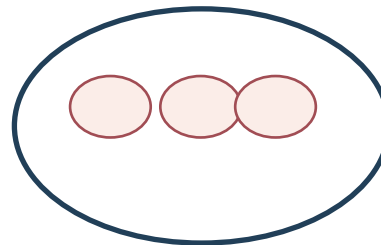


Structure of the Glomerulus

Normal architecture, the filtration barrier and the structural basis of protein retention



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Learning objectives

- Identify the endothelial, basement-membrane and epithelial components of the glomerular wall.
- Explain how podocyte junctions and the extracellular matrix contribute to selective filtration.
- Relate collagen IV, slit-diaphragm and mesangial structures to representative injury patterns.

Endothelium

Fenestrated cellular lining

GBM

Specialized extracellular scaffold

Podocyte

Foot processes + slit diaphragm

Why glomerular structure matters

- Disturbance of a particular glomerular component can produce a characteristic clinical manifestation.
- The filtration barrier normally retains plasma proteins while permitting water and small solutes.
- Recognizing normal compartments is prerequisite to understanding glomerular disease.

Collagen IV

Inherited GBM structural defects

NC1 domain

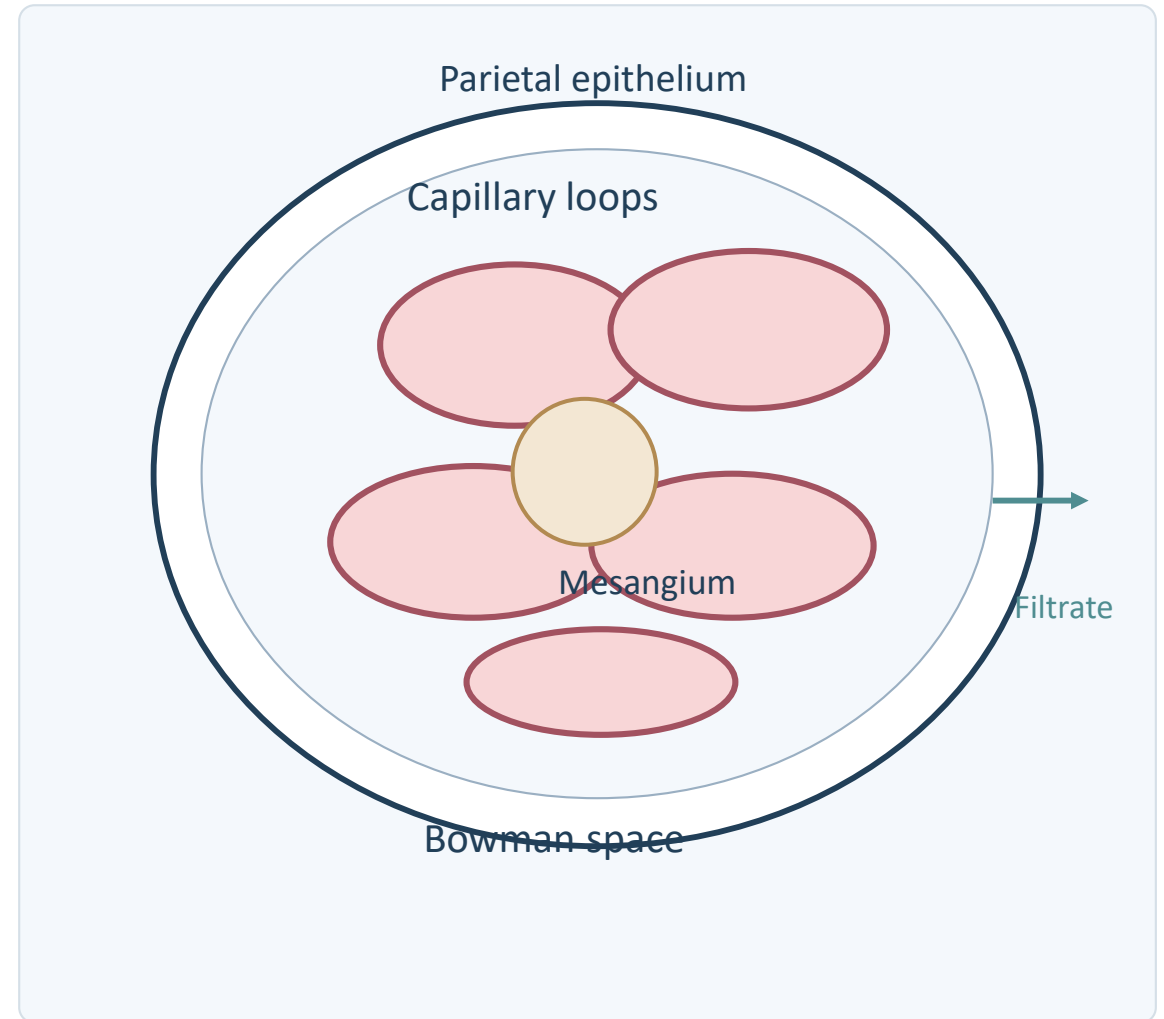
Target in anti-GBM nephritis

Slit proteins

Familial proteinuric disorders

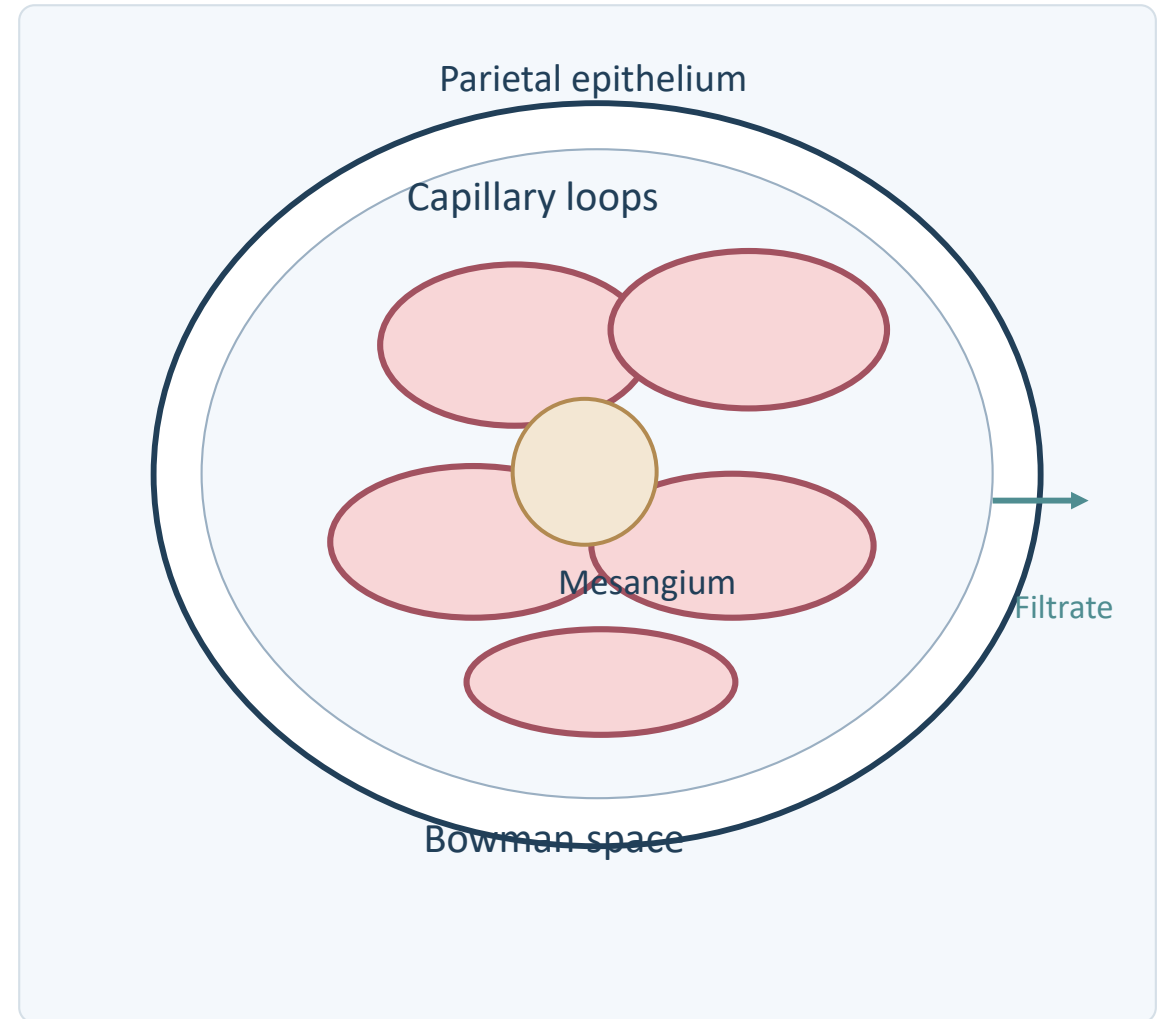
The glomerulus is an interconnected capillary tuft

- Anastomosing capillaries provide the structural core of the glomerulus.
- Fenestrated endothelial cells line individual capillary loops.
- Podocytes and a shared basement membrane invest the capillary wall.



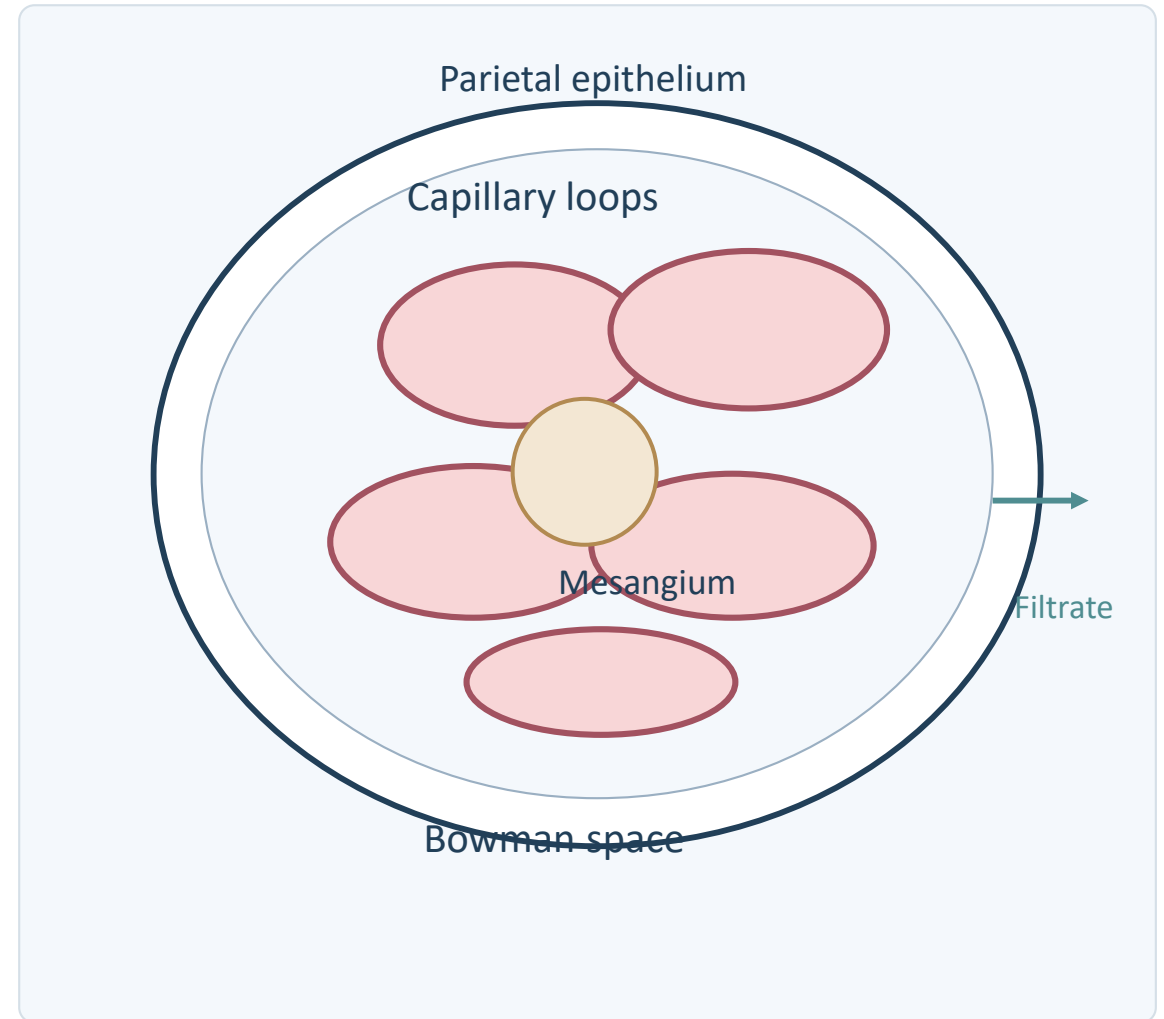
Two epithelial layers occupy different positions

- Visceral epithelial cells are podocytes: An intrinsic element of the capillary wall.
- Parietal epithelium lines the inner aspect of Bowman capsule.
- These layers face opposite aspects of the newly formed filtrate compartment.



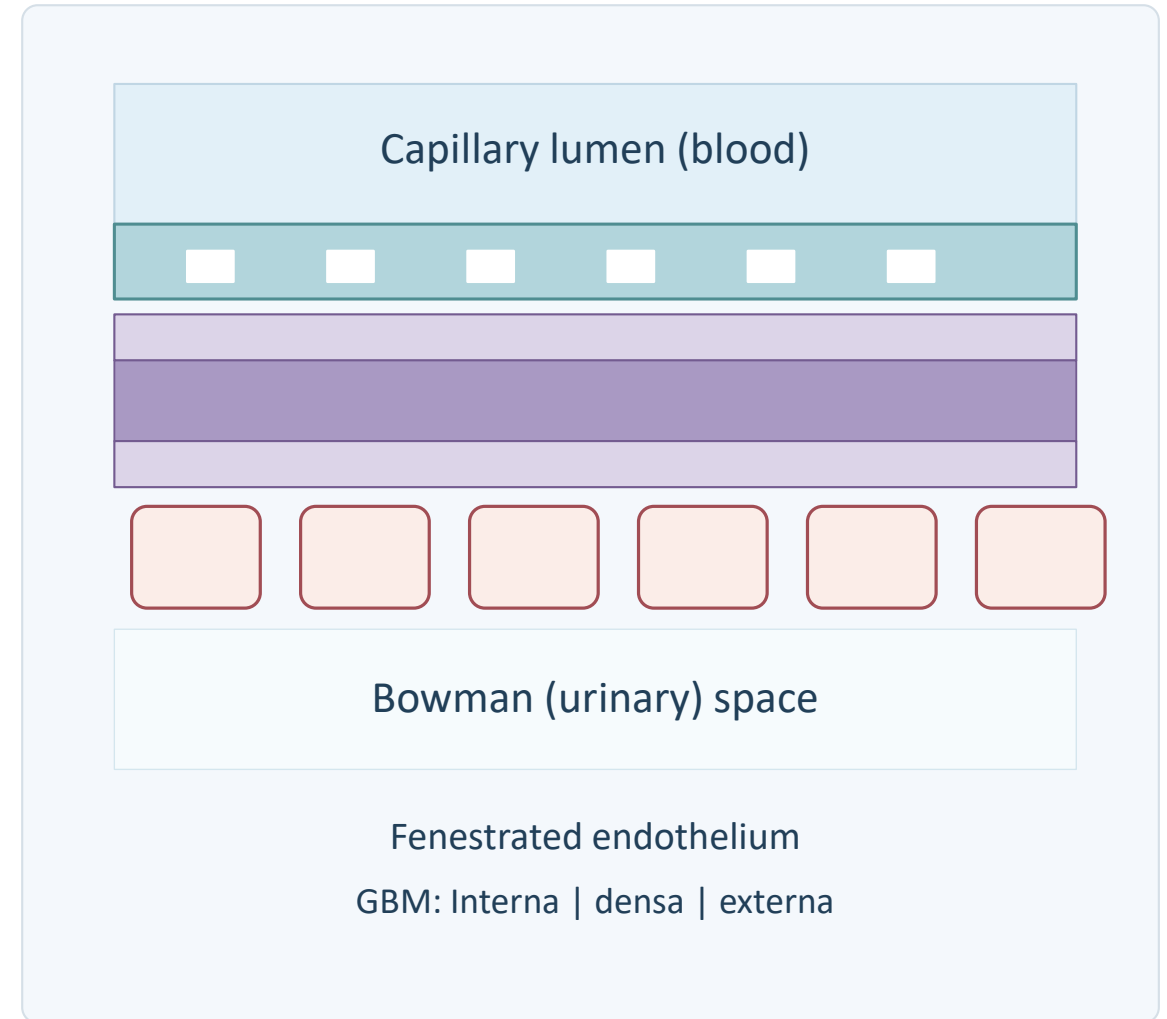
Bowman space is the first filtrate compartment

- The urinary space is bounded externally by parietal epithelium.
- Filtrate crosses the capillary wall before accumulating in Bowman space.
- The podocyte surface faces the space into which the filtrate emerges.



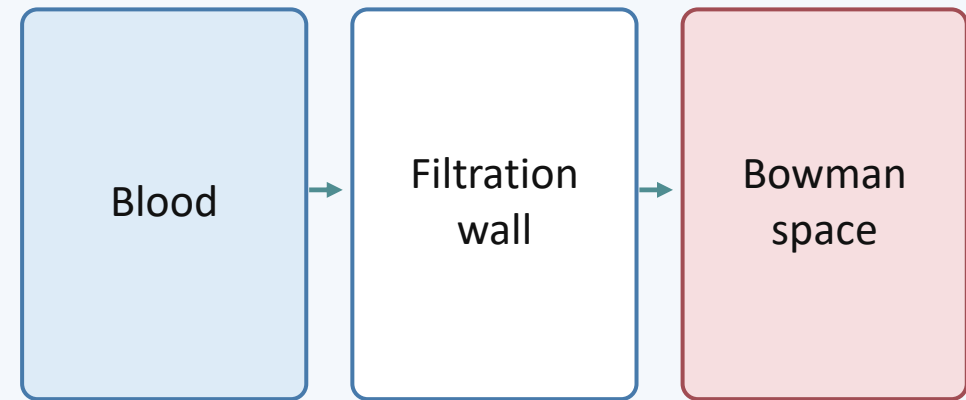
Three structural compartments must be distinguished

- Intracapillary compartment: The blood-containing capillary lumen.
- Capillary wall: Endothelial layer, shared GBM and visceral epithelium.
- Extracapillary urinary compartment: Bowman space enclosed by parietal epithelium.



The direction of glomerular filtration

- Filtrate moves from capillary blood across the endothelial layer.
- It then traverses the basement membrane and podocyte slit region.
- It emerges into Bowman space rather than into mesangial matrix.



Functional sequence

The capillary wall forms the filtration barrier

- The barrier is a composite structure, not a single cell membrane.
- Endothelium, GBM and slit-bearing podocyte processes contribute different structural features.
- A defect in any major component can disturb normal permeability.

Endothelium

Fenestrated cellular lining

GBM

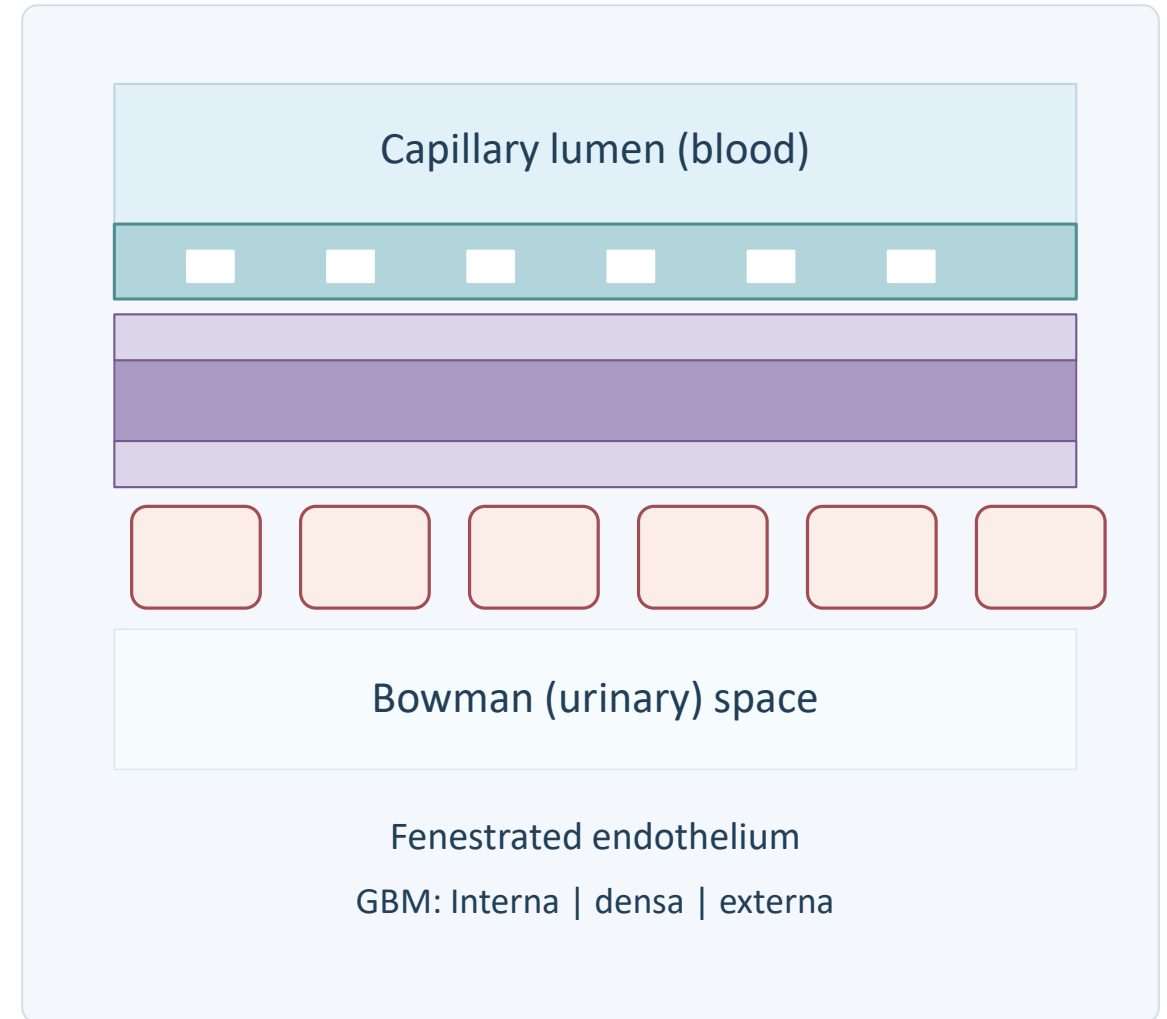
Specialized extracellular scaffold

Podocyte

Foot processes + slit diaphragm

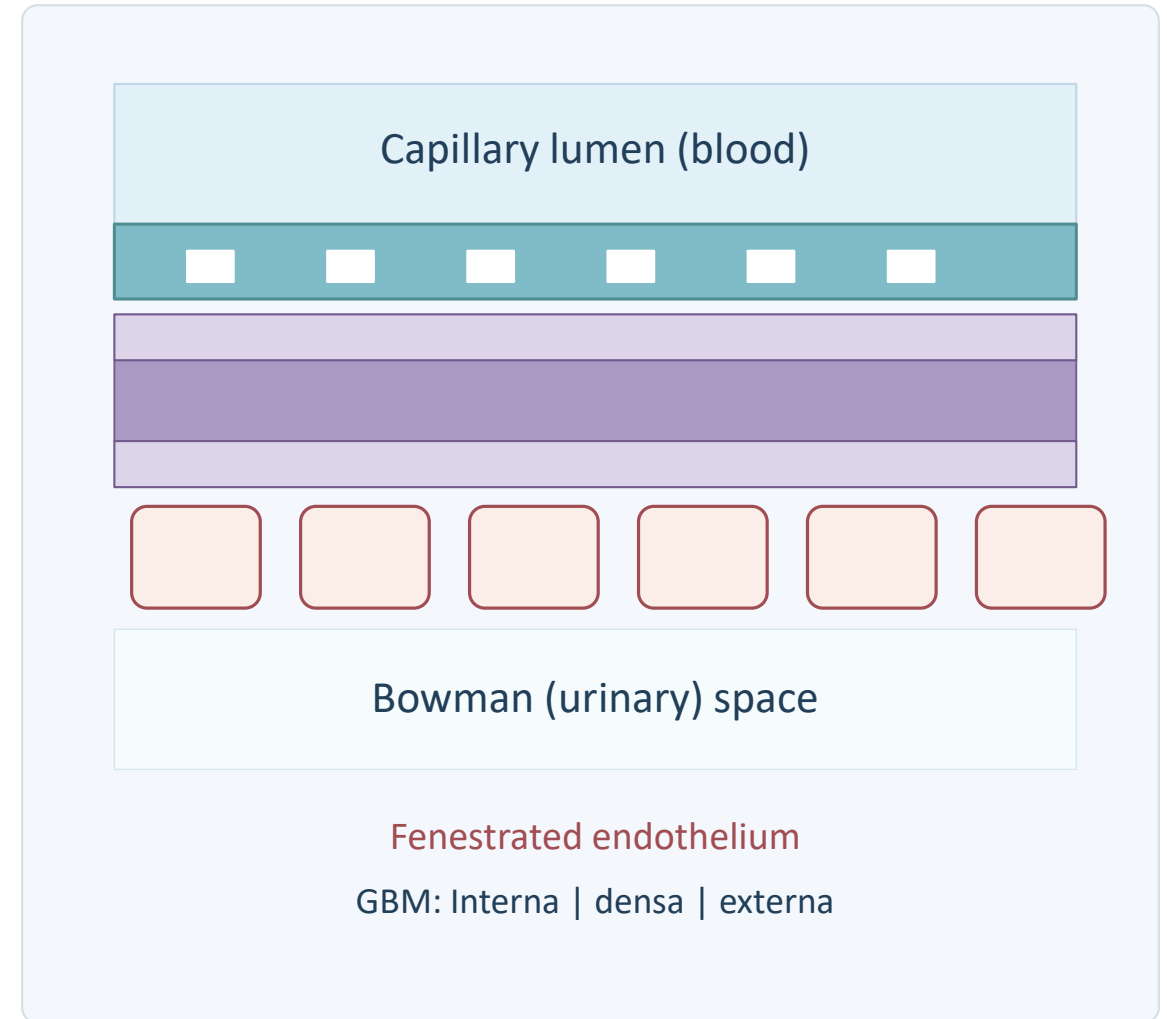
The filtration layers have a fixed order

- Endothelium lies nearest the capillary lumen.
- The GBM is shared by endothelium and podocytes.
- Podocyte foot processes face the urinary aspect of the GBM.



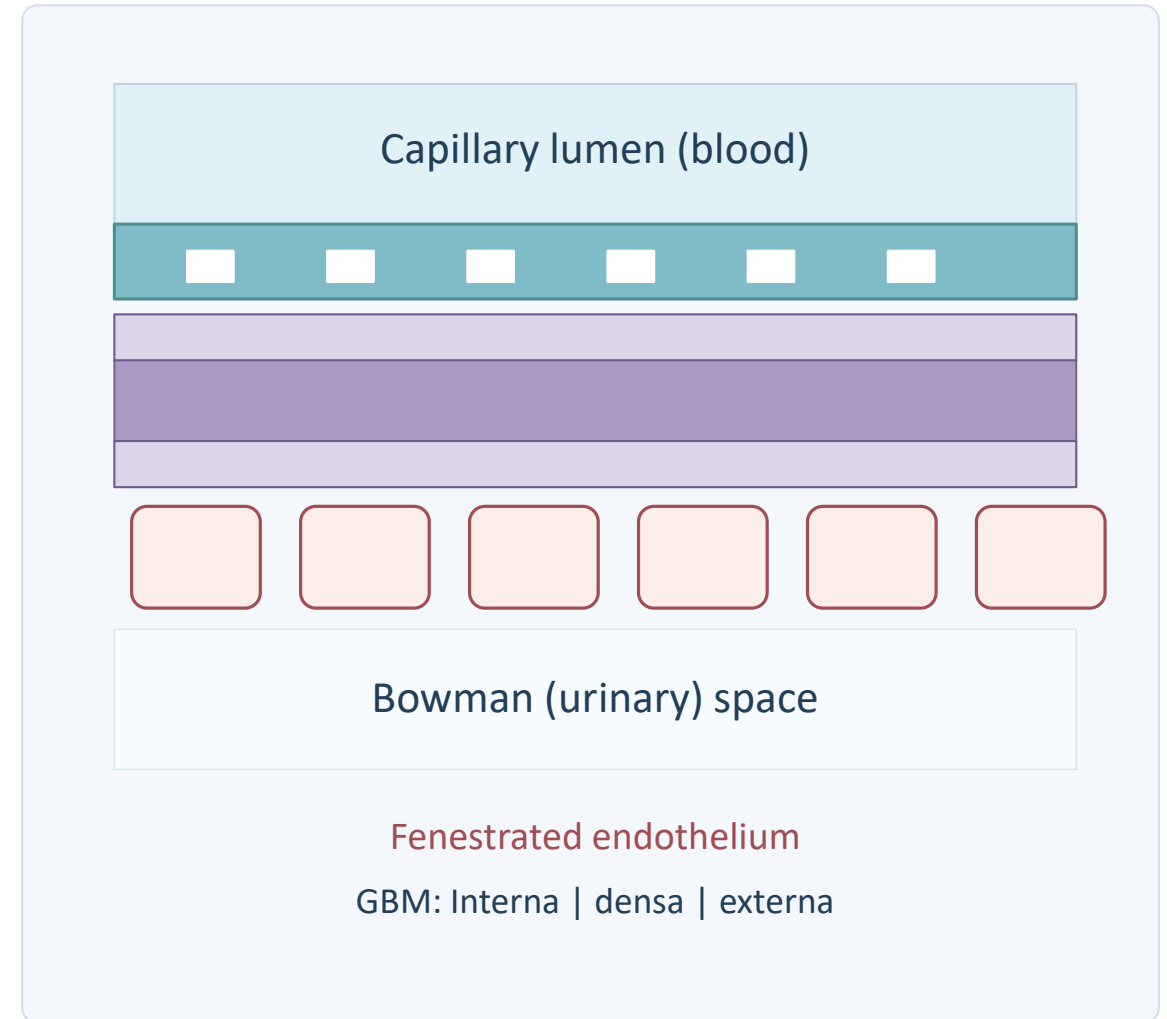
Fenestrated endothelium lines the capillaries

- Glomerular endothelial cells form a thin lining along the capillary lumina.
- Numerous fenestrae interrupt their cytoplasm.
- This arrangement supports high permeability to water and small solutes.



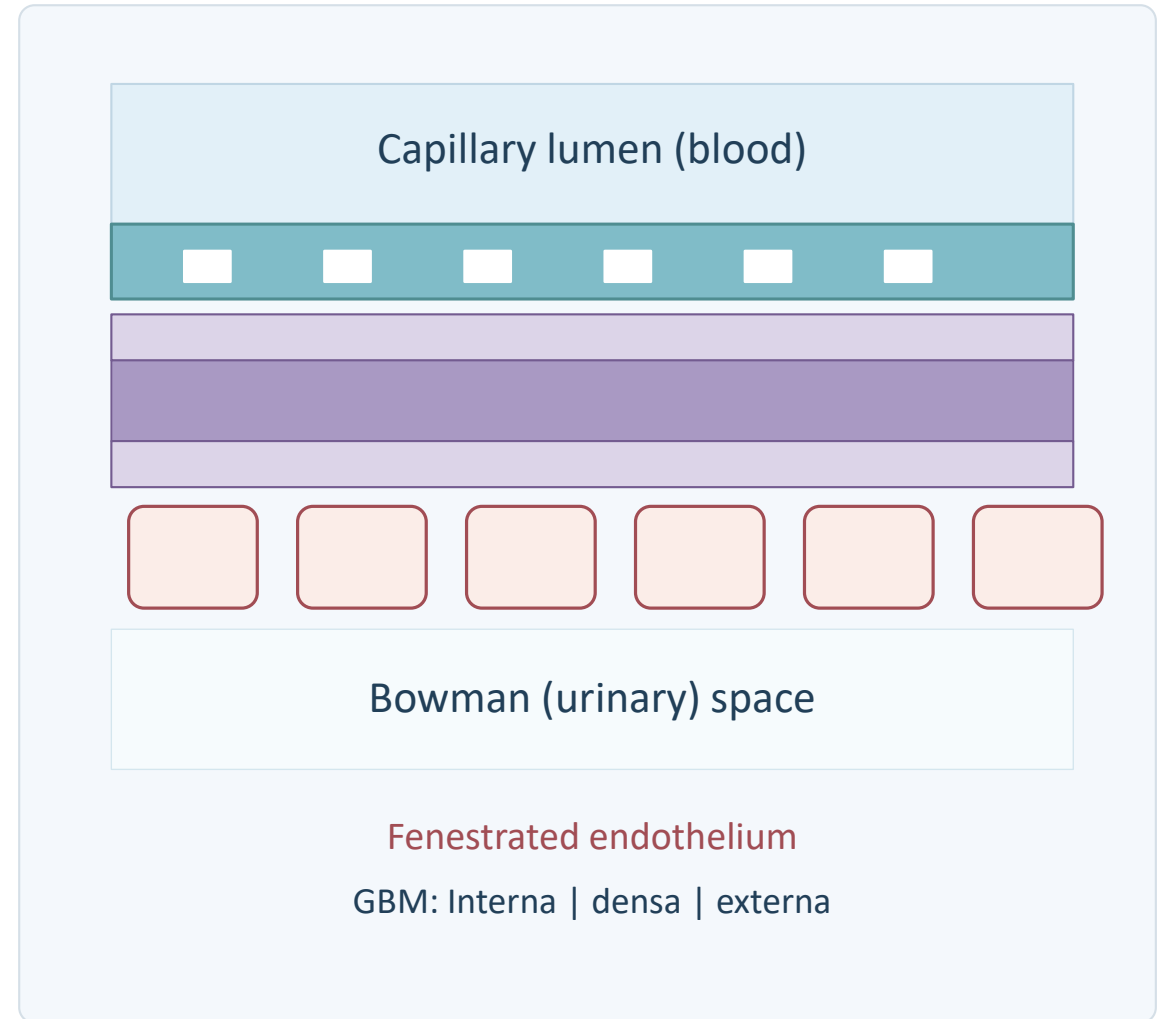
Endothelial fenestrae: A defined ultrastructural scale

- Fenestrae approximately 70–100 nm in diameter.
- These openings are far larger than the adjacent molecular-level junctions of podocytes.
- Fenestra diameter is a structural observation, not a complete explanation of protein sieving.



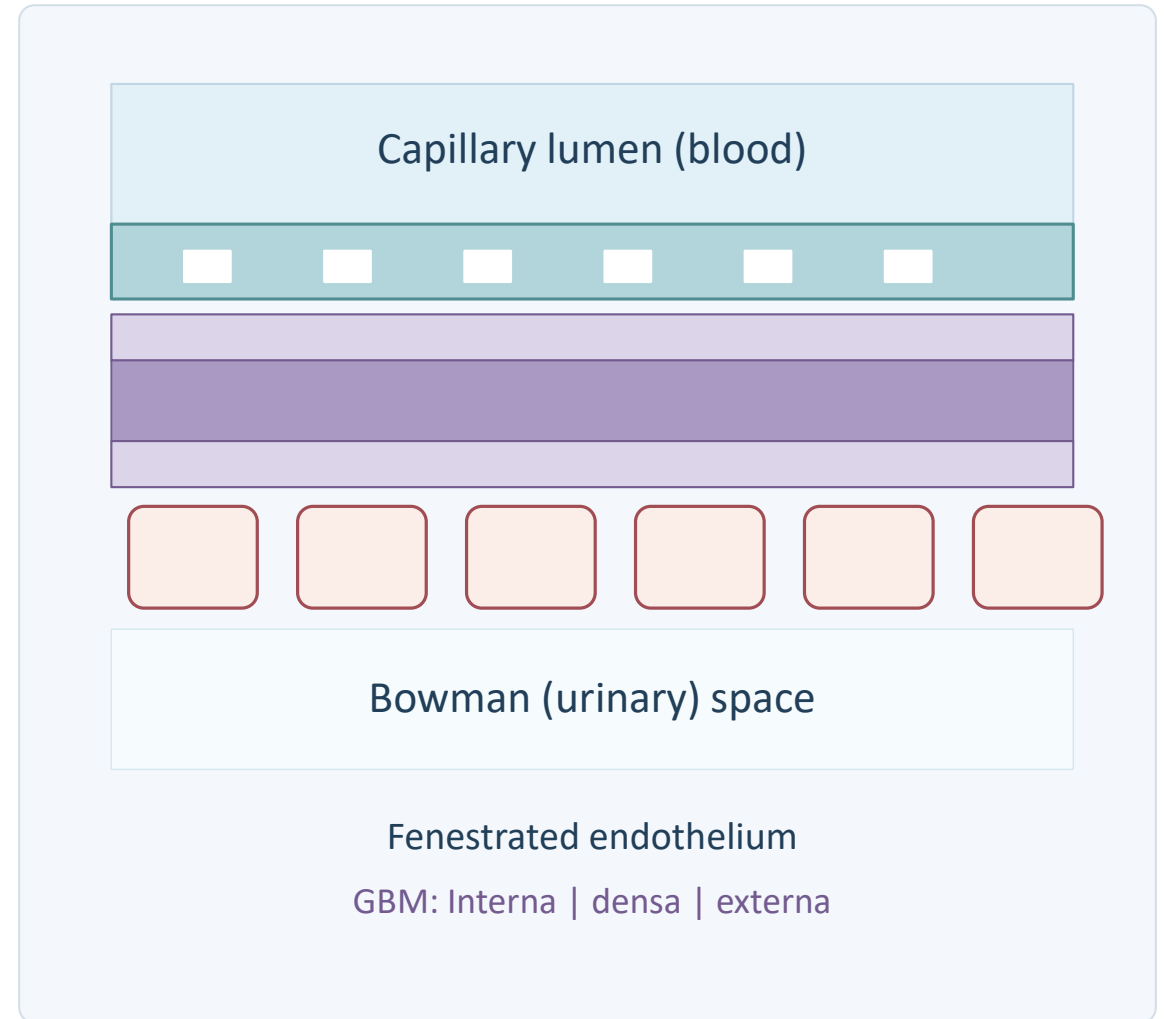
Endothelial fenestration favors fluid passage

- The fenestrated layer presents relatively little resistance to water and small-solute transit.
- Protein retention depends on the integrated filtration wall.
- The endothelial layer must be interpreted together with GBM and podocytes.



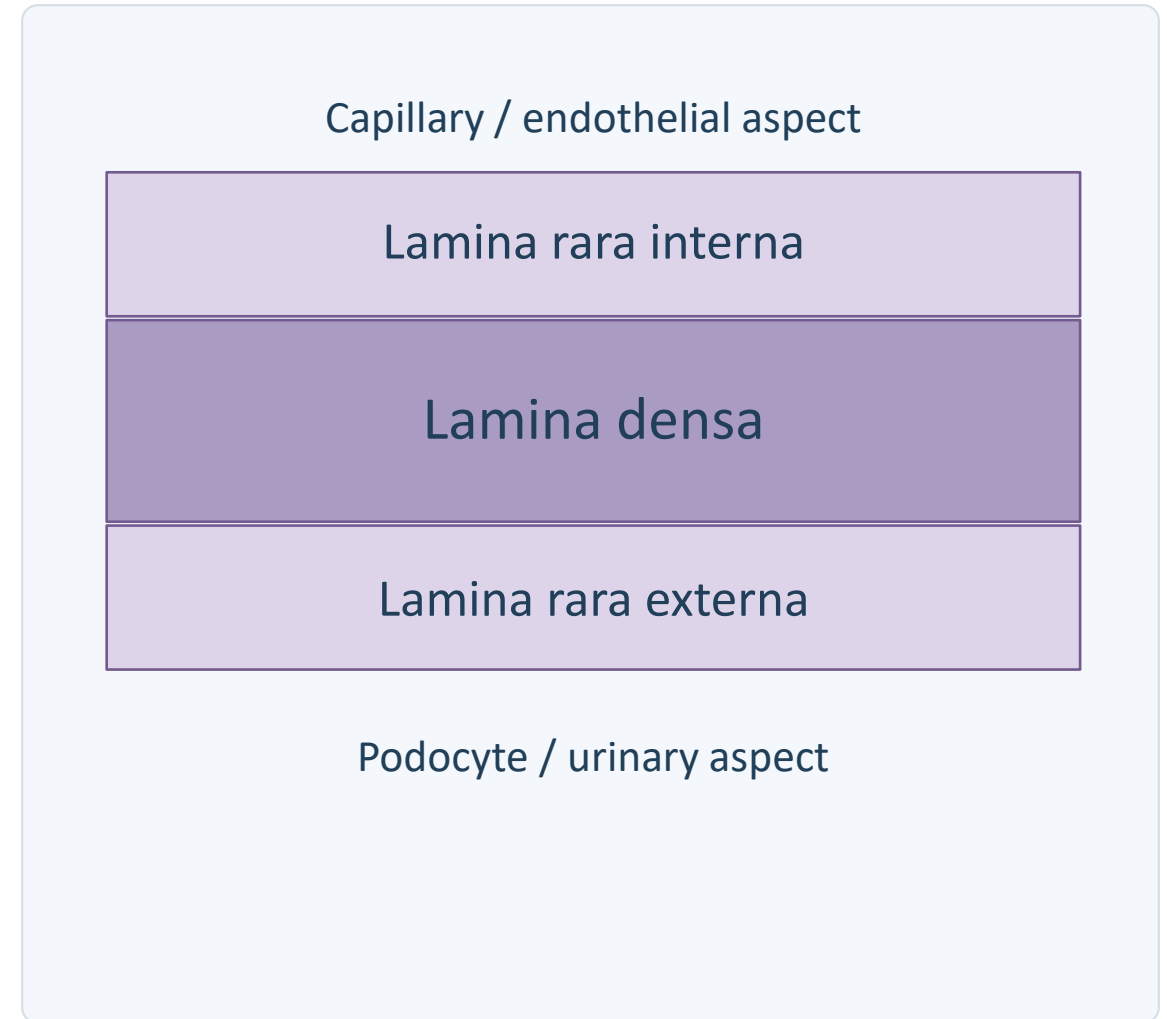
The GBM lies between endothelium and podocytes

- The glomerular basement membrane is a specialized extracellular matrix.
- Both endothelial cells and podocytes face this common membrane.
- Molecular composition and spatial organization of the GBM influence barrier function.



Electron microscopy resolves three GBM layers

- A central electron-dense lamina densa is flanked by two more electron-lucent layers.
- The inner layer is the lamina rara interna; The outer is the lamina rara externa.
- The three-layer description refers to ultrastructural electron density.



Lamina rara interna faces the endothelium

- The lamina rara interna occupies the endothelial aspect of the GBM.
- It is thinner and relatively electron-lucent compared with the lamina densa.
- Orientation is essential when localizing glomerular capillary-wall changes.



Lamina densa forms the central dense layer

- The lamina densa is the thick central electron-dense band of the GBM.
- It is situated between the two laminae rarae.
- This pattern is a description of the normal GBM in electron microscopy.



Lamina rara externa contacts podocytes

- The lamina rara externa lies on the podocyte-facing aspect of the GBM.
- Podocyte foot processes are adherent to this region.
- The outer GBM interface connects the matrix scaffold to cellular foot processes.



The GBM contains several matrix constituents

- Type IV collagen forms a major component of the matrix scaffold.
- Laminin, heparan-sulfate-rich proteoglycans, fibronectin and entactin are also present.
- Other glycoproteins participate in this specialized extracellular network.

Architecture

Fenestrated loops

Scaffold

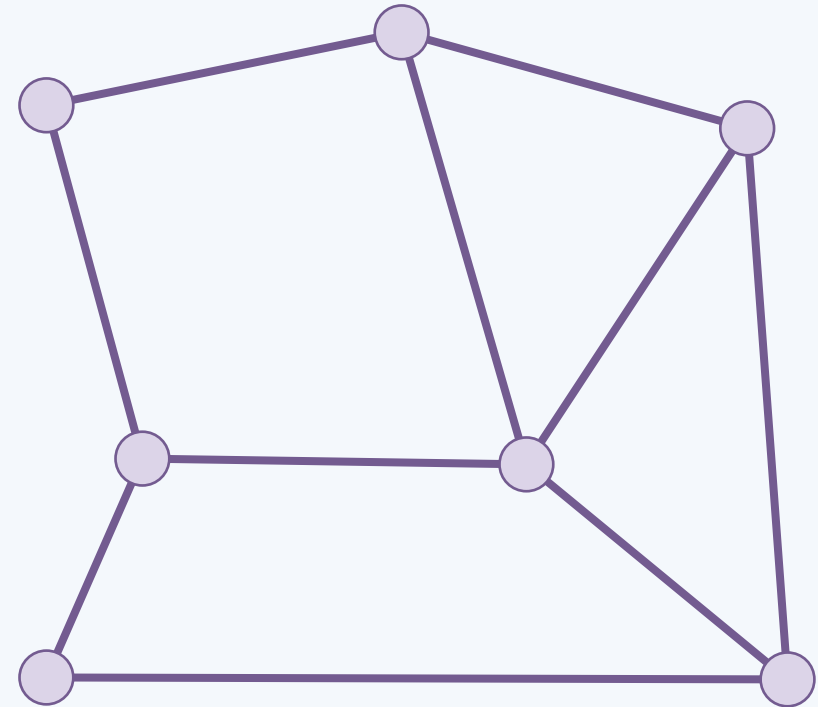
GBM + mesangium

Junctions

Slit diaphragms

Type IV collagen forms a supporting network

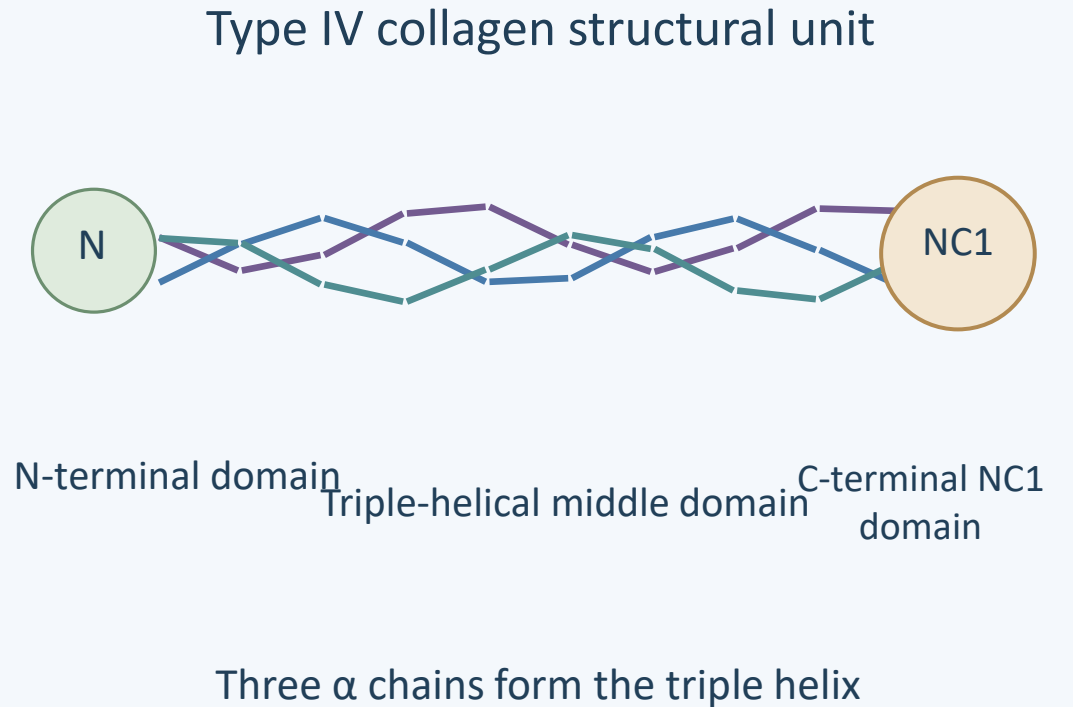
- Type IV collagen contributes a branching molecular network in the GBM.
- Other basement-membrane glycoproteins associate with this scaffold.
- Alterations in its molecular structure can compromise normal GBM architecture.



Type IV collagen network

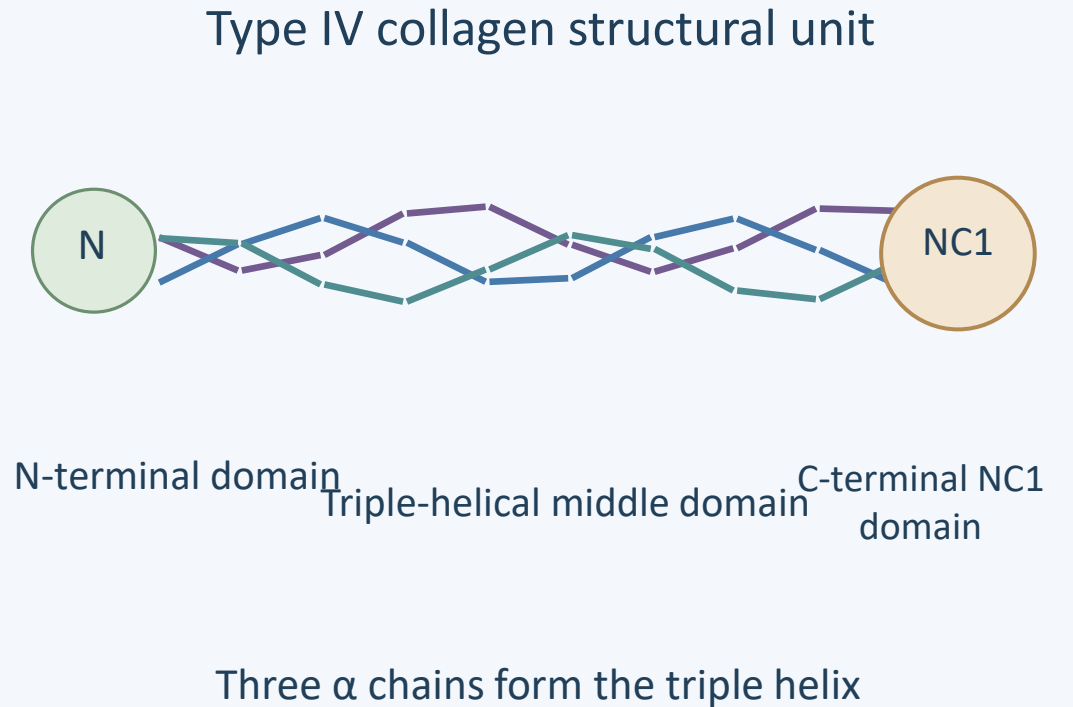
Six COL4A genes specify α -chain types

- Type IV collagen monomers contain one or more of six α -chain types.
- The genes are designated COL4A1 through COL4A6.
- The identity of these chains matters for inherited glomerular basement-membrane disorders.



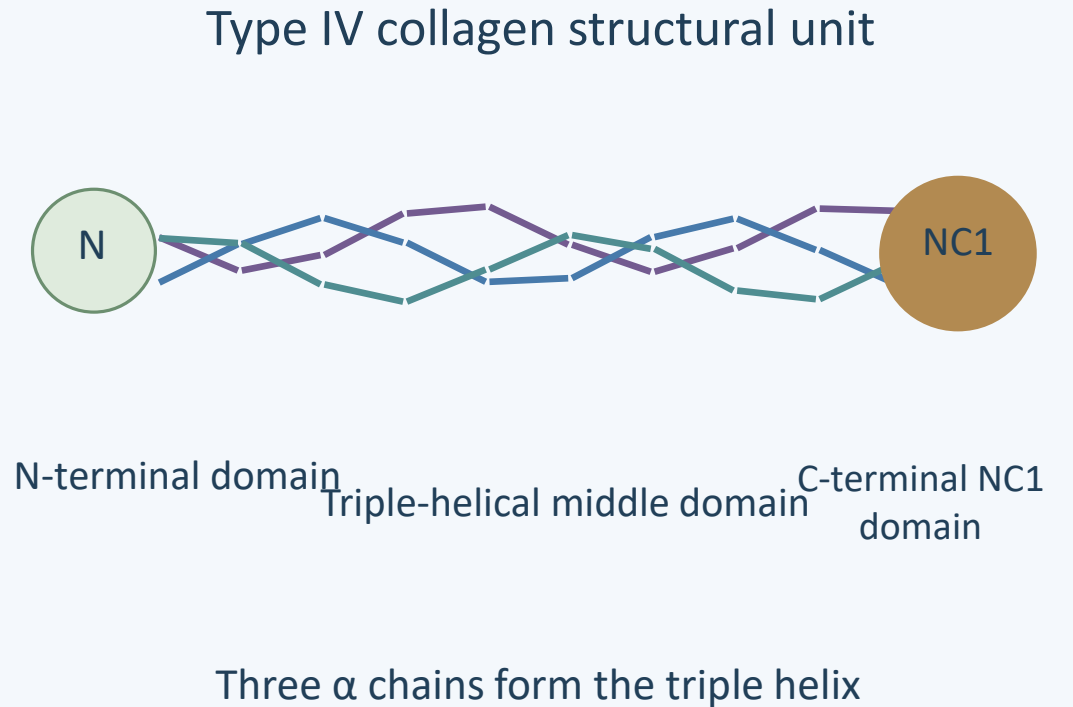
A type IV collagen monomer has three domains

- The N-terminal domain occupies one molecular end.
- A triple-helical domain forms the middle portion of the molecule.
- A globular noncollagenous NC1 domain occupies the C terminus.



The NC1 domain has clinical significance

- NC1 is the C-terminal noncollagenous domain of type IV collagen.
- Specific antigens in this domain are recognized in anti-GBM nephritis.
- This illustrates how an extracellular structural domain can also be an immune target.



Anti-GBM nephritis targets a matrix antigen

- The disease-relevant immune target lies in the type IV collagen NC1 domain.
- The glomerular basement membrane is therefore an antigenic tissue compartment.
- The example links normal molecular structure to a mechanism of glomerular injury.

Collagen IV

Inherited GBM structural defects

NC1 domain

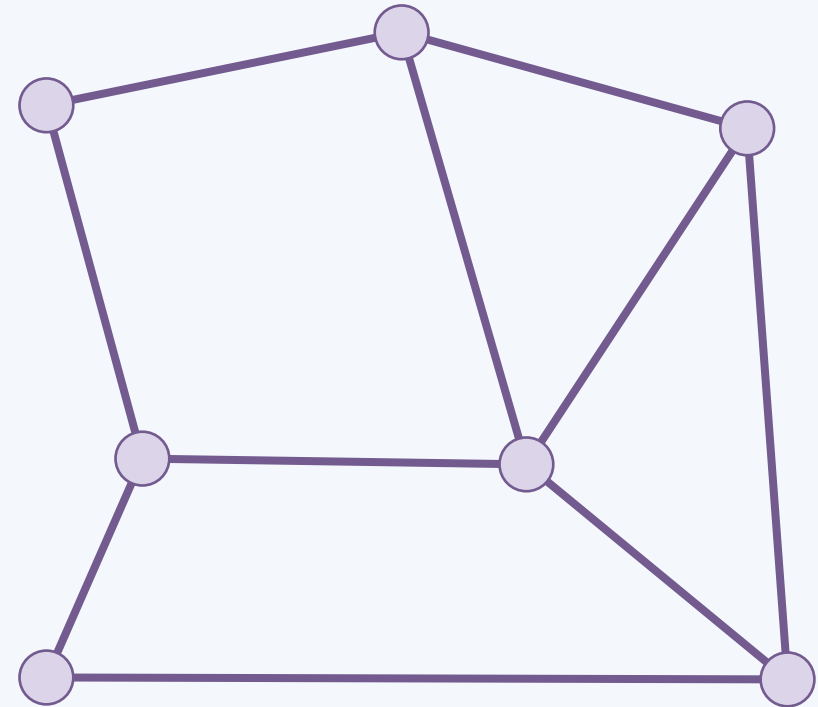
Target in anti-GBM nephritis

Slit proteins

Familial proteinuric disorders

Alport-spectrum disorders involve collagen IV

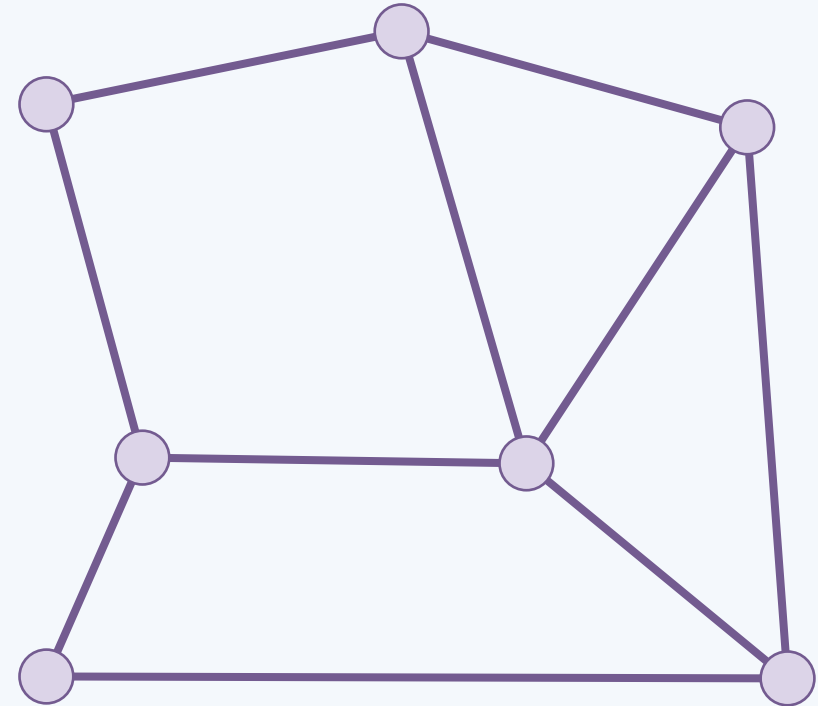
- Defects affecting type IV collagen α chains are linked to Alport-spectrum disease.
- The underlying structural component is the GBM collagen network.
- Molecular integrity of the basement membrane is critical for glomerular function.



Type IV collagen network

Laminin is part of the GBM matrix

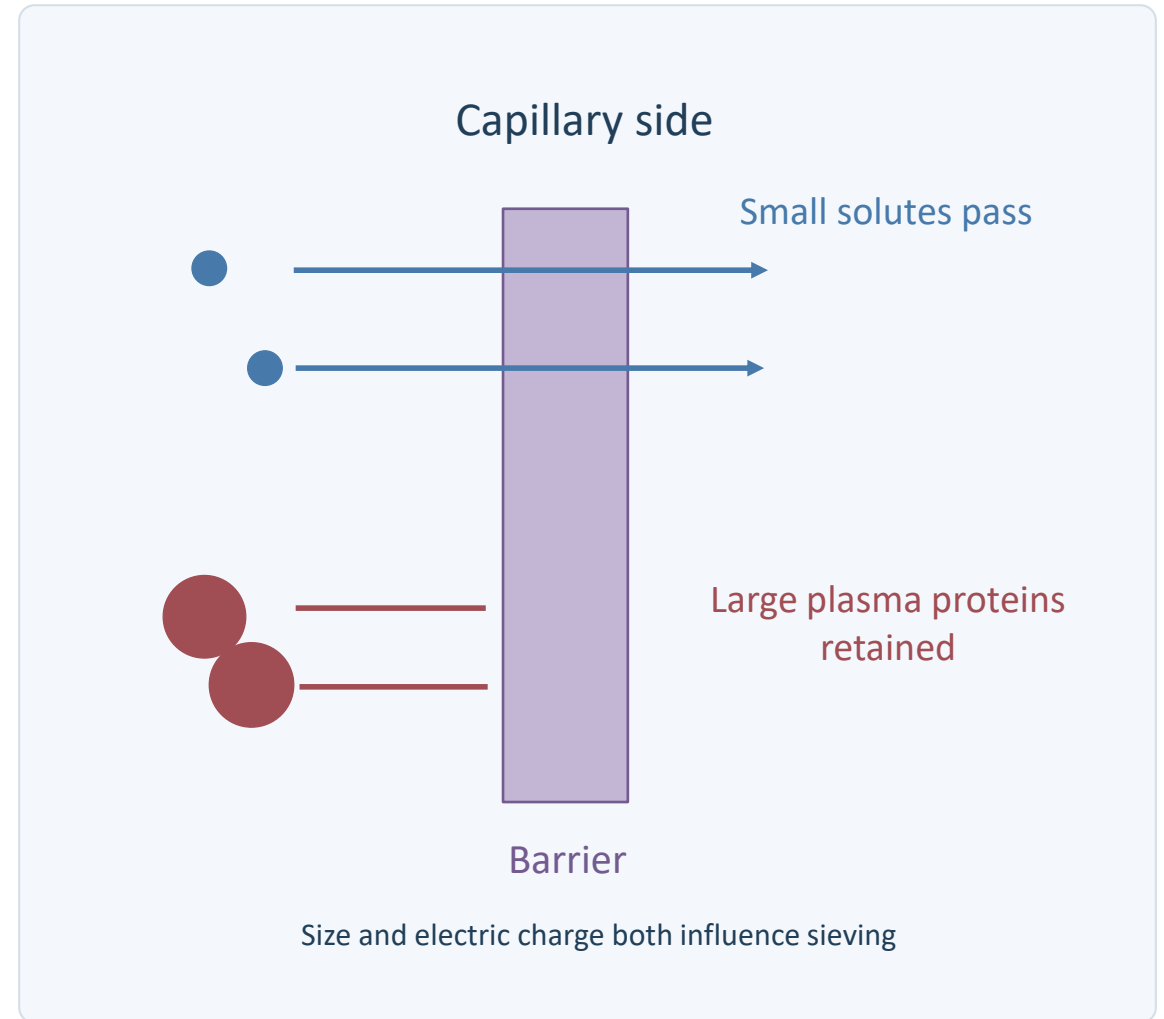
- Laminin is one of the glycoproteins composing the glomerular basement membrane.
- It is associated with the type IV collagen matrix scaffold.
- A basement membrane is a multi-component assembly, not simply deposited collagen.



Type IV collagen network

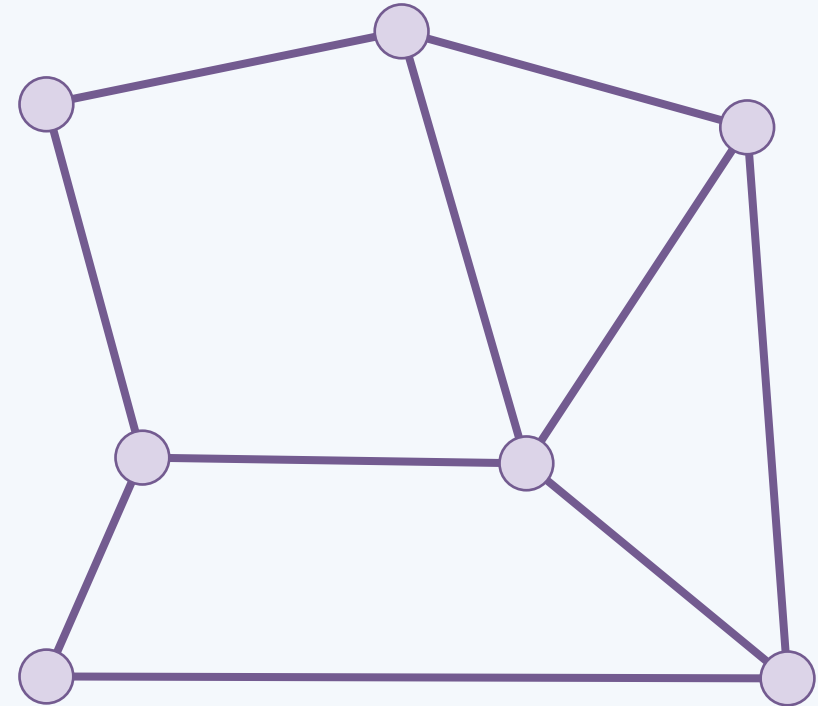
Proteoglycans contribute to GBM properties

- The basement membrane contains polyanionic proteoglycans.
- Heparan sulfate is identified by Robbins as a major proteoglycan component.
- The source describes their contribution to permeability characteristics as a possible role.



Fibronectin and entactin add matrix complexity

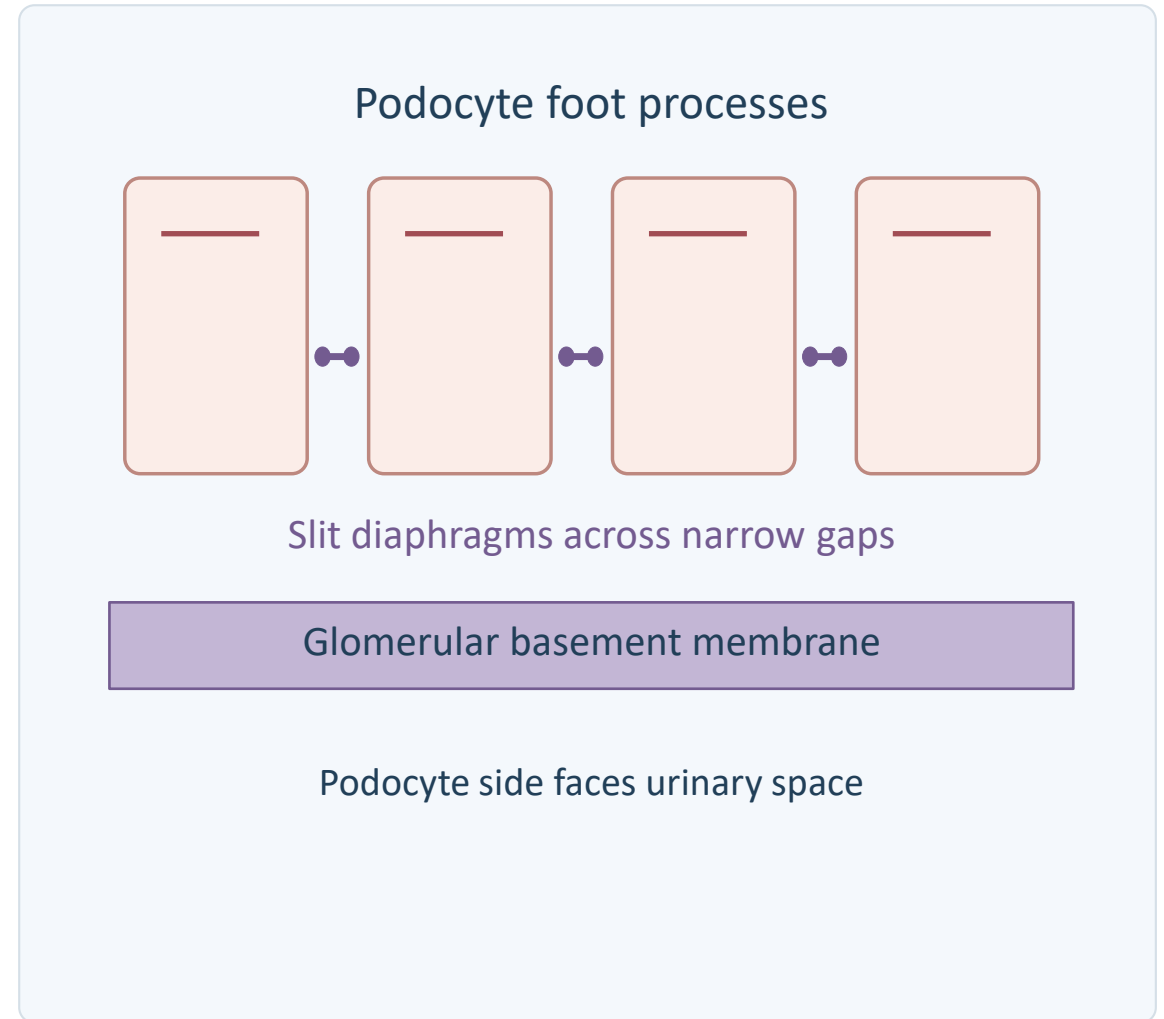
- Fibronectin and entactin occur among GBM glycoproteins.
- They belong to a molecularly heterogeneous network with type IV collagen and laminin.
- No individual matrix protein alone reproduces the intact filtration barrier.



Type IV collagen network

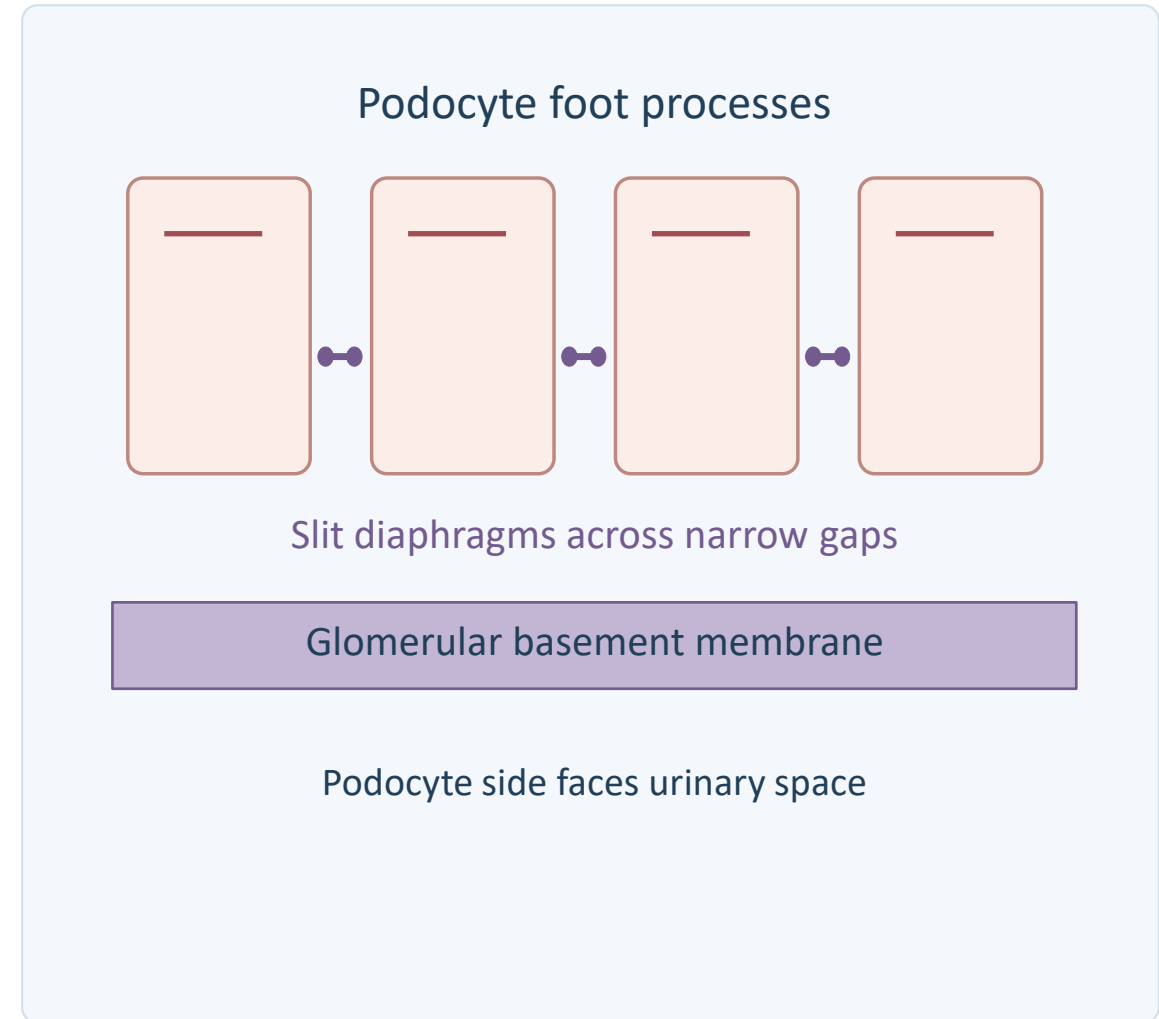
Podocytes are the visceral epithelial cells

- Podocytes are specialized epithelial cells integrated into the capillary wall.
- Their cellular processes abut the urinary side of the GBM.
- They are distinct from the parietal epithelium lining Bowman capsule.



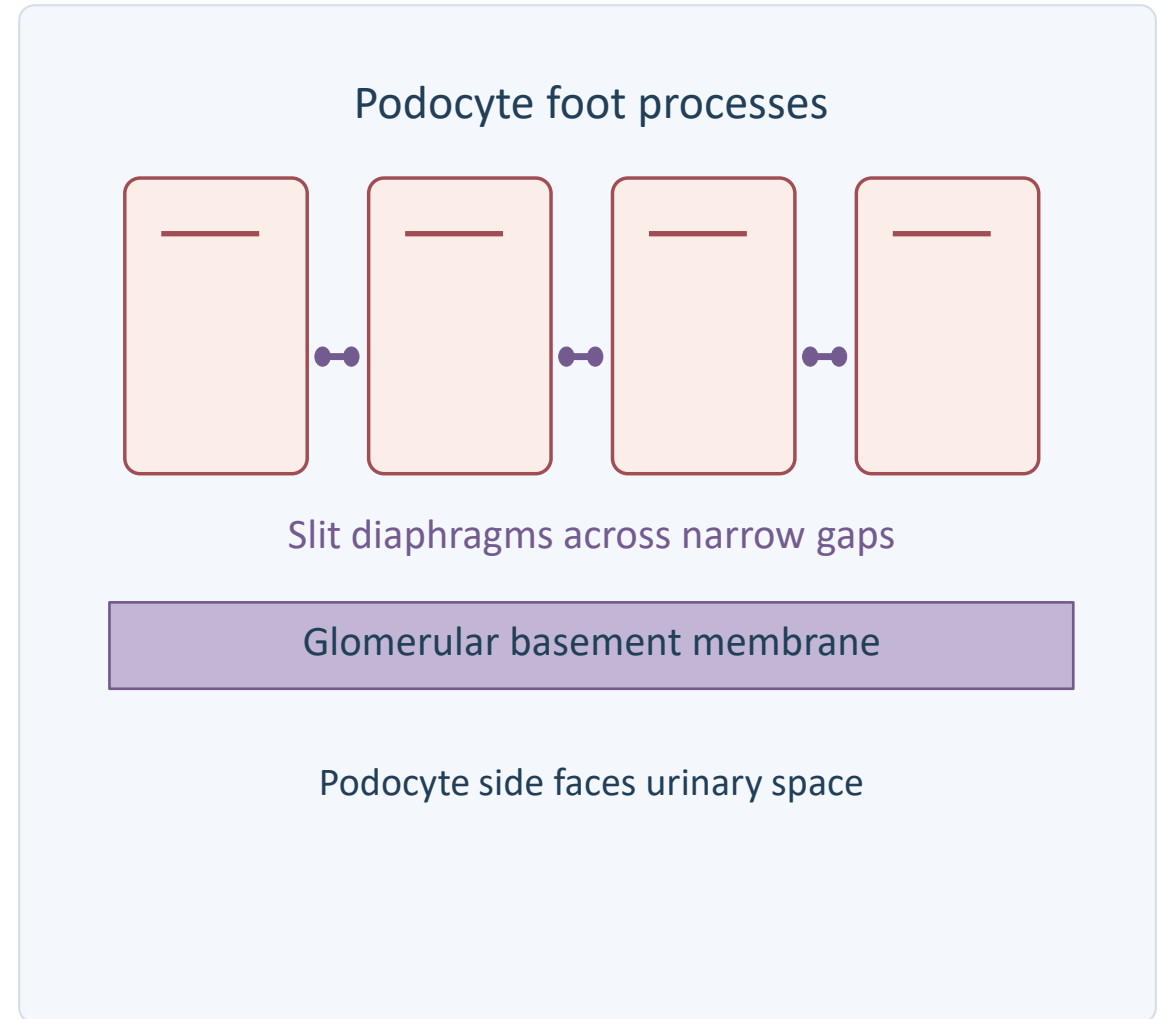
Podocyte adhesion links cells to GBM

- Podocyte foot processes adhere to the lamina rara externa.
- Their stable interface with matrix is essential to the structure of the outer capillary wall.
- The attachment interface is connected with the podocyte cytoskeletal apparatus.



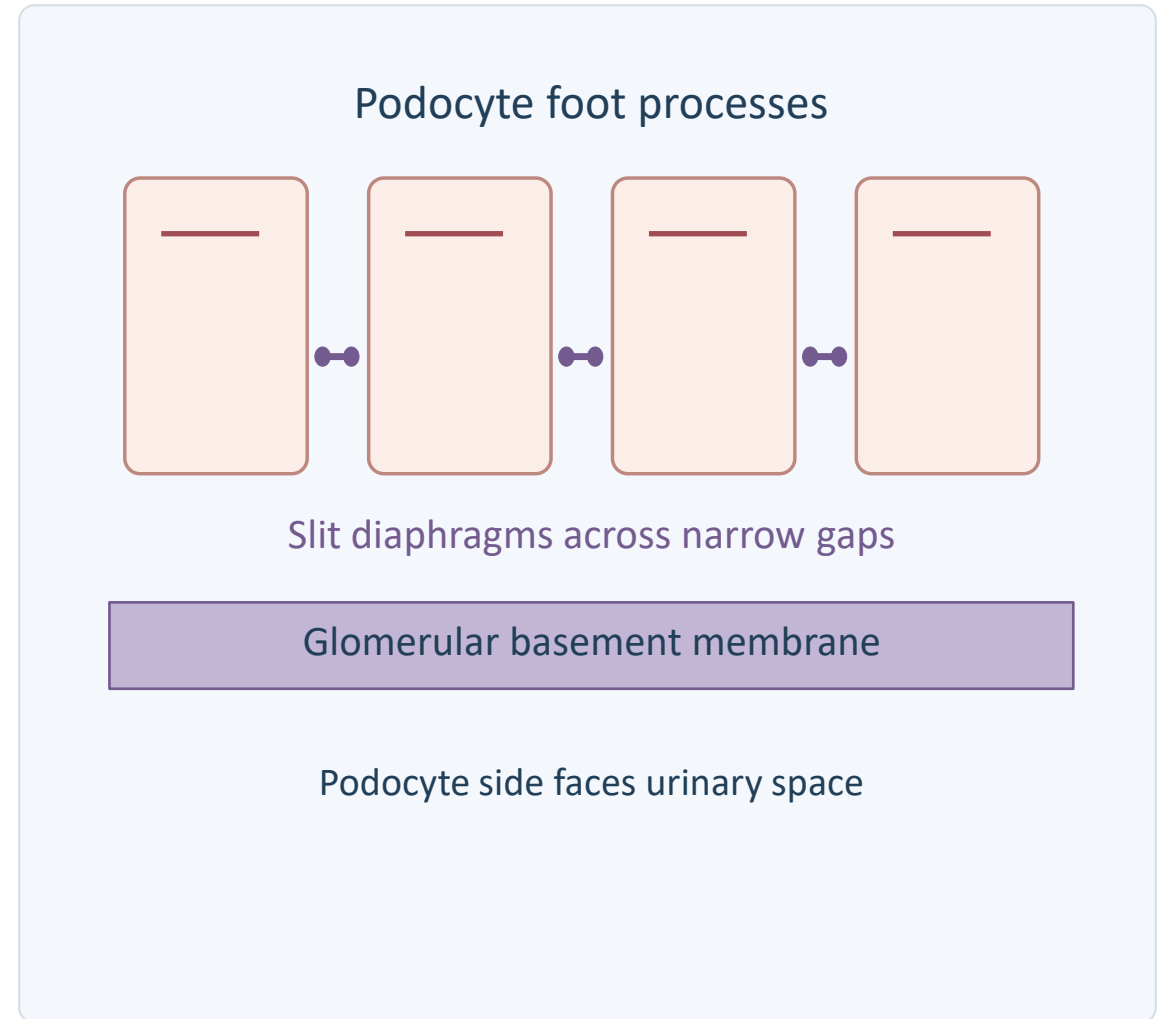
Foot processes interdigitate

- Adjacent podocytes send processes that interlock along the GBM.
- Interdigitation creates narrow spaces between neighboring foot processes.
- The arrangement enables formation of repeated filtration slits.



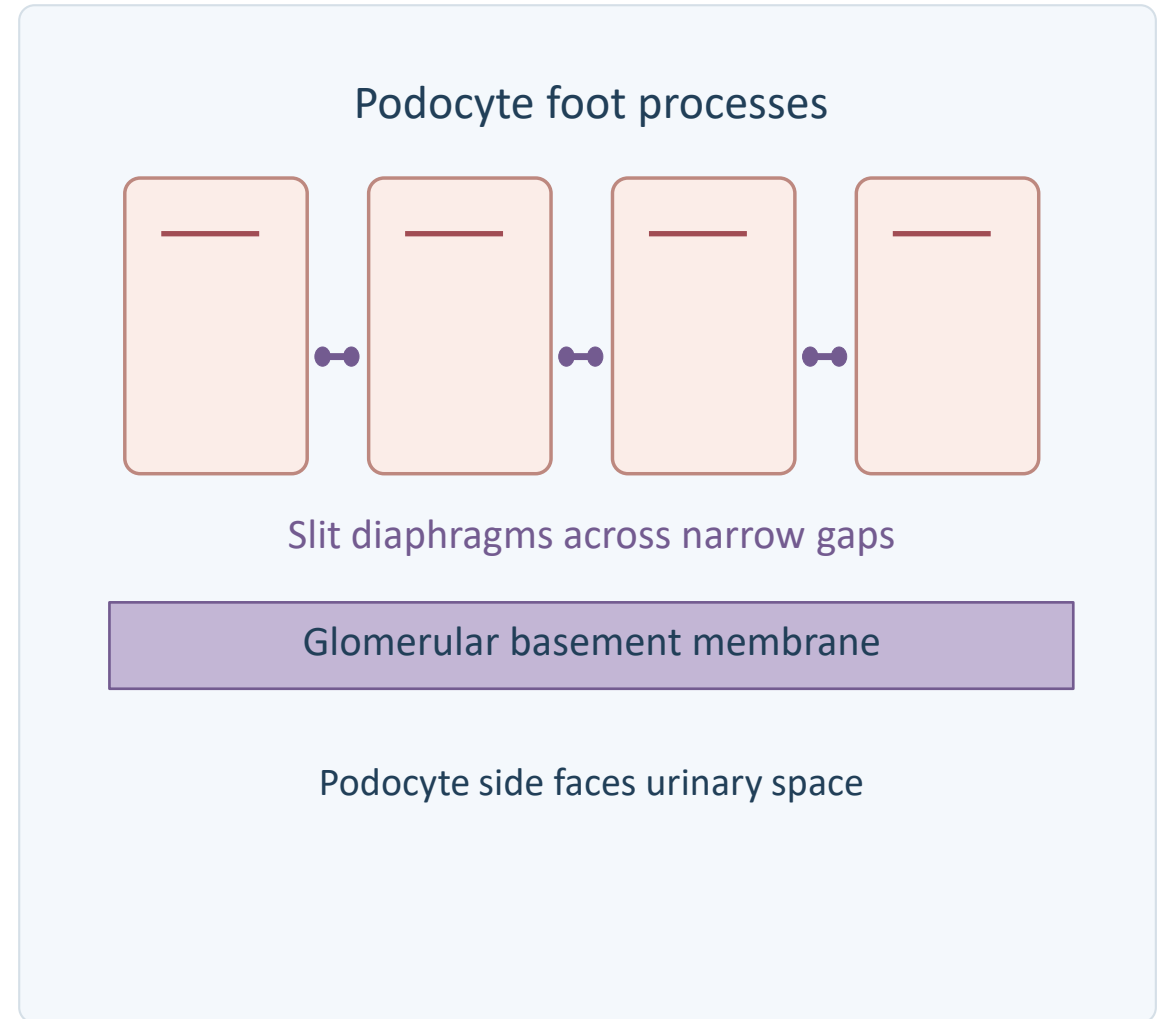
Filtration slits occupy nanometer-scale gaps

- Filtration slits approximately 20–30 nm wide.
- These gaps lie between adjacent podocyte foot processes.
- A specialized diaphragm bridges each slit; It is not an unprotected opening.



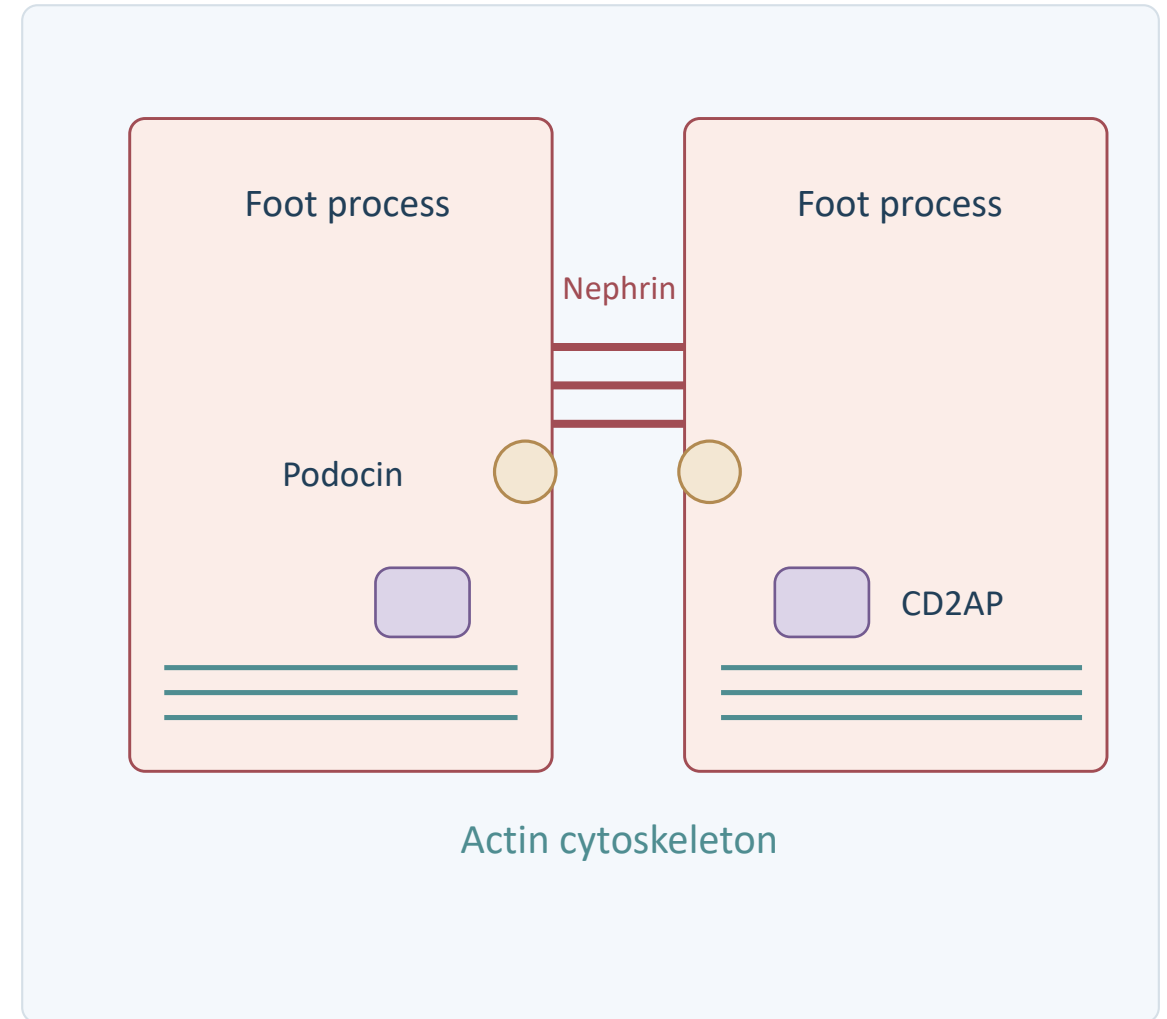
The slit diaphragm is a specialized junction

- Unlike a simple physical gap, the filtration slit has a molecular cell–cell junction.
- This slit diaphragm acts as a size-selective distal barrier to plasma proteins.
- It is a crucial component of normal glomerular permeability.



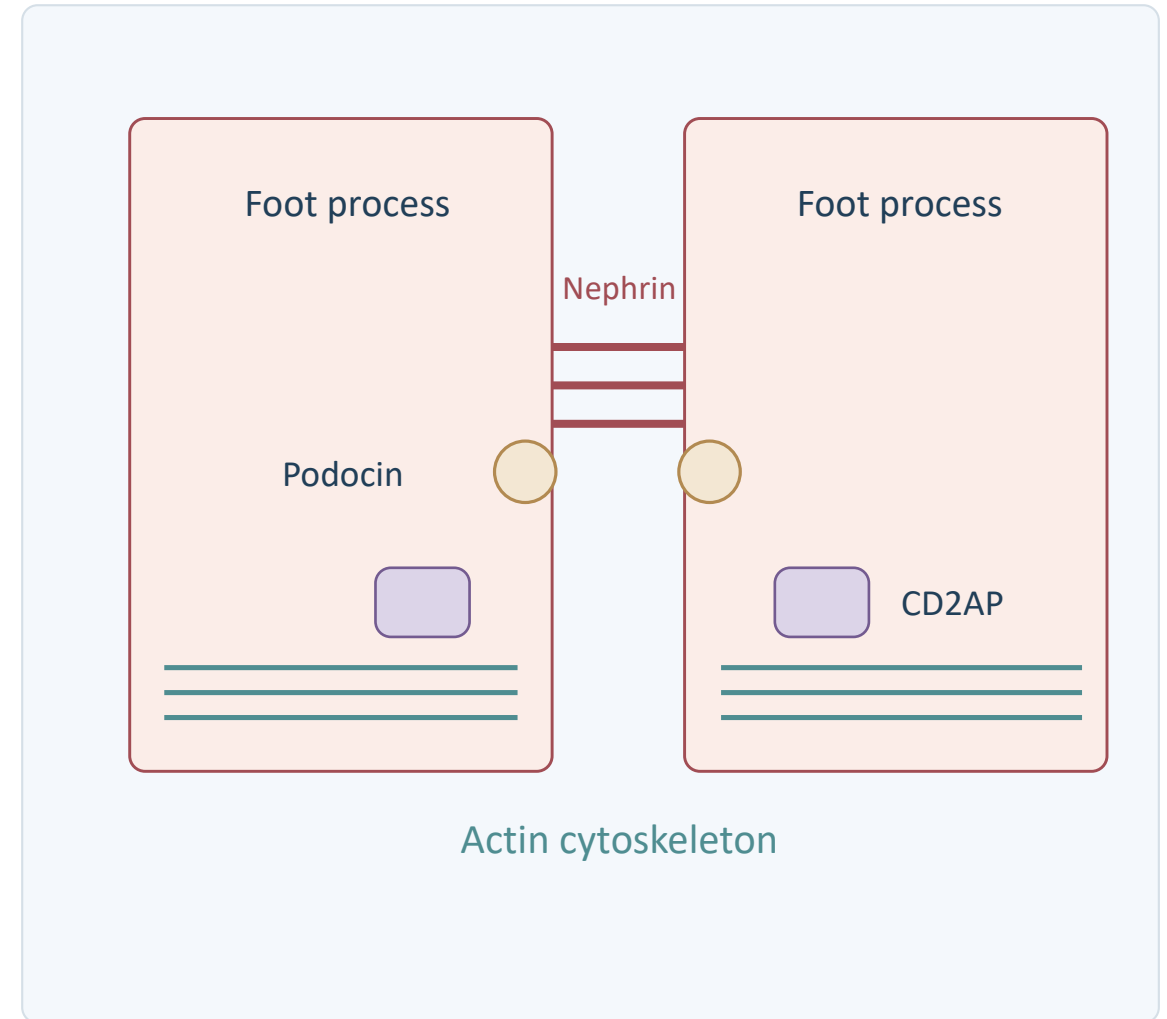
Nephrin spans the slit diaphragm

- Nephrin is a transmembrane protein with a large extracellular portion.
- Its extracellular region contains immunoglobulin-like domains.
- Nephrin molecules project from opposing foot processes into the slit.



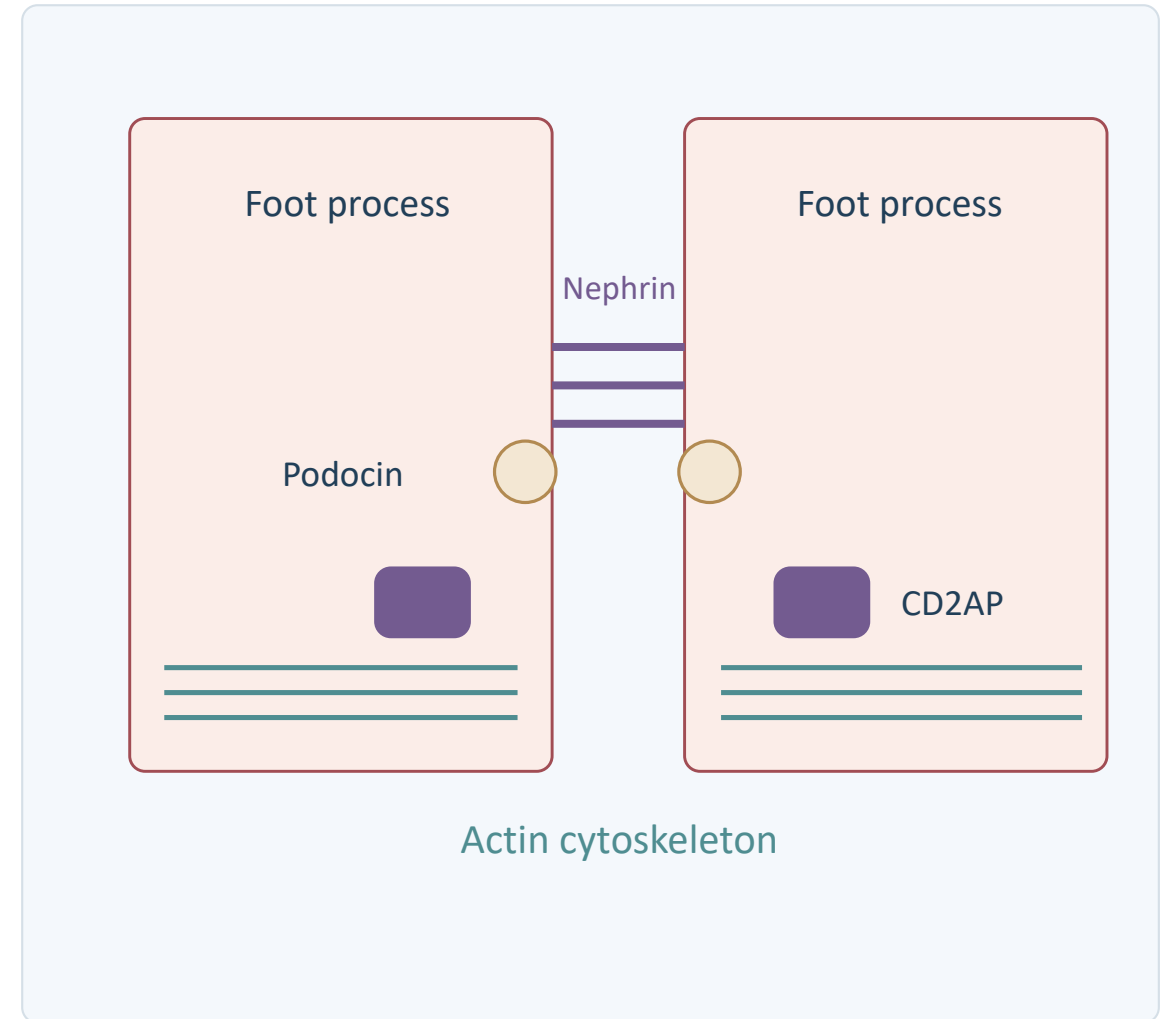
Nephrin molecules couple across neighboring cells

- Nephrin molecules from adjacent foot processes extend toward each other.
- Their dimerization across the filtration slit.
- This transcellular connection contributes directly to the slit diaphragm.



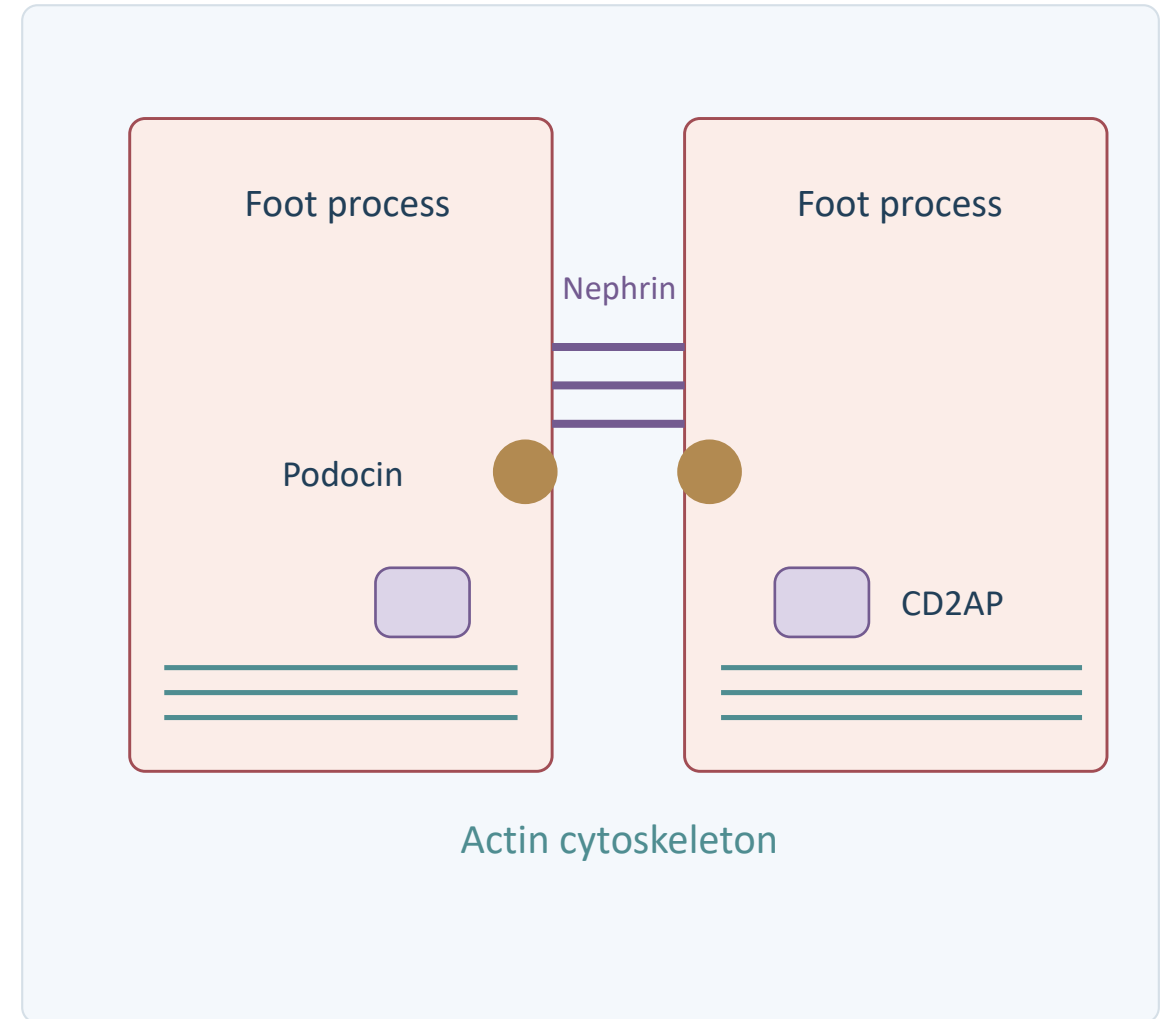
Nephrin also has intracellular partners

- The nephrin junction is mechanically integrated with the podocyte interior.
- Nephrin connects with proteins including podocin and CD2-associated protein.
- These links ultimately connect the junctional complex to the actin cytoskeleton.



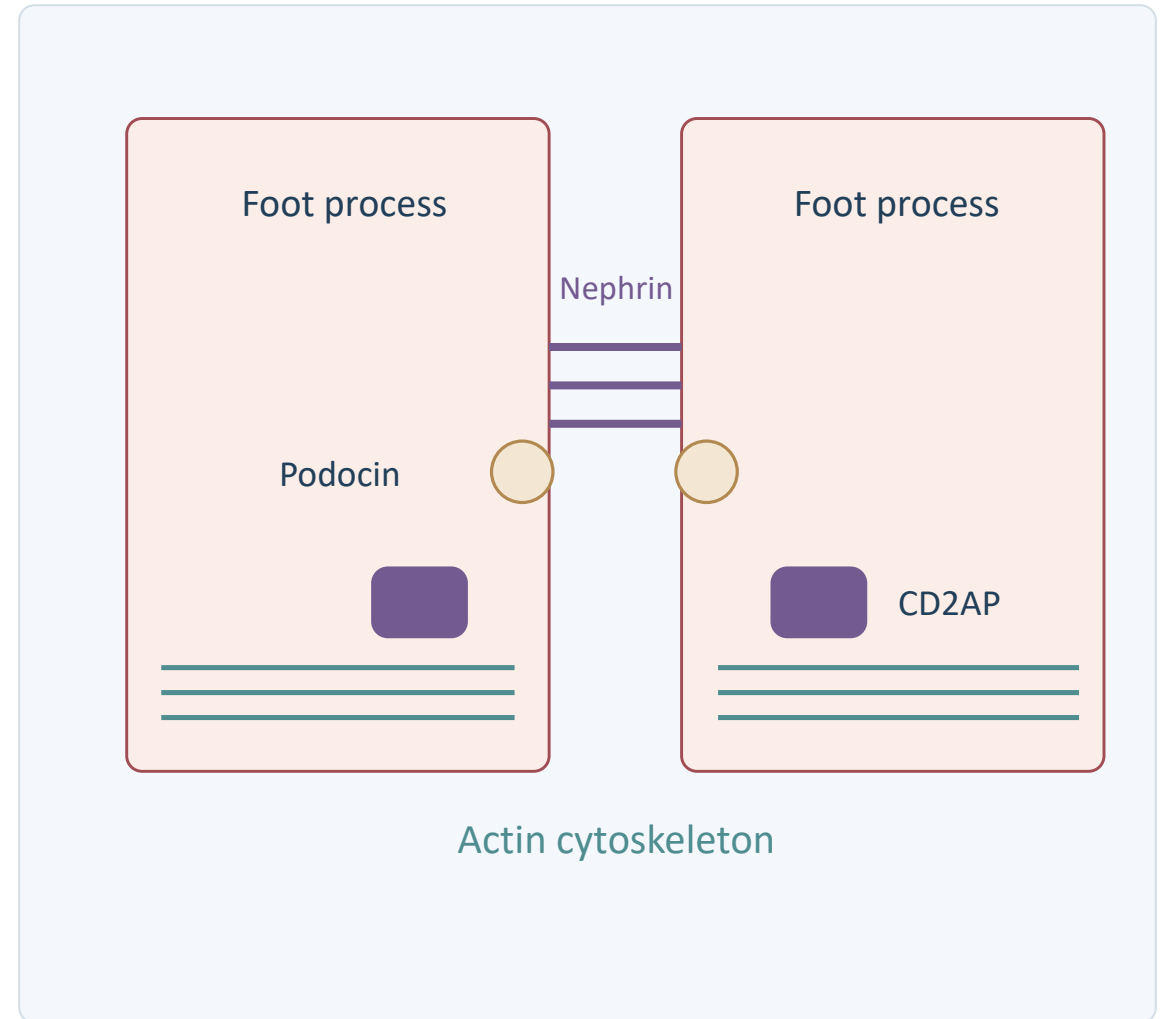
Podocin is a slit-complex partner

- Podocin participates in the intracellular molecular apparatus associated with nephrin.
- Its position helps link extracellular slit organization to cellular machinery.
- Defects involving slit-diaphragm proteins can impair permeability control.



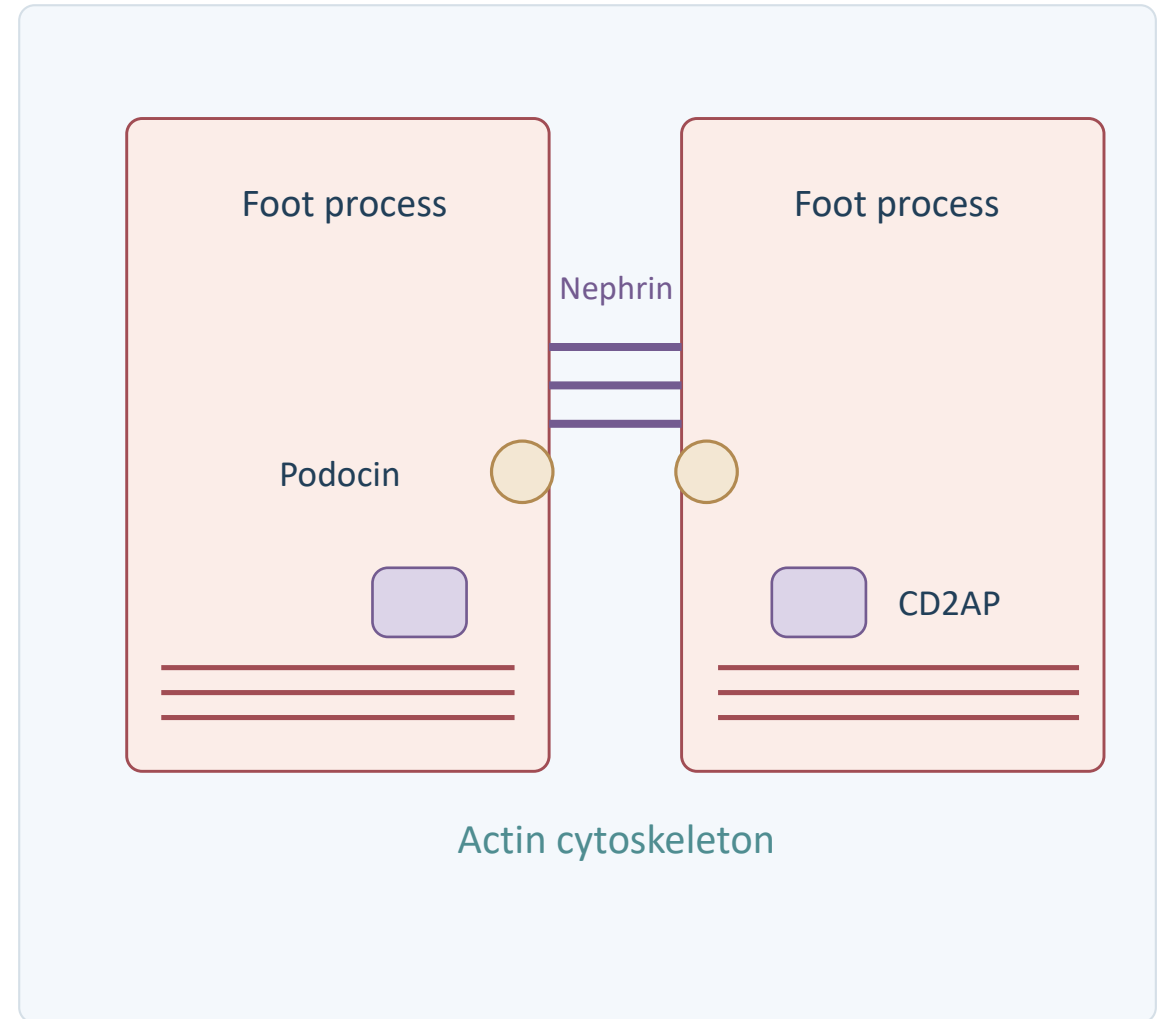
CD2AP contributes to the intracellular linkage

- CD2-associated protein (CD2AP) is an intracellular component of the slit complex.
- It lies in the connection between the junctional apparatus and actin.
- The molecular barrier depends on a coordinated protein assembly.



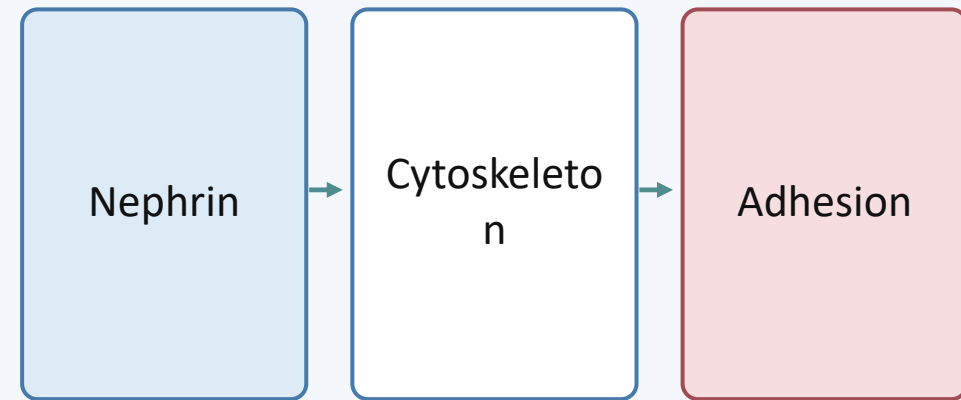
The actin cytoskeleton anchors slit architecture

- Nephrin-associated complexes connect ultimately to actin.
- The actin framework supports the architecture of podocyte foot processes.
- Junctional stability and the cytoskeletal scaffold are functionally connected.



Focal adhesion hubs complete the mechanical chain

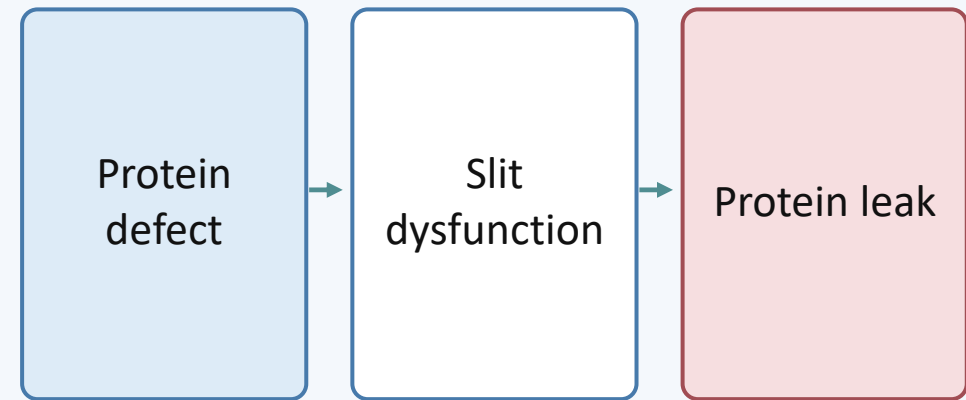
- Robbins traces the nephrin complex through intracellular partners to actin.
- The actin cytoskeleton is anchored on focal adhesion hubs.
- Barrier integrity thus requires coordination between junction, cytoskeleton and adhesion.



Functional sequence

Slit-protein mutations can produce proteinuria

- Mutations in genes encoding slit-diaphragm-associated proteins disrupt permeability.
- These molecular defects lead to familial nephrotic syndromes.
- A structural junction defect can therefore present as a clinical protein-leak phenotype.



Functional sequence

Podocytes also support GBM composition

- Under normal circumstances, podocytes synthesize a substantial share of GBM components.
- Their role extends beyond an outer cellular cover and slit diaphragm.
- A podocyte abnormality may consequently affect both cellular and matrix elements of the wall.

Endothelium

Fenestrated cellular lining

GBM

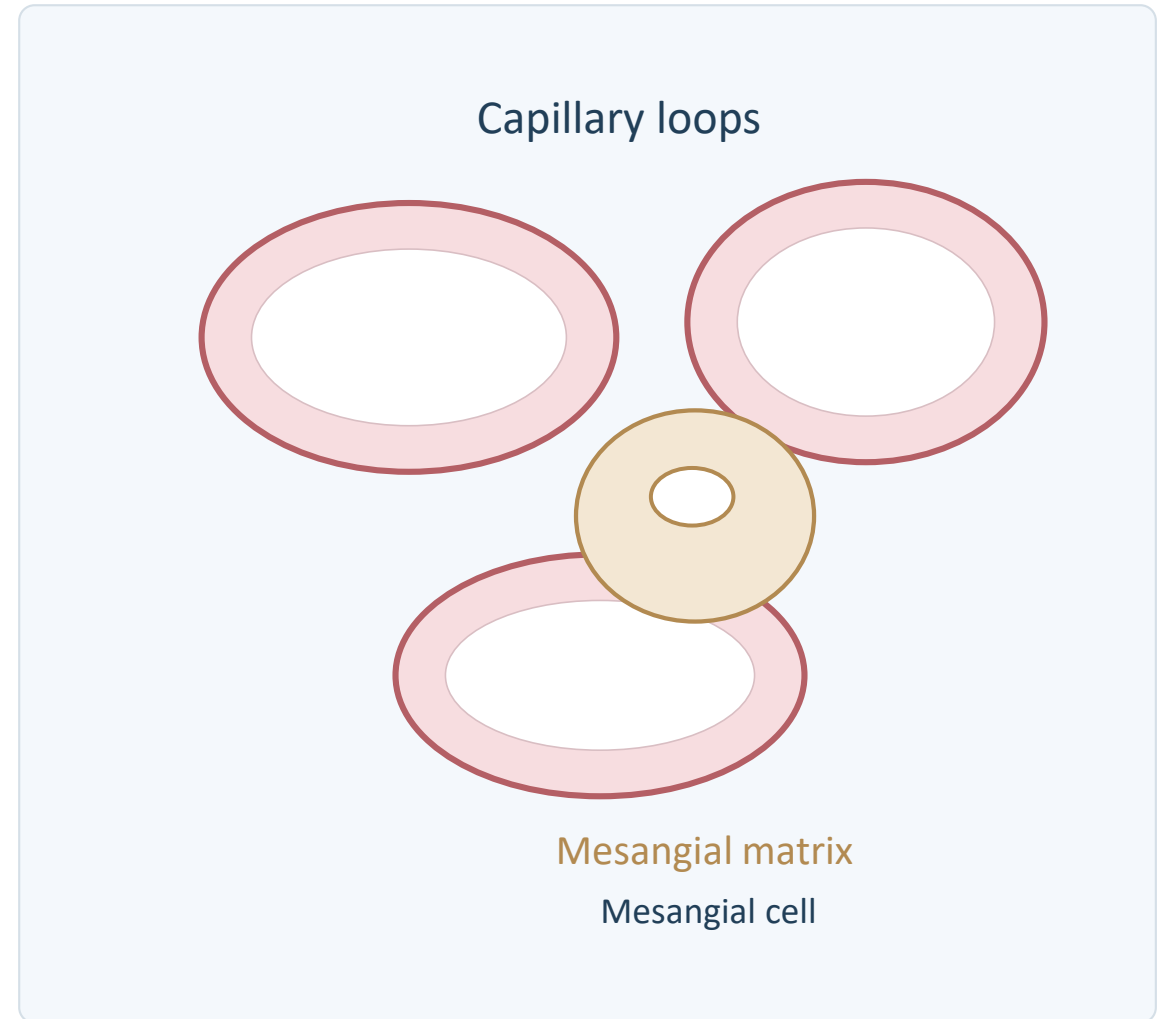
Specialized extracellular scaffold

Podocyte

Foot processes + slit diaphragm

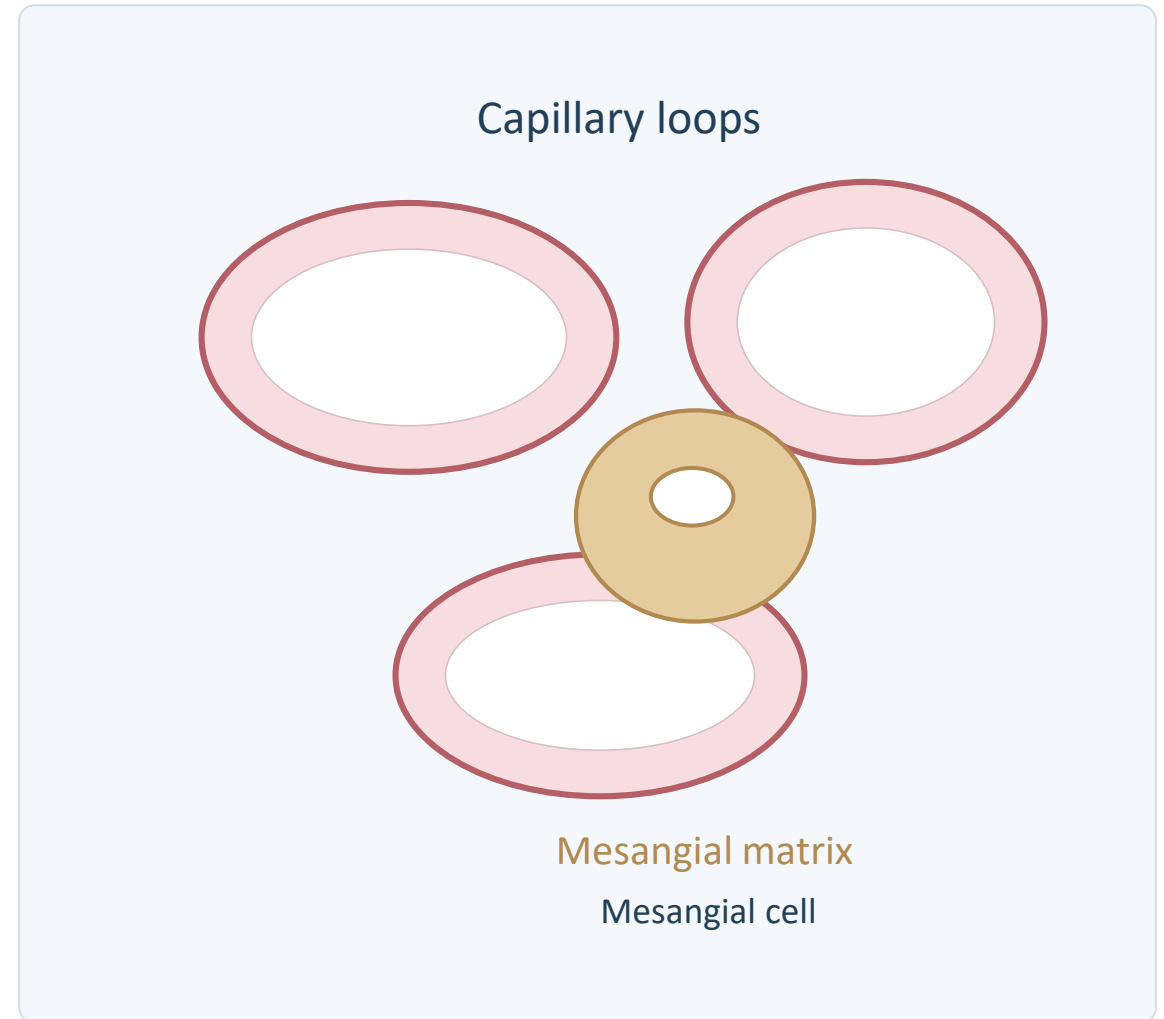
The mesangium supports the entire tuft

- Mesangial tissue occupies spaces between glomerular capillary loops.
- It provides structural support for the interconnected capillary network.
- It contains specialized cells within a basement-membrane-like matrix.



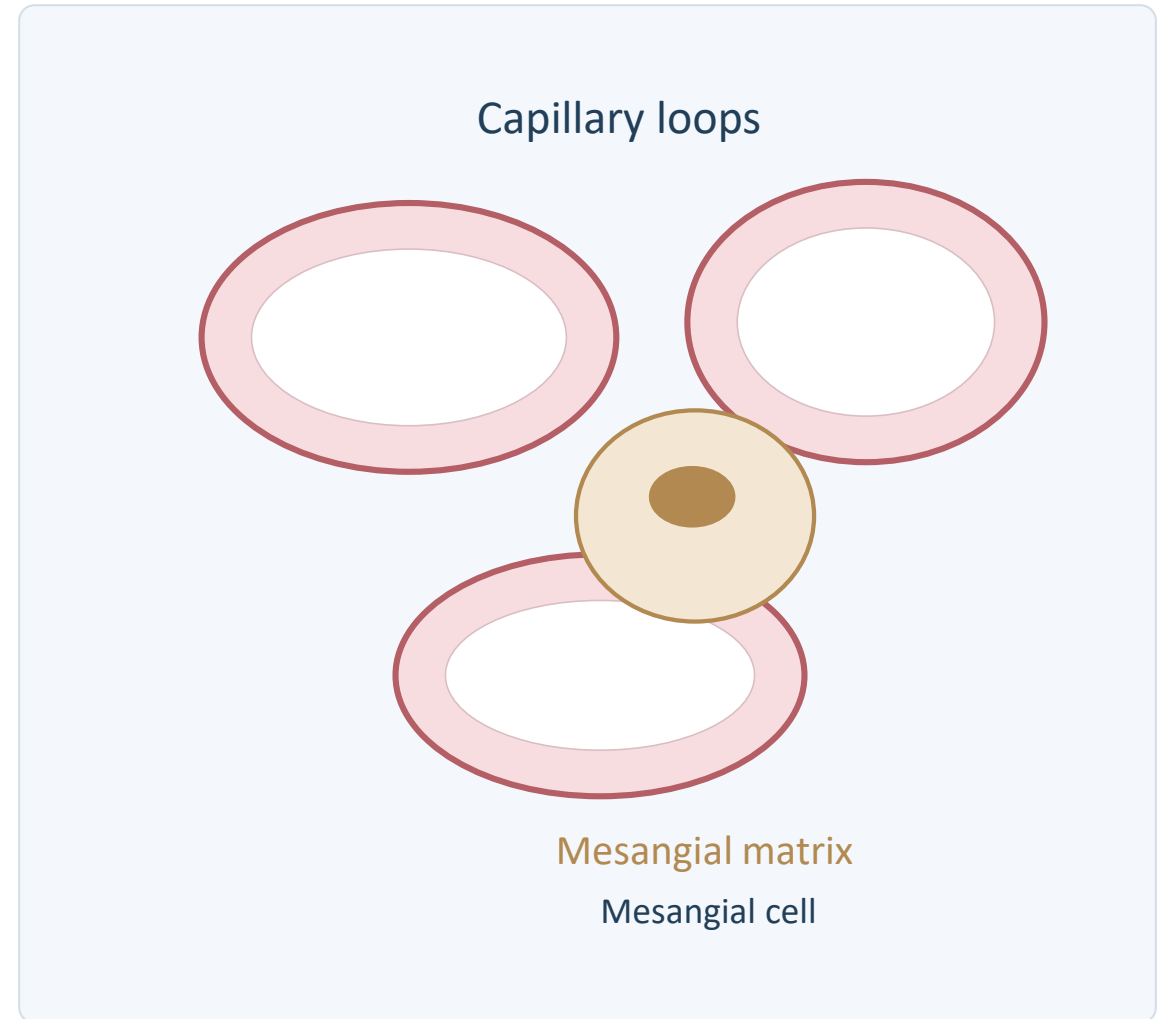
Mesangial matrix forms an intercapillary meshwork

- Mesangial matrix resembles basement-membrane material.
- It occupies a supporting rather than primary transcapillary-filtration location.
- Mesangial cells are embedded within this extracellular matrix network.



Mesangial cells are mesenchymal in origin

- Mesangial cells arise from mesenchymal lineage.
- Functionally they resemble vascular smooth muscle cells and pericytes.
- Their biological repertoire is broader than passive structural support.



Mesangial cells are contractile

- Contractility is an intrinsic property of mesangial cells.
- Their resemblance to pericytes and vascular smooth muscle cells is functionally relevant.
- This feature contributes to their dynamic role in the glomerular tuft.

Contractility

Alter local capillary geometry

Phagocytosis

Clear material in the tuft

Synthesis

Produce matrix and collagen

Mesangial cells perform phagocytic functions

- Mesangial cells can phagocytose material in their microenvironment.
- Their function is not confined to matrix production or contractile support.
- This activity adds a clearance function to the glomerular mesangial compartment.

Contractility

Alter local capillary geometry

Phagocytosis

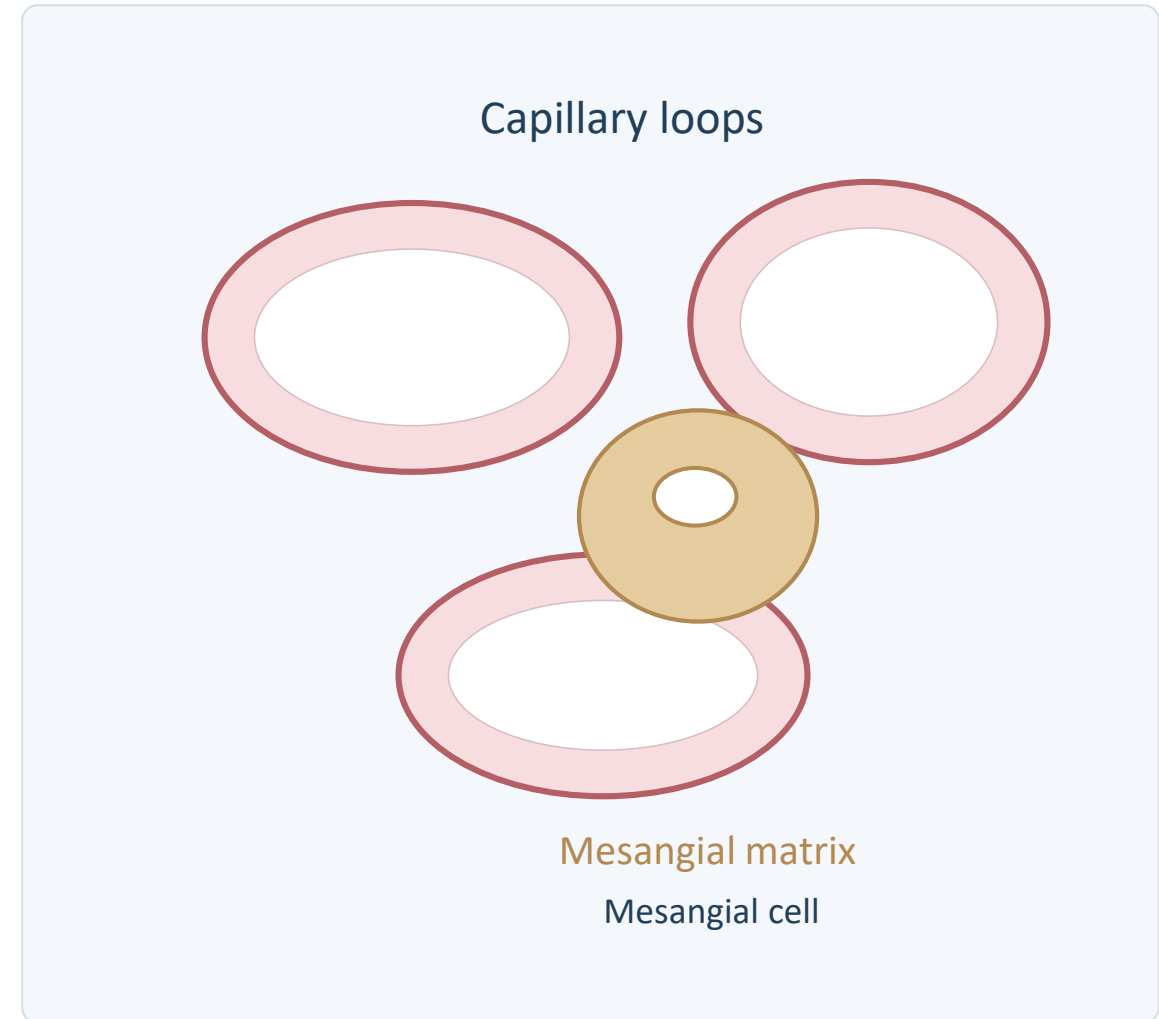
Clear material in the tuft

Synthesis

Produce matrix and collagen

Mesangial cells can proliferate and synthesize matrix

- These cells have proliferative capacity.
- They produce both mesangial matrix and collagen.
- Their proliferative and synthetic behavior explains the mesangium's potential for expansion in injury.



Mesangial cells secrete active mediators

- Mesangial cells are capable of releasing biologically active mediators.
- They participate in local glomerular responses, not merely structural maintenance.
- Contractile, phagocytic, synthetic and secretory capacities coexist in this cell type.

Contractility

Alter local capillary geometry

Phagocytosis

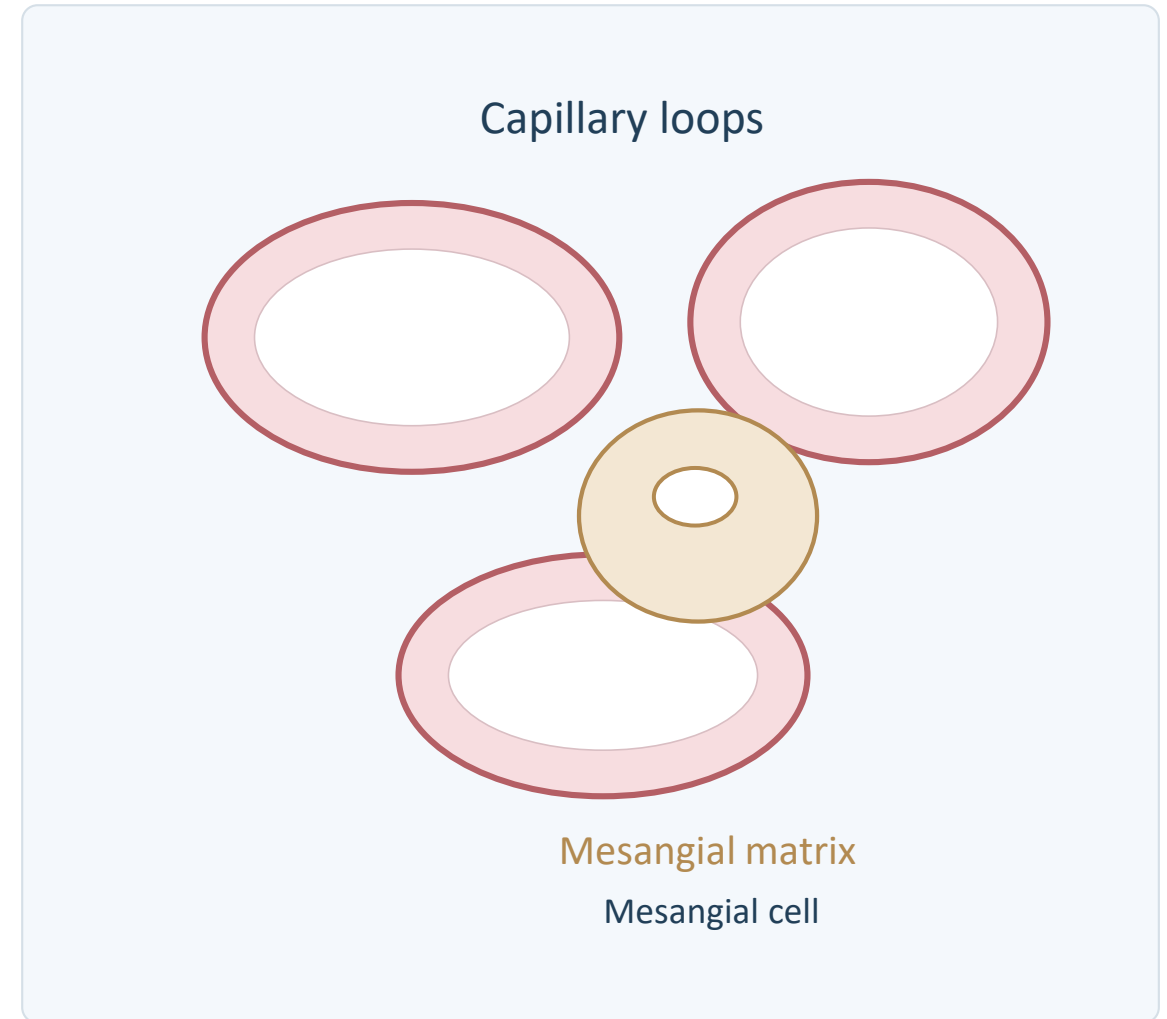
Clear material in the tuft

Synthesis

Produce matrix and collagen

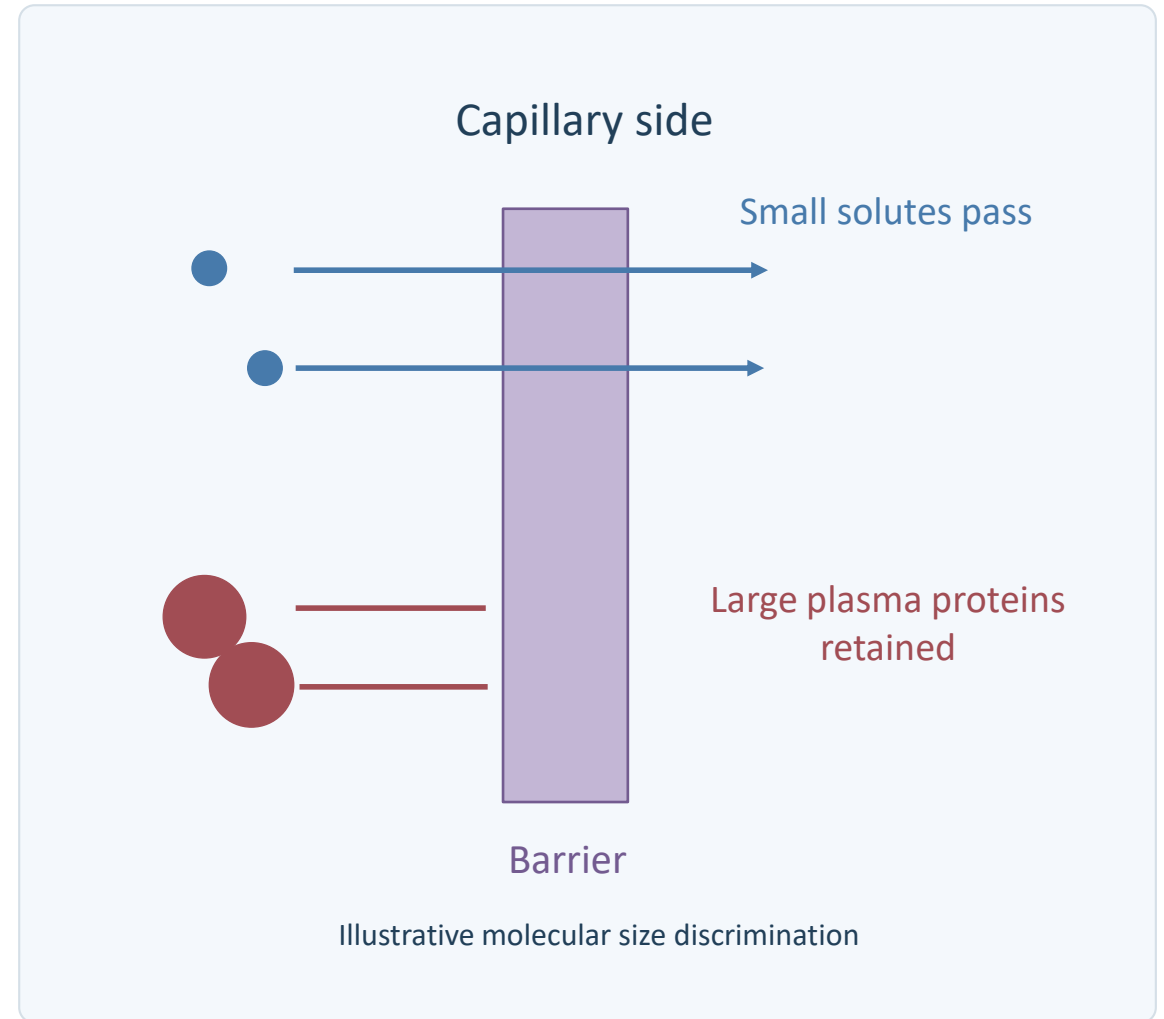
Mesangial and intracapillary lesions often coexist

- No basement membrane separates mesangial cells from adjacent capillary loops.
- This anatomical continuity permits overlap between mesangial and intracapillary involvement.
- Both compartments as commonly affected in glomerulonephritis.



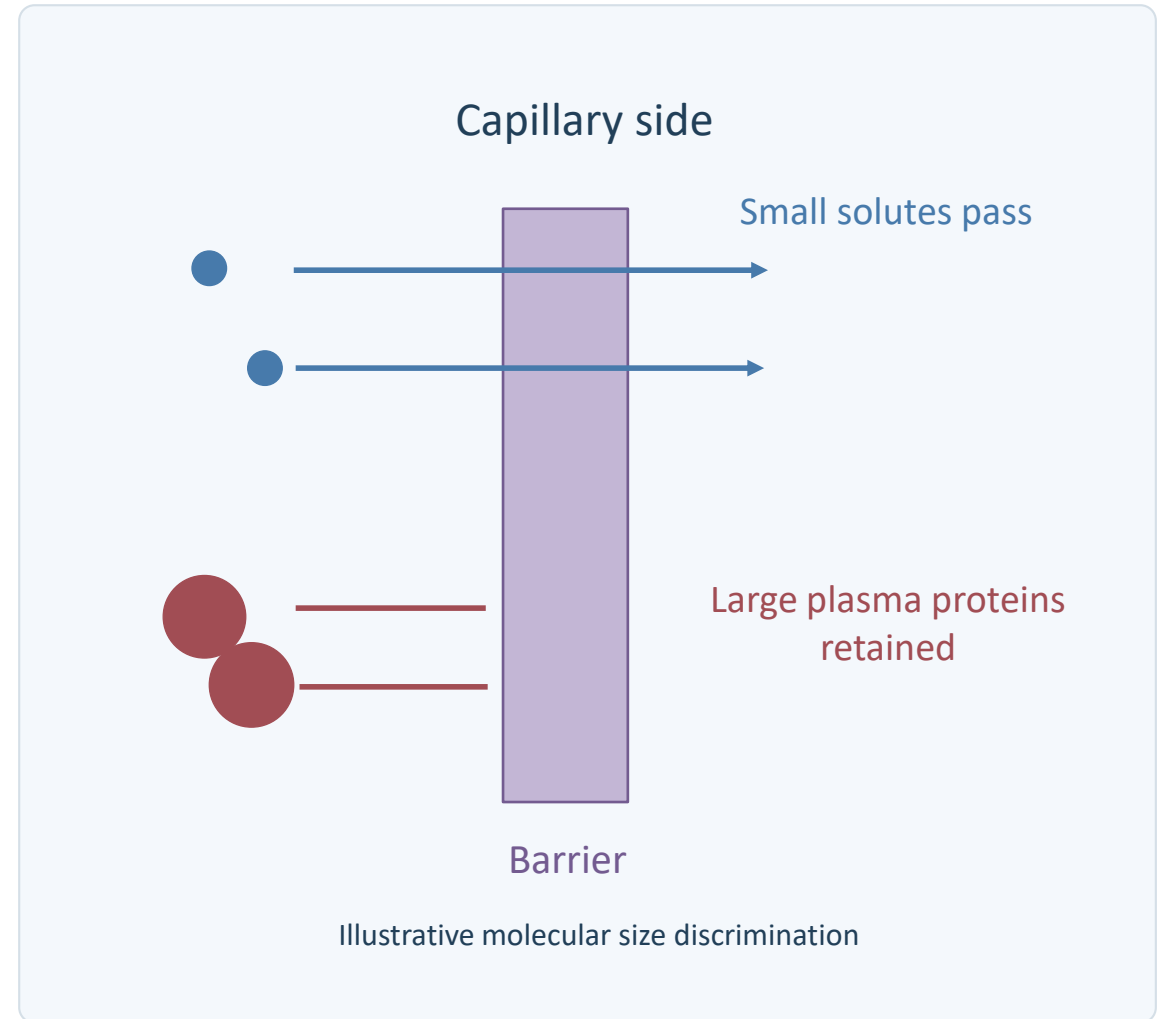
Normal filtration discriminates between solutes

- The intact glomerular wall is highly permeable to water and small solutes.
- Larger protein molecules cross much less readily.
- Permselectivity emerges from the intact composite capillary wall.



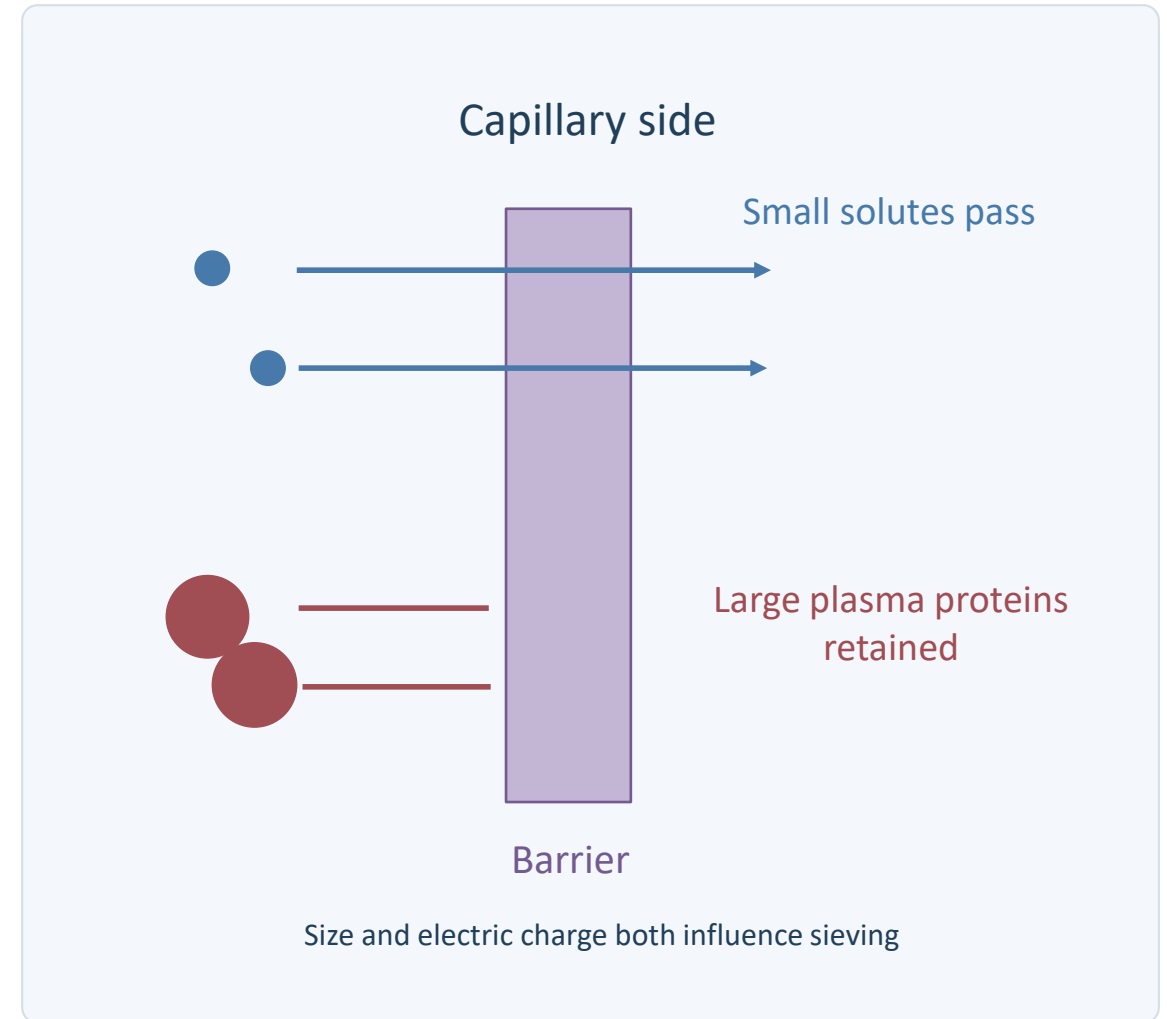
Molecular size influences permeability

- As molecular size increases, normal filtration-barrier permeability generally decreases.
- The slit diaphragm is an important distal size-selective component.
- Fenestrae alone do not account for retention of macromolecular proteins.



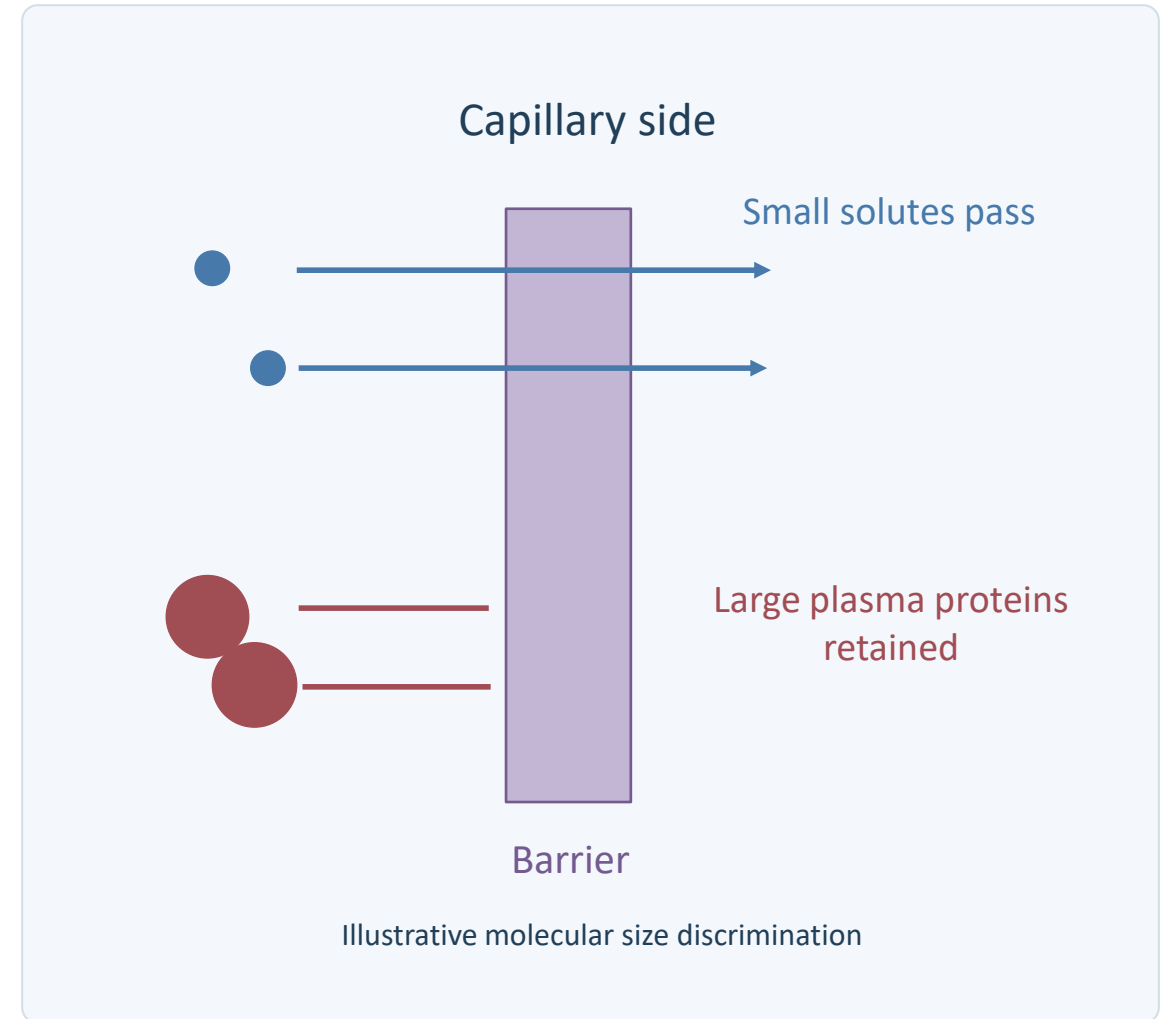
Electric charge also affects protein passage

- A charge-dependent component of glomerular permeability.
- At a comparable size, cationic molecules are described as more permeable than anionic ones.
- The relative contribution of GBM proteoglycans is presented in the source as potentially important.



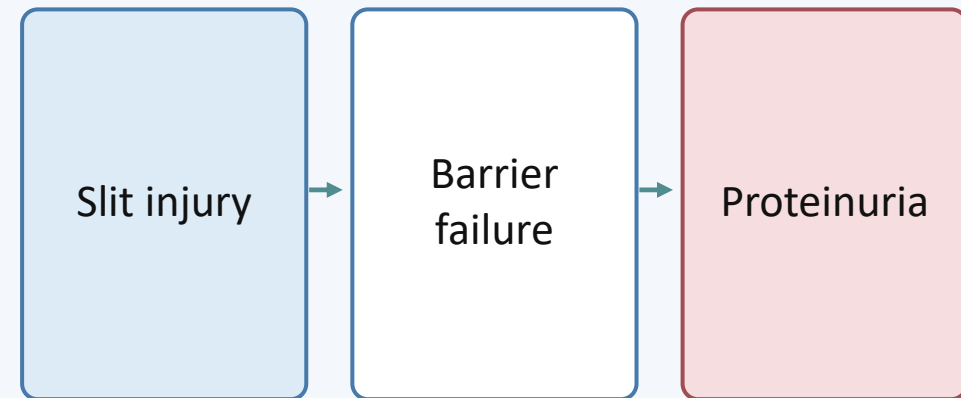
Albumin illustrates normal protein retention

- Albumin is a negatively charged plasma protein of approximately 70 kDa.
- The normal filtration barrier retains nearly all albumin.
- Its restricted passage reflects integrated size and charge selectivity account.



Structural injury can impair protein retention

- Podocyte junction abnormalities can increase protein permeability.
- A major clinical consequence is proteinuria, and severe glomerular leakage can produce nephrotic syndrome.
- Relating protein leakage to the responsible structural compartment is a core pathology task.



Functional sequence

Integrating the three filtration-wall elements

- Fenestrated endothelium provides a highly permeable luminal lining.
- The collagen-rich GBM is a specialized molecular matrix scaffold.
- Podocyte foot processes and their slit diaphragm contribute the distal selective barrier.

Endothelium

Fenestrated cellular lining

GBM

Specialized extracellular scaffold

Podocyte

Foot processes + slit diaphragm

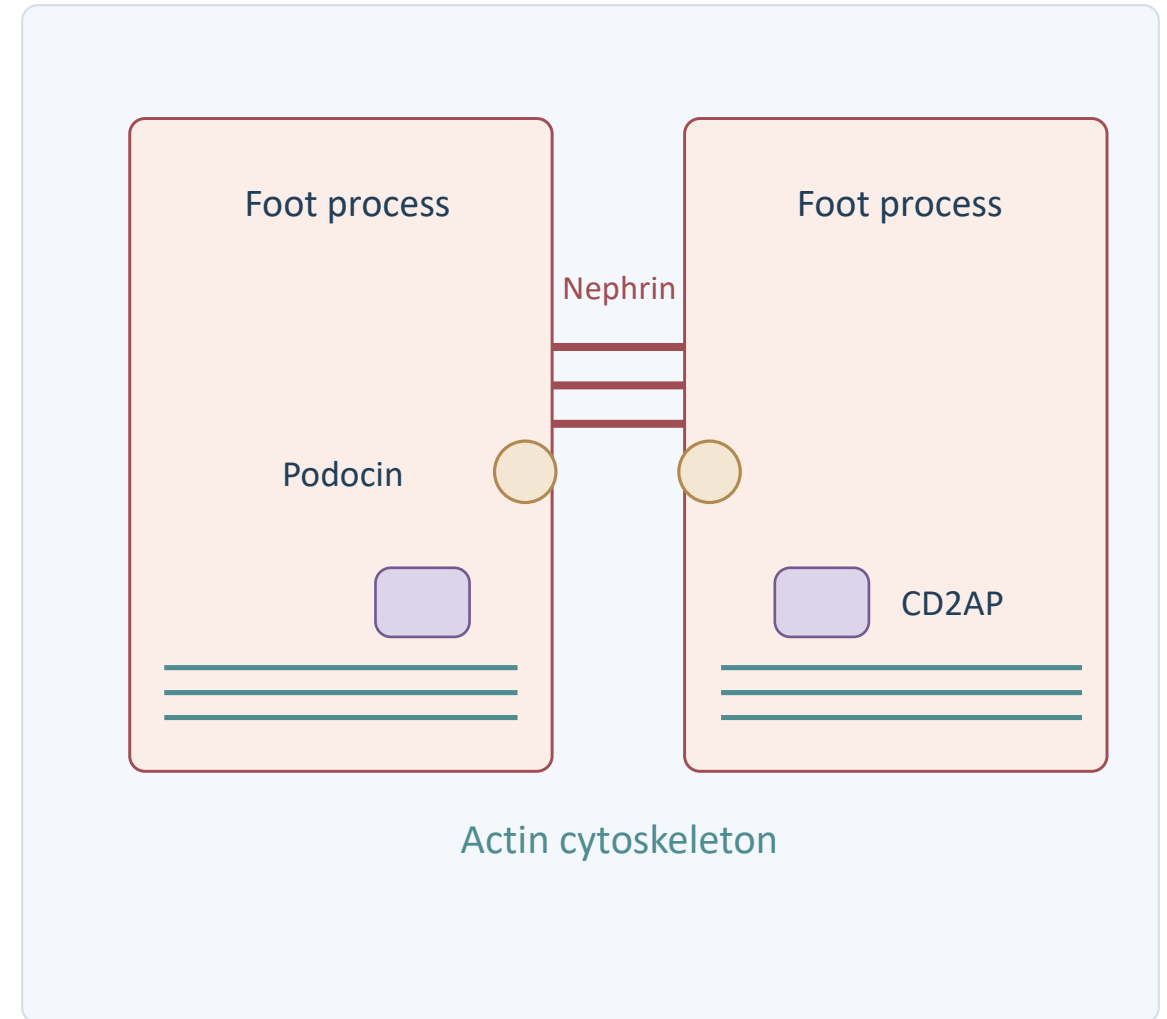
Structure–disease relationships

- Type IV collagen α -chain abnormalities illustrate hereditary GBM structural disease.
- NC1 epitopes illustrate immune targeting of a basement-membrane constituent.
- Nephrin-related junctional abnormalities illustrate inherited barrier-protein defects.

Structure	Pathologic link
COL4A α chains	Alport-spectrum disorders
Type IV collagen NC1	Anti-GBM nephritis
Slit protein complex	Familial nephrotic syndromes

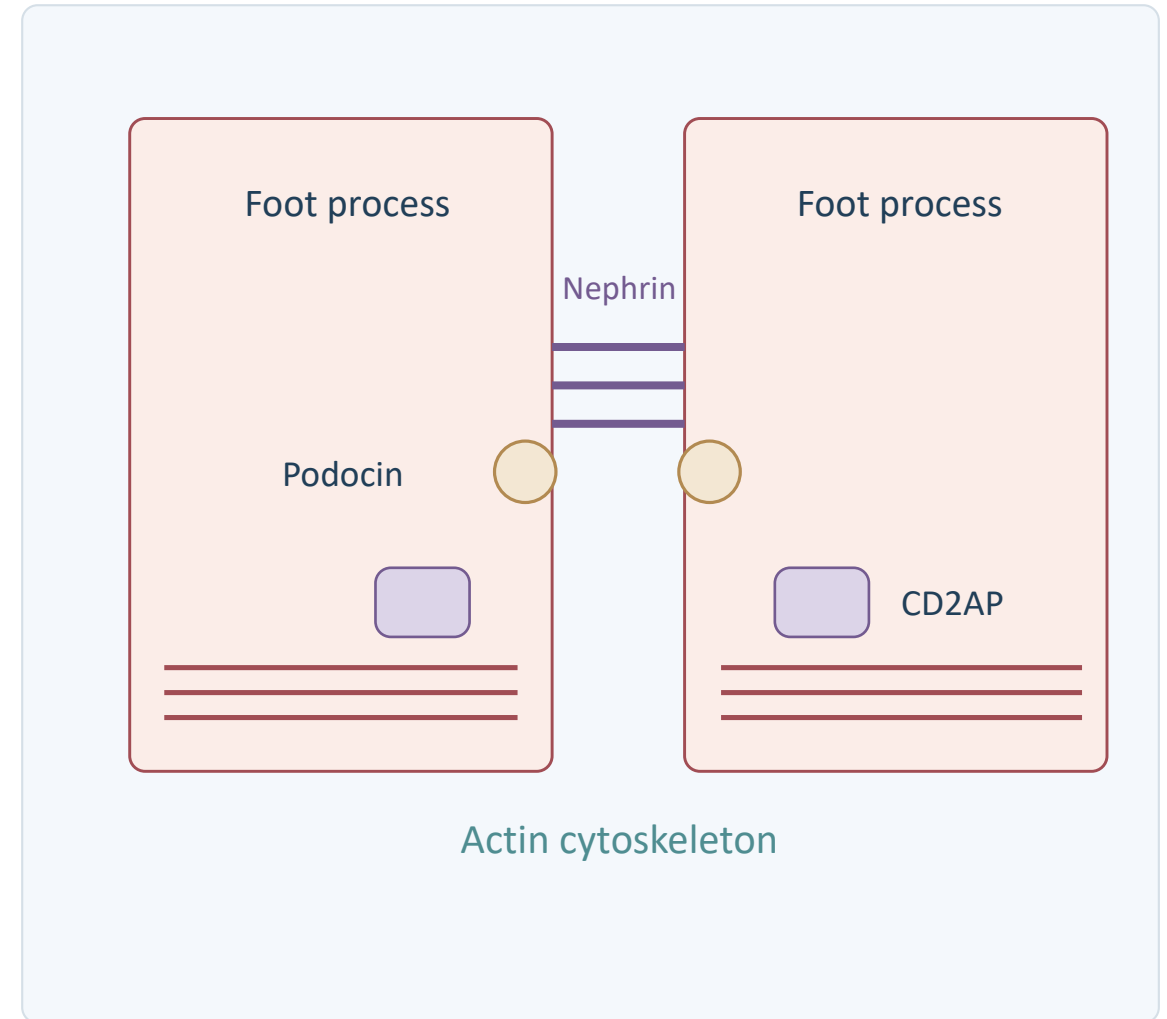
Apply the anatomy: A molecular case

- A child has severe proteinuria and an inherited defect of a slit-diaphragm protein.
- Which cellular compartment directly contains the defective junction?
- Why might light-microscopic capillary-wall appearance fail to reveal the molecular defect?



Case resolution: Podocyte slit apparatus

- The relevant compartment is the podocyte foot-process slit diaphragm.
- The defect involves a molecular junctional complex linked to actin.
- Protein permeability can be abnormal without a visible gross change in glomerular organization.



Synthesis: Four anatomical priorities

- Identify capillary endothelium, GBM, podocytes and mesangium separately.
- Orient filtration from blood toward Bowman space.
- Recognize collagen IV/NC1 and nephrin-associated complexes as clinically consequential structural targets.
- Link permeability to the intact composite barrier rather than to a single isolated pore.

Architecture

Fenestrated loops

Scaffold

GBM + mesangium

Junctions

Slit diaphragms

Reference and image provenance

Primary textbook

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. Chapter 20, “The Kidney”; “Structure of the Glomerulus,” pp. 815–816.

Illustrations

All diagrams are original, native editable PowerPoint schematics. They are not clinical specimens or representations drawn to measured anatomical scale.