# Pathogenic mechanisms in giant cell arteritis

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Giant cell arteritis (GCA) is a systemic vasculitis affecting medium-size and large arteries. In contrast to vasculitides of capillaries and small arteries, the inflammation does not accumulate in the perivascular space but directly attacks structures that are part of the arterial wall.[1] Besides the vascular lesions, an intense systemic inflammatory syndrome characterizes GCA. This systemic inflammatory syndrome also exists in the absence of fully developed vascular inflammation in patients diagnosed with polymyalgia rheumatica (PMR). Patients with PMR can have a forme fruste of vessel wall inflammation that escapes detection by histomorphology and requires molecular methods to document activation of immunopathways in the artery.[2]

Despite the systemic character of GCA, inflammatory injury of blood vessel walls is not a random process. To the contrary, this arteritis displays a stringent tissue tropism with clear preference for specific arterial trees. Intriguingly, the extracranial branches of the carotid arteries (superficial temporal, occipital, ophthalmic and posterior ciliary arteries), the vertebral arteries, and the subclavian arteries are most frequently affected. Also, the aortic wall, itself, is a well-recognized site of GCA. Coronary arteritis has been described and femoral arteries can be involved, but the likelihood that these vascular territories are attacked by the inflammatory disease is low. Most impressively, GCA essentially spares the intracranial arteries and GCA in mesenteric arteries is extremely unlikely. The mechanisms underlying the selective targeting of vascular beds are not understood, but molecular and structural characteristics of the arteries must play a role in defining susceptibility towards intrawall inflammation. A selection of structural features displayed by GCA-susceptible arteries is listed in **Table 1**. Molecular approaches will be necessary to identify the underlying principles of how molecular composition can translate into tissue tropism.

Vascular manifestations in GCA are a reflection of the affected vascular beds. Reduction in blood flow in the extracranial arteries causes jaw claudication, tongue claudication, scalp tenderness, or transient ischemic attacks. If the compromise of flow is severe enough, the patient will present with ischemic optic neuropathy, stroke, or, infrequently, with myocardial infarction or gangrene. Vascular complications of aortitis are generally related to aneurysm formation and aortic insufficiency.[3] Because of the irreversibility of ischemic tissue damage and the risk to vision and the central nervous system, GCA qualifies as a medical emergency. However, it is important to note that most of the clinical manifestations of GCA are not a direct reflection of arteritis but rather are connected to the syndrome of systemic inflammation, manifesting with a profound acute phase response, fever, anorexia, malaise, and myalgias.

## UNCONTROLLED INTIMAL HYPERPLASIA – THE PATHOGENIC LESION OF GCA

Focal arteritic lesions in extracranial arteries do not cause rupture and hemorrhage but instead cause vasoocclusion with subsequent ischemia. Luminal thrombosis is uncommon. Stenosis and occlusion are generated by excessive intimal hyperplasia, a process in which myofibroblasts migrate towards the lumen, settle in the subendothelial layer, begin to proliferate, and deposit extracellular matrix. Intimal hyperplasia is not unique to the vascular injury pattern in GCA. To the contrary, it is a shared mechanism in a diverse set of vasculopathies, including atherosclerotic disease and vascular-occlusive syndrome in transplantation. Of all the different mechanisms leading to vascular injury **(Table 2)**, uncontrolled hyperproliferation of the intimal layer produces clinically the most significant consequences of GCA, particularly blindness and stroke. As such, this mechanism has a key position in the pathogenic events of this arteritis.

As a rule, hyperplasia of the intima never precedes the accumulation of inflammatory cells in the arterial wall. From that timely relationship, it follows that T cells and macrophages infiltrating into the layers of the artery's wall directly or indirectly regulate the process of myofibroblast proliferation and matrix deposition. Studies in temporal arteries from patients with GCA have established that platelet-derived growth factor (PDGF) is a critical growth factor in arteries with lumenal occlusion.[4] PDGF is sup-

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**TABLE 1**
CHARACTERISTICS OF ARTERIES TARGETED BY GCA

- Topography—extracranial carotid branches, vertebral arteries, and upper extremity arteries
- Well-developed elastic membranes
- Multilayered wall
- Vasa vasorum network

plied from several different cellular sources, the most significant being multinucleated giant cells and macrophages located at the media-intima border. These cells not only produce PDGF, they also provide vascular endothelial growth factor (VEGF).[5] This angiogenesis factor appears to be required in supporting structural adaptations necessitated by the hyperplastic intima, specifically the growth of neocapillaries. The release of PDGF and VEGF from giant cells and macrophages emphasizes the central position of macrophages in mechanisms of vascular injury. The question then arises how macrophages are triggered to secrete potent growth and angiogenesis factors.

VEGF production in the arterial wall has been closely correlated with the concentration of interferon (IFN)-γ in the tissue.[5] Not all patients develop lumenal stenosis; in some patients, the intima is only minimally thickened and blood flow is not compromised. The subset of patients with clinically relevant loss of blood flow, identified by ischemic manifestations, is characterized by production of large amounts of PDGF and VEGF in the tissue. Other tissue cytokines associated with clinical evidence of compromised blood flow are IFN-γ and interleukin (IL)-1β.[6] If jaw claudication and visual symptoms occur in patients who generate higher tissue concentrations of IL-1β, IFN-γ, VEGF, and PDGF, it is likely that these mediators are mechanistically linked. One possible link derives from the fact that PDGF and VEGF are found in multinucleated giant cells. Such specialized macrophages are most frequent in IFN-γ–containing tissue samples. This finding suggests that it is not macrophages but IFN-γ–producing cells that are the primary decision makers in injury-induced intimal hyperplasia.

IFN-γ has been traced back to a relatively small population of T lymphocytes that lie in the adventitia of the inflamed artery.[7] IFN-γ–producing T cells undergo clonal expansion in the artery, are highly selected, and boost the disease process when adoptively transferred.[8,9] Their eradication eliminates the disease, yet IFN-γ production has been shown to be relatively resistant to standard corticosteroid treatment.[10] Recent data have indicated that IFN-γ production in the artery is susceptible to aspirin, providing this non-steroidal anti-inflammatory drug a possible role as a steroid-sparing agent in GCA.[11] IFN-γ–producing T cells are far removed from the growth factor–producing macrophages at the media-intima junction. Possibly, cells or matrix molecules serving as intermediaries are involved in transporting the information from the adventitia to the proximal layers of the arterial wall. Alternatively, it has been proposed that fibroblasts positioned in the adventitia are the precursors of the cells that migrate towards the intima to become hyperplastic myofibroblasts. These myofibroblasts, which compose the expanding intima, may receive their initial instructions directly from activated T cells.

**TABLE 2**
CELLULAR AND MOLECULAR TARGETS IN GCA

| Cellular target | Effect | Pathogenic consequence |
|---|---|---|
| Endothelial cells | Activation | Increased adhesiveness, increased cell recruitment |
| Smooth muscle cells | Smooth muscle cell death | Media degeneration |
| Myofibroblasts | Dedifferentiation (secretory → migratory) | Intimal hyperplasia |
| Elastic membranes | Loss of contractility, fragmentation, loss of tissue compartments | Myofibroblast migration |

Based on these data, we have proposed that the formation of multinucleated giant cells is under the control of the adaptive immune system through the release of IFN-γ.[12,13] Once formed, these multinucleated giant cells provide PDGF, thus fueling the process of intimal proliferation. Adaptive immune responses in inflamed temporal arteries do not necessarily lead to giant cell formation, growth factor secretion, and lumenal occlusion. In patients whose clinical presentation is dominated by PMR, temporal artery specimens predominantly contained the T-cell cytokine IL-2 and not IFN-γ.[6] Differences in cytokine production are not a reflection of the stage of disease. Patients who presented with primarily subclavian GCA and who had disease for several months before the biopsy was performed and the diagnosis was established, had non-occlusive disease in the temporal arteries and preferential production of IL-2.[14] The different cytokine response pattern regulating the extent of intimal hyperplasia may reflect genetic host factors. As an additional host factor, the vascular response to the inflammatory injury may be genetically diverse and may or may not induce the proliferation of myofibroblasts and the formation of intimal hyperplasia.

## ■ ARTERIAL MEDIAL WALL DESTRUCTION – A PREREQUISITE FOR INTIMAL HYPERPLASIA

Gene expression profiling of temporal arteries of patients with GCA has been used to identify novel pathways of tissue injury. This approach demonstrated a gene cluster related to oxidative damage that was upregulated in inflamed arterial specimens when compared with normal ar-

terial specimens. One of the first signs for oxidative stress derived from the observation that mitochondrial genes were expressed at extremely high levels in the arteritic lesions.[15] Immunohistochemical confirmation revealed that mitochondrial activation was particularly evident for macrophages in the medial layer. Considering the potential damage by oxygen radicals released in the medial layer, specific antibodies to lipid peroxidation products (4 hydroxy-nonenal) were used to examine smooth muscle cell membrane damage. Toxic aldehydes were detected on the surface of smooth muscle cells, often with widespread expression throughout the muscle cell layer. Inflammatory cells sitting between the smooth muscle cells were not entirely protected from oxidative attack.

Macrophages that served as the cellular source of reactive oxygen species were also shown to be specialized in the production of matrix metalloproteinase (MMP)-2.[15] Such macrophages coexpressing MMP-2 and high levels of mitochondrial antigens were localized directly adjacent to the disintegrated elastic lamina and may be pivotal in the formation of intimal hyperplasia.[16] They are equipped with two powerful mechanisms of tissue attack. They oxidize macromolecules, including matrix proteins, lipids, proteins, and DNA, thus mediating profound cellular damage. They also digest matrix molecules and cell membranes through the release of proteolytic enzymes. Such proteolytic enzymes are almost certainly needed to fragment the elastic membranes that separate the intima and the media and form a border between the media and adventitia. Fragmentation of the elastic lamina interna is often considered a histologic hallmark of GCA.

Myofibroblasts must be mobilized from their neighboring cells and matrix. On their path to the subendothelial space, they migrate through the tissue. An intact lamina elastica interna would be a barrier unless this membrane has been digested to allow for the passage of myofibroblasts. The MMP–and oxygen intermediates–producing macrophages in the media thus gain a key position in the events leading to the hyperplastic reaction of the intima.

## PROTEIN NITRATION AS A MECHANISM OF TISSUE INJURY IN GCA

Most avenues of tissue destruction in GCA depend on macrophage effector functions, with T-cell derived cytokines controlling the activity/differentiation of such macrophages. Inflammation-related upregulation of macrophage products includes inducible nitric oxide synthase, NOS-2.[16] In vitro, NOS-2 can be induced by proinflammatory cytokines such as IFN-γ, IL-1, TNF-α, and IL-2. NOS-2 was found in wall-infiltrating macrophages, specifically in those homing to the hyperplastic intima. The presence of NOS-2 has raised the question whether protein nitration contributes to vascular disease damage in GCA. The reactive nitrogen intermediate, peroxynitrite, can nitrate tyrosine residues, leading to protein dysfunction. Expression of nitrated proteins was examined in temporal arteries (Borkowski A, Younge BR, Szweda L, Mock B, Björnsson J, Moeller K, Goronzy JJ, Weyand CM. Am J Pathol, in press). Surprisingly, little evidence for NOS-2–associated nitration was detected. Structures in the intima remained free of this protein modification. Nitrotyrosine was found on endothelial cells of microcapillaries in the media. Such capillaries emerge by inflammation-induced neoangiogenesis; under physiologic conditions, the media is avascular. We hypothesized that the selective nitration of endothelial targets in the media resulted from an interaction between reactive nitrogen and oxygen intermediates. Reactive oxygen species are characteristically present in the media. We depleted the cellular source of such radicals by treating temporal artery grafts in SCID mice with cell-specific antibodies. Elimination of macrophages disrupted nitrotyrosine formation, confirming that oxygen radical formation by macrophages was crucial in the process of nitration. Of note, these medial macrophages did not express NOS-2, and the NO derived from NOS-3–expressing endothelial cells. The functional consequences of nitration in medial endothelial cells need to be investigated. Tyrosine nitration may harm tyrosine phosphorylation pathways critically involved in intracellular signaling. Changes in adhesion molecule expression or alterations in the secretory activity of endothelial cells could be envisioned. The remarkable selectivity of nitration, sparing intimal and adventitial capillaries, suggests heterogeneity of microvessels in the disease.

## MOLECULAR PATHWAYS COUNTERACTING TISSUE DAMAGE IN GCA

The inflammation-induced injury in GCA causes cell death, loss of microstructures, and functional impairment of the artery. It also initiates a response pattern of resident arterial cells that attempts to prevent and repair the damage.[1] Intimal hyperplasia is a maladaptive response-to-injury, intended to rebuild wall structures, but instead leading to excessive tissue production. Some of the reactions induced by the injury, however, will be protective and limit the negative consequences of inflammation. One such protective response, the upregulation of aldose reductase, has been studied in detail.[17]

Gene profiling of inflamed temporal arteries demonstrated abundant expression of aldose reductase. Transcription and tissue expression of aldose reductase occurred exclusively in arteries with characteristic inflammatory infiltrates. Aldose reductase is an oxidoreductase with broad substrate specificity for carbonyl compounds. Immunohistochemical studies revealed that the enzyme was produced by smooth muscle cells and by T cells and macrophages that infiltrated into the medial layer. A close relationship between the presence of lipid peroxidation products and aldose reductase was discovered. Given the substrate specificity of the reductase for carbonyl substrates, aldose reductase was examined as a possible detoxification system for toxic aldehydes formed during the process of lipid peroxidation. We experimentally approached this question by treating temporal artery-SCID mouse chimeras with aldose reductase inhibitors. After enzyme blockade, the amount of toxic aldehydes increased in the artery and the frequency of apoptotic medial smooth muscles cells increased threefold. We concluded that induction of aldose reductase is a protective

mechanism in that the enzyme metabolizes toxic aldehydes and protects cells from oxidative damage. This mechanism could prove therapeutically useful, particularly when considering that oxidative stress of the media is critical in initiating intimal hyperplasia.

## TISSUE INJURY IN THE ATHEROSCLEROTIC PLAQUE – A NEW PARADIGM FOR ACUTE CORONARY SYNDROMES

Inflammation-associated degradation of tissue in arteritic lesions is expected, considering the intensity of the cellular infiltrate and the granulomatous reaction. Tissue damage in the arterial wall, mediated by T cells and macrophages, however, is not limited to frank vasculitis. Atherosclerosis, traditionally understood as a degenerative disease with mechanical factors dominating pathogenesis, is now emerging on the list of immune-mediated syndromes.[18] Compelling evidence has accumulated that the sudden rupture of the atherosclerotic plaque giving rise to atherothrombosis and luminal occlusion causes acute coronary syndromes. The precise events leading to the surface defect in the atherosclerotic plaque are not understood. However, detailed work has demonstrated that plaque rupture occurs in lesions that are infiltrated by inflammatory cells, including T cells and macrophages. Parallel to the scenario in GCA, it is to be expected that effector macrophages, by virtue of the wide spectrum of mediators they can release, have a role in injuring the cap overlying the atherosclerotic plaque. Metalloproteinases have been suspected to contribute to plaque destabilization. Oxidative damage could also participate in cellular and matrix damage, leading to erosion of the plaque cover. As in the arteritic infiltrate characteristic of GCA, the ultimate question relates to the signals that orchestrate macrophage recruitment, function, and activation.

We have examined T-cell populations recruited to the unstable plaque.[19] Plaque harvested by atherectomy or after fatal myocardial infarction contains T cells that have undergone clonal expansion and can be identified by the unique sequence of their T-cell receptor. The most interesting population so far contains CD4 T cells that have lost expression of the CD28 surface receptor. $CD4^+CD28^-$ T cells share with classic helper T cells the memory phenotype, yet they display a profile of surface receptors that distinguishes them from classic helper T cells. CD28-deficient CD4 T cells efficiently release IFN-γ. They expand to large clonal size and routinely circulate in the blood of the patient. By gene profiling, they were found to express the cytotoxic molecules perforin and granzyme B, which they use to induce death of target cells. $CD4^+CD28^-$ T cells display several defects in apoptosis, explaining why they expand to gigantic clonal size. High frequency $CD4^+CD28^-$ T cells is a biological marker for patients with unstable angina and is rarely found in patients with stable coronary artery disease.[20] The association between $CD4^+CD28^-$ T cells and plaque instability has given rise to the notion that these T cells may be directly involved in plaque inflammation and plaque erosion.

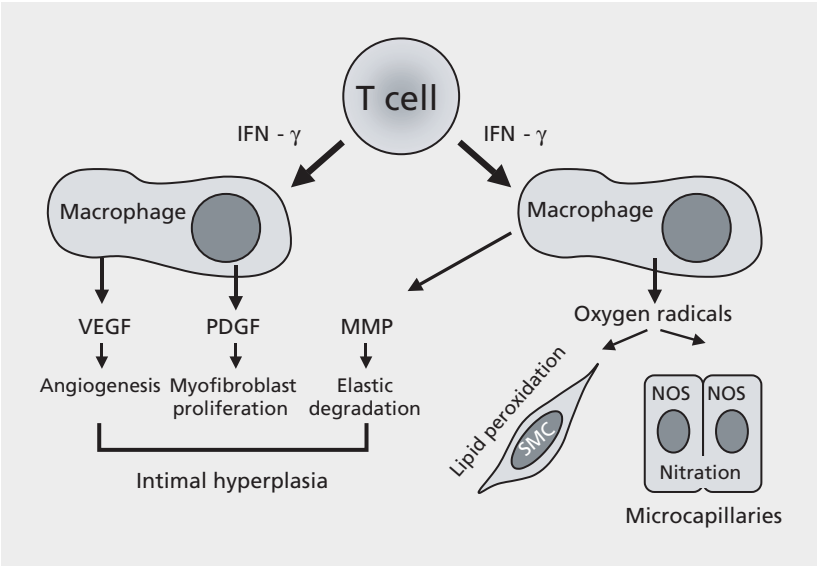


**Figure 1. Mechanisms of vascular injury in GCA.**

Potentially disease-relevant functions of $CD4^+CD28^-$ T cells in acute coronary syndromes have been carefully studied. In the peripheral blood, functional activity of $CD4^+CD28^-$ T cells seems to be predominantly related to their ability to secrete IFN-γ. Monocytes freshly isolated from patients with unstable angina have a molecular fingerprint of recent stimulation of the IFN-γ receptor with nuclear translocation of STAT-1 duplexes.[21] As a consequence, STAT-1–driven genes such as the chemokine IP-10 and the Fc receptor CD64 are upregulated.

Recent findings suggest that, in the arterial wall, $CD4^+CD28^-$ T cells may have yet other functional activities, those of cell-mediated cytolysis. In patients with unstable angina, $CD4^+CD28^-$ T cells assemble a cytolytic machinery and acquire cytotoxic capabilities. T-cell clones isolated from patients with acute coronary syndrome can effectively kill endothelial target cells. Endothelial injury is amplified in the presence of physiologic concentrations of CRP, suggesting a possible interaction between acute phase proteins and T lymphocytes in tissue damage.[22] How could endothelial death, induced by CD4 T lymphocytes, endanger the integrity of the atherosclerotic plaque?[23] As in GCA, atherosclerotic disease is associated with neoangiogenesis. Newly formed capillaries supply oxygen to the thickened wall. Injury to these microvessels could disrupt supply to the relatively hypoxic plaque tissue and induce ischemic damage.

## SUMMARY

T lymphocytes, encountering stimulatory signals in the adventitia of medium-size arteries, emerge as the key players in inflammation-associated injury pathways. In GCA, all injury mechanisms have been related to effector

macrophages. Regulated by IFN-γ–producing T cells, macrophages commit to distinct avenues of differentiation and acquire a spectrum of potentially harmful capabilities **(Figure 1)**. Macrophages in the adventitia focus on production of pro-inflammatory cytokines. Macrophages in the media specialize in oxidative damage with lipid peroxidation attacking smooth muscle cells and matrix components. These macrophages also supply reactive oxygen intermediates that, in combination with nitrogen intermediates, cause protein nitration of endothelial cells. Production of oxygen radicals is complemented by the production of metalloproteinases, likely essential in the breakdown of elastic membranes. With the fragmentation of the internal elastic lamina, the intimal layer becomes accessible to migratory myofibroblasts that, driven by PDGF, form a hyperplastic intimal layer and cause occlusion of the vessel lumen. Expansion of the hyperplastic intima is accompanied by intense neoangiogenesis, supported by angiogenesis factors that again derive from specialized macrophages.

Similarities in injury pathways between GCA and another arterial disease, atherosclerosis, are beginning to be recognized. Specifically, activated T cells and macrophages are increasingly appreciated as key players in the process of instability and rupture of atherosclerotic plaque. A specialized subset of CD4 T cells, $CD4^+CD28^-$ T cells, are suspected to participate in tissue injury in the plaque. These T cells are equipped with cytolytic capabilities and release large amounts of IFN-γ. Comparative studies between patients with GCA and those with acute coronary syndromes should enhance our ability to define the principles of arterial wall inflammation, the specifics of injury in that microenvironment, and help in the identification of the eliciting signals.

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