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Importance of platelets in VEGF-mediated agiogenesis in tumors

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We read with interest the article published by Selheim and colleagues [1]. They demonstrate that activated platelets expose both VEGF receptors, Flt-1 and KDR. Katoh and colleagues have previously demonstrated the presence of the mRNA of the VEGF receptor, KDR, in platelets and Salgado and colleagues showed with immunoelectron microscopic techniques that platelets might bind VEGF [2,3]. Selheim et al. provide additional data supporting a role for VEGF in enhancing thrombin-mediated platelet activation and aggregation. Their results add to the importance of platelet VEGF in tumoural angiogenesis. Previous studies have demonstrated that platelets of cancer patients acquire a higher VEGF load parallel to tumour progression [3]. We elaborated on how platelets acquire this higher VEGF load. Two mechanisms were proposed: endocytosis of circulating VEGF, and/or enhanced VEGF production in the platelet precursors, the megakaryocytes. The presence of VEGF on the platelet membrane might suggest that endocytosis could occur since receptor-mediated endocytosis of circulating proteins, e.g. fibrinogen, into the α-granules of platelets has been described. We analysed the distribution of [^{125}I]VEGF in the platelets of five healthy individuals and five cancer patients after adding [^{125}I]VEGF to whole blood. Median counts per minute in the platelet fraction was $50.9/10^3$ platelets (S.D. 15.4) for the cancer patients compared with $21.8/10^3$ platelets (S.D. 8.4; $P = 0.08$, paired t-test) for the healthy persons, indicating enhanced VEGF binding on the platelets of the cancer patients. As the authors noticed, activation of platelets exposes both VEGF receptors. It is known that circulating platelets of cancer patients are activated, indicated by the increased expression of adhesion molecules on the platelet membrane and of high circulating levels of platelet activation markers, e.g. β-thromboglobulin, in the plasma of cancer patients [4]. This may account for a higher exposure of the VEGF receptors on the membrane and thus for a higher probability of scavenging circulating VEGF. It remains to be identified whether membrane-bound VEGF, after transmitting signalling into platelets, may also be endocytosed and transported to the platelet α-granules accordingly. We did not succeed in demonstrating incorporation of exogenously added VEGF to platelet-rich plasma into platelets, which may be partly explained by incomplete activation of the platelets necessary to express the VEGF receptors. On the other hand, we have demonstrated that platelet VEGF may also be derived from enhanced VEGF expression in platelet precursors, megakaryocytes, mediated by tumour-derived interleukin-6 (unpublished data). Furthermore, immunohistochemistry for platelets demonstrated adhesion and aggregation on tumoural endothelium, which is invariably related to the release reaction of VEGF [5]. We elaborated on the additional importance of the higher platelet VEGF load in enhancing in an autocrine manner the platelet activation, aggregation and thus local release of VEGF at sites of coagulation, in this case tumours. A higher platelet VEGF load is associated with fast tumour growth kinetics and is associated with worse survival in patients with cancer [6]. The observations of Selheim and colleagues therefore add to the importance platelets can have in intra-tumoural angiogenesis. Moreover, since anti-angiogenic trials aimed at inhibiting the VEGF receptor tyrosine kinase pathway are currently undergoing clinical trial, additional indirect anti-angiogenesis effects might also be achieved by blocking the MAPK and PI-3 kinase pathways in platelets. Since these pathways are, as Selheim demonstrated, equally involved in endothelial cells as well as platelets, blocking the VEGF-mediated activation and aggregation may diminish the intra-tumoural local release of platelet VEGF.

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