Possible New Role of Vascular Endothelial Growth Factor-D During the Acute Phase of Kawasaki Disease

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Kawasaki Disease (KD) was first reported in 1967, yet the cause has not been established. A relationship between KD and vascular endothelial growth factor (VEGF) was initially established 13 years ago.¹⁻³ In this issue of the Journal, Ebata et al describe a role for VEGF-D during the acute stage of KD and report that its expression increased during lymphangiogenesis.⁴ Here we review the role of VEGF in KD and its possible role during the acute phase of KD, especially in the development of coronary artery lesions (CAL).

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KD is the most common systemic vasculitis syndrome primarily affecting small and medium sized arteries, particularly the coronary artery. Although timely treatment with high-dose intravenous immune globulin (IVIG) is now accepted as reducing the incidence of CAL, approximately 15% of patients do not respond to IVIG treatment and are at the highest risk for developing CAL.

The etiologic nature of KD and the pathogenesis of CAL largely remain to be determined. Previous histopathologic studies revealed that early coronary vascular lesions are infiltrated by a large number of mononuclear cells, such as macrophages and lymphocytes, leading to the assumption that these cells play a key role in the progression of CAL. In acute KD, the migration and proliferation of endothelial cells have been demonstrated to be markedly enhanced by cytokines. As a matter of fact, during the acute phase of KD, serum levels of proinflammatory cytokines are elevated.⁵ In addition to these proinflammatory cytokines, expression of VEGF, and of markers of local inflammation, including the family of damage-associated molecular pattern molecules, such as myeloid-related protein (MRP) 8/MRP14 and S100A12, which respond to initiation of the innate immune response, increases during acute KD and plays a crucial role in inflammation.^{3,6,7}

VEGF and their endothelial tyrosine kinase receptors are central regulators of vasculogenesis, angiogenesis and lymphangiogenesis. VEGF is expressed by a variety of cell types, including aortic smooth muscle cells, macrophages, and myocytes. In addition, lymphocytes, neutrophils, and platelets have recently been shown to express VEGF. Currently, 7 members in the VEGF family have been identified: VEGF-A, -B, -C, -D, -E (viral VEGF analogs), -F (snake venom VEGFs),

and placental growth factor. VEGFs belong to the platelet-derived growth factor/VEGF superfamily of secreted dimeric glycoprotein growth factors that contain a cysteine knot motif consisting of 8 regularly spaced cysteine residues. The VEGF ligands bind with differing specificities to 3, mostly endothelial transmembrane tyrosine kinase, receptors: VEGFR-1/fms-like tyrosine kinase (Flt) 1, VEGFR-2/human kinase insert domain receptor/mouse fetal liver kinase 1 and VEGFR-3/Flt 4 (Figure). All VEGFRs have a conserved intracellular split tyrosine kinase domain and a series of extracellular Ig-like domains. Neuropilins-1 and -2, originally identified as semaphoring receptors, function as coreceptors for specific VEGFs. They share a common structure, yet they bind VEGFs with distinct affinities and specificities.

VEGF-D (also known as *c-fos*-induced growth factor) is secreted into the extracellular space as a full-length VEGF-D homodimer. After secretion, proprotein convertases cleave the C- and N-terminal propeptides from the VEGF-homology domain to form the mature VEGF-D, which binds to VEGFR-2 and -3 with higher affinities than the full-length unprocessed VEGF-D (Figure). However, as VEGF-D seems to be largely dispensable for the development of the lymphatic system, its physiological role remains unclear. Vascular endothelial cells express VEGFR-2, and its expression is upregulated *inter alia* by angiogenesis. VEGF-D exerts angiogenic effects on binding to VEGFR-2, whereas when bound to VEGFR-3 on lymphatic endothelium it stimulates lymphangiogenesis (Figure). VEGFR-3 is initially widely expressed in endothelial cells during murine embryogenesis, but later in development its expression becomes largely restricted to the lymphatic endothelium.⁸ In adult human tissues, VEGFR-3 is specific to the lymphatic endothelium, with the exception of some fenestrated and discontinuous blood capillary bed.⁹ VEGFR-3 phosphorylation has been shown to lead to PI3K-dependent Akt activation and PKC-dependent activation of the p42/p44 MAPK pathway.¹⁰

It has been suggested in several studies¹⁻³ that VEGF has a key role in the deterioration of vasculitis in the acute phase of KD. The studies have shown that serum and plasma levels of VEGF are significantly elevated in both the acute and subacute phases of KD and that circulating levels could be associated with the risk of developing CAL. It has been hypothesized that the high levels of VEGF could contribute to the pathologic findings observed in vascular tissue in KD,

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such as subendothelial edema, gap formation, and fenestrations of endothelial cells.¹¹ Several single-nucleotide polymorphisms in the *VEGF* gene have been found to be associated with differences in VEGF protein production.¹²

There have been many studies reporting a role for VEGF in KD, but the study by Ebata et al represents the first report of a relationship between VEGF-D and KD. They conclude that serum VEGF-D levels increased after IVIG therapy in patients with acute KD and were significantly lower in patients with CAL compared to those without CAL. They also showed that the cross-sectional areas of lymphatic vessels in cardiac tissues were enlarged in patients with acute KD while VEGF-D protein was detected on the endothelium of the enlarged lymphatic vessels. Lymphatic vessels are thought to be maintained in a collapsed state and are important for the drainage of interstitial fluid under pathological conditions.¹³ Therefore, these new findings might reflect disruption or insufficiency of the regulation of lymphangiogenesis mediated by VEGF-D during the acute stage of KD.

Although further studies are required to elucidate the mechanism of how VEGF-D affects the outcome of KD, the evidence so far suggests that VEGF-D plays an important role and may serve as a biomarker for KD, as well as providing a novel therapeutic target.

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