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Review article

Plasticity and heterogeneity of Th17 in immune-mediated kidney diseases

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ABSTRACT

Anti-neutrophil cytoplasmatic antibody (ANCA)-associated glomerulonephritis, anti-glomerular basement membrane (GBM) glomerulonephritis and lupus nephritis are the most common causes of rapid progressive glomerulonephritis (RPGN) in the Western world. These aggressive forms of autoimmune kidney diseases significantly contribute to end-stage renal disease and are associated with high morbidity and mortality. Moreover, patients show significant heterogeneity with respect to clinical outcome and response to therapy. T cell infiltration is a morphological hallmark of RPGN and it is a critical driver of kidney injury. Different $CD4^+$ T cell subsets that are endowed with distinct regulatory and effector functions are involved in this detrimental inflammatory process. In particular, the identification and functional characterization of IL-17-expressing $CD4^+$ Th17 cells have substantially advanced our understanding of organ-specific autoimmunity. In experimental models of crescentic and proliferative GN, including ANCA-associated GN, anti-GBM-GN and lupus nephritis, the Th17/IL-17 axis significantly contributes to renal tissue damage. In patients with ANCA-associated GN or lupus nephritis, IL-17 serum levels correlated with disease activity. Moreover, Th17 cells are present in the kidneys of these patients and represents a topic of intense ongoing clinical and basic research. Importantly, recent studies have challenged the view of $CD4^+$ T cells subsets as terminally differentiated homogenous cells, showing that T cells, in particular Th17 cells, are much more flexible and heterogeneous than previously thought. However, analysis of Th17 cell fate in mouse models of autoimmune kidney disease revealed a high degree of stability within these cells, an observation that is in contrast to Th17 cells in other models of autoimmune diseases including experimental autoimmune encephalomyelitis. Interestingly, anti-CD3 treatment interferes with stable Th17 cells and induces a potential regulatory phenotype in Th17 cells, highlighting the therapeutic potential of targeting pathogenic Th17 cells in autoimmunity. In this review, we discuss the current knowledge of Th17 cell plasticity and heterogeneity in autoimmune kidney diseases with a special focus on the underlying mechanisms of this process and debate if Th17 cell plasticity is beneficial or harmful to renal inflammation.

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1. Introduction

Immune-mediated glomerular diseases (glomerulonephritis, GN) are a leading cause for the development of end-stage renal failure. Glomerular injury mediated by the immune system can be a consequence of systemic diseases, such as ANCA-associated vasculitis or systemic lupus erythematosus (SLE), or can be due to kidney-restricted diseases, such as IgA nephropathy, membranous nephropathy and some forms of anti-GBM-GN. These entities differ substantially from one another in their primary localization of glomerular injury, clinical course and manifestations. The clinical symptoms in patients range from asymptomatic hematuria to nephrotic syndrome with massive urinary protein loss or even worse rapidly progressive glomerulonephritis (RPGN) with irreversible renal failure. The underlying immunopathogenesis of the various forms of GN is complex and in large parts not well understood, but fundamental to all forms of immune-mediated glomerular injuries is a disturbed immune reaction, which leads to local pathogenic inflammatory responses resulting in progressive glomerular and tubulointerstitial destruction and ultimately to loss of kidney function. Several studies have now clearly demonstrated the critical role of $CD4^+$ T cells, in addition to the well characterized impact of glomerular autoantibody and immune complex deposition, in glomerulonephritis [1–4].

$CD4^+$ T helper cells orchestrate the immune response and play a central role in infection, inflammation, and autoimmunity. Distinct types of $CD4^+$ T cell subsets endowed with distinct migratory capacities and effector functions perform these tasks. The identification and functional characterization of distinct T cell subsets, such as Th1, Th2 [5] and Th17 cells [6,7] have substantially advanced our understanding of organ-specific autoimmune diseases. These different $CD4^+$ T cell subsets are characterized by their unique cytokine expression profile and specific key transcription factors. For example, T-bet initiates the development of IFNγ-expressing Th1 cells [8]. These cells were assumed to be largely responsible for initiating and driving tissue injury in autoimmune disorders [5]. This paradigm was, however, faced in 2005 following the first identification of a pathogenic IL-17A-producing subset of $CD4^+$ effector T cells, named to as Th17 cells [6,7].

Th17 cells are best characterized by their master transcription factor RORγt [9], the production of the cytokines IL-17A, IL-17F and IL-22 [10,11], and expression of the chemokine receptor CCR6 [12]. Today their critical role in the pathogenesis of numerous autoimmune disorders is definitely established [13,14].

2. T cells in human autoimmune diseases of the kidney

Immune-mediated kidney diseases encompass a heterogeneous group of disorders that cause inflammation within the glomerulus and other compartments of the kidney. Rapidly progressive (or crescentic) glomerulonephritis (RPGN) is the most aggressive form of glomerular diseases and, despite immunosuppressive treatment, is associated with a poor prognosis. Different disease entities may lead to the development of RPGN. The most common cause is anti-neutrophil cytoplasmatic antibody (ANCA)-associated small vessel vasculitis, while the most rapid and severe form is anti-glomerular basement membrane (GBM) nephritis. Furthermore, immune complex-mediated diseases, such as systemic lupus erythematosus (SLE), may present as RPGN (Table 1) [15]. T cell infiltration is a morphological hallmark of crescentic glomerulonephritis [1].

2.1. ANCA-associated glomerulonephritis

Anti-neutrophil cytoplasmic antibody (ANCA)-associated small vessel vasculitides includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA), and renal involvement is a typical and potential life-threatening finding in these diseases [16]. Data primarily gained from the peripheral blood of patients with ANCA-associated glomerulonephritis supports a role for Th1 and Th17 cells in the disease [17–22]. Importantly, we recently identified $CCR6^+ROR\gamma t^+$ Th17 cells by flow cytometry in the kidney of patients with ANCA-associated glomerulonephritis [23].

2.2. Lupus nephritis

Systemic lupus erythematosus (SLE) is a relatively frequent autoimmune disease that can affect almost every organ including the kidney. Renal involvement (lupus nephritis), in particular, is of major importance for the long-term prognosis of patients SLE [24–26]. Of note, T cell-mediated immune responses are activated in the peripheral blood of patients with SLE [27], and lupus flares might be correlated with the presence of Th17 and the absence of regulatory T cells [28]. Furthermore, IL-17 cytokine levels are elevated in peripheral blood [29,30].

Despite these numerous studies, the role of kidney-infiltrating T cells and the underlying mechanisms of renal injury in lupus nephritis remains to be fully elucidated. To get more insight into the role of the Th17 immune response in lupus nephritis, we therefore analyzed IL-17A-deficieny and IL-17A blockade in mouse models of systemic lupus erythematosus. Although IL-17A-expressing cells accumulate in the kidney of MRL/*lpr* and NZB/W mice, deficiency or neutralization of IL-17A did not affect the severity of the disease in these models [31]. However, anti-IFN-γ treatment ameliorated the clinical course of nephritis. It is therefore important to note, that targeting of the Th17/IL17 pathway resulted in mixed outcomes, most likely as a result of major differences in the Th17 response between different lupus nephritis models. On the basis of these

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