CARDIOLOGY—IN-DEPTH LOOK: ADVANCES IN ANTIPLATELET THERAPY

Karin Mauer and Jorge F. Saucedo
Department of Medicine, Cardiovascular Section, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma

1 PLATELET PHYSIOLOGY IN CARDIOVASCULAR DISEASE

Platelets have a central role in the pathophysiology of atherosclerotic vascular disease. The interaction of platelets, atherosclerotic lesions, and the coagulation system is crucial in the transition from stable coronary artery disease (CAD) to unstable coronary syndromes such as unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation infarction (STEMI) [1]. During acute coronary syndromes (ACS) and percutaneous coronary intervention (PCI), there is disruption of the natural protection provided by the endothelium with exposure to the subendothelial matrix. The hemodynamic and biochemical environment of circulating platelets changes, inducing the aggregation process. Binding of platelet surface receptors to von Willebrand's factor and collagen promotes platelet adhesion to the vessel wall, with subsequent platelet activation, granule secretion, and activation of the glycoprotein (GP) IIb/IIIa receptors. Irreversible platelet aggregation and additional recruitment of platelets eventually lead to occlusive thrombus generation. In addition to factors in the subendothelial matrix, thrombin is a primary agonist responsible for platelet activation. Following activation, arachidonic acid (AA) is released from membrane phospholipids and converted to thromboxane (Tx)A2 by cyclooxygenase (COX)-1 and Tx synthase. Secreted TxA2 binds to specific receptors on the platelet membrane surface activating surrounding platelets as a positive feedback mechanism. Once activated, adenosine diphosphate (ADP) is released from dense granules in platelets, which amplifies the platelet activation and recruitment phenomenon. The binding of ADP to the P2Y12 receptor triggers intracellular signaling pathways that result in GPIIb/IIIa receptor activation. In addition, platelet activation is characterized by the expression of surface adhesion molecules, such as P-selectin and CD40 ligand, and aggregation of platelets with leukocytes, which contributes to inflammation and amplification of thrombin generation [2, 3].

The binding of fibrinogen to the platelet surface via the calcium-dependent GPIIb/IIIa complex on the platelet surface is necessary for platelet aggregation induced by any agonist. The aggregation mechanism reflects the importance of a rapid and effective response to hemorrhage, which explains the high density of GPIIb/IIIa on the surface of platelets and the high concentration of circulating fibrinogen. The conformational change in GPIIb/IIIa results in its high affinity for the adhesive glycoprotein ligands and is the final common effector for platelet aggregation [4].

There is a well-known interindividual variation in platelet reactivity, which may contribute to the risk for thrombosis in certain individuals but protection in others. Enhanced platelet reactivity (i.e., platelet hyperreactivity) can prospectively identify subjects who are at risk for thrombotic events. The mechanisms responsible for the hyperreactivity are not well

Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing
Edited by Shayne C. Gad