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## Platelets: The Universal Killer?

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**Abstract**

For many, the final terminal event in life is cessation of the heart beat. In turn, this is generally because this organ has been deprived of oxygen and glucose as the blood can no longer deliver these requirements to the myocardium. The principal reason for this is blockage of one or more coronary arteries or arterioles by platelet rich thrombus. A similar process exists for the pathophysiology of stroke – a debilitating and often fatal event caused by occlusion or rupture of arteries in, or feeding, the brain. These scenarios are best developed in cardiovascular disease, but apply to almost all human disease. Therefore, the ultimate culprit for these major life events is the overactive platelet - too ready to form an inappropriate thrombus. Thus, one way forward in postponing an occlusive thrombotic event is to minimise platelet activation, new tools and treatments for which are eagerly sought.

Have platelets caused the greater proportion of human mortality and morbidity? What is their role in the cardiovascular, connective tissue and neoplastic disease that will strike the majority of the Western world and an increasing proportion of those in the developing world? Historically, pathophysiological aspects of platelet biology have focussed on their relatively passive and reactive roles in minimising blood loss after injury (desirable thrombosis), in contributing to the final stages of cardiovascular disease and its risk factors (largely in the inappropriate formation of life-threatening undesirable thrombosis), and on attempts in the out-patient and General Practice clinic, the cardiac catheter suite, and on the ward to reduce the risk of these thromboses with anti-coagulant and anti-platelet agents. Indeed, some data (e.g. adhesion of platelets to the endothelium prior to the development of manifest atherosclerotic lesions) have prompted the placement of platelets much closer to the centre of cardiovascular disease, hypothesising that platelets actually trigger atherosclerosis (1-3). But perhaps the most compelling evidence of the importance of this cell are the beneficial results of trials of anti-platelet drugs, of which the principles are aspirin and clopidogrel (4-6).

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 (7). Indeed, several commentators have mused that hypercoagulability precedes cancer (8). However, a more cancer-specific role for the platelet in this type of disease has been proposed by Pinedo et al (9), who suggest that differences in the release of pro-angiogenic (e.g. platelet derived growth factor, angiopoietin) and anti-angiogenic (e.g. platelet factor 4, thrombospondin) factors by this cell modifies the angiogenic balance of a tumour and its ability to metastasise. Data supporting this hypothesis has been produced by several groups, who have showed not only

that platelets carry the pro-angiogenic vascular endothelial growth factor but also release it upon activation by thrombin (10,11). Similarly, Caine *et al* have reported that the inflammatory cytokine IL-6 will cause the dose-dependent release of VEGF from normal platelets *in vitro* (12), whilst Rosselli *et al* (13) 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. It is therefore possible (at least in theory) that platelets may be important in angiogenesis and in wound healing.

Thrombocytosis and abnormalities in platelet function have long been a recognised feature of connective tissue diseases such as rheumatoid arthritis and systemic lupus erythematosus and, of course, aspirin is for many the first line of treatment (14-16). Increased numbers of platelet microparticles (fragments of cytoplasm) with pro-thrombotic potential (17) may contribute to the increased risk of disease in this group. However, the latter stages of the disease certainly involve thrombosis, such that the terminal events are cardiovascular (e.g. pulmonary embolism, myocardial infarction and stroke). Accordingly, rheumatoid disease may indeed be seen as an additional risk factor for cardiovascular disease in the same light as is diabetes and hypertension. Finally, inflammation (in the absence of a connective tissue component) has been strongly promoted as a player in the complex pathophysiology of atherosclerosis, and this extends to the platelet (12,18,19).

Thus the platelet and coagulopathy are target for each of the major disease processes that afflict our species (Table 1), but what tools do we have to study the pathophysiology of this cell? A major problem with the study of the isolated platelet (when obtained from venous

blood for studies such as aggregometry or adhesion) is that their fragile nature leads to the strong likelihood of an ex-vivo (and therefore artifactual) effect. Complex analyses such as are offered by flow cytometry may also provide useful, although possibly also artefactual, data, although this approach, by its nature, does not lend itself to high-throughput research. However, flow cytometry, directed towards surface molecules such as CD63 and gpIIb/IIIa (which binds fibrinogen), can be performed on whole blood, thus avoiding the preparation artefact of a purified population of platelets. A third opportunity to study this cell is by its secreted products. When activated (by, for example, thrombin or adenosine diphosphate), platelets release the contents of their alpha granules, such as beta thromboglobulin and platelet factor four, which can be measured in plasma by enzyme linked immunosorbent assay (ELISA). A parallel event in this degranulation is the appearance, at the cell surface, of the adhesion molecule CD62P, also known as P selectin, which can be detected by flow cytometry. However, using ELISA, a form of P selectin can also be found in the plasma (i.e. soluble P-selectin), and this product is becoming recognised as a valuable tool for assessing platelet activation *in vivo* and *in vitro* (20). This molecule may also, under certain circumstances, be found on the surface of the endothelial cell, leading to confusion in some minds regarding the origin of the plasma form. However, it is now clear that the platelet is the major source of soluble P selectin (20, and references therein).

These tools therefore, provide the opportunity to study the pathophysiology of thrombosis. However, some crucial questions can only be answered in animal model (presuming, of course, that the biology of the particular species reflects that of our species, which is frequently not the case (21)), and in this respect the P selectin knock-out mouse has proved fascinating (22). Nevertheless, some tools cannot easily be carried across species, and monoclonal antibodies (mAbs) are good example of this problem as those directed towards

humans invariably fail to react to the same molecules of common laboratory animals, frustrating the clinical scientists. But one source of frustration has recently been relieved by the production of a series of mAb's specific for rat P selectin. In the current issue of this Journal, Hirose et al report the development and application of such reagents from hybridoma cell lines using rat platelets stimulated with thrombin as immunogens (23). They use it to demonstrate that soluble P selectin could serve as a marker of lung inflammation and thus, by extrapolation, a new tool for studying thrombosis in this and other settings. An additional point of interest in the large variation in soluble P selectin between different strains of rat – a phenomenon not (yet) reported in our own species. These anti-rat P-selectin antibodies therefore may well open up a new field of potential research in this most common pathophysiology of human diseases.



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**Table 1****The Platelet in Human Disease**Cardiovascular disease

- Platelets are present in atheroma
- Rupture of the atheroma, alongside circulating thrombus, are responsible for acute coronary syndromes such as myocardial infarction and angina
- Platelets contribute to deep vein thrombosis and pulmonary embolism
- Anti-platelet drugs effective in postponing major clinical events such as myocardial infarction and stroke

Cancer

- Platelets carry vascular endothelial growth factor (although it is unclear whether or not this is clinically relevant)
- Patients with existing cancer are at risk of venous thrombosis
- Patients with an unexplained venous thrombosis are often found later to have an asymptomatic cancer

Connective tissue disease

- Raised platelet count often present in rheumatoid arthritis
- Increased numbers of pro-thrombotic platelet microparticles in systemic lupus erythematosus
- Connective tissue disease inevitable progresses to the cardiovascular system and thus major event such as venous and arterial thrombosis