Tipping the Balance in Glomerulonephritis

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Many forms of glomerulonephritis (GN) are believed to be autoimmune in origin, with both humoral and cellular immune responses directed against resident or planted glomerular antigens. In a proportion of cases the antigens are known, such as the a3 chain of type IV collagen constituent of the glomerular basement membrane (GBM) and the immune target in anti-GBM disease (1). In some diseases, antigens from outside the kidney may localize within the glomerulus and subsequently become the target of the immune response, while in others preformed immune complexes consisting of antigen and antibody may deposit directly. Clearly, because GN remains relatively uncommon, most individuals are able to prevent this immunological insult from occurring. This is a result of multiple factors, including the genetic makeup of the individual, their exposure to particular environmental insults, and the state of their “natural” immune protective mechanisms.

We now appreciate that in addition to the deletion of most autoreactive lymphocytes during immune development (central or thymic tolerance), other active mechanisms must keep in check any cells that are positively selected in the thymus but have autoreactive potential. One particular mechanism, which seems to be especially potent and ubiquitous, is the suppression of autoreactive effector lymphocytes by suppressive T regulatory cells (Treg). Different populations of Treg have been recognized. Some are exported from the thymus early on in the post natal period (natural Treg) while others develop in the periphery after antigen encounter under particular circumstances and after exposure to certain cytokines (adaptive Treg). Natural Tregs are characterized by the expression of foxp3, a key transcription factor in their development, and a number of cell surface markers including CD4, CD25, CTLA-4 and GITR (a member of the TNF superfamily). Natural Treg make up approximately 10% of circulating CD4+ T cells. Deficiency of these cells because of deletion of the foxp3 gene or following neonatal thymectomy results in numerous autoimmune phenomena and is mirrored in a human condition in which foxp3 is absent, termed immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance (IPEX) (2). This rare and aggressive autoimmune disease is characterized by thyroid abnormalities, enteropathy, diabetes, eczema, hematologic abnormalities, lymphadenopathy, and premature death. Most adaptive Tregs also appear to express foxp3, although their expression of other cell surface markers is more variable. The mechanisms of Treg action are only partly understood, and in many models rely on production of suppressive cytokines (such as TGF-β and IL-10). However, at least in vitro, natural Tregs employ an as yet unknown cell–cell contact mechanism.

These regulatory cells have been shown to play a role in the prevention of autoimmune diseases using animal models and have been implicated in disease pathogenesis in patients with rheumatoid arthritis (3), Goodpasture’s disease (4), diabetes (5), and multiple sclerosis (6). They have also been shown to play a role in transplantation tolerance (7). In this issue of JASN, Wolf et al. report on the role of Treg in preventing crescentic GN using a well-established disease model (8).

Unraveling the mechanisms of crescentic GN has to a large extent relied on the development of animal models, as human disease is uncommon, often presents at an advanced stage, and is quite heterogeneous. Interestingly, it has proven rather difficult to induce many forms of GN in mice, suggesting that the protective mechanisms that are in place to prevent autoimmunity are particularly efficient in the strains tested.

The authors chose to use a model of nephrotoxic nephritis, produced by localizing (or planting) an antigen to the GBM and targeting the immune response toward it. This results in a crescentic GN, with histologic similarities to human crescentic nephritis. In this model, crescentic GN is a typical delayed-type hypersensitivity reaction, dependent on a T helper1 cell phenotype (producing IFN-γ and IL-12) (9) and requiring macrophages expressing activating Fcγ receptors (10), complement, as well as interactions with resident renal cells expressing other pro-inflammatory cytokines such as TNF-α and co-stimulatory molecules such as CD40 (11,12). Many immune modifiers can attenuate or even abrogate disease in this model, including alteration of the cytokine environment, inhibition of cellular recruitment via integrins (13), and now, after the paper by Wolf et al., tipping the balance in favor of Treg (8).

The authors took cells expressing CD4 and CD25 from healthy, nonimmunized mice and after their purification transferred them to mice in which nephritis was induced. Despite a relatively modest number of Treg cells (1 × 10^6), there was a profound effect on decreasing the glomerular injury and proteinuria, associated with a reduction in renal infiltration of macrophages, CD4 and CD8 T cells, and a decrease in the pro-inflammatory cytokines. Interestingly, there was no alter-
ation in glomerular Ig deposition. Treg did not localize to the kidney; rather, they were maintained within the secondary lymphoid organs, at least at the time points that were examined. These data suggest that normal animals have a population of regulatory cells that are capable of preventing crescentic GN, and that under certain circumstances these cells are ineffective and disease ensues. Are the cells lost, overwhelmed by effector cells, or altered by the methods of inducing disease in the model? When CD4\(^+\)CD25\(^+\) expressing cells were obtained from nephritic (rather than healthy) animals and transferred, the resulting nephritis was augmented, not surprisingly, as the population contained a significant proportion of activated (effector) cells, suggesting that a balance of activated cells to regulators is a critical determinant of disease development. Had the authors obtained cells after disease treatment (reducing the number of effector cells), perhaps disease would have been diminished. These data corroborate our own data in anti-GBM disease, which demonstrate that during disease convalescence, but not at the time of acute presentation, Treg are capable of suppressing the autoimmune effector T cell response (4). Discovery of surface markers that better differentiate between Treg and activated T effector cells might help determine if Treg are present and functional during acute nephritis. One issue that remains untested by Wolf et al. (8), and other animal studies in general, is whether delayed therapy with Treg would be effective. This more realistically mimics the human condition when patients present with established renal inflammation. Nonetheless, by increasing the size of the Treg pool (and not by much), it was possible to tip the balance between immunity and tolerance back in favor of tolerance, demonstrating that these cells may be of therapeutic use.

In this paper, the cells transferred were not antigen-specific and the effect of Treg transfer on other immune parameters was not examined. Current treatment of human crescentic GN is based on suppression of the activation of autoreactive cells, reducing their clonal expansion and shifting the balance away from the damaging autoimmune response. However, adoptive transfer of Treg as shown by Wolf et al. (8) suggests an alternative way of tipping the balance in favor of resolution. Treg can be driven to enter cell cycle and proliferate given the right stimulus, and so they may be expanded in vitro. Importantly, Treg have been shown to suppress memory (recall) responses (14), which predominate in autoimmunity and which have proven more resistant to immunomodulation by conventional means. Hence, expanding the number of Treg may prove to be a useful therapy in a number of autoimmune glomerulonephritides, especially those that occur with a relapsing remitting course, such as systemic lupus erythematosus or systemic vasculitis (which currently require prolonged immunosuppression) or those for which there are limited established therapeutic options, such as crescentic IgA disease. Cellular therapy is already well established in the hematologic world, with T cell infusions after bone marrow transplantation. Therefore, making them a reality in the treatment of autoimmune disease is not so far-fetched.

What is now needed is assessment of which human renal diseases are capable of being regulated by Treg, and which antigen-specific lymphocytes are required for disease development so that the most appropriate conditions can be targeted. As always, there remain a number of questions to be answered. For example, although suppression induced by Treg in immune-mediated GN lasts at least two weeks in the mouse, it is unclear how long-lived this effect would be in patients. What effects would concurrent immunosuppression have and are there some therapies that are more permissive of Treg function? Our own data and that of others suggest that conventional maintenance immunosuppression, used in transplantation or autoimmunity, does not preclude the development of Treg (7,15), however, more data are required. Finally, do we need to be concerned about nonspecific immunosuppression induced by Treg, for example, in the face of concurrent viral infection?

Autologous transfusion of antigen-specific natural regulators for autoimmunity appears to be an attractive form of therapy, especially when compared with the adverse effects that our current immunosuppressive arsenal can induce. Capitalizing on these findings and taking them forward is an exciting prospect for the years to come.

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References


See related article, “CD4+CD25+ Regulatory T Cells Inhibit Experimental Anti–Glomerular Basement Membrane Glomerulonephritis in Mice,” on pages 1360–1370.