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Review

The role of platelets in hemostasis and the effects of snake venom toxins on platelet function

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ABSTRACT

The human body has a set of physiological processes, known as hemostasis, which keeps the blood fluid and free of clots in normal vessels; in the case of vascular injury, this process induces the local formation of a hemostatic plug, preventing hemorrhage. The hemostatic system in humans presents complex physiological interactions that involve platelets, plasma proteins, endothelial and subendothelial structures. Disequilibrium in the regulatory mechanisms that control the growth and the size of the thrombus is one of the factors that favors the development of diseases related to vascular disorders such as myocardial infarction and stroke, which are among the leading causes of death in the western world. Interfering with platelet function is a strategy for the treatment of thrombotic diseases. Antiplatelet drugs are used mainly in cases related to arterial thrombosis and interfere in the formation of the platelet plug by different mechanisms. Aspirin (acetylsalicylic acid) is the oldest and most widely used antithrombotic drug. Although highly effective in most cases, aspirin has limitations compared to other drugs used in the treatment of homeostatic disorders. For this reason, research related to molecules that interfere with platelet aggregation are of great relevance. In this regard, snake venoms are known to contain a number of molecules that interfere with hemostasis, including platelet function. The mechanisms by which snake venom components inhibit or activate platelet aggregation are varied and can be used as tools for the diagnosis and the treatment of several hemostatic disorders. The aim of this review is to present the role of platelets in hemostasis and the mechanisms by which snake venom toxins interfere with platelet function.

Contents

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1. Role of platelets in hemostasis

1.1. Platelets

Platelets are anucleate cell fragments in the form of a disk with diameter ranging from 1 to 4 μm derived from megakaryocytes. Megakaryocytes are found in the bone marrow and extend processes into the blood vessels where proplatelets are released (Bluteau et al., 2009; Hall, 2011; Jurk and Kehrel, 2005). Although anucleate, platelets are structures with an active metabolism and they have some functional features of whole cells, such as the presence of a cytoskeleton, mitochondria, Golgi residues and the endoplasmic reticulum, which synthesize enzymes and stores calcium ions as well as storage granules (dense granules, α-granules and lysosomes) (Gawaz, 2004; Hall, 2011; Saluk et al., 2014).

The platelet membrane has many receptors on its surface, such as GPIb-V-IX, GPVI, 5HT2A, TP, α_{2A}, protease activated receptors (PARs), $P2Y_1$, $P2Y_{12}$, and integrins, among others (Jurk and Kehrel, 2005; Nieswandt et al., 2009). These receptors are essential for the role that platelets play in hemostasis (Hall, 2011; Jurk and Kehrel, 2005; Nieswandt et al., 2009). The integrins play a critical role in platelet function. They are heterodimeric transmembrane glycoproteins formed by two subunits (α and β) linked by non-covalent bonds. There are five types of α subunits (α_2, α_{IIb}, α_V, α_5, α_6) and two types of β subunits (β_1 and β_3) comprising platelet integrins: $\alpha_{IIb}\beta_3$ (fibrinogen receptor), $\alpha_V\beta_3$ (vitronectin receptor), $\alpha_2\beta_1$ (collagen receptor), $\alpha_5\beta_1$ (fibronectin receptor) and $\alpha_6\beta_1$ (laminin receptor) (Nieswandt et al., 2009; Varga-Szabo et al., 2008).

Under normal physiological conditions, the platelets continuously flow within the blood vessel, without interacting with the vascular wall. However, when the vessel is injured, platelets are subjected to a response in a highly regulated manner which includes adhesion of circulating platelets to endothelial and subendothelial structures, activation, and platelet aggregation (Harrison, 2005).

1.2. Platelet adhesion

Platelet adhesion (Fig. 1) is a complex process that occurs when a vessel is injured and requires the coordinated interaction of receptors present on the surface of platelets and adhesive macromolecules of the extracellular matrix (Nieswandt et al., 2009; Savage et al., 1998; Varga-Szabo et al., 2008). When the vascular wall is injured, platelets are recruited from the circulation to the exposed subendothelial matrix (Jurk and Kehrel, 2005; Kamiguti, 2005). This process is dependent on shear stress. Under conditions of high shear stress, as seen in small arteries and arterioles, the initial recruitment of platelets to the exposed subendothelium is mediated by the interaction of von Willebrand factor (vWF) with the GPIbα subunit of the glycoprotein GPIb-V-IX complex. Binding between this receptor and vWF, immobilized on the surface of activated platelets, is also essential for the capture of circulating platelets (Andrews and Berndt, 2004; Savage et al., 1998; Varga-Szabo et al., 2008). Under low shear stress, platelets predominantly adhere to collagen by binding to glycoprotein VI (GPVI) and $\alpha_2\beta_1$ integrin, or adhere to fibronectin and laminin by other β_1 integrins (Jurk and Kehrel, 2005; Kamiguti, 2005). Under these shear conditions, the FvW-GPIbα interaction also plays a relevant role since it may favor the initial interaction of circulating platelets with the thrombus undergoing formation (Kulkarni et al., 2000).

vWF is a protein exclusively synthesized by megakaryocytes and endothelial cells. This molecule is stored in the Weibel-Palade bodies of endothelial cells and in platelet α-granules. vWF is released constitutively from endothelial cells (Ruggeri and Ware, 1993). Hemostatically, vWF is the major determinant of platelet adhesion and aggregation because it has several binding sites that can interact with the vascular wall, subendothelial matrix, and platelet receptors. There is little information regarding the nature of vWF binding sites. However, it is known that they interact strongly with the GPIb-V-IX complex during the capture of platelets (Jurk and Kehrel, 2005). vWF monomers present a structure comprised of the D1-D2-D′-D3-A1-A2-A3-D4-B1-B2-B3-C1-C2 domains, which are formed by 2050 amino acids and present an apparent molecular mass of 250 kDa (Bonthron et al., 1986; Jenkins, 1999; Sadler, 1991).

The C1 domain has the arginine-glycine-aspartate (RGD) sequence that binds to β_3 integrin, called $\alpha_V\beta_3$ and $\alpha_{IIb}\beta_3$ (Gawaz, 2004; Varga-Szabo et al., 2008). Under high shear stress, the A3 domain binds to fibrillary collagen, which results in a subsequent conformational change to the A2 domain. This conformational change leads to activation of the A1 domain, which binds to GPIbα (Andrews and Berndt, 2004). The A1 domain binds exclusively to collagen type VI, while the A3 domain binds to type I and III collagen (Farndale et al., 2004; Hoylaerts et al., 1997).

The interaction between VWF and the platelet glycoprotein (GP) Ib-IX-V receptor complex has a rapid rate of dissociation, which is insufficient to promote a stable platelet adhesion. This interaction requires unfolding of the VWF A1 domain and allows platelets to decelerate until they attach firmly in a process assisted by platelet integrins (Schneider et al., 2007). This unfolding provides a physical force, which keeps the platelets in intimate contact with the surface of the vessel, although they continuously translocate in the direction of blood flow (Varga-Szabo et al., 2008). During rolling, platelet receptors interact with the thrombogenic surface, inducing the activation of intracellular signals (Ozaki et al., 2005; Varga-Szabo et al., 2008). Therefore, the main role of the vWF-GPIbα interaction is to recruit platelets and to reduce their velocity to enable interaction with other receptors (Varga-Szabo et al., 2008).

The collagen located in the subjacent matrix of the endothelial cells is not exposed to blood flow. When a vascular injury occurs, blood comes into direct contact with subendothelial structures,