

# Complement in Lupus: Biomarker, Therapeutic Target, or a Little Bit of Both?



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*Kidney Int Rep* (2021) 6, 2031–2032; <https://doi.org/10.1016/j.ekir.2021.06.016>

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Systemic lupus erythematosus (SLE) is an autoimmune disease with complex pathogenesis involving genetic, hormonal, and environmental factors.<sup>1</sup> Mechanistically, evidence shows that dysfunctional apoptotic cell clearance and intracellular autoantigen exposure, together with abnormalities in lymphocyte signaling and interferon production pathways, are key drivers leading to formation of autoantibodies and pathogenic immunocomplexes. Immunocomplex accumulation in multiple tissues, further increased by their defective clearance, promotes inflammatory responses that impair organ function and structure. In the kidney, these processes produce lupus nephritis (LN), a dire disease complication.<sup>1</sup>

Immunocomplex deposition activates the complement cascade, leading to the deposition of split products in affected tissues and to consumption of circulating complement components. Initial

studies published in the 1950s have shown a correlation between complement consumption and SLE flares, supporting C3, C4, and CH50 (complement activity) measurement as biomarkers of disease activity.<sup>1</sup> More recently, associations between complement consumption and disease activity led to interest in targeting complement components as treatment for SLE.

The current SLE paradigm hypothesizes that effector mechanisms of complement activation enact damage through promotion of uncontrolled inflammation. In murine lupus models, unrestricted alternative complement pathway activation worsens disease severity; accordingly, anti-C5 monoclonal antibody in lupus-prone mice delays development of LN and prolongs survival compared to control animals.<sup>2,3</sup> Besides proinflammatory effects and membrane attack complex (MAC) formation, complement split products (e.g., C3a and C5a) directly injure podocytes<sup>4</sup> and tubular cells<sup>5</sup> acting on their respective receptors.

However, the role of complement in SLE is complex. Although its activation contributes to

SLE-associated inflammation and direct kidney injury, complement deficiency is a risk factor for SLE development. Complement activation is key for clearance of apoptotic bodies, a process altered in SLE.<sup>6</sup> Therefore, genetic deficiencies of the classical complement pathway components are associated with increased risk of SLE.<sup>6</sup>

In this issue, Toy *et al.*<sup>7</sup> report how a common C5 polymorphism (rs17611, 2404G>A) alters risk for developing LN in a cohort of 155 patients with SLE. The C5 variant is more susceptible to cleavage by leukocyte elastase producing a C5a-like molecule slightly larger than C5a derived from C5 convertase activity, but with comparable biological function.<sup>8</sup>

The authors found that the 2404G allele and 2404-GG genotype were associated with LN in Afro-American individuals with SLE, but not in white SLE patients. The reason for this association is unclear and needs confirmation in larger independent studies.

They further analyzed the impact of C5 polymorphism on C5a and MAC levels during LN flares, observing that urine C5a level increases were greater in 2404-GG patients. Importantly, only a subset of patients — approximately one-quarter of the cohort — had increased C5a and MAC in the urine. The patients with highest urinary C5a levels also had most severe proteinuria. Although the authors interpret this finding to support causative relationships between disease activity and urinary complement, it may also reflect high urinary complement filtration due to loss of permselectivity.

Intriguingly, increased urinary C5a levels during flares in patients with C5 polymorphism seem not to be related to the augmented

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cleavage by neutrophil elastase; urine C5a size is identical to C5a derived from C5 convertase. As urinary C5a increased in only a fraction of the LN flares in patients with the 2404-GG genotype, this indicates that whatever protease is cleaving this C5 variant, its involvement is sporadic.

No increase in urinary C5a was detected during SLE remission or during intervals between renal flares. Although this may indicate that urinary C5a truly reflects intrarenal complement activation, it also limits the role of C5a as a biomarker for risk-stratifying renal or nonrenal relapses.

The authors conclude that determining the 2404G>A genotype of LN patients could identify those who would benefit from complement-targeting therapies. Theoretically, gene sequencing could identify functional polymorphisms to precisely tailor treatments for patients with SLE. To date, however, little evidence supports such an approach.

Despite a theoretical risk of worsening autoimmune disease blocking complement-mediated apoptotic body clearance, blockade of the terminal common complement pathway activation with eculizumab, a monoclonal antibody against C5, did not worsen disease severity in patients with SLE-associated thrombotic microangiopathy.<sup>9</sup> Case reports of patients with SLE and other complement-mediated conditions also supports safety of this treatment.<sup>S2,S3</sup>

High disease heterogeneity makes SLE trials extremely challenging.<sup>S4</sup> Studies focusing on complement-targeting therapies may be further complicated by temporal dissociation between local complement activation in target organs and clinically evident disease flares.<sup>7</sup> Should treatment be guided by C5a and/or

MAC urinary levels? Should C5 or C5a receptor targeting therapies be used to treat disease flares or prevent their occurrence independent of urinary C5a levels? Is there a role for a genetic-based approach, testing the hypothesis that different genotypes define phenotypic responses to complement targeted therapies?

The answers to these critical questions will drive design of studies on complement targeting therapies in SLE. Ongoing trials are testing efficacy and safety of anti-C5 antibody (NCT04564339) and C5a receptor (C5aR) antagonists (NCT02151409) in patients with SLE. These studies will help design future trials with similar treatments. Importantly, if urinary C5a and/or MAC are to be used as disease severity biomarkers, standardized assays will be critical to widespread implementation.

In sum, despite the key role of complement in SLE pathogenesis, its complex and paradoxical effects on disease activity make it a challenging therapeutic target in the absence of selective tools. Unique molecules targeting complement components, regulators, and receptors are being developed and need to be followed by clinical studies testing their safety/efficacy profile in patients with SLE. Regardless of outcomes, these studies will clarify the pathogenic role of complement in human SLE. In this perspective, studies similar to the one by Toy *et al.*<sup>7</sup> should be welcome as they help identify new factors to risk-stratify patients and personalize treatments for this complex, heterogenous disease.

## DISCLOSURE

The authors declared no competing interests.

## ACKNOWLEDGMENTS

PC is supported by NIH NIAID grant R01 AI132949.

## SUPPLEMENTARY MATERIALS

[Supplementary File \(PDF\)](#)

[Supplementary References](#)

## REFERENCES

1. Tsokos GC, Lo MS, Reis PC, et al. New insights into the immunopathogenesis of systemic lupus erythematosus. *Nat Rev Rheumatol.* 2016;12:716–730.
2. Li NL, Birmingham DJ, Rovin BH. Expanding the role of complement therapies: the case for lupus nephritis. *J Clin Med.* 2021;10:626.
3. Wang Y, Hu Q, Madri JA, et al. Amelioration of lupus-like autoimmune disease in NZB/WF1 mice after treatment with a blocking monoclonal antibody specific for complement component C5. *Proc Natl Acad Sci U S A.* 1996;93:8563–8568.
4. Angeletti A, Cantarelli C, Petrosyan A, et al. Loss of decay-accelerating factor triggers podocyte injury and glomerulosclerosis. *J Exp Med.* 2020;217:e20191699.
5. Thurman JM, Lenderink AM, Royer PA, et al. C3a Is Required for the production of CXC chemokines by tubular epithelial cells after renal ischemia/reperfusion. *J Immunol.* 2007;178:1819.
6. Macedo ACL, Isaac L. Systemic lupus erythematosus and deficiencies of early components of the complement classical pathway. *Front Immunol.* 2016;7:55.
7. Toy CR, Song H, Nagaraja HN, et al. The influence of an elastase-sensitive complement C5 variant on lupus nephritis and its flare. *Kidney Int Rep.* 2021;6:2105–2113.
8. Giles JL, Choy E, van den Berg C, et al. Functional analysis of a complement polymorphism (rs17611) associated with rheumatoid arthritis. *J Immunol.* 2015;194:3029.
9. Wright RD, Bannerman F, Beresford MW, et al. A systematic review of the role of eculizumab in systemic lupus erythematosus-associated thrombotic microangiopathy. *BMC Nephrol.* 2020;21:245.