Unraveling the Role of Complement in Focal Segmental Glomerulosclerosis Pathogenesis: Insights and Challenges

To the Editor: We thank Dr Zagorec *et al*. for their interest in our study and for adding additional patient data supporting a plausible role for complement activation in the pathogenesis of focal segmental glomerulosclerosis (FSGS). Immunofluorescence and immunohistochemistry are invaluable in assessing complement in glomerulonephritis. C4d deposition in nonsclerotic glomeruli segments in 55 of 58 of their FSGS subjects indicates classic or lectin pathway activation. This, coupled with the lack of C1q deposition, supports lectin initiation. However, the absence of C1q has been described in glomerulonephritis and known to activate the classic pathway; and other studies have found greater C1q in FSGS biopsies with little mannose-binding lectin.[1] In addition, we previously found a greater relationship between the terminal pathway and urinary Ba, a marker of alternative pathway activity, compared to urinary C4a.[2] Although overlapping pathway activation in glomerulonephritis is expected, many questions remain. Why is C3 not found by immunofluorescence in nonsclerotic glomeruli segments? What triggers the cascade, and where is it initiated? Antinephrin antibodies targeting podocytes support local activation[3]; however, plasma Bb and C4a levels, which are significantly higher in FSGS than in lupus nephritis, support a systemic trigger.[4]

The lack of activation in minimal change disease (MCD) is also remarkable. In contrast to the absent urinary complement fragments in MCD in our cohort, a recent study found C4d in glomeruli by immunohistochemistry in 46 of 47 FSGS biopsies but in 6 of 15 MCD biopsies.[5] In addition, background C4d was found in some controls without glomerular disease. Similarly, C4d was found by immunohistochemistry in 73%, 21%, and 10% of FSGS, MCD, and controls in another cohort.[1] Although C4d deposition in MCD could reflect unsampled FSGS, the value of faint staining is uncertain and could represent passive trapping rather than ongoing complement activation. Contrary to the above group and the findings from Abedi *et al*.,[5] our study and 3 others found strong associations between complement activation and proteinuria.[1,3,4] With the lack of a unified FSGS pathogenesis and the variable findings using plasma, tissue, or urinary markers of complement activation, future studies are warranted to determine how the complement system can influence the podocyte pattern of injury.

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