Another Possibly Important Function of VEGF Related to Polyneuropathy

**Key words:** dematomyositis, polyneuropathy, vasculopathy, VEGF

Polyneuropathy occurs in collagen diseases such as polyarteritis nodosa (1), rheumatoid arthritis (RA) (2) and systemic lupus erythematosus (SLE) (3), which are also accompanied by vasculitis. Several reports of patients with polyneuropathy have referred to involvement of the peripheral neurons in vasculitis, and to expression of adhesion molecules (2).

In this article, I refer to the important function of vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) in accentuating the permeability of blood vessels and in destructing the blood-neuron barrier related to polyneuropathy.

VEGF was first detected in tumor ascites in promoting vascular permeability in an animal model in 1983 (4), thereafter Ferrara and Henzel (5) and Plouet et al (6) independently reported that this protein upregulates vascular endothelial proliferation. This protein was named VEGF or vasculotropin. These two proteins were revealed to be the one in the same, and it has been mainly called VEGF, and is known to be one of the most potent vascular proliferating factors (7). VEGF comprises dimers and the molecular structure is similar to that of PDGF. VEGF is produced by endothelial cells and many kinds of cells around the blood vessels, acting as paracrine and also as autocrine. Although the multifunction of VEGF such as gene expression for the induction of proteolytic enzymes, promotion of cell migration, upregulation of proliferation and suppression of apoptosis are well known, another function which is not widely known is that VEGF has very potent vascular permeability of more than 50 thousand times over histamine (8). Although the mechanism of vascular permeability by VEGF has not been well analyzed, it is thought to be due to upregulation of vesiculovascular organelle (VVO) formation in the endothelial cytoplasm and enlargement of the intercellular gap junction of each endothelial cell (9). When stimulated by VEGF, VVO filled cytoplasm are released to outside with transportation of serum and intracellular substances. Proteins comprising the gap junction and adherence junction are the targets of VEGF when enlarging, and signals for vascular permeability are mediated by KDR/FLK-1 receptor (10). From the experimental studies src is thought to be one of the candidates that mediates the signals for accentuating vascular permeability (11).

Crow-Fukase syndrome is a well known disease with an intimate relationship between VEGF and polyneuropathy that is also called POEMS syndrome accompanied by Polyneuropathy, Organomegaly, Endocrinopathy, M-proteinemia and Skin changes. Clinically, patients present neuroedema and exudation of plasma components by elevation of vascular permeability, polyneuropathy, pulmonary hypertension, glomerulosclerosis, dermal sclerosis, hepatosplenomegaly, and accentuation of coagulo-fiblynolytic system associated with elevation of VEGF level in serum (12). If we have more interest and carefully observe the patients from the point of relationship between expression of VEGF and polyneuropathy, the reports related to such cases will increase.

Polyneuropathy with demyelination is associated with the expression of VEGF and VEGFR in the blood vessels, muscle and skin in dermatomyositis (13). VEGF and VEGFR may co-activate the elevation of vascular permeability and lead to the destruction of the blood-neuron barrier. This case showed the local expression of VEGF and VEGFR in the blood vessel, skeletal muscles and skin, but no systemic effects as seen in Crow-Fukase syndrome. The local expression of VEGF and VEGFR on blood vessel wall and surrounding tissue associated with polyneuropathy has not been discussed in many reports except for RA until now. Only a few cases with RA were reported in expressing VEGF on the synovial cells and endothelial cells in inflammatory synovia (14), in which some kinds of adhesion molecules are suggested as candidates that induce polyneuropathy. If the production and expression of VEGF on blood vessels is concerned with polyneuropathy in collagen disease, some kinds of antibodies such as antiendothelial cell antibody (AECA) or other some growth factors such as TGF-β may also participate in stimulating VEGF expression.

It will be important to study more clinical cases and carefully examine the relationship between polyneuropathy and expression of VEGF and VEGFR in dermatomyositis and other collagen diseases. Apart from the differentiation and proliferation of blood vessels, if we carefully observe the expression of VEGF from the point of vascular permeability,
the number of polyneuropathy cases with local expression of VEGF and VEGFR may increase in collagen disease. Whether or not the polyneuropathy is due to vasculopathy mediated by VEGF depends on documenting further clinical evidence as well as experimental proof.

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References