

Preview

Lupus nephritis and beyond: Kidney-intrinsic genetic risk for antibody deposition

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SUMMARY

Antibody deposition is a defining pathological feature of multiple kidney diseases including lupus nephritis. In this issue of *Cell Reports Medicine*, Jiang and colleagues¹ identify a novel genetic risk factor, *VANGL1*, which predisposes individuals toward antibody deposition via a kidney-intrinsic mechanism.

The kidney is the most commonly affected major organ in patients with the autoimmune disease systemic lupus erythematosus (SLE, lupus), with 10% of those afflicted progressing to end-stage kidney disease.² Although mechanisms of kidney damage remain incompletely understood, autoantibody deposition and inflammation with immune cell infiltration are hallmarks of the disease and serve as targets of most therapies for lupus nephritis (LN). Treatment has centered around broad immunosuppression with more recent treatments, e.g., belimumab, directed toward depletion of autoantibody-producing B cells.³ A deeper understanding of the drivers behind autoantibody deposition in lupus nephritis and other antibody-mediated kidney diseases is critically important to improving clinical care.

Multiple genetic risk factors, primarily HLA susceptibility in concert with common polymorphisms identified by tagging single nucleotide polymorphisms in gene regulatory regions, confer lupus susceptibility.⁴ Mutations leading to loss of gene function, such as C4 deficiency, which is strongly associated with SLE onset, by contrast are much less common culprits. The known genetic risk factors can be broadly subdivided into 3 gene categories: (1) those affecting the immune system, (2) genes affecting programmed cell death and autoantigens, and (3) kidney-expressed genes promoting intrarenal pathogenesis.⁵ First, dysregulation of both the innate and adaptive immune systems has been implicated in LN pathogenesis with

variants in pattern recognition receptors, immune complex clearance, T and B lymphocyte activation all playing a role. Second, abnormalities in programmed cell death processes allow for the externalization of normally concealed antigens (e.g., nuclear proteins) and their recognition as non-self by the immune system. Notably, these two large categories involve extra-renal processes. The third, smaller category is comprised of intrarenal genes that fall into two subgroups: chemokine pathways that facilitate immune cell infiltration of the kidney⁶ and genes associated with co-morbidities such as hypertension that make the kidney more susceptible to injury overall.^{7,8}

In this issue of *Cell Reports Medicine*, Jiang and colleagues describe a genetic risk factor that does not fall neatly into one of the above categories and bridges the gap between kidney-intrinsic and immune risk factors: a gene predisposing to antibody deposition in a kidney-intrinsic manner.¹ The authors identify an association between copy number variation of the gene *VANGL1* and lupus nephritis and characterize the same loss in an indigenous population with a significantly higher rate of kidney disease than non-indigenous groups. Notably, lupus nephritis is not the primary cause of the high rate of kidney disease among the indigenous population, suggesting a role for *VANGL1* in multiple kidney diseases and emphasizing the broad implications of this work. Hemizyosity of *Vangl1* in mice led to spontaneous antibody depo-

sition within the glomerulus, and serum transfer experiments strongly suggest that *Vangl1* acts in the kidney to prevent antibody deposition, perhaps analogous to that conferred by lupus susceptibility loci in recombinant inbred lupus-prone mice.⁹ While mechanistic details are not fully elucidated, the inferred endothelial barrier function of *Vangl1* would position it in a new category of lupus nephritis susceptibility genes. Finally, the authors demonstrated that antibody deposition in the *Vangl1* hemizygous mouse model was not accompanied by inflammation, a key insight suggesting that antibody deposition itself is insufficient to drive pathology and must be accompanied by a “second hit.” Together, these findings identify a genetic risk factor with likely broad applicability to numerous kidney diseases and an uncommon kidney-intrinsic mechanism.

While the study provides strong complementary human and mouse genetic approaches to define the role of *VANGL1*, there are some limitations and unaddressed questions ripe for future study. First, the association between *VANGL1* mutations and specific kidney disorders remains incompletely characterized. Importantly, the initial association with lupus nephritis that the authors describe was not observed in a validation cohort, potentially due to ethnic differences between the studied populations. The authors also describe a higher mutation prevalence in an indigenous group with higher rates of kidney disease, but the



kidney diseases affecting this population are heterogenous, making it difficult to elucidate the specific role of *VANGL1* while at the same time increasing the applicability of the group's finding. Furthermore, this population had no association between mutation frequency and stage of chronic kidney disease. Future population studies will be essential to parse the associations between ethnicity, specific kidney disease etiologies, disease chronicity, and *VANGL1*. Next, the specifics of *VANGL1* genetics and mechanism remain to be elucidated. How a deletion in intron 7 leads to alterations in protein structure is one such question, and the presence of a cryptic splice site postulated by the authors deserves further consideration. Access to biopsy data from patients with kidney disease who have intact *VANGL1* or are hemizygous or homozygous for the deletion would be another crucial step toward understanding the contribution of this mutation to tissue pathology. Finally, experiments in well-established mouse models of kidney disease, particularly lupus nephritis, will be critical to defining the role *Vangl1* has in maintaining kidney-

intrinsic barrier defenses to antibody deposition. Overall, this study represents an important step forward in our understanding of the genetic, kidney-intrinsic risk factors for kidney disease and opens many avenues for investigation into the role of *VANGL1* in human health and disease.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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