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Th17 cells in renal inflammation and autoimmunity

Sebastian Dolff[a], Oliver Witzke[a], Benjamin Wilde[b,*]

[a] Department of Infectious Diseases, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
[b] Department of Nephrology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

ABSTRACT

Th17 cells are a distinct lineage of T-cells. These T-cells express IL-17A and the lineage-defining transcription factor RORγt. Th17 cells have a pivotal, physiological role in host defense against pathogens. These pro-inflammatory T-cells are also key players in autoimmunity and a pathogenic role has been demonstrated in several diseases such as rheumatoid arthritis or psoriasis. Recently, there is evidence that Th17 cells may drive renal inflammation and renal autoimmunity in anti-neutrophil-cytoplasmic-antibody-(ANCA)-vasculitis and systemic lupus erythematosus. The aim of this review is to discuss the possible involvement of Th17 cells in renal autoimmunity and its value for future therapeutic approaches.

1. Introduction

The IL-17 cytokine family consists of six cytokines termed IL-17A-F [1]. The first member of this family, IL-17A (also termed "IL-17" in this review), was originally named „CTLA8 "after its discovery in the 90s by Rouvier et al. [2]. IL-17A is -in contrast to the other cytokines of this family- very well studied and its function has been characterized extensively under healthy and diseased conditions. It is produced by a specific and distinct T-cell lineage (Th17 cells) but it is also secreted by other immune cells such as neutrophils, mast cells, natural killer cells and innate lymphocytes [3,4]. Recent evidence also suggests that parenchymal cells have the capacity to produce IL-17 [5,6]. The respective receptor is also expressed on immune and parenchymal cells [7]. This expression pattern already reveals effector functions: IL-17 acts as chemoattractant and has direct effects on tissues and immune cells. The pro-inflammatory characteristics were initially studied in an animal model of multiple sclerosis and in models for rheumatoid arthritis [1]. In these experimental studies, Th17 cells were proven pathogenic by disrupting the blood-brain-barrier or by bearing detrimental effects on cartilage. This sparked an avalanche of experimental studies in other autoimmune diseases and revealed a principal role for IL-17 and Th17 cells in systemic autoimmunity. It is the aim of this review to discuss the pathogenic role of Th17 cells in renal inflammation and autoimmunity. Furthermore, the tissue-specific effects of Th17 cells on renal parenchymal cells will be enlightened.

2. Effector functions of Th17 cells under healthy and diseased conditions

T-cells are divided into different T-cell lineages [8]. Th17 cells are characterized by the expression of its signature cytokine IL-17A and the master transcription factor retinoid-related orphan receptor (RORγt) [3,9]. Th17 cells are potent pro-inflammatory cells and may co-express several other cytokines like IL-21, IL-22, IFNγ or IL-10. Depending on the co-expression of cytokines or transcription factors, subtypes of Th17 cells can be defined (Fig. 1) [10]. Th17 cells exert a certain degree of plasticity and conversion into regulatory T-cells (Treg) or vice versa has been reported [4,10,11]. Under physiological conditions, Th17 cells mediate immunity against fungal infections and some evidence suggests that protective granuloma formation depends on Th17 responses [12]. IL-17 has also effects on parenchymal cells i.e. epithelial and endothelial cells inducing chemotactic factors and anti-microbial peptides [13]. In addition, Th17 cells co-producing IL-21 regulate B-cell responses, induce plasma cell differentiation and drive antibody formation [14]. In the context of autoimmunity, these effector mechanisms may take a turn for the worse. Th17 cells may promote and maintain formation of autoantibodies, mediate tissue destruction via upregulation of metallo-matrix-proteases or have other tissue-specific effects [1]. Accordingly, Th17 cells have emerged as key players in several autoimmune diseases; next to rheumatoid arthritis and multiple sclerosis, these cells became a therapeutic target in psoriasis and blockade of IL-17 itself or its maturation factors has been proven as a very efficient treatment strategy [15]. The major mechanisms and contribution of Th17 cells to the pathogenesis of renal autoimmunity have been identified very recently and have not been translated into treatment approaches yet.

* Corresponding author at: Department of Nephrology, University Hospital Essen, University of Duisburg-Essen, Hufelandstr. 55, 45122 Essen, Germany.
E-mail address: benjamin.wilde@uk-essen.de (B. Wilde).

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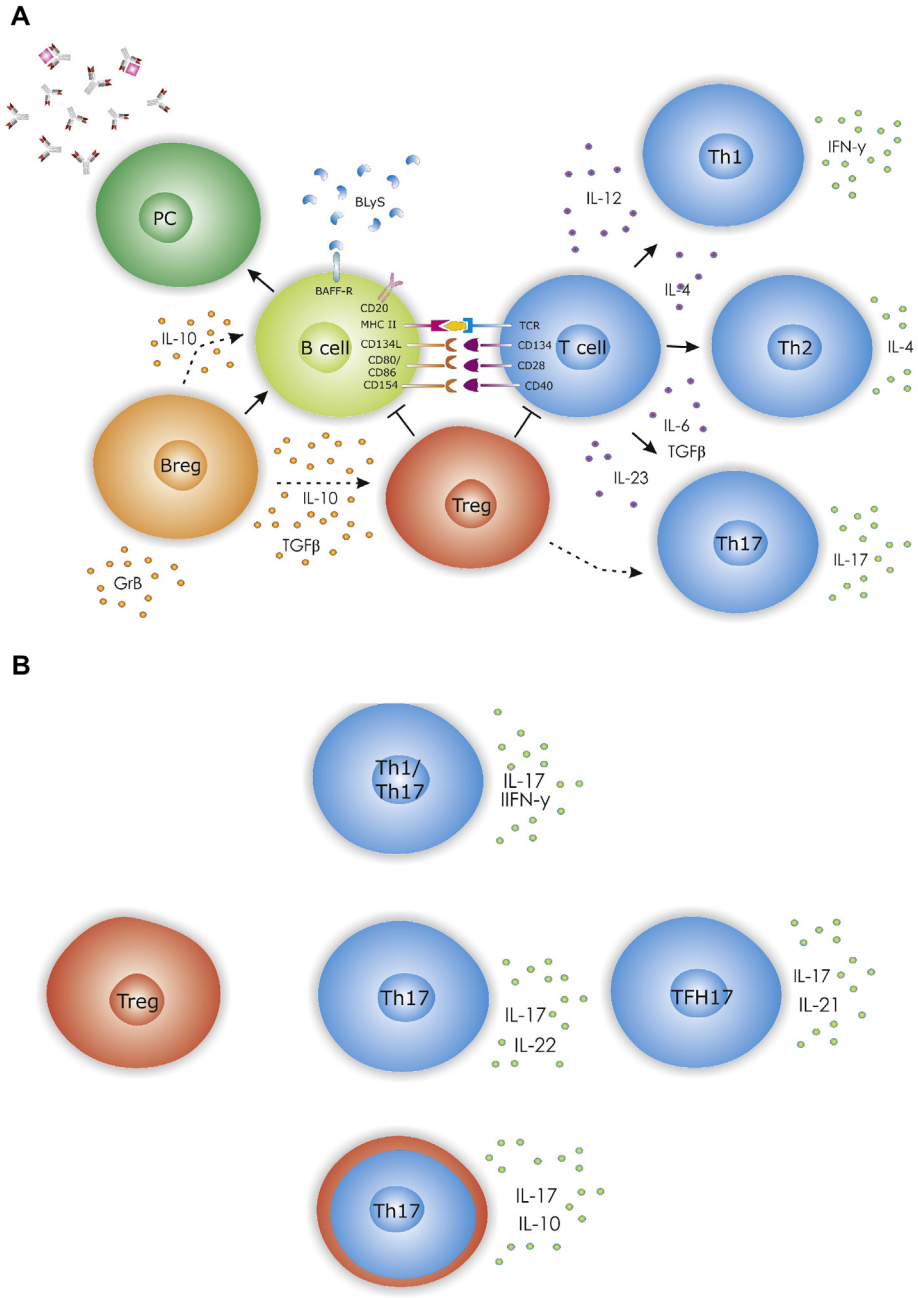

Fig. 1. Th17 T-cell differentiation, plasticity and effect of IL-17 on renal parenchymal cells. (A) Auto-antibody production by plasmacells (PC) is T-cell dependent. B-cell/T-cell interaction via T-cell receptor and co-stimulatory molecules also promotes T-cell differentiation orchestrated by various cytokines. T-cells differentiate into effector T-cells which are characterized by a specific cytokine profile. To maintain B-cell/T-cell homeostasis, cell subsets with inhibitory capacities, so called regulatory B- cells (B_{regs}) and regulatory T-cell (T_{regs}) exert immunosuppressive function. (B) Th17-cells are defined by the signature cytokine IL-17 and the transcription factor RORγt. Th17 are able to convert into other T-cell lineages. This process is called plasticity. Therefore, Th17 cells with Th1 features, i.e. secretion of IFNγ, have been identified. In addition, Th17 cells may convert into T_{regs} and acquire the capacity to secret IL-10. (C) A schematic illustration of specific renal compartments is shown. Th17 trafficking into the kidney is supposed to be dependent on receptors like CXCR3, CCR6. The respective chemokines are released by renal parenchymal cells. Il-17 exposure then results in further chemokine release by renal tubular cells (TEC), podocytes (POD) and endothelial cells promoting leukocyte transmigration. IL-17 exposure may also directly damage the integrity of TEC and POD. TEC and POD itself may secrete IL-17 upon exposure to specific stimuli such as complement factors or advanced glycation end products.

3. Effects of IL-17 and IL-17-related cytokines on renal parenchymal cells

It has been demonstrated that renal parenchymal cells respond to IL-17 in various ways and it may even lead to direct renal injury [16]. Human proximal renal tubular cells (hPTEC) can be activated in culture by IL-17A and subsequently release high amounts of IL-6 and IL-8 [17–19]. G-CSF and GM-CSF production by hPTEC is also induced by culture in presence of IL-17 [20,21]. Synthesis of IL-6, MCP-1 and RANTES synthesis is significantly upregulated in cultured human podocytes (hPOD) after challenge with IL-17 [5]. Similar observations were made for mesangial and endothelial cells [22–26]. Moreover, upregulation of adhesion molecules such as VCAM and *E*-Selectin enhancing transmigration was described for human endothelial cells as response to IL-17 [24]. Thus, renal parenchymal cells amplify IL-17A driven inflammation by upregulation of chemoattractants for

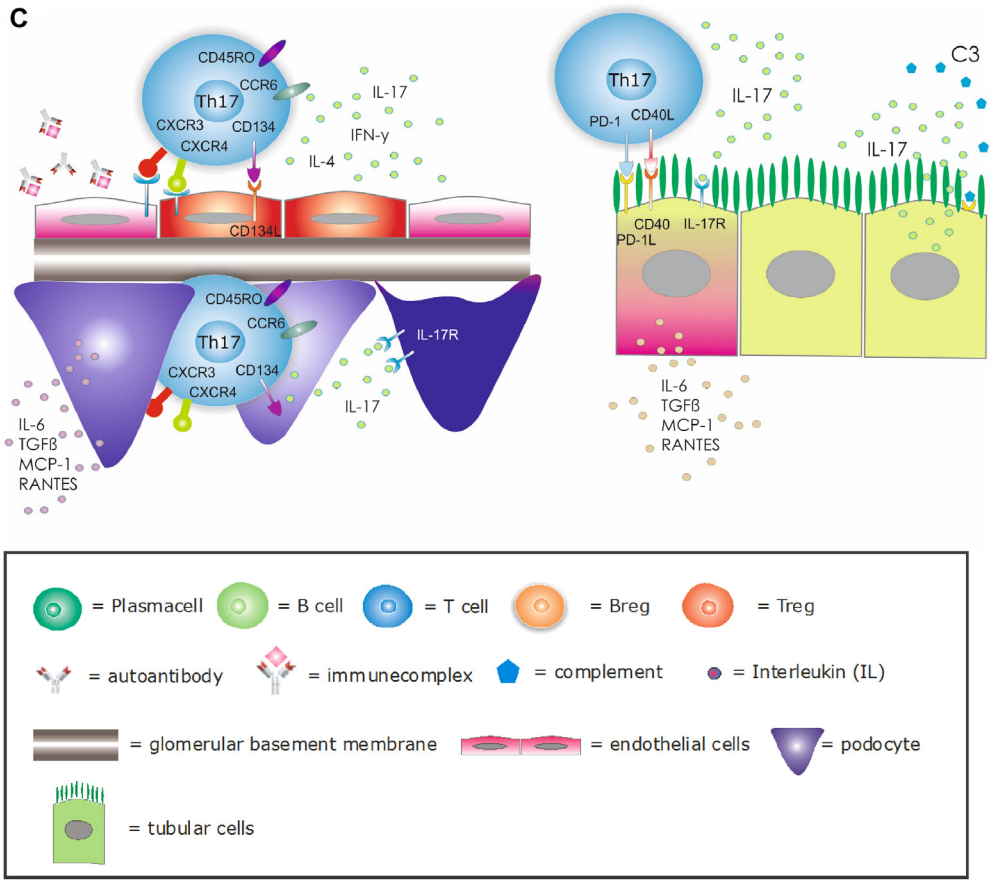

Fig. 1. (*continued*)

leukocytes and by facilitating transmigration. IL-17A exposure also upregulated CD40 expression of primary human tubular epithelial cells (TEC) and hPOD thereby enabling interaction with T-cells [5,27]. Ligation of CD40 with its cognate ligand induced synthesis of MCP-1 and RANTES in both types of renal cells [5,27]. Other costimulators or -inhibitors, namely ICOS and PDL-1, were not impacted by IL-17 [28]. However, the structural integrity of the kidney may also be influenced directly as a response to IL-17. It was reported that tubular epithelial cells show signs of disrupted cell-cell junctional integrity and loss of E-cadherin expression after exposure to IL-17 [21,29]. Two recent reports demonstrated signs of disintegration of the podocyte cytoskeleton accompanied by increased apoptosis when POD were cultured in presence of IL-17 [30,31]. Furthermore, there are some hints that renal fibrosis might be promoted by IL-17 driven inflammatory processes. Kuo et al. demonstrated that IL-17 enhances TGF-β1 production of cultured hPOD [5]. hPTEC produce extracellular matrix proteins and aSMA induced by IL-17 [29]. Interestingly, TEC and POD are in principle able to secrete IL-17 triggered by complement factors and advanced glycation end products [5,6]. Recently, it was shown that IL-17C is expressed by renal resident cells in an animal model for nephrotoxic nephritis and in a murine lupus model. This cytokine seems to specifically attract Th17 cells to sites of inflammation [32]. Therefore, IL-17 has several direct effects on renal parenchymal cells facilitating leukocyte transmigration, promoting interaction with T-cells and impacting renal integrity. These effects are inherent to the pathophysiological cascade in renal autoimmunity [33].

4. Th17 cells in crescentic glomerulonephritis: evidence from animal models

A number of studies have been conducted in murine models resembling crescentic glomerulonephritis to unravel the significance of Th17 mediated immunity. Gan et al. immunized mice against murine MPO followed by a sub-nephritogenic dose of anti-glomerular-basement-membrane (GBM) globulin to induce crescentic glomerulonephritis [34]. Crescent formation was virtually absent in IL-17A knock-out mice and the renal leukocyte infiltrate was significantly reduced as compared to the wild-type condition. While a cellular immune response against MPO was not detectable in knock-out mice, antibodies against MPO were present. This study demonstrated that crescent formation was -at least in this model- Th17-dependent. Another study by Odobasic et al. further extended these findings [35]. In a similar murine model, crescentic glomerulonephritis was induced by application of a nephritic dosage of sheep anti-GBM globulin in wild-type mice, IL-17 KO mice, IL23 (p19) KO mice and IL12 (p35) KO mice [35]. In accordance to the study by Gan et al., IL-17 KO mice were protected from disease during the early phase of disease on day six but finally developed severe crescentic glomerulonephritis beyond day 20 after disease induction. The same was observed for mice lacking the Th17 differentiation factor IL23 (p19). Mice lacking the Th1-promoting factor IL-12 suffered from less severe glomerulonephritis [35]. Therefore, Th17 cells may have a time-dependent dual role in the pathogenesis of crescentic glomerulonephritis. Early Th17 responses induce glomerulonephritis whereas in the later phase of disease Th17 responses may restrain Th1 mediated immunity attenuating renal injury. In a later study, this temporal course was confirmed; recruitment of Th17 and Th1 to the kidney was based on differential expression of CCL20 and CXCL9 by renal parenchymal cells regulated by IL-17/IFNγ [36]. Recently, Krebs et al. could track the origin of renal Th17 cells back to the intestine in a murine nephrotoxic nephritis model indicating that Th17 cell differentiation and survival may depend critically on the microbiota of the gut. Interestingly, treatment with oral vancomycin resulted in milder renal damage and less severe renal Th17 infiltration [37].

5. Th17 cells in Lupus nephritis

Systemic lupus erythematosus is an autoimmune disease which affects various organs, including skin, joints, central nervous system and kidneys. Renal involvement is a frequent and severe manifestation [38]. The precise pathogenesis of this clinically heterogenous disease in particular the development of lupus nephritis is still not completely understood. The deposition of antigen-antibody complexes was traditionally thought to initiate renal inflammation [39,40].

Several cell subsets of the adpative immune system have been identified to be dysregulated or altered in systemic lupus erythematosus. Abnormal B- and T-cell responses are responsible for the pathogenesis of lupus nephritis (LN). B-cells as a source of auto-antibody production promote the deposition of immune complexes in the kidneys [41]. Recently, B-cells with regulatory functions have been described [42]. An impaired regulatory capacity might contribute to a hyperactive B-cell compartment leading to characteristic auto-antibody formation and immune-complex mediated end-organ injury. Murine and human lupus studies demonstrated that the auto-antibody formation is a T-cell dependent process. The T-cell B-cell interaction promoted by costimulation seems to be crucial.

Over the last decade our understanding of B-cell and T-cell immunology increased through the increasing body of evidence and discovery of new distinct B- and T-cell populations. Recent studies have found T-cells as a pivotal subset in the development of LN. T-cells are central regulators of the adaptive immune system [43]. They were traditionally differentiated in regulatory T-cells (Tregs) and T-cells with effector function so called effector T-cells (TEff). A breakdown of the healthy T-cell homeostasis is thought to be a main reason for the development of autoimmune diseases.

It has been hypothesized that Th17-cells play an important role in the initiation and development of autoimmunity. Several human and murine studies support the essential role of effector T-cells, including Th17-cells, in the pathogenesis of SLE. In serum of SLE-patients, IL-17 level above the detection limit was more frequently found in patients who had active lupus nephritis compared to healthy controls [44]. The authors did not find any correlation with activity or chronicity score and ISN/RPS criteria class among patients with active lupus nephritis. However, this study confirmed results of a previous study by Wong et al. where elevated IL-17 concentrations were found in plasma of SLE patients [45]. The authors also found a positive correlation between IL-17 plasma concentration and disease activity assessed by SLEDAI.

Apart from detection of circulating IL-17, peripheral lymphocytes were studied to evaluate their capacity to secrete IL-17 upon *ex vivo* stimulation. In the presence of IL-6, TGFβ and IL-23 T-helper cells differentiate into Th17 cells. Phorbol myristate acetate (PMA) and ionomycin stimulated $CD3^+$ $CD8^-$ T-cells secrete significantly more IL-17A in active SLE-patients as compared to inactive patients and healthy controls [46]. Patients with renal involvement showed no differences in the proportion of circulating Th17 cells. However, the authors could demonstrate that Th17 cells were associated with vasculitis which was supported by the presence of infiltrating IL-17 lymphocytes in skin lesions of SLE-patients [46]. Similar results were reported by other groups [47,48, 49,50].

Koenen et al. described the phenomenon of a transitional T-cell type whichhas both Th17 and Tregcharacteristics [51]. Plasticity of T-cells and switch of lineage causes the occurrence of these T-cells with "dual identity". Thus we assessed the T-cell plasticity in SLE, by analyzing the intracellular expression of IFN-γ, IL-4 and IL-17A within the $CD4^+$ $CD25^{high}FoxP3^+$ subset. In our study we observed that Tregs are able to produce effector cytokine such as IL-17A but this production was relatively decreased in SLE [50].

The novel class I cytokine IL-21 is a member of the common γ-chain receptor family. The production of IL-21 is mainly restricted to $CD4^+$ T-cells, Th17- and T-follicular helper (TFH)-cells. High expression of the transcription factor RORγt and B-cell lymphoma-6 (BCL6) in T-cells is considered to define specifically Th17- and TFH -cell lineages, respectively. Interestingly, also $TCR\alpha\beta^+CD4^-CD8^-$ T-cells have been reported to produce significant levels of IL-17 and IL-21 after *ex vivo* stimulation in SLE patients [52]. Additionally, Crispin et al. further described this population of double-negative T-cells ($TCR\alpha\beta^+CD4^-CD8^-$) which are expanded in SLE patients. After stimulation with plate-bound anti-CD3, a significant proportion of these DN T-cellssecretes IL-17 [53]. We found a strong positive correlation between percentages of $IL\text{-}21^+$ $CD4^+$ T-cells and percentages of $IL\text{-}17^+$ $CD4^+$ T-cells in SLEpatients. These data might indicate that IL-21 drives differentiation of naïve T-cells into Th17-cells in human SLE [54]. Accordingly, IL-21 and TGF-β have been described as potent promoters of T-cell differentiation towards Th17 via induction of ROR-γt and IL-23R expression.

T-cell migration to the kidney as target organ has been postulated to cause and perpetuate renal inflammation. Early evidence came from histopathological findings of $CD8^+$ and $CD4^+$ mononuclear inflammatory cells infiltrating the renal interstitium of human LN biopsies [55]. More recent studies have demonstrated that $CD8^+$ and $CD4^+$ T-cells which infiltrate kidney during active lupus nephritis are detectable in the urine of these patients [56–58]. Thus, urinary T-cells might provide a non-invasive tool to assess renal activity in particular in patients with renal relapses where traditional markers such as proteinuria are often difficult to interpret. The mechanism of T-cell migration is not unraveled so far. Costimulatory molecules which are expressed on activated T-cells might be involved in T-cell trafficking into inflamed tissue. The glomerular expression pattern of CD134L (OX40L), predominantly along the glomerular capillary wall, fits complementary to our observation of increased CD134 expression on T-cells in LN patients [59]. The observation that CD134 (OX40) is upregulated on peripheral Th17 cells of LN patients combined with our histopathological finding of $CD134^+$ T-cells in perivascular infiltrates suggests a pivotal role of the CD134 (OX40) - CD134L (OX40L) axis for the Th17 recruitment to the kidney [48,59,60]. However, not only costimulatory molecules but also chemokine receptors have been identified as key receptors for T-cell migration. Murine and human studies demonstrated that mainly Th1 but also Th17-cells highly express the chemokine receptor CXCR3. Both histopathological stainings of renal specimens from MRL/lpr mice as well as human kidney biopsies showed the presence of $CXCR3^+$ T-cells within the inflammatory infiltrate [56,61]. A remarkable study by Poissonier et al. revealed that CD95-CD95L interaction induces an intracellular calcium response mediating a Ca^{2+} −dependent endothelial transmigration in inflamed organs in lupus-prone mice [62]. Taken together there is a growing body of evidence that a skewed T-cell balance towards IL-17 might be responsible for the development of LN. Tissue damage by Th17 cells might be caused by direct recognition of the antigen-specific target, or it can result from the recruitment of other cell subsets such as neutrophils and macrophages into the microenvironment. Local cell-cell interactions via various receptor axis obviously orchestrates Th17 recruitment and migration.

6. Th17 cells in ANCA-associated vasculitis

ANCA-associated vasculitis (AAV) is a necrotizing –depending on the type of vasculitis also granulomatous- small-vessel vasculitis of autoimmune origin [63]. This small-vessel vasculitis is characterized by the presence of autoantibodies directed against neutrophil-derived antigens. Anti-neutrophil-cytoplasmic-antibodies usually have specificity for either Proteinase-3 (PR3) or Myeloperoxidase (MPO) [63]. AAV comprises three different diseases: Eosinophilic Granulomatosis with polyangiitis (EGPA), Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) [63]. These diseases differ with respect to clinical presentation, organ involvement and autoantibody pattern. However, recent studies suggest that AAV should be rather stratified by the type of ANCA i.e. PR3-AAV or MPO-AAV [64]. This is also supported by outcome data indicating that relapse propensity is greater in

PR3-AAV than in MPO-AAV [65]. All three diseases are associated with systemic vasculitis and pauci-immune crescentic, necrotizing glomerulonephritis [66]. Many patients with GPA/EGPA also present with necrotizing granulomatous inflammation of the airways. The disease entities also show different histological features: eosinophil-rich infiltrates are mainly found EGPA whereas neutrophils are found in GPA. Several findings indicate that apart from autoantibodies T-cells have a major role in disease pathogenesis. T-cells are usually present in tissue lesions [67–69]. Furthermore, granuloma formation is a T-cell-dependent process [70]. Biomarkers of T-cell activity such as soluble IL-2-receptor (sIL2r), neopterin and soluble CD30 are elevated in AAV correlating with disease activity [71–73]. ANCA predominantly show an IgG1 and IgG4 isotype meaning a T-cell mediated class switch must have taken place [74]. Ruth et al. demonstrated in an animal model of AAV that T-helper-cell depletion ameliorates the course of the disease [75]. Specific T-cell targeted therapy in refractory cases was reported as beneficial [76]. In summary, these findings suggest that T-cells are involved in the pathogenesis of AAV.

Several alterations of the T cell compartment have been described in AAV. Effector memory T-cells are expanded in AAV and in a persistent state of activation [69,71,72,77–83]. The fraction of T-cells with dim expression of IL-2-α-chain is increased in AAV [84,85].

These T-cells are a major source of IL-17, show high expression of CCR6 enabling migration to target organs expressing CCL20 and resist suppression by Treg [85]. Treg in AAV patients also show a specific alteration which may account for the expansion of Th17 cells. The exon-2-deficient splice variant of the transcription factor FoxP3 is expressed disproportionally and to a higher extent in patient-derived Treg being associated with diminished suppressive function [85]. This splice-variant does not repress the Th17 transcription factor RORγt and may cause increased plasticity i.e. conversion of Treg into Th17 cells. Indeed, an expanded fraction of Th17 cells with characteristics of Treg has been identified in AAV patients [86]. Elevated numbers of Th17 cells are present in patients independent of disease activity [86–89]. Antigen-specificity of Th17 cells was studied by Abdulahad et al. and Nogueira et al. [87,88]. Both found that PR3- and MPO-specific T-cells were harboured within the Th17 cell population in AAV patients with quiescent disease. Two studies followed patients longitudinally during active disease and after having entered remission [67,90]. Induction therapy and remission maintenance therapy did not normalize Th17 expansion in AAV which is different from other autoimmune diseases such as SLE or giant cell arteritis (GCA) [91,92]. In GCA, Th17 cells are very susceptible to steroids and rapid normalization of Th17 cell expansion is observed during therapy. Thus, Th17 cells might be less susceptible to standard therapeutic approaches in AAV. Interestingly, a specific subset of Th17 cells expresses the multi-drug resistance type 1 membrane transporter conferring in vitro resistance to natural and synthetic glucocorticoids [93]. However, whether and to which extend this specific subset contributes to pathology in AAV remains to be studied. On tissue level, IL-17 was detected in orbital lesions of patients with GPA and was lacking in other granulomatous diseases [94]. Likewise, Th17 cells were detected in human renal tissue of patients with AAV [95]. Surprisingly, the majority of cells expressing IL-17 were neutrophils. Data from animal models suggests that Th17 driven renal inflammation occurs very early during the initial phase of glomerulonephritis (as discussed in the respective chapter of this review) and is curtailed by a Th1 dominant effector phase [35]. As renal biopsies are usually taken in advanced stages of glomerulonephritis (especially in case of diagnostic biopsies), it has to be considered that renal inflammation has already entered the Th1 dominant phase at the time of biopsy sampling.

The cause for expansion of Th17 cells remains unknown. It is conceivable that a lack of immunological control is promoting the aberrant polarization of T-cells. In line with this, functional defects of Treg have been reported in AAV [85,96–98]. Malfunction of Treg in AAV might be caused by diminished responsiveness to IL-2 serving as survival factor for Treg. This is supported by the finding that the expression of the IL-2-receptor-β-chain is diminished on Treg of AAV patients [99]. Moreover, the expression of a specific splice variant of FOXP3 -as discussed above- may further facilitate unfavourable effector Th17 cell expansion [85]. In addition, failing co-inhibition may have a role in the pathogenic cascade. Co-inhibition interferes with T-cell stimulation and prevents T-cell activation by rendering T-cells anergic [100]. Co-inhibition is mediated by several different molecules; the co-inhibitor PD-1 has been studied in AAV [69]. Interestingly, despite over-expression of PD-1 on T-cells in AAV, the PD-1/PDL-1 system fails to control T-cell proliferation in patients with AAV [69]. Interestingly, therapeutic blockade of PD-1/PDL-1 led to development of AAV in rare cases [101]. Thus, one may speculate that Th17 cells escape co-inhibition in AAV due to an intrinsic defect of the PD1/PDL1 system. Furthermore, persistent challenge with antigen could drive Th17 expansion in AAV. Nasal carriage of *Staphylococcus aureus* is common in GPA and associated with a higher relapse propensity [102–104]. *S. aureus* derived antigens induce polarization towards Th17 and may also have a role in Th17 skewing in AAV [105]. However, sufficient evidence in support of this hypothesis is currently lacking [89]. Granulomas are thought to be a niche for immune cells and lymphocyte maturation is thought to take place in these lesions [106]. Macrophages within granulomas secrete IL-6 and TGFβ potentially providing a specific local cytokine environment for T-cell differentiation. Therefore, granulomas frequently found in lesions of GPA patients may drive Th17 expansion. Accordingly, high amounts of factors promoting Th17 differentiation such as IL-6, TGFβ and IL-23 are found in sera of patients [107,108]. Thus, Th17 cells are persistently expanded in AAV due to lack of immunological control on several levels. Th17 cells may drive autoantibody formation, tissue destruction and renal inflammation in AAV.

7. Th17 cells in other renal autoimmune diseases

There is limited data available providing experimental evidence for a pathogenic role of Th17 cells in other renal autoimmune diseases.

IgA nephropathy (IgAN) is the most common cause of primary (idiopathic) glomerulonephritis. Deposition of galactose-deficient IgA1 deposits in the glomerular mesangium is a hallmark of IgAN [109]. Several studies indicate an important role for T-cells in this disease. In a murine model of IgAN, the role of Th17-cells and the chemokine receptor CCL20 was investigated [110]. The authors reported an increased percentage of intrarenal Th17-cells as compared to the control group. In IgA patients, peripheral circulating T-cells were first studied regarding the expression of IL-22 and IL-17 after ex vivo stimulation. Th17 cells were found to be increased in patients with IgAN as compared to non-IgA mesangial proliferative glomerulonephritis patients. Especially the proportion of IL-22 T-cells was associated with the degree of proteinuria [111]. In another study, human mesangial cells cultured with purified IgA1 for 24 h showed a significantly higher CCL20 release as compared to controls. Interestingly, the authors also demonstrated that CCL20 attracts CCR6+ T-cells which where $IL17^{+}IFN\gamma^{-}$. Next, kidney biopsies revealed the presence of CCL20 as well as $CCR6^{+}$/$IL-17^{+}$ T-cells. Thus, the authors concluded that CCL20 produced by HMC recruits $CCR6^{+}$ Th17 cellsmediating renal damage [112]. Taken together, there are a few studies reporting the importance of Th17 cells in the pathogenesis of IgAN. Nevertheless, more studies are necessary to clarify the exact role of Th17 dependent renal injury.

In minimal change nephropathy (MCN), an expansion of circulating Th17 cells is reported by Liu et al. [113]. Th17 expansion was accompanied by a reduction of circulating Treg. Skewing of the Th17/Treg balance was associated with proteinuria in patients and normalized in steroid-sensitive patients. In line with these findings, Wang et al. showed an increase of RORc and IL-23p19 transcripts in PBMC of patients with MCN. IL-17 expression was found in renal tissue of MCN patients [114]. The same authors could also demonstrate that exposure of podocytes to IL-17 led to increased apoptosis.

8. Conclusion

Th17 cells are key players in renal autoimmunity by mediating fundamental inflammatory cascades. These cells promote formation of autoantibodies which are pivotal to most renal autoimmune diseases, enhance tissue inflammation and have direct effects on renal parenchymal cells. Thus, it is conceivable to translate these findings into therapeutic approaches. Several agents blocking IL-17A, its receptor or differentiation factors which are already licensed mainly for use in psoriasis or psoriasis arthritis [15]. There is only one phase 2a study that has been conducted in patients with SLE to assess the efficacy of anti-IL-12p40 antibody treatment as addon to standary therapy (NCT02349061). Patients treated with anti-IL-12p40 showed an enhanced clinical response compared to placebo. However, patients with active lupus nephritis (class III/IV) were excluded from this study. To the best of our knowledge, there are no further studies running or underway investigating Th17 targeting agents in renal autoimmune diseases. Given the clear evidence for Th17 cells as key players in renal autoimmune disease and considering the -in comparison to other medical disciplines- limited treatment options for these diseases, there is a need to investigate the efficacy of Th17 targeting agents in patients with AAV and SLE.

Take home messages

- Th17 cells are potent pro-inflammatory cells with physiological function in host defense. In the context of autoimmunity, Th17 cells may promote autoantibody formation, tissue inflammation and destruction.
- Th17 cells have distinct, direct impact on renal parenchymal cells which is potentially detrimental.
- Th17 cells are key players in renal autoimmunity and may serve as future therapeutic target.

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Conflict of interest

Nothing to declare.

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