

The Emergence of Th17 Cells as Effectors of Renal Injury

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ABSTRACT

IL-17-producing Th17 effector cells directly induce renal inflammation by activating neutrophils or by participating in macrophage-mediated tissue injury. Th17 cells and cytokines participate in human and experimental renal disease, especially in proliferative glomerulonephritis where Th17 effector cells are active. Although growing evidence suggests Th17 cells are particularly relevant to effector responses involving neutrophils, there are still important questions to address before the complete functions of Th17 cells in renal disease are understood fully.

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The kidney is affected by organ-specific, systemic, and dysregulated immunity as an innocent bystander in host defense, and in transplantation through targeted allogeneic responses. Therefore, how CD4⁺ T helper (Th) cells direct these events is of central importance to immune-mediated renal disease. The discovery that CD4⁺ cells differentiate into different T helper cell subsets promoting various immune effector pathways revolutionized our understanding of host defense and immunopathology. For 20 years, only Th1 (expressing IFN- γ) and Th2 (expressing IL-4) subsets were known. The realization that another effector subset, called Th17 (as it produces IL-17A), contributes to both host defense and immunopathology is a major new development in how we view adaptive immunity.¹

Although many features of the Th1/Th2 hypothesis were validated by observations in humans and in experimental models of disease, there were significant flaws relating to protection from extracellular pathogens or in the pathogenesis of organ-specific autoimmunity.¹ Nonetheless, the variable po-

larization of T helper cell subsets in nephritogenic immunity (Th1 and Th2) helps explain both the patterns and severity of injury in a number of immune-mediated renal diseases, with cell-mediated immunity in the kidney generally associated with Th1 responses.^{2,3} The realization that cell-mediated injury could also result from activity of the Th17 subset calls for a re-evaluation of T helper cells and their role in renal immunopathology.

The discovery of the Th17 subset (originally called “Th_{IL-17}” as it expresses IL-17A and IL-17F) came through awareness that discordant results in organ-specific autoimmunity could be explained by the existence of another cytokine, IL-23, important in stabilizing Th17 responses.⁴ Before IL-23’s discovery, it was known that IL-12, the cytokine that induces Th1 responses, was a heterodimer composed of IL-12p40 and IL-12p35 subunits. Although IL-12p40-deficient mice were protected in experimental autoimmune encephalomyelitis, and in experimental autoimmune glomerulonephritis, IFN- γ -deficient mice were not.^{5–7} IL-23, although not critical for the differ-

entiation of Th17 cells, maintains and expands the Th17 subset.⁴ IL-23 shares the IL-12p40 chain with IL-12, but it has its own unique IL-23p19 subunit, and IL-23p19-deficient mice are protected from both autoimmune encephalomyelitis and glomerulonephritis.^{5,8} Therefore, by virtue of its importance in both Th1 and Th17 responses, IL-12p40 occupies a privileged place in the biology of T cell-mediated disease.⁴ Anti-IL-12p40 therapy has been approved for the treatment of psoriasis and is being evaluated in other autoimmune diseases, and its ability to modify dual proinflammatory pathways may also afford therapeutic advantage in rapidly progressive glomerulonephritis.

The differentiation of Th17 cells involves two pleiotropic cytokines, IL-6 and TGF β . IL-6 and TGF β together (often with IL-21) direct T cells to a Th17 phenotype, whereas TGF β alone (in the absence of IL-6 in inflammation) instructs T cells to function as anti-inflammatory T cells known as T regulatory cells (Tregs).⁹ Th17 cells and Tregs share CCR6 receptors;¹⁰ however, neither Th17 nor Treg cells are as stably committed as Th1 or Th2 cells.^{11,12} Th17 cells

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express particular transcription factors, cytokines, and chemokine receptors, some of which are common to other cell types. A simplified schema of the increasing complexity in T helper cell subsets is shown in Figure 1A.

These four well-defined subsets can also cross-regulate each other. Although Tregs exert regulatory effects over Th17, Th1, and Th2 cells, and there is some reciprocal inhibition between Th1 and Th2, the relationship between Th17 and Th1 cells is less clear. Evidence exists for both synergism and reciprocal inhibition between Th17 and Th1 subsets.^{13,14} Synergism between these two arms of the effector immune response enhances host defense, but in immunopathology the combined actions of Th1 and Th17 cells result in tissue injury from a variety of

activated mechanisms. The time course of Th17-mediated injury is also uncertain, and early Th17-mediated renal injury could be followed later by Th1-mediated disease.¹⁵ Furthermore, Th17 cells can acquire a mixed Th17/Th1 phenotype. Human T cell clones producing both IL-17A and IFN- γ have been defined,¹⁶ and murine Th17 cells do not have a particularly stable phenotype, expressing IFN- γ with time.^{17,15}

Th17 cells have diverse effects on innate effectors and somatic cells. They mobilize and activate neutrophils, directly affect resident somatic cells, and induce macrophage production of IL-1 β and TNF.^{9,18} Neutrophils, important in host defense, in renal ischemia reperfusion injury, and in ANCA-associated glomerulonephritis, are all targets of

Th17 cytokines. Several Th17 cytokines directly affect tissue cells. IL-17A stimulates tubular cells¹⁹ and mesangial cells^{20,21} to produce T cell, macrophage, and neutrophil chemoattractants (Figure 1B). Renal microvascular endothelial cells are also likely to be IL-17A-responsive, given the expression of IL-17 receptor components on microvascular endothelial cells in other organs.²² One Th17 cytokine that particularly illustrates the effects of Th17 cell on tissues is IL-22; it is produced by Th17 cells but, belying its status as an IL, affects only somatic cells, particularly epithelial cells.²³ In other organs, IL-22 is important in host defense and potentially important in some forms of damaging inflammation.^{24,25} Although IL-17A has a role in experimental pyelonephritis,²⁶ the role of IL-22 in renal disease is unknown.

Observational human studies and functional studies in experimental systems support the concept that rapidly progressive glomerulonephritis involves both humoral and cellular effectors, with CD4⁺ cells participating in most severe, crescentic forms of glomerulonephritis.² Evidence has accumulated over the years that Th1 responses mediate these lesions.² But are Th17 responses involved? Th17 cells promote experimental anti-myeloperoxidase glomerulonephritis,²⁷ and humans with ANCA-associated vasculitis have elevated IL-23 and IL-17A levels and IL-17A production by T cells.^{28,29} Serum IL-17A levels in patients with systemic lupus erythematosus are elevated and correlate with disease activity.^{30,31} IL-17A is present in glomeruli of patients with lupus nephritis, and double negative (CD4⁻, CD8⁻) T cells are a major source, underscoring the need to discriminate between IL-17A production by Th17 cells and IL-17A from other cell types.³² Both Th1 and Th17 effector T cells have the capacity to induce immune-mediated glomerular injury.^{20,15} Several studies implicate IL-17A, IL-23, and Th17 responses in experimental glomerulonephritis, including studies in planted antigen models of glomerulonephritis, anti-glomerular basement membrane glomerulonephritis, anti-myeloperoxidase glomerulonephritis, and lupus nephritis.^{27,20,33,34} In

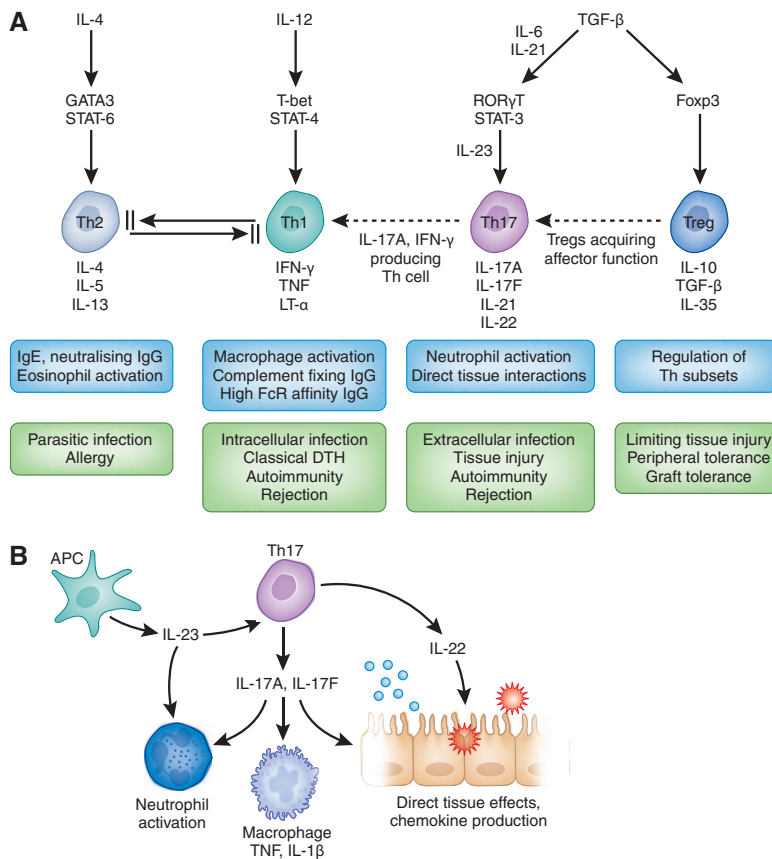


Figure 1. (A) Simplified diagram of the Th1, Th2, Th17, and Treg subsets, showing key cytokines produced by these cells, and the cytokines and transcription factors critical to the development and expansion of these subsets. The biologic functions of Th cell subsets are briefly summarized. There is evidence that Th17 cells can acquire the capacity to produce IFN- γ , and Tregs can, at sites of inflammation, lose their Foxp3 expression and acquire effector function. (B) Summary of potential mechanisms by which Th17 cytokines could mediate immune renal injury.

Table 1. Complexities and questions in the biology of Th17 cells

Area	Complexities and Questions
Th17 cell plasticity	Do Th17 cells later acquire a Th1 phenotype? Is it inevitable that some Tregs will become Th17 cells in inflammation?
Th17 does not equal IL-17A IL-17A does not equal Th17	What are the roles of other Th17 cytokines? Other important cellular sources of IL-17A need to be assessed
Relationships between Th1 and Th17	Do Th1 and Th17 cells synergize with or antagonize each other?
Differences between mice and men?	How discrete is the Th17 subset in humans?
Renal injury mediated by Th17 responses	Do effector Th1 and Th17 responses reflect different pathways to similar renal end points?
Intrinsic kidney cells and Th17 cells	How do renal cells respond to (and potentially secrete) Th17 cytokines?
Further Th subsets (for example, Th22 and Th9)	How many subsets are there? Is there a continuum between them?

two of these models (planted antigen/nephrotoxic serum nephritis and experimental lupus nephritis) IFN- γ , the prototypical Th1 cytokine, is pathogenic.² Whether Th1 and Th17 cellular effectors operate synergistically or independently is unknown. It will be important to determine whether Th1 and Th17 subsets cross-regulate each other in immune-mediated renal disease, as excessively reducing Th17 responses conceivably might lead to increased injury from enhanced Th1 effector responses.¹⁴

What is the pattern of renal injury directed by Th17 responses? In some models of renal disease, the potential participation of humoral immunity and CD8⁺ cells can confound assessments of the role of T helper cell effector function. Clear proof of concept of the capacity of Th1 and Th17 cells themselves to induce injury has been provided using a cell transfer system.¹⁵ Th1 or Th17-polarized ovalbumin-specific CD4⁺ cells were transferred into *Rag1*^{-/-} mice (lacking adaptive immunity) with ovalbumin in their glomeruli. Th17 cells induced proliferative glomerulonephritis more rapidly than Th1 cells and injury in Th17 cell recipients was associated both with neutrophil recruitment and the expression of intrarenal CXCL1, the murine homologue of IL-8. In contrast, renal injury in Th1 cell recipients develops more slowly, is characterized by macrophage activation, but is ultimately more severe. From these data, and the biologic activities of Th17 cells, one might expect Th17 responses to be more prominent in human neutrophil-mediated glomerular injury, in particular, ANCA-associated glomer-

ulonephritis, as suggested by human observations and animal studies.^{27–29}

Although most of the focus on the role of the Th17 subset centers on cell-mediated effector responses, some, but not all, studies suggest that Th17 cytokines promote autoantibody production.^{27,31} Observations in human renal transplantation link the presence of IL-17A to rejection and allograft dysfunction^{19,35} and Th17 cells are important in experimental cardiac transplantation.³⁶ The obligatory involvement of ischemia reperfusion injury in renal transplantation provides another avenue by which Th17 cytokines influence the course of allogeneic responses. Neutrophil-derived IL-17A is a target in ischemia reperfusion injury that could reduce the chance of early graft dysfunction.³⁷ As strategies aimed at inducing tolerance by tipping the balance toward regulatory T cells—away from damaging effector responses—gain pace, a central issue is the plasticity of Tregs and how to prevent them acquiring an effector Th17 phenotype.

Th17 cells are undoubtedly important as one component of immune responses that leads to renal injury. However, there is still much to be learned about these cells (summarized in Table 1), the nuances of their effector functions, the timing of their participation, and their degree of plasticity. T cell subsets, especially Th17 cells and Tregs, are more fluid than we once thought, and the epigenetic changes in these cells on differentiation to a Th17 phenotype may not be stable. In the future, T cell subsets may be seen as broader entities that are tunable.¹² In host defense this would enable effector

functions to effectively manage infectious threats while simultaneously limiting bystander injury to tissue. When infection is controlled, subtle alterations in subset phenotype could assist in effectively resolving the inflammation and limiting secondary immune responses. The corollary of this notion is that in inflammatory kidney disease and renal transplantation observations in human disease need to be supported by careful experiments using well-characterized *in vivo* and *in vitro* systems. The relationship between Th17 cells and Th1 cells in cell-mediated renal injury needs better definition. On the basis of a detailed understanding of the pathogenesis of different forms of kidney disease, modulating the damage from Th17 (and other T cell) immune responses by delivering more targeted and less toxic therapy is an achievable future aim.

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DISCLOSURES

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