Vascular Endothelial Growth Factor and Platelets

Key words: VEGF, DIC, serum, platelets, megakaryocytes

Vascular endothelial growth factor (VEGF) is one of the potent angiogenic polypeptides produced by multiple tissues. This polypeptide is known to be overexpressed in pathological or physiological events of neovascularization; inflammatory diseases, autoimmune diseases, solid tumors or hematological malignancies, wound healing, ischemic diseases and cyclic changes of the ovary and endometrium.

The concept of neovascularization in adult tissues has recently been established, i.e. neovascularization may involve vasculogenesis previously thought to only be recognized in embryogenesis, in addition to angiogenesis. Angiogenesis is defined as the development of sprouts of new blood vessels from pre-existing vasculatures caused by fully differentiated endothelial cells (ECs) (1). Also, by the demonstrated existence of endothelial progenitor cells (EPCs) derived from bone marrow (BM) in adult peripheral blood, post-natal vasculogenesis has been thought to be involved in pathological and physiological neovascularization of adult tissues (2).

Not only has VEGF been shown to induce migration and proliferation in vascular fully differentiated endothelial cells, but also to mobilize EPCs from BM, leading to neovascularization (2).

Based on such roles of VEGF in neovascularization, consideration of the circulating level of VEGF in peripheral blood may be an essential clue especially to grasp the pathogenesis or prognosis, and to determine the therapy in pathophysiological situations. In fact, the level of circulating VEGF in peripheral blood has been shown to be associated with angiogenesis, growth, dissemination, metastasis, and poor outcome in solid or hematological malignancies (3-6). Accordingly, for clinicians, knowledge of measurement of the VEGF level in peripheral blood should be emphasized.

As stated; the present report by Murata et al (7), we must consider the origin in markedly high levels of serum VEGF, i.e. it should be considered that platelets (or megakaryocytes) could be a massive source of VEGF production, and that VEGF measurement using serum isolated through coagulation might have an effect on the level.

Additionally, VEGF-C, which specifically promotes lymphangiogenesis by receptor binding (VEGFR-3), mainly expressed in lymphatic endothelium (8), is demonstrated to also be released from activated platelets (9). The circulating VEGF-C level in the patient might be remarkably high, leading to swelling of endocapillary cells and proliferation of the capillary in the inguinal lymph node biopsy of this report.

Not only in systemic diseases such as hematological malignancies (5, 6) or the present reported clinical case (7), but also even in local diseases such as ischemia, solid tumors, or wound healing, activated platelets has been proposed as one of the critical origins of VEGF production (10).

Although there is no report which describes the upregulated circulating VEGF under disseminated intravascular coagulation (DIC), it is easily speculated that the extremely high value of VEGF in serum of the patient might be caused via VEGF release in activated platelets (or megakaryocytes) (11), other than monocytes or macrophages, induced by DIC. Thrombin produced in a coagulation abnormality such as DIC cleaves the N-terminus of the thrombin receptor as a substrate, exposing a new N-terminus. This newly exposed N-terminus (thrombin receptor activating peptide= TRAP) acts as a ligand and activates platelets (12). Experimentally, VEGF polypeptide was released from platelets activated by TRAP into the supernatant and the VEGF level of supernatant was over 10 fold as compared to that in resting platelets (9). Alternatively, it has recently been reported that in some subtypes of myelodysplastic syndrome, neovascularization in BM is promoted as recognized in acute myeloid leukemia and that VEGF is prominently expressed in activated megakaryocytes in BM (13). Myelodysplasia in that report might involve activated megakaryocytes overexpressing VEGF in BM, predictably leading to the production of activated platelets.

Furthermore, we have to consider the measurement of VEGF using serum from the patient, except for the pathophysiological situation described above. As previously reported by Banks et al, the process to isolate serum through blood coagulation causes the activation of platelets automatically, leading to the release of VEGF into serum. And also, even in healthy volunteers, VEGF level in serum was variable among interindividuals and remarkably high as compared to citrated plasma (10). For accurate measurements, they recommend citrated plasma processed within one hour of obtaining peripheral blood, using either glass or plastic tubes to avoid the secondary release of VEGF from activated platelets after puncture (10).

Conclusively, the markedly high level of circulating VEGF may be explained by the pathophysiological conditions of DIC inducing activated platelets in the patient and the measurement of circulating VEGF using serum. Data on the circulating VEGF level in DIC must be studied in the future.
References