Current Update on Giant Cells Arteritis

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Blood vessels and the immune system have an intimate relationship. Endothelial cells are important gatekeepers in the trafficking of lymphocytes and monocytes to tissue sites where they are engaged in localized immune reactions and tissue remodeling. In most cases, lymphocytes and monocytes, equipped with enormous destructive power, are able to slip through the vascular wall leaving it behind uninjured. Occasionally, the dialog between the vascular wall and immune cells is fundamentally disturbed and instead of innocuously passing by, T cells and macrophages target vascular structures. Almost always, the immune injury of blood vessels is accompanied by a vigorous systemic inflammatory syndrome.

The dialogue between the vascular wall and the immune system is exemplified in the arteritides of the large and medium-size arteries because these blood vessels have structural components beyond a thin endothelial cell layer on top of a thin lamina muscularis. Medium-size and large arteries, such as the aorta and its major branches, are structured organs supplied by a capillary network, and they possess well developed internal and external elastic laminae; lamina elastica interna defines the border to a multilayered muscular media. Due to the wall thickness of the large and medium-size arteries, the adventitia provides support tissues such as the vasa vasorum and the lymphatics. Two vasculitic entities, giant cell arteritis/temporal arteritis (GCA) and Takayasu's arteritis (TA), manifest in the large and medium-size arteries (1, 2). For both disease entities, the pathological hallmark is the formation of granulomas, often associated with giant cell accumulation. In clear distinction to other vasculitides, the inflammatory lesions in GCA and TA reside in the arterial wall itself and not in the perivascular region. Recent studies have broadened our horizon on the immunopathology of GCA, but it is likely that similar principles are relevant in TA. Despite similar pathogenic pathways in these two types of granulomatous vasculitis, there also exist remarkable differences. TA is a disease of the young, and its primary target is the aorta and its primary branches. GCA is a disease of the elderly that preferentially affects the second to fifth degree branches of the aorta.

The immune system against extracranial arteries – paying a price for long-lasting immunocompetence

Considering that humans live in an hostile environment under constant attack by infectious microorganisms, the immune system is a critical survival factor. Because the risk of dying from infection is high starting from birth, the immune system had strong evolutionary pressure to become highly active. Considerable redundancy has emerged to generate prompt and effective responses against pathogens, infected and malignant cells, and cellular debris. This is best attested by the relative safety of a large array of immunosuppressive agents that successfully weaken multiple facets of immunity. Effective immunosuppression, mostly very high doses of corticosteroids is also employed in the treatment of patients with GCA (1, 2). Within hours of treatment initiation, clinical symptoms improve and irreversible ischemic complications can be prevented. In essence, GCA is a persistent immune response that has unfolded in the wall layers of large arteries. Certainly, only hosts able to generate a vigorous immune response are susceptible to this disease. Yet, the microenvironment in which this immune response occurs and the particular response pattern of the artery, itself, to the immune injury are equally important. Progress has been made in determining the nature of the immune response that causes GCA. Although an instigator has not been detected, much has been learned of what goes wrong in the artery-immune system dialogue to give rise to GCA. We will briefly review the major elements of the immunopathology of GCA.

T cells in GCA

The granulomatous lesions in GCA are composed of T lymphocytes, highly activated macrophages, and multinucleated giant cells (3). CD4 T cells are the dominant lymphocyte populations, occasionally accompanied by CD8 T cells. B cells are suspiciously absent, an observation that lends meaning to the relative unimportance of antibodies in this disease process (4). Several lines of evidence support the concept that CD4 T cells infiltrating the artery are engaged in an antigen-driven immune response (5, 6). CD4 T cells with identical T-cell receptor sequences have been isolated from independent regions of the disease, demonstrating antigen driven selection of the T-cell infiltrate (7). CD4 T cells, in the process of clustering their T-cell receptors on the cell surface, produce interferon (IFN)-α (8). IFN-α has emerged as a key cytokine in GCA. The concentration of IFN-α in the lesion is closely correlated with the pattern of clinical manifestations (9). Temporal arteries from patients with polymyalgia rheumatica, which are supposedly free of vasculitis, contain the T-cell activation product interleukin (IL)-2 yet lack IFN-α (10). In contrast, arteries harvested from patients with lumen-occlusive vasculitis have high levels of in situ produced IFN-α; and, tissue IFN-α synthesis has been associated with the formation of multinucleated giant cells (9).

A remarkable characteristic of vasculitic CD4 T cells in GCA is their positioning in the artery. The majority of tissue destruction occurs in the medial layer and in the internal elastic lamina. While giant cells have a strong tendency to accumulate at the border of the media and the intima, IFN-α–producing CD4 T cells prefer the adventitia (8). The preference of CD4 T cells for this microenvironment may be that this is the only part of the artery containing capillaries that allow them to enter the wall. Alternatively, T-cell activation in the vasculitic lesions is accomplished by a specialized antigen-presenting cell, which shares a preference for the adventitia.

The disease process in GCA depends on CD4 T cells. Depletion of T cells in temporal artery-SCID mouse chimeras immediately disrupts vascular inflammation, including a shutdown of macrophages activity (11). Conversely, adoptive transfer of temporal artery-derived T cells boosts inflammation in the implanted arteries with accelerated production of proinflammatory cytokines. All currently available data strongly support the concept that GCA is a T-cell dependent disease (3, 5, 12-14).

Macrophages in GCA

While T cells have ultimate regulatory function, macrophages are the effector cells that facilitate the tissue-destructive actions. In recent years, we have dissected the pathways that contribute to the vasculitic process, paying particular attention to macrophage-mediated responses.

Macrophages accumulate in the adventitia of the artery, where they intermingle with IFN-α–producing CD4 T cells, are specialized in releasing IL-1α and IL-6 (15, 16). This macrophage population has also been described to transcribe high levels of transforming growth factor (TGF)-α. The disease relevance of TGF-α is not understood but IL-1α and IL-6 are assumed to amplify the inflammatory reaction and to contribute to activation of endothelial cells lining the vasa vasorum. IL-6 appears in the circulation and can be used to monitor disease activity in patients on immunosuppressive therapy (17, 18).

The media is the preferred homing place for macrophages committed to the production of matrix metalloproteinases (MMP) (3, 19). These enzymes may mediate the fragmentation of the elastic membranes. Molecular mediators involved in damage of medial smooth muscle cells (SMC) have only recently been identified. A gene profiling approach revealed the upregulation of multiple genes engaged in oxidative stress. Subsequent studies demonstrated toxic aldehydes, products of lipid peroxidation, on the surface of smooth muscle cells (19). Experimental evidence has implicated reactive oxygen intermediates (ROI) in SMC apoptosis and the loss of medial thickness (19, 20).

Multinucleated giant cells are one of the most remarkable macrophage populations in GCA. Quite unexpectedly, they actively secrete mediators that modulate the vascular inflammation. Specifically, giant cells produce platelet-derived growth factor (PDGF), a cytokine engaged in regulating the growth and migration of SMC (21). It is likely that this growth factor has a critical role in the process of intimal hyperplasia and lumenal occlusion. In parallel, giant cells contribute vascular endothelial growth factor (VEGF), thus promoting the growth of new capillaries required to supply the outgrowth of the neointima tissue (22).

Little information is available on macrophages recruited to the intima. They produce the enzyme nitric

oxide synthase (NOS)-2 and thus have the potential to regulate vascular tonus and endothelial function but could also be a contributor to tissue damage.

A series of questions regarding vasculitic macrophages are still unanswered and need attention. It is not known how these cells are recruited into the tissue. All evidence suggests that their port of entrance is the vasa vasorum in the adventitia and not the macroendothelial layer covering the arterial lumen. One of the intriguing observation is that a predictable relationship exists between the positioning of the macrophage and its functional commitment (16). Which mechanisms inform these macrophages where they are? How do macrophages sense the molecular details of their microenvironment and how can extracellular and cellular components of the distinct wall layers modulate the functional differentiation of macrophages invading into the vessel wall? Answers to these questions may ultimately provide clues to tissue target susceptibility of different vascular beds to immune attack.

The artery's contribution to GCA — the detrimental effects of insufficient restraint

Just as strong evolutionary pressures favor the emergence of a highly reactive immune system aimed at eliminating pathogens and malignancies, the vascular system must have been shaped by stringent selection pressures. Leakage of the artery wall must be prevented at all cost, because it is not compatible with survival. Medium-size arteries, transporting large volumes of blood, have a powerful mechanism of repair, which involves the mobilization of fibroblasts and their directed migration towards the lumen, where they seek out the subendothelial layer. Once in position, they proliferate and deposit extracellular matrix, eventually forming a hyperplastic intimal layer that can reduce the lumen and decrease blood flow. While intended to repair weak spots in the arterial tubing, this originally adaptive system can become maladaptive. Hyperactive intimal proliferation can obviously occlude the lumen leading to tissue ischemia. It is important to understand that most of the feared clinical complications of GCA, including blindness and stroke, result from arterial occlusion (23). The inciting factor is injury by T-cell–regulated macrophages. As a response, the artery initiates a response-to-injury-program that unfortunately harms the patient more than it protects (24).

Therapeutic utilization of this insight, in essence a rebalancing of the homeostatic arterial repair system, can only be achieved if the precise molecular events regulating the maladaptive arterial response are understood. A major clue has come from the observation that multinucleated giant cells can produce growth factors that drive the migration and proliferation of SMC (21, 22). Interestingly, tissue PDGF production is positively associated with the development of ischemic complications in patients. Further studies are needed to identify the respond-er cells to PDGF and their role in the physiological and pathological responses to injury. Equally important is VEGF, also supplied by the immune system but used to drive neoangiogenesis of capillaries in otherwise avascular regions of the arterial wall. Not all patients are able to generate neovessels in the blood vessel wall. Those patients that respond to a lesser degree may be protected from the formation of lumen-obstructive neointima.

Recognizing the contribution of the artery in the clinical manifestations of GCA has been an important conceptual advance (24). Not only has it provided new therapeutic targets, it has also set the stage for a disease model that proposes equal partnership between the misdirected immune system and the attacked vascular structure. If the artery determines how to respond to the immunological injury, the artery may be the ultimate decision maker in targeting particular vasculitic syndromes to defined arterial territories and may be instrumental in shaping the phenotype of the syndrome (23).

As can be expected from evolutionary forces shaping the arterial response pattern, there are also molecular pathways aimed at repairing and improving. One of these pathways has recently been investigated in detail. Upon inflammatory attack, vascular SMC express the aldose reductase (20). This enzyme is a ketoreductase with broad substrate specificity. Blocking aldose reductase in vivo in temporal artery-SCID mouse chimeras led to a striking increase in the number of apoptotic medial cells. In parallel, tissue lipid peroxidation was boosted with increased production of 4-hydroxy-nonenal (HNE). Somehow medial SMC must sense the need to induce aldose reductase, which is then used to metabolize toxic aldehydes, reducing downstream damage from oxidative stress.

Current and future therapies

The golden standard for treating GCA is the use of high doses of corticosteroids (18, 25). Although impressively powerful in improving the systemic manifestations of disease, literally within hours, these drugs must be given over several

years. Exper-imental evidence suggests that corticosteroids cannot clear the vascular infiltrates but rather paralyzes the lesional production of proinflammatory cytokines (26). Tissue cytokines have been classified into those responsive to corticosteroid inhibition and those persisting despite therapy. The macrophage products, IL-1α and IL-6, are highly sensitive to steroid-mediated repression; however, IFN-α is hardly affected by this mode of therapy. NF-κB appears to be the primary target of corticosteroids in the vascular lesions of GCA. Recent data suggest that aspirin may be useful in inhibiting IFN-α production by inhibiting the nuclear transcription factor AP-1 (27). Complementary action of corticosteroids and aspirin, building on the differential inhibition of nuclear transcription factors, may prove useful in the clinical management of GCA.

It is likely that other therapeutic opportunities lie in interfering with newly recognized and appreciated pathways of immune activation and tissue damage in the vascular infiltrates (Table 1). Suppression of IFN-α production must be a primary goal when treating GCA. This could be achieved by either blocking this highly powerful cytokine itself or preventing its production in the adventitial microenvironment.

New knowledge of arterial injury related to lipid peroxidation could possibly be translated into novel treatments. Optimizing what nature has already set in place, e.g., metabolizing toxic aldehydes to halt the chain reaction of lipid peroxidation and thus reduce tissue injury, could have promise. Similarly, minimizing the production of PDGF and VEGF could cut the lifeline of the proliferating intima, thus avoiding luminal occlusion of the artery and its ischemic consequences.

Progress in the management of GCA could have a positive impact on how we treat TA. TA is a disease with serious morbidity and possible mortality (2). The occurrence in young females and the need for long-standing immunosuppressive therapy calls for improvement of currently available treatment regimens. As in GCA,

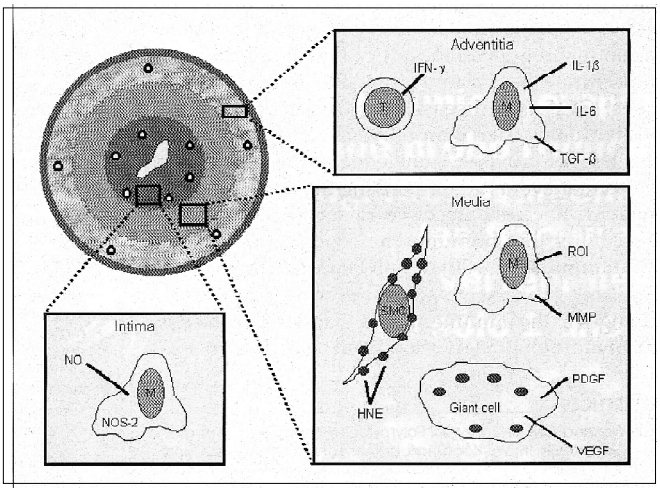

Figure 1. Topographically distinct types of inflammation in the arterial wall. *Adventitial inflammation is characterized by T cells (T) producing interferon (IFN)-α and macrophages secreting interleukin (IL)-1, IL-6, and transforming growth factor (TGF)-α. The medial infiltrate is dominated by effector macrophages (M) and giant cells producing reactive oxygen intermediates (ROI), matrix metalloproteinases (MMP), platelet-derived growth factor (PDGF), and vascular endothelium growth factor (VEGF). Oxidative stress leads to the formation of 4-hydroxy-nonenal (HNE) and lipid peroxidation of the cell membrane of smooth muscle cells (SMC). Intimal macrophages preferentially express nitric oxide synthase (NOS)-2, which leads for the production of nitric oxide (NO).*

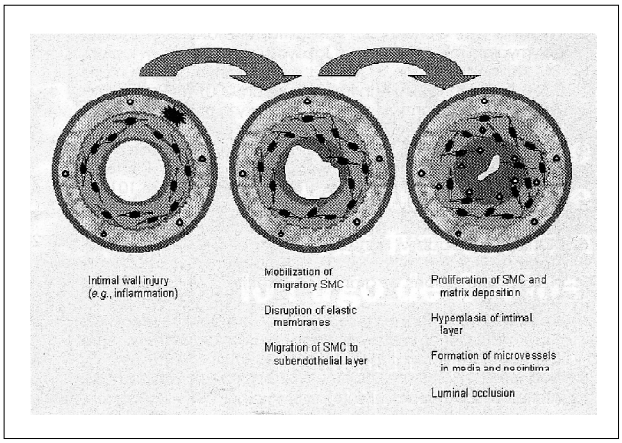

Figure 2. *Schematic diagram of the artery's response-to-injury program.*

Table 1. MOLECULAR TARGETS IN THE TREATMENT OF GCA

T-cell–derived mediators/pathways
- IFN-a
- IL-2

Macrophage-derived mediators/pathways
- IL-1a
- IL-6
- ROI
- MMP

Endothelial cell-related pathways
- VEGF
- Other angiogenic factors

Smooth muscle cell-related pathways
- PDGF
- Detoxification of ROI

immunosuppressive agent widely used in other autoimmune diseases have shown limited usefulness in TA. It may be easier to gain ground by interfering with the injury response program of the artery. Finally, efforts must concentrate on explaining how the immune system ages. GCA is a disease that exclusively affects individuals older than 50 years of age. There is limited but growing knowledge of the genetic and molecular events accompanying the aging immune system. Recent data have raised the intriguing possibility that immunosenescence contributes to autoimmunity (28-30). It will be fascinating to find out how progressive aging introduces functional changes in the immune system that increase the risk of an individual to develop giant cell arteritis.

REFERENCES

1. Weyand CM, Goronzy JJ. Polymyalgia rheumatica and giant cell arteritis. In: WJ Koopman, editor. Arthritis and Allied Conditions. A Textbook of Rheumatology. Baltimore, MD, Lippincott, Williams, and Wilkins; 1996. p. 1605-16.
2. Weyand CM, Goronzy JJ. Vasculitides: Giant cell arteritis, polymyalgia rheumatica, and Takayasu's arteritis. In: JH Klippel, CM Weyand, JH Stone, J Crofford, editors. Primer on Rheumatic Diseases. Atlanta, GA, Arthritis Foundation; 2001 (In Press).
3. Weyand CM, Goronzy JJ. Arterial wall injury in giant cell arteritis. Arthritis Rheum 1999; 42:844-53.
4. Martinez-Taboada V, Brack A, Hunder GG, Goronzy JJ, Weyand CM. The inflammatory infiltrate in giant cell arteritis selects against B lymphocytes. J Rheumatol 1996; 23:1011-4.
5. Weyand CM, Goronzy JJ. Giant cell arteritis as an antigen-driven disease. Rheum Dis Clin North Am 1995; 21:1027-39.
6. Martinez-Taboada V, Hunder NN, Hunder GG, Weyand CM, Goronzy JJ. Recognition of tissue residing antigen by T cells in vasculitic lesions of giant cell arteritis. J Mol Med 1996; 74:695-703.
7. Weyand CM, Schonberger J, Oppitz U, Hunder NN, Hicok KC, Goronzy JJ. Distinct vascular lesions in giant cell arteritis share identical T cell clonotypes. J Exp Med 1994; 179:951-60.
8. Wagner AD, Björnsson J, Bartley GB, Goronzy JJ, Weyand CM. Interferon-gamma-producing T cells in giant cell vasculitis represent a minority of tissue-infiltrating cells and are located distant from the site of pathology. Am J Pathol 1996; 148:1925-33.
9. Weyand CM, Tetzlaff N, Björnsson J, Brack A, Younge B, Goronzy JJ. Disease patterns and tissue cytokine profiles in giant cell arteritis. Arthritis Rheum 1997; 40:19-26.
10. Weyand CM, Hicok KC, Hunder GG, Goronzy JJ. Tissue cytokine patterns in patients with polymyalgia rheumatica and giant cell arteritis. Ann Intern Med 1994; 121:484-91.
11. Brack A, Geisler A, Martinez-Taboada V, Younge BR, Goronzy JJ, Weyand CM. Giant cell vasculitis is a T cell-dependent disease. Mol Med 1997; 3:530-43.
12. Weyand CM. The Dunlop-Dottridge Lecture: The pathogenesis of giant cell arteritis. J Rheumatol 2000; 27:517-22.
13. Weyand CM, Hunder NN, Hicok KC, Hunder GG, Goronzy JJ. HLA-DRB1 alleles in polymyalgia rheumatica, giant cell arteritis, and rheumatoid arthritis. Arthritis Rheum 1994; 37:514-20.
14. Weyand CM, Hicok KC, Hunder GG, Goronzy JJ. The HLA-DRB1 locus as a genetic component in giant cell arteritis. Mapping of a disease-linked sequence motif to the antigen binding site of the HLA-DR molecule. J Clin Invest 1992; 90:2355-61.
15. Wagner AD, Goronzy JJ, Weyand CM. Functional profile of tissue-infiltrating and circulating CD68+ cells in giant cell arteritis. Evidence for two components of the disease. J Clin Invest 1994; 94:1134-40.
16. Weyand CM, Wagner AD, Björnsson J, Goronzy JJ. Correlation of the topographical arrangement and the functional pattern of tissue-infiltrating macrophages in giant cell arteritis. J Clin Invest 1996; 98:1642-9.
17. Roche NE, Fulbright JW, Wagner AD, Hunder GG, Goronzy JJ, Weyand CM. Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. Arthritis Rheum 1993; 36:1286-94.
18. Weyand CM, Fulbright JW, Hunder GG, Evans JM, Goronzy JJ. Treatment of giant cell arteritis: interleukin-6 as a biologic marker of disease activity. Arthritis Rheum 2000; 43:1041-8.
19. Rittner HL, Kaiser M, Brack A, Szweda LI, Goronzy JJ, Weyand CM. Tissue-destructive macrophages in giant cell arteritis. Circ Res 1999; 84:1050-8.
20. Rittner HL, Hafner V, Klimiuk PA, Szweda LI, Goronzy JJ, Weyand CM. Aldose reductase functions as a detoxification system for lipid peroxidation products in vasculitis. J Clin Invest 1999; 103:1007-13.
21. Kaiser M, Weyand CM, Björnsson J, Goronzy JJ. Platelet-derived growth factor, intimal hyperplasia, and ischemic complications in giant cell arteritis. Arthritis Rheum 1998; 41:623-33.
22. Kaiser M, Younge B, Björnsson J, Goronzy JJ, Weyand CM. Formation of new vasa vasorum in vasculitis. Production of angiogenic cytokines by multinucleated giant cells. Am J Pathol 1999; 155:765-74.
23. Brack A, Martinez-Taboada V, Stanson A, Goronzy JJ, Weyand CM. Disease pattern in cranial and large-vessel giant cell arteritis. Arthritis Rheum 1999; 42:311-7.
24. Weyand CM. Vascular pathology: A dialogue between the immune system and the arterial wall. In: GS Hoffman, CM Weyand, editors. Inflammatory Diseases of Blood Vessels. New York, NY, Marcel Dekker; 2001 (In Press).
25. Weyand CM, Fulbright JW, Evans JM, Hunder GG, Goronzy JJ. Corticosteroid requirements in polymyalgia rheumatica. Arch Intern Med 1999; 159:577-84.
26. Brack A, Rittner HL, Younge BR, Kaltschmidt C, Weyand CM, Goronzy JJ. Glucocorticoid-mediated repression of cytokine gene transcription in human arteritis-SCID chimeras. J Clin Invest 1997; 99:2842-50.
27. Weyand CM, Kaiser M, Yang H-Y, Younge B, Goronzy JJ. Therapeutic Effects of Acetylsalicylic Acid in Giant Cell Arteritis. Arthritis Rheum 2001 (In Press).
28. Wagner UG, Koetz K, Weyand CM, Goronzy JJ. Perturbation of the T cell repertoire in rheumatoid arthritis. Proc Natl Acad Sci U S A 1998; 95:14447-52.
29. Koetz K, Bryl E, Spickschen K, O'Fallon WM, Goronzy JJ, Weyand CM. T cell homeostasis in patients with rheumatoid arthritis. Proc Natl Acad Sci U S A 2000; 97:9203-8.
30. Goronzy JJ, Weyand CM. Thymic function and peripheral T-cell homeostasis in rheumatoid arthritis. Trends Immunol 2001; 22:251-5.