arthritis research&therapy

REVIEW

T-helper cells as new players in ANCA-associated vasculitides

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Abstract

In anti-neutrophil cytoplasmic autoantibody-associated vasculitides (AAV), several observations support a key role of T-helper cells ($CD4^+$ T cells) in disease pathophysiology. An expanded population of effector memory $CD4^+$ T cells in AAV patients may contribute to tissue injury and disease progression. In addition, functional impairment of regulatory T cells (T_{Regs}) is reported in AAV patients. A fraction of T_{Regs} have the capacity to differentiate into Th17 cells in the context of a proinflammatory environment. Therefore, nonfunctionality of T_{Regs} described in AAV patients may be caused by their conversion into IL-17-producing cells that may contribute to granulomatous vasculitis. Further investigations directed at the plasticity of T_{Regs} in AAV patients are warranted.

Introduction

Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) constitutes a group of disorders characterized by autoimmune necrotizing inflammation of small blood vessels, which leads to systemic organ damage [1]. This group of systemic vasculitides includes Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and Churg–Strauss syndrome (CSS). These disorders are predominantly associated with the presence of circulating ANCAs that are directed against proteins in the cytoplasmic granules of neutrophils. ANCAs with specificity for proteinase-3 (PR3-ANCA) are associated with WG to a high degree, whereas ANCAs with specificity for myeloperoxidase (MPO-ANCA) are predominant in MPA and to a lesser degree in CSS [2]. Although it remains unknown how these conditions develop, it has been postulated that ANCA *in vivo* bind to surface-expressed autoantigens (PR3 or MPO) on primed neutrophils, which enhances neutrophil degranulation and the release of toxic products that cause endothelial damage, ultimately leading to necrotizing vasculitis [2].

In vivo experimental studies have clearly demonstrated that MPO-ANCAs are pathogenic factors. Xiao and colleagues have shown that immunization of MPO-deficient mice with mouse MPO results in an MPO-directed immune response, and transfer of splenocytes from these mice into immune-deficient mice leads to development of pauci-immune necrotizing crescentic glomerulonephritis and systemic necrotizing vasculitis reminiscent of MPA [3]. Further support for the pathogenicity of ANCA comes from a recent study by van Timmeren and coworkers [4]. They observed that administration of anti-MPO antibodies hydrolyzed by the bacterial enzyme endoglycosidase S, which abolishes IgG binding to Fcγ receptors, attenuated both neutrophil influx and formation of glomerular crescents in the above-described model of MPO-ANCA-induced glomerulonephritis. An immunopathogenic role for MPO-ANCA has also been strongly suggested by the occurrence of neonatal MPA in a child born to a mother with a history of MPO-ANCA-associated pulmonary renal syndrome [5].

In contrast to MPO-ANCA, *in vivo* evidence is still lacking for a direct vasculitic pathogenicity of PR3-ANCA. So far only PR3-induced and PR3-ANCA-induced enhancement of inflammation has been demonstrated in an animal model [6,7]. Recent findings by Primo and colleagues suggest that, under certain conditions, anti-PR3 antibodies can be pathogenic in rodents [8]. They showed that adoptive transfer of splenocytes from PR3-immunized mice into NOD-SCID mice resulted in the appearance of circulating anti-PR3 antibodies and crescentic glomerulonephritis in the recipient mice. However, it is unclear whether glomerulonephritis in recipient mice is mediated by the humoral or the cellular arm of the anti-PR3 response.

Of note, infiltrating T cells in granulomatous lesions as well as persistent T-cell activation have been reported in AAV patients [9-12]. Interestingly, T-cell-depleting therapy with anti-CD52 antibodies (alemtuzumab) and

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anti-thymocyte globulin can induce remission in refractory AAV patients [13,14]. Moreover, the IgG subclass distribution of ANCA, predominantly consisting of IgG_1 and IgG_4, implies isotype switching of ANCA for which CD4 T-helper cells are required [15]. T-cell-mediated immunity is thus thought to contribute to the pathogenesis of ANCA-associated vasculitis. In the present review we will summarize the currently available data on the role of T cells in AAV. We shall first discuss current thoughts about the contribution of T cells to tissue injury in AAV. The main emphasis will then be on the plasticity of regulatory T cells (T_{Regs}), their transition into Th17 cells, and the involvement of Th17 cells in granuloma formation and disease progression.

Involvement of CD4 T cells in AAV

Unlike other autoantibody-mediated diseases, AAV is characterized by an absence of deposited antibodies in affected tissue, in particular in glomeruli, designated as pauci-immune glomerular lesions [16]. Otherwise, immune effector cells such as $CD4^+$ T cells, macrophages and granulocytes are enriched in granulomatous lesions [9,10,17-20]. This suggests a primary role of cell-mediated immunity in initiating granuloma formation. Studies in mice and humans have demonstrated a key role of $CD4^+$ T cells in the generation of a granulomatous response. For instance, Saunders and colleagues have shown that CD4-deficient mice did not generate the typical mononuclear granulomatous lesions following *Mycobacterium tuberculosis* infection [21]. In humans, the extent of granuloma formation was correlated with peripheral CD4 T-cell counts in HIV patients with mycobacterial infection [22,23]. The important role of CD4 T cells in the expression of crescentic glomerulonephritis has been demonstrated by Ruth and colleagues [24]. They induced experimental anti-MPO-associated crescentic glomerulonephritis by immunizing C57BL/6 mice with human MPO followed by subsequent challenge with anti-glomerular basement membrane antibodies. Mice depleted of $CD4^+$ T cells at the time of administration of anti-mouse glomerular basement membrane developed significantly less glomerular crescent formation and less cell influx when compared with control mice. These data provide convincing evidence that $CD4^+$ T cells are crucial in granuloma formation and glomerulonephritis.

Studies in AAV patients also support this notion. Proliferation of $CD4^+$ T cells in response to the autoantigens PR3 and MPO have been reported in patients with AAV, although $CD4^+$ T cells from healthy controls also proliferated in response to PR3 and MPO, albeit to a lesser extent [25]. Persistent CD4 T-cell activation has also been observed in peripheral blood from AAV patients [26-28]. Importantly, Marinaki and colleagues observed an association between persistent $CD4^+$ T-cell activation and disease severity in both WG patients and MPA patients [29]. Recently, Seta and colleagues evaluated the effect of depleting CD4 or CD8 T cells on the proliferative response to MPO fragments of peripheral blood mononuclear cells isolated from MPA patients [30]. Strikingly, proliferation was completely lost after the depletion of $CD4^+$ T cells, but not after depletion of $CD8^+$ T cells. In our studies in WG patients, we observed a persistent expansion of a subset of memory $CD4^+$ T cells, termed effector memory T cells (T_{EM}), with a reciprocal decrease in naïve $CD4^+$ T cells [11]. Moreover, the $CD8^+$ T-cell compartment also appears to be altered [31,32]. In accordance, infiltrating T cells in lung lesions and glomeruli were shown to consist mainly of $CD4^+$ T cells with a memory phenotype [9,33,34]. Also in CSS patients, given the allergic background and hypereosinophilia in this disease, activated $CD4^+$ T cells producing Th2 cytokines are believed to be the disease inducer [35]. Taken together, these findings indicate that CD4 T cells can serve as effector cells in the pathogenesis of AAV.

$CD4^+$ effector memory T cells: a key player in tissue injury in AAV

As mentioned above, several observations support the involvement of $CD4^+$ T cells in the pathogenesis of AAV. Important evidence regarding their role in disease manifestations came also from the clinical observation that remission could be induced in WG patients by antibodies directed at T cells [36]. Indeed, an altered phenotype of $CD4^+$ T cells has been found in AAV patients. An increased proportion of $CD45RC^{Low}CD4^+$ memory T cells was reported in peripheral blood of AAV patients [37]. In addition, an expanded population of $CD4^+$ T cells lacking the co-stimulatory molecule CD28 was observed in peripheral blood and in granulomatous lesions of patients with WG [9,38]. These $CD28^-CD4^+$ T cells display up-regulation of the T-cell differentiation marker CD57 and show intracytoplasmic perforin expression, indicating the cytotoxic potential of these cells [9]. Based on phenotype and functional characteristics, $CD28^-$ T cells have been classified as a T_{EM} population that lacks the chemokine receptor CCR7 [39].

Consistent with these findings, we observed a significant increase in the frequency of circulating $CD4^+$ T_{EM} ($CD45RO^+CCR7^-$) in WG patients in remission compared with healthy individuals [11]. In addition, we have shown that the number of these circulating $CD4^+$ T_{EM} decreases during active disease compared with that during complete remission, which is consistent with their migration towards inflamed tissues [11]. Indeed, our cross-sectional and follow-up studies confirmed migration of $CD4^+$ T_{EM} during active renal disease into the diseased organs [40]. We observed a remarkable

increase in $CD4^+$ T_{EM} in the urinary sediment with a concomitant decrease of circulating $CD4^+$ T_{EM} of WG patients with active renal involvement [40]. These urinary $CD4^+$ T_{EM} decreased or disappeared from the urine during remission, which might reflect their role in renal injury. In accordance with these findings, Wilde and colleagues demonstrated that $CD4^+$ T_{EM} expressing CD134 are expanded in peripheral blood of patients with WG [41]. CD134 is thought to contribute to T-cell migration and tissue infiltration through its interaction with OX40L on vascular endothelial cells [42]. Indeed, Wilde and coworkers have shown that CD134-expressing T cells were localized within the inflammatory lesions of WG patients, supporting our hypothesis on migration of this T-cell subset to inflamed sites [41].

As mentioned, $CD4^+$ T_{EM} display natural killer (NK)-like features such as cytotoxicity [39]. They also mimic NK cells by their surface expression of the NKG2D molecule. NKG2D is an activating C-type lectin-like homodimeric receptor, which differs from other NKG2 members as it apparently lacks an antagonist and substitutes for CD28-mediated co-stimulatory signaling in $CD28^-$ T_{EM} [43]. One of the NKG2D ligands is the major histocompatibility complex class-I chain-related molecule A (MICA), which is expressed upon cellular injury and stress on target cells such as fibroblasts and epithelial cells [43]. Proof of concept for NKG2D-mediated tissue destruction was provided by Allez and colleagues [44], who demonstrated that $NKG2D^+CD4^+$ T-cell clones from patients with Crohn's disease kill target cells that express MICA via NKG2D–MICA interaction. Importantly, MICA is upregulated in peritubular endothelium and glomerular epithelial cells in AAV patients during active renal disease [45]. Strikingly, Capraru and colleagues have shown that NKG2D is preferentially expressed on expanded $CD28^-CD4^+$ T cells in the peripheral blood of WG patients [31]. Next, they showed that both NKG2D and MICA are expressed in granulomatous lesions in WG, but not in disease controls. Killing mechanisms via NKG2D–MICA interaction therefore probably contribute to vessel injury and disease progression in AAV patients (Figure 1). Accordingly, selective targeting of $NKG2D^+CD4^+$ T_{EM} or inhibiting MICA expression without impairing other parts of cellular immunity might have value in the treatment of AAV [46].

Th1/Th2/Th17 paradigm in AAV

Aberrant T-helper cell polarization has been described in AAV. Analysis of soluble markers for T-helper cell subsets in patient sera reveals a predominance of the Th1 pattern with expression of IFNγ and sCD26 in patients with localized WG and in patients with MPA, whereas a shift towards a Th2 pattern, with expression of IL-4, IL-5, IL-10, IL-13, sCD23, and sCD30, was observed in active generalized WG and CSS [47,48]. The same results were obtained from analysis of nasal granulomatous lesions in which abundant Th1-associated markers (IFNγ, sCD26, CCR5) were seen during localized WG, whereas Th1-associated and Th2-associated markers (IL-4 and CCR3) are found in generalized WG [20,49]. Besides the balance between Th1 and Th2, a recent breakthrough has revealed that IL-17-secreting T cells (Th17) are another major pathogenic effector subset involved in the induction of inflammation and autoimmunity [50,51]. It has been reported that induction of experimental autoimmune encephalomyelitis (EAE) was blocked in mice deficient in either IL-17 or the Th17 polarizing cytokine IL-23, whereas mice deficient in either IFNγ or the Th1 polarizing cytokine IL-12 show increased susceptibility to EAE [50,52,53]. Interestingly, Th17 cells in EAE infiltrate the brain prior to the onset of clinical symptoms, whereas Th1 cells dominate the cellular infiltrate thereafter when clinical disease develops [54]. It seems that T-cell-mediated disease manifestations are linked to Th17 cells and not primarily to Th1 responses.

The physiological role of Th17 cells lies in bacterial defense – for example, against *Staphylococcus aureus* – as shown in experimental pneumonia and the hyper-IgE syndrome [55,56]. Peptidoglycans as well as superantigens from *S. aureus* might have an immunomodulatory effect on dendritic cells by imprinting of a strong Th17 polarizing capacity [57]. In addition, *S. aureus* α-toxin was shown to induce IL-17A secretion in CD4 T cells [58]. Intriguingly, nasal *S. aureus* co-localization has been reported to be related to relapse and correlates with endonasal activity in WG [59,60]. Infection with *S. aureus* might therefore drive a Th17 response in AAV patients. Indeed, in patients with AAV we observed a skewing towards Th17 cells following *in vitro* stimulation of peripheral blood samples [61]. In line with this observation, Ordonez and coworkers have shown that the expanded $CD4^+$ memory T cells in AAV patients are a source of IL-17 [37]. Most importantly, we found a relative increase in autoantigen-specific Th17 cells in ANCA-positive patients in comparison with ANCA-negative patients and controls [61]. This observation suggests involvement of Th17 cells in the process of autoantibody production in AAV. These results were corroborated by Nogueira and colleagues, who reported elevated levels of serum IL-17A and increased autoantigen-specific Th17 cells in AAV patients during disease convalescence compared with healthy controls [62]. In addition, Saito and colleagues observed an increased frequency of circulating Th17 cells in patients with active CSS compared with in patients with inactive disease and healthy controls [63].

IL-17 has been reported to promote the release of pro-inflammatory cytokines, which are essential for triggering

the expression of PR3 and MPO on the surface of neutrophils (priming of neutrophils), and also to induce CXC chemokine release and expression of adhesion molecules responsible for the recruitment of neutrophils to the site of inflammation [64-66]. Indeed, WG granulomata (site of inflammation) are rich in neutrophils [20]. On the other hand, IL-17 has been shown crucial for the formation of an autoreactive germinal center in autoimmune BXD2 mice [67]. IL-17-producing T cells and B cells expressing the IL-17 receptor have also been reported to localize together in germinal centers [67]. This observation suggests that IL-17 not only induces tissue inflammation but also could function on B cells to promote the germinal center reaction. The lymphocyte clusters in granuloma structures can resemble germinal center-like structures that might be induced by IL-17 and may provide a place for ANCA production. IL-17 thus seems to be an important player in disease development in AAV and in early granuloma formation in WG, whereas Th1 and Th2 cells might prevail in later stages [20,49]. Of note, Th17 cells have not so far been demonstrated at inflamed sites in AAV.

Disturbance in the frequency and/or function of regulatory T cells in AAV

Natural T_{Regs}, a subset of thymus-derived $CD4^+$ T cells expressing a high level of IL-2Rα (CD25) and a unique transcription factor *FoxP3*, have been shown critical for preventing autoimmune responses. Defects in T_{Reg} function or reduced numbers of T_{Regs} have been documented in several autoimmune diseases [68]. Indeed, we found that the suppressive function of T_{Regs} was defective in WG patients as compared with healthy controls [69]. In this group of patients, however, we observed a significant increase of memory *FoxP3*$^+$CD25^{High} T_{Regs}. In line with these findings, Klapa and colleagues demonstrated an increased number of *FoxP3*$^+$ T cells as well as phenotypical and functional alterations of T_{Regs} in WG patients [70]. They reported an increased number of interferon receptor I-positive T_{Regs} in the peripheral blood of WG patients [70]. In addition, they showed that IFNα exaggerates functional T_{Reg} impairment *ex vivo* in response to the autoantigen PR3 [70]. T_{Regs} in WG patients might thus display functional anergy in the context of an inflammatory cytokine milieu.

Altered T_{Reg} function in WG patients has also been reported by Morgan and coworkers [71]. They observed that T_{Regs} from healthy controls and from ANCA-negative patients were able to suppress T-cell proliferation to PR3, whereas T_{Regs} from ANCA-positive patients failed to suppress this autoimmune response [71]. Dysfunction of T_{Regs} is thus believed to play a role in the development of WG. In contrast, T_{Reg} function in MPA patients was comparable with that in healthy controls, but *FoxP3* levels were diminished in MPA patients [72]. MPA seems to be associated with a numerical deficiency rather than a functional deficiency of T_{Regs}. Moreover, studies in CSS patients showed that both patients and controls have a similar number of $CD25^+CD4^+$ T cells with an equal percentage of *FoxP3*-expressing cells. However, the suppressive function of T_{Regs} in CSS patients still needs to be investigated [63,73].

Plasticity of T_{Regs} in AAV: conversion towards Th17 effector cells within an inflammatory milieu

A reciprocal relationship in the development of T_{Regs} and Th17 cells has recently been described. This may underlie the propensity of T_{Regs} to convert to Th17 cells in the context of proinflammatory stimuli, a phenomenon that has only recently been recognized [74-76]. Under neutral conditions *in vitro*, transforming growth factor beta can shift the balance towards functional *FoxP3*$^+$ T_{Regs} – whereas in the context of an inflammatory cytokine milieu (IL-1β, IL-2, IL-6, IL-15, IL-21, IL-23), functional T_{Regs} convert towards IL-17-producing, nonfunctional T_{Regs}. The relatively novel notion of T-cell lineage plasticity is of interest in relation to many papers describing nonfunctional T_{Regs} in several autoimmune conditions, including AAV. Our hypothesis is that these nonfunctional *FoxP3*$^+$ T cells have lost their suppressive function due to co-expression of a second Th17 lineage-associated transcription factor RORγt that interferes with *Foxp3* activity [77]. Recently, different isoforms of *FoxP3* have been investigated in human T_{Regs} that have been shown to impact T_{Reg} function and lineage commitment. More specifically, the full-length isoform (*FoxP3fl*) – but not the isoform lacking exon 2 (*FoxP3Δ2*) – interacts with RoRγt and inhibits the expression of genes that define Th17 cells [78-80]. Based on the aforementioned data, the putative nonfunctional T_{Regs} described in AAV may lack their suppressive function due to upregulation of the *FoxP3Δ2* isoform that fails to inhibit RORγt-mediated IL-17A mRNA transcription. Upon stimulation in an inflamed context, these cells convert into IL-17-producing effector T cells.

Evidence from several groups of investigators, including our own, support this hypothesis of conversion of T_{Regs} into effector IL-17-secreting cells in AAV. As mentioned before, we found a significant increase in the percentage of *FoxP3*$^+$CD25^{High} T_{Regs} with a defective regulatory function in AAV patients in remission as compared with healthy controls. Furthermore, we demonstrated a concurrent increase in the percentage of Th17 cells upon *in vitro* stimulation of peripheral blood samples from AAV patients. Consistent with this, patients with AAV had significantly higher serum levels of IL-17 compared with healthy controls [62]. Importantly, increased serum levels of IL-17 in AAV patients

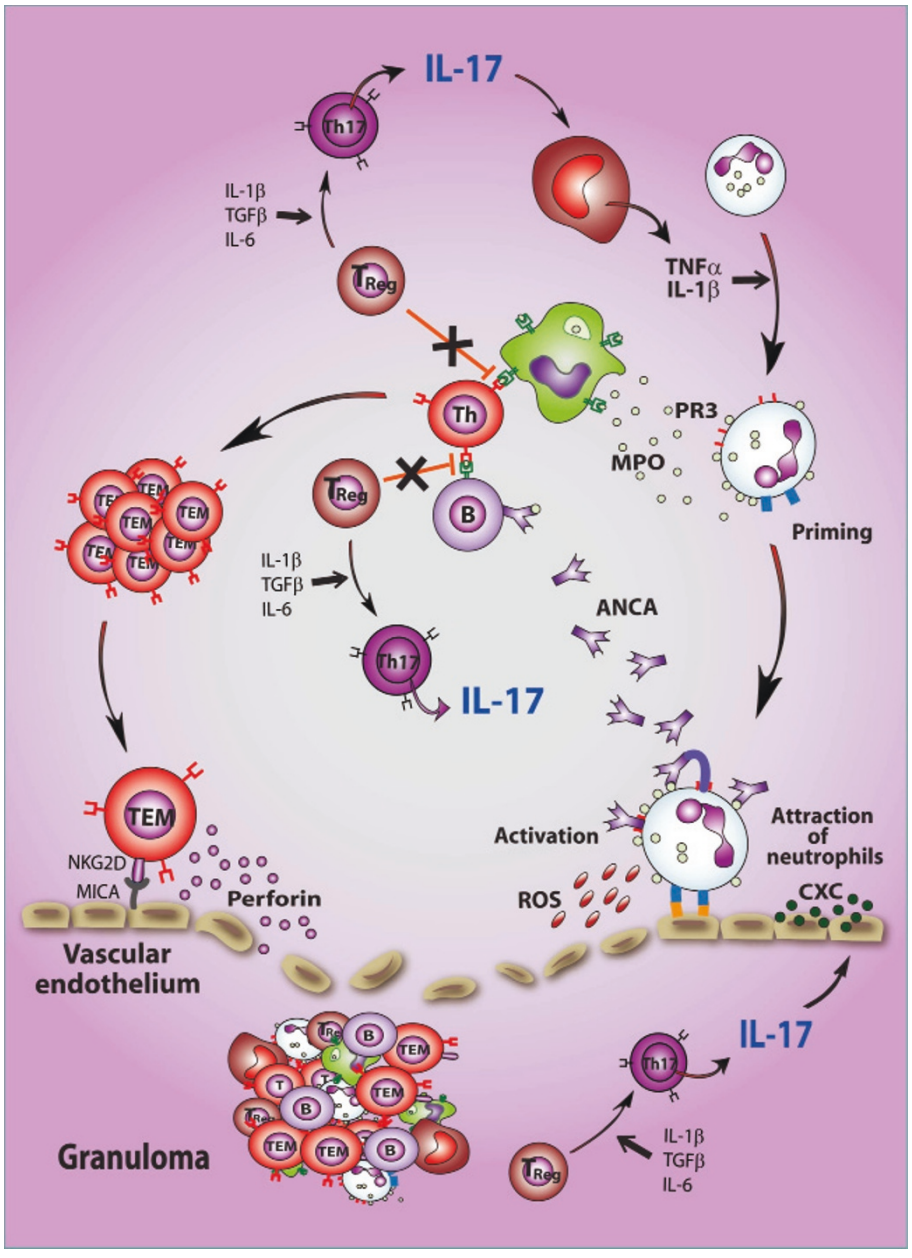

Figure 1. Proposed pathophysiological mechanisms of anti-neutrophil cytoplasmic autoantibody-associated vasculitides. Inflammatory cytokines (IL-1β, IL-6, transforming growth factor beta (TGFβ)) released due to bacterial or viral infections can promote skewing of a subset of functional regulatory T cells (T_{Regs}) towards IL-17-producing nonfunctional T_{Regs}. These IL-17-producing cells play a key role in disease onset through their cytokine IL-17. This cytokine induces CXC chemokine release from the target tissue that will attract neutrophils to the site of inflammation. In addition, IL-17 stimulates the release of IL-1β and TNFα from macrophages, which causes upregulation of the expression of endothelial adhesion molecules and induces translocation of proteinase-3 (PR3) and myeloperoxidase (MPO) to the neutrophil membrane (priming). Released PR3 and MPO can be processed and presented by antigen-presenting cells (APC) to T-helper cells. Since T_{Regs} are converted into nonfunctional IL-17-producing cells that fail to inhibit this autoimmune response, autoreactive T cells may undergo repeated stimulation by PR3-pulsed or MPO-pulsed APC, resulting in a pool of effector memory T cells (T_{EM}). In addition, PR3-stimulated T-helper cells act on B cells. The presence of IL-17 can enhance the production of anti-neutrophil cytoplasmic autoantibody (ANCA) by autoreactive B cells. Subsequently, ANCA binds to PR3 or MPO on primed neutrophils that adhere to endothelial cells, which enhances neutrophil activation resulting in degranulation and release of reactive oxygen species (ROS) and proteolytic enzymes that can damage vascular endothelial cells. Moreover, persistent activation of T-helper cells by PR3 or MPO, together with the breakdown of T_{Reg}-mediated self-tolerance mechanisms, will induce autoreactive $CD4^+$ T_{EM} expansion. Expanded $CD4^+$ T_{EM} upregulate their killer immunoglobulin-like receptor (NKG2D) and interact with their ligand (major histocompatibility complex class-I chain-related molecule A (MICA)) on vascular endothelial cells, which in turn enhances their cytotoxic function and kills target cells in a perforin-dependent and granzyme-dependent way, ending up in vasculitis.

correlated significantly with increased levels of the cytokines that are involved in the conversion of T_{Regs} into Th17 cells; that is, IL-1β, IL-23 and IL-6 [62]. In addition, patients with active CSS showed an increased frequency of Th17 cells with a decrease in the frequency of IL-10-producing T_{Regs}, whereas an inverse result was observed in CSS patients with inactive disease [63]. The aforementioned data appear to support a link between the conversion of T_{Regs} into Th17 cells and disease activity in AAV (Figure 1).

Therapeutic targets in patients with AAV

Because Th17 cells contribute to inflammation and granuloma formation, this T-cell subset could be a novel therapeutic target for AAV. Depletion of Th17 cells by targeting specific surface proteins may be difficult as Th17 cells share many surface markers with other T-cell subsets. A therapeutic approach targeting its cytokine (that is, IL-17) would therefore be more feasible. Indeed, neutralizing IL-17 by anti-IL-17 antibody or by soluble IL-17 receptors reduces inflammation and bone erosion in various animal arthritis models [81]. Interestingly, humanized anti-IL-17 mAbs – including AIN457 and LY2439821, which neutralize the biologic activity of IL-17 – are in clinical trials. These biologicals have been shown to induce clinically relevant responses in patients with psoriasis, rheumatoid arthritis, and non-infectious uveitis, compared with placebo without safety issues [82,83]. Neutralization of IL-17 could therefore represent a novel therapeutic approach for patients with AAV.

On the other hand, $CD4^+$ T_{EM} – supposed to act as a key trigger of disease expression and relapse in AAV – may also serve as a therapeutic target. Selective targeting of $CD4^+$ T_{EM} without impairing other parts of the humoral and cellular immune system could be a major step forward in the treatment of AAV. NKG2D blockade by anti-NKG2D antibodies has been reported to prevent autoimmune diabetes in NOD mice [84]. Blocking of NKG2D could be a new strategy in the treatment of AAV. Other studies have revealed that targeting of the voltage-gated Kv1.3 channel, which is highly expressed on activated $CD4^+$ T_{EM}, provides a specific immunomodulatory approach [85,86]. Blockade of the Kv1.3 channel by ShK(L5) amide effectively prevented autoimmune disease in the EAE model of multiple sclerosis and suppressed delayed-type hypersensitivity in rats [85,86]. The selective targeting of $CD4^+$ T_{EM} using ShK(L5) amide and/or blocking the NKG2D–MICA interaction by anti-NKG2D antibodies may therefore hold therapeutic promise for AAV.

Conclusion

$CD4^+$ T_{EM} seem to be involved in tissue damage and renal injury in patients with AAV. Besides $CD4^+$ T_{EM}, impaired T_{Reg} function and an increased Th17 response are also reported in AAV patients. During the past 2 years, multiple studies indicate a link between T_{Regs} and Th17 cells. Indeed, in the context of an inflammatory cytokine milieu, conversion of T_{Regs} into IL-17-producing cells has been demonstrated. Evidence from several studies supports this conversion in AAV patients. Defective T_{Reg} function in AAV patients can thus be explained by their conversion into effector Th17 cells. Instead of suppressing autoreactive responses, these converted T_{Regs} – through production of IL-17 – can participate in granuloma formation and tissue injury, which contribute to necrotizing granulomatous vasculitis in AAV patients. The mechanisms underlying the conversion of suppressive T_{Regs} into nonfunctional T_{Regs} in AAV await further investigation. This novel view into the role of converted T_{Regs} in the pathophysiology of vasculitis will improve our understanding of AAV pathogenesis, which may lead to the identification of new biomarkers and targets for therapeutic intervention.

Autoimmune Basis of Rheumatic Diseases

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Abbreviations

AAV, anti-neutrophil cytoplasmic autoantibody-associated vasculitides; ANCA, anti-neutrophil cytoplasmic autoantibody; CSS, Churg–Strauss syndrome; EAE, experimental autoimmune encephalomyelitis; *FoxP3*, transcription factor forkhead box P3; IFN, interferon; IL, interleukin; mAb, monoclonal antibody; MICA, major histocompatibility complex class-I chain-related molecule A; MPA, microscopic polyangiitis; MPO, myeloperoxidase; NK, natural killer; PR3, proteinase-3; T_{EM}, effector memory T cells; Th, T-helper type; TNF, tumor necrosis factor; T_{Reg}, regulatory T cell; WG, Wegener's granulomatosis.

Competing interests

The authors declare they have no competing interests.

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