The Importance of Platelet Counts and Their Contents in Cancer

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VEGF, a potent angiogenic growth factor, plays an important role in several pathophysiological processes including tumorigenesis. It is presumably involved in the angiogenic switch from the initial avascular phase of a microscopic tumor into a progressively, rapidly growing and metastasizing tumor by stimulation of new vessel formation. Because of this important role, many investigators have been studying whether circulating VEGF can be used as a prognostic marker in patients with different cancer types, including breast cancer. These kind of studies have been performed since the beginning of the 90s, reviewed by Hormbrey et al. (1). In this review, the differences between the methods that were used for obtaining and measuring plasma and serum VEGF in these studies were compared, and they proposed a standardized way to collect and measure VEGF in blood samples of cancer patients.

After initial reports that serum VEGF is increased in cancer patients, we published in this journal in 1997 that serum VEGF concentrations in breast cancer patients were determined by platelet counts and not by tumor burden (Fig. 1). We found that platelets release VEGF on activation. Therefore, we predicted that plasma VEGF instead of serum VEGF concentrations should be studied as a marker for tumor progression (2). In addition, we found evidence that platelets may be involved in tumor-induced angiogenesis because of their release of angiogenic growth factors on activation by angiogenic endothelium (3). Apart from VEGF, platelets contain several other angiogenic growth factors and inhibitors that are released on activation, including platelet-derived endothelial cell growth factor, transforming growth factor-β, hepatocyte growth factor, thrombospondin, and even endostatin (4).

In addition, other studies report an increased VEGF content of platelets from cancer patients compared with healthy volunteers (5, 6).

Now, 6 years later, the dispute is still ongoing whether serum VEGF or plasma VEGF should be used as a marker of tumor progression or prognosis. Some studies show that platelet-poor plasma reflect more accurate tumor progression (7), whereas others found that serum VEGF gives a better indication of tumor progression (6).

Heer et al. (8) published earlier in this journal that serum VEGF detects breast cancer preoperatively with a sensitivity of 62.1%. In addition, they show a relation with the estrogen positivity of the tumors and VEGF levels. In this issue of Clinical Cancer Research, Murphy et al. (9) question again whether these measurements of serum-VEGF are meaningful, because they published earlier that plasma VEGF but not serum VEGF is elevated in breast cancer patients when these levels were compared with healthy volunteers (10; see Letters to the Editor in this issue). Taken the different studies together, the question remains whether serum-VEGF or plasma-VEGF should be determined.

When taking these different opinions and findings together, what do they tell us about tumor biology? Is it possible that tumors stimulate the megakaryocytes in the bone marrow to generate increasing amounts of platelets that contain more VEGF? If so, which tumor-released factor is responsible for this, and secondly, what is the effect on tumor progression?

It is well known that tumors can stimulate the bone marrow; for example, it has been shown that tumors promote the mobilization of progenitor endothelial cells from the bone marrow, and presumably VEGF plays an important role in this pathway (11). In addition, it has been shown that tumors initiate intratumoral activation of the coagulation cascade including platelet activation (disseminated intravascular coagulation; Ref. 12). Furthermore, platelets have been shown to contain TPO and release it on activation. TPO is the specific cytokine that stimulates megakaryocytes in the bone marrow to generate platelets. Folman et al. (13) suggested a self-regulatory vicious circle of platelet counts and the bone marrow controlled by TPO. In response to an injury of the vessel wall or any other local thrombogenic process, platelets attach to the vessel wall and subsequently become activated and release their contents, including TPO. On its turn, this platelet-released TPO stimulates the bone marrow to generate new platelets into the circulation.

We hypothesize that activated platelets in the tumor vasculature release TPO, and thereby stimulate bone marrow generation of platelets (Fig. 2). As a consequence of our hypothesis, an increased number of platelets will reach the circulation as we often see in cancer patients. On the basis of this hypothesis both plasma VEGF and serum VEGF may be important to indicate tumor activity. Plasma VEGF may be increased because of direct tumor release of VEGF, and by tumor-induced intravascular platelet activation and subsequent VEGF release. On the other hand, elevated serum VEGF may be the consequence of increased platelet numbers in cancer patients caused by intratumoral platelet activation and subsequent release of TPO.

In conclusion, as mentioned before, we strongly recommend in any study regarding circulating VEGF to include plasma and serum levels, and platelet counts. Hopefully we will come to a better understanding of what role circulating growth factors and platelets play in tumor biology. In the end, it might well be that just a simple platelet count is a better prognostic

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2 The abbreviations used are: VEGF, vascular endothelial growth factor; TPO, thrombopoietin.
factor compared with plasma or serum VEGF concentrations in cancer patients (14, 15).

References


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