ical knee instability was significantly higher in the optional delayed reconstruction group. Although these findings were not generated by the primary research question, they suggest the potential risks associated with avoiding or delaying ACL reconstruction.

Given that no two patients and no two ACL injuries are identical, it is extremely difficult to recommend a single treatment strategy for all patients with ACL injuries. The study by Frobell et al. confirms that some patients who are not elite athletes can function with an ACL-deficient knee. However, it is difficult to predict which patients will have symptoms of instability that require surgery, and longer-term data are needed to truly understand the benefits and consequences of each of the two strategies described in this study. Ultimately, the decision about whether to reconstruct an ACL-deficient knee, and the timing of surgery when reconstruction is indicated, should be individually tailored to address the unique characteristics of each injured knee and to meet the specific needs of each patient.

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Goodpasture's Disease — New Secrets Revealed

David J. Salant, M.D.

In this issue of the *Journal*, Pedchenko et al.[1] increase our understanding of the pathogenesis of two forms of antibody-mediated glomerulonephritis. One, Goodpasture's disease, is an organ-specific autoimmune disease that is mediated by anti–glomerular basement membrane (anti-GBM) antibodies and has a pathology characterized by crescentic glomerulonephritis with linear immunofluorescent staining for IgG on the GBM. It typically presents as acute renal failure caused by a rapidly progressive glomerulonephritis, often accompanied by pulmonary hemorrhage, that may be life-threatening.

The other form of glomerulonephritis, so-called Alport's post-transplantation nephritis, occurs in a small proportion of patients with Alport's syndrome after kidney transplantation. Alport's syndrome is most often an X-linked disorder in which affected male patients have hematuria from infancy. Proteinuria and progressive renal failure occur during adolescence and early adult life and are often accompanied by deafness and sometimes by ocular abnormalities. Female carriers have hematuria from birth but are generally not subject to renal failure. Electron microscopy reveals splintering of the GBM in affected male patients and thinning of the GBM in female carriers.

Two observations suggested that the underlying mutation in Alport's syndrome is somehow related to the absence of the Goodpasture antigen in the affected GBM. First, patients with Alport's post-transplantation nephritis were found to have circulating anti-GBM alloantibodies and a rapidly progressive glomerulonephritis, with linear GBM deposits of IgG after transplanta-

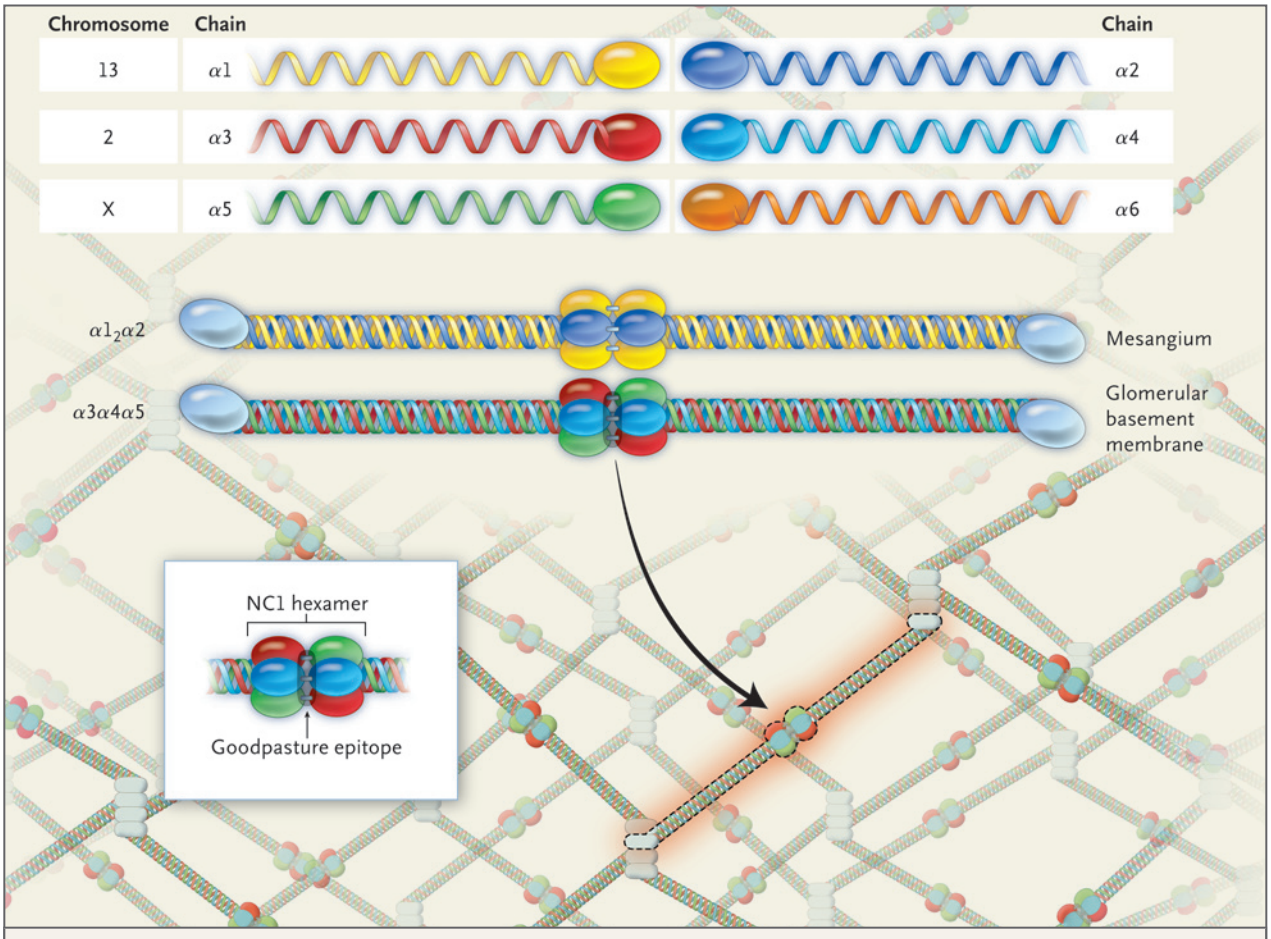

Figure 1. Structure and Composition of Type IV Collagen and the Chromosomal Location of the Genes Encoding Its Six Isoforms.

The genes for the α1 and α2, α3 and α4, and α5 and α6 isoforms share common promoters on their respective chromosomes. Individual type IV collagen chains form a triple helix and contain short noncollagenous domains (NC1 and NC2) at each end. The fibers are laid down as a lattice, joined end-to-end by sulfilimine bonds between the NC1 domains and linked in bow-tie fashion by their NC2 domains. Mesangial type IV collagen is composed of α1 and α2 chains, whereas the collagen of the glomerular basement membrane contains α3, α4, and α5 chains. The Goodpasture antigen is sequestered in the hexamer made up by adjacent NC1 domains.

tion with a normal kidney.[2] Second, anti-GBM antibodies from patients with Goodpasture's disease generally failed to stain the GBM of native Alport's kidney sections, suggesting that the antigen was missing.[3]

A new understanding of the molecular basis of these disorders emerged in the early 1980s after the discovery that basement membranes are made up of a unique form of collagen named type IV.[4] There are six isoforms of type IV collagen, encoded by three pairs of genes on chromosomes 2, 13, and X (Fig. 1). Mature GBM collagen forms a latticelike structure composed of heterotrimers of α3, α4, and α5 chains forming a triple helix and containing short noncollagenous domains 1 and 2 (NC1 and NC2) at each end (Fig. 1). Serum samples containing anti-GBM antibodies from patients with Goodpasture's disease were used to identify the reactive antigen on the NC1 domain of the α3 chain of collagen IV and to document its sequestration in the hexamer composed of the cross-linked NC1 domains of adjacent molecules of type IV collagen[5] (Fig. 1). A search for sequence homologies on the X chromosome identified the gene for the α5 chain of collagen IV and disclosed disease-associated mutations in several families with X-linked Alport's syndrome.[6] This finding, while defining the molecular basis of X-linked Alport's syndrome, failed to explain the apparent

link with Goodpasture's disease. The $\alpha 3\alpha 4\alpha 5$ heterotrimeric composition of the NC1 domain of type IV collagen, and the observation that Alport's post-transplantation nephritis is caused by alloantibodies to $\alpha 5$NC1, provided clues that are developed further by Pedchenko et al.

In their article, the investigators extend their previous observations on the nature and potential clinical importance of the NC1 epitopes identified by anti-GBM autoantibodies and Alport's post-transplantation nephritis alloantibodies. Whereas previous studies showed that serum samples from patients with Goodpasture's disease contain antibodies to $\alpha 5$NC1 (and $\alpha 4$NC1) as well as anti-$\alpha 3$ antibodies, this new work shows that such antibodies can be eluted from the affected tissues of patients with Goodpasture's disease, implicating the antibodies in a pathogenic role. Although only two cases are included in the study, the eluted Alport's post-transplantation nephritis alloantibodies react with $\alpha 5$NC1 and not $\alpha 3$NC1.

Like the anti-$\alpha 3$ antibodies, the anti-$\alpha 5$ antibodies from patients with Goodpasture's disease and from patients with Alport's post-transplantation nephritis are reactive with $\alpha 3\alpha 4\alpha 5$ hexamers purified from GBM; however, the reactivity of the anti-$\alpha 5$ (and anti-$\alpha 3$) antibodies from patients with Goodpasture's disease — but not the anti-$\alpha 5$ antibodies from patients with Alport's post-transplantation nephritis — require that the hexamer first be dissociated. This confirms previous observations that the epitopes identified by antibodies from patients with Goodpasture's disease and those identified from patients with Alport's post-transplantation nephritis are different. It appears that the $\alpha 5$ epitope in Alport's post-transplantation nephritis is exposed on the surface of the hexamer, whereas the $\alpha 3$ and $\alpha 5$ epitopes identified by Goodpasture's disease autoantibodies are cryptic (or hidden), enclosed in the quaternary structure of the hexamers created by previously shown sulfilimine cross-links between the trimers of adjacent NC1 chains.[7]

Applying a technique in which short, linear amino acid sequences of $\alpha 3$NC1 and $\alpha 5$NC1 are attached to a nonreactive $\alpha 1$NC1 backbone, the authors found that the anti-$\alpha 5$ Goodpasture's disease antibodies eluted from the kidney or lung react with a peptide termed E_A, whereas anti-$\alpha 3$ antibodies react with both E_A and an analogous peptide termed E_B from $\alpha 3$NC1. In contrast, Alport's post-transplantation nephritis alloantibodies react with both the intact $\alpha 5$NC1 and $\alpha 5E_A$. Using a computer-based, three-dimensional molecular model to identify the location of the E_A and E_B epitopes, the authors conclude that dissociation of the $\alpha 3\alpha 4\alpha 5$ hexamer causes a conformational change that exposes the epitopes on E_A and E_B, allowing the anti-$\alpha 3$ and anti-$\alpha 5$ autoantibodies to bind. On the other hand, the Alport's post-transplantation nephritis alloantibodies react with an exposed face of the $E_A\alpha 5$ epitope, allowing the anti-$\alpha 5$ alloantibodies to bind to the intact hexamer.

The authors suggest that dissociation of the NC1 hexamers and exposure of the pathogenic epitopes on the $\alpha 3$ and $\alpha 5$ chains may be the inciting event that leads to the production of the Goodpasture's disease autoantibodies. Certainly, there are environmental factors — such as exposure to hydrocarbons, tobacco, and viruses — that have been linked with the development of Goodpasture's disease that could bring about such a conformational change in the quaternary structure of the NC1 hexamers. The question of whether this exposure actually elicits the autoimmune response, or exposure to a pathogenic stimulus induces the autoantibodies and uncovers the epitope, will need further study.

The clinical importance of these findings is difficult to determine, given the retrospective and cross-sectional nature of the studies. The authors found a significantly higher level of autoantibodies (especially anti-$\alpha 5$ antibodies) in patients with Goodpasture's disease who subsequently required dialysis. However, this finding does not establish cause and effect, and other explanations are possible. Nevertheless, the observation may provide useful prognostic information and would be a fruitful line of investigation for prospective longitudinal studies.

Since anti-$\alpha 5$ antibodies are rarely, if ever, found in Goodpasture's disease in the absence of anti-$\alpha 3$ antibodies, one might question why it is important to identify them and their target epitopes. Possible applications of this knowledge might be the design of decoy antigens to block the antibodies from binding to the GBM or the use of immunoadsorbents to deplete the antibodies from serum. The specific epitopes might also be used to help restore self-tolerance.

As the authors note, several other autoimmune

diseases have conformation-dependent epitopes. In some instances genetic polymorphisms influence conformation of an epitope, rendering it susceptible to autoantibody binding.[8] In others, a variety of post-translational modifications create or expose neoepitopes,[9] perhaps the most prominent of which are those produced by the citrullination of several proteins in rheumatoid arthritis.[10] As proposed by Pedchenko et al., an autoantibody itself may also alter antigen conformation, thus exposing additional epitopes, a phenomenon called epitope spreading.

In summary, this article clarifies the probable pathogenic role of anti-α5NC1 autoantibodies in Goodpasture's disease and Alport's post-transplantation nephritis, establishes more clearly the difference between the epitopes identified by Goodpasture's disease autoantibodies and Alport's post-transplantation nephritis alloantibodies, and further advances our understanding of the conformational nature of the Goodpasture's disease epitopes. Remaining challenges include identifying the events that initiate the autoimmune response and induce conformational changes in the NC1 hexamer that enable the antibodies to bind.

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