Review

Angiogenesis in vasculitides

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ABSTRACT

Vasculitides, including Wegener's granulomatosis, Takayasu's arteritis, giant cell arteritis, Kawasaki disease, Behçet disease, thromboangiitis obliterans and erythema elevatum diutinum, are inflammatory diseases of blood vessel wall characterized by myointimal proliferation, fibrosis and thrombus formation leading to stenosis or occlusion of the vascular lumen, and finally to tissue ischemia. In these diseases the hypoxic environment subsequent to stenosis or occlusion of the vascular lumen is a potent signal for the generation of new blood vessels. Angiogenesis may be a compensatory response to ischemia and to the increased metabolic activity and may be also a further inflammatory stimulus because endothelial cells of newly-formed vessels express adhesion molecules and produce colony-stimulating factors and chemokines for leukocytes.

Angiogenesis

Angiogenesis is the formation of newly-formed capillaries from pre-existing vessels. It is characterized by a well-programmed cascade of events which contains a number of distinct steps (1). Angiogenic factors activate endothelial cells, inducing them to produce, in turn, proteolytic enzymes such as matrix metalloproteinases and plasminogen activators, which are responsible of the degradation of the basement membrane and of the perivacular extracellular matrix. The proliferation and migration of endothelial cells into the perivascular area and the subsequent lumenation of these "primary sprouts" forming "capillary loops" and the synthesis of new basement membrane, lead finally to new vessel formation. Endothelial cells of the "primary sprouts" proliferate and migrate to generate secondary and further generations of sprouts.

Angiogenesis is regulated by several angiogenic and anti-angiogenic factors (2) (Table I). Vascular endothelial growth factor (VEGF) family members, fibroblast growth factor (FGF) family members, platelet-derived growth factor (PDGF), transforming growth factor alpha and beta (TGF-α and β), tumor necrosis factor alpha (TNF-α), interleukins (IL), chemokines, angiogenin, and angiopoietins have a positive regulatory activity. On the contrary, angiostatin, endostatin, and thrombospondin have a negative regulatory activity (3-5). The net balance between these positive and negative factors, with a prevalence of positive regulators, or a downregulation of the expression of negative regulators, is responsible for inducing and regulating the angiogenic process (2) (Fig. 1).

Angiogenesis in chronic inflammation

Angiogenesis plays a key role in the pathogenic events leading to chronic inflammation. Chronic inflammatory lesions occuring in several diseases, such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, primary biliary cirrhosis, and vasculitides (6-10) are characterized by cellular infiltrates and newly-formed vessels involved in favouring inflammatory cells recruitment and providing a compensatory response to ischemia and to the increased metabolic activity (11, 12).

Angiogenic factors induce endothelial cells to express adhesion molecules, cytokines and chemokines, which may have additive stimulatory effects on chronic inflammation. VEGF promotes the migration of inflammatory cells, such as monocytes and lymphocytes, into the extracellular matrix via inducing vascular permeability and endothelial cells expression of adhesion molecules, such as VCAM-1 and ICAM-1 (13, 14). FGF-1 and FGF-2 promote endothelial cell production of

Table I. Main angiogenic and anti-angiogenic factors that regulate angiogenesis.

Angiogenic factors*	Angiogenic activity			
	In vitro assays			*In vivo* assays
	Proliferation	Migration	Capillary tube fromation	
Vascular endothelial growth factor (VEGF)	S	S	S	S
Fibroblast growth factor-2 (FGF-2)	S	S	S	S
Platelet derived growth factor (PDGF)	N	S	=	S
Transforming growth factors beta (TGF-β)	I	N	S	S
Angiopoietin-1	N	S	S	S
Anti-angiogenic factors*				
Thrombospondin-1	I	I	I	I
Angiostatin	I	I	I	I
Endostatin	I	I	I	I

*All the angiogenic and the anti-angiogenic factors may be considered as pleiotropic growth factors, which recognize several producing and effector cells, such as endothelial cells, pericytes, inflammatory cells and tumor cells.
I: inhibition; N: no effect; S: stimulation; =: no findings available.

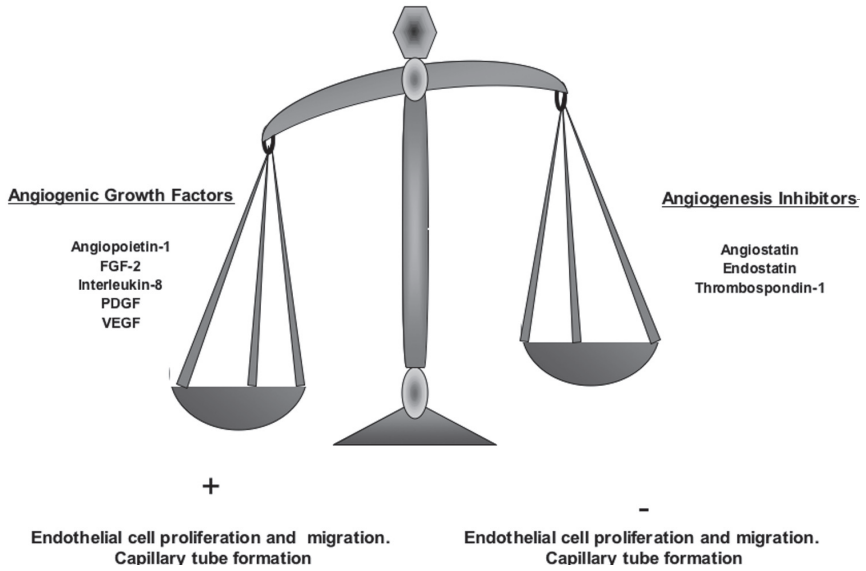

Fig. 1. Angiogenesis results from the balance between pro- and anti-angiogenic factors.

plasminogen activator and collagenase which allow the migration of inflammatory cells via degradation of the extracellular matrix (15). Other angiogenic factors involved in inflammatory cells recruitment are chemokines containing the ELR motif (glutamyl-leucyl-arginyl sequence), such as CXC chemokines (16, 17).

Most angiogenic factors, such as TNF-α, IL-1, IL-6, IL-8, and IL-18 are also inflammatory factors involved in increasing the production of other inflammatory cytokines and cell adhesion molecules, and in enhancing matrix metallo-proteinases and/or cyclooxygenase activity (18).

Vasculitides

Vasculitides are an heterogenous group of disorders including giant cell arteritis, Takayasu's arteritis, Cogan's syndrome, Behçet disease, polyarteritis nodosa, thromboangiitis obliterans, Kawasaki disease, primary angiitis of the central nervous system, Goodpasture's disease, cutaneous leukocytoclastic angitiis, Henoch-Schönlein purpura, hypocomplementemic urticarial vasculitis, essential cryoglobulinemia, erythema elevatum diutinum, Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, renal-limited vasculitis and secondary forms of vasculitis (19).

At the present time, the Chapell Hill Consensus Conference Nomenclature of primary vasculitides (Table II) provide a useful guide to clinician and pathologist for evaluating a patient with a idiopathic form of vasculitis. This classification is based on the predominant size of vessels affected and describes the main clinico-pathologic features of the various clearly defined types of systemic vasculitis.

Vasculitides are also classified on the basis of their histopathologic features into neutrophilic or leukocytoclastic vasculitis, lymphocytic vasculitis, and granulomatous vasculitis (20). Leukocytoclastic vasculitis is an inflammation of small-vessel characterized by segmental angiocentric neutrophilic inflammation, endothelial cell damage and fibrinoid necrosis. These histopathologic features may be found in cryoglobulinemia and rarely in multiple myeloma (21). Lymphocytic vasculitis, characterized by lymphocytic recruitment of inflammatory cells and cytotoxic reactions, is the histopathologic pattern of lymphocytic endovasculitis, lymphocytic lichenoid vasculitis and granulomatous vasculitis (22). Granulomatous vasculitis is a granulomatous inflammation with extensive necrosis and a variegated cellular infiltrate. Wegener's granulomatosis is an example of this histopathologic pattern (23).

These disorders are characterized by inflammation of blood vessel wall. The final result is myointimal proliferation, fibrosis and thrombus formation leading to stenosis or occlusion of the vascular lumen, and finally to tissue ischemia (24). Even if aetiology of vasculitides is still unknown, infections, inflammatory disorders, autoimmunitary disorders and drugs are involved as triggers for disease activity in vasculitides (25-27).

Because the etiologies of most from of vasculitis remain unknown, the most valid basis for classifying the vasculitides is the size of the predominant blood vessels involved. Large vessel vasculitis involves the aorta and its major branches; medium vessel vasculitis involves vessels large enough to be observed in gross pathological specimens or visualized by angiography; small

Table II. Names and definitions of vasculitides adopted by the Chapel Hill Consensus Conference.

Giant cell arteritis
Granulomatosis arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery.

Takayasu's arteritis
Granulomatosis arteritis of the aorta and its major branches.

Polyarteritis nodosa
Necrotizing inflammation of the medium-sized or small arteries.

Kawasaki's disease
Arteritis involving large, medium sized and small arteries. Coronary arteries are often involved.

Wegener's granulomatosis
Necrotizing vasculitis affecting small to medium-sized vessels.

Churg-Strauss syndrome
Necrotizing vasculitis affecting small to medium-sized vessels.

Microscopic polyangitis
Necrotizing vasculitis affecting small vessels.

Henoch-Schönlein purpura
Vasculitis affecting small vessels.

Essential cryoglobulinemia vasculitis
Vasculitis affecting small vessels

Cutaneous leukocytoclastic vasculitis
Isolated cutaneous leukocytoclastic angitis without systemic vasculitis.

vessel vasculitis involves capillaries, post-capillary venules and arterioles.

Several studies have demonstrated that angiogenesis is involved in the pathogenesis of vasculitides, such as Wegener's granulomatosis, Takayasu's arteritis, giant cell arteritis, Kawasaki disease, Behçet disease, thromboangiitis obliterans and erythema elevatum diutinum. The angiogenic response is more intense in small vessel vasculitis, as compared to medium- and large-vessels vasculitis, because angiogenesis generally involves capillary and post-capillary venules. The hypoxic environment subsequent to stenosis or occlusion of the vascular lumen is a potent signal for the generation of new blood vessels.

A dual role of angiogenesis in vasculitides has been proposed (9). On the one hand, angiogenesis may be a compensatory response to ischemia and to the increased metabolic activity above all in strong acute phase of disease. On the other hand, endothelial cells of newly-formed vessels express adhesion molecules and produce colony-stimulating factors and chemokines for leukocytes (28-32). In this way, circulating leukocytes arrive to sites of inflammation where constitute a further inflammatory stimulus (32, 33). Antineutrophil cytoplasmic antibodies (ANCA) potentiate neutrophil and monocyte mediated endothelial cell activation (34).

Angiogenesis in giant cell arteritis

Giant cell arteritis is a vasculitis that mainly affects extracranial medium-sized and large arteries, aorta and its principal branches (35, 36). The aorta typically demonstrates aortic root dilatation, with medial dissection in occasional cases of aortic rupture. The intima is wrinkled demonstrating a tree-back appearance. Histologically, the inflammatory infiltrate consists of lymphocytes, plasma cells and histiocytes. There is disruption of the internal elastic lamina with fragmentation and a giant cell reaction. The disruption may be accompanied by a significant degree of necrosis. Vessel occlusion occurring in giant cell arteritis causes ischemia. Cid *et al*. (9) have hypothesized that angiogenesis has an essential role in reducing ischemic tissue damage above all in giant cell arteritis target organs (37), such as small arteries supplying the optic nerve, and potentiates inflammation via expression of adhesion molecules and production of colony-stimulating factors and chemokines for leukocytes (28-32). Angiogenesis has been associated with severe inflammation in giant cell arteritis (32). On the other hand, severe inflammation, manifested by very high levels of erythrocyte sedimentation rate greater than 100 mm/1st hour or chronic anemia, has been associated with protection against visual ischemic manifestations or other severe ischemic manifestations of this vasculitis (38-40).

VEGF, FGF-2, TGF-β, PDGF, TNF-α, monocyte chemoattractant protein-1 (MCP-1) and IL-8 have been observed in giant cell arteritis lesions (41, 42). Moreover, high levels of VEGF, FGF-2 and soluble ICAM-1 have been found in sera of giant cell arteritis patients (43). TNF-α and IL-6 levels are higher in giant cell arteritis acute phase (44), when haptoglobin, a carrier for free hemoglobin with angiogenic properties, is highly produced (45).

Constitutive (PECAM-1, ICAM-1, ICAM-2, and P-selectin) and inducible (E-selectin and VCAM-1) endothelial cell adhesion molecules for leukocytes are over-expressed by endothelial cells of adventitial microvessels and neovessels in giant cell arteritis vascular lesions. Leukocytes interactions with these ligands are responsible for the formation of inflammatory infiltrates in giant cell arteritis lesions (32). In adventitia, $CD4^+$ T cells produce interferon-γ (IFN-γ). IFN-γ is correlated with multinucleated giant cells (MGCs) formation and intimal hyperplasia (46). MGCs are specialized fused cells derived by macrophages that accumulate in media-intima of arterial wall where are involved in VEGF production. VEGF and IFN-γ, in addition to tissue hypoxia subsequent to arterial wall thickening and luminal stenosis, are probably responsible of the angiogenesis in giant cell arteritis lesions (47). Blindness, stroke, and jaw claudication are often seen in giant cell arteritis patients with high levels of IFN-γ in their lesions (46). On the contrary, systemic manifestations in giant cell arteritis patients are well correlated with low levels of IFN-γ (47). Interestingly, a microsatellite dinucleotide (CA) repeat polymorphism in the first intron of the IFN-γ gene was associated with some differences between biopsy-proven giant cell arteritis, with or without visual ischemic manifestations. In this regard, an association between a high IFN-γ producer allele with giant cell arteritis patients who experienced visual ischemic events, and an inverse correlation with individuals carrying a low IFN-γ producer allele was found (48). Also, a functional VEGF-634 G→C gene polymorphism was found to be associated with severe ischemic complications in giant cell arteritis patients from Northwestern Spain (49). The low VEGF producer VEGF-634 G allele of this genetic polymorphism was significantly overexpressed in giant cell arteritis

patients with ischemic complications and additionally, a higher risk of developing severe ischemic complications was observed for VEGF-634 GG homozygous individuals (49).

MGCs are also involved in elastic membranes degradation via matrix metalloproteinase (MMP)-2 production (50-52). Moreover, MGCs produce PDGF-AA and PDGF-BB, both involved in intimal proliferation (53).

Giant cell arteritis is characterized by the release, in the systemic acute-phase, of proinflammatory cytokines, such as IL-1, TNF-α, and IL-6 (54), which may influence vascular responses such as vessel occlusion or regeneration, involved in the pathogenesis of giant cell arteritis inflammatory lesions (28, 55, 56). IL-6-induced angiogenesis is responsible of inflammation in giant cell arteritis and patients with elevated IL-6 levels needed higher corticosteroid dosage to limit their inflammatory activity (44, 57, 58).

Decorin, a chondroitin/dermatan sulfate proteoglycan of the extracellular matrix (59), has been found in giant cell arteritis lesions (60). Even if no factors responsible for the induction of decorin production have been still found, it is known that endothelial cells of newly-formed vessels in giant cell arteritis temporal artery may produce decorin. Decorin probably interacts with type I collagen (61, 62) and fibronectin (63, 64), two extracellular matrix proteins, and may induce endothelial cells proliferation by modifying the structural organization of these molecules (65, 66). It was found that when cultured endothelial cells spontaneously change their morphology from a polygonal shape to a sprouting phenotype they concomitantly initiate decorin synthesis and depostion, indicating that decorin is associated with angiogenesis (67). Decorin, a ligand for the epidermal growth factor receptor (EGF-R) (68), that is involved in endothelial cells proliferation, inhibits apoptosis of endothelial cells (69), induces collagenase expression (70) and phospholipase A2 activity (71), both involved in angiogenesis (72-74), inhibits TGF-beta (75, 76) and induces FGF-2 activity (77). Nelimarka *et al*. (78) have demonstrated that the intimal thickening and angiogenesis are coupled in giant cell arteritis and that the capillary neovessels within the inflamed temporal artery wall contain decorin.

Angiogenesis in Kawasaki disease

Kawasaki disease is a vasculitis of young childhood, characterized by aneurysmal dilatation and acute thrombosis of coronary arteries (79-83). Kawasaki disease lesions are characterized by thinning of vascular media, inflammation and destruction of the extracellular matrix in the internal elastic lamina and in the trilaminar structure of the vascular wall (79, 80, 83, 84). Fibrosis, granulation and angiogenesis have been seen in these lesions (79, 80, 83-85). Increased VEGF levels have been found in Kawasaki disease and TGF-β1 has been demonstrated to upregulate VEGF expression in acute phase of disease (86). Moreover, endothelial cells of newly-formed blood vessels in myointima and adventitia of Kawasaki disease coronary artery aneurysms produce high levels of MMP-2 (84). Moreover, Gavin *et al*. (84) have demonstrated that in Kawasaki disease coronary aneurysms, MMP-9 was also expressed, but its expression is not confined to aneurysmal arteries. Systemic arterial expression of MMP-9 in acute Kawasaki disease, even in absence of inflammatory changes in the vessel, suggests induction by a circulating factor, or by an infectious agent with tropism for arterial tissue. Moreover, the significantly elevated MMP-9 levels during acute phase of Kawasaki disease may reflect vascular remodeling or an inflammatory response to a microbial agent, suggesting a pathophysiological role for MMP-9 in coronary aneurysm formation (87).

Miura *et al*. (88) have demonstrated that endothelial cells of newly-formed blood vessels in coronary artery aneurysm in Kawasaki disease express E-selectin, involved in leukocytes adhesion on endothelial cells, and VCAM-1, important in leukocytes adhesion and extravasation into tissues. On the contrary, luminal endothelial cells of coronary arteries without aneurysms do not express E-selectin and VCAM-1, such as endothelial cells of newly-formed blood vessels in polyarteritis nodosa and giant cell arteritis (29, 32). This particular feature may be due to the vasculitic process on luminal endothelial cells.

Angiogenesis in Behçet's disease

Behçet's disease is characterized by increased VEGF expression in oral aphthous lesions and in the ocular inflammation (89, 90) and by increased interleukin-8 levels in synovial fluids (91). Moreover, increased levels of VEGF and MCP-1 were detected in sera of Behçet disease patients (92).

Recombinant human interferon alpha-2a is effective in ocular Behçet's disease, leading to significant improvement of vision and complete remission of ocular vasculitis in the majority of patients (93). The mode of action of interferon may be explained by an anti-angiogenic effect, as it has been demonstrated since 1980, when interferon alpha was shown to inhibit endothelial cell migration in a dose-dependent manner (94).

Angiogenesis in thromboangiitis obliterans

Angiogenesis plays a crucial role in the inflammatory process of thromboangiitis obliterans. Vascular lesions are characterized by increased levels of TNF-α and ICAM-1-, VCAM-1- and E-selectin are expressed on the endothelial cells of thromboangiitis obliterans newly-formed vessels contributing to leukocyte adhesion (95).

Angiogenesis in leukocytoclastic vasculitis

Erythema elevatum diutinum, a variation of leukocytoclastic vasculitis, is characterized by cutaneous lesions over the shins, buttocks and extensor surfaces of the knees, elbows, and finger joints (96). Macroscopically, erythema elevatum diutinum lesions in the acute inflammatory phase are raised erythematous plaques, resolving in fibrous nodules with storiform or concentric fibrosis (97). Microscopically, three stages are described: a first stage characterized by capillary proliferation and fibrinoid degeneration of vessel wall; a

second stage characterized by fibrosis, dermal aggregates of neutrophils and areas of granulation tissue; a third stage characterized by fibrosis of the dermis with small foci of persistent leukocytoclastic vasculitis.

Dermal dendrocytes (DD), present in the adventitial and reticular dermis, have phagocytic and antigen presenting function and may modulate the regulatory mechanisms of deposition of extracellular macromolecules in the dermis. Moreover, DD are involved in the tissue repair mechanisms, fibrogenesis and angiogenesis (98, 99). Pacheco *et al*. (100) have demonstrated that DD may play a role in inflammatory skin diseases and found that DD in erythema elevatum diutinum and leukocytoclastic vasculitis are increased in number, hypertrophic and show stellate morphology. Even if erythema elevatum diutinum was characterized by a higher number of newly-formed blood vessels than leukocytoclastic vasculitis, no statistically significant difference in the number of DD has been observed between these two pathological conditions (100).

Angiogenesis in lymphocytic vasculitis

Lymphocytic vasculitis can be secondary to treatment of rheumatoid arthritis and Crohn's disease with infliximab, etanercept, or adalimumab (26, 27). These drugs rarely cause autoimmune disorders, such as vasculitis and lupus, probably due to low TNF-α levels (101-106), which are unable to suppress autoreactive B and T cells responsible in turn of autoimmune reactions (107).

Srivastava *et al*. (27) found an increase of VEGF and chemokine levels, especially RANTES, in serum of a patient with T-cell lymphocytic vasculitis secondary to treatment with etanercept, which worsened significantly with switch to infliximab. Moreover, angiogenic mediators, including TNF-α, IL-1β, IL-15, IL-18, were found in the vasculitic lesions of the patient.

Further evidences of angiogenesis in vasculitides: haptoglobin

Haptoglobin, a carrier for free hemoglobin, has angiogenic properties and is probably involved in endothelial cell differentiation and proliferation in systemic vasculitis, including Wegener's granulomatosis, Takayasu's arteritis and giant cell arteritis. Cid *et al*. (45) found a potent angiogenic activity in association with high levels of haptoglobin in sera from patients affected by Wegener's granulomatosis, Takayasu's arteritis and giant cell arteritis, using both *in vitro* and *in vivo* angiogenesis models. Haptoglobin levels are particularly high in Wegener's granulomatosis patients in the period of clinically active disease characterized by intense angiogenic activity.

Concluding remarks

In vasculitides, angiogenesis may be a compensatory response to ischemia and to the increased metabolic activity and may be also a further inflammatory stimulus because endothelial cells of newly-formed vessels express adhesion molecules and produce colony-stimulating factors and chemokines for leukocytes (28-33). Even if further studies are needed to elucidate the pathogenic mechanism of vasculitides, the emergency of angiogenesis as a key player in the pathogenic events leading to Wegener's granulomatosis, Takayasu's arteritis, giant cell arteritis, Kawasaki disease, Behçet's disease, thromboangiitis obliterans and erythema elevatum diutinum vasculitides, may provide a basis for a rational approach to the development of an anti-angiogenic therapy.

It is well established that the angiogenic phenotype results from the imbalance between positive and negative regulator factors, so that the contribution of each angiogenic factor may play a different role in the definition of the angiogenic phenotype in vasculitides, when increased production of angiogenic stimuli and/or reduced production of angiogenic inhibitors may lead to abnormal neovascularization.

The development of a clinical trial requires the identification and characterization of the physiological targets involved in angio-stimulatory and angio-inhibitory activities.

Angiogenesis inhibitors are now being approved and introduced into medical practice throughout the world. Much research has been concentrated on the role of angiogenesis in cancer, and inhibition of angiogenesis is a major area of therapeutic development for the treatment of this disease. It is conceivable that this therapeutical approach might involve also the treatment of chronic inflammatory diseases, such as vasculitides.

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