Tolerance and Autoimmunity in Anti-GBM Disease

ALAN D. SALAMA and JEREMY B. LEVY
Renal Unit, Division of Medicine, Charing Cross Hospital, Hammersmith Hospitals Trust, London, UK.

Anti-glomerular basement membrane (GBM) or Goodpasture’s disease is an uncommon cause of acute renal failure, with an incidence of only 0.5–1 cases/million per year, making it an unfamiliar clinical entity to many physicians. It has two recognized disease peaks in the third and seventh decades of life and is associated with exposure to hydrocarbons. Like many other autoimmune diseases, it has a strong genetic linkage to human leukocyte antigens (HLA), particularly HLA-DR15 and HLA-DR4; however, unusually for an autoimmune disease, it does not follow a relapsing-remitting course (1,2). Despite its rarity, it has been much studied as a model of autoimmune diseases and is preeminent in terms of understanding the immune basis of renal disease. Following its initial description as a clinical entity, Goodpastures disease underwent a more precise diagnostic definition with the identification of deposited and circulating anti-GBM antibodies (3–5). The antibodies were identified as pathogenic following adoptive transfer experiments, and their removal was associated with clinical recovery (6). Pioneering work defined the molecular structure of the GBM and conclusively demonstrated that the autoantigen was a single fraction of a type IV collagen chain in the majority of patients, the NC1 portion of the α3 chain of type IV collagen (α3(IV)NC1), a molecule found only in basement membranes in the kidney, lung, cochlear, and eye (7). Despite the importance of antibody in anti-GBM disease, there is significant evidence that the autoimmune response is driven and orchestrated by T lymphocytes.

Why does a structural protein present throughout an individual’s life suddenly become a target for immune attack? Why is the precise immunologic tolerance to GBM broken in certain individuals at certain times of life?

The immune system has a number of non–mutually exclusive mechanisms to prevent autoimmune phenomena developing. The first and most important is the elimination of self-reactive cells during a period of “immunological education” that occurs in the thymus and bone marrow in fetal and neonatal life. This permanently deletes any lymphocytes that demonstrate strong reactivity to self-proteins. However, the system is not foolproof and certain cells that have the potential to bind epitopes from self-proteins emerge into the peripheral circulation, where a number of other mechanisms usually prevent them from initiating an immune response. These mechanisms include sequestration of the antigen from the immune system, apoptosis and anergy (a switching off of cellular proliferation) of any cells that do react to self-antigens, and active regulation of autoreactive cells by soluble factors such as cytokines or professional regulatory cells.

The detailed characterization of the autoantigen in human anti-GBM disease makes it unique among immunologic renal diseases and human autoimmune diseases in general. Despite the sparse clinical material available from patients with anti-GBM disease, much has been learned regarding the immunopathology of the disease as well as establishing general concepts regarding the development and control of renal autoimmunity.

Analysis of the α3(IV)NC1 molecule was undertaken to define the precise molecular epitopes that constitute the target of the autoimmune response, in an attempt to discover why immunologic tolerance to these proteins is lost and also potentially develop new therapeutic strategies for treating the disease. Using patients’ sera as a source of autoantibody, a number of groups have identified specific regions of the α3(IV)NC1 molecule that are common autoantibody targets (8–10). Some of these regions are poorly exposed in health, and this has led to the suggestion that these more cryptic epitopes are only exposed after a primary insult to the kidney or lung, which allows them to be recognized by the immune system. Interestingly, this may explain the association of clinical disease with hydrocarbon exposure and smoking (causing pulmonary hemorrhage), since both of these environmental toxins may directly damage either pulmonary or renal architecture and expose the previously cryptic α3(IV)NC1 epitopes.

More recent attention has focused on the T-cell responses to the autoantigen. The demonstration of α3(IV)NC1 expression in the thymus of normal individuals suggested that thymic deletional mechanisms should be active, at least in healthy individuals, and result in the elimination of most autoreactive cells generated during the development of the immune system (11,12). This mechanism is clearly not perfect, since circulating T cells from patients have been found to react with the α3(IV)NC1 autoantigen. High cell frequencies are found at the time of disease, but these decrease during the recovery and convalescent periods (12). This result is consistent with peripheral deletion or regulatory mechanisms playing a role in the control of the autoimmune response, again possibly linking with the clinical findings of rare disease relapses. More recently, the role of professional regulatory cells capable of suppressing the autoimmune response has become apparent, with two groups reporting on a population of α3(IV)NC1 autoantigen-specific cells that are capable of modulating the T cell response to the autoantigen. These regulatory cells develop from the time of disease onset and emerge during the convalescent period. Our group defined these by limiting...
dilution and ELISPOT analysis and demonstrated them to be CD25\(^+\) regulatory cells reactive to \(\alpha_3(IV)\)NC1 (13). In this edition of *JASN*, Cairns et al. (14) have defined a group of \(\alpha_3(IV)\)NC1-reactive T cells that have apparently switched their immunologic profile from a proliferative and IFN-\(\gamma\)-producing (Th1) phenotype during the acute disease to a regulatory IL-10–producing (Th2) phenotype during convalescence. The same peptides can stimulate both T-cell responses in the same patient at different times. Moreover, their paper demonstrates that T cells react to only a minority of peptides derived from \(\alpha_3(IV)\)NC1, and the peptides to which the T cells react most strongly do not correspond to those found when \(\alpha_3(IV)\)NC1 is processed and presented by HLA-DR15–expressing antigen-presenting cells in vitro. The authors conclude that the autoimmune T-cell response in anti-GBM disease is therefore targeted toward epitopes on the antigen that are not usually (or inefficiently) processed and presented by antigen-presenting cells. However there are caveats to this. First, the elution experiments were carried out using recombinant bacterial proteins, lacking mammalian posttranslational modifications, as well as EBV-transformed antigen-presenting cells. Both posttranslational modifications and EBV cell transformation are known to strongly influence antigen processing and presentation and have been shown to affect significantly T-cell responses in other autoimmune models. Second, there may be differences between patients and healthy subjects in thymic expression of autoantigen, and thus deletion of autoreactive T cells. Nonetheless as suggested by Cairns *et al.*, changes in peptide processing and presentation may generate epitopes previously not tolerated by the immune system and thus initiate disease.

Reestablishing an operational tolerance to the \(\alpha_3(IV)\)NC1 appears to occur in patients, as disease relapses are uncommon. We now have some indication as to how this may be happening; through an active process in which \(\alpha_3(IV)\)NC1-specific T cells become regulatory rather than pathogenic. Identifying the triggers and controls for the change in T cell cytokine expression and induction of regulatory cells has the potential significantly to impact on our understanding and treatment of Goodpasture’s disease. Are the regulatory IL-10–producing cells described by Cairns *et al.* CD25\(^+\) T cells, or do they simply represent a shift in response of the auto-aggressive \(\alpha_3(IV)\)NC1-specific T cells, which may be induced by regulatory cells or through other signals from antigen-presenting cells? Further work is required to define the basis of this regulatory shift. Moreover, it would be of great interest to compare these data with responses of cells taken from those rare anti-GBM patients with clinical relapses who would be predicted not to demonstrate regulation.

The benefits of such work are that potential new therapies may be developed, with altered peptide ligands, cytokine therapies, or propagation of antigen-specific regulatory cells. Such studies lay the ground for taking us away from the nonspecific immunosuppressive sledgehammer that we currently rely on to a more specific and targeted therapeutic design.

Although significantly harder to perform, with smaller subject numbers and greater variability than animal models, it is reassuring that such experimental studies on patients are performed to provide important information on human disease mechanisms and validate the correlation from animal data. What is now required is that some of these experimental strategies be applied to other more common immune-mediated renal diseases, some of which also have known autoantigenic targets and others with only potential candidates.

References