T-Lymphocytes and Disease Mechanisms in Wegener’s Granulomatosis

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Introduction

Wegener’s granulomatosis (WG) is a granulomatous-necrotizing small vessel vasculitis [1]. WG forms together with microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS), a disease complex named ANCA-associated vasculitis (AAV). All forms of AAV share common features like the presence of anti-neutrophil-cytoplasmic antibodies (ANCA). In WG, ANCA are usually directed against proteinase-3 (PR3) whereas patients with MPA and CSS have myeloperoxidase-specific ANCA. However, there are also cases reported in which ANCA were not detectable [2, 3]. Although MPA and CSS show the same class of ANCA, the type of inflammation is different. Like WG, CSS is a granulomatous vasculitis whereas MPA is not. If and in what way this is related to the different types of ANCA is not clear. AAV is a life-threatening disease and adequate treatment is essential [4].

Both the innate and adaptive immune system play a role in disease mechanisms of WG, although the pathogenesis is not well understood [5]. Basically, it is believed that ANCA have a pathogenic role in disease mechanisms: the interaction of ANCA with its target antigen causes degranulation of neutrophils resulting in endothelial and finally vasculitic damage. There is evidence from in vivo experiments on the pathogenicity of MPO-ANCA [6]. Transfer of anti-MPO IgG in rodent models leads to necrotizing crescentic glomerulonephritis whereas administration of anti-PR3 IgG fails to induce granulomatous inflammation and glomerulonephritis [6–9]. Nevertheless, there is some evidence pointing at a patho-

Key Words
Anti-neutrophil cytoplasmic antibodies · T-cells · Regulatory T-cells · Vasculitis · Wegener’s granulomatosis

Abstract
The mechanisms underlying Wegener’s granulomatosis (WG) are not well understood. The role of T-cells in the pathogenesis of WG has only recently come into focus of research. This review presents recent developments regarding the role of T-cells in WG. The occurrence of anti-neutrophil-cytoplasmic antibodies (ANCA) directed against proteinase-3 (PR-3) is a hallmark of WG. ANCA seem to mediate vasculitic damage in WG. Apart from ANCA, T-cells are involved in disease mechanisms. T-cells might participate in ANCA formation. Furthermore, T-cells are observed in affected tissue and granulomatous lesions. T-cells are indispensable for granuloma formation in other diseases and this might apply to WG too. In line with this, several aberrations of T-cell populations and alterations of the T-cell response were recently discovered in patients suffering from WG. Therefore, the impact of T-cell polarization, genotypic alterations modifying T-cell function and specific T-cell subsets on disease pathogenesis is discussed. Moreover, the influence of Staphylococcus aureus on T-cells and self-tolerance in WG is further elucidated. Finally, therapeutic options and implications with regard to T-cell-mediated pathogenesis are highlighted.
The expression level of membrane-bound PR3 on neutrophils is reported to have impact on the relapse rate in WG [14]. Last but not least, B-cell-targeted therapy with rituximab seems to be efficacious in refractory disease and is accompanied by a decrease of autoantibody titer [15]. However, apart from autoantibodies and B-cells, T-cells play an important role in disease mechanism. The IgG subclass of ANCA indicates that a T-cell-dependent subclass switch has occurred [16]. In addition, granuloma-like formations are usually found in affected tissue. These granulomas are a source of autoantibodies [17, 18]. Granuloma formation is driven by T-cells and T-cell-derived cytokines [19, 20]. T-cells are found in these lesions suggesting a role in the inflammatory process of WG [21]. Furthermore, Schmitt et al. [22] reported a strong correlation of disease activity and markers of T-cell activation such as soluble IL-2 receptor. T-cells are reported to be persistently expanded in WG [23]. Further evidence on the role of T-cells in AAV is provided by Ruth et al. [7] in an MPO animal model. Glomerular crescent formation was reduced after CD4+ T-cell depletion. These facts and the capacity of T-cells to control and induce immune responses gave rise to investigations of the role of T-cells in WG.

**Table 1. Overview on different T-cell subsets important in WG**

<table>
<thead>
<tr>
<th>T-cell subset</th>
<th>Properties and phenotype</th>
<th>Function in WG</th>
<th>References</th>
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<tr>
<td>Naturally occurring regulatory T-cells (T&lt;sub&gt;reg&lt;/sub&gt;)</td>
<td>CD4+CD25&lt;sup&gt;bright&lt;/sup&gt;FoxP3+CD127&lt;sup&gt;low&lt;/sup&gt;</td>
<td>Presumably defective in function, do not suppress sufficiently</td>
<td>Abdulahad et al. [49]</td>
</tr>
<tr>
<td>Induced regulatory T-cells (iT&lt;sub&gt;reg&lt;/sub&gt;)</td>
<td>CD4+FoxP3–IL-10+ CD4+FoxP3+TGF-β</td>
<td>Not studied yet, mainly limit immune responses in a physiologic context</td>
<td>Piccirillo [51] Roncarolo et al. [52]</td>
</tr>
<tr>
<td>Naive T-cells</td>
<td>CD4+CD45RO–CD45RA+</td>
<td>Diminished in WG, skewing towards memory phenotype</td>
<td>Marinaki et al. [55]</td>
</tr>
<tr>
<td>Effector T-cells (T&lt;sub&gt;eff&lt;/sub&gt;)</td>
<td>Displaying effector function, e.g. IFN-γ or TNF-α production</td>
<td></td>
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<tr>
<td>Effector memory T-cells (T&lt;sub&gt;em&lt;/sub&gt;)</td>
<td>CD4+CD45RO+CCR7– CD4+CD25+CD45RO+CD134+ CD4+CD25+CD45RO+GITR+</td>
<td>Expanded T-cell population, maybe driver for granuloma formation and vasculitis</td>
<td>Abdulahad et al. [23] Wilde et al. [59]</td>
</tr>
<tr>
<td>Terminally differentiated effector memory T-cells (T&lt;sub&gt;tEM&lt;/sub&gt;)</td>
<td>CD4+CD45RO+CD28–CTLA4+</td>
<td>Abundantly present in granulomas, main source of proinflammatory cytokines</td>
<td>Lamprech et al. [25, 26, 64] Hoff et al. [96]</td>
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**Granuloma Formation and T-Cells in WG**

Fienberg [24] described WG-associated granulomas in detail. Macrophages, neutrophils and lymphocytes form granulomas usually observed in WG. Interestingly, most of the T-cells residing within granulomas display features of terminally differentiated effector memory T-cells (T<sub>tEM</sub>) (table 1) [25–27]. T<sub>tEM</sub> show a downregulation of CD28 whereas the cytotoxic T-lymphocyte antigen-4 (CTLA-4) is overexpressed (table 1) [28]. Despite the regulatory functions of CTLA-4 in CD28-dependent T-cell activation, this molecule seems to confer protection against induced cell death by upregulation of anti-apoptotic BCL-2 as shown by Pandiyan et al. [29]. T-cells found in granulomas mainly show a Th1-cytokine pattern with secretion of IFN-γ and TNF-α [30]. A recent report showed that PR3 antigen elicits strong Th1-responses via dendritic cell maturation and subsequent antigen presentation to T-cells [31]. As granuloma formation is driven by Th1 responses, DC maturation and activation pathways might be important in disease pathogenesis. Intriguingly, PR3 antigen is usually present in granulomas and antigen-presenting cells (APC) are found in these lesions as well. Therefore, T-cells might be primed in granulomas. B-cells are also located in these lesions [17].

Thus, the question arises whether granulomas sustain the immune response in WG or even provide conditions favorable to overcome tolerance.
Genotypic Alterations in WG

Genetic background is proven for some of the autoimmune diseases. Some findings point at a genetic disposition for WG as well. The coding gene for CTLA-4 was studied extensively as this molecule plays a key role in the T-cell activation processes and shows an aberrant expression pattern in WG [27, 28]. CTLA-4 is able to shut down and limit T-cell activation. It is expressed on T-cells and binds to CD80/CD86 on APC. Distinct polymorphisms of the CTLA-4 gene are associated with WG and correlate with the renal outcome of patients [32]. Some of the polymorphisms associated with WG were also shown to impair the regulatory function of CTLA-4 [33]. Dinucleotide expansions within the CTLA-4 gene in WG might cause instability of mRNA and hence interfere with the expression as well as functionality of CTLA-4 [33–35].

A study on polymorphisms of the protein tyrosine phosphatase non-receptor type 22 (PTPN22) was published in 2005 [36]. PTPN22 is a tyrosine phosphatase that is involved in T-cell receptor signaling [37]. Jagiello et al. [36] revealed that a particular allele of the PTPN22 gene is a risk factor for WG. This specific allele is supposed to be less functional [36]. Enhanced proliferation of memory T-cells and formation of ectopic germinal centers in rodent models with complete deficiency of PTPN22 was demonstrated [38, 39]. Since similar phenomena such as memory T-cell expansion are observed in WG, a role for PTPN22 has to be considered [23].

Polymorphisms of genes coding for cytokines were studied in the past. Although TNF-α and IL-2 levels are usually increased in WG, no association with polymorphisms was found [40]. However, gene analysis for IL-10 revealed an increased frequency of a specific allele within the promoter region of IL-10 in WG [41]. This specific allele is associated with decreased production of the immunoregulatory cytokine IL-10 and thus might promote break of tolerance [42].

Disease Pathogenesis and Specific T-Cell Subpopulations

Regulatory T-cells (T\textsubscript{reg}) and effector T-cells (T\textsubscript{eff}) are major players in T-cell-mediated immunity (table 1). The role of both T\textsubscript{reg} and T\textsubscript{eff} in the pathogenesis of WG will be discussed below. T\textsubscript{reg} and T\textsubscript{eff} have different phenotypes and functions (table 1). T\textsubscript{reg} control immune responses and limit inflammatory processes that are initiated and sustained by T\textsubscript{eff}. Thus, T\textsubscript{reg} seem to have a key role in maintaining self-tolerance [43–47]. T\textsubscript{reg} are usually found within the CD25+ T-cell population and express high levels of Foxp3 allowing differentiation from activated effector lymphocytes. T\textsubscript{reg} depletion in animal models leads to autoimmunity and defective regulatory function was also seen in patients suffering from multiple sclerosis and rheumatoid arthritis. The role of T\textsubscript{reg} has been investigated in WG. Marinaki et al. [48] assessed FoxP3 mRNA expression in T-cells from patients with AAV but did not find differences as compared with healthy controls. Abdulahad et al. [23] analyzed FoxP3 expression of effector memory T-cells (T\textsubscript{em}) defined as CD4+CD45RO+CCR7– in WG (table 1). It was shown that patients in remission have a slightly higher frequency of FoxP3+ T\textsubscript{em} accompanied by an increase of FoxP3– T\textsubscript{em} than patients with active disease. Active patients did not show any differences in frequency of FoxP3+ T\textsubscript{em}. Calculated ratios for FoxP3–/FoxP3+ T lymphocytes did not differ in comparison to healthy controls. Again, these findings did not point at a role for T\textsubscript{reg} in the pathogenesis of WG. The latest report in this matter was published by Abdulahad et al. An increased frequency of CD4+CD25\textsuperscript{bright} FoxP3+ and CD4+CD45RO+CD25\textsuperscript{bright} FoxP3+ cells was detected in peripheral blood lacking correlation with clinical features. These T\textsubscript{reg} were less efficient in inhibiting proliferation of responder T-cells than T\textsubscript{reg} from HC [49]. The authors concluded that T\textsubscript{reg} from WG patients are impaired in function. It has to be stressed that FoxP3 was recently reported to be transiently upregulated in activated lymphocytes [50]. Therefore, these findings need to be confirmed. Nevertheless, this is a first hint pointing at a role of T\textsubscript{reg} in disease pathogenesis. A different subset of T\textsubscript{reg}, so-called ‘induced regulatory T-cells’ (iT\textsubscript{reg}), have not been studied yet in WG but may be impaired in function, too (table 1) [51, 52].

Apart from T\textsubscript{reg}, T\textsubscript{eff} have been investigated as well. T\textsubscript{eff} are controlled by T\textsubscript{reg} and have the capacity to promote and initiate immune responses. In general, all T-cells displaying effector functions belong to T\textsubscript{eff} [53]. Thus, T\textsubscript{em} and T\textsubscript{IEM} are subsets of T\textsubscript{eff} (table 1). It was shown earlier that the circulating T\textsubscript{IEM} with no or little CD28 expression are expanded. T\textsubscript{IEM} were also found in granulomas and are a major source of IFN-γ and TNF-α. The expansion is associated with disease progression and organ involvement [25, 30, 54].

Recent reports show a significant increase of whole T\textsubscript{em} along with a decrease of naive T-cells in WG patients [23, 55]. The cause for the expansion of T\textsubscript{em} has been investigated by several groups. Data from Czernok et al. [31] suggest a role for dendritic cells in initial stages of WG,
but increased expression of CTLA-4 followed by protection from induced cell death might contribute to $T_{em}$ expansion as well. Persistent antigen stimulation could also favor expansion of the $T_{em}$ compartment. A role for $T_{reg}$ should be considered. Furthermore, differences between patients in remission and those with active disease were revealed. Patients in remission show higher levels of circulating $T_{em}$ than patients with active disease. It is speculated that these $T_{em}$ migrate from peripheral blood to sites of inflammation causing a decrease in circulating $T_{em}$ during active disease [23, 31]. Memory T-cells also express receptors belonging to the tumor necrosis factor receptor (TNFR) superfamily (CD134 and glucocorticoid-induced tumor-necrosis factor receptor, GITR); these receptors are known to confer resistance against immunoregulation [56–58]. In WG, CD134+/GITR+ T-cell subsets are expanded and associated with disease activity. These T-cell subsets are also present in inflamed tissue and might contribute to tissue damage in WG [59]. However, the importance of these T-cells as markers of disease activity needs further investigation. The pathogenic potential of these T-cells has to be elucidated further. As $T_{em}$ and $T_{tem}$ respond rapidly and establish a powerful immune response, they might account for relapsing disease course; a contribution to granuloma formation seems to be likely. New therapeutic options might arise from targeting these T-cells.

**T-Cell Cytokines and Chemokines in WG**

It is stated that there are differences in Th1/Th2 polarization depending on disease and disease stage [60–62]. Some authors support the idea that localized disease is associated with a Th1 response whereas a Th2 response is observed in systemic disease. Schonermack et al. [63] assessed sCD26 plasma levels as a marker for Th1 response in patients with localized and systemic WG. Levels were elevated in patients with localized disease suggesting a preferential Th1 response. Lamprecht et al. [64] compared CCR5 (Th1) and CCR3 (Th2) expression on T-cells from patients with WG. In localized disease, there was a higher expression of CCR5 as compared to CCR3 whereas both markers were expressed at equal levels in systemic disease. This was confirmed by observations made in biopsy studies. Muller et al. [65] characterized the cell infiltrates from nasal biopsies. These cells were mainly positive for CD26 and IFN-γ in localized WG indicating a preferential Th1 response. In systemic disease, an increase of IL-4 mRNA was detected. Accordingly, Balding et al. [60] found upregulation of IL-4 and failed to detect IFN-γ in biopsies suggesting a Th2 response in systemic WG. In contrast to these studies, Csernok et al. [61] detected high levels of IFN-γ mRNA and low levels IL-4 mRNA in granulomas in systemic WG. The majority of granuloma-derived T-cells were IFN-γ producers. Hence, data on Th1/Th2 polarization is inconclusive.

TNF-α levels are also increased in WG [30]. T-cells found in granulomas and in the circulation are sources of TNF-α [30]. TNF-α acts as a proinflammatory cytokine on lymphocytes and neutrophils. It primes neutrophils, making them susceptible for ANCA-mediated degranulation and oxidative burst. Furthermore, it promotes upregulation of adhesion molecules on endothelial cells thus facilitating migration to the tissue. Thus, TNF-α is of particular importance promoting vasculitic inflammation in several different ways.

IL-17-producing T-cells (Th17 cells) are major players in autoimmunity [66–68]. IL-17 is suggested to be involved in autoantibody formation as well as in recruitment and activation of neutrophils [69, 70]. Little data is available on the role of IL-17 in WG. However, a skewed Th17 response observed in WG might contribute to disease pathogenesis [71].

In conclusion, there is evidence for a disturbed cytokine axis promoting inflammation.

**Staphylococcus aureus-Induced Immune Alterations and WG**

Nasal carriage of *S. aureus* and the staphylococcal toxic shock syndrome toxin-1 (TSST-1) are risk factors for new onset and relapsing disease [72, 73]. Anti-*S. aureus* treatment with cotrimoxazole reduces the rate of relapses [74]. Therefore, the impact of *S. aureus* on pathogenesis in WG is discussed below. A study of outstanding interest was conducted by Pendergraft et al. [75], who investigated the role of complementary proteins in WG. In brief, the amino acid sequence of a specific protein is generally coded by the ‘sense’ strand of DNA [76]. Transcribing and translating this information results in a ‘sense’ protein. The opposite strand of the coding DNA is the so-called ‘anti-sense’ strand. The anti-sense strand carries genetic code of the complementary peptide that is the counterpart of the ‘sense’ protein [76]. Pendergraft et al. [75] hypothesize that the initial immune response in autoimmunity is directed against complementary PR3 (cPR3), resulting in the formation of antibodies against cPR3 (idiotypic response). Later on, an anti-idiotypic response
against anti-cPR3 antibodies evolves. The antibodies formed during this anti-idiotypic response react to the sense autoantigen PR3. Indeed, Pendergraft et al. demonstrated the presence of anti-cPR3 antibodies in a minority of WG patients. These antibodies were specific for cPR3 and also bound specifically to anti-PR3. After having shown that anti-cPR3 and anti-PR3 antibodies from human WG sera form idiotypic pairs, mice were immunized with recombinant or synthetic human cPR3 in order to test the hypothesis in vivo. After immunization, anti-cPR3 as well as anti-PR3 antibodies were detected in mice supporting the idea of idiotypic and anti-idiotypic responses. Furthermore, Pendergraft et al. [75] searched for sources of cPR3 in WG patients. cPR3 transcripts were found in none of the healthy controls, ANCA-negative or lupus patients. However, cPR3 mRNA could be detected in leukocytes of PR3-ANCA patients. The origin of the cPR3 transcripts has not been unraveled so far. It could be of endogenous origin or exogenous origin, the latter introduced by pathogens. Indeed, genetic sequences complementary to human PR3 gene were detected in pathogens like S. aureus, Ross River virus and Entamoeba histolytica [75]. In conclusion, Pendergraft et al. provided substantial evidence for an involvement of cPR3 in disease mechanisms of WG; the idea is supported that microbial pathogens are of importance in different stages of autoimmunity.

Apart from classic ANCA, a different type reactive to lysosomal membrane protein-2 (LAMP-2) has been described by Kain et al. [77]. Anti-LAMP2 was present in WG patients with active disease and renal involvement; having entered remission, anti-LAMP2 was no longer detectable in the majority of patients. Kain et al. also provide evidence for in vitro and in vivo pathogenicity of anti-LAMP2. Anti-LAMP2 showed similar pathogenic potential in vitro as compared to anti-PR3. Shape change and degranulation of neutrophils was induced by anti-LAMP2; in addition, apoptosis could be induced in human vascular endothelial cell culture by adding this antibody [77]. Furthermore, LAMP2 shows homology to the bacterial protein FimH, which is involved in adhesion to epithelial cells and is usually found on common bacterial pathogens such as Escherichia coli and Klebsiella pneumonia. Therefore, the in vivo pathogenicity of anti-LAMP2 was tested in two different ways. First, anti-human rabbit IgG with specificity to LAMP2 were injected into Wistar-Kyoto (WKY) rats [77]. These rats developed focal necrotizing glomerulonephritis (FNGN). Thus, anti-LAMP2 antibodies seem to be pathogenic in vivo and promote FNGN. Then, in a second approach, WKY rats were immunized using recombinant FimH fusion protein. Subsequently, antibodies to FimH could be detected. However, standard ANCA assays were also positive. Antibodies to FimH cross-reacted with rat and human LAMP2. Furthermore, these rats developed FNGN and in some cases hemorrhagic pulmonary vasculitis occurred. Therefore, immunization with FimH induces antibodies to LAMP2 and provokes vasculitis. Finally, this study by Kain et al. [77] suggests that bacterial infections with common bacteria such as E. coli might trigger the development of autoantibodies and thus promote pauci-immune glomerulonephritis.

Exotoxins from S. aureus were suggested to be responsible for persistent activation and expansion of T-cells [78]. Some of the bacterial exotoxins are able to activate lymphocytes by binding to Vβ regions of the T-cell recep-
tor independent of antigen specificity; these exotoxins are so-called superantigens (SAg). SAg bind to MHC class II on APC and to T-cell receptor on T-cells outside the antigen-binding groove [79]. Especially expansion and activation of autoreactive T-cells could contribute to autoimmune disease. Popa et al. [78] analyzed the frequency of Vβ-expressing T-cells. Although T-cell subsets expressing Vβ regions with affinity to SAg were expanded, no correlation with presence of SAg or S. aureus was seen.

**Therapeutic Implications**

There is a rationale for therapeutic lymphocyte depletion as T-cells contribute to disease mechanisms. For this purpose, anti-thymocyte globulin (ATG) was administered to patients with refractory disease in the context of clinical studies. At least partial remission could be induced, but in view of severe side effects also known from transplant studies, ATG treatment is not the first choice.

**Fig. 2.** Teff trigger granuloma formation. Granulomas provide an inflammatory environment that sustains inflammation and might facilitate break of tolerance. Granulomas are sources for proinflammatory cytokines and autoantibodies; whether B- and/or T-cell maturation takes place is not fully proven. PR3 is also present in granulomas. PR3 acts on DCs and promotes maturation. Autoreactive T-cells might be activated by these DCs. ANCA produced by granuloma-resident B cells bind to primed neutrophils that express PR3 on their surface. Subsequently, degranulation of neutrophils is caused provoking vasculitic damage.
of therapy [80–82]. An antibody (alemtuzumab) directed against CD52 (displayed on mature lymphocytes) was also used for T-cell depletion in some small studies with patients suffering from WG. Responses and even sustained remissions were achieved in these patients. In line with the experience on ATG administration, alemtuzumab was used only in an experimental setting because of the risk for infections, malignancies and allergic reactions. No sufficient long-term data is available [83–86].

Targeting cytokines is a more specific therapeutic opportunity. Anti-TNF-α biologics were used abundantly in many different autoimmune diseases. It is also administered in WG in selected cases. There are different forms of anti-TNF-α biologics: (1) etanercept is a fusion protein with two TNF-α receptors bound to the Fc part of a human IgG; (2) infliximab is a chimeric monoclonal IgG-antibody able to bind soluble and membrane-bound TNF-α, and (3) adalimumab is a human monoclonal IgG antibody with two binding sites for soluble or already bound TNF-α.

Etanercept was tested against a placebo in a large, controlled trial named WGET [87]. Either etanercept or the placebo was added to the standard therapy. In this trial, both arms were comparable with regard to induction of remission or relapse rate. Interestingly, the incidence of malignancies was higher in the etanercept arm [88]. Some small studies were conducted with infliximab; a total of 48 patients were included in these uncontrolled trials [89–92]. 38 patients received infliximab in addition to a standard treatment regimen. 33 of these 38 patients entered remission. However, a relapsing disease course was observed frequently. In one of these trials, 10 patients received sole infliximab treatment with corticosteroids; complete remission (5) and partial remission (5) were induced [89]. Right now, no data is available on adalimumab. The efficacy of anti-TNF-α agents in WG remains uncertain. Additional controlled clinical trials are needed to assess the potency and safety of anti-TNF-α agents in WG.

Attenuation of T-cell-dependent immune responses by blocking the CD28/CD80 pathway is effective in animal models. The CTLA-4Ig was tested recently in human clinical trials on rheumatoid arthritis (RA). So far, CTLA-4Ig seems to be a promising therapeutic option for refractory disease in RA [93, 94]. Even though disease pathogenesis is not comparable to WG, T-cell activation and CD80 expression pattern is altered in AAV [27]. Hence, modifying costimulatory pathways might be a new and effective therapeutic approach [95].

Conclusion

T-cells contribute to disease mechanisms in WG. Both the pathogenesis as well as the key events leading to the break of tolerance have not been uncovered yet. Potentially, Treg are not able to control Tem sufficiently. Thus, defective Treg function, persistent antigen stimulation, protection from induced cell death and activated DCs might cause an expansion of Tem (Fig. 1). Hence, Tem might be major players in disease mechanisms by promoting granuloma formation (Fig. 2). Thereafter, granulomas provide a proper environment for a break of tolerance and sustained autoantibody as well as T-cell-mediated inflammation (Fig. 2). Further efforts in unraveling the disease pathogenesis of WG will finally result in new and effective therapeutic strategies.

References


T-Lymphocytes and Disease Mechanisms in WG


