Constructing an Immune System for Glomerulonephritis Studies

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Th17 cells mediate various immune-mediated diseases and have recently been proposed to contribute also to GN. A paper in this issue of the Journal of the American Society of Nephrology provides further evidence for this notion and identifies the transcription factor RORγT as an important regulatory element. Because this transcription factor is also active in several innate lymphocyte populations, the authors had to exclude alternative interpretations by generating an animal model in which only T cells were RORγT deficient. To this end, they constructed an immune system in mice by adoptive transfer of defined components. This approach is faster than cell-specific genetic targeting and may turn out useful also for studying other forms of nephritis.

Scientific theories contrary to established dogma usually take long to become textbook knowledge. This certainly applies to the notion that T cells directly cause renal injury. It required three decades to gather sufficient mechanistic evidence in murine models of GN. Many of these studies originated from the laboratories of Holdsworth, Tipping, and Kitching in Melbourne, Australia, who showed in elaborate studies that Th17 cells drive intrarenal delayed-type hypersensitivity reactions and thereby promote certain rapid-progressive forms of glomerular disease, such as pauci-immune or crescentic GN. This concept is widely accepted today, and the attention of scientists has turned toward clarifying the underlying molecular mechanisms, such as identifying the T cell subtypes, the antigen-presenting cells, and the molecular mediators involved. Detailed mechanistic information is essential not only for understanding immunopathophysiology, but also for designing novel therapeutic approaches.

The Th subset causing crescentic GN are the Th type 1 (Th1) cells, which produce mediators like IFNγ to stimulate macrophages that cause renal injury. Normally, this is important for anti-viral and anti-bacterial defense. By contrast, Th2 cells activate eosinophils that mediate anti-parasite immunity. However, if dysregulated or autoreactive, both Th cell types may cause disease, such as Th1 cell–dependent contact dermatitis or Th2 cell–dependent asthma. An important extension of the Th1/Th2 dichotomy was the discovery of Th17 cells as a third differentiation type of Th cell. Th17 cells have been implicated primarily in immune-mediated diseases, especially in multiple sclerosis and rheumatoid arthritis, whereas their anti-infectious role remains unclear. While this unresolved question continues to puzzle basic scientists, clinical immunologists have realized that a T cell subset mainly involved in disease offers therapeutic opportunities: selective inhibition of Th17 cells should not result in serious immunosuppressive side effects if Th1 and Th2 cells remain functional. However, developing such approaches requires exact mechanistic knowledge on Th cell subsets and their regulation in immune-mediated diseases.

From this perspective, the simultaneous discovery from Ulf Panzer’s group in Hamburg, Germany, and Richard Kitching’s group in Melbourne, Australia, that Th17 cells can mediate kidney disease represents a major step forward in nephroimmunology. These two groups have joined forces and present in this issue of the JASN further evidence for an involvement of these cells in nephritis: Oliver Steinmetz from Hamburg discovered during a postdoctoral sojourn to Melbourne that the transcription factor RORγT, which is important in Th17 cell differentiation, regulates nephritogenic Th17 cell responses. These authors induced accelerated crescentic GN in mice deficient for RORγT and found that clinical symptoms and renal infiltration with immune cells were much attenuated. Systemic IgG titers and macrophage responses were unaffected in these mice, confirming that Th1-dependent immunity was preserved. Until here, the study might be considered straightforward or even simple. However, RORγT knockout mice feature several other alterations, so that an observed phenotypic difference cannot be automatically attributed to the lack of Th17 cells. Most importantly, these mice lack lymph nodes, because lymphoid tissue-inducer–like (LTI) cells, which mediate fetal lymphoid tissue organogenesis, depend on this transcription factor and are therefore absent in RORγT knockout mice. Furthermore, LTI cells can produce IL-17, and so does another recently discovered RORγT-dependent population of natural killer (NK)–like cells that occur in the intestine. Therefore, it remained to be investigated that the attenuation of disease in RORγT knockout mice was caused by the absence of lymph nodes or of IL-17–producing LTI and/or NK cells.

To rule out these alternative explanations, Steinmetz et al. took advantage of an elegant immune system construction kit approach,
where RAG-knockout mice (which lack T and B cells but possess LTi and NK cells) are reconstituted with splenocytes or with isolated CD4+ Th cells from wild-type or RORγT-deficient mice. This allowed creating an experimental situation where lymph nodes were present and where only the Th cells lacked RORγT. After confirming that such mice have an operational cellular immune system, they showed that the selective lack of this transcription factor in Th cells was sufficient to attenuate crescentic nephritis. However, there was still one more alternative explanation that needed to be excluded: RORγT operates also in regulatory T cells, which may be explained by a developmental similarity with Th17 cells. To address this issue, they reconstituted RAG-deficient mice with RORγT-deficient Th cells depleted of CD25+ T cells. Also in this setting, crescentic nephritis was attenuated, ruling out that regulatory cells had been responsible. These experiments allow the conclusion that T cell–expressed RORγt supports nephritogenic Th17 responses.

This experimental system of reconstituting RAG-deficient mice with lymphocyte populations from knockout mice may look complicated and even contrived at first glance. However, it has proven very useful in immunology, because it allows rapid assembly of an immune system from defined components to clarify which components are important in a disease model and which are not. The alternative approach of genetically generating mice whose Th cells selectively lack RORγT (for example, by generating and crossing mice with a floxed RORγT gene to mice expressing Cre under a Th cell–specific promoter) is far more labor- (and cost-) intensive and time-consuming. This study is the first to apply this reconstitution approach in nephritis research. In doing so, Steinmetz et al. have provided further support for a role of T cells in general and especially for Th17 cells in GN. Moreover, they identified RORγT as a potential therapeutic target, which in theory should allow less immunosuppressive side effects, because anti-infectious Th1 and Th2 cells should remain unharmed. The future will show whether this exciting new concept will hold its promise in clinical translation.

DISCLOSURES
None.

REFERENCES

HIV-1 Entry into Renal Epithelia

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Presence of HIV-1 nucleic acid in both glomerular and tubular cells indicates that the kidney may serve as a reservoir for HIV-