When a blood vessel is injured, platelets adhere to the exposed subendothelium (platelet adhesion). The platelets are activated (platelet activation) and secrete their granule contents (platelet secretion). The granule contents include platelet agonists (adenosine diphosphate [ADP] and serotonin) that, by interacting with specific platelet receptors, contribute to the recruitment of additional platelets to form aggregates (platelet aggregation). Platelets also play a role in coagulation, providing the necessary surface of procoagulant phospholipids (platelet procoagulant activity). Congenital or acquired abnormalities of platelet numbers or functions are associated with a heightened risk of bleeding, proving that platelets play an important role in haemostasis. Patients with platelet disorders typically have mucocutaneous bleedings of variable severity and excessive haemorrhage after surgery or trauma.

Classification of the Congenital Disorders of Platelet Function

Inherited disorders of platelet function are generally classified based on the type of abnormal function. Platelet functions are intimately related and a clear distinction between the disorders of platelet adhesion, aggregation, activation, secretion and procoagulant activity may be problematic. We propose a classification of the inherited disorders of platelet function based on the shared common characteristic abnormalities of platelet components:

- platelet receptors for adhesive proteins;
- platelet receptors for soluble agonists;
- platelet granules;
- signal transduction pathways; and
- procoagulant phospholipids.

Those inherited disorders of platelet function that are less well characterised will be placed in a separate category of miscellaneous disorders.

Abnormalities of the Platelet Receptors for Adhesive Proteins

Abnormalities of the Glycoprotein Ib–V–IX Complex

Bernard-Soulier Syndrome

Bernard-Soulier syndrome (BSS) is associated with both quantitative and qualitative defects of the platelet glycoprotein complex GPIb-IX-V. The complex is formed of four glycoproteins. GPIbα and GPIbβ. Characterised by an autosomal recessive inheritance (only one case has been characterised by autosomal dominant inheritance), BSS also exhibits prolonged bleeding times, variable degrees of thrombocytopenia, giant platelets, decreased platelet adhesion and abnormal prothrombin consumption. Electron microscopy shows cytoplasmic vacuoles and membrane complexes in the giant platelets. These abnormalities extend to megakaryocytes (MK). With an estimated prevalence of 1/1,000,000 cases, BSS is a relatively severe bleeding disorder. Typical bleeding manifestations of the disorder include epistaxis, gum bleeding and both post-surgical and post-traumatic bleeding. Most heterozygotes have intermediate amounts of the GP complex and may have some giant platelets without a bleeding diathesis.

In primary haemostasis initial platelet adherence and recruitment depends on GPIbα binding to immobilised von Willebrand factor (VWF). BBS platelets are characterised by a significantly reduced ability to adhere to the subendothelium. The disease phenotype is primarily due to the inability of VWF to bind to GPIbα. The absence of GPIbα-related binding sites for thrombin, P-selectin, thrombospondin-1 (TPS-1), factor XI, factor XII, α-Mβ-2 and high-molecular-weight kininogen may play an additional role in the impairment of haemostasis. BSS platelets do not agglutinate in vitro when exposed to the antibiotic ristocetin or to the snake venom protein botrocetin. This defect is not corrected by the addition of normal plasma. In this instance the platelet responses to physiological agonists are normal, with the exception of low concentrations of thrombin. Diagnosis of BSS is based on the demonstration of a GPIbα-V deficiency by either flow-cytometry or immunoblotting. BSS is associated with genetic defects in GPIbα, GPIbβ and GPVI, preventing the constitution and trafficking of the receptor through the both the Golgi apparatus and the endoplasmic reticulum. Mutations within GPV do not lead to BSS. The molecular defects responsible for BBS include frame shifts, deletions and point mutations.

Platelet-type or Pseudo-von Willebrand Disease

Platelet-type von Willebrand disease (VWD) or pseudo-VWD is an autosomal-dominant disease associated with amino acid substitutions that...
Coagulation Disorders  Platelet Disorders

Abnormalities of the Platelet Thromboxane A₂ Receptor

Defects of the Platelet Granules

Abnormalities of the Platelet Adenosine Diphosphate Receptor P2Y₁₂

Abnormalities of the Platelet Receptors for Soluble Agonists

Abnormalities of Glycoprotein IIb and Glycoprotein III-a (α₁bβ₃)

Glanzmann’s Thrombasthenia

Defects of the Delta Granules

Defects of the Platelet Disorders

Abnormalities of the Platelet Thromboxane A₂ Receptor

Thromboxane-A₂ (Tx-A₂) formation on platelet activation is due to the action of phospholipase-A₂. It releases arachidonic acid (AA) from membrane phospholipids, as well as cyclo-oxygenase-1 (COX-1), which transforms arachidonic acid into endoperoxides, metabolised to Tx-A₂ by thromboxane synthase (TxAR5). Released Tx-A₂ binds to its Gq-coupled TxAR. Several homozygous and heterozygous patients suffering from lifelong mucosal bleeding and easy bruising have been found to have an Arg60 Leu mutation in the first cytoplasmic loop of the TxAR, affecting both receptor isoforms.17,18 The mutation was inherited as an autosomal-dominant trait and the heterozygous patients did not differ from the homozygous patients in terms of aggregation and secretion responses of platelets to Tx-A₂.

Defects of the Platelet Granules

Defects of the platelet granules comprise a heterogeneous group of disorders, including deficiencies of the delta and/or alpha granules, or their constituents (delta- and alpha-storage pool deficiency) and other less common defects of the alpha granules.

Abnormalities of the Platelet Receptors for Soluble Agonists

Abnormalities of Glycoprotein IIb and Glycoprotein III-a (α₁bβ₃)

Glanzmann’s thrombasthenia (GT) is an autosomal recessive disease caused by a lack of expression or qualitative defects in one of the two GPs forming the integrin αIIbβ₃. In activated platelets the integrin αIIbβ₃ binds the adhesive glycoprotein (fibrinogen at low shear, VWF at high shear) that bridges adjacent platelets and secures platelet aggregation. The diagnostic hallmark of the disease is the lack (or severe impairment) of platelet aggregation induced by all agonists. Severe forms (GT-type-I) are characterised by a lack of fibrinogen in the platelet α-granules. GT patients display a phenotype that is similar to that of BSS patients, albeit less severe. Heterozygotes do not have a bleeding diathesis.24,4 Diagnosis of GT is based on the presence of typical abnormalities in platelet function and on the demonstration that GPIIb/IIIa is absent or severely reduced on the platelet membrane. Flow cytometry is used as a screening test and clot retraction is often absent. Genetic defects can occur along the length of both genes. In the GPIIb (α₂bβ₃) subunit, splice site mutations and non-sense mutations, involving frame-shifts and giving rise to truncated proteins, are usually associated with severe forms of GT (type-I GT, according to early nomenclature).3,4 Missense mutations may give rise to a less severe deficiency of the complex or to dysfunctional proteins.3,4 Deletions, splice mutations and inversions in GPIII-a (β₃) involving frame-shifts and giving rise to truncated proteins, are usually associated with severe forms of GT.3,4 A comprehensive list of mutations can be found in the GT database at sinaicentral.mssm.edu/intranet/research/glanzmann.

In citrated platelet-rich plasma, primary aggregation induced by ADP or epinephrine and the agglutination response to ristocetin are normal. The second wave of aggregation and the aggregation in response to collagen are generally absent or greatly reduced.22,24 The production of arachidonate metabolites can be defective after stimulation with epinephrine or collagen but normal with arachidonate.24 The aggregation induced by sodium arachidonate or prostaglandin endoperoxides may be normal or decreased,24,25 depending on the severity of ADP deficiency in platelet granules.25 Normal responses to ADP or epinephrine have been observed in some patients;26 indicating that there is a large variability in platelet aggregation in patients with β-SPD. This has been well documented in a large study of 106 patients with β-SPD.21 Platelets from patients with isolated platelet β-SPD had normal amounts of the granule membrane protein granulophysin, suggesting a qualitative rather than a quantitative type of β-granule defect.19

Lumiaggregometry, which measures platelet aggregation and secretion simultaneously, may prove a more accurate technique than platelet aggregometry for diagnosing patients with β-SPD and platelet secretion defects. The diagnosis of β-SPD is essentially based on the finding of defective platelet secretion induced by several agonists, decreased platelet content of total ADP and adenosine triphosphate (ATP), an increase in the ATP/ADP ratio of >2.5–3.17 and a normal serum concentration of the stable
In contrast to soluble proteins, the \( \alpha \)-granule membrane proteins are normal in GPS, consistent with the demonstration of the presence of empty \( \alpha \)-granules in the GPS platelets and the normal production of precursors of \( \alpha \)-granules in GPS megakaryocytes. A decrease in secondary granules and secretory vesicles in neutrophils was recently described in some GPS patients. Circulating platelets are reduced in number, relatively large and vacuolated, and contain normal numbers of mitochondria, \( \delta \)-granules, peroxisomes and lysosomes. They specifically lack \( \alpha \)-granules. The degree of thrombocytopenia is usually mild, although cases with platelet counts as low as 20,000/\( \mu l \) have been described. Platelet aggregation studies show variable results in GPS patients. Platelet aggregation induced by ADP and adrenaline in citrated plasma was usually normal. Impaired aggregation responses induced by ADP or low concentrations of thrombin or collagen have been described in some patients.

**Quebec Platelet Disorder**

Quebec platelet disorder (QPD) is an autosomal dominant qualitative platelet abnormality characterised by the abnormal proteolysis of \( \alpha \)-granule proteins, normal platelet counts and a markedly decreased platelet aggregation induced by epinephrine. Patients with QPD experience severe post-traumatic and post-surgical bleeding complications, joint bleeds and large bruises that are unresponsive to platelet transfusion but are well controlled by the administration of antifibrinolytic agents. Multimerin, one of the largest proteins found in the human body, is present in platelet \( \alpha \)-granules and in endothelial cell Weibel-Palade bodies. It binds with factor V and its activated form, factor Va. Its deficiency in patients with the QPD is probably responsible for the defect in platelet factor V. This is likely to be degraded by abnormally regulated platelet proteases.

**Paris-Trousseau Syndrome Thrombocytopenia and the Jacobsen Syndrome – 11q Terminal Deletion Disorder**

Paris-Trousseau syndrome (PTS) and Jacobsen syndrome (JS) are related disorders presenting a mild haemorrhagic diathesis. They are characterised by congenital thrombocytopenia, a normal platelet life span and an increased number of marrow megakaryocytes, many of which present with signs of abnormal maturation and intramedullary lysis. A fraction of the circulating platelets have giant \( \alpha \)-granules that are unable to release their content upon platelet stimulation with thrombin. While the platelet defect is predominant in PTS, JS has a more severe phenotype, which includes congenital heart defects, mental retardation, gross and fine motor delays, trigonocephaly, facial dysmorphism and ophthalmological, gastrointestinal and genito-urinary problems.

**Defects of the Alpha Delta Granules**

Alpha- and delta-storage pool deficiency is a heterogeneous congenital disorder of platelet secretion characterised by deficiencies of both \( \alpha \)- and \( \delta \)-granules. It is important to note that blood samples should be collected in sodium citrate for measurement of platelet granule content as platelets from some individuals may undergo degranulation in vitro when blood is collected in ethylenediaminetetraacetic acid (EDTA), resembling \( \alpha, \delta \)-SPD. Approximately 80% of platelets from the patient with severe \( \alpha, \delta \)-SPD expressed little or no P-selectin after stimulation. The remaining 20% expressed normal amounts. Compared with \( \delta \)-SPD platelets, which have a normal density, \( \alpha, \delta \)-SPD platelets show a shift to the left of the
density distribution, suggesting that α-granules are a major determinant of platelet density. The clinical picture and the platelet aggregation abnormalities are similar to those of patients with GPS or α-SPD.

Abnormalities of the Signal–Transduction Pathways

Congenital abnormalities of the arachidionate thromboxane A2 pathway raise an impaired liberation of arachidonic acid from membrane phospholipids. In these patients TXB2 production, after stimulation with ADP or thrombin, was impaired. It was normal with arachidonic acid stimulation. Patients with congenital abnormalities in cyclo-oxygenase have been also been identified. Platelets from these patients have the same functional defect as normal platelets treated with aspirin: impaired aggregation and secretion induced by ADP, epinephrine, collagen or arachidonic acid, normal responses to Thromboxane A2 (TXA2) endoperoxides analogues and absent platelet TXA2 production.

Abnormalities of Membrane Phospholipids

Scott Syndrome

Scott syndrome is a very rare bleeding disorder associated with the maintenance of the asymmetry of the lipid bi-layer in the membranes of blood cells, including platelets. It leads to reduced thrombin generation and defective wound healing. The cause of the defect is still not clearly understood.

Miscellaneous Disorders of Platelet Function

Primary Secretion Defects

The term ‘primary secretion defect’ was probably used for the first time by Weiss to indicate all those ill-defined abnormalities of platelet secretion not associated with platelet granule deficiencies. It was later broadened to include the platelet secretion defects not associated with platelet granule deficiencies and abnormalities of the arachidonic pathway or, more generally, all of the abnormalities of platelet function associated with defects of signal transduction. With the progression of our knowledge in platelet pathophysiology, this heterogeneous group of patients with congenital disorders of platelet function will become progressively smaller. Patients with better-defined biochemical abnormalities responsible for their platelet secretion defect will be classified correctly. As an example, patients with heterozygous P2Y12 deficiency were included in this group of disorders until their biochemical abnormality was identified.
Editor’s Recommendations

Platelet P2 Receptors – Old and New Targets for Antithrombotic Drugs
Cattaneo M

Platelets possess three P2 receptors for adenine nucleotides: P2Y1 and P2Y12, which interact with ADP, and P2Y13, which interacts with ATP. The interaction of adenine nucleotides with their platelet receptors plays an important role in thrombogenesis. The thienopyridine ticlopidine, an antagonist of the platelet P2Y12 ADP receptor, reduces the incidence of vascular events in patients at risk, but it also has some important drawbacks: a relatively high incidence of toxic effects, delayed onset of action and high inter-individual variability in response. Another thienopyridine, clopidogrel, has superseded ticlopidine because it is an efficacious antithrombotic drug and is less toxic than ticlopidine. However, the high inter-patient variability in response still remains an important issue. These drawbacks justify the continuing search for agents that can further improve the clinical outcome of patients with atherosclerosis through greater efficacy and/or safety. A new thienopyridyl compound, prasugrel, which is characterised by higher potency and faster onset of action compared with clopidogrel, is currently under clinical evaluation. Two direct and reversible P2Y12 antagonists, cangrelor and AZD6140, have very rapid onset and reversal of platelet inhibition, which makes them attractive alternatives to thienopyridines, especially when rapid inhibition of platelet aggregation or its quick reversal is required. Along with new P2Y12 antagonists, inhibitors of the other platelet receptor for ADP, P2Y1, and of the receptor for ATP, P2X1, are under development and may prove to be effective antithrombotic agents.

Inherited Traits Affecting Platelet Function
Salles II et al.

Inherited platelet disorders constitute a large group of diseases involving a wide range of genetic defects that can lead to bleeding symptoms. They are associated with defects in surface membrane glycoproteins, resulting in, for example, Bernard-Soulier syndrome and Glanzmann thrombasthenia, causing defects in platelet adhesion and aggregation, respectively, as well as in receptors for agonists (P2Y12, TXA2) disrupting platelet signalling. Defects affecting platelet granules can be characterised by abnormalities of alpha-granules as in the grey platelet syndrome or dense granules in congenital storage pool deficiency. 

55. Hayward CP, Richardson GE, Kane WH, An autosomal dominant, qualitative platelet disorder associated with multimerin deficiency, abnormalities in platelet factor V, thrombomodulin, von Willebrand factor, and fibrinogen, and an epinephrine aggregation defect, Blood, 1996;87:4967–78.