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Complement and Podocytopathies: Do We Have a New Biomarker?

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Minimal change disease (MCD) is defined by the absence of visible glomerular lesions on light microscopy and effacement of foot processes on electron microscopy. MCD is the main cause of nephrotic syndrome (NS) in children (75%–90%),[1] with most cases responding to corticosteroid treatment; kidney biopsy is thus typically not performed in children with NS unless steroid resistance is observed. However, MCD only explains 10% to 15% of NS in adults,[2] who demonstrate higher incidence of steroid resistance or dependence and poorer kidney survival. In contrast to MCD, focal segmental glomerulosclerosis (FSGS) shows segmental solidification of the glomerular tuft. Its prevalence and incidence are difficult to approximate, but FSGS seems to be increasing worldwide and is a major contributor to end-stage kidney disease.[3] Plasma factors, adaptive changes, genetic predisposition, infections, and drugs, among others, have been linked to the development of various forms of FSGS. Treatment guidance and prognostic insights in FSGS rely on integration of findings from clinical history, kidney biopsy, laboratory values, and increasingly, genetic testing.

Both MCD and FSGS are histological lesions in the broad spectrum of podocytopathies. However, in these morphologic descriptions, the podocyte injury can be caused by multiple pathological pathways[4] (Figure 1). Moving forward from histological description to an etiologic classification would offer clear benefits, not only at the diagnostic level, but especially in therapeutic management and long-term prognosis improvement. The development of biomarkers with high sensitivity and specificity to discriminate the different pathogeneses of podocytopathies therefore remains a holy grail.

Uncontrolled complement activation can cause or contribute to glomerular injury in multiple kidney diseases such as atypical hemolytic uremic syndrome or C3 glomerulopathy, with clear therapeutic implications. However, in MCD and FSGS, complement-level data from studies analyzing plasma, urine, and kidney biopsies, both in patients and animal models,[5,6] is limited and can be confounded by other phenotypic variations (infections, drugs, etc.).

In this issue, Cambier *et al.*[7] analyzed urinary terminal complement components—membrane attack complex (C5b-9), cytolytic effectors of innate and adaptative immunity, and C5a, a potent anaphylatoxin and chemotactic agent—as potential biomarkers for different podocytopathies. Fifty-six patients with biopsy-proven MCD ($n = 15$) or FSGS ($n = 41$) and proteinuria >1 g/g creatinine were recruited in 4 Canadian hospitals from 2006 to 2023. Compared to FSGS, patients with MCD were younger at the time of urinary sampling (33 ± 22 vs. 48 ± 19 years, $P = 0.02$), with higher estimated glomerular filtration rate (99 ± 32 vs. 53 ± 37 ml/min per 1.73 m^2, $P < 0.001$), lower albuminemia (22 ± 9 vs. 31 ± 10 g/l, $P = 0.002$), and lower proteinuria (3.1 vs. 5.1 g/g, $P = 0.40$). Patients with FSGS were classified as primary disease in up to 58% of cases (24/41); of the remainder, 2 were drug-induced, 1 genetic, 1 maladaptive (previous different GN), and 13 uncertain cause. All patients with MCD achieved complete remission with preserved kidney function, whereas only 25 of 41 patients with FSGS (60.9%) experienced partial remission (with frequent relapses) and 15 of 41 developed kidney failure. Kidney biopsies were reviewed by a blinded nephropathologist within a median of 2 (0–18) months from urinary sampling. Five patients with glomeruli showing only adhesions but no evidence of segmental sclerosis were classified

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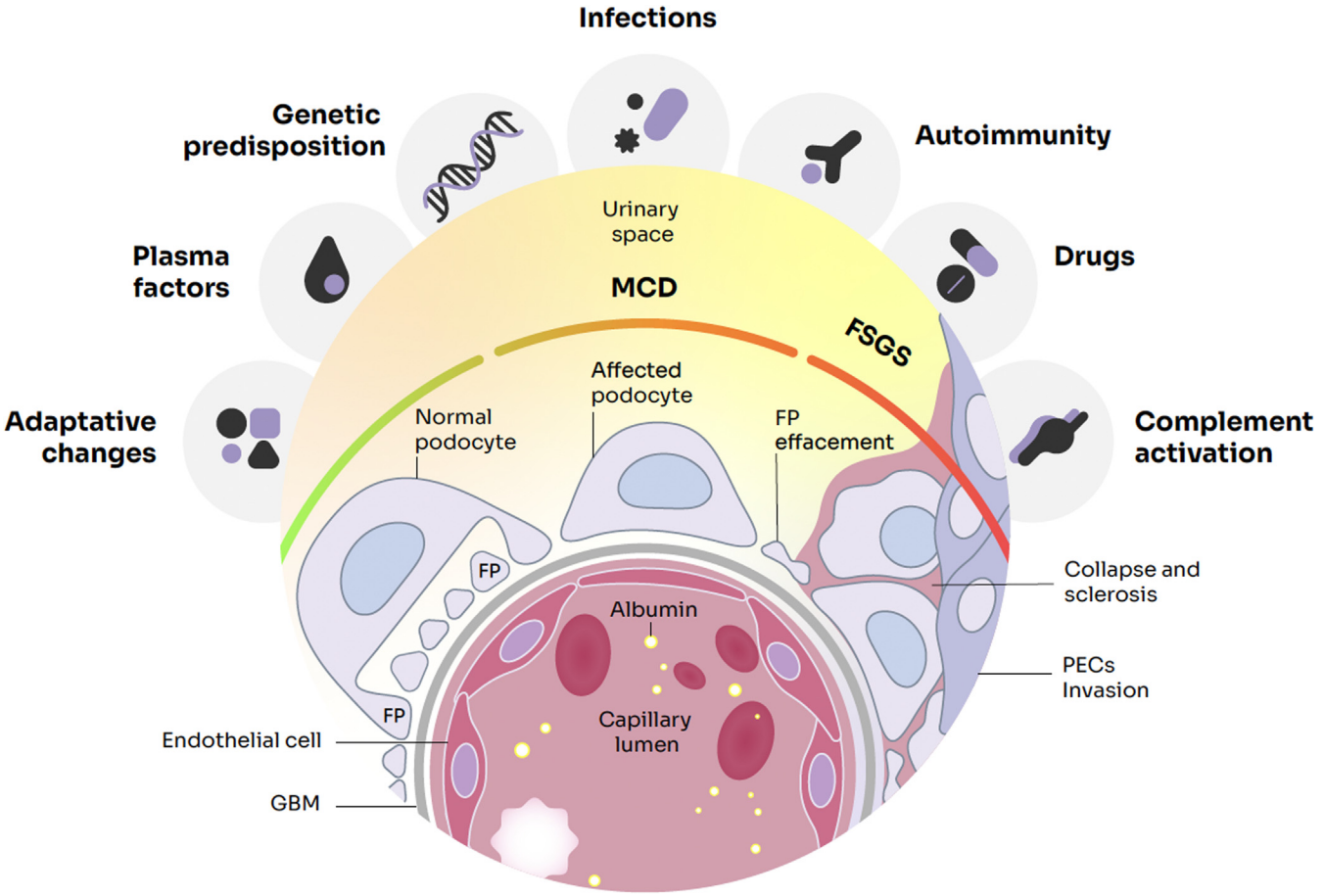

Figure 1. Potential pathogenic mechanisms related to podocyte damage. In the broad spectrum of podocytopathies, different mechanisms have been linked to the development of minimal change disease and focal segmental glomerulosclerosis. These mechanisms include adaptative changes (such as obesity or low weight at birth), plasma factors (e.g., cardiotrophin-like cytokine factor 1, apoA1b [an isoform of ApoA1], anti-CD40 antibody, and serum urine–type plasminogen activator receptor [suPAR]), genetic predisposition (e.g., *APOL1*, *COL4A3-5*, and *PDSS1*), infections (e.g., HIV, cytomegalovirus, and parvovirus B19), autoimmunity, drugs (e.g., heroin, bisphosphonates, and interferon) and complement activation. FP, food process; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; MCD, minimal change disease; PECs, parietal epithelial cells.

as a "potential FSGS." In addition, histology evaluated interstitial fibrosis and tubular atrophy, arteriosclerosis and arteriolar hyalinosis (scaled 0 to 3+), and foot process effacement by electron microscopy (diffuse ≥75% vs. segmental <75%).

In the analysis of complement factors, patients with FSGS presented higher urinary membrane attack complex (C5b-9) levels (8.7 μg/mmol of creatinine) than MCD cases (0.8 μg/mmol of creatinine; $P < 0.001$). Likewise, higher levels of membrane attack complex were found in primary FSGS (12.5 μg/mmol of creatinine) compared to those considered secondary or of undetermined cause (4.8 μg/mmol of creatinine), although the difference was not statistically significant ($P = 0.09$). Urinary membrane attack complex threshold >2 μg/mmol of creatinine in the entire cohort was 73% sensitive and 93% specific for FSGS, increasing its sensitivity up to 93% in cases with proteinuria ≥3g/g creatinine. Patients with FSGS also showed significantly higher urinary levels of C5a (1.26 μg/mmol of creatinine) than patients with MCD (0.06 μg/mmol of creatinine; $P < 0.001$), with high sensitivity and specificity.

Cambier *et al.*[7] propose that these results support a role of complement activation in the pathogenesis of FSGS, and consequently, a potential therapeutic intervention. The search for pathophysiological mechanisms and new therapeutic targets in diseases without specific treatments is undoubtedly a crucial driving force for investigations like theirs. However, enthusiasm should not outweigh caution. First, in the present cohort, the FSGS population is significantly older, and many patients already had advanced chronic kidney disease (5 with stage G3a; 15 with stage G3b; 7 with stage G4; and 3 with stage G5) compared to patients with MCD. In addition, in the FSGS group, several patients had

borderline or normal albuminemia, proteinuria less than 3 g/g creatinine, and higher histological chronicity findings (interstitial fibrosis and tubular atrophy, arteriosclerosis and arteriolar hyalinosis) than patients with MCD (11/15 showed no chronic changes). Furthermore, the patients with secondary FSGS had higher urinary complement component levels than MCD cases. Do terminal complement components in the urine reflect the activity of FSGS lesions or are they just reflective of the severity and chronicity of kidney injury? To reduce these confounding factors, investigations like this should aim to study populations with FSGS and MCD balanced by age and kidney function.

In this observational study,[7] the authors reported no urinary complement activation in patients MCD. However, previous studies[6] showed an increase in blood and urinary C4a levels in patients with NS compared with healthy controls (with no differences between patients with MCD and FSGS). Urinary C5b-9 levels were higher in patients with NS (part of NEPTUNE cohort) and trended higher in 15 pediatric patients with idiopathic NS (validation cohort). These previous studies[8] suggest that the degree of urinary complement fragments could be a nonspecific result of plasma complement proteins spilling into the urinary space and may be influenced by impairment of kidney function, level of proteinuria, and metabolic acidosis.

Complement activation frequently occurs in physiological situations, is not harmful in all conditions, and is most frequently self-limiting. A study of a larger cohort of patients, with the inclusion of patients with different clinical presentations (steroid-resistant and steroid-responsive NS) and degrees of kidney damage, alongside inclusion of a control group, would allow a better assessment of the potential role of complement activation in the podocytopathies. Because glomerular diseases are dynamic processes, the time between biopsy and urinary complement components collection should be as short as possible when evaluating the possible correlation between histology and biomarkers. Finally, a prospective study of the evolution of complement-level biomarkers, reflecting the patient's clinical parameters and treatments received, could allow greater opportunities to evaluate a biomarker's ability to predict outcome.

The search for new biomarkers in podocytopathies is crucial and will offer better pathophysiological knowledge of these entities and improvements in the diagnostic process that, hopefully, allow the development of novel therapeutic targets to improve kidney outcomes. The work by Cambier *et al.*[7] is a valuable contribution to this field in promoting the hypothesis that complement is implicated in FSGS development. Nevertheless, more studies are necessary in a broader population of podocytopathy patients, at varying time points of the disease course, before we can move beyond interesting studies like this towards therapeutic trials of complement-targeting therapies.

DISCLOSURE

MB has received honoraria for presentations, advisory boards, and funding to attend courses and conferences from Otsuka, Chiesi, Alnylam, Astrazeneca, Novartis, and Alexion in the last 36 months. ASB has received consulting honoraria from Apellis, Novartis, Alexion, Q32, Amgen, and Silence.

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