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Review

# Pro-inflammatory and anti-inflammatory T cells in giant cell arteritis

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ABSTRACT

Giant cell arteritis is an autoimmune disease defined by explicit tissue tropism to the walls of medium and large arteries. Pathognomic inflammatory lesions are granulomatous in nature, emphasizing the functional role of CD4 T cells and macrophages. Evidence for a pathogenic role of antibodies and immune complexes is missing. Analysis of T cell populations in giant cell arteritis, both in the tissue lesions and in the circulation, has supported a model of broad, polyclonal T cell activation, involving an array of functional T cell lineages. The signature of T cell cytokines produced by vasculitic lesions is typically multifunctional, including IL-2, IFN-γ, IL-17, IL-21, and GM-CSF, supportive for a general defect in T cell regulation. Recent data describing the lack of a lymph node-based population of anti-inflammatory T cells in giant cell arteritis patients offers a fresh look at the immunopathology of this vasculitis. Due to defective $CD8^+NOX2^+$ regulatory T cells, giant cell arteritis patients appear unable to curtail clonal expansion within the CD4 T cell compartment, resulting in widespread CD4 T cell hyperimmunity. Why unopposed expansion of committed CD4 effector T cells would lead to invasion of the walls of medium and large arteries needs to be explored in further investigations.



## 1. Introduction

Giant cell arteritis (GCA) is a vasculitis of medium and large arteries typically combined with an intense systemic inflammatory syndrome [1–4]. Systemic inflammatory syndrome may occur in the absence of frank vasculitis, mostly presenting muscle pain and stiffness known as polymyalgia rheumatica (PMR). GCA is an immune-mediated disease, involving the innate and adaptive branch of the immune system and characterized by granuloma formation in the mural layers of inflamed arteries. By definition, granulomas are organized lymphoid microstructures, composed of two major cell populations: macrophages, sometimes called histiocytes, which may fuse to form giant cells and CD4 T cells. Granulomas have been implicated in containment of intracellular bacterial infections and difficult-to-digest irritants, but convincing data implicating either in the pathogenesis of GCA are missing [5,6].

While there is no doubt that excess activation of immune cells drives GCA, the original stimulus leading to aberrant immune activation has remained undefined. Granulomatous tissue inflammation is a typical complication of immunodeficiency syndromes [7,8], exemplifying the coexistence of defective immunity with autoimmune and granulomatous manifestations. In such immune-deficient patients, susceptibility to bacterial and fungal infections is combined with a high risk for excessive inflammation, promoting granuloma formation in essentially any organ system.

Here, we will review current evidence for a fundamental immunodysregulation in GCA, with formation of non-infectious arterial wall granulomas representing a consequence of insufficient immunosuppression and aberrant threshold setting in CD4 T cell homeostasis.

### 1.1. GCA – more than one immunopathology

When assessing the immunopathology of GCA, it is important to recognize that the disease has several components, which may be partially independent. GCA's vasculitic component is characterized by granulomatous infiltrates in the wall layers of arteries of sufficient size to have a vasa vasorum network. Data from the last two decades best fit a model in which immune cells enter the target artery through the vasa vasorum network, encounter professional and vessel-specific antigen-presenting cells, are locally stimulated and form granulomatous arrangements of highly activated

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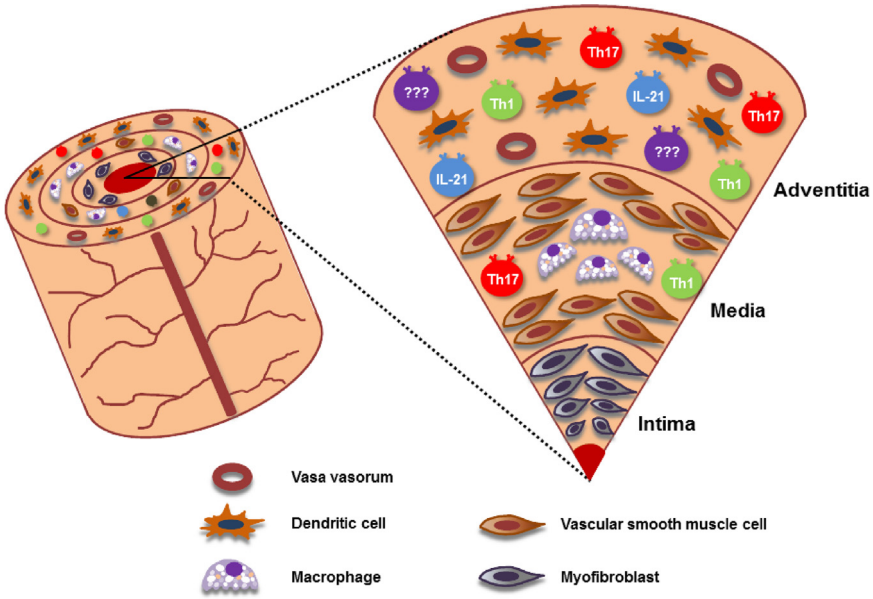


**Fig. 1.** Multiple T helper cell lineages participate in GCA. CD4 T cells are the dominant cell population in the vasculitic lesions of GCA, where they partner with macrophages to build granulomatous infiltrates. Based on the production of signature cytokines, CD4 T helper cells are subcategorized into distinct effector cell lineages. Vessel wall infiltrates in GCA patients are characterized by a broad array of T helper cell types, suggestive for a broad defect in T cell biology.

macrophages and T cells. In line with this model, the vast majority of tissue-residing lymphocytes are CD4 T cells, which have converted to effector and memory status. A multitude of other immune cells are present in low frequencies, including CD8 T cells, mast cells, NK cells, eosinophils, and occasional B cells. Clinical manifestations of vascular inflammation are dominated by vaso-occlusive events that lead to tissue ischemia, most prominently to vision loss due to ischemic optic neuropathy. Recent data suggest that aortic involvement is frequent amongst GCA patients, which may result in dissection or aneurysm formation and rare fatal complications.

GCA's systemic component has not been localized to a specific tissue site and may occur widespread within lymphoid organs. Fever of unknown origin can be the presenting symptom. Constitutional symptoms, such as weight loss, night sweats, malaise, are not unusual. The muscle pain and stiffness clinically known as PMR can be present early in the disease process and often appear after corticosteroids are reduced during chronic disease management. The underlying immune abnormalities leading to PMR are not understood. Clinically, the intensity of the systemic inflammation is captured by acute phase reactants, measured as elevated C-reactive protein (CRP), acute phase serum amyloid A protein (A-SAA), erythrocyte sedimentation rate (ESR). Such acute phase reactants may, in turn, have functions in driving disease relevant processes, as supported by a recent study demonstrating that A-SAA induced IL-6 and IL-8 production by temporal artery explants, fostered angiogenic tube formation and promoted myofibroblast outgrowth [9]. Besides hepatocytes, which are also a major producer of CRP, A-SAA can also be released within inflammatory infiltrates, as has been shown for rheumatoid arthritis and psoriatic arthritis [10,11]. Elevation of such acute phase reactants in the circulation gives them widespread access to numerous organ systems, particularly the vascular tree. Accordingly, A-SAA serum levels have been identified as a predictor of coronary artery disease [12] and as an amplifier of atherosclerosis in mice [13]. Acute phase reactants respond well to corticosteroid therapy and one of the benefits of this therapy may lie in disrupting non-specific feed-forward inflammatory amplifier loops. In GCA patients, corticosteroids are excellent suppressors of IL-6, IL-1, IL-17 and IL-23, all products of the innate immune system [14]. However, adaptive immunity appears much more resistant to corticosteroids, making GCA a chronic condition, the chronicity of which will require therapeutic interventions counteracting vasculitogenic T cells and their role in granuloma formation.

Accepting the disease model of partially independent disease components has important consequences for the design of explorative studies, the utilization of diagnostic tests (which may only capture one component) and the therapeutic management [15]. Ultimately, the immunopathologic processes, vascular inflammation and systemic inflammation, need to be controlled to successfully treat the disease.

### 1.2. *Pro-inflammatory T cells in GCA*

Molecular studies of tissue-residing T cells in temporal artery biopsies have demonstrated expansion of individual T cell clones shared amongst disconnected disease lesions; strongly suggestive for antigen-reactive immunity [16]. Functional studies in temporal artery tissues support a model of multiple T cell lineages acting as pro-inflammatory effector cells (Fig. 1). A multitude of T cell cytokines have been detected in GCA tissue lesions; including IL-2, IFN-γ, IL-17, IL-9, IL-21 and GM-CSF [17–19]. Notably, IL-4, the marker cytokine for Th2 cells, has been consistently missing. Either effector T cells packed into the granulomatous lesions are multifunctional and are capable of producing a variety of cytokines or the T cell infiltrate is composed of many different specified T cell populations. Both scenarios suggest a fundamental defect in the regulation of the CD4 T cell compartment.

Th1 cells are a stable participant in the granulomatous infiltrates of GCA and are also elevated in the circulation [14,18]. IFN-γ has been implicated in a number of pathogenic events in the inflamed vessel wall, predominantly by functioning as a strong activator of endothelial cells, stromal cells, dendritic cells and macrophages (Fig. 2). IFN-γ appears critical in inducing vascular endothelial growth factor (VEGF) and promoting neoangiogenesis [20]. IFN-γ has been identified as a major chronicity factor in GCA [14]. Th1-committed T cells remain the predominant population in both the tissue and the blood [14]. Th1 cells are also the most frequent population of differentiated T cells in the blood of healthy individuals, probably a reflection of their critical role in a functional immune system.