Hotline Editorial

Polymorphisms of platelet receptors as risk factors in coronary thrombosis

Platelet participation in coronary artery disease has long been recognized. The formation of platelet-rich thrombi at the sites of fissured atherosclerotic plaques is a primary cause of unstable angina and, when the result is vessel occlusion, of myocardial infarction. Recent years have seen advances in our understanding of the molecular pathways through which platelets first attach then spread on exposed subendothelium[1-2]. In the coronary artery, vessel wall-bound von Willebrand factor and collagen are probably the primary substrates for platelets. Platelet adhesion to von Willebrand factor occurs through a major receptor, termed glycoprotein Ib, which exists on the platelet surface in the form of a complex formed by four gene products. Other receptors mediate platelet adhesion to collagen. Shear rate-dependent adhesion of platelets to von Willebrand factor (or collagen) leads to platelet activation and the expression of binding sites for fibrinogen and other adhesive proteins (also including von Willebrand factor) on another major glycoprotein complex, glycoprotein IIb-IIIa. This step is the key to platelet aggregation. The rapid binding of fibrinogen by way of identified peptide sequences leads to the formation of protein bridges that cross-link platelets together via glycoprotein IIb-IIIa complexes which are present at a high density on the platelet surface[3]. Soluble agonists present in the vicinity of the fissured plaque, such as ADP, thrombin or thromboxanes, also induce this process, acting through specific receptors and intracellular signalling pathways.

Inhibition of platelet function has long been considered to be an essential part of anti-thrombotic therapy in coronary artery disease. Aspirin has figured prominently in this strategy and provides substantial benefit, acting by inhibiting the formation of the active metabolites of arachidon acid by platelets[4]. Ticlopidine is also frequently used and acts on the ADP-induced activation pathway in platelets[4]. By inhibiting specific elements of the multiple activation pathways, these drugs leave others untouched, even when used in the presence of heparin, an inhibitor of soluble thrombin. The inhibition of glycoprotein IIb-IIIa function provides a way of inhibiting platelet aggregation as induced by all agonists. Nonetheless, the fact that an inherited haemorrhagic disorder, Glanzmann's thrombasthenia, is characterized by the presence of qualitative or quantitative defects of glycoprotein IIb-IIIa on platelets suggested that bleeding could be a problem in this approach[1].

Pioneering studies were performed using monoclonal antibodies to glycoprotein IIb-IIIa in in vitro studies and in animal models[5]. Fab fragments of one such antibody, 7E3, were synthesized in a chimeric, humanized, form (c7E3, ReoPro) and shown in the EPIC study to induce a significant additional benefit when administered with heparin as an infusion prior to angioplasty in patients with unstable angina[6]. Somewhat surprisingly, the benefit extended up to 6 months after the angioplasty, suggesting that c7E3 was inhibiting not only acute thrombotic events linked to the physical removal of the stentotic material with the balloon catheter, but also the process of late restenosis. Perhaps a clue to this effect lies in the fact that c7E3 interacts not only with glycoprotein IIb-IIIa, but also with Mac-1 and the vitronectin receptor, which, as part of the integrin family of receptors, share sequence homologies with glycoprotein IIb-IIIa. Although the bleeding tendency was increased in the EPIC study, the benefits appeared to outweigh the risks which, it was suggested, would be reduced by carefully controlling the heparin dose. Here, c7E3 was given as a way of preventing arterial thrombosis. However, just as fibrinolytic agents are administered to disperse fibrin-rich clots, the future of agents such as c7E3 may be in dispersing platelet-rich thrombi in acute situations. A whole series of new compounds are being tested as anti-glycoprotein IIb-IIIa drugs, including integrelin, a peptide inhibitor of fibrinogen binding to glycoprotein IIb-IIIa, other cyclic constructs of RGD peptides and chemically synthesized peptide mimetics some of which may be taken orally[4]. Time will tell which will be the most successful in a clinical context.

Diverse plasmatic risk factors such as an elevated plasma fibrinogen content, deficiencies of protein C or protein S, and the presence of the factor V Leiden mutation have received much publicity largely in the context of venous thrombosis. However, until now, little has been known about risk
factors on platelets in arterial disease, even though the platelet aggregation response to low doses of agonists varies appreciably among donors. This situation has now changed with the report in the New England Journal of Medicine by Weiss and his colleagues showing a high frequency of a particular polymorphism of glycoprotein IIIa in a group of 71 patients with myocardial infarction or unstable angina. The gene for glycoprotein IIIa is highly polymorphic. Among the changes is the leucine => proline substitution that accounts for the P1^A2/P1^A2 (HPA-1a/1b) alloantigen system. It is the prevalence of the P1^A2 allele, 2-1 times higher in the case patients of the present study (and 3.6 times higher among patients whose coronary artery disease was detected before the age of 60), that is creating so much interest as it was more predictive for arterial thrombosis in the study group than major cardiac risk factors such as hypertension, smoking, hypercholesterolaemia or diabetes. This paper is quite controversial for, up to now, incompatibility within this alloantigen system has been associated with the development of rare alloimmune thrombocytopenias.

Many questions are posed by the findings of the Johns Hopkins group. Firstly, their results should be confirmed in a much larger group of patients. Then it would be necessary to look at the way in which the presence of the P1^A2 polymorphism influences platelet function, since it cannot be ruled out that P1^A2 is bilaterally linked to another unidentified genetic marker which is the active factor. Perhaps it is not even platelets that are being affected because glycoprotein IIIa is also found as the second subunit of the vitronectin receptor (see above), a receptor widely distributed among endothelial cells, smooth muscle cells and chondrocytes among others. The vitronectin receptor has also been highly implicated in angiogenesis so perhaps the structure of the cardiac vasculature should be examined in P1^A2 positive individuals.

One wonders whether this interesting finding is the veritable tip of the iceberg. As I have noted previously, known size differences within glycoprotein Ib could also influence platelet function, whereas the seven transmembrane domain receptor family, which includes receptors for such platelet stimuli as thrombin, PAF, thromboxanes, and adrenaline is notoriously polymorphic. The influence of these other genetic variations also needs to be examined in a cardiovascular disease setting. Polymorphisms can also control the number of receptors and cells as well as affect function and it may be predicted, for example, that patients with a low circulating platelet count or a low platelet glycoprotein IIb-IIIa content may be less susceptible to forming an occlusive thrombus than those with high numbers. It may be that a high 'score' of cellular and plasmatic risk factors will prove to be an efficient way of selecting patients for adjunctive (and relatively expensive) new generation anti-platelet therapy, such as that provided by c7E3. For the present, it is important that studies such as those conducted by Weiss et al, be continued and expanded to include other categories of patients, such as those with platelet-rich thrombi resistant to fibrinolytic therapy. The molecular biology tests are relatively simple and should be performed in combinations (P1^A2, factor V Leiden etc). I think that we are now on the right track, but that the train is not yet in the station.

A. T. NURDEN
UMR 5533 CNRS,
Hôpital Cardiologique, Pessac, France

References