# Immunological Aspects of Renal Disease

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# The renal system

The kidney is a major filtering organ.

Urine is produced after a complex process of glomerular filtration, tubular transport, and reabsorption.

Cellular elements involved in immunity have a high probability of interacting with glomerular and tubular cells that may or may not cause renal disease.

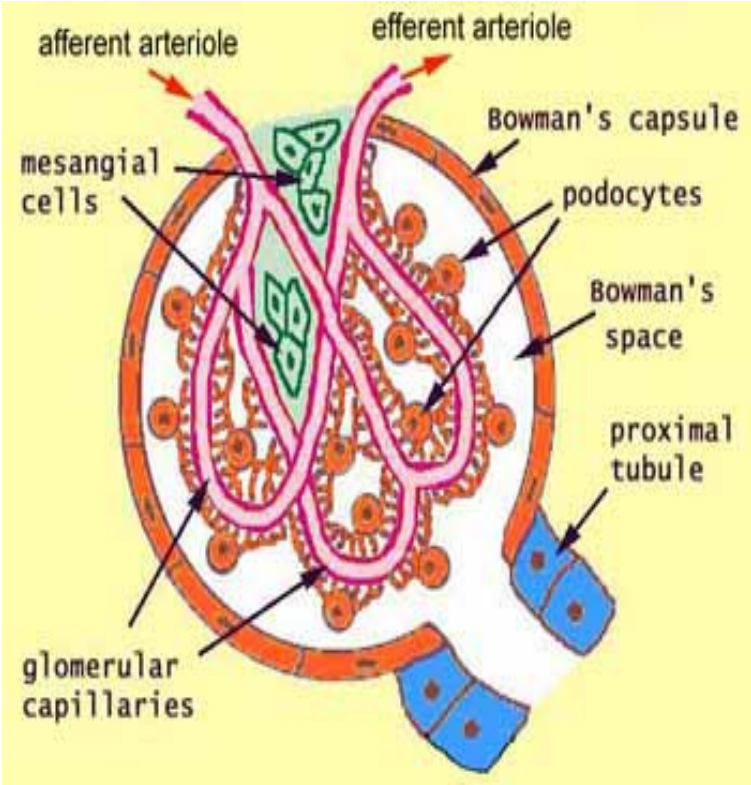
# The renal system

The **nephron** is the functional unit of the kidney.

Each nephron consists of one renal corpuscle and its associated tubule.

The **renal corpuscles** are the sites where the process of urine formation begins.

Renal corpuscles consist of Bowman's capsule enclosing a knot of



# The renal system

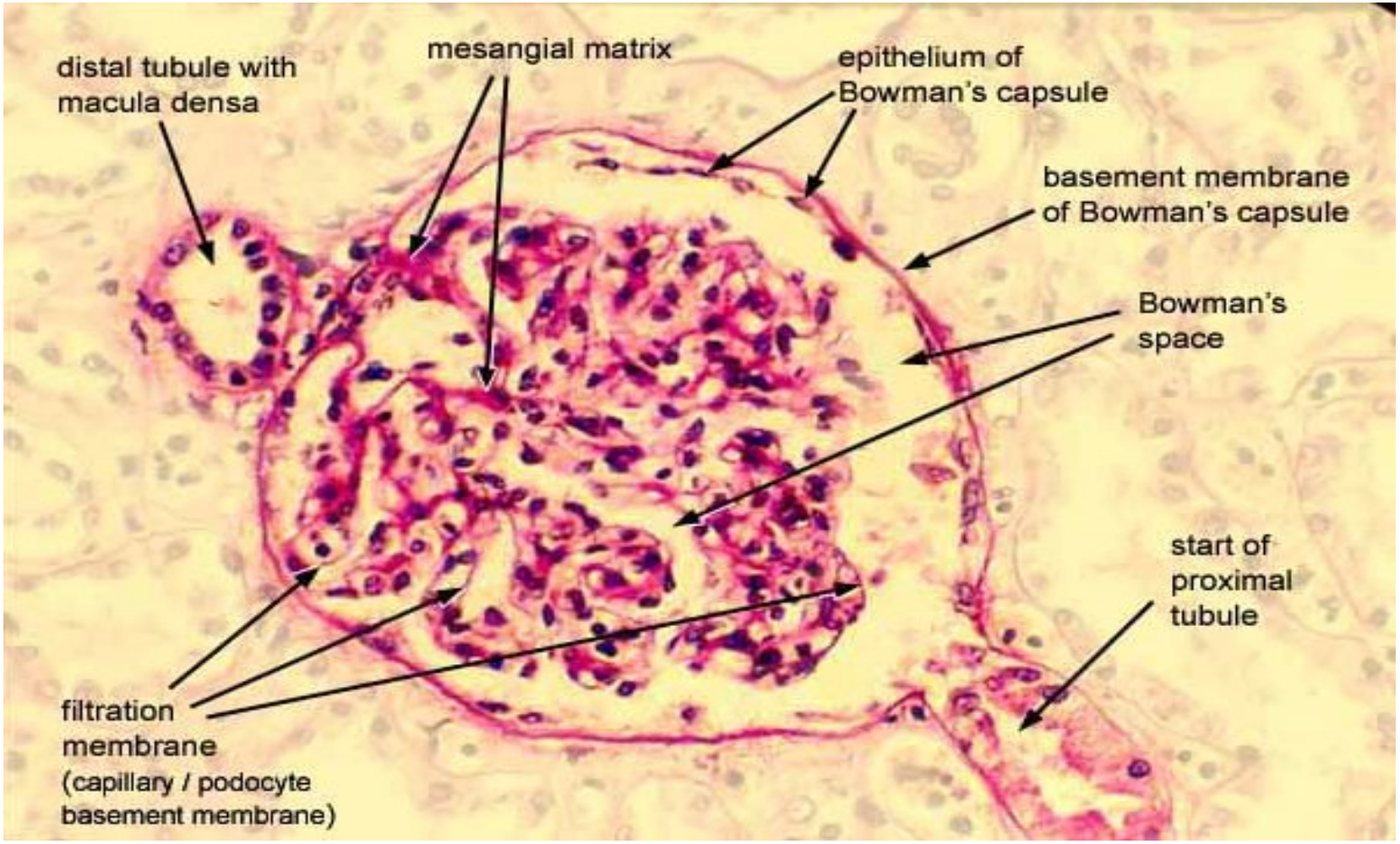
Each **renal corpuscle** has several parts.

Bowman's capsule is the outer, epithelial wall of the corpuscle with underlying space.

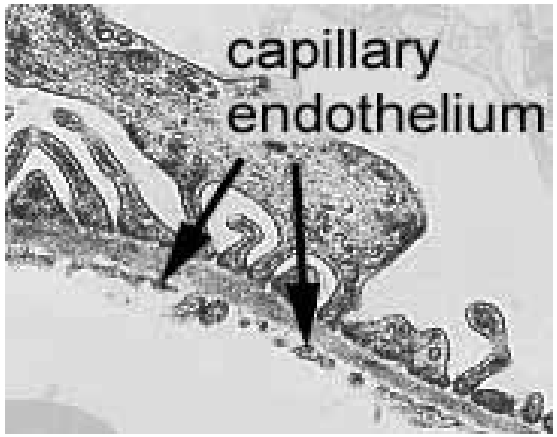
The glomerulus consist of:

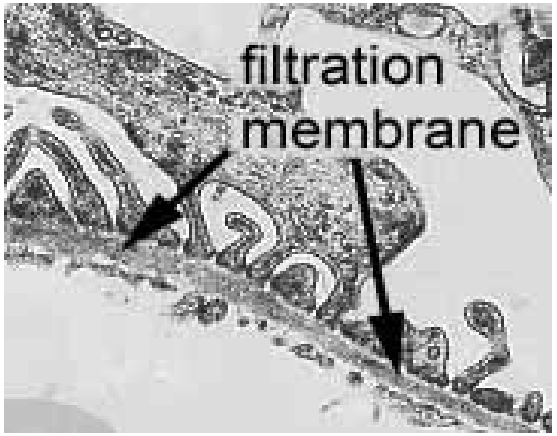
- Glomerular capillaries: with fenestrated endothelium.
- Podocytes are epithelial cells covering the capillaries.
- The filtration membrane in between the podocytes and the capillary endothelium.
- Mesangium is a supporting tissue consisting of mesangial cells and matrix.

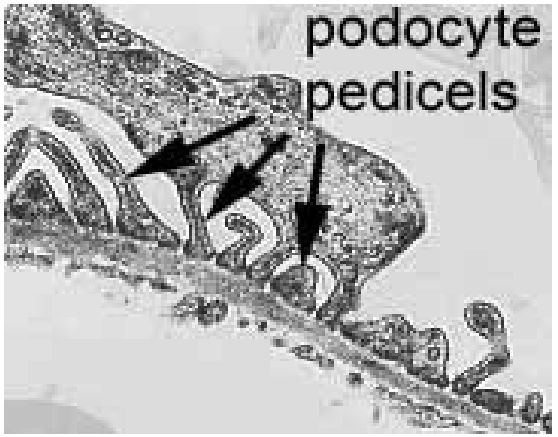
# The renal system

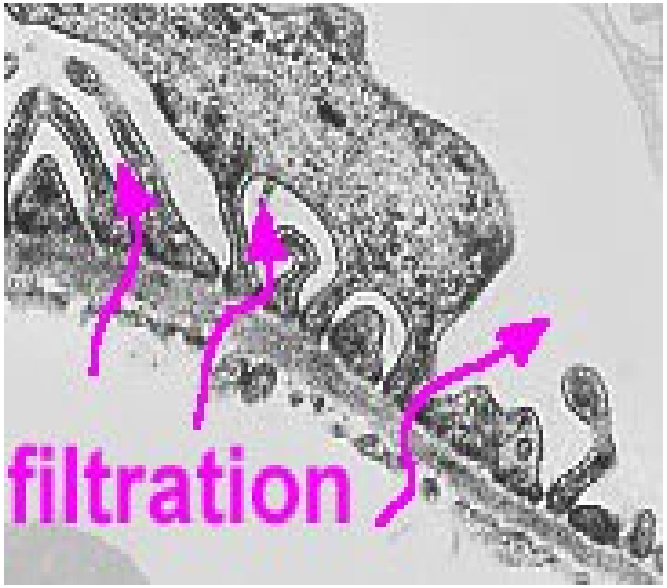


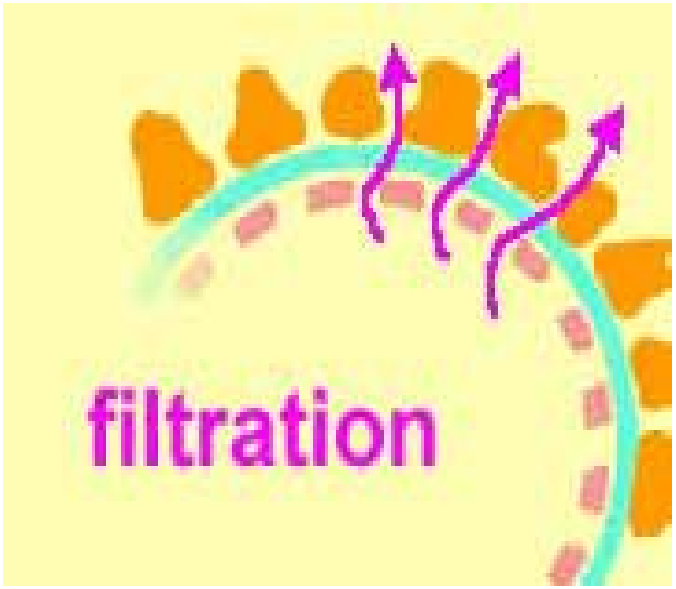
# The renal system



# The renal system

The GBM is formed by the fusion of the endothelial and epithelial basement membrane.

**Type IV collagen** is the major constituent of the GBM.

GBM woks as a sieve that is both size and charge selective.

The endothelial cells produce NO and endothelin-1 they are implicated in inflammatory – processes.

Mesangial cells have phagocytic properties — endocytosis of immune complexes, intracellular production of prostaglandins and reactive oxygen species cause injury to the glomerulus.

# Immune mediated kidney diseases

## Allergic interstitial nephritis

Usually drug-induced: e.g methicillin, nonsteroidal agents, rifampin, sulfa, cimetidine, cephalosporins, and 5-aminosalicylates.

Patient present with acute renal failure 7-0 days post initial drug intake.

Kidney injury corresponds to type IV hypersensitivity reaction.

# Allergic interstitial nephritis

**Clinical findings** : fever, rash, proteinuria, haematuria, eosinphpilia.

**Histological findings**: tubulointerstitial inflammation rich in T cells, plasma cells with occasional eosinophils.

The glomeruli are spared from any inflammatory effects.

**Treatment**: stop the drug+ early steriods.

# IgA Nephropathy

Known as Berger’s disease.

It is the most common cause of glomerulonephritis in the world.

It usually occur after a respiratory infection ?days??

The hallmark of this disease is deposition of IgA in the mesangium leading to focal mesangial expansion.

# IgA Nephropathy-Pathogenesis

It is thought that a defect in IgA regulation secondary to environmental stimuli may contribute to disease pathogenesis.

This is supported by high level of circulating IgA in ~50% of patients, increased circulating immune complexes and increased number of IgA-specific B and T lymphocytes.

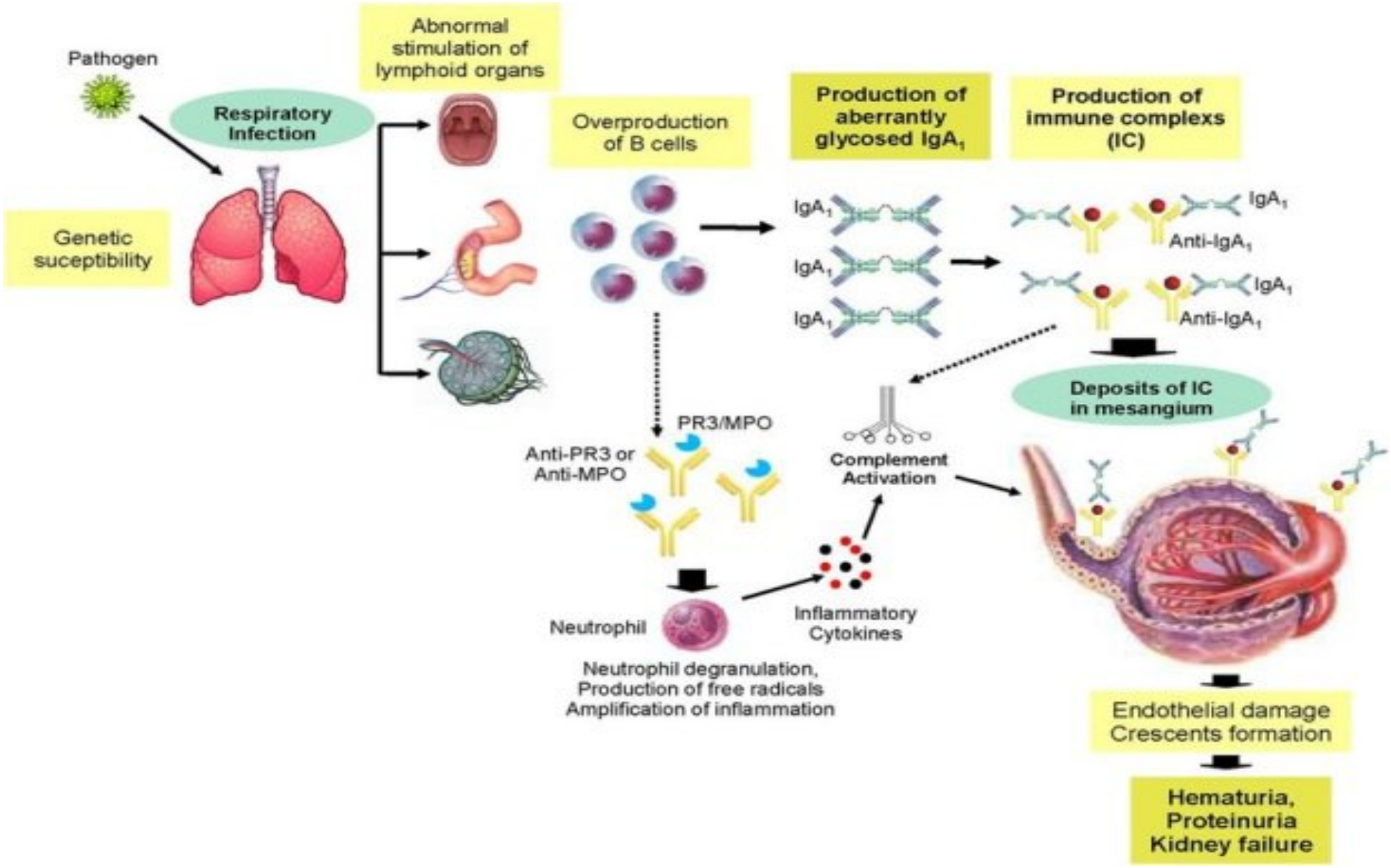
# IgA Nephropathy- Pathogenesis

The association with respiratory tract infections may also infer that mucosal immunity may play a role exaggerated — mucosal IgA response or decreased clearance may explain the elevated levels of plasma IgA in this disease.

Circulating IgA-containing complexes binds to fibronectin (a component of the GBM).

In the glomeruli, these immune complexes activate the alternative complement pathway causing inflammation that — damages kidney tissues.

# Pathogenesis



# IgA Nephropathy

**Diagnosis**: kidney biopsy.

**Prognosis**: usually follows benign course.

15% & 20% of patients may reach end stage renal disease at 10&20 years respectively.

**Treatment:**

ACEI±ARBs: to decrease the proteinuria and for their renoprotective properties.

Cytotoxic agents and steroids for aggressive renal disease.

# Acute post-streptococcal glomerulonephritis

APSGN is an immune complex disease that follows pharyngitis and skin infections from nephritogenic strains of group A streptococci.

It occur 10 days after streptococcal pharyngitis or 21 days after streptococcal skin infection (impetigo).

# APSGN

Circulating immune complexes appear early in the course of the disease and are associated with hypocomplementemia.

Subendothelial IC deposits are primarily responsible for complement activation and influx of inflammatory cells.

Damage to the epithelial cells results in proteinuria.

# APSGN

Two prominent proteins have been implicated in the pathogenesis of APSGN: streptokinase (Ska) and streptococcal pyrogenic exotoxin B (SPEB).

They are proposed to be the streptococcal antigen involved in the immune complexes.

For example: SPEB can bind plasmin to form a complex that can activate the complement cascade.

# APSGN

SPEB and other streptococcal pyrogenic exotoxins (SPEA and SPEC) are considered superantigens, which can stimulate T-cell proliferation.

The result is excessive production of cytokines, which mediate inflammation and tissue injury.

**Clinical course**: benign, mostly resolves spontaneously.

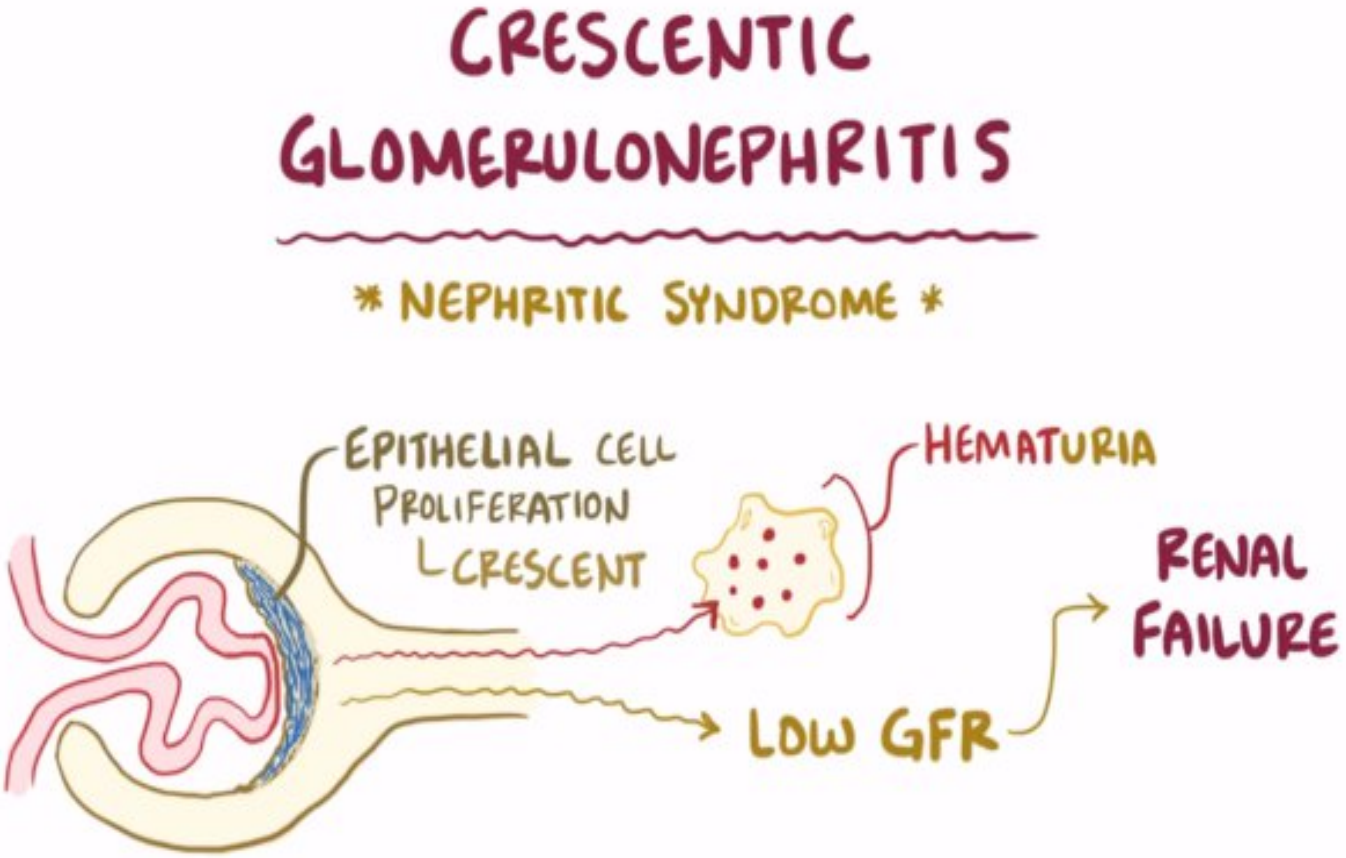
# Rapidly progressive glomerulonephritis

RPGN is a severe form of glomerulonephritis that leads to end-stage renal disease invariably in a matter of weeks.

Patients present with acute nephritis picture associated with progressive loss of renal function.

There are three types of RPGN, depending on the mechanism of injury.

# RPGN

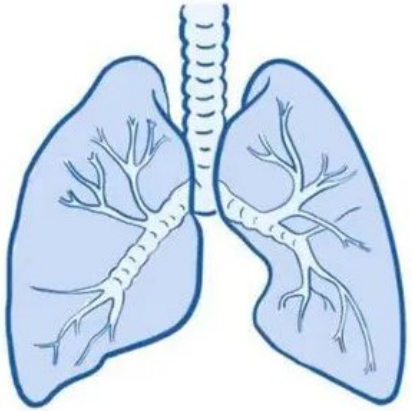

CRESCENTIC
GLOMERULONEPHRITIS
* NEPHRITIC SYNDROME *
EPITHELIAL CELL
PROLIFERATION
└CRESCENT
HEMATURIA
RENAL
FAILURE
LOW GFR

# RPGN- Goodpasture's syndrome

Goodpasture's syndrome is RPGN type I or anti-GBM disease.

Characterized by the presence of circulating antibodies to an antige in the GBM.

The circulating antibody also bin to the alveolar BM



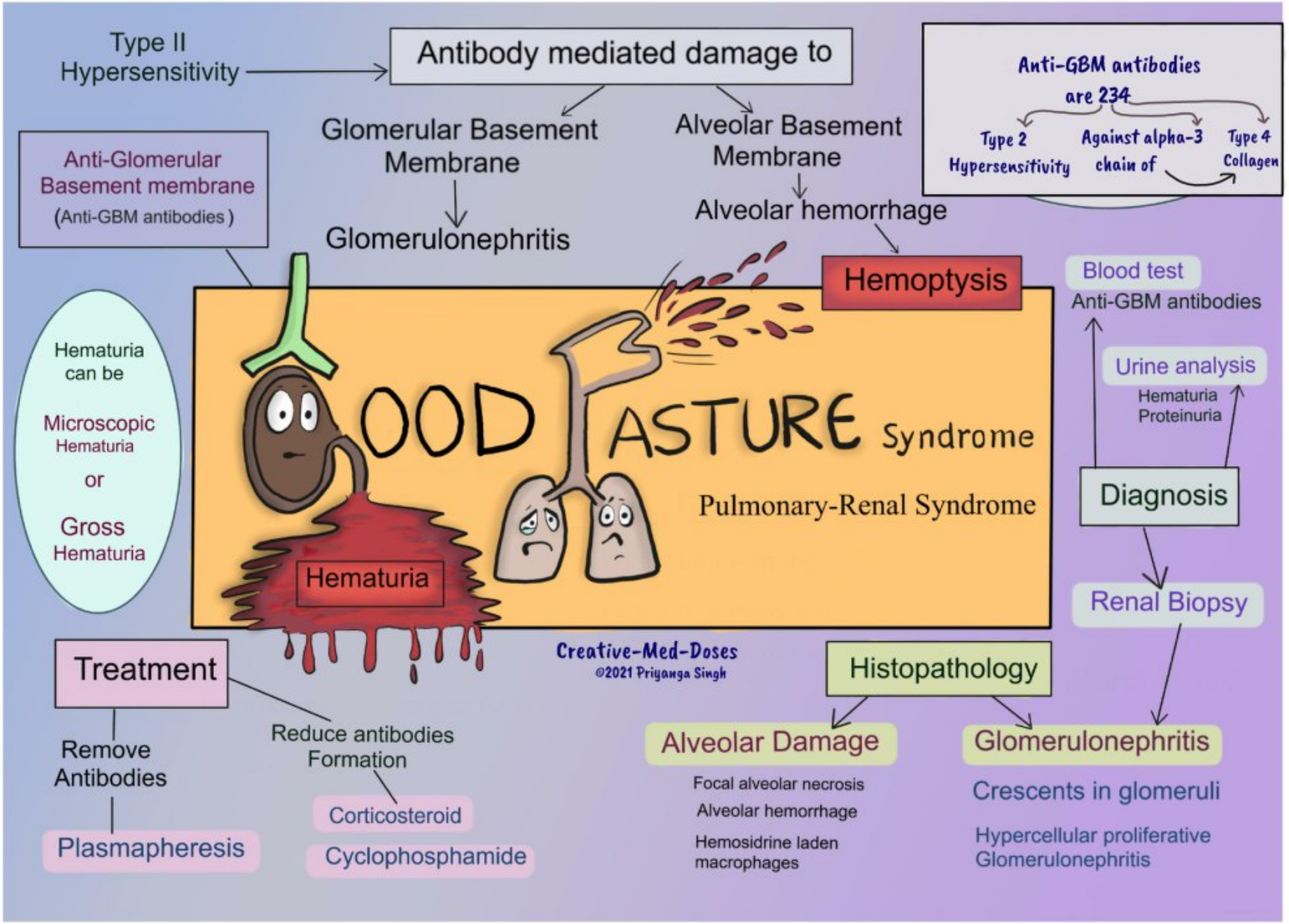
# GPS- Pathoimmunogenesis

The autantigen  has been identified to be part of the alpha-3 chain of type IV collagen.

The alpha-3 chain is common for both alveolar and glomerular BMs.

Autoreactive B-&T-lymphocytes are involved in production of autoantibodies to this antigen.

The result is renal failure, pulmonary hemorrhage and hemoptysis.


Type II Hypersensitivity
Antibody mediated damage to
Glomerular Basement Membrane
Alveolar Basement Membrane
Anti-GBM antibodies are 234
Type 2 Hypersensitivity
Against alpha-3 chain of
Type 4 Collagen
Anti-Glomerular Basement membrane
(Anti-GBM antibodies)
Glomerulonephritis
Alveolar hemorrhage
Hemoptysis
Blood test
Anti-GBM antibodies
Urine analysis
Hematuria
Proteinuria
Diagnosis
Renal Biopsy
Hematuria can be
Microscopic Hematuria
or
Gross Hematuria
OOD ASTURE Syndrome
Pulmonary-Renal Syndrome
Hematuria
Creative-Med-Doses
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Treatment
Remove Antibodies
Plasmapheresis
Reduce antibodies Formation
Corticosteroid
Cyclophosphamide
Histopathology
Alveolar Damage
Focal alveolar necrosis
Alveolar hemorrhage
Hemosidrine laden macrophages
Glomerulonephritis
Crescents in glomeruli
Hypercellular proliferative Glomerulonephritis

# Goodpasture's syndrome

Diagnosis: measurement of anti-GBM antibody titer and other immune tests.

Treatment: The main treatment includes a combination of plasmapheresis, steroids, and cyclophosphamide.

Plasmapheresis is to remove circulating antibodies.

Steroids and cyclophosphamide prevent further antibody production.

# RPGN- Pauciimmune glomerulonephritis

Pauci-immune glomerulonephritis is type III RPGN.

It is a form of necrotizing glomerulonephritis.

Characterized by minimal or absence of immune deposits in the kidney.

Patients presents with renal failure, and systemic symptoms related to the respiratory tract, skin, nervous, and musculoskeletal systems.

# RPGN- Pauciimmune glomerulonephritis

Most patients will have ANCA antibody that is invariably present in other form of vasculitides.

Two target antigens have been identified by ANCA – proteinase 3 (PR-3) and myeloperoxidase.

About 75–80 % of pauciimmune glomerulonephritis cases exhibit the P-ANCA pattern (Antibodies to the myeloperoxidase Antigen).

# RPGN

## TYPE I

* ANTI-GBM ANTIBODY
  - Goodpasture Syndrome

## TYPE II

* IMMUNE-COMPLEXES

ANTIGEN — ANTIBODY

- Poststreptococcal glomerulonephritis
- Lupus
- IgA nephropathy
- Henoch-Schonlein purpura

## TYPE III

* PAUCI-IMMUNE
  - NO ANTI-GBM
  - NO IMMUNE COMPLEXES
* ANCA in BLOOD

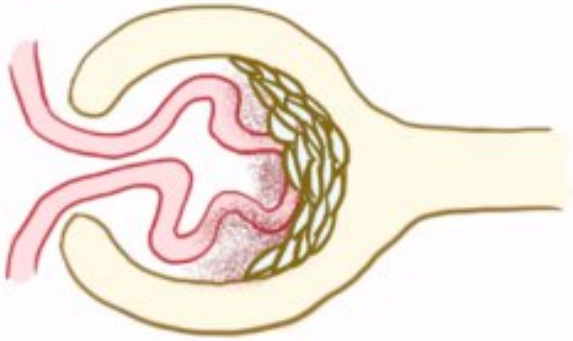
ANTI NEUTROPHILIC CYTOPLASMIC ANTIBODY

- cANCA
  - Wegener granulomatosis
- pANCA
  - Microscopic polyangiitis
  - [Churg-Strauss syndrome]

→ Granulomatous inflammation, asthma, eosinophilia

## IDIOPATHIC

* NO IDENTIFIABLE CAUSE



# Mempranoprolifrative glomerulonephritis

MPGN is a severe type of glomerulonephritis that is often idiopathic in nature.

It affects patients from age 8 to 30.

Patients usually present with a nephritic picture :hematuria with red cell casts, nonnephrotic- range proteinuria, hypertension, and renal insufficiency.

# MPGN

**MPGN is classified into three types:**

(depending on the location of dense deposits seen on EM)

**Type I:**

The most benign lesion.

There is immune deposits in the mesangium and subendothelial space.

Can be associated with systemic disease e.g. hepatitis C & B infection, SLE, subacute bacterial infection (SBE).

# MPGN

**Type II MPGN:**

Characterized by the lack of immune complexes and the presence of circulating C3 nephritic factor (C3NeF): an IgG autoantibody against the alternative complement pathway C3 convertase.

C3NeF binding to the enzyme creates a stable C3bBb complex that is resistant to enzymatic inactivation and allows consumption of C3.

The persistent hypocomplementemia and accumulation of terminal C5b-9 complement complex deposits in the glomeruli cause tissue damage.

# Minimal change disease

MCD is the most common cause of nephrotic syndrome in children under age 10.

**Histologically** there is effacement of the epithelial foot processes and absence of immune deposits.

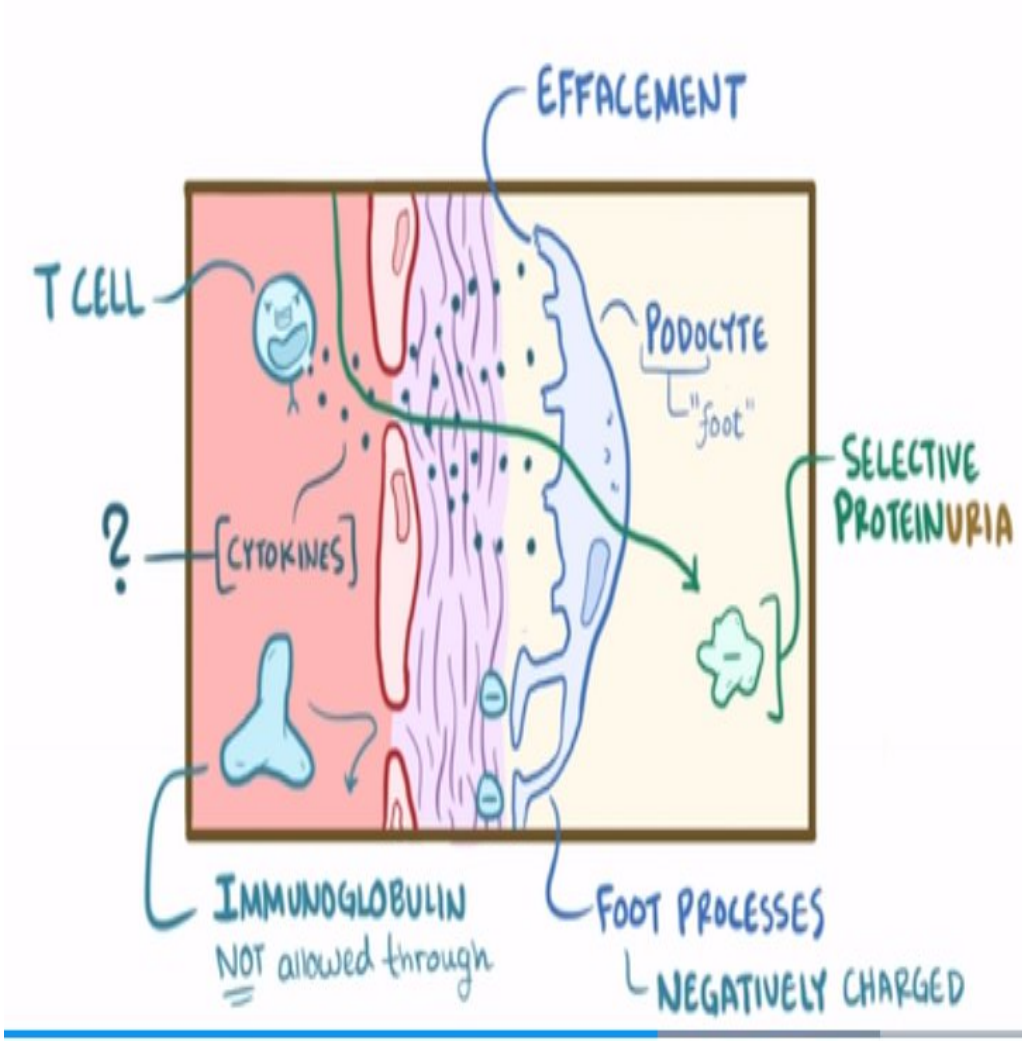
It is suggested that MCD is a T-lymphocyte disease: respond to steroids and cyclosporine.

It is strongly associated with Hodgkin's lymphoma .increased cytokines production? —

# Minimal change disease

A glomerular permeability factor (GPF) derived from T-cells is suggested to cause damage to the foot processes and result in proteinuria this —

GPF has TNF-like activity causing epithelial damage and loss of the negative charge of the podocytes.



# Focal segmental glomerulosclerosis

FSGS is a common cause of idiopathic nephrotic syndrome in adults.

FSGS is classified as primary or secondary

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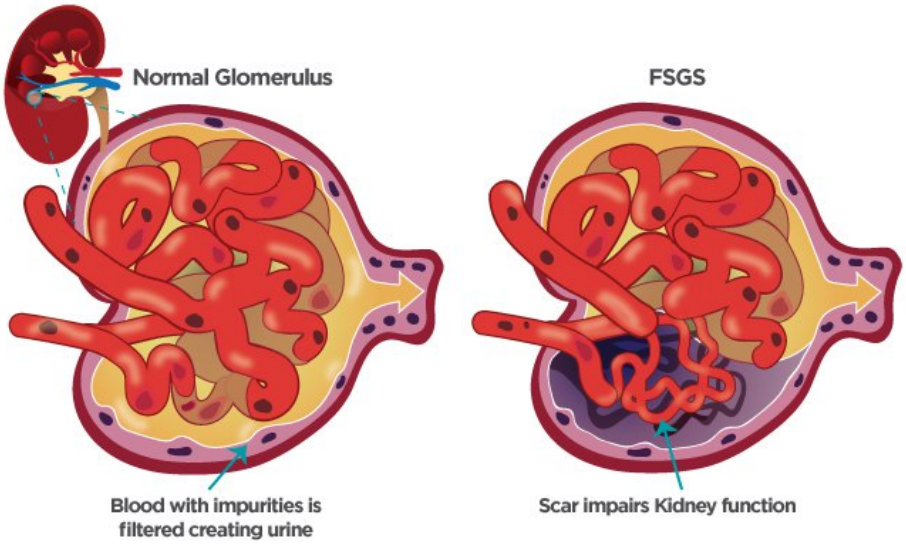
TGF-β contribute t
glomerulosclerosis



# Focal segmental glomerulosclerosis

It is histologically similar to MCD: effacement of foot processes and lack of immune deposits FSGS may be a more severe form of the MCD.

A circulating toxin found in the serum of FSGS patients that can increase permeability of isolated glomeruli to albumin.

This toxin (or cytokine) appears to cause injury to the podocytes similar to the GPF found in MCD.

# Membranous nephropathy

Membranous nephropathy (MN) is a type of nephrotic syndrome characterized by thickening of the capillary walls of the glomeruli.

Classification: idiopathic or secondary

Secondary is associated with SLE, malignancy, infections, drugs e.g. penicillin, NSAID, gold.

Histologically: there is immune deposits of IgG and C3 along the capillary walls.

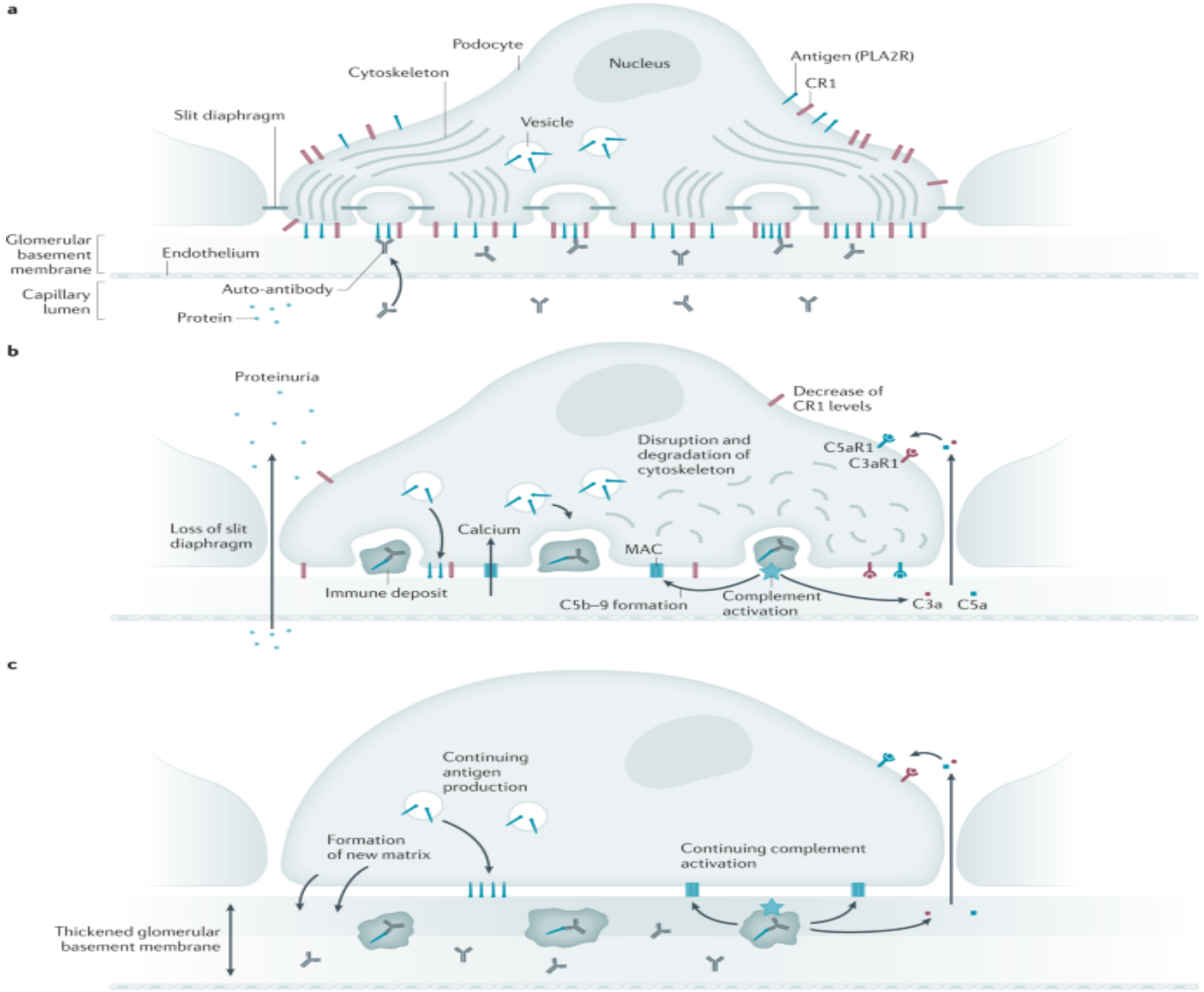
# Membranous nephropathy

There is immune complex mediated damage to the GBM.

Autoantibodies binds autoantigens (in the GBM/podocytes) forming immune complexes.

**Possible autoantigen**: PLA2R, NEP.

PLA2R is a podocytes antigen, and antibodies to PLA2R are specific for MN (found in ~80% of cases).


a
Podocyte
Nucleus
Antigen (PLA2R)
CR1
Cytoskeleton
Slit diaphragm
Vesicle
Glomerular basement membrane
Endothelium
Capillary lumen
Auto-antibody
Protein
b
Proteinuria
Decrease of CR1 levels
Disruption and degradation of cytoskeleton
C5aR1
C3aR1
Loss of slit diaphragm
Calcium
MAC
Immune deposit
C5b–9 formation
Complement activation
C3a
C5a
c
Continuing antigen production
Formation of new matrix
Continuing complement activation
Thickened glomerular basement membrane

# Lupus Nephritis

Lupus nephritis is a form of renal disease that occur in SLE patients.

SLE is an autoimmune disease mediated mostly by autoantibodies and immune complexes.

**Autoantigens**: components of the cell nucleus mainly DNA resulting in antinuclear antibodies ANA, anti-dsDNA antibodies.

# Lupus Nephritis

**Target organ/s**: systemic, secondary to immune complex deposition in the skin, joints, lungs, blood vessels, heart, kidney, and brain.

Almost **all** SLE patients will have renal involvement on renal biopsy, however only 50–70% of patient will have clinically detectable disease: abnormal urinalysis, hematuria, proteinuria, or pyuria, hypertension, renal insufficiency.

# Lupus Nephritis

Immune complex deposits in the glomeruli are primarily responsible for the inflammatory process that causes glomerular damage IC activate — complement and recruits inflammatory cells.

Immune complexes identified in lupus nephritis include anti-nuclear antigens, Sm, La (SS-B), Ro (SS-A), ribosomes , and C1q.

# Lupus Nephritis

**Lupus nephritis is currently classified into six types-** based on kidney biopsy findings:

1. Class I: mesangial deposits without mesangial hypercellularity.
2. Class II: mesangial deposits with mesangial hypercellularity.
3. Class III: focal glomerulonephritis.
4. Class IV: diffuse glomerulonephritis.
5. Class V: membranous nephropathy.
6. Class VI: advanced sclerosing lesions (ESRD).