Teaching Day EMCHD 2022

Bench to bedside Topic: Complement in renal disorders

Objective

To define the role of complement in a spectrum of kidney diseases, starting from the prototypical complement-related diseases: hemolytic uremic syndrome, C3 glomerulopathy and immunoiglobulin-associated membranoproliferative glomerulonephritis, and moving to other glomerular diseases including lupus nephritis, and anti-neutrophil cytoplasmic antibody (ANCA)-associated renal vasculitis and IgA nephropathy.

For each disease, we will review :

- The evidence indicating whether complement plays a primary or secondary role.
- The biomarkers of complement activity in monitoring disease course.
- Whether specific drivers (i.e., genetic or acquired) dysregulate complement activity
- Whether any anti-complement therapies currently under investigation may be potential treatments

Bullet points

1) **Hemolytic uremic syndrome**

1. What is the definition and the spectrum of different forms of HUS?
2. Which complement pathways—and to what extent—are involved in complement-mediated HUS?
3. What biomarkers and/or tests are helpful to diagnose and monitor complement-mediated forms of HUS?
4. Which is the role of complement genetic abnormalities (common and rare variants, copy number variation, etc…) and acquired autoantibodies (i.e. anti-factor H autoantibodies) in the disease?
5. How do genetic results and test for acquired autoantibodies (i.e. anti-factor H autoantibodies) impact on the management of complement-mediated HUS, including in the setting of renal transplantation and in the choice of living related donors?
6. Does the renal microenvironment contribute to the pathogenesis of renal involvement in complement-mediated forms of HUS?
7. What is the optimal use of current therapies and what are the emerging therapies for complement-mediated HUS?

2) **C3G, IC-MPGN, and Postinfectious Glomerulonephritis (PIGN)**

1. What is the state of the art of the classification of C3G, IC-MPGN and PIGN ?
2. Which complement pathways—and to what extent—are involved in each condition?
3. Which is the role of complement genetic abnormalities (common and rare variants, copy number variation, etc…) in the diseases and which are the difference vs HUS-associated genetic risk factors?
4. Which is the origin and function of C3NeF? Which is their impact on pathogenesis and clinical outcome of IC-MPGN, C3G, PIGN?
5. What is the prevalence of anti-factor H, anti-factor B, and anti-C3b antibodies in IC-MPGN, C3G, and PIGN?

6. Is there a rationale for complement inhibition in IC-MPGN, C3G, and PIGN?
7. Do we have enough information to tailor the choice of complement inhibitor based on the serological, genetic and biomarker work-up of patients with C3G and IC-MPGN?

3) **Other emerging conditions : Lupus nephritis, ANCA-Associated Vasculitis (AAV) and IgA nephropathy**

Lupus Nephritis

1. What is the contribution of complement activity to kidney injury in relation to the other effector mechanisms active in lupus nephritis?
2. Is complement activation a driver of kidney injury or a consequence of immunoglobulin deposition in the kidney?
3. Is there a role of genetic complement abnormalities in lupus nephritis? What is the relevance of the link between complement deficiencies and lupus (the "systemic lupus erythematosus [SLE] paradox")?
4. What is the place for anti-complement protein antibodies in lupus nephritis (e.g., anti-C1q antibodies); are they useful biomarkers with relevance for diagnosis and prognosis?

ANCA-Associated Vasculitis (AAV)

1. Which complement pathways—and to what extent—are involved in AAV?
2. What have we learned from use of avacopan in AAV?
3. Is there a role for targeting other parts of the complement system (e.g. C3) in AAV?

IgAN

1. What is the evidence (from preclinical models and human and genetic studies) that complement activation plays a role in kidney injury in IgAN?
2. Is complement-mediated injury a primary driver of disease or a generic downstream consequence of glomerular immunoglobulin deposition?

3. Is there a role of genetic complement abnormalities in IgAN?
4. Is there a rationale for complement inhibition in IgAN

Suggested readings

1. Fakhouri F, Fremeaux-Bacchi V. Thrombotic microangiopathy in aHUS and beyond: clinical clues from complement genetics. *Nat Rev Nephrol* 2021; **17:** 543-553.

2. Galbusera M, Noris M, Gastoldi S, Bresin E, Mele C, Breno M, Cuccarolo P, Alberti M, Valoti E, Piras R, Donadelli R, Vivarelli M, Murer L, Pecoraro C, Ferrari E, Perna A, Benigni A, Portalupi V, Remuzzi G. An Ex Vivo Test of Complement Activation on Endothelium for Individualized Eculizumab Therapy in Hemolytic Uremic Syndrome. *Am J Kidney Dis*. 2019;**74**:56-72.

3. Noris M, Daina E, Remuzzi G**.** Membranoproliferative glomerulonephritis: no longer the same disease and may need very different treatment. *Nephrol Dial Transplant*. 2021 Oct 1:gfab281. doi: 10.1093/ndt/gfab281. Online ahead of print.

4. Noris M, Remuzzi G. Glomerular Diseases Dependent on Complement Activation, Including Atypical Hemolytic Uremic Syndrome, Membranoproliferative Glomerulonephritis, and C3 Glomerulopathy: Core Curriculum 2015. *Am J Kidney Dis*. 2015;66:359-75.

5 Noris M, Remuzzi G. Challenges in Understanding Acute Postinfectious Glomerulonephritis: Are Anti-Factor B Autoantibodies the Answer? *J Am Soc Nephrol.* 2020; **31**:670-672.

6 Smith RJH, Appel GB, Blom AM, *et al.* C3 glomerulopathy - understanding a rare complement-driven renal disease. *Nat Rev Nephrol* 2019; **15:** 129-143.

7 Iatropoulos P, Daina E, Curreri M, *et al.* Cluster Analysis Identifies Distinct Pathogenetic Patterns in C3 Glomerulopathies/Immune Complex-Mediated Membranoproliferative GN. *J Am Soc Nephrol* 2018; **29:** 283-294.

9. Noris M, Remuzzi G. Genetics of Immune-Mediated Glomerular Diseases: Focus on Complement. *Semin Nephrol*. 2017;37:447-463.

10. Quintana LF, Kronbichler A, Blasco M, *et al.* ANCA associated vasculitis: The journey to complement-targeted therapies. *Mol Immunol* 2019; 112: 394-398.

11. Song D, Guo WY, Wang FM, *et al.* Complement Alternative Pathways Activation in Patients With Lupus Nephritis. *Am J Med Sci* 2017; 353: 247-257.

12. Rizk DV, Maillard N, Julian BA, *et al.* The Emerging Role of Complement Proteins as a Target for Therapy of IgA Nephropathy. *Front Immunol* 2019; 10: 504.