Platelet function and arterial thrombosis

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Over the last decade, efforts aimed at unraveling the mechanisms responsible for arterial thrombosis and developing new antithrombotic treatments have led to a clearer definition of the role that platelets play in the acute complications of ischemic cardiovascular and cerebrovascular diseases. As a result, there is now a more precise understanding of the molecular events that underlie platelet adhesion to the damaged vessel wall and the complex interplay of intracellular signals and cell surface adhesive interactions that support aggregation and thrombus growth. The multifaceted platelet contribution to hemostasis and thrombosis includes the specific recognition of multiple reactive substrates, including altered endothelial cells and exposed subendothelial constituents, the ability to respond to stimuli by secreting and synthesizing active substances that amplify aggregation; and the participation in the assembly of the procoagulant pathways that lead to the generation of fibrin necessary for thrombus stability. Building on this mechanistic knowledge, clinical trials have established the efficacy of new antiplatelet strategies in the primary and secondary prevention of life-threatening arterial thrombotic events. Moreover, platelet studies have contributed to relevant information with respect to risk assessment and may ultimately lead to the possibility of prevention by demonstrating that specific polymorphisms in the genes encoding for certain platelet adhesive receptors are associated with an increased incidence of thrombotic episodes. Therefore, at present, the conclusion that platelets are of key importance in the genesis of the acute complications of ischemic cardiovascular and cerebrovascular diseases is supported by pathophysiological, pharmacological, and epidemiological data.

In this issue of the *Italian Heart Journal*, a minisymposium of four invited articles provides an update in selected areas of platelet research likely to have an impact on clinical practice. Two reviews – one by Santoso and Kunicki, the other by Clemetson – provide independent evaluations on how to interpret what is currently known about platelet receptor polymorphisms and risk for arterial thrombosis. It is an area in rapid development – as attested by the fact that new information on yet another receptor, glycoprotein VI, has recently become available[1,2] – but the results of these epidemiological studies are not fully consistent, thus are not definitive. At first glance, the existence of a causative link may seem reasonable when a given polymorphism is not only associated with increased risk but has also an impact on specific platelet functions. This, in turn, may focus attention on the usefulness of laboratory assays in predicting platelet activities *in vivo*, an area where new developments have occurred but clear answers have not yet been found. In fact, the value of genetic population studies is to suggest previously unsuspected cause-effect relationships that are not reflected in established functional tests, an outcome that may be particularly relevant in the heterogeneous syndromes of vascular instability. For example, selected aspects of the platelet adhesive and reactive repertoires, geared to respond to a variety of stimuli possibly vascular-bed specific, may be differentially important in the context of distinct pathogenetic conditions. Important clues to understanding such a complexity may be more easily derived from genetic studies than from the use of *in vitro* tests, which by their own nature tend to be selective, *a priori*, with respect to the response pathways being tested.

The third review in the minisymposium, by Bouchard and Tracy, explores the current knowledge on the pathophysiological links between platelet activation and thrombin generation. The process leading to the assembly of tenase and prothrombinase complexes on the platelet surface is complex and involves receptors and transduction systems likely to have considerable genetic and functional variability. This issue has bidirectional relevance, as activated platelets favor thrombin generation and thrombin activates platelets in addition to forming fibrin, two key events in thrombosis. Finally, the last review by Marcus and collaborators focuses on the vascular production of ecto-ADPase, one of the important physiologic mechanisms that maintain and regulate platelet reactivity. This enzyme, also known as CD39, degrades ADP, which is a platelet agonist, to AMP, which cannot stimulate platelets, and may have a dual physiologic role. By removing small amounts of ADP generated in the vasculature, it may prevent desensitization of the platelet ADP receptors, thus maintaining reactivity[3], but it may also control thrombus propagation by regulating the amounts of released ADP available for the amplification of platelet responses to a thrombogenic stimulus. The latter property makes ecto-ADPase a potential pharmacological tool for antithrombotic intervention.

The topics addressed in this minisymposium are necessarily limited, but indicative of the complex interrelationships between platelets and all the other components of the vascular hemostatic system. Platelet function is finely tuned to achieve hemostasis without risking thrombosis, and a recent example concerning von Willebrand factor (VWF) demonstrates how this delicate balance is likely to be implemented at multiple, if not at all levels of the platelet response to thrombogenic stimuli. The multimeric VWF mediates platelet adhesion to collagen and platelet aggregation under high shear stress conditions, as may occur in stenosed coronary arteries, and increased levels of this adhesive protein are associated with high recurrence rates of ischemia in coronary patients. It has been known for a long time that the size of VWF multimers is directly correlated with the ability to induce platelet thrombus formation. Equally well established is the fact that normal blood contains cleaved VWF multimers, evidence of a proteolytic mechanism possibly devoted to the functional regulation of this prothrombotic protein. Indeed, the protease responsible for the specific cleavage of VWF has recently been identified[4,5], and its genetic abnormalities have been associated with the occurrence of arteriolar thrombosis in patients with thrombotic thrombocytopenic purpura[6]. This information will undoubtedly result in future studies aimed at evaluating whether changes in the activity of this enzyme contribute to increasing the thrombogenic potential of VWF and, with this, the incidence of ischemic cardiovascular and cerebrovascular diseases. We hope that the critical synthesis of basic and clinical research data presented in this minisymposium, although limited to selected topics, will contribute to an improved understanding of the mechanisms of arterial thrombosis and delineate an approach to the design of more effective antithrombotic drugs.

References

1. Kunicki TJ, Ruggeri ZM. Platelet collagen receptors and risk prediction in stroke and coronary artery disease. Circulation 2001; 104: 1451-3.
2. Croft SA, Samani NJ, Teare MD, et al. Novel platelet membrane glycoprotein VI dimorphism is a risk factor for myocardial infarction. Circulation 2001; 104: 1459-63.
3. Enjyoji K, Sevigny J, Lin Y, et al. Targeted disruption of CD39/ATP diphosphohydrolase results in disordered hemostasis and thromboregulation. Nat Med 1999; 9: 1010-7.
4. Gerritsen HE, Robles R, Lämmle B, Furlan M. Partial amino acid sequence of purified von Willebrand factor-cleaving protease. Blood 2001; 98: 1654-61.
5. Fujikawa K, Suzuki H, McMullen B, Chung D. Purification of human von Willebrand factor-cleaving protease and its identification as a new member of the metalloproteinase family. Blood 2001; 98: 1662-6.
6. Levy GG, Nichols WC, Lian EC, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. Nature 2001; 413: 488-94.