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Complement C5a and C5a Receptor 1 Mediates Glomerular Damage in Primary Focal Segmental Glomerulosclerosis

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Objectives : Clinical data and animal models have provided compelling evidence indicating the pathogenic role of complement activation in the progression of primary focal segmental glomerulosclerosis (FSGS). However, the precise mechanism underlying complement-induced podocyte injury and parietal epithelial cells (PECs) activation requires clarification.
Methods : We examined the glomerular expression of C5aR1 (CD88) in patients with primary FSGS. Mice with Adriamycin nephropathy were administered a C5aR1 antagonist (PMX205) either from day 0 or day 15. The impact on PECs and podocytes was evaluated following exposure to recombinant C5a or FSGS plasma, with or without the C5aR1 antagonist.
Results : Our findings revealed an overexpression of C5aR1 on PECs and podocytes in FSGS patients, with levels positively correlated to serum creatinine, the percentage of segmental glomerulosclerosis, and the prognosis of refractory nephrotic syndrome. In Adriamycin nephropathy mice, the C5aR1 antagonist attenuated proteinuria, blood urea nitrogen, and the percentage of segmental and global glomerulosclerosis. It also alleviated PECs activation and proliferation, along with podocyte loss. Furthermore, there was a reduction in glomerular IgM deposits, followed by decreased deposits of C3d and C5b-9. In vitro, PECs exposed to recombinant C5a exhibited an upregulated expression of CD44 and Notch1, along with increased secretion of COL4A2. Podocytes exposed to FSGS plasma displayed impaired cell viability and downregulation of synaptopodin. These effects were reversed by the C5aR1 antagonist.
Conclusions : These results underscore the pathogenic role of complement system in primary FSGS development through the C5a-C5aR1 axis on podocytes and PECs. The C5aR1 antagonist emerges as a potential therapeutic intervention for FSGS patients.