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Vasculitogenic T Cells in Large Vessel Vasculitis

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Vasculitis is an autoimmune disease of unknown etiology that causes inflammation of the blood vessels. Large vessel vasculitis is classified as either giant cell arteritis (GCA), which occurs exclusively in the elderly, or Takayasu arteritis (TAK), which mainly affects young women. Various cell types are involved in the pathogenesis of large vessel vasculitis. Among these, dendritic cells located between the adventitia and the media initiate the inflammatory cascade as antigen-presenting cells, followed by activation of macrophages and T cells contributing to vessel wall destruction. In both diseases, naive $CD4^+$ T cells are polarized to differentiate into Th1 or Th17 cells, whereas differentiation into regulatory T cells, which suppress vascular inflammation, is inhibited. Skewed T cell differentiation is the result of aberrant intracellular signaling, such as the mechanistic target of rapamycin (mTOR) or the Janus kinase signal transducer and activator of transcription (JAK-STAT) pathways. It has also become clear that tissue niches in the vasculature fuel activated T cells and maintain tissue-resident memory T cells. In this review, we outline the most recent understanding of the pathophysiology of large vessel vasculitis. Then, we provide a summary of skewed T cell differentiation in the vasculature and peripheral blood. Finally, new therapeutic strategies for correcting skewed T cell differentiation as well as aberrant intracellular signaling are discussed.

Keywords: CD4+ T cells, CD8+ T cells, giant cell arteritis, regulatory T cells, Takayasu arteritis

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INTRODUCTION

Vasculitis is an autoimmune disorder that causes inflammation of blood vessels and multiple organ damage. Large vessel vasculitis (LVV) primarily affects the aorta and its major branches and can be divided into two disease categories: giant cell arteritis (GCA) and Takayasu's arteritis (TAK) (1). GCA is common in individuals over 50 years of age, especially in their 60s to 80s (2). Symptoms related to GCA include fever, headache, jaw claudication, and visual disturbances (3). Polymyalgia rheumatica is often accompanied by extravascular manifestations (4). In contrast, TAK is common in patients under 50 years of age, especially in Asian women in their 20s to 40s (5). TAK results in fever, general malaise, pulselessness, renovascular hypertension, and aortic regurgitation (6). Ulcerative colitis and erythema nodosum are well-known extravascular manifestations (7, 8).

The pathological findings of these two diseases are indistinguishable and the pathological hallmark of these diseases is chronic granulomatous inflammation, which primarily involves activated $CD4^+$ T cells and macrophages (9) (**Figure 1**). Cytokines released from activated $CD4^+$ T cells are the main triggers of macrophage activation (10). In addition, genome-wide association studies (GWAS) have revealed that human leukocyte antigens are critically involved

in the pathomechanisms of both GCA and TAK (11, 12). These findings suggest that antigen presentation to T cells, particularly $CD4^+$ T cells, plays a central role in the development of LVV.

Recent studies have revealed remarkable heterogeneity in $CD4^+$ T cells, leading to the discovery of T helper 1 (Th1), Th2, Th9, Th17, Th22, and T follicular helper (Tfh) cells, as well as regulatory T cell subsets (13, 14). Each T cell subset plays a unique role by expressing specific transcription factors and cytokines. Technological advances at the single-cell level have allowed further subdivision of these subsets and have led to the discovery of novel T cell subsets. Accordingly, several T helper cell subsets have been identified in LVV (15, 16). Moreover, aberrant cellular signaling pathways in activated T cells and new T cell subsets, such as tissue-resident memory T cells, have been identified in LVV (17).

In this mini-review, we first outline the current knowledge regarding the immunopathogenesis of LVV, followed by a discussion of the roles of each T cell subset, newly discovered T cell subsets, and aberrant signaling pathways in T cells. Finally, we provide future therapeutic perspectives for LVV based on targeting of T cells.

THE UPDATED IMMUNOPATHOGENESIS OF GCA

Vascular inflammation begins with antigen recognition in vascular dendritic cells (vasDCs) (18, 19). Essentially every artery contains vasDCs, which allow for early detection of foreign antigens. Proliferation of T cells with the shared T cell receptor is confirmed in distinct vascular lesions of GCA (20), which indicates that T cells undergo clonal expansion after recognizing certain antigens. Herpes zoster virus and others have been proposed as antigens (21), but this has not yet been verified. VasDCs express unique Toll-like receptor patterns in each artery (22). In non-inflamed temporal arteritis, the vasDCs are immature and located at the media-adventitia border (23). Once activated, vasDCs expand and express costimulatory molecules such as CD80 and CD86. They also produce excess chemokines and cytokines, which prime naive $CD4^+$ T cells and facilitate monocyte migration (24, 25). A recent study demonstrated that defective expression of programmed death ligand 1 in vasDCs also contributes to the maintenance of T cell activation (26, 27). Monocytes then differentiate into tissue macrophages, which are activated by cytokines, particularly interferon (IFN)-γ, released by activated T cells. Activated macrophages in turn start to produce large amounts of cytokines (e.g., IL-6) (28), chemokines (29, 30), proteolytic enzymes (e.g., matrix metalloprotease) (31, 32), and various growth factors, such as vascular endothelial growth factors (VEGF), fibroblast growth factor, and platelet-derived growth factor (33). These growth factors act on endothelial cells (ECs) and vascular smooth muscle cells (VSMCs), transforming them into myofibroblasts, and accelerate intimal hyperplasia and adventitial neoangiogenesis (34–36). Thus, the conventional inflammatory cascade in GCA includes three major players:

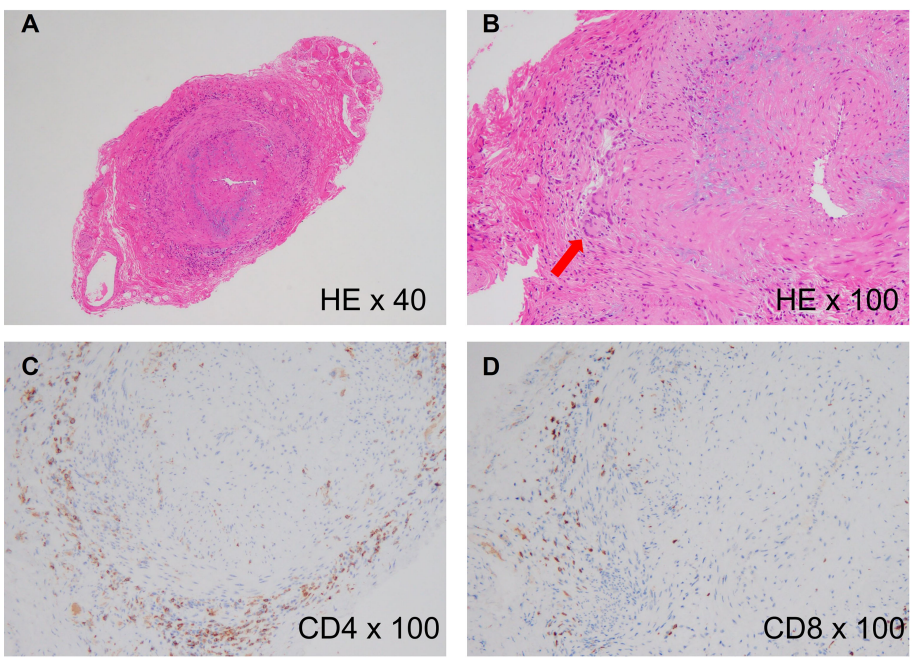

FIGURE 1 | Histology of giant cell arteritis. **(A)** Histological findings of a temporal artery biopsy from an 82-year-old woman with giant cell arteritis (hematoxylin and eosin staining, x40), showing intense cellular infiltration in the adventitia and luminal narrowing due to intimal hyperplasia. **(B)** High-power image of the biopsy (hematoxylin and eosin staining, x100). The red arrow indicates multinucleated giant cells. **(C)** CD4 staining of the biopsy (anti-CD4 staining, x100), showing accumulation of $CD4^+$ T cells in the adventitia. **(D)** CD8 staining of the biopsy (Anti-CD8 staining, x100), showing slight accumulation of $CD8^+$ T cells in the adventitia.

vasDCs, CD4$^+$ T cells, and macrophages. However, several new cell populations have emerged in the pathomechanisms of GCA.

First, neutrophils are not only important mediators of host defenses against pathogens but also contribute to many autoimmune diseases through neutrophil extracellular traps (NETs) (37). Until recently, the role of neutrophils has been underestimated because of the rarity of vascular lesions in GCA; however, mapping of immune cell populations from GCA patients has shown that immature neutrophils generate high levels of reactive oxygen species and enhance protein oxidation, leading to endothelial barrier dysfunction in vascular lesions (38). These findings link the function of immature neutrophils to disease mechanisms.

Second, intimal hyperplasia is thought to be caused by transformation and expansion of ECs and VSMCs into myofibroblasts. Recently, however, it has been proposed that fibroblasts located in the adventitia start to produce α smooth muscle actin and collagen by an unknown trigger, phenotypically change into myofibroblasts, and migrate toward the intimal layer (39). As fibroblasts are also abundant in the vascular lesions of TAK (40), these cells could be therapeutically targeted in LVV.

VASCULITOGENIC T CELLS IN GCA

Th1 Cells

Analysis of the T cell population in vascular tissues and the circulatory system suggests polyclonal T cell activation (41–43) (**Figure 2**). Among these, Th1 cells appear to be the dominant cell population and are highly enriched in vascular tissues and the circulatory system in GCA (15, 44). Naive CD4$^+$ T cells are induced to express transcription factor T-bet and differentiate into Th1 cells in the presence of IL-12 (13), which is abundant in GCA-affected arteries (45). IFN-γ released by Th1 cells not only stimulates macrophages and provides protective immunity against intracellular pathogens but also affects ECs, VSMCs, and fibroblasts. Although IFN-γ impairs the proliferation and survival of ECs in the tumor microenvironment (46, 47), it promotes angiogenesis *via* VEGF produced by tissue macrophages in GCA (10). IFN-γ induces VSCM proliferation in atherosclerosis (48). The direct effect on fibroblasts residing in blood vessels is unknown. However, upon stimulation with IFN-γ, synovial fibroblasts upregulate MHC class II expression and increase IL-6 production (49). Thus, IFN-γ derived from Th1 cells is implicated in several pathogenic events in GCA.

Th17 Cells

Compared to Th1 cells, all other functional T cell lineages occur at much lower frequencies (42), although Th17 cell numbers are increased in GCA (15). Naive CD4$^+$ T cells express the master transcription factor RORγt and differentiate into Th17 cells in the presence of IL-6 and transforming growth factor β, which are abundant in the vascular lesions (50, 51). IL-23 appears to function in the expansion and maturation of Th17 cells at a late stage (13). Th17 cells produce IL-17, IL-21, and IL-22, and the IL-17 family includes six isoforms (IL-17A to IL-17F) (52). IL-17A not only provides host defense against extracellular pathogens, including bacteria, fungi, and mycobacteria but also participates in autoimmunity (53, 54). IL-17A acts on ECs, resulting in the secretion of proinflammatory cytokines, such as IL-6 and chemokines (55). IL-17 is also involved in the proinflammatory response of VSMCs, inducing the release of cytokines such as IL-6 and granulocyte–macrophage colony-stimulating factor (GM-CSF) (56).

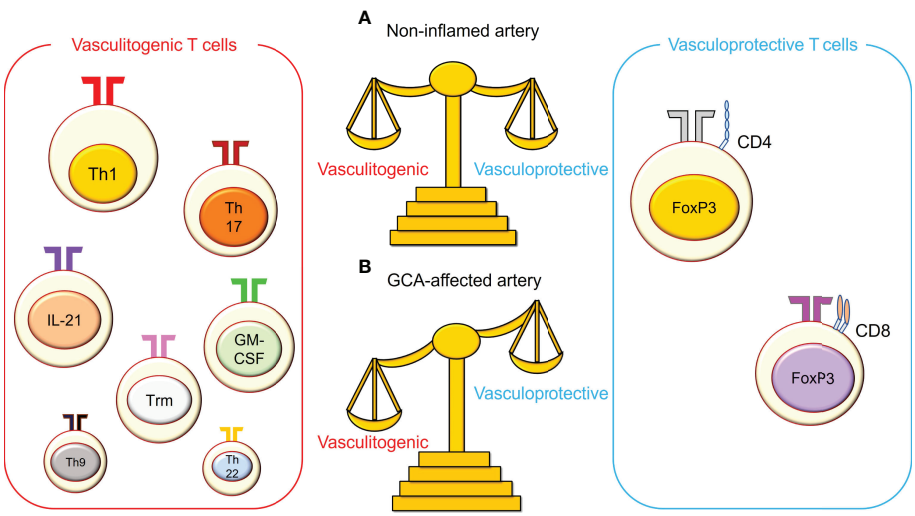

FIGURE 2 | The imbalance between vasculitogenic T cells and vasculoprotective T cells in giant cell arteritis. **(A)** In non-inflamed arteries, vasculitogenic T cells and vasculoprotective T cells are well balanced in the blood, and both cell types are rare in the vasculature. **(B)** In giant cell arteritis (GCA), this balance is perturbed, and vasculitogenic T cells accumulate, while the number of vasculoprotective T cells decreases in the tissue and the blood. Vasculitogenic T cells include T helper 1 (Th1) cells, Th17 cells, IL-21-producing T cells, granulocyte macrophage-colony stimulating factor (GM-CSF)-producing T cells, tissue-resident memory T (Trm) cells, Th9 cells, and Th22 cells. On the other hand, vasculoprotective T cells include CD4$^+$ regulatory T cells and CD8$^+$ regulatory T cells.

What is the molecular basis for the increase in Th1 and Th17 cells in GCA? A recent study revealed that the VEGF-NOTCH1 axis plays a role in skewed T cell polarization (57). VEGF is primarily derived from tissue macrophages and is enriched in GCA plasma (58). The innermost ECs of the vasa vasorum respond to VEGF and upregulate the expression of NOTCH1 ligand, which in turn stimulates NOTCH1 receptor expressed on GCA $CD4^+$ T cells. This NOTCH1 ligand-NOTCH1 interaction induces activation of the mechanistic target of rapamycin (mTOR), shifting T cell differentiation toward Th1 and Th17 cells (57). mTOR is a serine/threonine protein kinase that constitutes the catalytic subunit of two distinct complexes: mTOR complex 1 (mTORC1) and mTORC2 (59). The mTOR pathway integrates a diverse set of environmental factors to direct cellular growth and is implicated in metabolic disorders, neurodegeneration, cancer, and aging (60). Recent studies have shown that mTORC1 regulates the differentiation of T helper cells and is involved in Th1 and Th17 development (61). Thus, the VEGF-NOTCH1-mTORC1 axis contributes to skewed T cell differentiation.

IL-21-Producing $CD4^+$ T Cells

The number of IL-21-producing $CD4^+$ T cells is also increased in vascular lesions and in the blood (44). IL-21-producing $CD4^+$ T cells account for approximately 2.5% of the peripheral blood cells in healthy individuals, whereas this proportion increases to approximately 8% in patients with GCA, which cannot be explained by the frequency of Th17 cells. IL-21 is the main cytokine produced by Tfh cells, which help B cells to secrete IgG antibodies, but the Tfh-B cell signature is not upregulated in GCA (62). Thus, the cellular origin of IL-21 remains unclear. However, since IL-21 is able to shift T cell differentiation toward Th1 and Th17 phenotypes and decrease the number of regulatory T cells (Tregs) (44), this cytokine could be a therapeutic target for GCA.

GM-CSF-Producing T Cells and Other T Helper Cells

Recently, GM-CSF has emerged as a key cytokine in the pathogenesis of GCA (63–65). GM-CSF and GM-CSF receptors are highly expressed in GCA-affected arteries. Although Th1 and Th17 cells are the major sources of GM-CSF in the joints with rheumatoid arthritis (RA) (66, 67), GM-CSF is produced by endothelial cells, macrophages, and T cells in vascular lesions of GCA. In ex vivo cultured arteries, anti-GM-CSF receptor antibodies have shown promise, decreasing T cell and macrophage numbers as well as proinflammatory cytokine expression (63). Other T helper cell subsets, such as Th9 and Th22 cells, are also implicated in the amplification of vascular inflammation (68, 69), although their precise role is still unclear.

Tissue-Resident Memory T Cells

The results of a study that enrolled patients with GCA confirmed by temporal artery biopsy (TAB) and prospectively performed a second TAB from the contralateral side to the first TAB showed residual inflammation in approximately half of the patients even after one year of treatment (70). The pathological analysis showing that T cells were the main residual cells prompted us to investigate tissue-resident memory T (Trm) cells. A subset of effector T cells resides in lymphoid and non-lymphoid tissues without recirculation through the blood and gives rise to Trm cells (71, 72). A key feature of Trm cells is their ability to be retained in barrier tissues for prolonged periods of time and their rapid response when encountering the same antigen (73). Trm cells are characterized by the expression of C-type lectin CD69 and integrin CD103 (74). In our mouse model of LVV, approximately 10% of the $CD4^+$ T cells infiltrating the vascular tissue expressed CD103. Interestingly, tissue residency of Trm cells requires signals from the JAK-STAT pathway and CD28 stimulation from tissue niches (17, 75). Further characterization of these Trm cells may lead to the development of therapeutic strategies to specifically eliminate them.

VASCULOPROTECTIVE T CELLS IN GCA

Naturally occurring $CD4^+$ Tregs, which express the transcription factor FoxP3 in the nucleus and CD25 on the cell surface, are a functionally distinct T cell subset actively engaged in the maintenance of immunological tolerance (76). Since IL-6 and IL-21 have been reported to inhibit Treg differentiation (44, 77) and these cytokines are highly enriched in the plasma of patients with GCA, the number of $CD4^+$ Tregs is reduced in patients with GCA compared to healthy controls (44). However, accumulating evidence suggests that tocilizumab (TCZ), an IL-6 receptor inhibitor, restores not only the number of $CD4^+$ Tregs but also the function of these cells (78–80). Accordingly, TCZ decreases relapse and has a steroid-tapering effect on GCA (81).

While $CD4^+$ Tregs are well recognized and established, their $CD8^+$ counterparts are still controversial in many regards, including their phenotypic identity and mechanisms of suppression (82); however, the immunosuppressive effects of $CD8^+$ Tregs have been proven in some experimental models such as inflammatory bowel disease and graft-versus-host disease (83, 84). Compared with younger individuals, the number of $CD8^+$ Tregs is reduced in the elderly, and these cells are significantly reduced in number and function in GCA patients (85). The functional defect of $CD8^+$ Tregs is attributed to inadequate release of exosomes containing NADPH oxidase 2 (NOX2), which inhibits neighboring $CD4^+$ T cell activation by blocking the phosphorylation of ZAP-70, a proximal molecule directly involved in T cell receptor signaling (85, 86).

VASCULITOGENIC AND VASCULOPROTECTIVE T CELLS IN TAK

Similar to GCA, an increase in Th1 and Th17 cells has been reported in TAK (16, 87). This increase may stem from overactivation of the NOTCH1-mTOR pathway (88, 89) and/or an increase in the number of $CD4^+$ IL-21-producing T cells (89, 90). In parallel, a decrease in $CD4^+$ Treg numbers has also been documented (91). In contrast, unlike GCA, microarray analysis

has demonstrated that the Tfh signature that includes CXCR5 and CCR6 is significantly increased in the blood and the aorta (62). Tfh cells may be partly responsible for the elevated levels of IL-21 in TAK. Moreover, it has been reported that $CD8^+$ T cell infiltration is more common in TAK than in GCA (92). Recent immunophenotyping analysis using flow cytometry has added another piece of evidence showing that circulating $CD8^+$ T cells were increased only during the active phase in TAK, but the number of these cells in GCA was stable irrespective of the disease activity (93). The contribution of $CD8^+$ T cells to the pathomechanisms of TAK may be greater than their contribution in GCA.

DISCUSSION

$CD4^+$ T cells undoubtedly play a central role in LVV pathogenesis. Additionally, $CD8^+$ T cells and natural killer cells actively engage in the disease mechanism of TAK, making it more complex than that of GCA (40). Indeed, abatacept (ABT), which selectively inhibits T cell activation by blocking the co-stimulatory signal, has been shown to improve the disease activity of RA and reduce the relapse rate in patients with GCA (94), but it failed to exhibit efficacy in TAK (95). However, the high relapse rate even in the ABT treatment arm in patients with GCA prompts us to explore better therapeutic options for LVV.

Considering the disease mechanism, the VEGF-NOTCH1-mTOR pathway as well as T cell polarizing cytokines, such as IL-12, IL-23, and IL-21, could be therapeutic targets to correct biased $CD4^+$ T cell differentiation and suppress LVV. Anti-VEGF antibody, an mTOR inhibitor, and an IL-12/IL-23 inhibitor (e.g., ustekinumab) are on the market. Ustekinumab has been tested for GCA and TAK (96, 97), but the results obtained to date are not encouraging (98, 99).

Other therapeutic options include inhibition of released cytokines, including IL-17, GM-CSF, and IFN-γ. The efficacy and safety of anti-IL-17 and anti-GM-CSF receptor antibodies against GCA are being actively pursued in clinical trials, and the results obtained to date appear promising (100, 101). Signaling downstream of GM-CSF and IFN-γ involves the JAK-STAT pathway, and the efficacy of JAK inhibitors is widely recognized in RA (102), which raises expectations for the treatment of LVV (103). Indeed, in addition to IFN-γ, type I IFN is also highly expressed in the vascular lesions, and there have been several reports of increased activation of the JAK-STAT pathway in GCA- and TAK-T cells (17, 104–106).

Furthermore, GWAS has identified *IL-12B* as a susceptibility gene for TAK (12, 107), and the *IL-12B* risk allele is associated with vascular damage in TAK (108). IL-12 relies on the JAK-STAT pathway for intracellular signal transduction. Although the results of ustekinumab are not encouraging, JAK inhibitors may have potential for treating TAK (109).

In conclusion, recent research advances have shed new light on the role of T cells in the disease mechanisms of LVV. Several treatment options targeting T cells are expected to emerge in the near future.

AUTHOR CONTRIBUTIONS

RW drafted the manuscript. MH revised and finalized the manuscript. All authors contributed to the article and approved the submitted version.

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