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PI3K/Akt in platelet integrin signaling and implications in thrombosis

Gianni F. Guidetti, Ilaria Canobbio, Mauro Torti*

Department of Biology and Biotechnology, Laboratories of Biochemistry, University of Pavia, Pavia, Italy

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ABSTRACT

Blood platelets are anucleated circulating cells that play a critical role in hemostasis and are also implicated in arterial thrombosis, a major cause of death worldwide. The biological function of platelets strongly relies in their reactiveness to a variety of extracellular agonists that regulate their adhesion to extracellular matrix at the site of vascular injury and their ability to form rapidly growing cell aggregates. Among the membrane receptors expressed on the cell surface, integrins are crucial for both platelet activation, adhesion and aggregation. Integrin affinity for specific ligands is regulated by intracellular signaling pathways activated in stimulated platelets, and, once engaged, integrins themselves generate and propagate signals inside the cells to reinforce and consolidate platelet response and thrombus formation. Phosphatidylinositol 3-Kinases (PI3Ks) have emerged as crucial players in platelet activation, and they are directly implicated in the regulation of integrin function. This review will discuss the contribution of PI3Ks in platelet integrin signaling, focusing on the role of specific members of class I PI3Ks and their downstream effector Akt on both integrin inside-out and outside-in signaling. The contribution of the PI3K/Akt pathways stimulated by integrin engagement and platelet activation in thrombus formation and stabilization will also be discussed in order to highlight the possibility to target these enzymes in effective anti-thrombotic therapeutic strategies.

* Corresponding author. Department of Biology and Biotechnology, Laboratories of Biochemistry, University of Pavia, via Bassi 21, 27100 Pavia, Italy. Tel.: +39 0382 987238.
E-mail address: mtorti@unipv.it (M. Torti).

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Introduction

Myocardial infarction and stroke, which are caused by arterial thrombosis in heart and brain, represent one of the most common causes of mortality and morbidity in the western world. Arterial thrombosis is a also major complication of atherosclerosis (Badimon and Vilahur, 2014; Jackson, 2011). It is well established that circulating platelets play a central role in the pathogenesis of cardiovascular thrombosis (Furie and Furie, 2008; Weyrich et al., 2007). Under physiological conditions, platelets are involved in primary hemostasis. Their arrest at the site of an injured vessel wall initiates a process of cell aggregation, which leads to the formation of a platelet plug, promptly arresting excessive bleeding. By contrast, platelet hyper-reactivity and pathologic events, such as the rupture of an unstable atherosclerotic plaque, can produce intravascular platelet aggregation, a process that leads to the formation of an occlusive thrombus preventing oxygen supply to heart or brain, and thus resulting in myocardial infarction or stroke.

Platelets promote thrombus formation through three specific actions: adhesion, activation and aggregation (Jackson et al., 2003). To fulfill these functions, platelets are extremely reactive to extracellular stimuli and are equipped by a number of membrane receptors specialized in the interaction with soluble agonists (typically G-protein-coupled receptors), and adhesive proteins (including platelet specific receptors such as GPIb-IX-V complex and GPVI). Cell-matrix and cell–cell interaction during hemostasis and thrombosis is also assured by the action of several integrins expressed on the platelet surface. Integrins are heterodimer receptors, composed by α and β subunits, whose assembly defines the specificity and selectivity of ligand binding (Barczyk et al., 2010). Integrins are critical for mediating stable platelet adhesion to extracellular matrix, but they also transmit signals bidirectionally through the plasma membrane.

Upon the interaction with their specific ligands, integrins transmit signals from the extracellular environment to the cell. Through a complex array of integrated signal transduction pathways known as outside-in signaling, the cell elaborates a proper reaction to the stimulus. In particular, integrin engagement and clustering typically result in the generation and transduction of signals inside the cell to modulate the cytoskeletal reorganization and to alter cellular function (Shattil and Newman, 2004). Conversely, integrin function is strictly related to the activation state of the cell, which can control the integrin conformational changes that regulate its binding properties through a process generally referred to as inside-out signaling pathway (Shattil and Newman, 2004; Shen et al., 2012).

Platelets express members of the integrin β_1 and β_3 families, including $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$, $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$ (Broos et al., 2011). Of these, $\alpha_2\beta_1$ and $\alpha_{IIb}\beta_3$ are among the most abundant adhesive receptors on the platelet surface. Integrin $\alpha_2\beta_1$ is a receptor for collagen, but also bind tenascin and the proteoglycan decorin (Guidetti et al., 2002; Schaff et al., 2011), while integrin $\alpha_{IIb}\beta_3$, which is exclusively expressed in platelets, binds several adhesive proteins, including fibrinogen, von Willebrand factor (VWF) and fibronectin (Bennett, 2005; Ruggeri et al., 1999). These integrins are differently involved in specific phases of platelets adhesion, are able to initiate intracellular signaling pathways for platelet activation and are involved in establishing cell–cell contact during platelet aggregation and thrombus formation (Estevez et al., 2015).

At the site of vascular injury, the mechanism for initial tethering and subsequent arrest of platelets to the exposed subendothelial matrix is largely influenced by the specific rheological conditions and blood flow rates (Cosemans et al., 2013). At shear rates typical of large arteries and arterioles (500–1600 s^{-1}) the rapid but transient interaction of GPIb-IX-V to VWF immobilized on the subendothelial collagen fibers is essential for initial platelet recruitment, but is unable to guarantee stable platelet adhesion (Ruggeri, 2009). Nevertheless, this essential step allows the subsequent binding of integrins to their respective ligands, thus firmly arresting platelets to the injured site. In this process binding of integrin $\alpha_{IIb}\beta_3$ to VWF itself or to fibronectin, integrin $\alpha_2\beta_1$ (and GPVI) to collagen or decorin, and integrin $\alpha_6\beta_1$ to laminin contribute to consolidate shear-resistant platelet attachment to the extracellular matrix. Importantly, initial GPIb-IX-V ligation can initiate platelet activation leading to inside-out stimulation of several integrins, thus increasing their affinity for the ligands (Kasirer-Friede et al., 2004; Wu et al., 2000). In platelets, inside-out activation has been proven to be essential to stimulate integrin $\alpha_{IIb}\beta_3$ function, but has also been shown to regulate the activity of integrin $\alpha_2\beta_1$