Endothelial cell biology, perivascular inflammation, and vasculitis

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1. INTRODUCTION

Endothelial cells are among the most dynamic and biologically active cellular components of blood vessels and play a crucial role in the pathogenesis of systemic vasculitis. The participation of endothelial cells in the pathogenesis of vascular inflammation is complex. On one hand, vascular endothelium may be the main target for injury. On the other hand, endothelial cells may actively participate in amplifying and maintaining the inflammatory process. The role of endothelial cells as a target for injury seems to be more prominent in small-vessel vasculitis, namely hypersensitivity vasculitis and vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA). In large-vessel vasculitis, endothelial cells are crucial protagonists of what we have called vascular response to inflammation, a complex constellation of changes that occur in the vessel wall in response to inflammatory mediators released by infiltrating leukocytes.[1,2] Vascular response to inflammation leads to the amplification of the inflammatory response, vessel remodeling and repair, and eventually, vessel occlusion, source of some of the most severe complications in patients with systemic vasculitis.

2. ENDOTHELIAL CELL AS A TARGET FOR INJURY

2.1 Vasculitis triggered by infectious agents

Although most of the infection-related vasculitides are immune-complex–mediated (i.e., hepatitis B virus [HBV]-related polyarteritis nodosa, and hepatitis C virus [HCV]-associated cryoglobulinemia), some pathogens are able to directly infect the endothelial cell. Rickettsiae and Herpesvirus family members, particularly cytomegalovirus, are the best documented.[3,4] Serious infections by these agents frequently include vasculitic lesions.

2.2 Immune-complex–mediated endothelial cell injury

In immune-complex–mediated vasculitis, endothelial cell morphology is altered and the luminal endothelium is eventually destroyed. Complement-mediated lysis as well as neutrophil-mediated endothelial cell damage are the main mechanisms of endothelial cell injury in these processes.[5] The membrane attack complex C5b-9, final product of the complement activation cascade, has been detected in necrotizing vasculitis of polyarteritis nodosa type.[6]

2.3 ANCA-mediated vasculitis

ANCA stimulate many neutrophil functions resulting in endothelial cell damage. ANCA may recognize myeloperoxidase (MPO) or proteinase-3 (PR3) translocated to the neutrophil membrane by the effects of cytokines such as tumor necrosis factor (TNFα) or interleukin-8 (IL-8) or may bind to Fc receptors through their Fc portion. Both interactions, specific and Fc-mediated, appear to be functionally relevant.[7,8] Experimental work by several groups has demonstrated that ANCA binding to neutrophils may stimulate or amplify many neutrophil functions including respiratory bursts with generation of reactive oxygen intermediates,[7] degranulation and protease release,[7] nitric oxide production,[9] and chemotactic activity.[10] ANCA binding also stimulates integrin expression and integrin-mediated homotypic adhesion and adhesion to endothelial cells, partially through an Fc-mediated mechanism.[11-13] Studies with blocking monoclonal antibodies have shown that enhancement of TNF-induced neutrophil activation by ANCA is, at least, partially dependent on homotypic interactions mediated by neutrophil integrins.[14]

In several experimental settings it has been demonstrated that ANCA-stimulated neutrophil function results, indeed, in an augmentation of neutrophil-mediated endothelial cell injury.[15,16] ANCA-stimulated neutrophils are able to produce endothelial cell detachment and lyse endothelial cells previously damaged by other mediators.[15,16] In addition, in an inflammatory microenvironment, enzymes released by activated neutrophils, including MPO and PR3, may induce endothelial cell apoptosis.[17]

2.4 Anti-endothelial cell antibodies

Circulating anti-endothelial cell antibodies have been detected in several vasculitides including Wegener's granulomatosis, microscopic polyangiitis, Kawasaki disease, thromboangiitis obliterans, Behçet's disease, and

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Takayasu's arteritis.[18-20] Antigens recognized by anti-endothelial cell antibodies seem to be highly heterogeneous and have not been well characterized. Some anti-endothelial cell antibodies, such as those detected in Kawasaki disease, recognize cytokine-inducible molecules,[21] whereas others, such as those detected in Wegener's granulomatosis and microscopic polyangiitis, recognize constitutive endothelial cell antigens.[18]

In vitro studies have shown that some anti-endothelial cell antibodies may trigger complement activation or antibody-dependent cellular cytotoxicity.[5,18,22] Therefore, anti-endothelial cell antibodies might contribute to endothelial cell damage in systemic vasculitis. However, their precise pathogenic role has not been fully characterized.

3. THE ENDOTHELIAL CELL AS AN INFLAMMATION AMPLIFIER

Rather than being passive spectators of leukocyte infiltration, vessel wall components, particularly endothelial cells, actively and dynamically react to the products released by infiltrating leukocytes. Endothelial cells are able to amplify the inflammatory response by three main mechanisms: adhesion molecule expression, cytokine production, and angiogenesis.

3.1 Endothelial adhesion molecules

Vessel infiltration by leukocytes requires finely regulated interactions among leukocytes, endothelial cells, and the underlying matrix mediated by adhesion molecules.[23]

3.1.1. Immunopathogenic mechanisms of vessel damage and adhesion molecules. Most of the primary immunopathogenic mechanisms which are thought to play a role in the pathogenesis of blood vessel inflammation in vasculitis have been shown to influence adhesion molecule expression or function.[23]

In vitro studies have shown that complement activation products induce adhesion molecule expression by cultured endothelial cells. C1q induces E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1),[24] and C5a has been shown to up-regulate P-selectin expression.[25] Adhesion molecule expression and function are required for immune-complex– and complement-mediated vessel damage in vivo.[26,27]

Recent studies have shown that ANCA binding to endothelial cell membrane-associated PR 3[28] or related epitopes on the endothelial cell surface[29] may induce E-selectin and VCAM-1 expression by endothelial cells.[30,31] In an inflammatory context, PR3 released by neutrophils in the vicinity of endothelial cells is able to induce endothelial cell ICAM-1 expression.[32] In vitro studies have shown that anti–endothelial cell antibody binding to endothelial cells also induces endothelial adhesion molecule expression.[33]

In vasculitis, activated lymphocytes and macrophages actively produce IL-1, TNFα, and interferon γ,[34,35] the main inducers of endothelial adhesion molecules. Topographical relationship between inducer cytokines and endothelial adhesion molecule expression has been demonstrated in tissue samples from patients with microscopic polyangiitis.[36]

3.1.2. Tissue expression of endothelial adhesion molecules. Expression of endothelial adhesion molecules in lesions has been investigated in sizeable and homogeneous series of patients with cutaneous leukocytoclastic vasculitis, Kawasaki disease, classical polyarteritis nodosa, and giant-cell arteritis.[37-40] In all of them, expression of inducible adhesion molecules E-selectin and VCAM-1 by endothelial cells can be detected at some point and constitutive expression of ICAM-1 is usually up-regulated. In glomerular lesions of Wegener's granulomatosis and microscopic polyangiitis, as well as in ANCA-associated necrotic and crescentic glomerulonephritis, VCAM-1 and ICAM-1 expression can be observed at the glomerular tuft as well as in tubular epithelial cells and peritubular capillaries.[41-43]

In small-vessel vasculitis, endothelial adhesion molecule expression occurs in the luminal endothelium.[37] However, in medium-sized vasculitis such as classical polyarteritis nodosa, the luminal endothelium only expresses constitutive or inducible adhesion molecules at early stages. As the inflammatory process proceeds, the luminal endothelium is damaged and the vascular lumen is occluded. Endothelial adhesion molecules are then strongly expressed by adventitial neovessels.[39] In kidney lesions of ANCA-associated vasculitis, glomerular expression of ICAM-1 and VCAM-1 also declines in sclerotic glomeruli.[43] In large-vessel vasculitis such as giant-cell arteritis, adhesion molecule expression occurs in neovessels at the adventitia and within the inflammatory lesions, mainly at the intima/media junction. These observations suggest that, in large- and medium-sized vessels, infiltrating leukocytes do not come from the vascular lumen. Rather, inflammatory cells penetrate the vessel wall through the adventitial vasa vasorum and neovessels.

3.1.3. Functional relevance of endothelial adhesion molecules in vasculitis. Immunohistochemical studies usually disclose a close topographical relationship between endothelial expression of adhesion molecules and expression of their ligands by infiltrating leukocytes, suggesting that interactions mediated by adhesion molecules actively participate in the development of inflammatory infiltrates in vasculitis.[39,40] The functional relevance of interactions mediated by adhesion molecules in the pathogenesis of vessel inflammation has been investigated in in vitro studies exploring adhesion of T lymphocytes to glomeruli in tissue sections from patients with renal vasculitis,[44] and in animal models. In a murine model of systemic vasculitis induced by immunization against *Mycobacterium butyricum*, the administration of blocking monoclonal antibodies and the application of vital microscopy have demonstrated the important participation of interactions mediated by selectins and by α4 integrins in leukocyte adhesion and transmigration through postcapillary venules.[45] Similarly, ICAM-1 deficiency considerably reduces the development of vasculitis in MRL/lpr mice,[46] and blocking E-selectin ligands or α4 integrins prevents the development of β-glucan–induced granulo-

matous vasculitis.[47,48] Although none of these models satisfactorily represents specific human vasculitic syndromes, these findings underline the functional importance of interactions mediated by adhesion molecules in the development of vascular inflammation.

3.1.4. Effects of treatment on endothelial adhesion molecule expression. In vitro studies have shown that corticosteroids may suppress endothelial cell adhesion molecule expression induced by endotoxin or by cytokines.[49] In addition, corticosteroids inhibit the production of proinflammatory cytokines which are the main inducers of adhesion molecule expression.[50]

The effect of treatment on adhesion molecule expression in patients with vasculitis is not well defined. Immunoglobulin therapy decreases endothelial cell adhesion molecule expression in skin samples from patients with Kawasaki disease.[38] Preliminary cross-sectional studies show a substantial decrease in E-selectin and VCAM-1 expression in lesions from patients with giant-cell arteritis treated with corticosteroids for up to one month, but some expression still persists,[40] indicating a persistent exposure of endothelial cells to an inflammatory microenvironment. A decrease in endothelial adhesion molecule expression in synovial biopsies from patients with polymyalgia rheumatica treated with corticosteroids has also been observed.[51] Corticosteroid and immunosuppressive treatment of patients with polyarteritis nodosa for just a few days does not substantially modify adhesion molecule expression.[39]

3.2 Cytokine production

Endothelial cells have the potential to produce a variety of cytokines, chemokines and growth factors in an inflammatory microenvironment. Through the production of IL-1α and IL-6, endothelial cells may contribute to the systemic acute-phase reaction which is characteristically prominent in many systemic vasculitides compared with other immune-mediated diseases.[1]

Endothelial cells are able to produce colony-stimulating factors and these may be able to prolong the half-life of infiltrating leukocytes as suggested by in vitro studies.[52] In fact, the occurrence of leukocytoclastic vasculitis in association with granulocyte colony-stimulating factor therapy has been reported.[53]

Several chemokines such as IL-8, RANTES, Gro α, and SLC, among others, can be produced by endothelial cells.[54] Chemokines selectively attract leukocyte subpopulations bearing specific receptors. Chemokine production by endothelial cells may contribute to tissue targeting in systemic vasculitis, and by attracting additional leukocytes may perpetuate and amplify vessel inflammation.[55]

As for adhesion molecules, ANCA binding to endothelial cells,[30,31] some anti–endothelial cell antibodies,[24] and cytokines released by infiltrating cells[52] stimulate endothelial cell production of cytokines and chemokines such as IL-8. PR3 binding to endothelial cells may also increase endothelial cell production of IL-8 and monocyte chemoattractive protein-1 (MCP-1).[32]

3.3 Angiogenesis

Angiogenesis, new vessel formation, is a relevant phenomenon in systemic vasculitis. Immunohistochemical studies have shown that, in vasculitis, extensive neovascularization occurs in inflammatory lesions, particularly in the adventitial layer or surrounding tissues.[56,57] In large-vessel vasculitis, neovessels also appear within the inflammatory infiltrates, particularly at the intima/media junction.[40]

We have proposed that angiogenesis may play a dual role in systemic vasculitis. On one hand, in medium-sized and large-vessel vasculitis such as giant-cell arteritis and polyarteritis nodosa, newly formed vessels intensively express adhesion molecules for leukocytes and provide new sites through which leukocytes may invade the vessel wall.[39,40] In addition, new vessels provide a wider endothelial cell surface and provide a new source of cytokines, chemokines, and growth factors, amplifying and perpetuating the inflammatory process.

On the other hand, in small-vessel vasculitis and at distal sites supplied by large or medium-sized vasculitis, angiogenesis may be a compensatory mechanism to avoid ischemia. The relevance of angiogenesis as a compensatory mechanism is illustrated by the fact that interferon α, a potent angiogenesis inhibitor, may worsen cryoglobulinemia-related ischemic complications.[58] Similarly, in giant-cell arteritis, the magnitude of the angiogenic response measured in temporal artery samples inversely correlates with the development of ischemic complications.[59] Even though giant-cell arteritis is considered a large-vessel vasculitis, we have shown that small cranial arteries are frequently involved and, in fact, characteristic ischemic complications such as blindness or scalp necrosis usually occur in territories supplied by small arteries.[57] These observations suggest that angiogenic activity might have a compensatory function in giant-cell arteritis. Detection of neovessels by imaging techniques may be of clinical interest in assessing disease activity. In this regard, preliminary studies suggest that, in Takayasu's disease, intramural neovascularization can be detected by computed tomography after bolus injection of contrast material, and this may reflect active inflammation.[60]

Angiogenesis results from a delicate balance between the influx of angiogenic and anti-angiogenic factors and the regulation of the expression and function of their respective receptors. A large variety of molecules may exhibit angiogenic activity. These include growth factors, chemokines, thymosins, acute-phase proteins and extracellular matrix protein fragments.[61] Several angiogenic factors such as vascular endothelial cell growth factor (VEGF), fibroblast growth factor (FGF-2),[62] IL-8, and thymosin β4 (Cid et al, unpublished) have been detected in temporal artery lesions from patients with giant-cell arteritis but their functional relevance is incompletely understood. Other factors such as TNFα and transforming growth factor beta (TGFβ), also produced in giant-cell arteritis lesions,[63] may also have angiogenic activity in vivo, probably through indirect mechanisms requiring the participation of additional cell types.

4. ENDOTHELIAL CELLS AND VESSEL OCCLUSION

Vascular inflammation frequently leads to vessel occlusion with the ensuing ischemia of supplied tissues. Ischemic complications often result in organ dysfunction and major disabilities in patients with vasculitis. Major contributors to vessel occlusion are thrombosis and intimal hyperplasia. Thrombosis is more frequently seen in small/medium-sized vessel vasculitis, whereas in large-vessel vasculitis lumen reduction usually occurs as a consequence of intimal hyperplasia.[1]

Several cytokines and growth factors produced in inflamed vessels have prothrombotic and fibrogenic effects. IL-1 and TNFα have procoagulant activity by inducing endothelial expression of tissue factor.[52] However, both IL-1 and TNFα can also induce prostacyclin synthesis, which is a potent inhibitor of platelet aggregation, and TNFα may increase the production of plasminogen activators.[64,65] The final impact of these opposite interactions on the coagulability status is complex and is probably determined by many interactions in the inflammatory microenvironment at a given time point.

Endothelial cells may produce fibrogenic factors able to stimulate myointimal cell proliferation and matrix deposition leading to intimal hyperplasia. These include IL-1α, FGFs, TGFβs and platelet-derived growth factors (PDGFs), among others.[52] However, in large-vessel arteritis, macrophages, rather than endothelial cells, are probably the main producers of fibrogenic growth factors,[66,67] and the fibrogenic impact of endothelial cells is probably less relevant in these diseases.

5. CONCLUDING REMARKS

Endothelial cells have a relevant and complex participation in vasculitis pathogenesis, both as target for injury and as active protagonists of the inflammatory process. Endothelial cell response to inflammatory mediators may be both harmful and beneficial, given that endothelial cells have proinflammatory functions and may actively participate in vessel remodeling and repair. A better understanding of the endothelial response to inflammation may lead to new therapeutic approaches in the future.

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