Immunologic Basis of Kidney Disease

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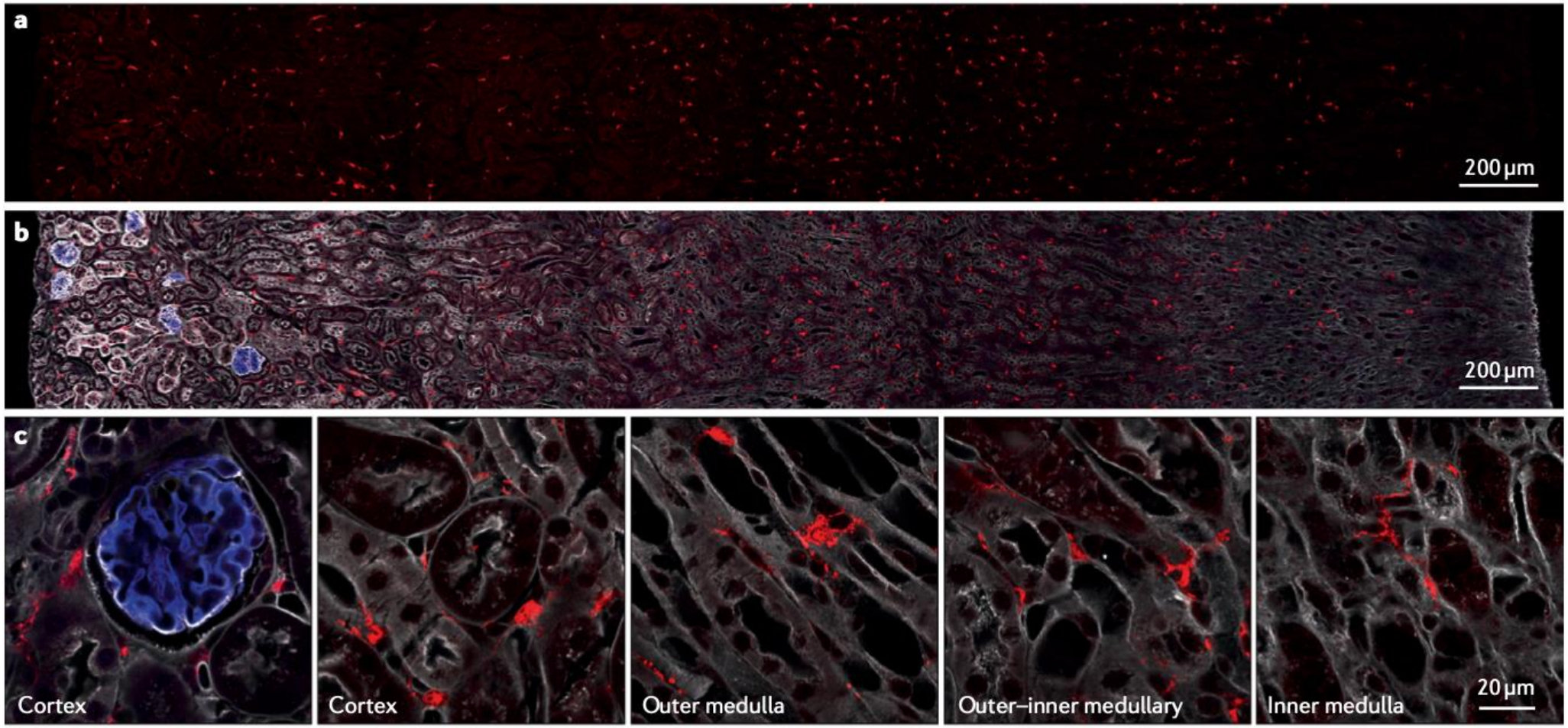
Disclosures

- I have no financial disclosures

Objectives

- Understand the role of lymphatics in the interplay between the innate and adaptive immune responses following kidney injury
- Understand how specific disorders in the immune system result in the pathogenesis of various glomerular diseases

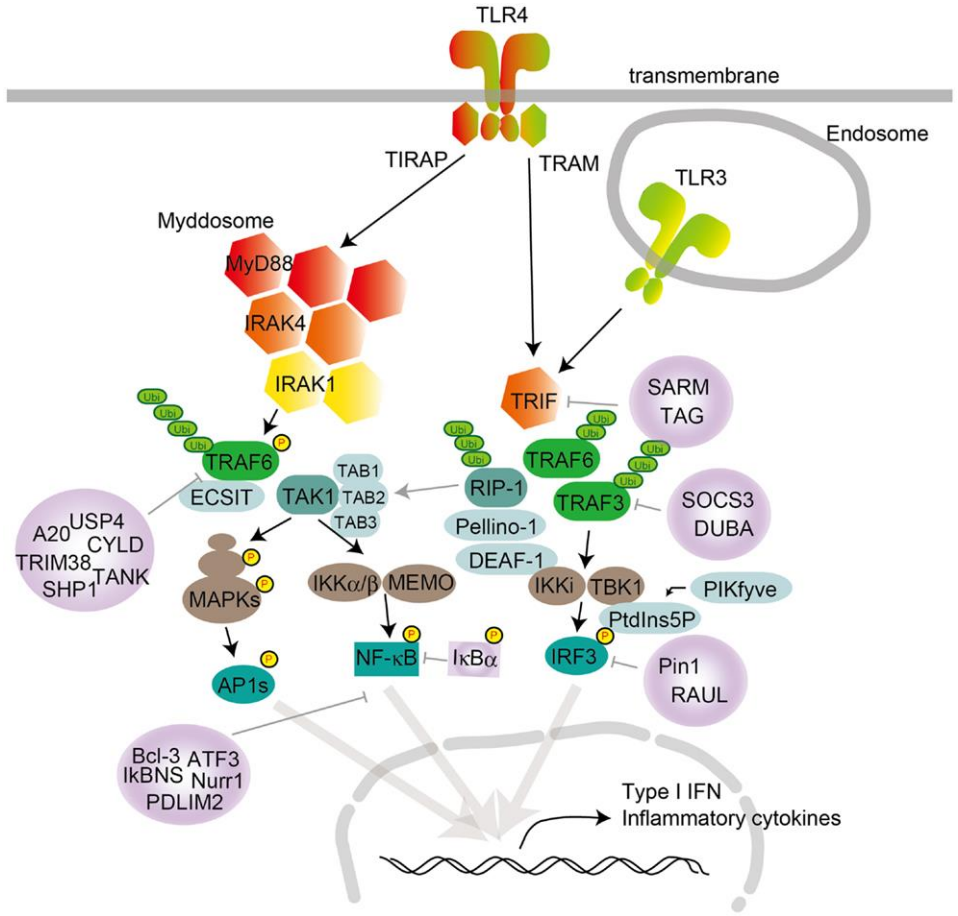
Dendritic cells in kidney



CX3CR1

Source: Kurts C, Ginhoux F, Panzer U. Nat Rev Nephrol. 2020;16(7):391-407.

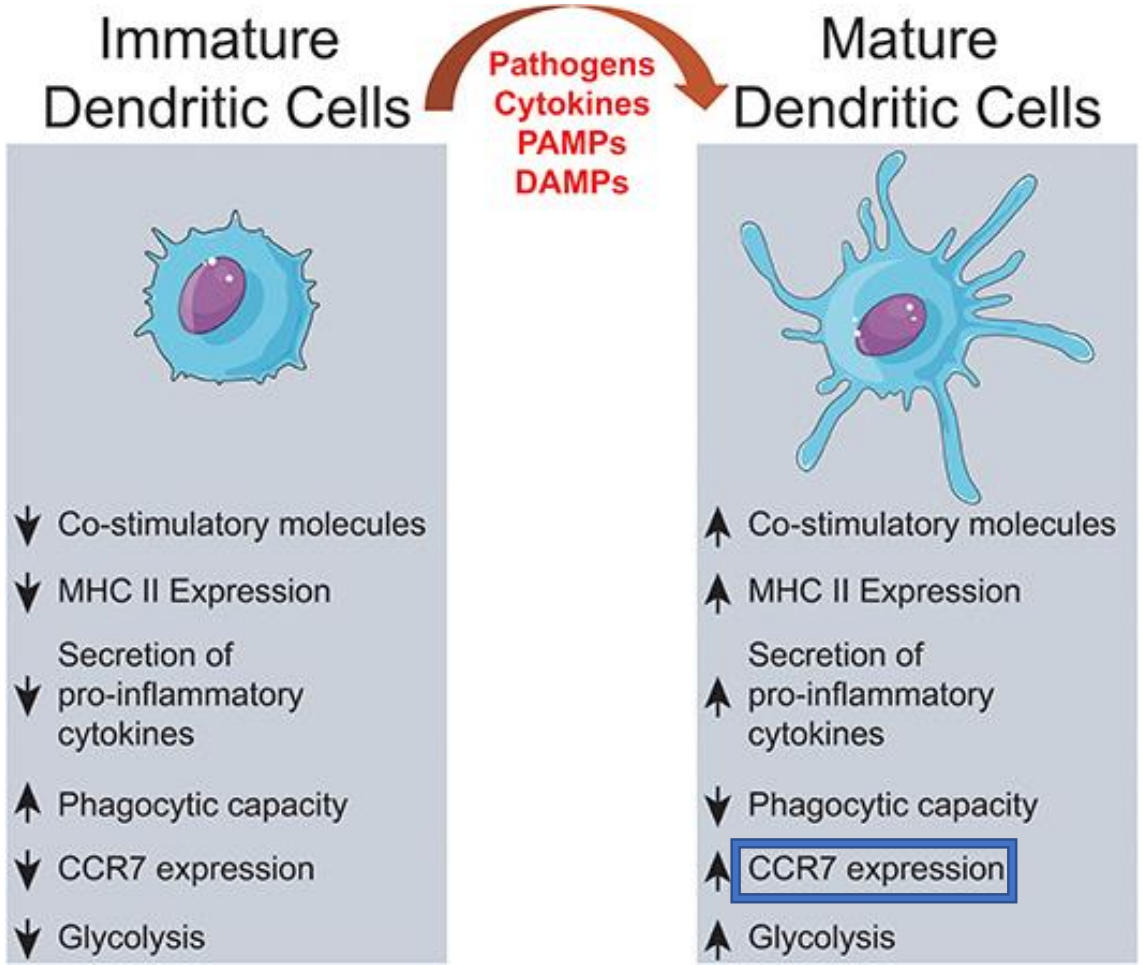
Tissue-resident dendritic cell biology



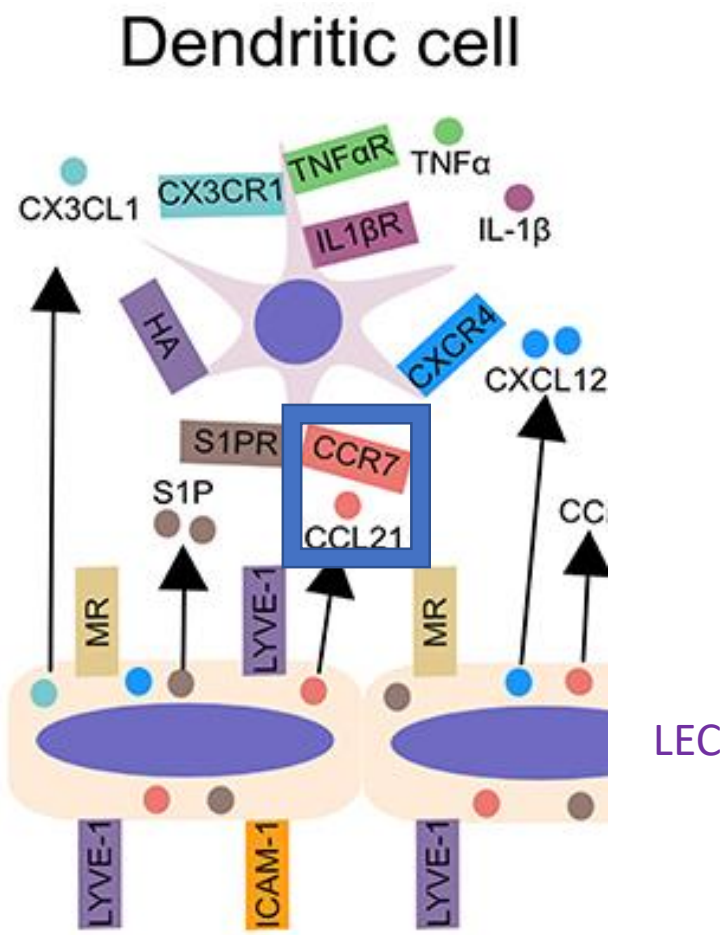
- Toll-like receptors (TLRs)
- Pathogen-associated molecular patterns (PAMPS)
  - Lipopolysaccharide (LPS)
  - Viral nucleic acids
- Damage-associated molecular patterns (DAMPS)
  - Heat shock proteins
  - Histones

Source: Kawasaki T, Kawai T. Front Immunol. 2014;5:461.

Dendritic cell activation and migration

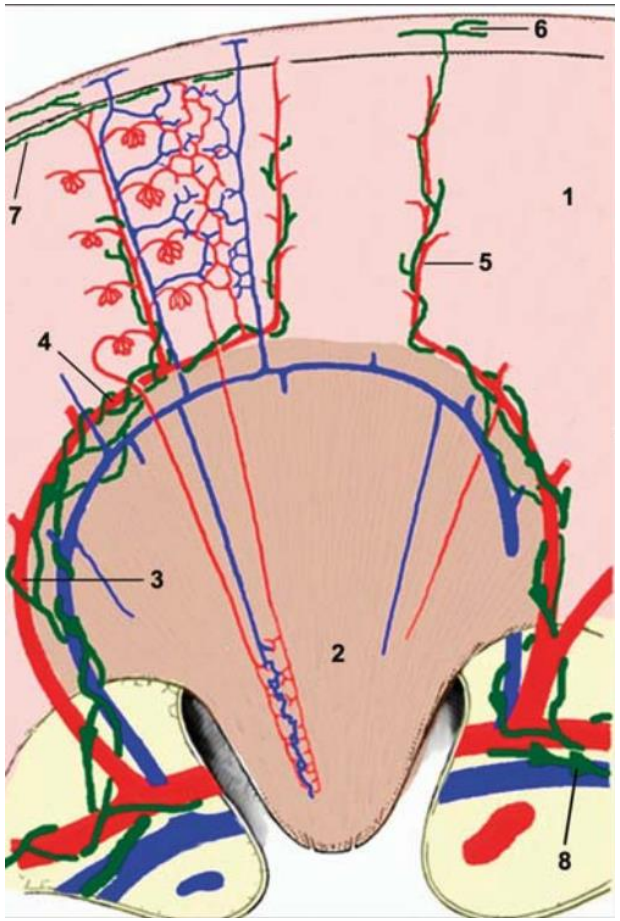


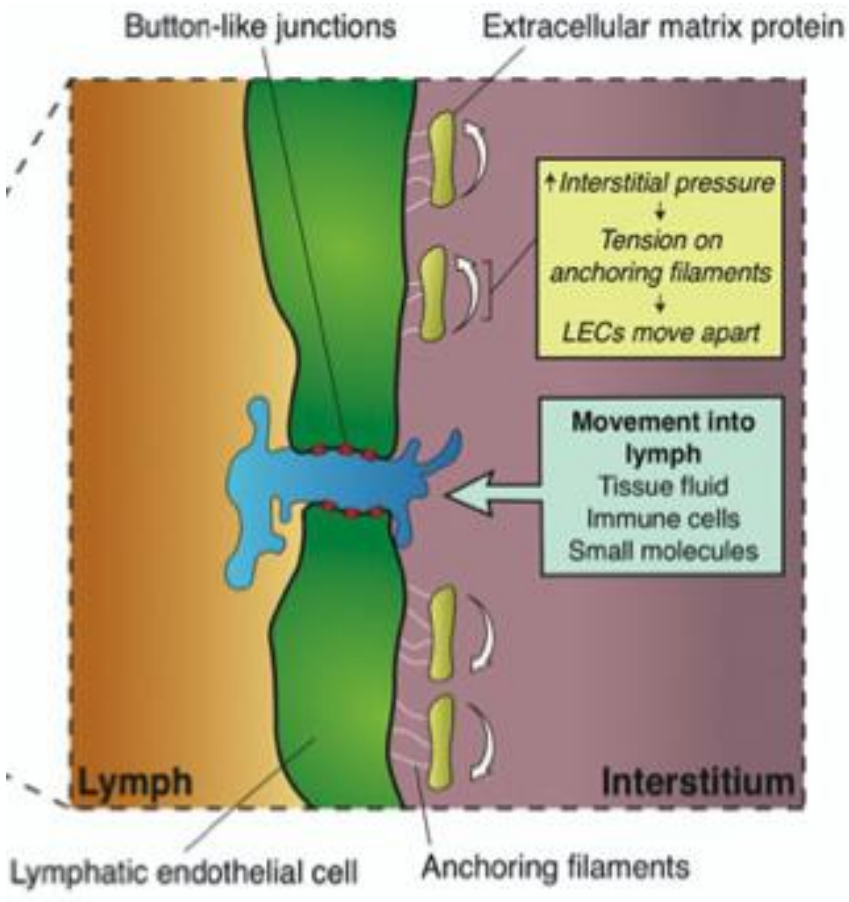
Source: Patente TA et al. Front Immunol. 2018;9:3176



Source: Hampton HR, Chtanova T. Front Immunol. 2019;10:1168

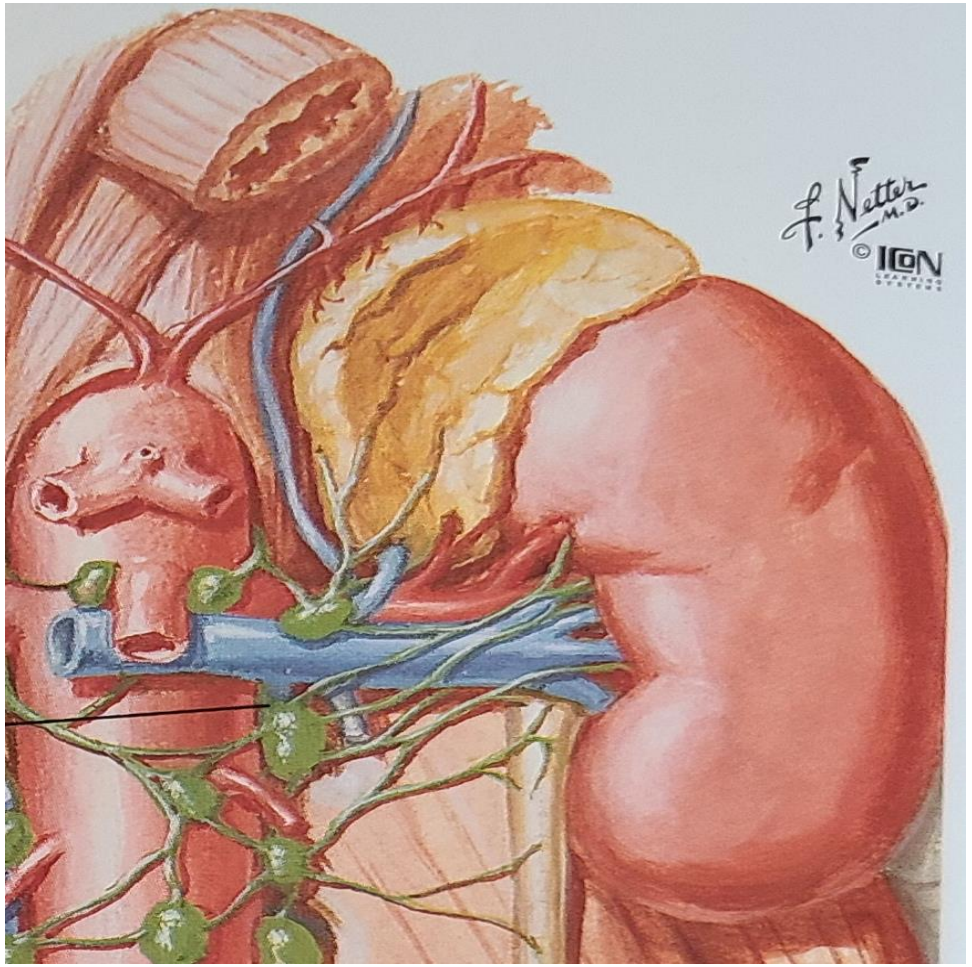
Kidney: Lymphatic microanatomy

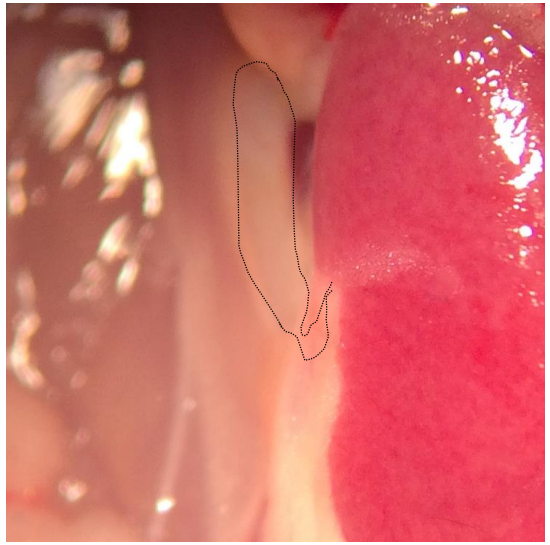


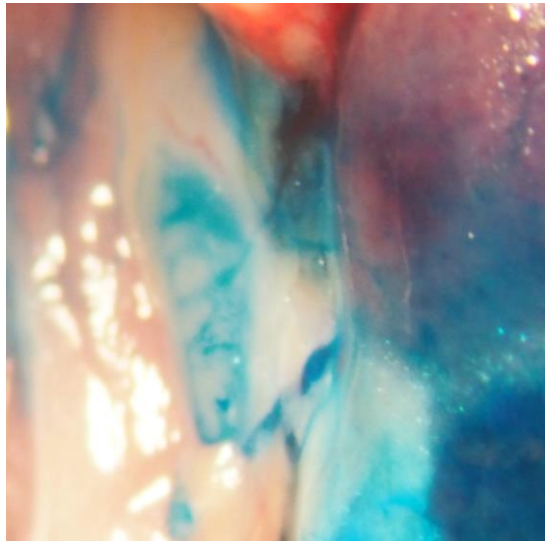


Sources: Seeger H, Bonani M, Segerer S. Nephrol Dial Transplant. 2012;27(7):2634-41.
Jafree DJ, Long DA. J Am Soc Nephrol. 2020;31(6):1178-90.

Kidney-draining Lymph Node (KLN)

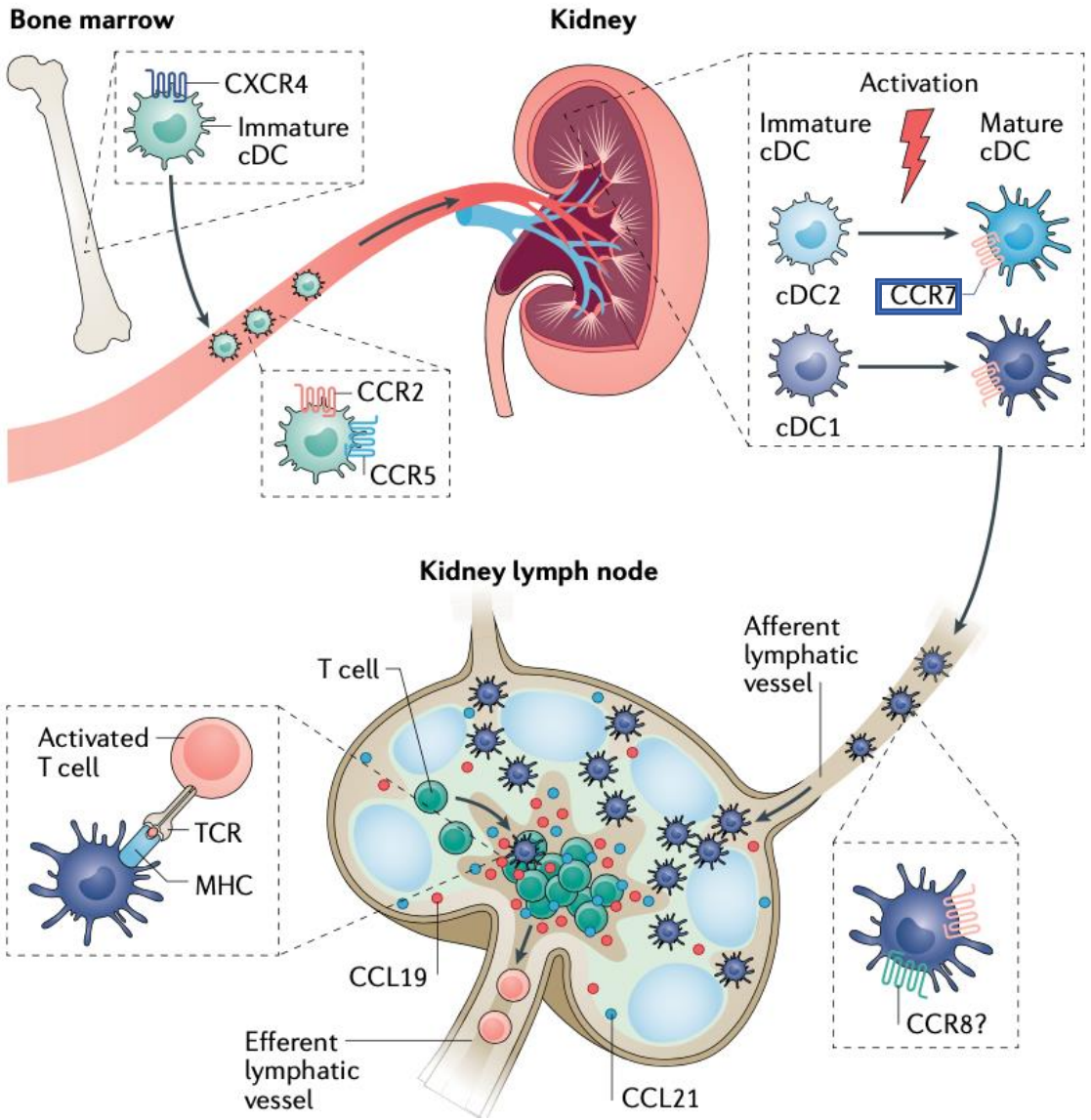






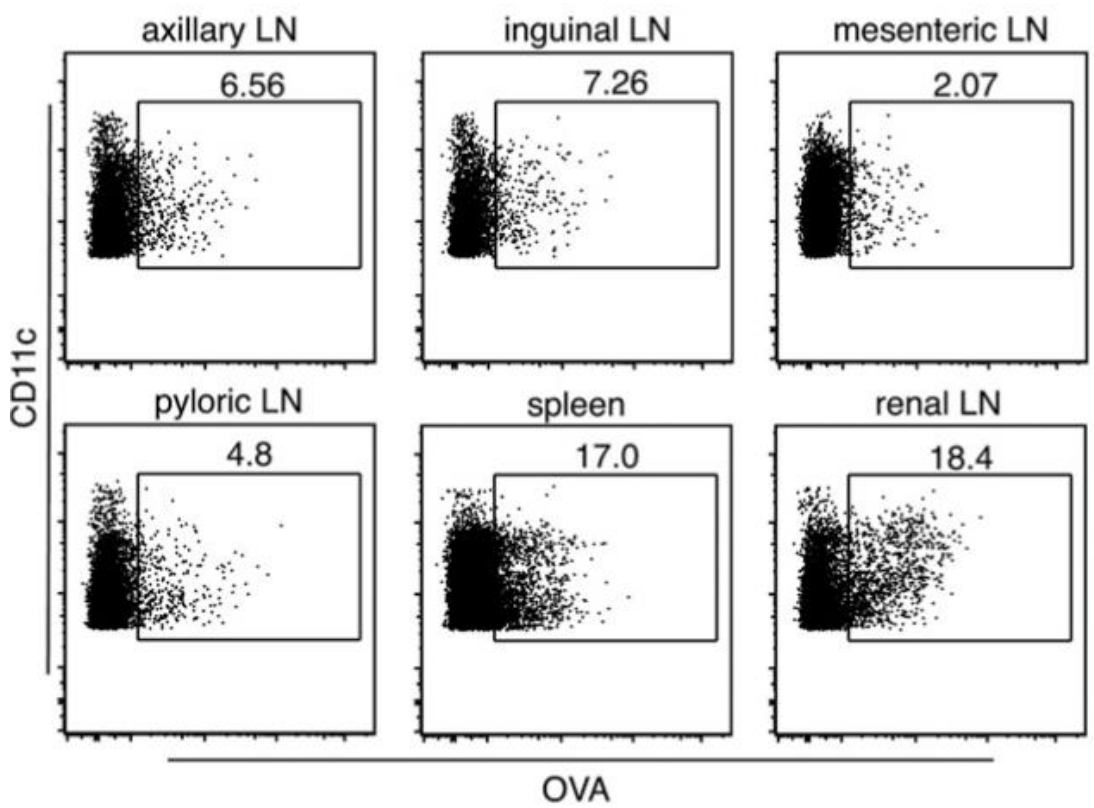
Source: Netter F. Atlas of Human Anatomy, 3rd edition. 2003: Plate 329.

Cellular Migration to KLN



Source: Kurts C, Ginhoux F, Panzer U. Nat Rev Nephrol. 2020;16(7):391-407.

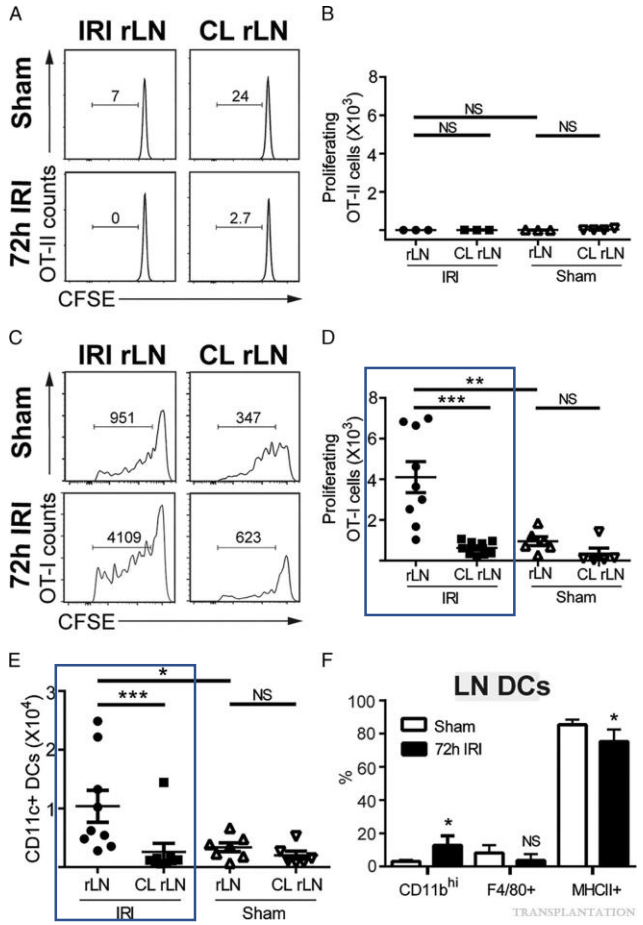
Role of Kidney and KLN in Tolerance Induction



- Filtered antigens from kidney traffic to KLN via afferent lymphatics
- BATF3^{+} KLN-resident dendritic cells internalize filtered antigens and induce apoptosis of CD8^{+} T cells→**tolerance**

Source: Gottschalk C, Damuzzo V, Gotot J, Kroczek RA, Yagita H, Murphy KM, Knolle PA, Ludwig-Portugall I, Kurts C. J Am Soc Nephrol. 2013;24(4):543-9.

KLN after Kidney IRI (Day 3): Dendritic cells cross-present antigen to CD8$^+$ T cells



Source: Snelgrove SL, Lo C, Hall P, Lo CY, Alikhan MA, Coates PT, Holdsworth SR, Hickey MJ, Kitching AR. Transplantation. 2017;101(5):1013-24.

Objectives

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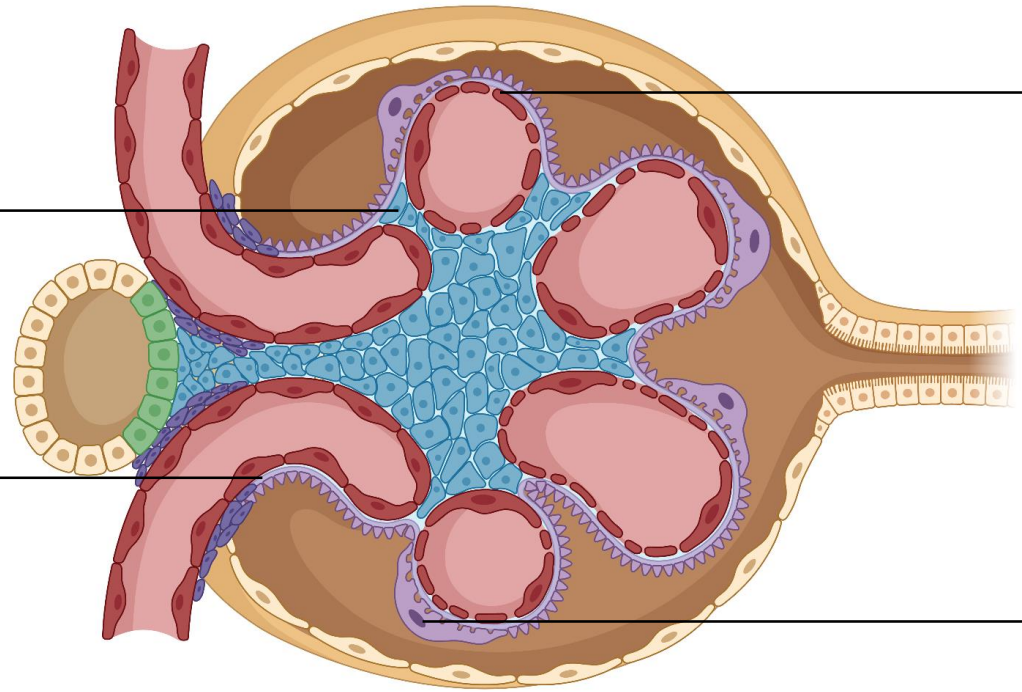
- Understand how specific disorders in the immune system result in the pathogenesis of various glomerular diseases

Immunological Basis of Glomerular Diseases: Primary sites of injury

Mesangial injury
- IgA nephropathy

Glomerular basement membrane (GBM) injury
- Anti-GBM disease
- Post-infectious glomerulonephritis



Vascular injury
- Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis
- Atypical hemolytic-uremic syndrome

Podocyte injury
- Membranous nephropathy
- Minimal change disease/idiopathic focal segmental glomerulosclerosis (FSGS)

General injury
- Lupus nephritis
- Deposition diseases

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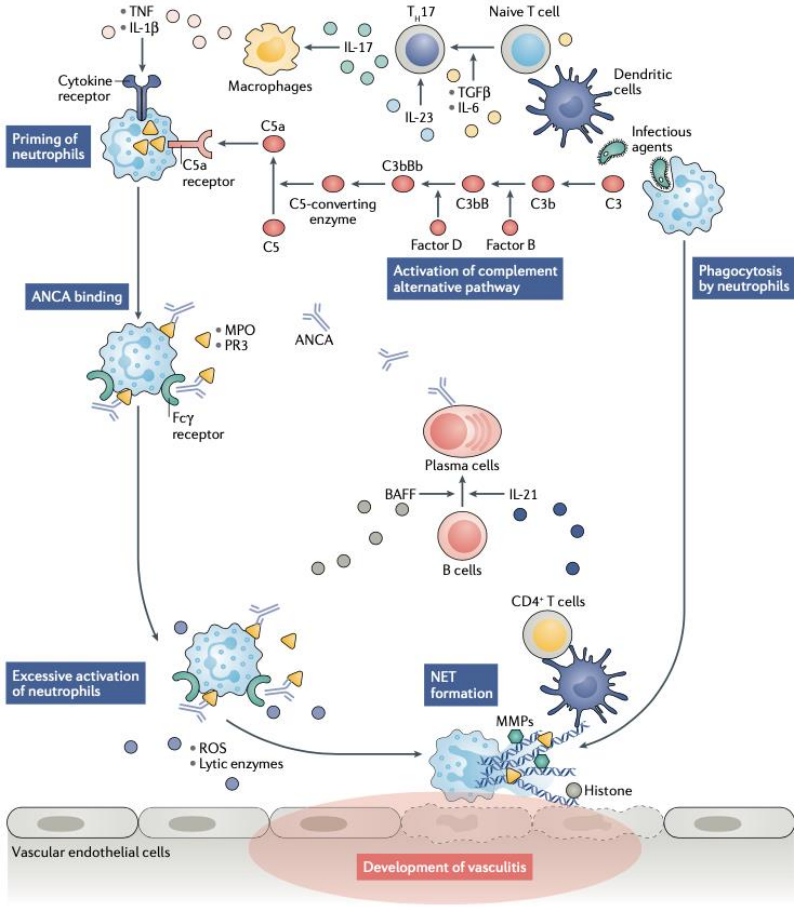
Vascular Injury: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis

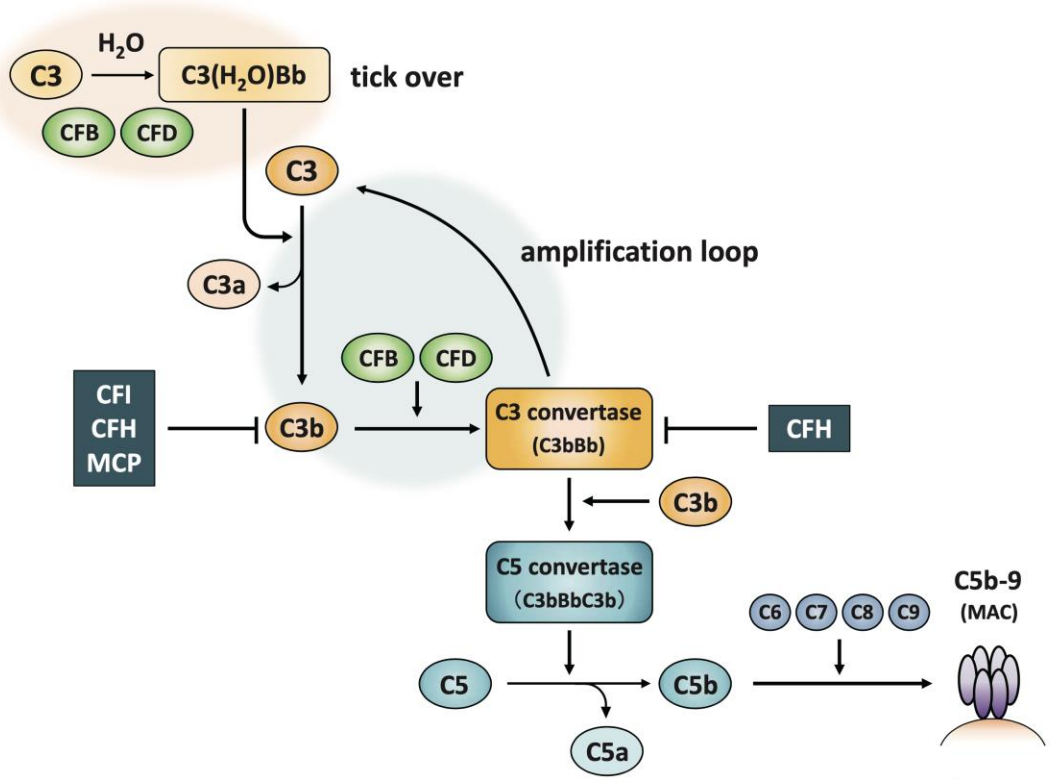
- Neutrophil priming after immune stimulus (e.g., infection)
- Binding of antibodies against myeloperoxidase (MPO) or proteinase 3 (PR3) to antigens on neutrophil cell membrane
  - Sustained neutrophil activation
- Excessive formation and decreased degradation of neutrophil extracellular traps (NETs)
- Damage to endothelium by NETs
  - ANCAs degraded by NETs-->pauci-immune



Source: Nakazawa D, Masuda S, Tomaru U, Ishizu A. Nat Rev Rheumatol. 2019;15(2):91-101.

Vascular Injury: Atypical Hemolytic-Uremic Syndrome (aHUS)

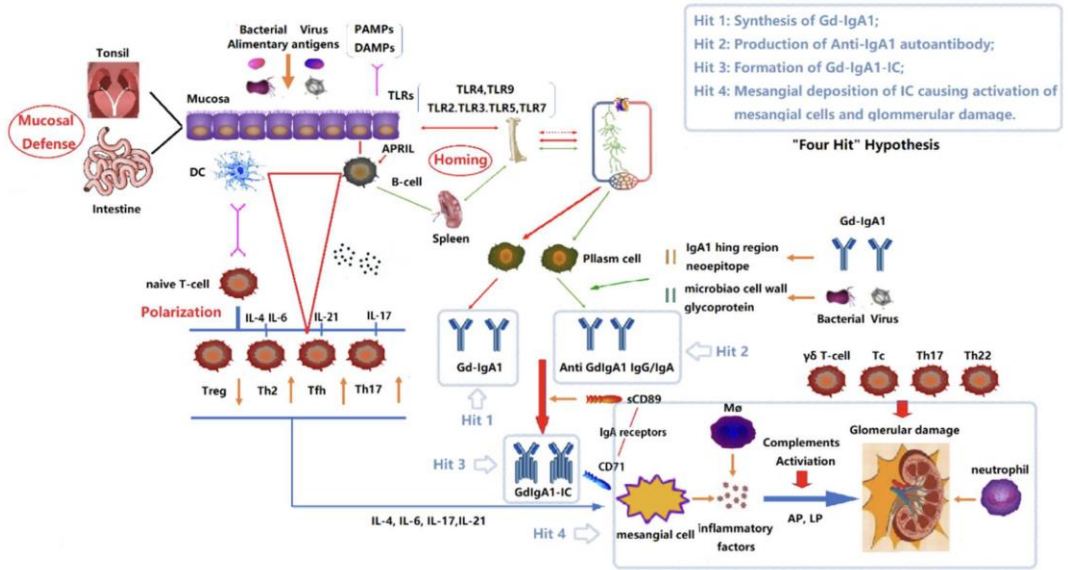
- Excessive activation of alternative complement pathway
- Most common cause is mutation in regulatory protein complement factor H (CFH) (20-30% of cases)
  - Mutations in factor I and membrane cofactor protein (MCP)
  - Antibodies to factor H
  - Excessive activation of C3
- Endothelial damage, microvascular thrombi→thrombocytopenia, microangiopathic hemolytic anemia, organ damage



Source: Yoshida Y, Kato H, Ikeda Y, Nangaku M. J Atheroscler Thromb. 2019;26(2):99-110.

Mesangial Injury: IgA Nephropathy

- Four-hit hypothesis
  - Synthesis of undergalactosylated IgA1 by mucosal lymphoid tissue
    - Tonsils in oral mucosa
    - Peyer's patches in intestines
  - Production of anti-IgA1 autoantibodies
  - Formation of IgG-IgA1 and IgA1-IgA1 immune complexes
  - Mesangial deposition of immune complexes-->cytokine production and glomerular damage



Source: Chang S, Li XK. Front Med (Lausanne). 2020;7:92.

GBM Injury: Post-infectious GN

- Post-infectious (streptococcal)
  - Deposition of either circulating or *in situ* immune complexes in glomerulus
  - Culprit antigens include glyceraldehyde phosphate dehydrogenase (GAPDH) and streptococcal cationic proteinase exotoxin B (SpeB)
    - Can degrade GBM themselves or activate procollagenase and matrix metalloproteinases (MMPs)

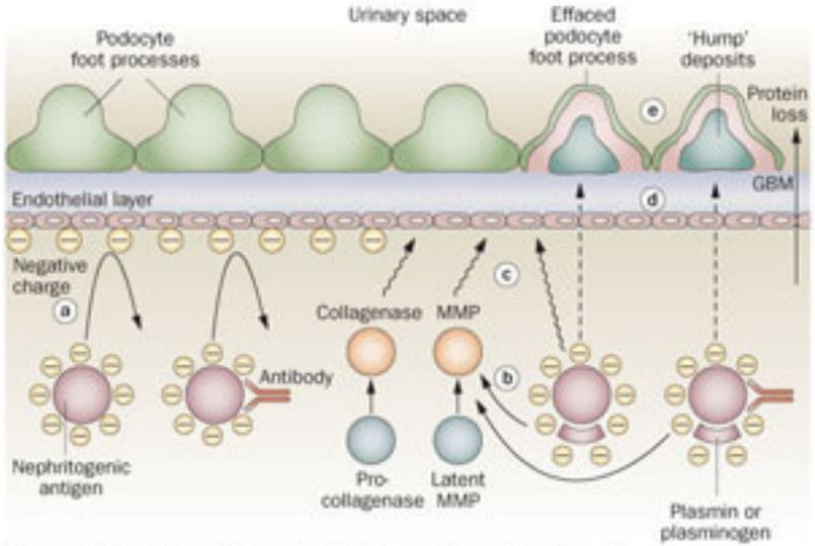
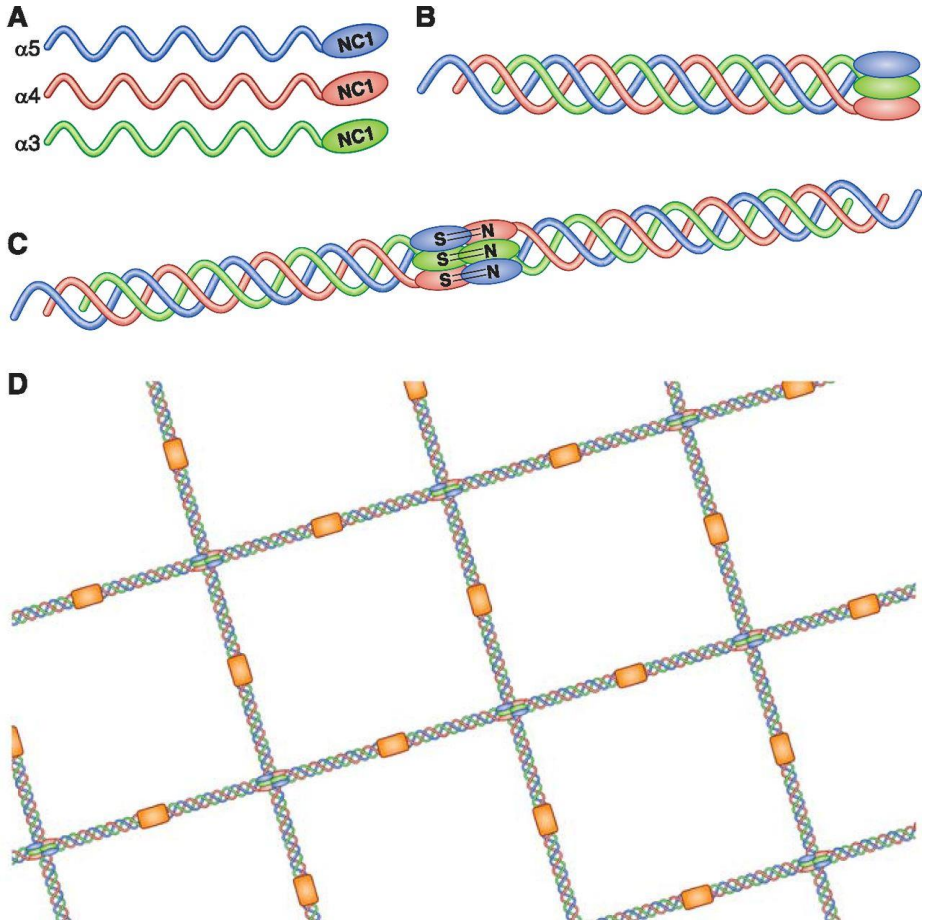


Figure 5 | Possible pathogenic mechanism of poststreptococcal glomerulonephritis. **a** | The putative nephritogenic antigens SpeB or zymogen and GADPH are normally repelled in both their free and antibody-bound forms by the negatively charged GBM. **b** | However, these antigens can interact with plasmin or plasminogen to activate procollagenase and latent MMPs. **c** | The active enzymes (and the nephritogenic antigen itself, in the case of SpeB or zymogen) degrade the GBM, and abolish its negative charge. **d** | The nephritogenic antigen and immune complexes can then pass through the damaged GBM and form the characteristic 'hump'-like deposits under the podocyte processes. **e** | Damage to the GBM also causes effacement of podocyte foot processes, which leads to loss of protein in the urine. Abbreviations: GADPH, streptococcal glyceraldehyde phosphate dehydrogenase; GBM, glomerular basement membrane; MMP, matrix metalloproteinase; SpeB, streptococcal cationic proteinase exotoxin B.

Source: Kanjanabuch T, Kittikowit W, Eiam-Ong S. Nat Rev Nephrol. 2009;5(5):259-69.

GBM Injury: Anti-Glomerular Basement Membrane (GBM) Disease

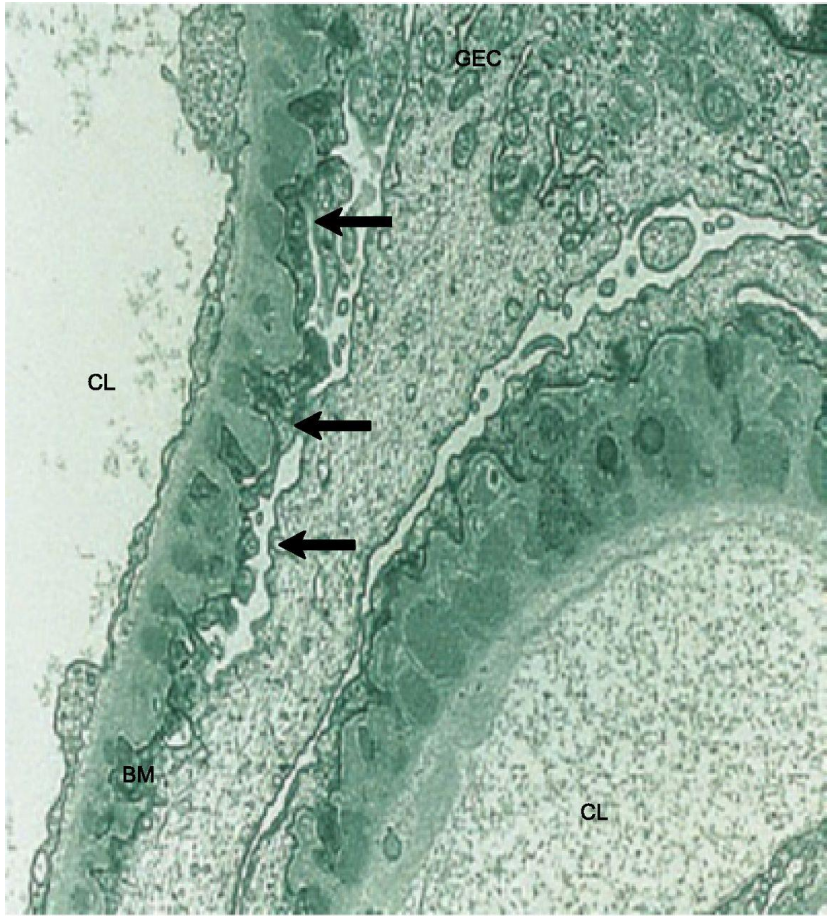
- Binding of circulating antibodies to NC1 domain of α3 chain of collagen IV
- Typically, quaternary structure sequesters epitope
  - Requires initial event that induces conformation change
- ?Geographical clustering
  - Link to influenza A or environmental exposures?



Source: McAdoo SP, Pusey CD. Clin J Am Soc Nephrol. 2017;12(7):1162-72.

Podocyte Injury: Membranous Nephropathy

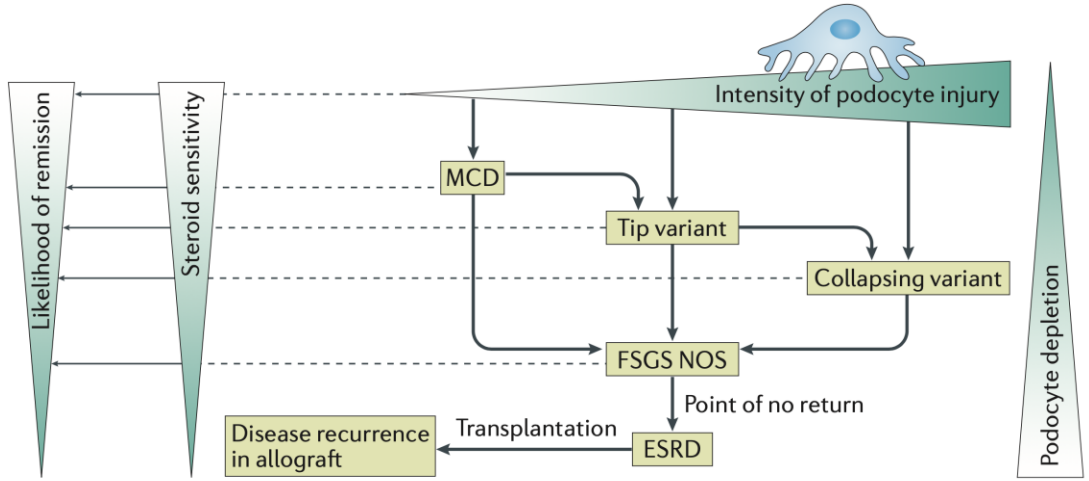
- Primary membranous nephropathy (~80%)
  - IgG4 antibody circulating against M-type receptor of secretory phospholipase A2 (PLA2R) (85%)
  - Antibodies directed against thrombospondin type 1 domain containing 7A (THSD7A) (3-5%)
- Antibody binds to podocyte proteins
  - PLA2R binding may disrupt adhesion of collagen type IV fibers
  - THSD7A binding may disrupt intercellular adhesion
- Secondary membranous nephropathy
  - HBV, HCV, HIV, solid tumors, SLE class V, GVHD
- Homology between genes for PLA2R and LTLENCK domain in some Gram^{+} bacterial enzymes



Source: Zhao et al. Front Immunol. 2021;12:665629

Podocyte Injury: Minimal Change Disease (MCD)/Idiopathic Focal Segmental Glomerulosclerosis (FSGS)

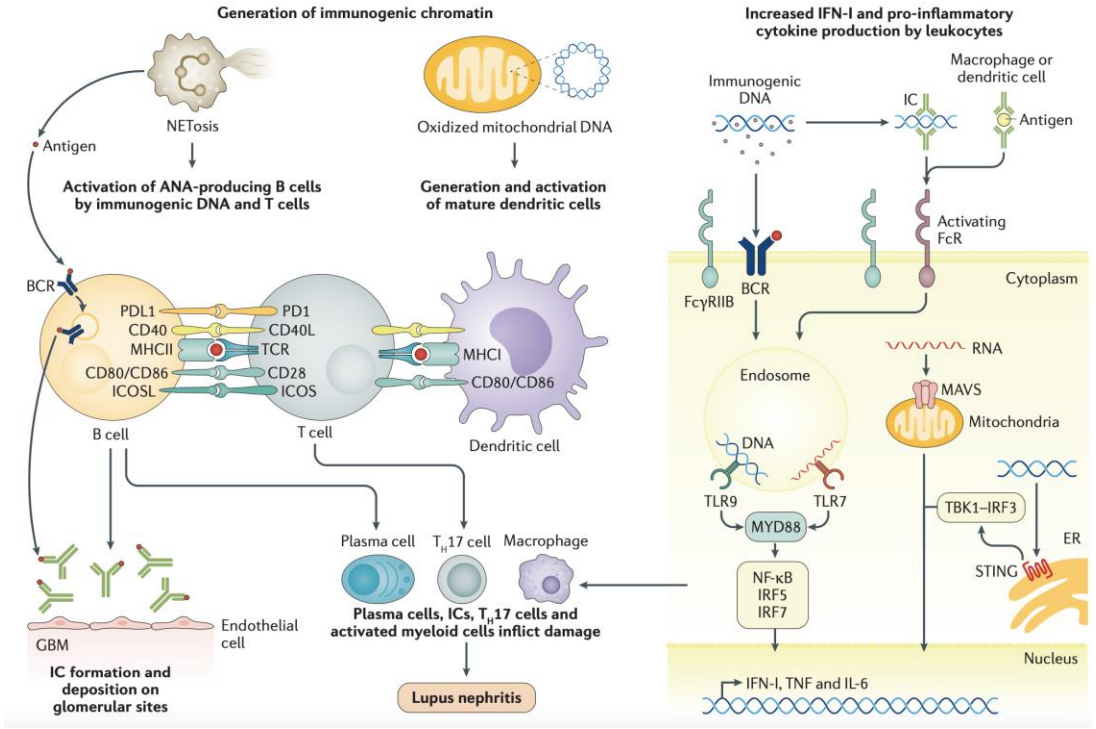
- MCD and idiopathic FSGS likely forms of same disease characterized by foot process effacement
  - Idiopathic FSGS marked by more severe podocyte injury/loss, and less steroid-responsive than MCD
- Likely etiology is soluble circulating factor toxic to podocytes
  - Identity unknown
- Association with decreased Tregs and altered cytokine production
- Association with missense coding variants in HLA-DQA1



Source: Maas RJ, Deegens JK, Smeets B, Moeller MJ, Wetzels JF. Nat Rev Nephrol. 2016;12(12):768-76.

General Injury: Lupus Nephritis (SLE)

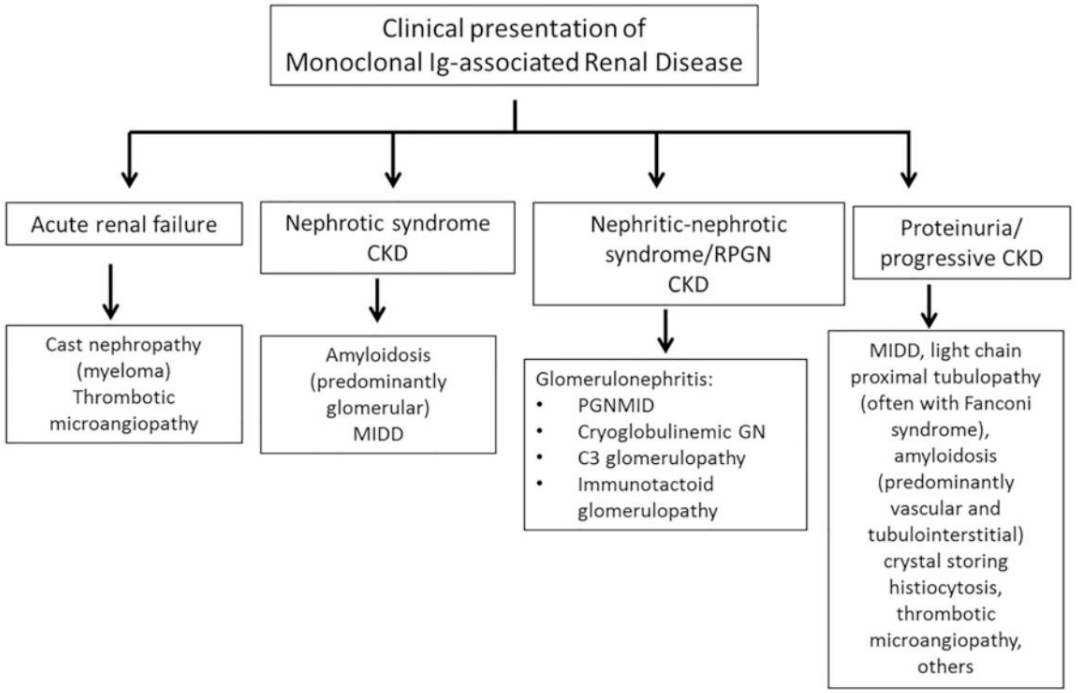
- Hyperactivation of leukocytes by endogenous chromatin (e.g., oxidized mtDNA)
  - TLR7 has been implicated→production of type 1 interferon
  - Chromatin-reactive B cells→production of anti-nuclear antibodies (ANA)
  - Activation of complement (classical and alternative pathways)



Source: Anders HJ, Saxena R, Zhao MH, Parodis I, Salmon JE, Mohan C. Nat Rev Dis Primers. 2020;6(1):7.

General Injury: Deposition Diseases

- Monoclonal Immunoglobulins
  - Light chain deposition disease (most common) (GBM, tubule basement membrane)
    - 80-90% **K** light chains
  - Amyloid (vessel walls, tubular basement membrane, mesangium/interstitium)
    - **λ > K** light chain predominance for AL; most commonly IgG for AH
  - Heavy chain deposition disease (GBM, tubule basement membrane)
    - Most commonly **truncated γ-chains**, deposit with C3 and C1q
  - Membranoproliferative GN (MPGN) (GBM)
    - **Intact** monoclonal antibodies with light chains (**IgG3** is most common subclass)



Source: Sethi S, Rajkumar SV, D'Agati VD. J Am Soc Nephrol. 2018;29(7):1810-23.

General Injury: Deposition Diseases

- Cryoglobulins (GBM)
  - MPGN; most commonly **IgM**, less commonly IgG
  - Type 1 (single monoclonal Ig due to malignancy)
  - Type 2 (monoclonal Ig complexed to polyclonal Ig) (HBV, HCV, HIV, SLE, RA)
  - Type 3 (polyclonal Ig) (HBV, HCV, HIV, SLE, RA)
- Fibrillary GN (GBM, mesangium)
  - Fibrils of IgG between 16-24 nm in diameter; **DNAJB9^{+}** (?autoantigen)
  - Various patterns of injury: MPGN, mesangial, membranous, sclerosing
- C3 GN/Dense Deposit Disease (GBM, mesangium)
  - Dysregulation of alternative complement pathway (like aHUS)

Case #1

A 20-year-old woman presents to the hospital with sudden onset of peripheral edema 7 days following an upper respiratory infection. Her serum Cr is 1.1 mg/dL, serum Alb is 1.8 g/dL, and urine protein:Cr is 12 g/g. She has had two previous episodes of similar presentation at ages 10 and 15, both of which resolved following a 2-month course of corticosteroids. Her BP is 147/90, and physical exam is significant for anasarca. Urinalysis shows 4+ protein and no blood.

Case #1

What is the most likely cause of her glomerular disease?

A. Hyperactivity of the alternative complement pathway
B. Production of antibodies against the NC1 domain of α3 chain of collagen IV in the GBM
C. Deficiency in attachment of galactose moieties to the hinge regions of IgA1 molecules
D. Presence of a soluble circulating factor in the blood that is toxic to the podocytes
E. Formation of immune complexes against bacterial antigens with deposition in the GBM

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Pure nephrotic syndrome presentation and resolution of past episodes with steroid therapy are the clues to the likely diagnosis of minimal change disease. Minimal change disease is believed to be caused by an unidentified (as of yet) soluble circulating factor that is toxic to podocytes.

Case #2

A 37-year-old man of Southeast Asian ancestry presents to your clinic with a 4-day history of a diarrheal illness, accompanied by fever, a rash over both legs, and fatigue. His serum Cr is 1.3 mg/dL, and urinalysis is significant for 2+ protein and 1+ blood, with several red blood cells visualized in the urine sediment. Urine protein:Cr is 1.9 g/g. A kidney biopsy is performed, which is significant for mesangial enlargement on light microscopy, and multiple electron-dense deposits are visualized in the mesangium on electron microscopy.

Case #2

What is the most likely cause of his glomerular disease?

A. Hyperactivity of the alternative complement pathway
B. Production of antibodies against the NC1 domain of α3 chain of collagen IV in the glomerular basement membrane
C. Deficiency in attachment of galactose moieties to the hinge regions of IgA1 molecules
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E. Formation of immune complexes against bacterial antigens with deposition in the GBM

Presence of concurrent diarrheal illness, skin rash, hematuria, and non-nephrotic range proteinuria, along with visualization of electron-dense deposits in mesangium are all clues to the likely diagnosis of IgA nephropathy. IgA nephropathy is caused by deposition of immune complexes consisting of IgA or IgG antibodies directed against IgA1 antibodies with hinge regions that are deficient in galactose molecules.

Summary/Take Home Points

- Communication between the innate and adaptive arms of the immune response is critical to the pathogenesis of kidney disease
- Dysregulation and abnormalities in the systemic immune response are common causes of various forms of glomerular injury
- Understanding how disorders in the immune system result in these different types of glomerular injury can aid in the formation of an accurate differential diagnosis

Brief References

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- Any questions?
- Please email me at vkasinath@bwh.harvard.edu