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REVIEW

Platelets at work in primary hemostasis

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ABSTRACT

When platelet numbers are low or when their function is disabled, the risk of bleeding is high, which on the one hand indicates that in normal life vascular damage is a rather common event and that hence the role of platelets in maintaining a normal hemostasis is a continuously ongoing physiological process. Upon vascular injury, platelets instantly adhere to the exposed extracellular matrix resulting in platelet activation and aggregation to form a hemostatic plug. This self-amplifying mechanism nevertheless requires a tight control to prevent uncontrolled platelet aggregate formation that eventually would occlude the vessel. Therefore endothelial cells produce inhibitory compounds such as prostacyclin and nitric oxide that limit the growth of the platelet thrombus to the damaged area. With this review, we intend to give an integrated survey of the platelet response to vascular injury in normal hemostasis.

1. Introduction

Platelets are involved in many processes ranging from fighting microbial infection and triggering inflammation to promoting tumor angiogenesis and metastasis[1]. Nevertheless, the main function of platelets still is stopping hemorrhage following vascular injury. In normal circumstances platelets do not interact with the intact vessel wall. However, upon tissue trauma platelets adhere to the extracellular matrix in a process that involves the coordinated action of different platelet receptors, leading to initial tethering and rolling of platelets over the damaged vessel wall, eventually resulting in firm adhesion. Platelet adhesion triggers a signaling cascade mediated by tyrosine kinases and G-protein coupled receptors, which guide full activation of the platelet and concomitant granule release, in turn resulting in recruitment and activation of additional platelets. Platelet adhesion and activation leads to platelet aggregation and the presentation of a procoagulant surface promoting formation of a fibrin-rich hemostatic plug at the injured site. Platelet activation, in addition, also triggers endothelial cells to synthesize and secrete molecules which tightly control and limit thrombus formation.

This review summarizes our current understanding of the basic platelet reactions upon vascular injury.

2. Platelet adhesion to the vessel wall

In normal circulation within intact vasculature, most platelets never undergo significant interaction with the endothelial surface during their entire lifetime. However, at sites of vascular injury, the subendothelial extracellular matrix is exposed to the blood, to which platelets promptly adhere in order to limit hemorrhage and promote tissue healing. This matrix contains several adhesive macromolecules such as collagen, von Willebrand factor (VWF), laminin, fibronectin and thrombospondin, all of which serve as ligands for different platelet surface receptors. Among these subendothelial substrates, the thrombogenic fibrillar collagens type I and III are by far the most potent mediators of platelet adhesion due to their strong platelet activating potential and affinity for VWF[2].

Stable platelet adhesion to the extracellular matrix occurs in a coordinated process that involves tethering, rolling, activation and firm adhesion. The initial adhesive interactions between platelets and the extracellular matrix are highly dictated by the local rheological conditions. At low shear rates ($<1000\ s^{-1}$, such as in veins and larger arteries) platelet adhesion primarily involves binding to collagen, fibronectin and laminin. At higher shear rates however ($>1000\ s^{-1}$, such as in small arteries and microvasculature, but also in atherosclerotic/stenotic vessels), the interaction between the platelet surface receptor glycoprotein Ibα (GPIbα) and VWF (either in the extracellular matrix or immobilized on exposed collagen) becomes

Abbreviations: CEACAM1, carcinoembryonic antigen cell adhesion molecule-1; COX, cyclo-oxygenase; DAG, 1,2-diacylglycerol; DTS, dense tubular system; GP, glycoprotein; ERK, extracellular signal-regulated kinase; Fg, fibrinogen; GPCR, G-protein coupled receptor; IP, prostacyclin receptor; IP3, inositol 1,4,5 trisphosphate; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibition motif; MLC, myosin light chain; NO(S), nitric oxide (synthase); PECAM-1, platelet endothelial cell adhesion molecule-1; PG, prostaglandin; PGI_2, prostacyclin; PKC, protein kinase C; PL, phospholipase; PtdSer, phosphatidylserine; SNARE, soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor; SH3, SRC Homology 3; STIM1, stromal interaction molecule 1; TMEM16F, transmembrane protein 16F; TXA_2, thromboxane A_2; VWF, von Willebrand factor.

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critically important to slow down fast-flowing platelets (Fig. 1). This slow motion allows the establishment of additional bonds (see below), leading to definitive arrest of platelets and subsequent thrombus formation.

2.1. GPIbα–VWF

Among the platelet–extracellular matrix interactions, binding of GPIbα to VWF is unique for its capability of recruiting fast flowing platelets in a high shear blood flow. VWF is a large, multimeric adhesive glycoprotein synthesized by endothelial cells and megakaryocytes[3]. Platelet VWF is stored in α-granules whereas endothelial VWF is either stored in Weibel–Palade bodies or secreted constitutively in both the blood and subendothelium. At sites of vascular damage, circulating VWF rapidly binds to exposed collagen, via collagen binding sites in its A1 and especially A3 domain[4,5]. Another mechanism of VWF immobilization is via self-association, where circulating VWF multimers bind to matrix-bound[6], platelet-bound[7] or endogenous subendothelial VWF, a process that involves multiple domain interactions[8].

After immobilization, VWF is able to capture platelets from the circulation via binding of its A1 domain with GPIbα, the only receptor on a non-activated platelet with a significant affinity for activated VWF. GPIbα (25,000 copies per cell) is part of the GPIb/IX/V complex consisting of the leucine-rich repeat glycoproteins GPIbα (130 kDa), GPIbβ (25 kDa), GPIX (22 kDa) and GPV (88 kDa)[9] in a 2:4:2:1 stoichiometry.

Under normal conditions, there is no interaction between native VWF and GPIbα because the GPIbα binding site on VWF A1 is cryptic. However, VWF immobilization and/or high fluid shear forces in the blood abolish the shielding effect of other VWF domains on the A1 GPIbα binding site, allowing platelets to bind[10–12].

Recent studies have shed more light on the specialized mechano-chemical force-resistance properties of the GPIbα–VWF interaction[13,14]. The bond is characterized by fast on- and off-rates, resulting in transient interactions that permit platelet rolling in the direction of the blood flow. Thus, whereas GPIbα–VWF is not sufficient to mediate stable adhesion, it rather decelerates platelets, maintaining them in close contact with the exposed subendothelium, allowing engagement of other platelet receptors leading to activation and eventually firm adhesion via high affinity β1 and β3 integrins (see 'Platelet activation' and 'Platelet aggregation'). Nevertheless, under very high shear conditions (>10,000 s^{-1}) (see 'Platelet aggregation'), it has been demonstrated that non-activated platelets can attach firmly to immobilized VWF, which could favor the establishment of thrombi in very high shear environments where shear forces and rapid flow limit adhesive bond formation and/or local agonist concentration[15].

The essential role of the GPIbα–VWF interaction becomes evident in patients having deficiencies of either VWF or GPIbα, which results in severe bleeding disorders known as von Willebrand disease[3] and Bernard–Soulier syndrome[16] respectively. Furthermore, studies using mice lacking the GPIb/IX/V complex[17,18] or mice in which the extracellular domain is replaced by one of the human interleukin-4 receptor (IL4Rα/GPIbα)[19] all confirm the defects in platelet dependent hemostasis. Interestingly, whereas virtually no tethering platelets and complete inhibition of thrombus formation was observed in mice lacking the extracellular part of GPIbα[19], platelets can still adhere and initiate arterial thrombus formation in VWF deficient mice[20,21]. This suggests that GPIbα can interact with other ligands to initiate platelet adhesion. Thrombospondin-1 might be a likely candidate[22].

2.2. Direct collagen receptors

Collagen is considered one of the most potent vessel wall components in the initiation of platelet adhesion and aggregation[2]. Platelets have two receptors that play a defined role in platelet–collagen interactions, namely glycoprotein VI (GPVI) and the integrin α2β1 (Fig. 1). Despite extensive studies, their exact relative roles in platelet adhesion and activation remain a matter of intense debate, questioning whether GPVI alone can mediate all aspects of collagen-dependent platelet adhesion and activation or whether the two receptors function independently in their interaction with collagen but operate synergistically for optimal function[23]. Interestingly, patients with GPVI or α2β1[24,25] deficiency only have a mild bleeding diathesis[26–29].

2.2.1. GPVI

The platelet-specific GPVI (62 kDa) is a member of the immunoglobulin superfamily consisting of a transmembrane complex formed

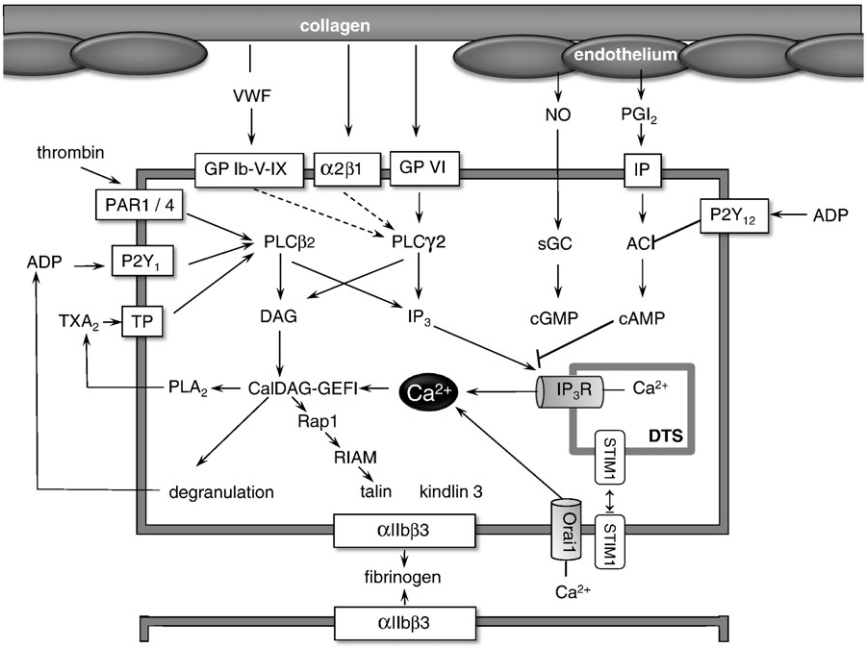

Fig. 1. Schematic overview of the main platelet receptors and effectors involved in platelet signaling.