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EDITORIAL

Soluble Fms-Like Tyrosine Kinase-1

– A Novel Marker for Atherosclerotic Progression? –

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Angiogenesis is the sprouting of new capillaries from pre-existing microvasculature that supports tissue growth and repair under physiological conditions.[1,2] Although a dynamic equilibrium exists between pro-angiogenic and anti-angiogenic factors, impairment of this balance accompanies many different diseases. For example, while pathological excessive neovascularization is characteristic for tumors, diabetic retinopathy, rheumatoid arthritis, psoriasis, endometriosis and atherosclerotic plaques, the presence of impaired ineffective angiogenesis is a common feature in patients with cardiac (or peripheral limb) ischemia, diabetes, hypertension, pre-eclampsia and nephropathy.

Article p2211

Among a myriad of factors, implicated in the regulation of different aspects of angiogenesis, vascular endothelial growth factor (VEGF) represents a key promoter of the generation of new vessels. VEGF is a potent hypoxia-regulated angiogenic factor and multifunctional cytokine for endothelial cells, which express 2 main types of VEGF receptors: VEGF receptor type 1 (soluble fms-like tyrosine kinase-1) (VEGFR-1/flt-1) and VEGF receptor type 2 (flk-1/KDR), which might have important roles in angiogenesis.[3] Ischemia accompanied by increased oxidative stress and expression of hypoxia-inducible factor-1 markedly upregulates the production of VEGF by ischemic tissues, which is subsequently followed by the induction of angiogenesis.[4]

VEGFR-1 is expressed on endothelial cells, monocytes and macrophages.[5] Stimulation of the receptor triggers intracellular tyrosine kinase activity thus regulating monocyte/macrophage mediated processes that have been implicated in the pathogenesis inflammatory disorders, cancer metastasis, and atherogenesis. The soluble form of flt-1 is overexpressed in the placenta of pre-eclamptic pregnant women, and believed to be associated with maternal hypertension and renal dysfunction.[6] This might result from blockade of the 'physiological' VEGF function(s), some of which might not be fully elucidated.

A recent post-mortem study established the presence of strong links between the severity of the atherosclerotic lesions and intraplaque vascularization.[7] Noteworthy, in atherosclerotic lesions in human coronary arteries, VEGF released from smooth muscle cells and foamy macrophages acts as a local endogenous regulator of endothelial cell function and actively promotes intimal neovascularization[7,8]

However, possibly because of the complex nature of the processes regulated by VEGF and sFlt-1 no robust evidence exists on the direct relationship between their levels and angiographically defined disease severity in patients with coronary atherosclerotic disease. One recent experimental study found that abnormal adventitial angiogenesis can promote intimal thickening and atherogenesis.[9] However, the available evidence does not support the hypothesis that excessive adventitial vascularization might serve as a trigging factor of intimal thickening.[9]

VEGF has also been shown to influence vascular remodeling given that its abnormal levels are associated with restenosis after percutaneous coronary interventions.[10] In contrast, a recent study has demonstrated that sFlt-1 might act as an endogenous antagonist of the pro-atherogenic placental growth factor and thus, delay the progression of atherosclerosis in patients with renal dysfunction.[11] An experimental animal model has since been employed to confirm the hypothesis, showing that reduced levels of the sFlt-1 are associated with the accelerated progression of atherosclerosis that accompanies renal dysfunction.[11]

In this issue of Journal, the study by Shin et al evaluates the association between sFlt-1 and the progression of carotid intima-media thickness (IMT) in hypertensive patients.[12] High levels of sFlt-1 predicted carotid IMT progression in hypertensive patients and the authors propose that this biomarker can be used as an indicator for the progression of atherosclerosis.[12] A multivariate analysis identified sFlt-1 levels and low high density lipoprotein cholesterol levels as predictors of carotid IMT progression.

Although recent experimental studies indicated that adventitial angiogenesis could stimulate intimal thickening,[9] the study by Shin et al[12] is the first prospective follow-up study that assessed the potential relationship between carotid IMT progression (a widely accepted marker of atherosclerosis) and sFlt-1. The association between the carotid atherosclerosis and VEGF and sFlt-1 levels were also investigated in 909 healthy middle-aged participants of a cross-sectional substudy of the 'Salzburg Atherosclerosis Prevention Program in Subjects at High Individual Risk (SAPHIR)' study.[13] This study found significant gender differences in VEGF and sFlt-1 concentrations, whereby VEGF levels were lower and sFlt-1 levels were higher in men when compared to women. Although VEGF was found to be significantly positively cor-

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related with age, body mass index, insulin resistance, white blood cell and platelet count, C-reactive protein, only a weak correlation was established between the plasma VEGF, sFlt-1 levels and carotid IMT.[13] Also, this substudy of SAPHIR trial was conducted on healthy participants and had no long-term follow-up results. Thus, the study by Shin et al has established similar cross-sectional findings with no difference in carotid IMT between lower, middle and high tertiles of sFlt-1 levels.[12]

The involvement of VEGF (especially VEGF-A) in the pathogenesis of atherosclerosis is not limited by the effects on the plaque and adventitial angiogenesis, and VEGF-mediated pathways appear to a play a role in the recruitment of atherogenic macrophages to the sites of plaque formation. Indeed, treatment with sFlt-1 in an animal model of atherosclerosis results in prominent suppression of the atherogenic process.[14] Additional evidence supporting the importance of VEGF-VEGFR-1 signaling comes from a model using VEGFR-1 Tyrosine kinase (–/–) mice, which have diminished accumulation of macrophages in the arterial wall and decreased atherogenesis.[15] VEGFR-1 plays also a critical role in the reconstitution of bone marrow, perhaps as a backup system when the M-CSF system is severely suppressed.

The balance of potentially beneficial effects of VEGF pathway (eg, angiogenesis and vasculogenesis in ischemic tissues) and presumably detrimental activities (eg, intraplaque angiogenesis and excessive macrophage mobilization) ultimately depends on myriads of biological and microenvironmental confounders. For example, soluble forms of flt-1 and flk-1 induce an endothelial nitric oxyde synthase (eNOS) with a mechanism dependent upon outgrowth of a mural cell network and in turn, this accelerates the mural cell coverage of neovessels, promote mural cell migration towards endothelial cells, and stimulate endothelial S1P1 overproduction and eNOS activation that is critical for the induction of the recruitment of neighboring mural cells.

The study by Shin et al[12] further advances the field providing evidence for an important role of sFlt-1 in the orchestration of cell recruitment (eg, pericytes, smooth muscle cells) into the vascular wall. Although these cells might be important for both angio-/vasculo- genesis and atherogenesis, the precise mechanisms driving and potentially separating these processes are beyond the scope of the last study and need further investigation. Indeed, soluble receptors of VEGF appear to regulate the interactions between VEGF and its membrane connected receptors, and might thus represent a physiological feedback mechanisms responsible for the prevention of the excessive VEGF stimulation. Hovewer, more research is required to shed further light on the regulation of (anti)angiogenic processes in ischemic tissues and establish approaches to their therapeutic manipulation.

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