IL-17A in Experimental Glomerulonephritis: Where Does It Come from?

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The immune system comprises specialized cells and molecules that are capable of combating nearly any pathogen. Innate immunity provides a first line of defense, whereas adaptive immunity, collectively T and B lymphocytes, provides antigen-specific mechanisms that keep the body pathogen-free. Much has been learned about T cell recognition of peptide antigen and subsequent co-stimulatory signals that instruct T cells to mature and differentiate into a number of subsets. T cell subsets have varying functions and effects. For decades, it has been known that T cells can develop into either Th1 or Th2 effector cells, each better suited to combat particular types of pathogens. A new T cell subset, Th17 cells, that may have a pivotal role in the context of autoimmunity has recently been identified.

The Th17 subset, first characterized in 2005,[1] correlates with autoimmune disease. These implications have run the gamut from protection of mice that are deficient in the cytokine IL-17A from experimental autoimmune encephalomyelitis to the finding that synovial fluid from patients with rheumatoid arthritis contains increased levels of IL-17A.[2,3] The study by Gan *et al.*[4] in this issue of *JASN* suggests Th17 cells play a role in the pathogenesis of experimental anti-myeloperoxidase (anti-MPO) glomerulonephritis. In this study, Gan *et al.* detected systemic IL-17A production after inducing an antibody response directed against MPO found in neutrophils. This IL-17A production is mainly derived from Th17 cells. Wild-type mice develop necrotizing glomerulonephritis, whereas IL-17A$^{-/-}$ mice are protected.

The experimental model used by Gan *et al.*[4] elucidates a new role for IL-17A production in the pathogenesis of anti-MPO glomerulonephritis; however, several questions remain unanswered. In this study, it is unclear which cell type is producing IL-17A. Does anti-MPO glomerulonephritis develop from the direct effects of IL-17A or from downstream responsive pathways? The overarching question is, "How can these findings translate to human disease?"

In human ANCA disease, much is known about T cell responsiveness, including recognition of MPO or proteinase 3.[5,6] Although the proportion of regulatory T cells (Tregs) increases,[7] these Tregs from patients with ANCA seem defective in that they are unable to suppress proliferation of effector cells and their cytokine production.[8] The most intriguing of the T cell findings is that in ANCA disease, there is an increased percentage of T cells secreting IL-17 in the periphery, and serum levels of the Th17-associated cytokine IL-23 correlates with ANCA titers and propensity to relapse; therefore, some human data correspond to the murine studies.[9]

Are Th17 cells really participating in the pathogenesis of ANCA disease, or are Th17 cells the byproduct of another underlying mechanism? Studies in mice revealed that Th17 cells and Tregs are very closely related within the immunologic family tree, although they have opposing functions. Both cell types require TGF-β for differentiation, and both initially express the transcription factor ROR-γt.[10] Slight alterations in the cytokine milieu can push a cell toward a Th17 or Treg phenotype. Some studies suggested that Th17 cells are unstable in that they have the ability to convert into a Th1-like phenotype.[11] Likewise, FoxP3^{+} Tregs may differentiate into IL-17–producing cells.[12] Treg conversion to Th17 has been observed in instances of persistent infection and inflammation.[13] Evidence suggests that components of pathogens themselves and the type of inflammation they incur can initiate this switch. These studies provide biological data supporting the accumulation of epidemiologic data correlating certain infections preceding the onslaught of autoimmunity. Thus, it is possible that the accumulation of Th17 cells in autoimmunity is merely a reflection of decreased Treg activity.

The study by Gan *et al.*[4] suggests neutrophil accumulation in the kidney is dependent on IL-17A and chemokines induced by the IL-17A pathway. Th17 cells produce and secrete CXCL8, a chemotactic ligand for neutrophils. Supernatants from cultured Th17 cells induce activation of neutrophils while promoting their survival. Neutrophil activation is dependent on GM-CSF, TNF-α, and IFN-γ production from Th17 cells.[14] Although there is an ongoing debate as to whether IL-17 can directly modulate neutrophil responses, Th17 cells are certainly contributing to neutrophil activity, yet neutrophils themselves can produce CCL2 and CCL20—the main chemotactic ligands for Th17 cells.[14] In ANCA disease, ANCA activation of neutrophils could recruit Th17 cells, or do Th17 cells recruit neutrophils that are then activated by ANCA?

The pathogenesis of ANCA disease requires at least two hits: One of which is MPO or proteinase 3 ANCA–induced neutro-

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phil activation.[15] The data from Gan *et al.* suggest that Th17 cells could be another hit in the pathogenesis. In this model, ANCA disease did not progress in the absence of IL-17A.[4] Mice deficient in IL-17A had high anti-MPO titers, akin to humans who have autoantibodies but who are asymptomatic. Further explanation will be required to define precisely the role of IL-17A and IL-17A–producing cells in human ANCA disease.

DISCLOSURES

None.

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See related article, "Th17 Cells Promote Autoimmune Anti-Myeloperoxidase Glomerulonephritis," on pages 925–931.

Caspase-12 and Diabetic Nephropathy: From Mice to Men?

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Since the seminal observation that high glucose induces renal cell apoptosis in culture and *in vivo*,[1] investigators have sought to identify the molecular mechanisms of renal cell apoptosis in diabetic nephropathy. In this issue of *JASN*, Brezniceanu *et al.*[2] explore proapoptotic genes that are upregulated differentially by reactive oxygen species (ROS) in renal proximal tubular cells of diabetic (db/db) mice. Expression of caspase-12 and other endoplasmic reticulum (ER) stress genes, such as HSPA5/GRP78/BiP and CHOP, are increased in the proximal tubules of these mice compared with nondiabetic and diabetic catalase transgenic mice. Reduction of ROS generation also inhibits albumin-stimulated expression and activity of caspase-12 in a human proximal tubule cell line (HK-2). Furthermore, knockdown of caspase-12 with small interfering RNAs reduces albumin-induced apoptosis in HK-2 cells. The authors of this article conclude that albuminuria may induce ROS-mediated ER stress and subsequent tubular apoptosis in diabetic kidneys. The involvement of caspase-12 in this process, especially in human cells, stands out as the most original part of the article; however, no information is provided on human

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