Specialized Regulatory T Cells for Optimal Suppression of T Cell Responses in GN

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In the current issue of the Journal of the American Society of Nephrology, Nosko et al. describe novel experimental results that provide compelling evidence for peripheral-derived regulatory T cells (Tregs), which develop during crescentic GN (cGN) and are molecularly equipped to perfectly suppress their T-helper (Th) cell counterparts. GN remains the underlying cause of ESRD in a significant proportion of patients on dialysis, and in some countries comprises up to 40% of the dialysis population. In addition, de novo GN in renal transplant recipients or recurrence of GN frequently leads to allograft loss. In most forms of GN, the underlying mechanisms are still unclear and available therapy is mostly nonspecific and accompanied by a high burden of toxicity. Therefore, there is a need for novel therapeutic approaches, which can only be found by dissecting the course of GN in more detail. Due to limited access to human samples, animal models, like the cGN model used by Nosko et al., remain invaluable in efforts to broaden our understanding of this immunologically fascinating autoimmune disease.

The current cGN model is induced by injecting sheep antiserum directed against the glomerular basement membrane and results in a cGN with histopathologic features similar to human forms of rapid-progressive GN. Although many groups are using this model, it is still unclear what specific kidney and glomerular basement membrane antigen and epitopes are targeted by the antiserum, and if those antigens are the same or different from the human situation. Notwithstanding these limitations, studies using this model are important for furthering our understanding of inflammatory kidney disease. The pathogenesis has been shown to be dependent on innate as well as adaptive immune cells. The importance of γδ T cells has already been described 15 years ago, and recently those cells have been identified as the first cells in the course of cGN in the kidney, attracting neutrophils via IL-17 (reviewed by Kurts et al.). In the early phase, neutrophils are recruited via the chemokine ligand CXCL-1 and infiltrate the kidney, mainly the glomeruli, where they cause damage to glomerular cells. After an early phase of neutrophil infiltration, Th17 cells expressing CCR6 infiltrate the renal interstitium and glomeruli, and in turn recruit neutrophils which infiltrate mainly the interstitium (reviewed by Kurts et al.). This has been proven to be dependent on CXCL-5 rather than CXCL-1. The prolonged infiltration of even more immune cells seems to be dependent on cortical dendritic cells. Their migration to the injured kidney has been shown to be mediated by CCR2 and CX3CR1, and in turn those cells recruit Th1 cells, leading to the attraction of macrophages via IFN-γ (reviewed by Kurts et al.). Proinflammatory cells infiltrate the kidney in cGN, as well as regulatory immune cells, which limit the ongoing proinflammatory processes. Ten years ago, Tregs became the center of attention in cGN, when they were shown to ameliorate the course of cGN.

Since the discovery of CD4+CD25+ Tregs by Sakaguchi et al. in 1995, a number of subpopulations have been described. Soon after the initial description of CD4+CD25+ FoxP3+ Tregs, subsets of this population were identified by differential expression of cell surface markers such as CD103, PD-1, and CD62L. Several of these subsets probably represent different stages of activation or maturation, and—comparable to activated effector T cells—home to locations other than the secondary lymphoid organs. The current understanding is that Tregs develop, not only in the thymus, but also in the periphery from conventional T cells upon exposure to certain combinations of cytokines in an inflammatory environment. The latter, also called peripheral Tregs, might be a useful and very specific tool to counteract immune activation as well as chronic inflammation in secondary lymphoid organs, such as lymph nodes and spleen, and also in nonlymphoid tissues, such as gut and skin. The plasticity of conventional CD4+ T cells depending on the cytokine milieu has been shown clearly, and obviously this plasticity is also evident in peripheral Tregs. Within the respective cytokine milieu, peripheral Tregs coexpress transcription factors previously considered to be specific for conventional T cells, such as IRF4, GATA-3, and Tbet, and are thereby polarized toward Th2-, Th17-, or Th1-like Tregs, respectively. The coexpression of the appropriate transcription factors also results in the expression of specific chemokine receptors, such as CCR6 and CXC3, on Th17- or Th1-like Tregs. This chemokine receptor expression mirrors the expression profile of the distinct effector T cell subpopulation and thereby guides both effector and regulatory T cell subpopulations to the site of
inflammation. Hereby, the immune system generates polarized Treg cells that are molecularly equipped for optimal suppression of effector T cells under the specific inflammatory conditions in which they are generated.

The data published by Nosko et al. further support the concept of Th-specific Treg subsets in cGN. Evidence of the key role of Th-specific Tregs in cGN, namely Th17-like Tregs (which are likewise dependent on STAT-3 signaling and express CCR6), has been previously published. Here, Nosko et al. provide compelling evidence that Th1-specific Treg development by coexpressing Tbet, and that they robustly express FoxP3 and migrate to the site of Th1-prone inflammation by expressing the chemokine receptor CXCR3. Thereby, they effectively inhibit the phenotype of cGN in vivo. It is somewhat surprising that Tbet-expressing Th1-like Tregs have been shown not to play a role in other inflammatory disease models, such as autoimmune encephalitis and colitis, which have been implicated in Th1-dependent models. So far, it can only be speculated that different inflammatory milieus in the respective models are responsible for the observed outcome.

Nonetheless, it is still unclear how and where these Th-specific peripheral Tregs really develop. Nosko et al. speculate that the cells develop in the spleen and migrate to the site of inflammation—the kidney. However, this is questioned by the fact that splenectomy in mice does not have any effect on the phenotype of cGN. Since the lymph node has been proven to be an important site of immune regulation in the cGN model (reviewed Artinger et al.), it would be interesting to study further Th-specific Treg populations in this secondary lymphoid organ.

We all know the limitations of animal studies, especially in the field of cGN, but we also know that novel interventions are urgently needed. Whereas nephrologists are still reluctant to attempt a proof-of-concept study in humans, transplant physicians have already started the first clinical applications of Tregs in solid-organ transplantation. Nonetheless, the application in the transplant setting is much easier compared with cGN because of higher frequencies of transplantation and the possibility of time Treg therapy. Thus, the first clinical trials are already underway to test the safety and feasibility of Treg therapy in renal transplantation (reviewed by van der Net et al.). Work on the roles of different Treg subsets, such as that done by Nosko et al., is of utmost importance. On the basis of the first results of Treg therapy in solid-organ transplantation, we are confident that various engineered Treg subsets could be a therapeutic option in the future. The Treg subset used will probably be based on the state of progression of cGN.

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**REFERENCES**


See related article, “T-Bet Enhances Regulatory T Cell Function and Directs Control of Th1 Responses in Crescentic GN,” on pages 185–196.