Pathogenesis of Primary Glomerular Diseases

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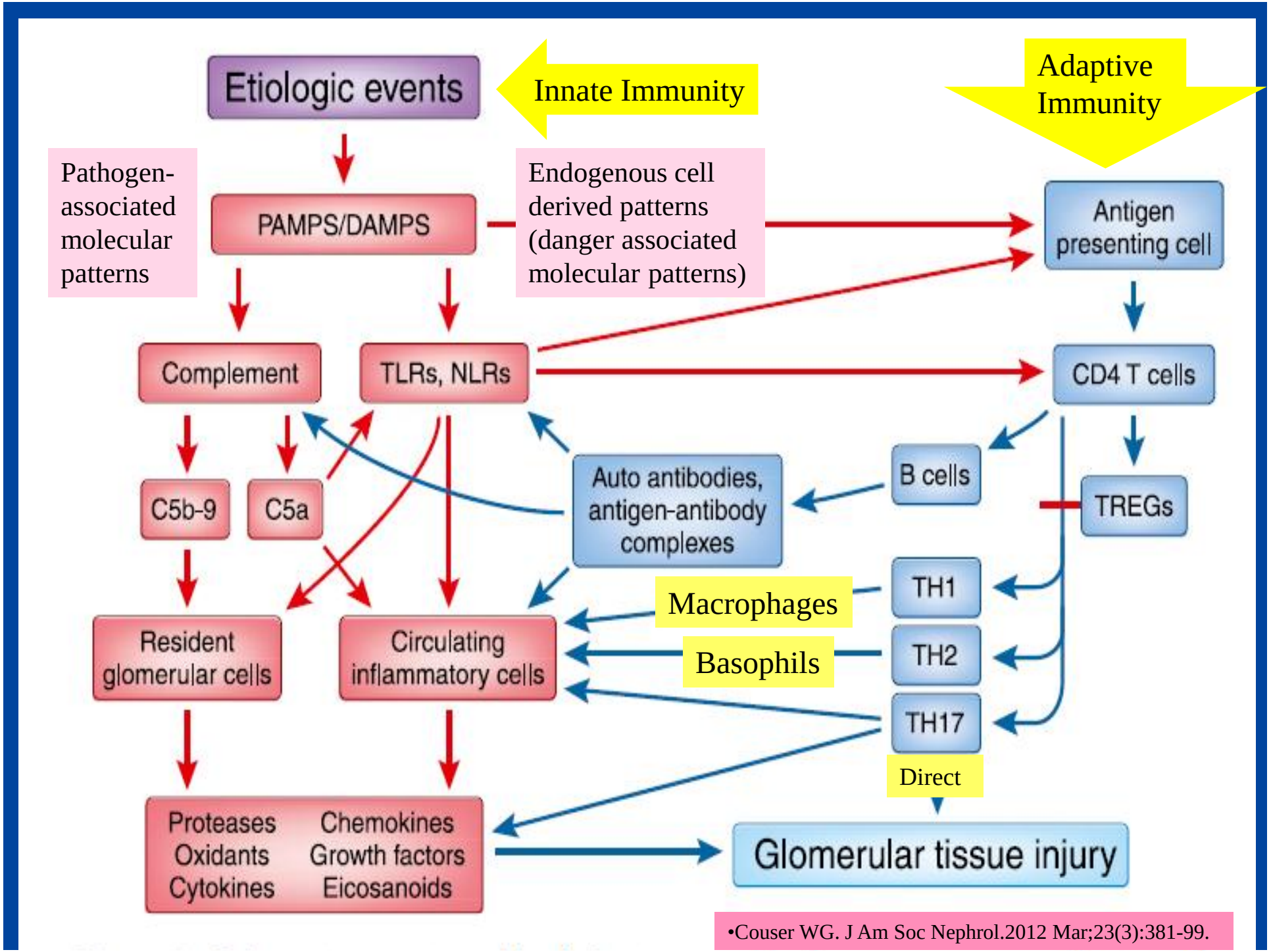
Introduction

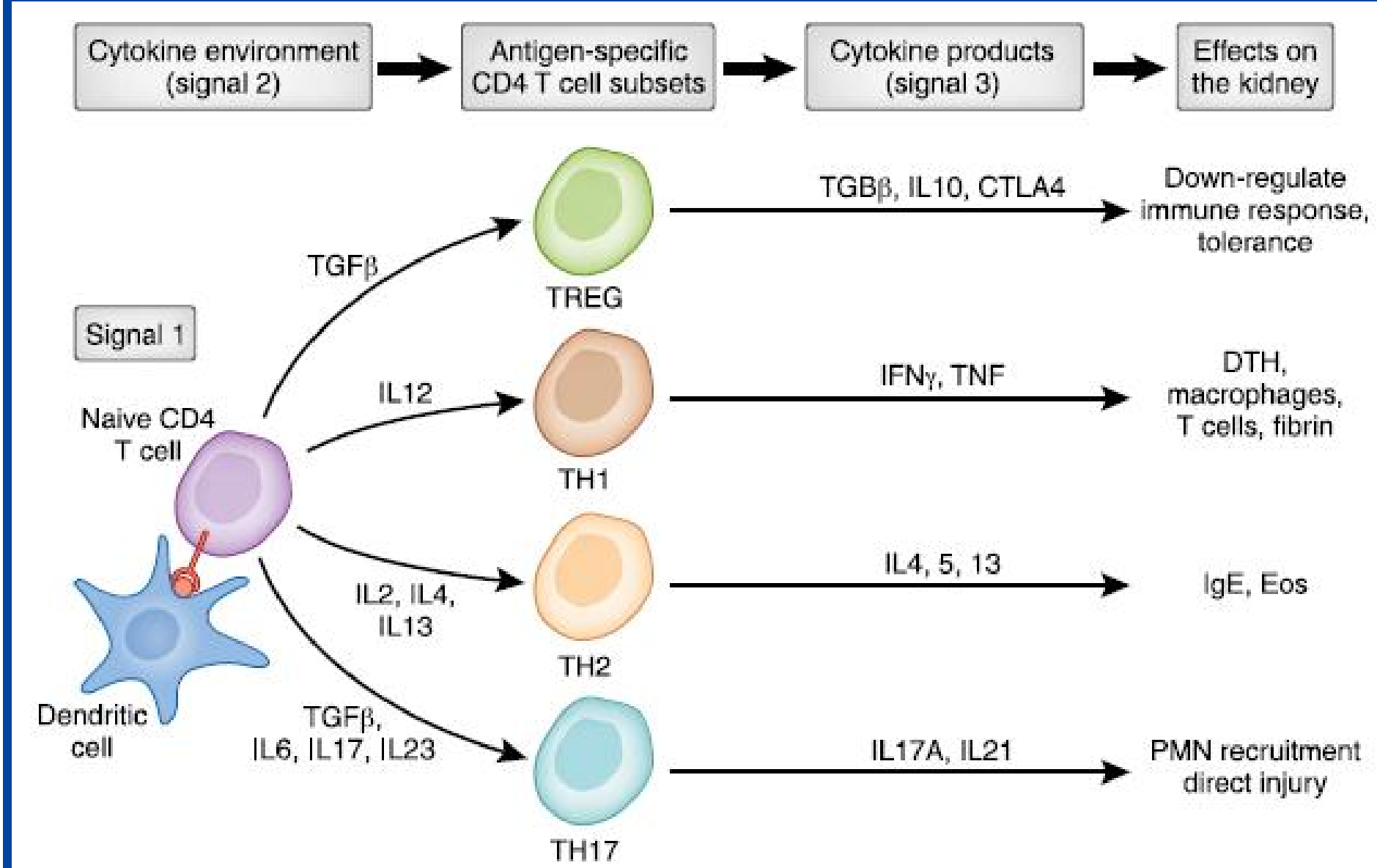
- Evidence show that most human GNs are due to Immunogenic mechanisms.
- Many pathogens of GNs like drugs, infections, toxins and unknown factors cause GN through activation of the immune system through common mechanisms
- The nature of immune response depends on immunogenic phenotypes.

- In mouse and human the differences between the number of Fcgr3 gene copies determines the occurrence of immunogenic GNs.
- Fcgr3-related sequence (Fcgr3-rs):determinant of macrophage overactivity and glomerulonephritis in Wistar Kyoto rats.
- In human, reduction in the number of these genes (FCGR3B)I s associated with occurrence of glomerulonephritis in the lupus erythematosus.

Aitman TJ . Nature.2006 Feb 16;439(7078):851-5.



•Couser WG. J Am Soc Nephrol.2012 Mar;23(3):381-99.


Cytokine environment (signal 2)
Antigen-specific CD4 T cell subsets
Cytokine products (signal 3)
Effects on the kidney
Signal 1
Naive CD4 T cell
Dendritic cell
TGFβ
TREG
TGBβ, IL10, CTLA4
Down-regulate immune response, tolerance
IL12
TH1
IFNγ, TNF
DTH, macrophages, T cells, fibrin
IL2, IL4, IL13
TH2
IL4, 5, 13
IgE, Eos
TGFβ, IL6, IL17, IL23
TH17
IL17A, IL21
PMN recruitment direct injury

Nephritogenic Response

- Cellular: Mediated by Th1
  - Mononuclear cell infiltration (lymphocytes and macrophages) into the glomerulus and crescent formation
- Humoral: Mediated by Th2
  - Initiation of B cell response, activation of complement and IC deposition

- The T helper subset Th1 tends to predominate in proliferative and crescentic forms of GN.
- Th2 predominates in MN and MCD.

Tipping PG. Clin Exp Immunol. 2005;142(2):207./ Kuroki A. Kidney Int. 2005;68(1):302.

Humoral Immunity

- IC and C’ deposition is seen in most GNs and this is a symptom of humoral response.
- Examples are:
  - PIGN, IgAN, AntiGBM disease, LN, MN, MPGN, many cases of RPGN

In situ IC formation

- Against normal glomerular Ags:
  - Ab to non-collagenous domain of α3 chain of type 4 collagen (Anti GBM disease after renal Tx in Alport Syndrome)
  - Ab to Megalin in Heymann Nephritis

In situ IC formation…

- Against non-renal Ags trapped in the glomerulus:
  - Poorly glycosylated IgA trapped in the kidney in IgAN
  - DNA- nucleosome complexes in LN

In situ IC formation…

- Against foreign Ags:
  - Hepatitis C Ag in cryoglobulins depoisted in MPGN, which may cause IC deposition
  - Toxins in MN including Cationic cow albumin in milk which may bind to anionic GBM

Circulating IC formation

- Another possible mechanism for immune complex deposition is the passive process of trapping circulating immune complexes within the glomeruli.

- Although this process has been studied in animal models, it appears to be less commonly seen in human GN than in situ glomerular immune complex formation.

Cellular Immunity: NO IC

- CD4+ cells increase monocyte/ macrophage activity→
  - ↑IL12, IL2,INF-γ, TNF-α →
  - Severe glomerular injury
- CD-8+ cells: cytotoxic activity, important in some diseases such as MCD, FSGS and Crescentic GN

Minimal Change Disease (MCD)

T cell dysfunction

- Cell-mediated immunity (CMI) is a major pathogenetic factor in MCD:
  - Remission can be induced by measles, an infection known to modify CMI.
  - The lesion of MCD occurs more frequently in patients with Hodgkin lymphoma than in the general population.
  - Atopic individuals are at higher risk for the development of MCD.
  - Glucocorticoids and cyclophosphamide, which modify CMI, have proven benefit in the treatment of MCD.

Shalhoub RJ. Lancet. 1974;2(7880):556

Humoral Immunity

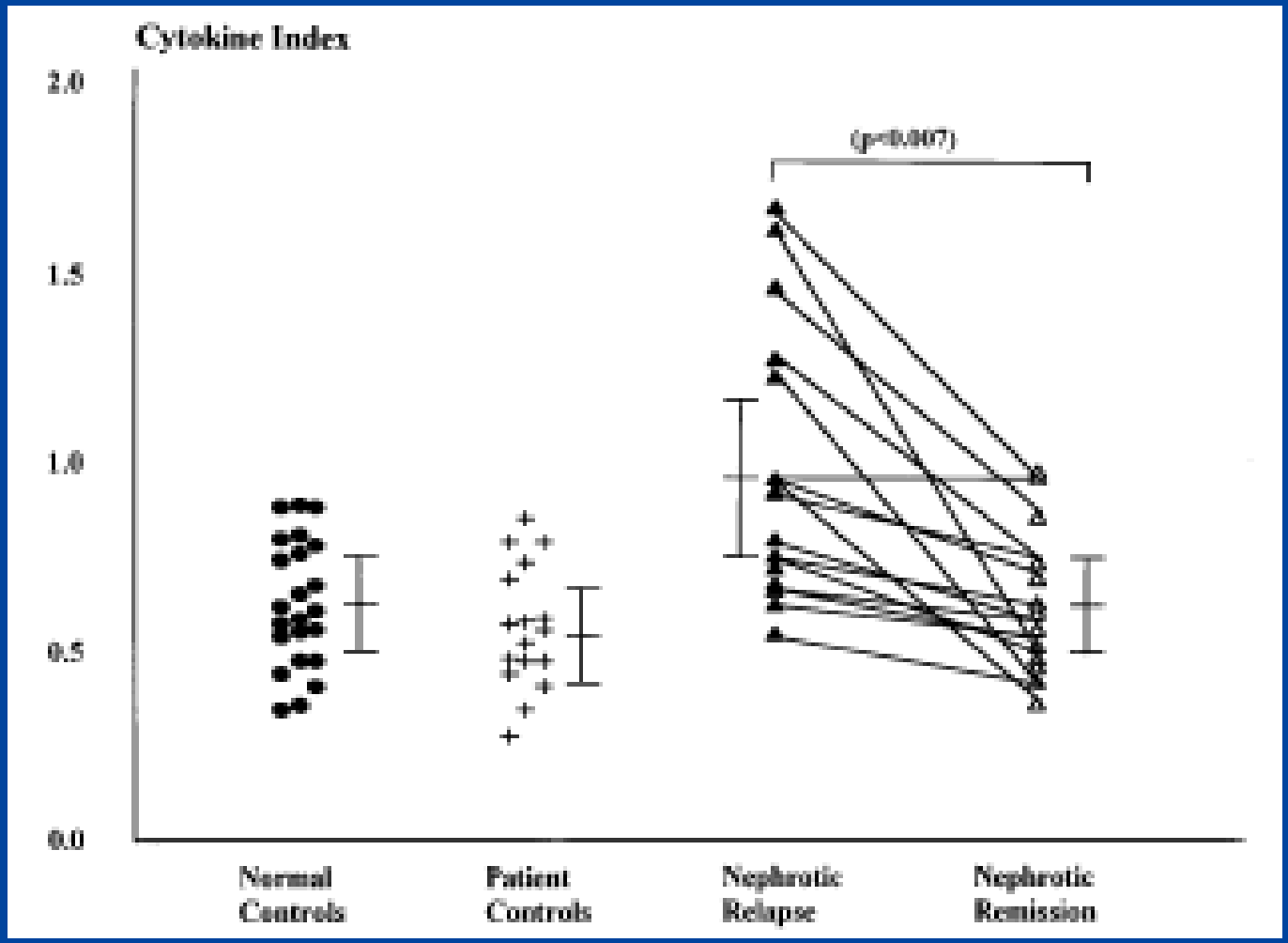
- The preliminary results of MCD treatment with rituximab suggest a role for B cells in addition to T cells in the pathogenesis of MCD in some patients.

Yang T. Nephrol Dial Transplant. 2008 Jan;23(1):377-80.

Permeability Factor

- The identity of the glomerular permeability factor in MCD has not been determined in humans.
  - Th2-derived cytokines, esp. IL-13

T cells from patients with relapsed MCD have increased expression of IL-13 compared to those from patients in remission



Yap HK .J Am Soc Nephrol. 1999;10(3):529.

S1

Minimal change disease: a CD80 podocytopathy?

- CD80 is increased in the urine of MCD patients & not commonly present in the urine of patients with other glomerular diseases.
  - IL-13 or microbial products via Toll-like receptors could induce CD80 expression on podocytes.
  - CTLA-4 appears to regulate CD80 expression in podocytes, and to be altered in MCD.
- Proteinuria in MCD may be caused by persistent CD80 expression in podocytes, possibly initiated by stimulation of these cells by antigens or cytokines.

Ishimoto T. Semin Nephrol. 2011 Jul;31(4):320-5

Slide 19

S1 Find the figure for this

Shahrzad, 1/23/2015

- Urinary CTLA-4 levels do not correlate with urinary CD80 excretion, suggesting the possibility that the CTLA4 response may be suboptimal in this disease during relapse.

- Persistent increased urinary CD80 excretion in patients with MCD in relapse is due to an ineffectual CTLA-4 response of the host to curtail the activation of CD80.

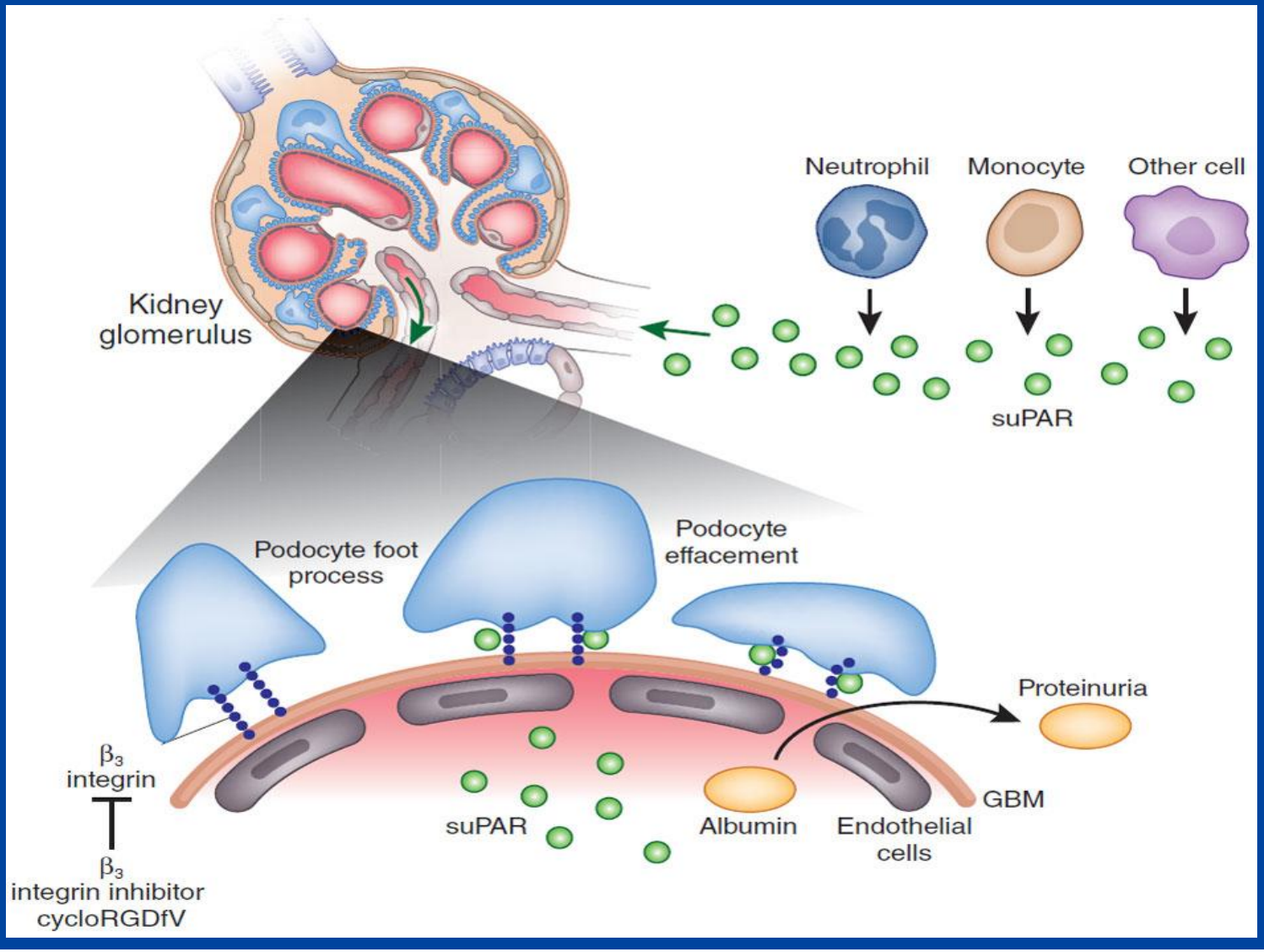
- CTLA-4 therapy?

Cara-Fuentes G. Pediatr Nephrol.2014 Dec;29(12):2333-40.

FSGS

- In FSGS also it seems that the injury is initiated by podocytes cells although parietal epithelial cell injury is also possible.
- The initial injury seems to be initiated by a circulating factor in most patient.
- The circulating factors are different from MCD
- Different circulating factors have been suggested in FSGS.

Soluble urokinase plasminogen activating receptor (suPAR)



Shankland SJ. Nature Medicine 17, 926–927 (2011)

- Mice exposed to some but not all forms of suPAR developed albuminuria and a progressive glomerulopathy characterized by effacement of foot processes, hypercellularity, mesangial expansion, mesangiolysis, and tuft adhesions.

- Serum from patients with recurrent FSGS, but not from those with nonrecurrent FSGS or normal controls, activated beta3 integrin activity *in vitro*, while inhibition of suPAR reduced beta3 integrin activity

Wei C. Nat Med. 2011;17(8):952

- Circulating suPAR activates podocyteβ(3) integrin in both native and grafted kidneys, causing foot process effacement, proteinuria and FSGS-like glomerulopathy.

- Renal disease only develops when suPAR sufficiently activates podocyteβ(3) integrin.

- Thus, the disease can be abrogated by lowering serum suPAR concentrations through plasmapheresis, or by interfering with the suPAR-β(3) integrin interaction through antibodies and small molecules targeting either uPAR orβ(3) integrin.

- This study identified serum suPAR as a circulating factor that may cause FSGS.

Wei C. Nat Med. 2011;17(8):952

Cardiolopin- like cytokine-1 (CLC-1)

- CLC-1 is a cytokine belonging to the IL6 family.
- The level of this factors is 100 times in relapsing FSGS patients than normal people.
- It mimics the effects of FSGS plasma on *albumin permeability*, and it decreases nephrin expression by glomeruli and cultured podocytes.
- Strikingly, a monoclonal antibody to CLC-1 blocks the *albumin permeability* effect of active FSGS sera.

McCarthy ET. Clin J Am Soc Nephrol.. 2010 Nov;5(11):2115-21.

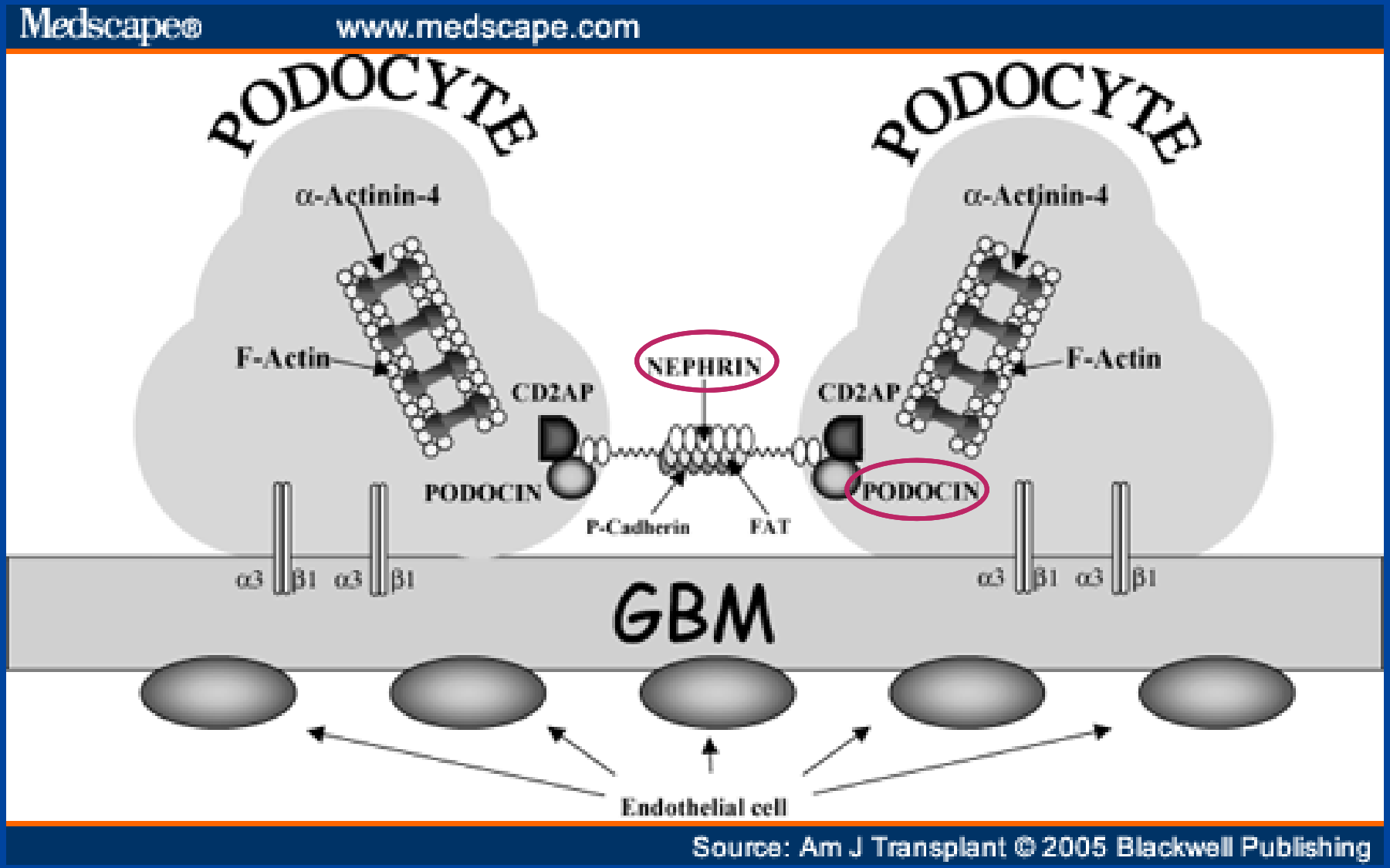
Other factors

- **MiRNA193-a** expression is increased in non-genetic FSGS.
- Increased expression of MiRNA193 may inhibit transcription of Wilm tumor protein- WT1 and down-regulation of target genes including podocalcin and nephrin.

Genetic FSGS

- Mutations in the gene for nephrin, called NPHS1, cause congenital nephrotic syndrome of Finnish type.
- NPHS1 mutations have also been identified in older children with steroid-resistant nephrotic syndrome.

- NPHS2, encodes podocin, which is found exclusively in glomerular podocytes.
- Patients with FSGS due to mutations in NPHS2 usually present with early-onset nephrotic syndrome but adult cases have also been reported.



Nephrin and Podocin are a transmembrane proteins that are structural components of the slit diaphragm.

Membranous Glomerulopathy

- IC are formed in situ and after passing the circulating antibodies through the GBM.
- Abs are formed against Ags expressed on podocytes or circulating low molecular weight or cationic Ags, which have passed through the anionic GBM.
- In Heymann Nephritis Abs are formed against an endocytic receptor called Megalin (gp330).

- The M-type phospholipase A2 receptor (PLA2R), a transmembrane receptor that is highly expressed in glomerular podocytes, has been identified as a major antigen in human idiopathic MN.
- Serum samples from 26 of 37 patients (70%) with idiopathic but not secondary membranous nephropathy specifically identified a 185-kD glycoprotein in nonreduced glomerular extract detected as the M-type phospholipase A(2) receptor (PLA(2)R) by mass spectrometry

Beck LH Jr . N Engl J Med. 2009;361(1):11.

- Anti-PLA(2)R autoantibodies in serum and glomeruli were mainly IgG4.
- PLA(2)R was expressed in podocytes in normal human glomeruli and colocalized with IgG4 in immune deposits in glomeruli of patients with membranous nephropathy.
- IgG eluted from such deposits in patients with idiopathic membranous nephropathy, but not in those with lupus membranous or IgA nephropathy, recognized PLA(2)R.

Beck LH Jr . N Engl J Med. 2009;361(1):11.

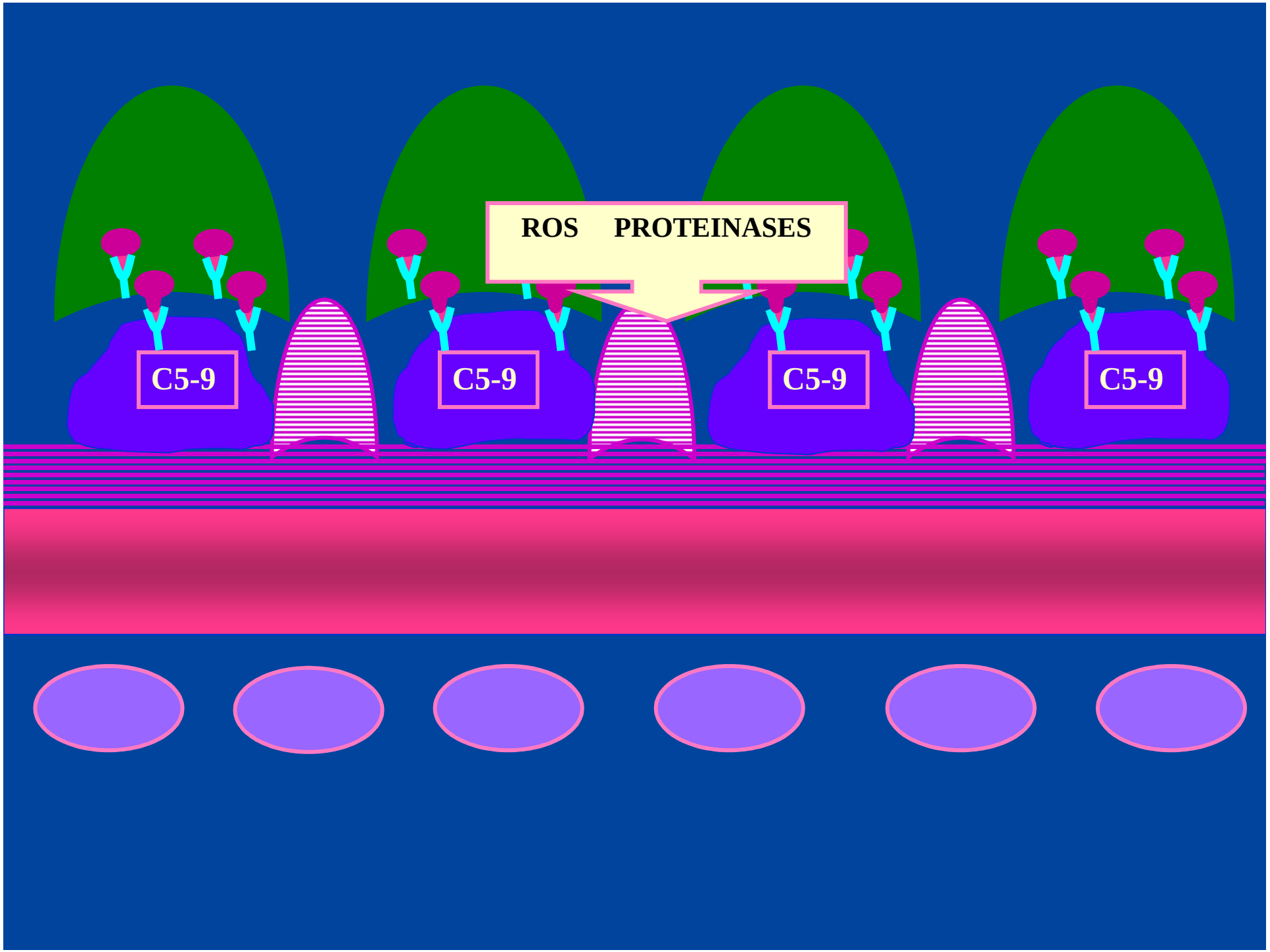
Thrombospondin type-1 domain-containing 7A

- THSD7A is, like PLA2R, a transmembrane protein expressed on podocytes.
- THSD7A may be the responsible antigen in approximately 10 percent of patients with idiopathic MN who are negative for anti-PLA2R antibodies

Tomas NM. N Engl J Med. 2014;371(24):2277

Other Ags

- Neutral endopeptidase: A rare antenetal form of MN
- Intracellular: alpha-enolase, aldose reductase, and superoxide dismutase 2
- Antibodies to a cationic form of bovine serum albumin (BSA) are present in a small number of children with MN.


ROS PROTEINASES
C5-9
C5-9
C5-9
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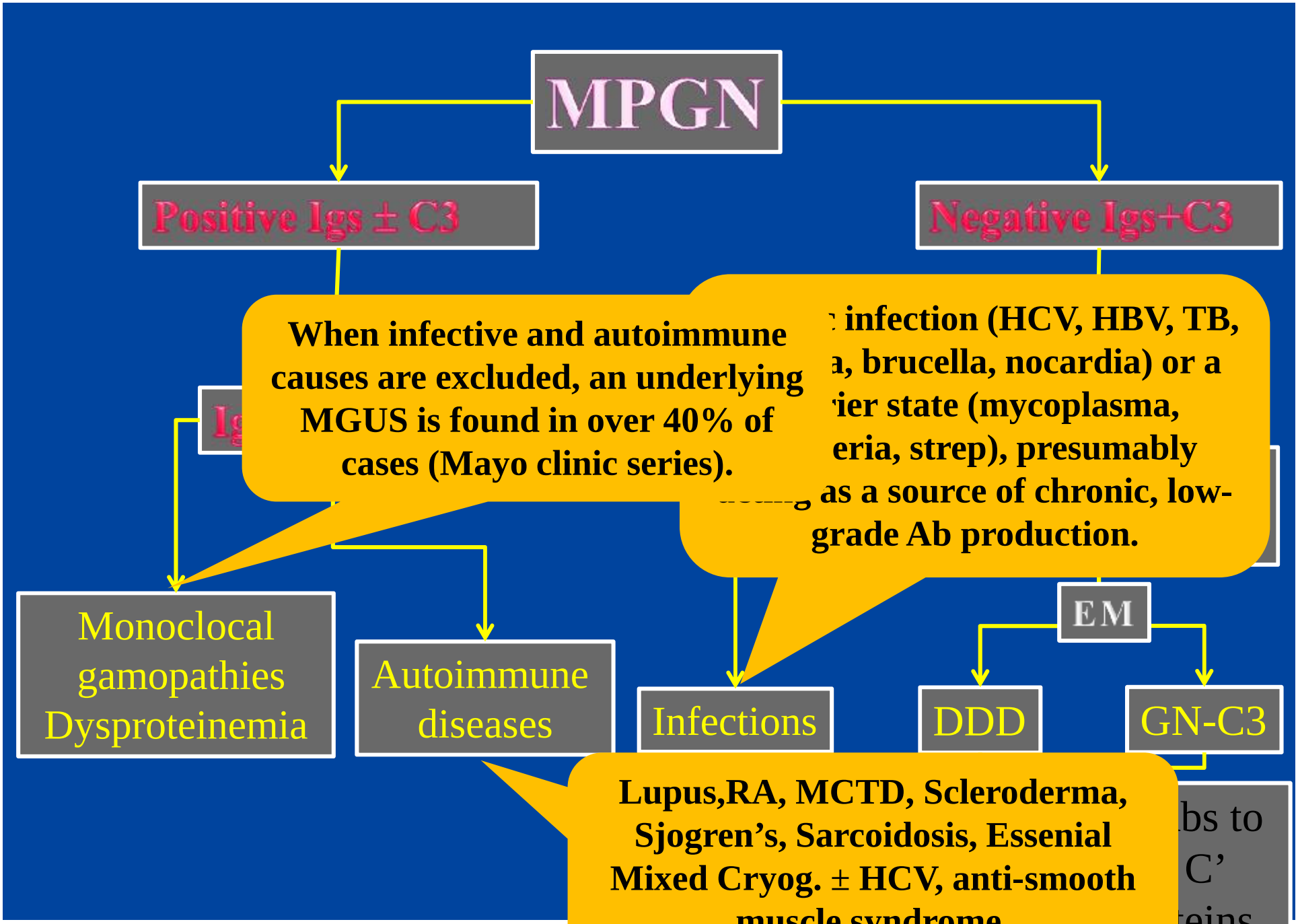
Membranoproliferative Glomerulonephritis (MPGN)

- IF based classification:
  - Immune complex- mediated MPGN
  - Complement- mediated MPGN



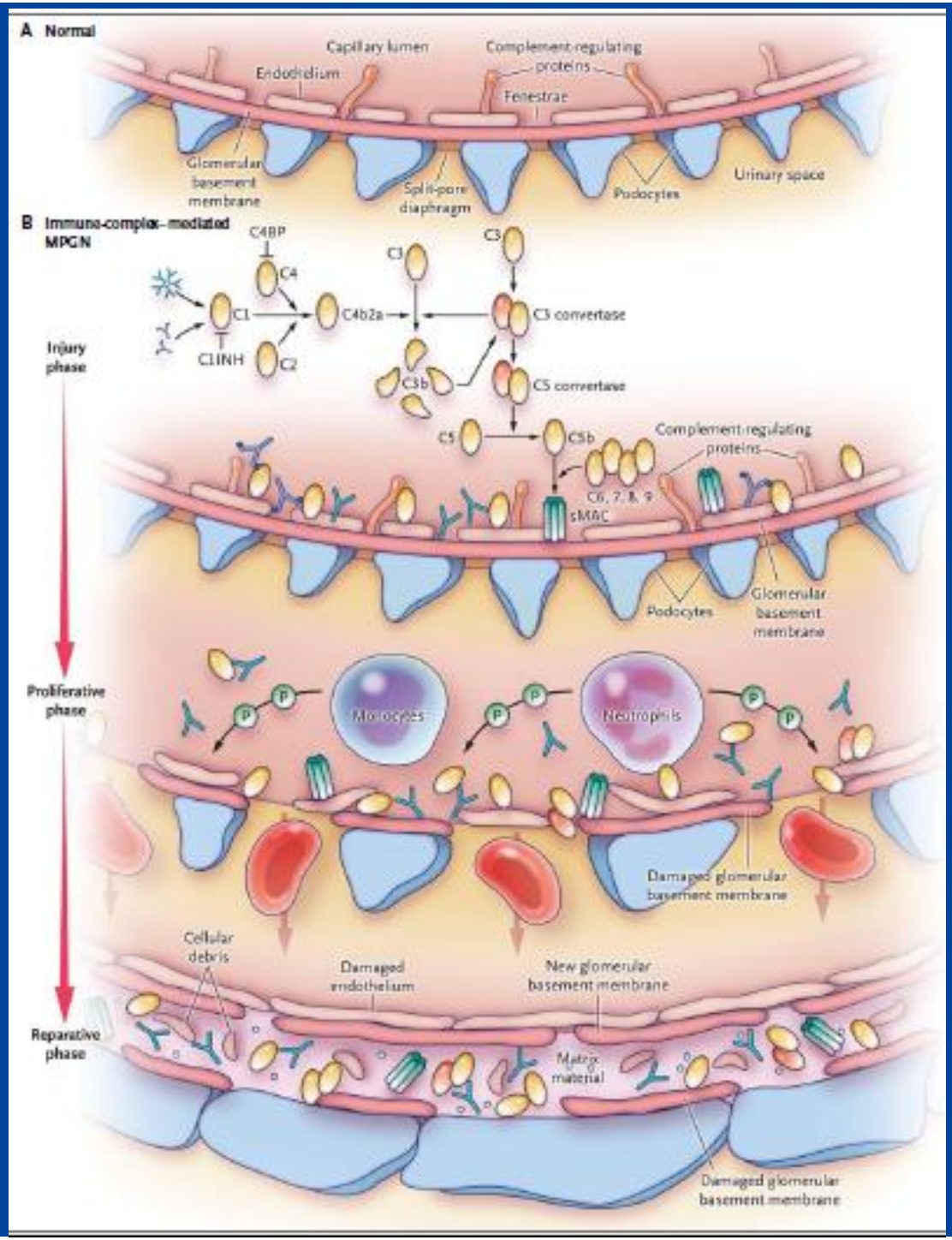
Fervenza C. NDT (2012) 27: 4288

Immune complex- mediated MPGN

- **Hepatitis C induced MPGN** (or other viral infections): Granular deposition of IgM, C3, and **BOTH κ** and **λ** light chains ± IgG, and C1q is typically negative. Rennke HG. Kidney Int. 1995;47(2):643.

- **Monoclonal gammopathy induced MPGN:** Monotypic **κ OR λ** light chains **but not both**. MPGN associated with heavy-chain deposition may show IG deposition (heavy-chain isotypes) in the absence of either light chain. Sethi S. Clin J Am Soc Nephrol. 2010;5(5):770

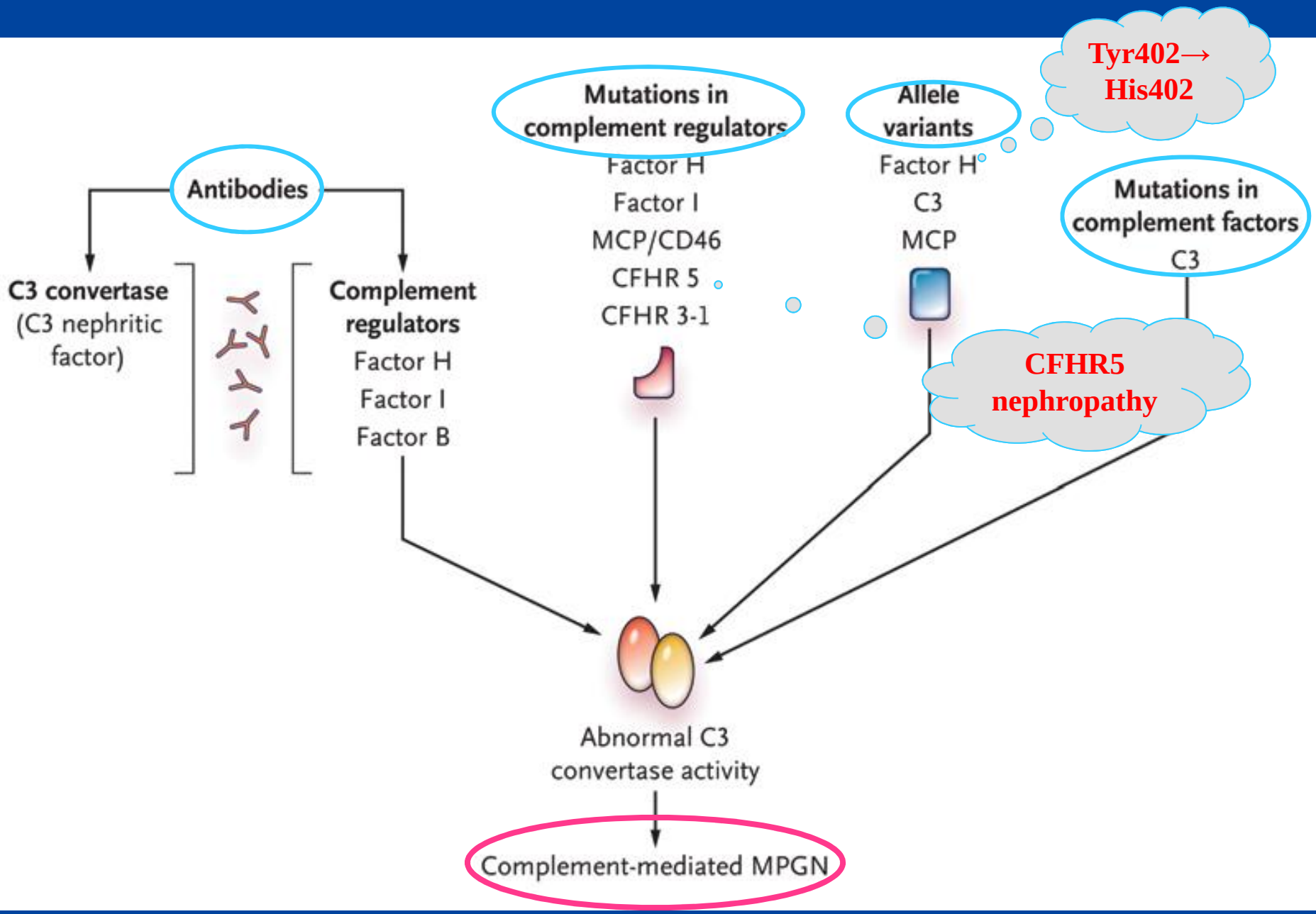
- **Autoimmune MPGN:** "Full house" pattern of Ig deposition, including IgG, IgM, IgA, C1q, C3, and **κ** and **λ** light chains . Weening JJ. J Am Soc Nephrol. 2004;15(2):241



Sethi S. N Engl J Med. 2012 Mar 22;366(12):1119

Complement Mediated MPGN

- Less common than IC-mediated MPGN
- Due to dysregulation and persistent activation of the alternative C’ pathway.
- Deposition of C’ products along the capillary walls and in the mesangium.
- IF: predominantly bright C3 staining but no significant Ig staining, in the mesangium and along the capillary walls.
- DDD or C3 Glomerulonephritis



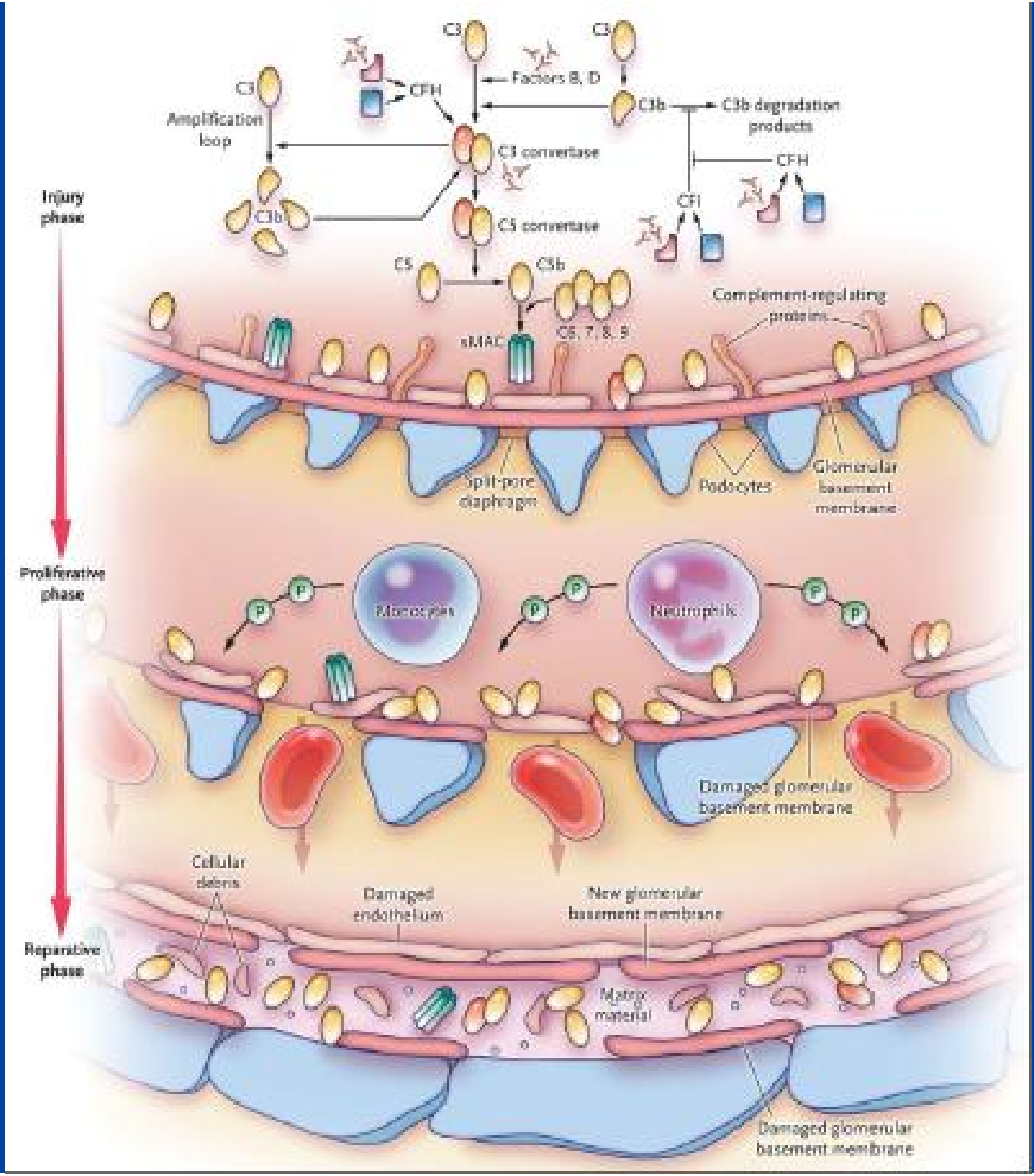
Sethi S. N Engl J Med. 2012 Mar 22;366(12):1119

Despite genetic risk factors,

- MPGN due to complement abnormalities often develops relatively late in life.
- MPGN does not develop in all genetically similar members of high-risk families.

- Redundant control mechanisms may be present.
- When an additional insult such as a complement-activating infection occurs, it may overwhelm the compensatory regulatory mechanism, triggering glomerular deposition of complement factors.

- Recurrent episodes of macroscopic hematuria associated with infections (synpharyngitic hematuria)
- Production of monoclonal proteins that act as autoantibodies to complement-regulating proteins in patients with MGUS



Sethi S. N Engl J Med. 2012 Mar 22;366(12):1119

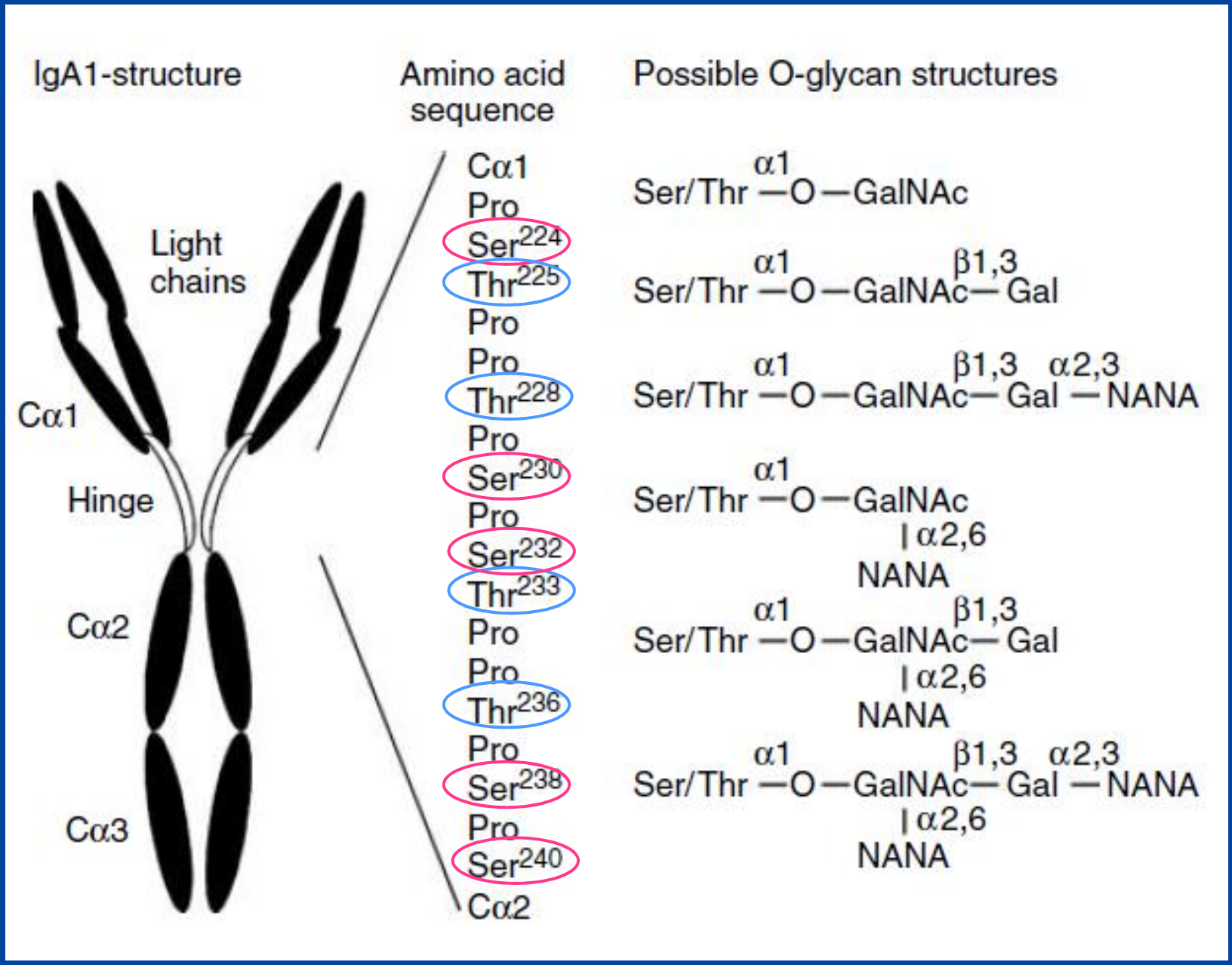
IgA nephropathy

- Is the most frequent GN in the world.
- Focal proliferative and matrix expansion, with IgA, and frequently IgG, C3, C5-C9,.
- Recurrent episodes of GN after viral infection.

Pathogenesis

1. Increased occurrence of IgA1 with poor galactosylation in the circulation.
2. Generation of IgG antibodies against poorly galactosylated IgA1.
3. Mesangial deposition and/or formation of IgG-IgA1 or IgA1-IgA1 complexes.
4. Activation of mesangial IgA receptors and/or complement
5. Mesangial cell damage and activation of secondary pathways, such as overproduction of platelet-derived growth factor.
6. Activation of pathomechanisms that are not specific for IgA nephropathy and that drive glomerulosclerosis and tubulointerstitial fibrosis.

Floege J. Am J Kidney Dis.2011 Dec;58(6):992-1004



Van Der Boog, PJM. Kidney International, Vol. 67 (2005), pp. 813–821

- Underglycosylated IgA1 exhibits altered biologic properties compared with normal IgA1 including

  1. increased tendencies to self aggregate,
  2. unmasking of MBL binding sites leading to complement activation,
  3. binding to other molecules like fibronectin, IgG, and collagen IV.

- In circulating macromolecular form, it evades removal from the circulation by asialoglycoprotein and CD 89 receptors, thus facilitating mesangial localization.
- Mesangial cells become activated through interactions between the IgA1 deposits and IgA Fca (CD89) receptors, TLRs, and transferrin receptors (TfR, CD71).

Role of Complement

- C5b-9 generated from complement activation induced by interaction of IgA1 aggregates with MBL, or in situ formation of ICs by IgG antiglycan antibodies, all resulting in mesangial cell proliferation and matrix expansion.

- The pattern of glomerular complement deposition in IgAN includes MBL, C4d, and C5b-9 (but not C1q) that co-localize with IgA1 and suggests both MBL and AP rather than classic pathway activation

Conclusion

- Innate and adaptive immunity are interactive in pathogenesis of GNs
- Th1 cells (cellular immunity) are more effective in proliferative and crescentic GNs
- Th2 cells (humoral immunity) are more effective in MN
- Th17 may cause direct glomerular injury

Conclusion…

1. MCD: CD80 glomerulopathy
2. FSGS: suPAR, CLC-1
3. MN: AntiPLA2R,
4. MPGN: IC mediated or comlement dependent
5. IgAN: poorly glycosilated IgA

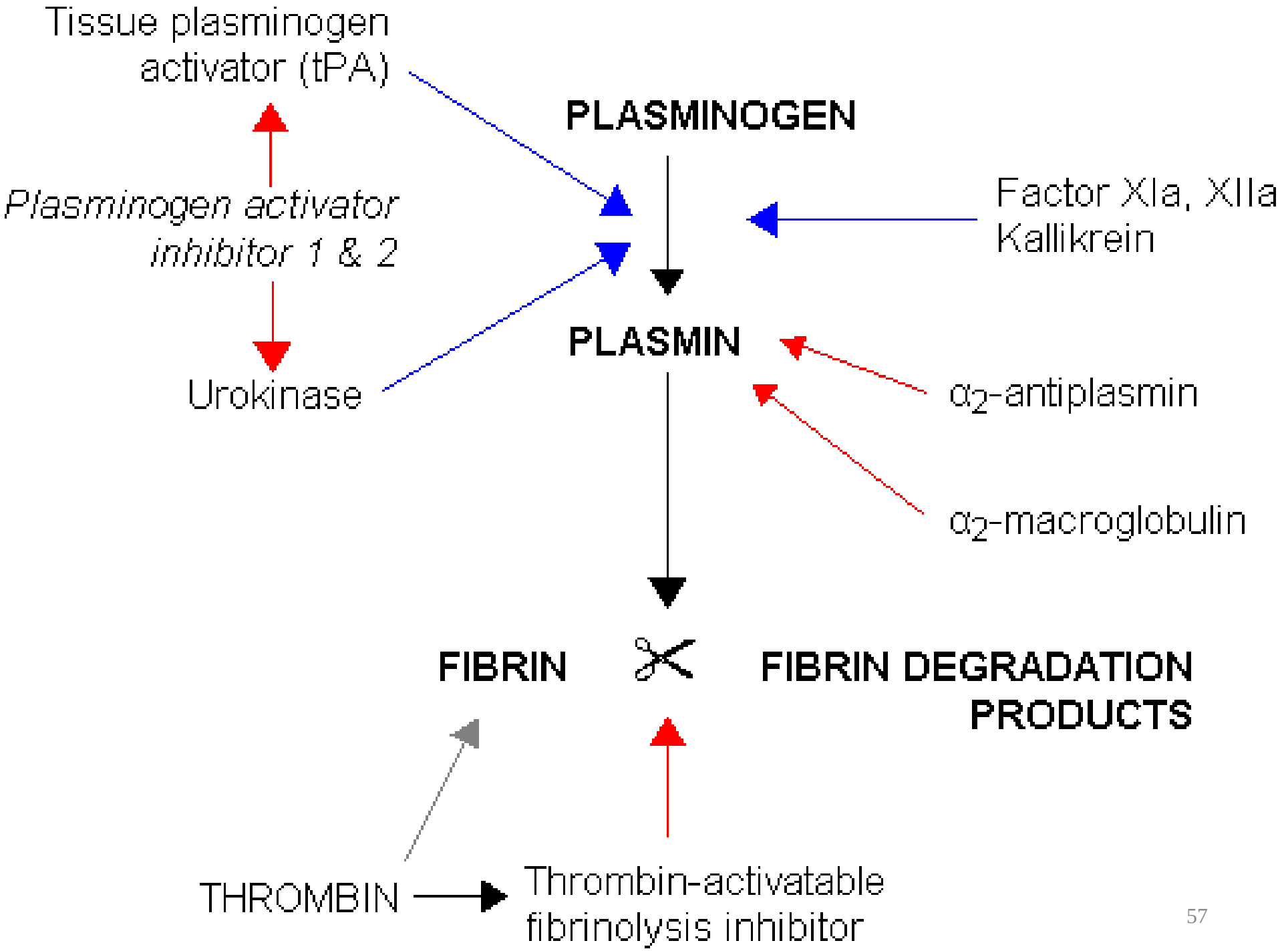
- The T helper subset Th1 tends to predominate in proliferative and crescentic forms of glomerulonephritis, whereas Th2 predominates in MN and minimal change disease [44,45].

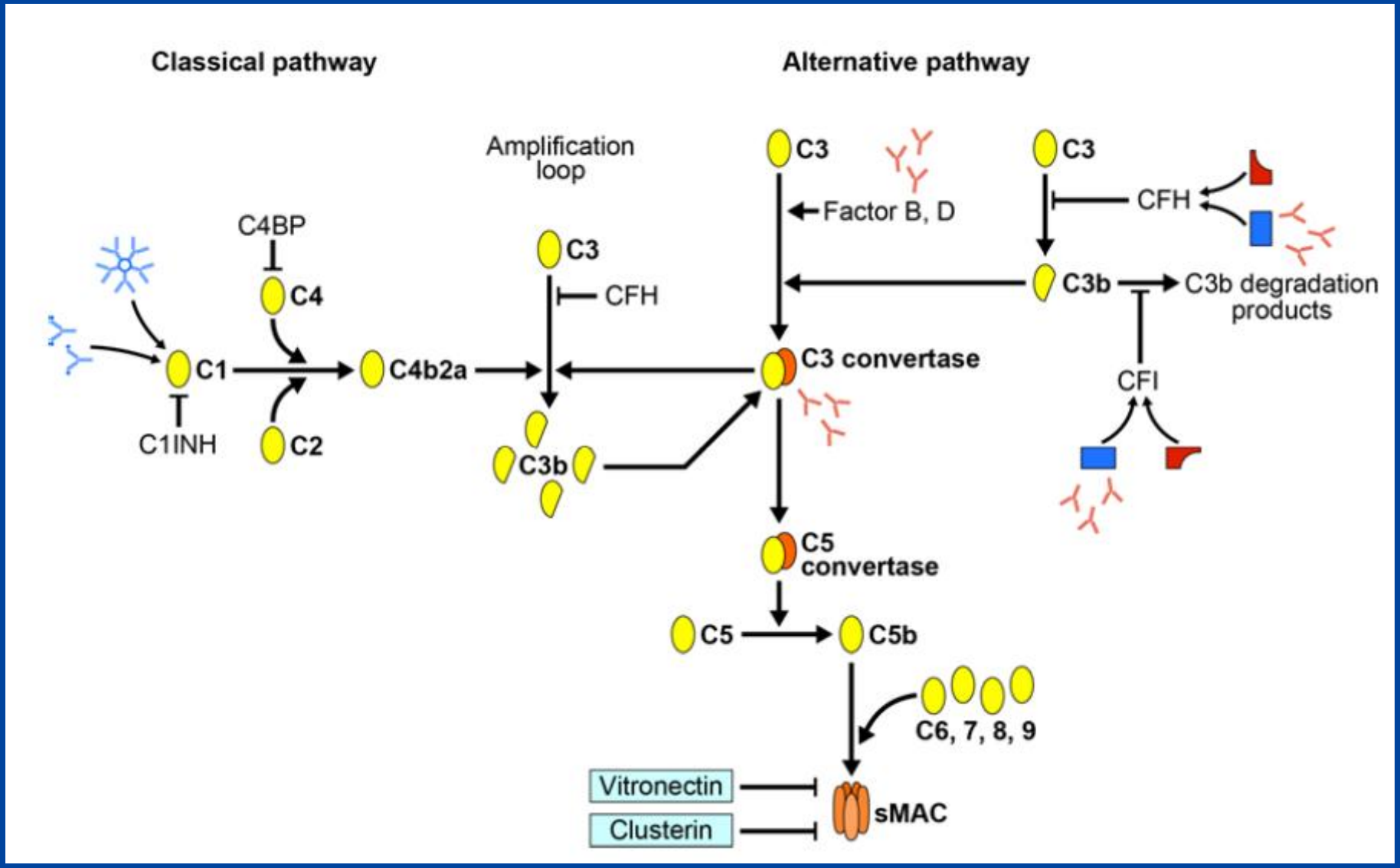
Tipping PG. Clin Exp Immunol. 2005;142(2):207.
Kuroki A. Kidney Int. 2005;68(1):302.

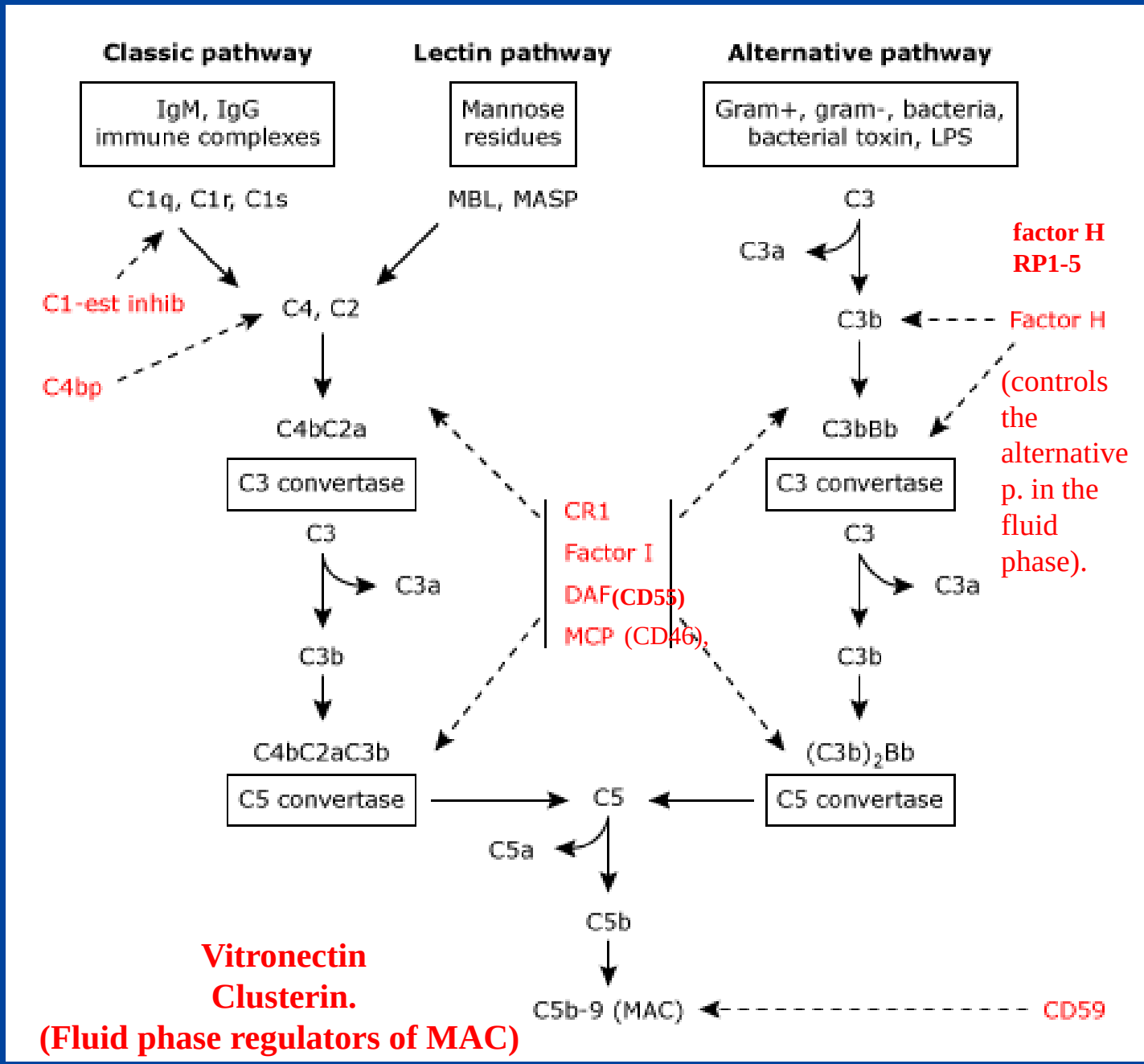
- In support of a pathogenetic role for Th2 in MN is the observation in a model of lupus nephritis that deletion of the WSX-1 gene (encoding a cytokine receptor integral for mounting a Th1 response) causes a shift toward a Th2 response, and converts the diffuse proliferative pattern that is typically seen to a membranous pattern [46]

Shimizu S. J Immunol. 2005;175(11):7185.

- SuPAR
- From Wikipedia, the free encyclopedia
- suPAR, soluble urokinase-type plasminogen activator receptor, is the soluble form of uPAR. uPAR is a membrane bound receptor for uPA, otherwise known as urokinase as well as Vitronectin. suPAR results from the cleavage and release of membrane-bound uPAR. suPAR concentration positively correlates to the activation level of the immune system and is present in plasma, urine, blood, serum, and cerebrospinal fluidsuPAR is a marker of disease severity and aggressiveness.
- Molecular characteristics
- suPAR has a secondary structure of 17 anti parallel β-sheets with 3 short α-helices. There are three homologous domains of suPAR: DI, DII, and DIII. In the comparison of cDNA sequences, DI differs from DII and DIII in its primary and tertiary structure, causing its distinct ligand binding properties.[
- The GPI-anchor inks uPAR to the cell membrane making it available for uPA binding. When uPA is bound to the receptor, there is cleavage between the GPI-anchor and DIII, forming suPAR.
- There are three different suPAR forms: suPARI-III, suPARII-III, and suPARI. Of these three forms suPARII-III is known to be a chemotactic agent for promoting the immune system.
- Application
- suPAR is a biomarker for activation of the inflammatory and immune systems. suPAR levels are positively correlated with pro-inflammatory biomarkers, such as tumor necrosis factor-α, leukocyte counts and C-reactive protein. Elevated levels of suPAR are associated with increased risk of systemic inflammatory response syndrome (SIRS), cancer, Focal segmental glomerulosclerosis cardiovascular disease, type 2 diabetes, infectious diseases, HIV, and mortality.
- suPARnostic is a prognostic test used to detect suPAR levels in blood plasma.


Tissue plasminogen activator (tPA)
PLASMINOGEN
Plasminogen activator inhibitor 1 & 2
Factor XIa, XIIa Kallikrein
PLASMIN
Urokinase
α2-antiplasmin
α2-macroglobulin
FIBRIN
FIBRIN DEGRADATION PRODUCTS
THROMBIN
Thrombin-activatable fibrinolysis inhibitor


Classical pathway
Alternative pathway
Amplification loop
C4BP
C4
C1
C1INH
C2
C4b2a
C3
CFH
C3b
Factor B, D
C3 convertase
C5 convertase
C5
C5b
C6, 7, 8, 9
Vitronectin
Clusterin
sMAC
C3
CFH
C3b
C3b degradation products
CFI



Noris M. JASN 2005; 16:1035.

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