caution
Light microscopy	Cellularity; Crescents; GBM thickening or sclerosis	Response pattern does not identify antigen alone
Immunofluorescence	Granular versus linear immune-reactant distribution	Does not prove in situ vs circulating route
Electron microscopy	Ultrastructural location of dense deposits	More than one compartment may be involved

Interpret granular IF with EM localization

- Start by identifying whether deposits are granular along loops, mesangium, or both.
- Use electron microscopy to classify the deposit compartment.
- Then connect the compartment to a plausible inflammatory or podocyte-dominant response.

IF: Granular capillary-wall / mesangial pattern



EM: Subendo / mesangial / subepi deposits



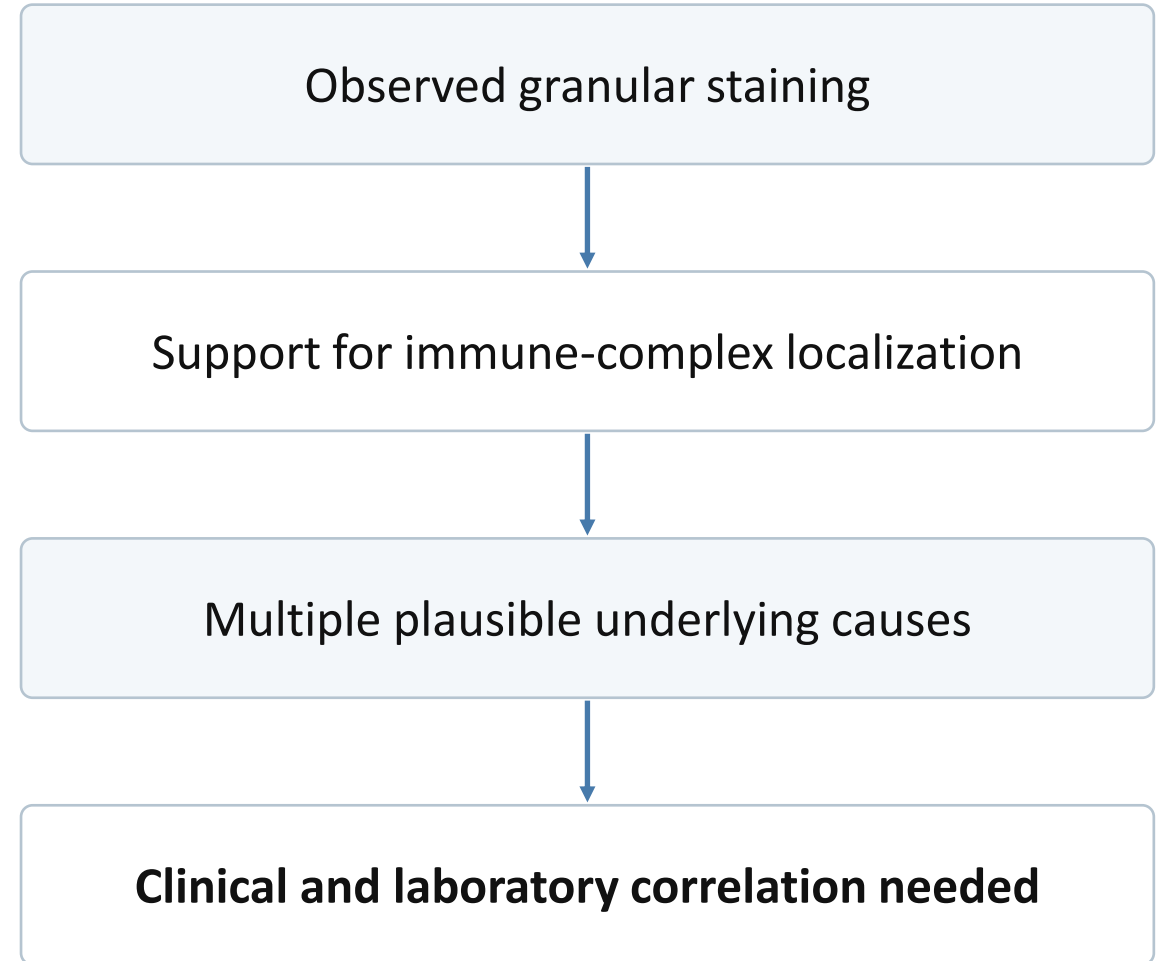
LM: Proliferation / GBM response / crescents



Clinicopathologic integration

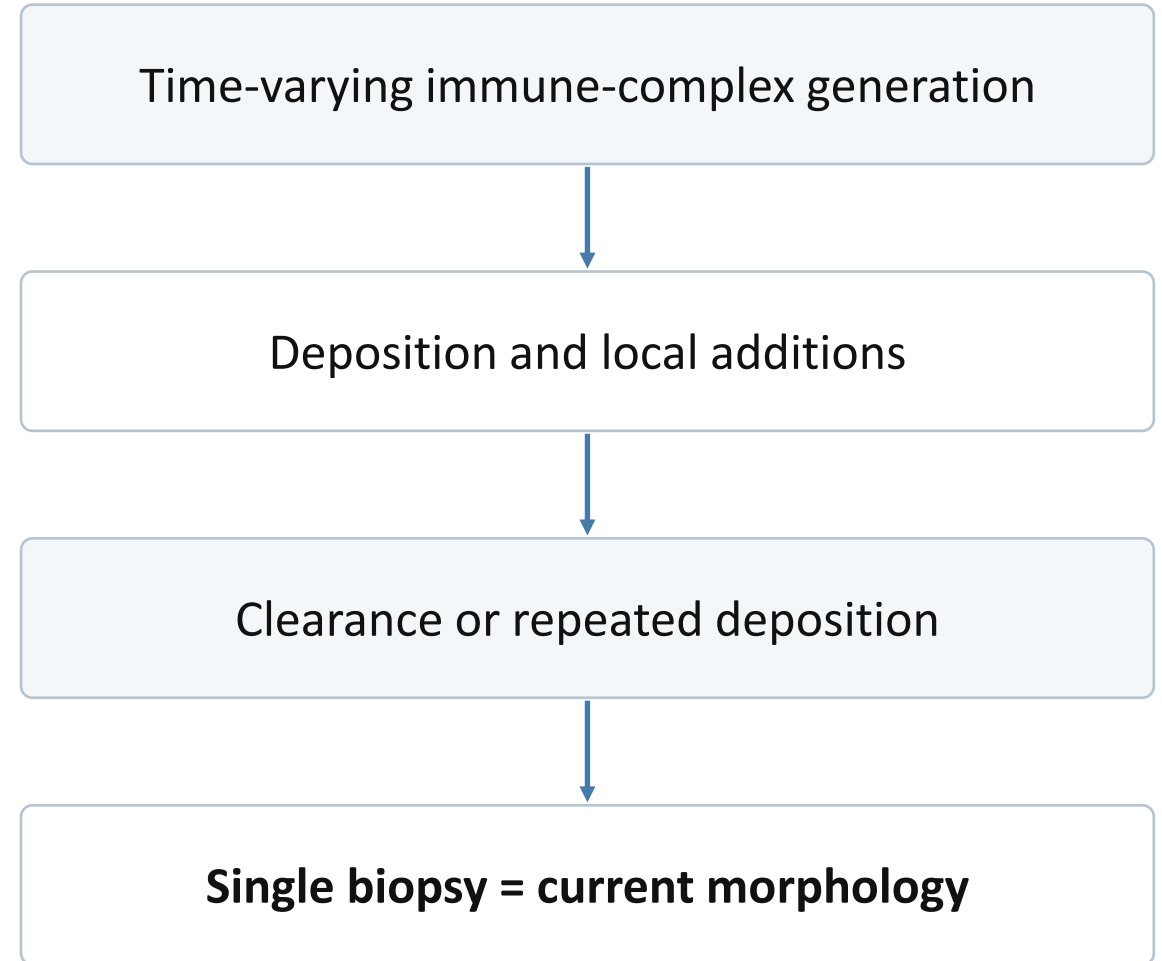
Diagnostic pitfall: Granularity is not etiology

- Granular IF establishes a distribution pattern compatible with immune-complex deposition.
- Multiple diseases share similar granular patterns.
- Neither morphology nor pattern alone identifies the precise antigen or its source.



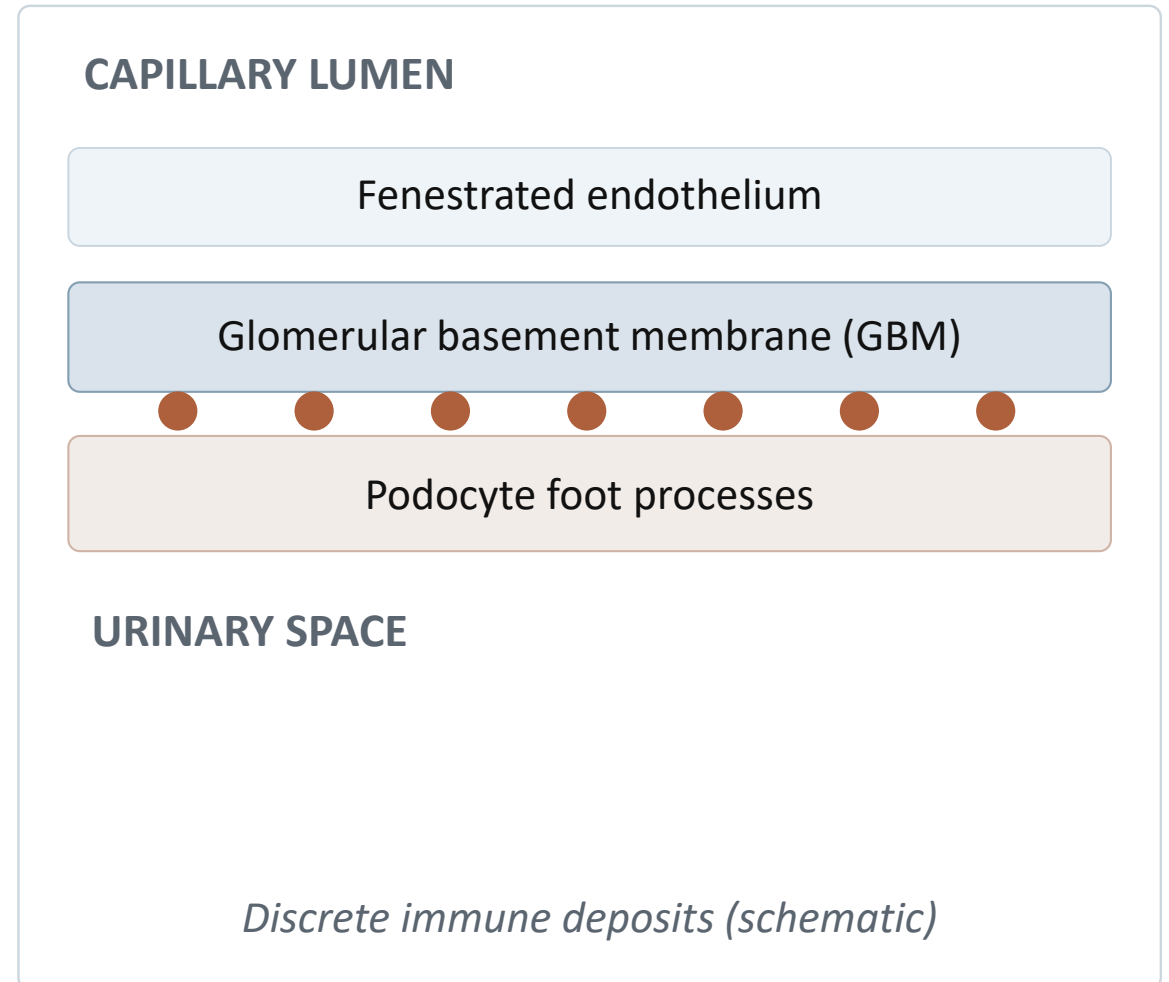
Diagnostic pitfall: IF cannot time deposition

- Deposits may persist after the initiating antigen exposure has changed.
- Local trapping can be followed by additional in situ immune-complex assembly.
- A static biopsy cannot reliably reconstruct every prior event in complex formation.



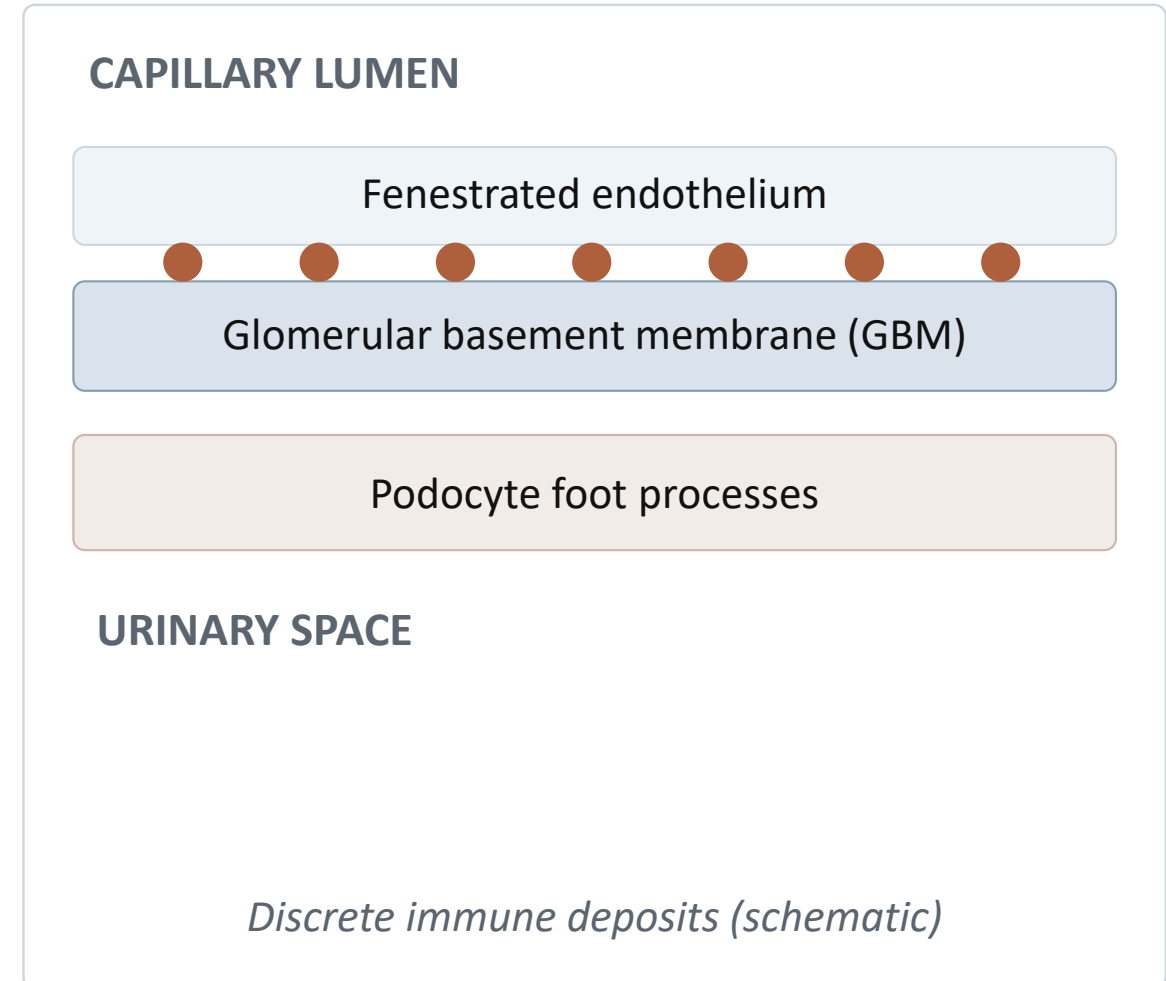
Clinicopathologic exercise: Subepithelial deposits

- Hypothetical biopsy: Granular capillary-wall IF with numerous subepithelial dense deposits.
- The absence of florid leukocytic exudation is mechanistically plausible.
- The key injury may involve podocytes and progressive GBM remodeling.



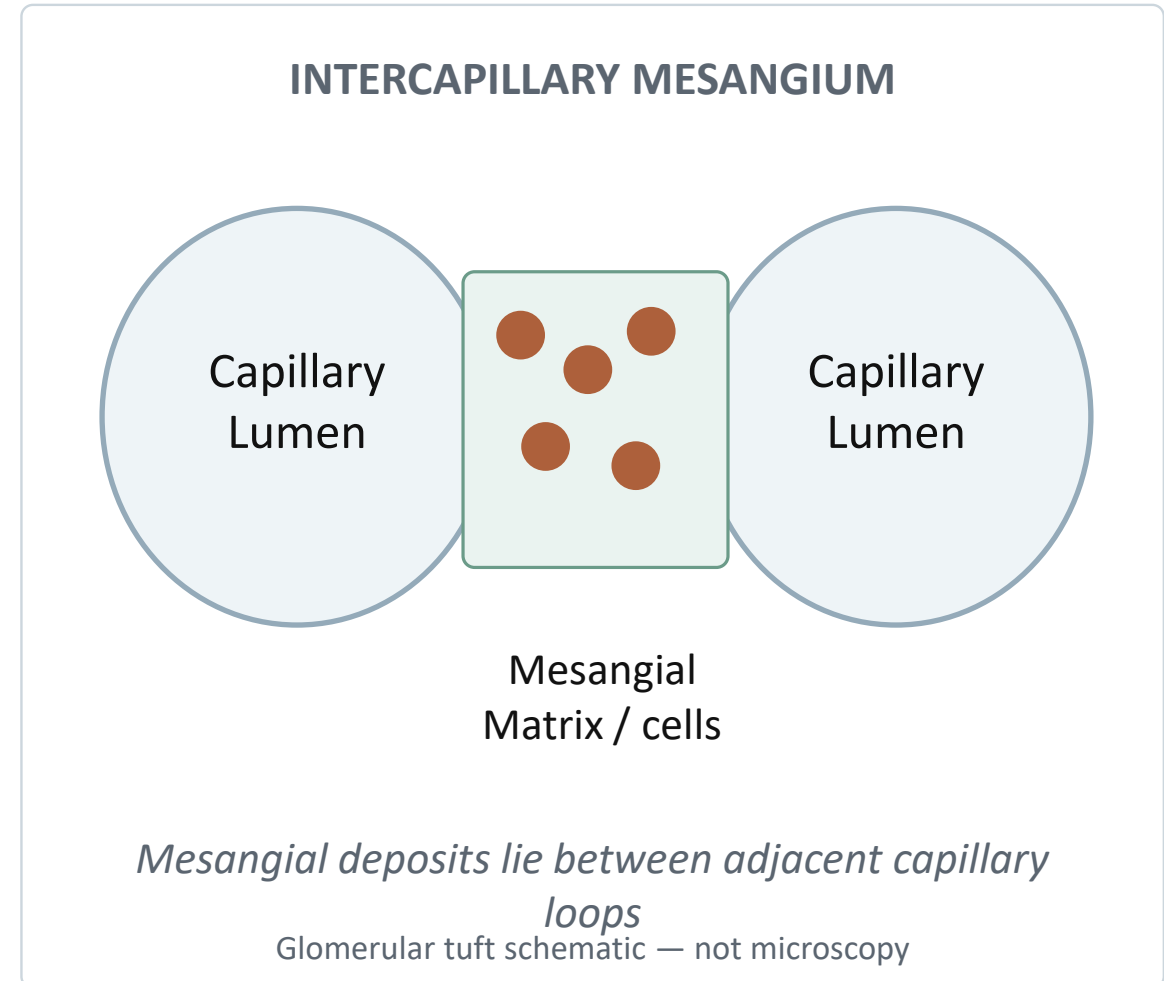
Clinicopathologic exercise: Subendothelial deposits

- Hypothetical biopsy: Subendothelial dense deposits and prominent endocapillary inflammation.
- Luminal proximity explains strong recruitment of leukocytes.
- Severe capillary injury may be associated with crescent formation.

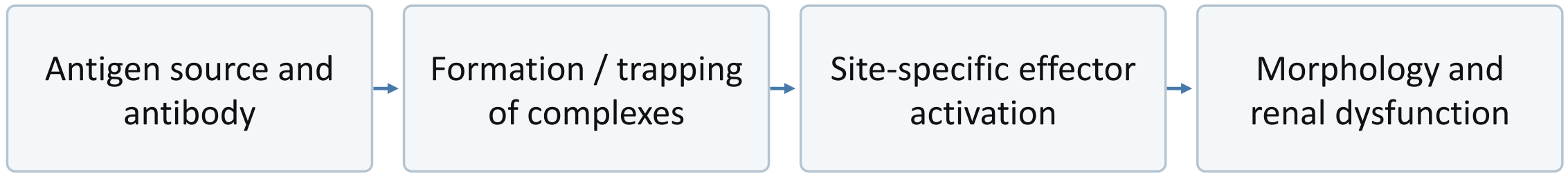


Clinicopathologic exercise: Mesangial deposits

- Hypothetical biopsy: Dominant mesangial immune deposits with mesangial hypercellularity.
- Mesangial accessibility to capillary blood permits inflammatory-cell responses.
- Intrinsic mesangial mediator production can add proliferative effects.



Mechanistic synthesis: Deposition to outcome



Localization and persistence together shape the resulting glomerular lesion.

Remember the four mechanistic discriminators

Question	High-yield answer
Where formed?	In situ or circulation; Both may contribute.
Where deposited?	Mesangial, subendothelial, subepithelial, or multiple sites.
How injured?	Complement, Fc receptors, recruited and resident cells, coagulation.
What determines outcome?	Exposure duration, deposit clearance, repeated injury, remodeling.

Primary reference and interpretive boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026), Chapter 20: The Kidney.
- Core section: “Mechanisms of Glomerular Injury Following Immune Complex Formation,” printed pp. 820–821.
- Adjacent glomerular-injury, mediator, and podocyte sections (pp. 817–822) supply essential mechanisms and context.
- All structural images in this lecture are original schematics, not patient specimens or reproduced textbook figures.