

## Involvement of Glycoprotein Ib, $\alpha$ Ib $\beta$ 3 and Von Willebrand Factor in Platelet Production

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Hematopoietic stem cells (HSCs) are differentiated into megakaryocytes (Mks), terminating in proplatelet formation and release of platelets [1-3]. Mks and platelets express specific receptors of extracellular proteins on their surface. Von Willebrand factor (VWF) is one of extracellular proteins that binds to platelets. VWF binds to glycoprotein Ib (GPIb) on the surface of platelets under high shear forces, subsequently platelet  $\alpha$ Ib $\beta$ 3 is activated and VWF and fibrinogen bind to activated  $\alpha$ Ib $\beta$ 3 resulting in platelet aggregation [4]. Thus interaction between VWF and platelet is important in hemostasis and patients with von Willebrand disease (VWD), those who are quantitative or qualitative deficient in VWF, have mild to moderate bleeding diathesis [5]. Mks also express both GPIb and  $\alpha$ Ib $\beta$ 3 [6], and VWF may bind to Mk GPIb and  $\alpha$ Ib $\beta$ 3.

GPIb is proved to be important in platelet production. Thrombocytopenia and giant platelets are found in Bernard-Soulier Syndrome (BSS), inherited bleeding disorders deficient in GPIb or carrying non-functional GPIb [7]. Impaired Mk synthesis and proplatelet formation was demonstrated in the animal models of BSS [8,9]. Involvement of GPIb in platelet production is also proved by the observations that anti GPIb antibodies from primary immune thrombocytopenia patients or quinidine-induced thrombocytopenia patients reduced Mk synthesis and proplatelet formation [10,11].

Compared to GPIb,  $\alpha$ Ib $\beta$ 3 seems to be less important in platelet production. Platelet count and size is normal in Glanzmann thrombasthenia (GT) characterized by severe quantitative or qualitative defects of  $\alpha$ Ib $\beta$ 3 [7]. However, recently patients with congenital macrothrombocytopenia having mutations in  $\alpha$ Ib $\beta$ 3 were reported. Constitutive activation of  $\alpha$ Ib $\beta$ 3-mediated outside-in signaling in Mks reduced proplatelet formation, resulting in macrothrombocytopenia in these cases [12].

Proplatelet formation from Mk occurred after Mk plating on VWF [13]. Proplatelet formation and subsequent platelet release was accelerated by MK exposure to high shear forces, and it was abolished by anti VWF antibody [14]. Anti  $\alpha$ Ib $\beta$ 3 antibody, abciximab, also strongly reduced proplatelet formation and completely abolished platelet release under high shear forces. In addition, proplatelet formation under high shear was reduced on a VWF of type 2B VWD coating surface [14]. Type 2B VWD is a relatively rare form of VWD characterized by VWF with increased affinity to GPIb and mild to moderate thrombocytopenia [15]. These results suggest that shear forces promote interaction between VWF and MK GPIb, subsequently  $\alpha$ Ib $\beta$ 3 is activated, resulting in proplatelet formation and platelet release. Spontaneous binding of VWF of type 2B VWD to GPIb may impair platelet production under high shear forces. Giant platelets often appear in type 2B VWD and they may be a cause of impaired platelet production [16,17]. Reduced platelet production from type 2B VWD patients' HSCs compared to that from healthy donors' HSCs was also demonstrated [18]. Addition of exogenous native VWF increased platelet production from type 2B VWD patients' HSCs [18]. These findings suggest that proper interaction between VWF and Mks plays important role in platelet production.

In summary,  $\alpha$ Ib $\beta$ 3 as well as GPIb may be involved in platelet production, however the mechanism how they affect the platelet production needs to be examined. VWF binding to these Mk receptors occurs under high shear forces *in vitro*, however considering platelet count and size is usually normal in patients with VWD except for type 2B VWD [5], the significance of interaction between VWF and Mks *in vivo* is still uncertain. Recent progress made it possible to produce platelets not only from HSCs but also from embryonic stem cells [19], induced pluripotent stem cells [20] and adipocyte precursor cells [21] *in vitro*, however yields of platelets are too low for clinical use. To reveal the roles of GPIb,  $\alpha$ Ib $\beta$ 3 and VWF in MK synthesis, proplatelet formation and platelet release may help to increase platelet production from these cells *in vitro*.

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