Posttransplant anti–glomerular basement membrane (GBM) nephritis is a rare but devastating complication of Alport syndrome. Although anti-GBM nephritis follows transplantation in only about 3 to 5% of Alport patients, about 75% of affected allografts are lost, and the risk of recurrence in subsequent allografts is very high. Posttransplant anti-GBM nephritis and anti-GBM nephritis in native kidneys (Goodpasture syndrome) are distinct diseases, distinguished by the disparate genetic backgrounds in which they occur, and by differences in the antigens targeted by anti-GBM antibodies.

The phenomenon of posttransplant anti-GBM nephritis in an Alport patient was first described in 1982 by McCoy and colleagues, who made the key observation that circulating antibodies in the patient’s serum reacted with normal GBM, but not GBM in his native kidneys or the kidneys of other males with Alport syndrome (1). They hypothesized that Alport GBM lacks a normal antigenic component that elicits an immune response upon introduction into the Alport patient in the form of a transplanted kidney. Their observations complemented a previous report by Olson et al. that anti-GBM antibodies from patients with Goodpasture syndrome failed to bind to Alport GBM (2). These findings suggested that identification of the targets of anti-GBM antibodies would help in uncovering the molecular defect in Alport syndrome. This work also raised a question: Were anti-GBM antibodies in Goodpasture and Alport patients targeting the same or distinct epitopes?

Studies performed in the 1980s revealed similarities and differences in Goodpasture and Alport anti-GBM antibodies. Both classes of antibodies were shown to target epitopes associated with noncollagenous domains of type IV collagen isolated from normal GBM (3,4). However, one- and two-dimensional immunoblotting studies demonstrated that the Goodpasture and Alport anti-GBM antibodies reacted with different peptide fragments within the noncollagenous fraction of normal GBM, although all of these peptide fragments appeared to be absent from Alport GBM (5). In addition, Alport anti-GBM antibodies were shown to react with epitopes in epidermal basement membranes, whereas Goodpasture antibodies showed no reactivity with these structures (3,6).

This confusing mass of data was greatly clarified by the molecular characterization of the six type IV collagen genes, COL4A1 to COL4A6, and their translational products, the α1(IV) to α6(IV) collagen chains (7). About 80% of Alport families have the X-linked form of the disease (XLAS), resulting from mutations in COL4A5, which encodes the α5(IV) chain (8). Because males with XLAS account for 80 to 90% of Alport patients who require transplantation, it is perhaps not surprising that the great majority of Alport patients who develop posttransplant anti-GBM nephritis are males with XLAS, or that their anti-GBM antibodies predominantly target the α5(IV) NC1 domain (9). About 15% of Alport families have autosomal recessive disease (ARAS), due to mutations in both alleles of COL4A3, which encodes the α3(IV) chain, or COL4A4, which encodes the α4(IV) chain (10,11). In those patients with ARAS who develop posttransplant anti-GBM nephritis, the predominant target of anti-GBM antibodies is the α3(IV) NC1 domain, the site of the Goodpasture epitope (9,12). Thus, the contrasting immunoblotting patterns of Goodpasture and Alport anti-GBM antibodies applied to normal human GBM extracts are explained by the fact that the antibodies target different epitopes: Goodpasture antibodies target the α3(IV) NC1 and Alport antibodies usually target the α5(IV) NC1. The α3, α4, and α5(IV) chains form a distinct type IV collagen network in a subset of basement membranes, including GBM (13). A component of this network is a hexamer composed of the NC1 domains of the α3, α4, and α5(IV) chains [(α3α4α5)5NC1]. This network is missing from GBM of most Alport patients, whether the pathogenic mutation is located in COL4A3, COL4A4, or COL4A5 (13). Absence of this network explains the failure of Alport GBM to bind both Goodpasture and Alport anti-GBM antibodies.

In this issue of JASN, Wang and colleagues add a new facet to the Alport anti-GBM story, showing that anti-GBM antibodies from an ARAS patient and Goodpasture antibodies targeted distinct epitopes on α3(IV) NC1 (14). Using col4a3−/− ARAS mice, the authors found that the target of antibodies generated against α3(IV) NC1 was influenced by the conformation of the α3(IV) NC1 immunogen. Their findings suggest a model in which the specificity of immune responses to α3(IV) NC1 is determined by a complex interplay involving the genetic complement of the host organism and the process by which α3(IV) NC1 epitopes are presented to the immune system. When an α3(IV) NC1–naïve individual, e.g., an ARAS patient with homozygous deletion of COL4A3, receives a kidney transplant, the immune system “sees” an allo-epitope (or “allotope”) located on the surface of the α3α4α5(IV) NC1 hexamer. This
The allotope recognized by the anti-αs(IV) NC1 antibodies generated in patients with X-linked Alport syndrome (XLAS) has yet to be identified. Will the XLAS allotope be relatively accessible, like the ARAS allotope, or sequestered, like the Goodpasture autotope? Autoantibodies to αs(IV) NC1 in non-Alport patients are very rare but have been reported, and are associated with anti-GBM nephritis and subepidermal blisters (16). Perhaps αs(IV) NC1 is also a “Janus-faced antigen” that, like α3(IV) NC1, carries autotopes and allotopes.

The αs(IV) chain is not detectable in basement membranes of most males with XLAS (17,18). Similarly, most patients with ARAS fail to express the α3(IV) chain in their tissues (19). Why isn’t posttransplant anti-GBM nephritis the rule, rather than the exception, in Alport patients? Some reports suggest that production of anti-GBM antibodies after transplantation occurs in most Alport patients, but rarely results in disease (20). Other reports have concluded that generation of anti-GBM antibodies is rare, and influenced by the nature of the causative COL4 gene mutation (9,21,22). By precisely defining the targets of posttransplant anti-GBM antibodies, studies like those of Wang and colleagues should help explain how and why these antibodies are generated, and may facilitate the development of effective prophylaxis against recurrent posttransplant anti-GBM nephritis.

References
