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New Insights Into the Treatment of Glanzmann Thrombasthenia

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ABSTRACT

Glanzmann thrombasthenia (GT) is a rare inherited autosomal recessive bleeding disorder of platelet function caused by a quantitative or qualitative defect of platelet membrane glycoprotein IIb/IIIa (integrin αIIbβ3), a fibrinogen receptor required for platelet aggregation. Bleeds in GT are variable and may be severe and unpredictable. Bleeding not responsive to local and adjunctive measures, as well as surgical procedures, is treated with platelets, recombinant activated factor VII (rFVIIa), or antifibrinolytics, alone or in combination. Although platelets are the standard treatment for GT, their use is associated with the risk of blood-borne infection transmission and may also cause the development of platelet antibodies (to human leukocyte antigens and/or αIIbβ3), potentially resulting in platelet refractoriness. Currently, where rFVIIa is approved for use in GT, this is mostly for patients with platelet antibodies and/or a history of platelet refractoriness. However, data from the prospective Glanzmann's Thrombasthenia Registry (829 bleeds and 206 procedures in 218 GT patients) show that rFVIIa was frequently used in nonsurgical and surgical bleeds, with high efficacy rates, irrespective of platelet antibodies/refractoriness status. The mechanisms underpinning rFVIIa effectiveness in GT have been studied. At therapeutic concentrations, rFVIIa binds to activated platelets and directly activates FX to FXa, resulting in a burst of thrombin generation. Thrombin converts fibrinogen to fibrin and also enhances GT platelet adhesion and aggregation mediated by the newly converted (polymeric) fibrin, leading to primary hemostasis at the wound site. In addition, thrombin improves the final clot structure and activates thrombin-activatable fibrinolysis inhibitor to decrease clot lysis.

Contents

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Glanzmann thrombasthenia (GT) is a rare inherited bleeding disorder of platelet function. For bleeding not responsive to local management and antifibrinolytics, treatment with systemic hemostatic agents is required. Platelet transfusion is the time-honored standard treatment for serious bleeding but is not without its shortcomings. Recombinant activated factor VII (rFVIIa) is emerging as an important therapeutic agent. This review provides an update on the general understanding of GT and its management, with emphasis on current thinking on the mechanisms of action of rFVIIa in GT. We will briefly touch on hemopoietic stem cell transplantation (HSCT) as a curative treatment in carefully selected patients with poor quality of life suffering from recurrent persistent bleeding. Finally, the prospect of gene therapy and the promising progress made in basic and animal research will be discussed.

GT: General Overview

Eduard Glanzmann, a Swiss pediatrician, first described GT in 1918 [1]. GT is characterized by absent or decreased platelet aggregation to physiologic agonists including adenosine diphosphate (ADP), epinephrine, collagen, and thrombin [2–4]; prolonged bleeding time or PFA-100 closure times [5,6]; and abnormal clot retraction [2,7] (Table 1). Platelet number and morphology are usually normal [2], as is platelet agglutination to ristocetin (Table 1) [8], although a few families with macrothrombocytopenia have been reported [2,9]. These laboratory findings are unique to GT. Although platelets in GT patients can undergo shape change upon stimulation, adhere to exposed subendothelial tissue, and initiate secretion from storage granules [4], they cannot form platelet aggregates and thrombi at the site of vascular injury [10].

Platelet dysfunction in GT is caused by a quantitative or qualitative defect of the platelet membrane glycoprotein (GP) IIb/IIIa (integrin αIIbβ3) complex [3,4,11]. αIIbβ3 is a heterodimeric molecular complex acting as a fibrinogen receptor [12,13], which is important for mediating platelet aggregation induced by physiologic agonists and for fibrin clot retraction. When platelets are activated, αIIbβ3 responds to inside-out signaling and transforms from its bent resting state to a straight active configuration required for fibrinogen binding [14–16]. Other αIIbβ3 ligands include the adhesive proteins von Willebrand factor, fibronectin, vitronectin, and CD40L [17–19]. Platelets with deficient or defective αIIbβ3 cannot bind to these adhesive proteins when stimulated (Figure), which accounts for the characteristic GT laboratory findings. GT is a rare autosomal recessive disorder with an incidence of approximately 1 per million. However, in areas where marriage between close family relatives is common, the incidence can be as high as 1:200000 [20]. The genetic defect resides on the *ITGA2B* or *ITGB3* gene encoding αIIb and β3, both located on chromosome 17 (12q21) [3,4,9,21,22]. Mutations affecting either gene can result in GT. The multitude of mutations reported and how they result in quantitative or qualitative αIIbβ3 defects in GT have recently been extensively reviewed by Nurden and colleagues [4,9]. Details are also available at http://sinaicentral.mssm.edu/intranet/research/glanzmann/menu. Currently (as of October 25, 2015), there are 255 mutation records on the *ITGA2B* gene and 164 mutation records on the *ITGB3* gene. Although the majority are missense mutations, nonsense mutations (causing premature termination), small deletions and insertions (with in- or out-of-frame shifts, some causing altered splicing or premature termination and loss of transcript), as well as intronic splice site alterations are also reported. Integrin synthesis occurs in the megakaryocytes with αIIbβ3 complex formation in the endoplasmic reticulum. Any noncomplexed or incorrectly folded gene products will fail to undergo processing in the Golgi apparatus and are rapidly degraded intracellularly [4,9,23,24]. In GT, homozygosity of the same mutation is often a result of consanguineous marriage, although many other patients may be compound heterozygous for different mutations from each parent. Bleeding symptoms are confined to GT patients who are homozygous or compound heterozygous for αIIbβ3 mutations, whereas simple heterozygotes are asymptomatic [11], so family bleeding history may be absent. Integrin subunit αIIb expression is exclusively for αIIbβ3 in platelets. However, subunit β3 is involved in other integrins outside platelets. The impact of β3 loss (that results in GT) on other tissues is currently unknown.

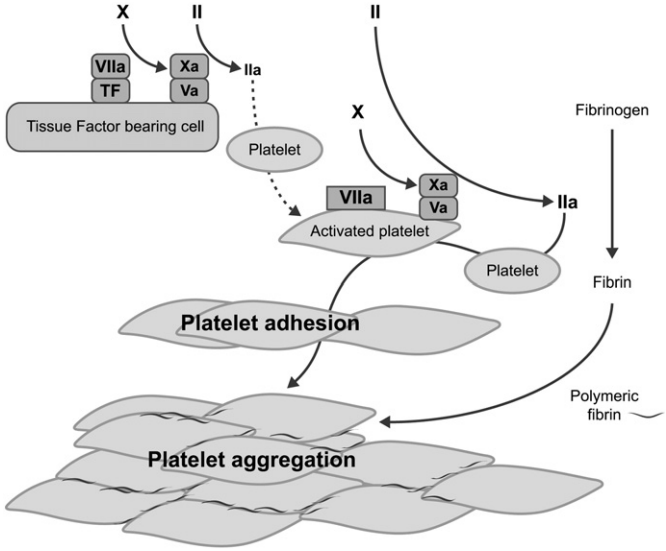

Figure. Adhesion and aggregation in GT platelets deficient in GPIIb-IIIa (integrin αIIbβ3): role of factor VIIa. FVIIa-Tissue Factor (TF) complex on TF-bearing cells at the site of vascular injury activates FX to FXa [25]. FXa-FVa on the TF-bearing cells initiates generation of a small amount of thrombin (FIIa) that is insufficient to provide fibrin formation but sufficient to activate GT platelets, causing degranulation and release of FV. FVIIa binds weakly to the negatively charged phospholipid surface [26] of the activated platelets, with the binding enhanced by the GPIb/IX/V complex [27]. FVIIa at high concentration (attained by high-dose rFVIIa therapy) can directly activate FX to FXa to mediate generation of a high concentration of thrombin (thrombin burst) [26]. The augmented thrombin generation results in an increased number of activated platelets deposited (adhesion) to the wound site and an increased available platelet procoagulant surface to facilitate more thrombin generation and more platelet activation [28,29]. The augmented thrombin generated also converts fibrinogen to fibrin. GT platelets lack the fibrinogen receptor (integrin αIIbβ3); therefore, these platelets cannot use fibrinogen for aggregation. However, binding of fibrin/polymeric fibrin to an unidentified platelet surface receptor can mediate aggregation of GT platelets at the wound site (albeit less potently than fibrinogen-mediated aggregation of normal platelets) [28,29] following the initial platelet adhesion, resulting in the formation of a primary hemostatic plug (adopted from Poon [30] with permission from the publisher).

GT can be classified according to platelet membrane αIIbβ3 protein levels measured using flow cytometry using monoclonal antibodies CD41 (for αIIb) and CD61 (for β3) [31,32]. As shown in Table 1,

Table 1
Diagnosis and classification of GT

Type	Proportion of GT patients	αIIbβ3 expression (platelet membrane)	αIIbβ3 (%) (flow cytometry: CD41: αIIb CD61: β3)	Platelet aggregation (ADP, EP, collagen, thrombin)	Platelet agglutination (ristocetin)	Bleeding time/ closure times (PFA-100)	Clot retraction	α-Granule pool fibrinogen
Type I	~75%	Absent or trace expression	0-5	Nil	Normal	Prolonged	Nil	Nil
Type II	~15%	Substantially reduced	5-20	Nil	Normal	Prolonged	Residual	Subnormal
Variant	~10%	Abnormal αIIbβ3 which cannot bind fibrinogen	>20	Nil/abnormal	Normal	Prolonged	Variable	Variable

Platelet count and morphology are usually normal, although a few families have been reported to have macrothrombocytopenia (see text). Abbreviations: ADP, adenosine 5'-diphosphate; EP, epinephrine.