Angiogenesis and platelets: the clot thickens further

Andrew D. Blann*

Haemostasis, Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Dudley Road, Birmingham, B18 7QH, UK

Received 10 May 2004; accepted 14 May 2004

Available online


Pathophysiological aspects of platelet biology have, until recently, focussed on their relatively passive and reactive roles in minimising blood loss after injury, in contributing to the final stages of cardiovascular disease (largely in the inappropriate formation of life-threatening thrombosis), and on attempts in the clinic, the cardiac catheter suite, and on the ward to reduce the latter with anti-coagulant and anti-platelet agents. However, there is currently a growing awareness that another pathophysiological process, inflammation, may be important in atherosclerosis and acute coronary syndromes and, as a result, could have a role in platelet biology [1]. Among the various lines of evidence supporting this concept include the expression by platelets of integrin and adhesion molecules (such as P-selectin and CD154, the ligand for CD40) designed to enhance contact with the endothelium and leukocytes (possibly activating the transcriptional factor nuclear factor-κB) and the presence within the platelet of vasoactive molecules such as prostacyclins and thromboxanes, platelet-derived growth factor (PDGF), transforming growth factor-beta, and nitric oxide. Indeed, these and other data (e.g. adhesion of platelets to the endothelium prior to the development of manifest atherosclerotic lesions [2]) have prompted Gawaz to place platelets much closer to the centre of cardiovascular disease, hypothesising that platelets actually trigger atherosclerosis [3].

Lest we forget, our colleagues in oncology have long had an interest in coagulation and the platelet, and thus, in thrombosis. For example, patients with cancer are at risk of venous thromboembolism, have raised plasma fibrinogen, von Willebrand factor, and fibrin degradation products, and thrombocytosis can be used as an independent prognostic indicator [4]. However, a more cancer-specific role for the platelet in this disease has been proposed by Pinedo et al. [5], who suggest that differences in the release of pro-angiogenic (e.g. PDGF, angiopoietin) and anti-angiogenic (e.g. platelet factor 4, thrombospodin) factors by this cell modifies the angiogenic balance of a tumour and its ability to metastasise. Data supporting this hypothesis have been produced by several groups that have shown not only that platelets carry the pro-angiogenic vascular endothelial growth factor (VEGF) but also that they release it upon activation by thrombin [6,7]. Similarly, Caine et al. [8] have reported that the inflammatory cytokine IL-6 can cause the dose-dependent release of VEGF from normal platelets in vitro, whilst Rosselli et al. [9] have demonstrated a strong correlation between VEGF and platelet counts as well as with a plasma marker of platelet activation (soluble P-selectin) in both squamous and adenoma variants of non-small cell lung cancer, suggesting that the platelet could be an important source of this growth factor.

But what of cardiovascular disease? Just as possible roles for inflammation have been developing, there has been an increasing realisation that angiogenesis may also be important in collateralisation, vascularisation of the media, and plaque formation [10,11]. In support of this is the report of increased levels of circulating VEGF in stable coronary artery disease, peripheral artery disease, and diabetes [12]. Whilst increased VEGF levels in these situations may be seen as valuable in promoting collateralisation [11,13], it may also reflect vascular dysfunction. Of more concern is the report that raised levels of VEGF predict an adverse prognosis, although this study may be marred by the measurement of the growth factor in serum [14]. Nevertheless, as a corollary of the above, it is entirely possible that platelets, either circulating freely or whilst deposited as a thrombus, may release VEGF, which may then act on nearby endothelium and thus contribute directly to angiogenesis. Indeed, the finding of VEGF localised within the fibrin net of a thrombus partially supports this hypothesis [7].
In an elegant series of in vitro and animal models, the report by Brill et al. [15] in the present issue of Cardiovascular Research provide additional evidence of the importance of the platelet. Using in vitro rat aortic ring and in vivo murine models, they show that endothelial cell outgrowths promoted by platelets are reduced by inhibition of VEGF receptor phosphorylation and promoted further by the blocking of platelet factor 4 or the activation of platelets by thrombin, providing an additional perspective of the potential for a role of platelets in angiogenesis. Attempts to block these effects with glycoprotein IIb/IIIa inhibitors was unsuccessful, suggesting other mechanisms, although platelets treated with agents suppressing ADP and cAMP did result in significantly weaker angiogenesis. Of course, purists may argue that these models fail to address the effects of other cells and systems, particularly of the endothelium itself in vivo, that are likely to have an impact on angiogenesis. Of further note is the possibility that their rodent models for angiogenesis may not accurately reflect the process in our own species, although this criticism can be levelled at all animal work. However, what is clear from this work is that it provides additional evidence of the need to continue to study the platelet and find means to prevent inappropriate activation.

In the beginning, the platelet was viewed as being simply a mechanism for staunching blood loss. Later, roles in inflammation [1] and in nitric oxide biology were proposed [16]. We are currently witnessing an accumulation of data suggesting that this cell has an additional role, i.e. in angiogenesis, which may be related to classical growth factors such as VEGF and angiopoietins or to certain phospholipids such as sphingosine-1-phosphate [17]. We already know that aspirin is beneficial in certain cancers [18], and it is now tempting to contemplate mechanism(s) for this [16], but whether or not this translates into new cardiovascular therapies and thus improved patient care can only speculated upon.

References