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 regions have been 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

Correspondence to Dr. Alan D. Salama, Renal Unit, Division of Medicine, Charing Cross Hospital, London W6. Phone: +44 (0)2088461754; Fax: +44(0)2083830692; E-mail: asalama@tiscali.co.uk

1046-6673/1411-2988
Journal of the American Society of Nephrology
Copyright © 2003 by the American Society of Nephrology
DOI: 10.1097/01.ASN.0000096785.86791.68
Tolerance and Autoimmunity in Anti-GBM Disease

References


See related article, “The Fine Specificity and Cytokine Profile of T-Helper Cells Responsive to the α3 Chain of Type IV Collagen in Goodpasture’s Disease,” on pages 2801–2812.