Inherited platelet-based bleeding disorders

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Summary. Inherited platelet-based bleeding disorders include abnormalities of platelet number and function, and are generally classified based on the abnormal functions or responses. However, a clear distinction is problematic, and in this review, the classification has been based on abnormalities of platelet components that share common characteristics.

Inherited thrombocytopenias are rare, but probably underdiagnosed. They are usually classified according to both platelet size and the presence or absence of clinical features other than those deriving from the platelet defect. Hereditary disorders of platelet function can be classified as resulting from: (i) abnormalities of the platelet receptors for adhesive proteins; (ii) abnormalities of the platelet receptors for soluble agonists; (iii) abnormalities of the platelet granules; (iv) abnormalities of the signal-transduction pathways; (v) abnormalities of the membrane phospholipids; and (vi) miscellaneous abnormalities of platelet function. The literature on these disorders is reviewed, and the underlying defects discussed.

Keywords: inherited bleeding disorders, inherited thrombocytopenias, platelet abnormalities, platelets.

Introduction

When a blood vessel is injured, platelets adhere to the exposed subendothelium (platelet adhesion), are activated (platelet activation) and secrete their granule contents (platelet secretion), including some platelet agonists (adenosine diphosphate (ADP), serotonin) which, by interacting with specific platelet receptors, contribute to the recruitment of additional platelets to form aggregates (platelet aggregation). In addition, platelets play a role in the coagulation mechanism, providing the necessary surface of procoagulant phospholipids (platelet procoagulant activity). Congenital or acquired abnormalities of platelet number or function are associated with a heightened risk for bleeding, proving that platelets play an important role in hemostasis. Typically, patients with platelet disorders have mucocutaneous bleedings of variable severity, and excessive hemorrhage after surgery or trauma. In this brief chapter, I shall review the main inherited platelet-based bleeding disorders. Abnormalities of platelet function due to defects of plasma proteins [e.g. von Willebrand disease (VWD), afibrinogenemia] will not be considered in this review. Due to space limitations, I shall focus on the more recently described and less well-known abnormalities of the platelet receptors for ADP, referring the interested reader to very good and recent reviews for more details on the remaining disorders [1–4].

Classification

Inherited platelet-based bleeding disorders include abnormalities of platelet number (inherited thrombocytopenias) and function (inherited disorders of platelet function) (Table 1). Some disorders are characterized by both thrombocytopenia and abnormalities of platelet function. Inherited disorders of platelet function are generally classified based on the functions or responses that are abnormal. However, since platelet functions are intimately related, a clear distinction between disorders of platelet adhesion, aggregation, activation, secretion and procoagulant activity is in many instances problematic. For example, platelets that are deficient in the glycoprotein (GP) complex Ib/IX/V, which is a receptor for von Willebrand factor (VWF), do not adhere normally to the subendothelium and for this reason are generally included in the group of abnormalities of platelet adhesion. However, they also do not undergo normal activation and aggregation at high shear, do not aggregate normally to thrombin, and display abnormal procoagulant responses. For this reason, I chose a classification of the inherited disorders of platelet function based on abnormalities of platelet components that share common characteristics: (i) platelet receptors for adhesive proteins; (ii) platelet receptors for soluble agonists; (iii) signal transduction pathways; and (iv) procoagulant phospholipids. Inherited disorders of platelet function that are less well characterized are grouped in a fifth category of miscellaneous disorders.

Inherited thrombocytopenias

Although inherited thrombocytopenias are rare, their frequency is probably underestimated because of diagnostic difficulties. Moreover, not all the existing forms have yet been identified, and some patients remain without a definite diagnosis.
despite accurate investigation. The Italian Gruppo di Studio delle Piastrine has recently proposed an algorithm to assist clinicians in the diagnosis of inherited thrombocytopenias [5]. A correct diagnostic approach is essential, not only to avoid the use of potentially harmful treatments that are generally given to patients with acquired thrombocytopenias, but also to classify patients with known disorders and to identify families with uncharacterized forms. The study of these new entities by the coordinated efforts of physicians, biologists and geneticists will improve diagnostic skills and provide insights into the molecular basis of platelet production and function.

Inherited thrombocytopenias are usually classified according to both platelet size and the presence (syndromic) or the absence (non-syndromic) of clinical features other than those deriving from the platelet defect [Table 1]. For a detailed discussion of the clinical and biological features of hereditary thrombocytopenias see [6,7].

Table 1 Inherited platelet-based bleeding disorders

<table>
<thead>
<tr>
<th>Inherited thrombocytopenias*</th>
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<tr>
<td>With small platelets</td>
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<td>Wiskott–Aldrich syndrome</td>
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<td>X-linked thrombocytopenia</td>
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<td>Familial platelet disorder and predisposition to acute myelogenous leukemia</td>
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<td>Congenital amegakaryocytic thrombocytopenia</td>
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<td>Velo-cardio-facial syndrome</td>
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<td>Platelet-type von Willebrand disease</td>
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<td>Benign mediterranean macrothrombocytopenia</td>
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<td>Dyserythropoietic anemia with thrombocytopenia</td>
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<td>X-linked thrombocytopenia with thalassemia</td>
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<td>Paris–Trudeau –Jacobsen’s syndrome</td>
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<td>MYH9-related disease (May–Haegglin anomaly, Sebastian syndrome, Fechtner syndrome, Epstein syndrome)</td>
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<td>Gray platelet syndrome</td>
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<td>Montreal platelet syndrome</td>
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<td>Macrothrombocytopenia with platelet expression of glycoporphin A</td>
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Inherited disorders of platelet function

Abnormalities of the platelet receptors for adhesive proteins
- GP IIb/IIIa (αIIb/β3) (Glanzmann’s thrombasthenia)
- GP Ia/IIa (α2/β1)
- GPVI
- GPIV

Abnormalities of the platelet receptors for soluble agonists
- Thromboxane A2 receptor
- α2-adrenergic receptor
- P2Y12 receptor

Abnormalities of the platelet granules
- δ-granules (δ-storage pool deficiency, Hermansky–Pudlak syndrome, Chediak–Hygashi syndrome, thrombocytopenia with absent radii syndrome, Wiskott–Aldrich syndrome)
- γ-granules (gray platelet syndrome, Quebec platelet disorder, Paris–Trudeau–Jacobsen syndrome)
- α- and δ-granules (α,δ-storage pool deficiency)

Abnormalities of the signal-transduction pathways
- Abnormalities of the arachidonate/thromboxane A2 pathway
- Gαq deficiency
- Partial selective PLC-β2 isozyme deficiency
- Defects in pleckstrin phosphorylation
- Defective Ca2⁺ mobilization
- Hyperresponsiveness of platelet Gαs

Abnormalities of membrane phospholipids
- Scott syndrome
- Stormorken syndrome

Miscellaneous abnormalities of platelet function
- Primary secretion defects
- Other platelet abnormalities (Montreal platelet syndrome, osteogenesis imperfecta, Ehlers–Danlos syndrome, Marfan’s syndrome, hexokinase deficiency, glucose-6-phosphate deficiency)

*Syndromic forms are in *italics* (for details, see reference [5]).
Abnormalities of the GP Ib-V-IX complex

**Bernard–Soulier syndrome (BSS)** BSS is caused by defects in the genes for GPIb, GPIbβ or GPIX, while defects in the gene for GPV are not associated with BSS. The molecular defects that are responsible for BSS, including frame shifts, deletions, point mutations have recently been reviewed [2]. Characterized by autosomal recessive inheritance (only one case has been characterized by autosomal dominant inheritance), prolonged bleeding time, thrombocytopenia, giant platelets and decreased platelet survival, the syndrome is associated with quantitative or qualitative defects of the platelet glycoprotein complex GPIb/IX/V. The degree of thrombocytopenia may be overestimated when the platelet count is performed with automatic counters, because giant platelets, which may be as frequent as 70–80% in occasional patients, may reach the size of red blood cells and consequently are not recognized as platelets by the counters. Typically, Bernard–Soulier syndrome (BSS) platelets do not agglutinate with ristocetin and this defect is not corrected by the addition of normal plasma. The platelet response to physiological agonists is normal, with the exception of low concentrations of thrombin, because GPIb (one of the two components of GPIb) plays a critical role in platelet aggregatory, secretory and procoagulant responses to thrombin [8–11]. *In vitro* studies have shown that the interaction of BSS platelets with the subendothelium is impaired at both high and low shear rates.

Bleeding events, which may be very severe, can be controlled by platelet transfusion. Most heterozygotes, with few exceptions, do not have a bleeding diathesis. BSS is caused by defects in the genes for GPIb, GPIbβ or GPIX, while defects in the gene for GPV are not associated with BSS. The molecular defects that are responsible for BSS, including frame shifts, deletions, and point mutations have recently been reviewed [2].

**Platelet-type, or pseudo, von Willebrand disease (VWD)** VWD is a disorder of primary hemostasis that is due to complete or partial defects of VWF, an adhesive protein that plays an essential role in platelet adhesion and aggregation under high shear rates [12]. Platelet-type (or pseudo) VWD is not due to defects of VWF, but to gain of the functional phenotype of the platelet GPIb, which has an increased avidity for VWF, leading to the binding of the largest VWF multimers to resting platelets and to their clearance from the circulation. Since the high molecular weight VWF multimers are the most hemostatically active, their loss is associated with bleeding risk, as in type 2B VWD, which is caused by a gain of function abnormality of the VWF molecule. Platelet-type VWD is an autosomal dominant disease, which is associated with amino acid substitutions occurring within the disulfide-bonded double loop region of GPIb (G233V and M239V) [13–15].

**Abnormalities of GP IIb/IIIa (αIIb/β3), Glanzmann’s thrombasthenia (GT)** This is an autosomal recessive disease that is caused by lack of expression of or qualitative defects in one of the two glycoproteins forming the integrin αIIb/β3, which in activated platelets binds the adhesive glycoproteins (fibrinogen at low shear, VWF at high shear) that bridge adjacent platelets, securing platelet aggregation. The diagnostic hallmark of the disease is the lack, or severe impairment, of platelet aggregation induced by all agonists; severe forms are characterized by lack of fibrinogen in the platelet granules. Platelet clot retraction is defective. GT platelets normally bind to the subendothelium, but they fail to spread. The disease is associated with bleeding manifestations that are similar to those of patients with BSS, although of lower severity.

The defect is caused by mutations or deletions in the genes encoding for one of the two glycoproteins forming the αIIb/β3 integrin. In GT due to mutations in the β3, the levels of platelet vitronectin receptor (αv/β3) are also decreased, but the phenotype of these patients is no different from that of the other GT patients [2]. The molecular defects that are responsible for GT have been recently reviewed [2] and are available on an Internet database (http://med.mssn.edu/glanzmanndb).

**Abnormalities of GP Ia/IIa (α/β1)** Two patients with mild bleeding disorders associated with deficient expression of the platelet receptor for collagen GP Ia/IIa (α/β1) and selective impairment of platelet responses to collagen have been described [18,19]. Their platelet defect spontaneously recovered after the menopause, suggesting that α/β1 expression is under hormonal control.

**Abnormalities of GPVI** A selective defect of collagen-induced platelet aggregation was also described in another mild bleeding disorder, characterized by deficiency of platelet GPVI [20], a member of the immunoglobulin superfamily of receptors, which mediates platelet activation by collagen [21]. The molecular defects that are responsible for the platelet abnormality have not been characterized in the patients described so far. The possibility should be explored that the molecular abnormality lies in the gene encoding for the Fcγ receptor, which is the signaling subunit of GPVI [22].

**Abnormalities of GPIV** GPIV binds collagen, thrombospondin and probably other proteins. Its physiologic role is unclear, because its deficiency, which is common in healthy individuals from Japan and other East Asian populations, is not associated with an abnormal phenotype [2].
Abnormalities of the platelet receptors for soluble agonists

Thromboxane A2 (TXA2) receptor In 1981, three reports of impaired platelet responses to TxA2 in patients with bleeding disorders were published [23–25]. In one patient, the stable TxA2 mimetic U46619 was tested and found to be unable to elicit normal platelet responses [26], providing convincing evidence that the platelets had a defect at the receptor level. In 1993, a similar patient with a mild bleeding disorder was described, whose platelets had normal number of TxA2-binding sites and normal equilibrium dissociation rate constants [26]. Despite the normal number of TxA2 receptors, TxA2-induced IP3 formation, Ca2+ mobilization and GTPase activity were abnormal, suggesting that the abnormality of these platelets was impaired coupling between TxA2 receptor, G protein and PLC. These last two patients were subsequently found to have an Arg60→Leu mutation in the first cytoplasmic loop of the TxA2 receptor [27], affecting both isoforms of the receptor [28,29]. The mutation was found exclusively in the affected members of the two unrelated families and was inherited as an autosomal dominant trait.

α2-adrenergic receptors Subjects with selective impairment of platelet response to epinephrine, decreased number of the platelet α2-adrenergic receptors and mildly prolonged bleeding times have been described. However, the relationship between this defect and the bleeding manifestations still needs to be defined [3].

P2 receptors The P2 receptors interact with purine and pyrimidine nucleotides. Human platelets express at least three distinct P2 receptors stimulated by adenosine nucleotides: P2Y1 [30], P2Y12 [31,32], and P2X1 [33–36].

Adenosine triphosphate (ATP) is the physiological agonist of the P2X1 receptor, the role of which in platelet activation is controversial. The failure by many studies to show that α,β-methylene-ATP promotes platelet shape change or aggregation is attributable to rapid desensitization of the receptor by adenine nucleotides released during the preparation of platelet suspensions [37]. Recent studies showed that P2X1 plays an important role in platelet aggregation and thrombus formation under high shear rates [38]. A dominant-negative mutation in the P2X1 receptor gene has been described in a patient with a severe bleeding disorder, which, however, was associated with impaired platelet aggregation induced by adenosine diphosphate (ADP), suggesting that other defects were probably responsible for the bleeding diathesis in this patient [39].

Binding of ADP to P2Y1 leads to the Gq mediated activation of β isoforms of PLC, which leads to a transient increase in the concentration of intracellular calcium, platelet shape change and aggregation [40–42]. Stimulation with ADP of normal platelets in the presence of P2Y1 antagonists [30,40–47] or of P2Y1−/− murine platelets [48,49] does not induce shape change and normal aggregation, but inhibits adenylyl cyclase and elicits a slowly progressive and sustained platelet aggregation not accompanied by shape change. These platelet responses are mediated by the other platelet receptor for ADP, P2Y12 [31]. Therefore it appears that, while P2Y1 has a role in the initiation of platelet activation, P2Y12 is essential for a sustained, full aggregation response to ADP. The concurrent activation of the Gq and Gi pathways is necessary for full platelet aggregation induced by ADP.

P2Y12 also mediates the potentiation of platelet secretion by ADP [50,51] and the stabilization of thrombin-induced platelet aggregates [52,53].

Congenital defects of the platelet ADP receptors Only patients with congenital defects of the platelet P2Y12 receptors have been described. The first patient was described in 1992 by Cattaneo et al. [54]. He had a lifelong history of excessive bleeding, prolonged bleeding time and abnormalities of platelet aggregation that are similar to those observed in patients with defects of platelet secretion (reversible aggregation in response to weak agonists and impaired aggregation in response to low concentrations of collagen or thrombin), except that the aggregation response to ADP was severely impaired. Other abnormalities of platelet function found in this patient were: (i) no inhibition by ADP of PGE1-stimulated platelet adenylyl cyclase; (ii) normal shape change and normal (or mildly reduced) mobilization of cytoplasmic ionized calcium induced by ADP; (iii) presence of about 30% of the normal number of platelet-binding sites for 33P-2MeSADP [55] or 3H-ADP. After the identification and cloning of P2Y12, it was possible to characterize this defect at a molecular level. The patient’s P2Y12 gene displayed a homozygous 2-bp deletion in the open-reading frame, located at bp294 from the start methionine, thus shifting the reading frame for 33 residues before introducing a stop codon, causing a premature truncation of the protein [3].

Three additional patients, one male (patient 2) [57] and two sisters (patients 3 & 4) [50] with very similar characteristics were later described. Similar to patient 1, patients 3 and 4 displayed a homozygous single bp deletion in P2Y12 gene occurring just beyond the third transmembrane domain, thus shifting the reading frame for 38 residues before introducing a stop codon, causing a premature truncation of the protein [31]. In contrast, the molecular defect responsible for the abnormal phenotype of patient 2 is less well defined. The patient has one mutant and one wild-type allele. The mutant allele contains a deletion of 2 bp within the coding region, at position 240, thus shifting the reading frame for 33 residues before introducing a stop codon, causing a premature truncation of the protein [31].

As biochemical studies of patient 2’s platelets indicated that he was completely defective for the G1-linked receptor, it is likely that he has a second, as yet unidentified mutation that silenced his wild-type allele [31].

A new patient (5) with congenital bleeding disorder associated with abnormal P2Y12-mediated platelet responses to ADP has more recently been characterized [58]. The platelet phenotype is very similar to that of other patients with P2Y12 deficiency, except that the number and affinity of 33P-2Me-SADP binding sites was normal. Analysis of the patient P2Y12
gene revealed, in one allele, a G→A transition changing the codon for Arg256 in the sixth transmembrane domain to Gln and, in the other, a C→T transition changing the codon for Arg265 in the third extracellular loop to Trp. Neither mutation interfered with receptor surface expression but both altered function, since ADP inhibited the forskolin-induced increase of cAMP markedly less in Chinese hamster ovary (CHO) cells transfected with either mutant P2Y12 type than with the wild-type receptor. In accordance with previous studies of the P2Y1 receptor [59,60], these findings identify regions corresponding to the extracytoplasmic end of TM6 and EL3, whose structural integrity is necessary for normal functioning of a G protein-coupled receptor.

The study of the children of patient 2 and patient 5 allowed the characterization of a heterozygous P2Y12 defect [50,58]. Their platelets underwent a normal first wave of aggregation after stimulation with ADP, but did not secrete normal amounts of ATP after stimulation with different agonists. This secretion defect was not caused by impaired production of thromboxane A2 or low concentrations of platelet granule contents, and is therefore very similar to that described in patients with an ill-defined and probably heterogeneous group of congenital defects of platelet secretion, sometimes referred to with the general term primary secretion defect (PSD, see below), which is the most common congenital disorder of platelet function. The results of this study therefore confirm the hypothesis that (some) patients with PSD are heterozygous for the severe defect of P2Y12 [51].

Based on the hypothesis that PSD is due to heterozygous P2Y12 deficiency, it is likely that the severe defect is relatively common and that, due to its characteristics and to the fact that it is not yet well known, it is currently underdiagnosed, being confused with other platelet function abnormalities [61,62]. It is therefore important to emphasize that this condition should be suspected when ADP, even at relatively high concentrations (10 μM or higher), induces a slight and rapidly reversible aggregation that is preceded by normal shape change. Of the two possible confirmatory diagnostic tests, measurement of the platelet-binding sites for radiolabeled 2MeSADP and inhibition of stimulated adenyl cyclase by ADP, the second is preferred because it is easier to perform, cheaper, more specific, and sensitive not only to quantitative abnormalities of the receptor but also to functional defects.

Abnormalities of the platelet granules

Abnormalities of the δ-granules (δ–storage pool deficiency) The term δ–storage pool deficiency (δ–SPD) defines a congenital abnormality of platelets characterized by deficiency of dense granules in megakaryocytes and platelets. It may present as an isolated platelet function defect, or be associated with a variety of congenital disorders. Between 10% and 18% of patients with congenital abnormalities of platelet function have SPD [63,64]. The inheritance is autosomal recessive in some families and autosomal dominant in others [1].

δ–SPD is characterized by a bleeding diathesis of variable degree, mildly to moderately prolonged skin bleeding time, abnormal platelet secretion induced by several platelet agonists, and impaired platelet aggregation. Typically δ–SPD platelets have decreased levels of δ-granule constituents: ATP and ADP [65,66], serotonin, calcium and pyrophosphate [67,68]. The bleeding time is usually prolonged, and the extent of its prolongation is inversely related to the amount of ADP or serotonin contained in the granules [69,70].

Normal aggregation responses to ADP or epinephrine have been observed in some patients [71], indicating that there is a large variability in platelet aggregation in patients with δ–SPD. This has been well-documented in a large study of 106 patients with δ–SPD, which showed that about 25% of the patients had normal aggregation responses, while only 33% had aggregation tracings typical for a platelet secretion defect [63]. Lumia aggregationometry, which measures platelet aggregation and secretion simultaneously, may prove a more accurate technique than platelet aggreometry for diagnosing patients with δ–SPD and, more generally, with platelet secretion defects.

The Hermansky–Pudlak syndrome (HPS) and the Chediak–Hygashi syndrome (CHS) are rare syndromic forms of δ–SPD. HPS is an autosomal recessive disease of subcellular organelles of many tissues, involving abnormalities of melanosomes, platelet δ-granules and lysosomes [1]. It is characterized by tyrosinase-positive ocucutaneous albinism, a bleeding diathesis due to δ–SPD and ceroid–lupofuscin lysosomal storage disease. HPS can arise from mutations in different genetic loci [1,72–74]. CHS is also an autosomal recessive disorder, characterized by variable degrees of oculocutaneous albinism, very large peroxidase-positive cytoplasmic granules in a variety of hemopoietic (neutrophils) and non-hemopoietic cells, easy bruising due to δ–SPD, and recurrent infections, associated with neutropenia, impaired chemotaxis and bactericidal activity, and abnormal NK function [75]. The syndrome is lethal, leading to death usually in the first decade of life. The gene responsible for CHS is very large and several mutations have been described (reviewed in [1]).

Two types of hereditary thrombocytopenia: thrombocytopenia and absent radii syndrome [76], and the Wiskott–Aldrich syndrome [77] may be associated with δ–SPD.

Abnormalities of the α-granules

Gray platelet syndrome The condition owes its name to the gray appearance of the patient platelets in peripheral blood smears caused by the scarcity of platelet granules. Since its first description [78], about 40 new cases have been reported in the literature, many belonging to a single family in Japan. The inheritance pattern seems to be autosomal recessive, although in one family it seemed to be autosomal dominant. Affected patients have a lifelong history of mucocutaneous bleeding, which may vary from mild to moderate in severity, prolonged bleeding time, mild thrombocytopenia, abnormally large platelets and isolated reduction of the platelet α-granule content. Mild to moderate myelofibrosis has been described.
in some patients and hypothetically ascribed to the action of cytokines that are released by the hypogranular platelets and megakaryocytes in the bone marrow [79,80]. The basic defect in GPS is probably defective targeting and packaging of endogenously synthesized proteins in platelet α-granules.

**Quebec platelet disorder** The Quebec platelet disorder is an autosomal dominant qualitative platelet abnormality, characterized by severe post-traumatic bleeding complications unresponsive to platelet transfusion, abnormal proteolysis of α-granule proteins, severe deficiency of platelet factor V, deficiency of multimerin, reduced-to-normal platelet counts, and markedly decreased platelet aggregation induced by epinephrine [81,82]. Multimerin, one of the largest proteins found in the human body, is present in platelet α-granules and in endothelial cell Weibel–Palade bodies. It binds factor V and its activated form, factor Va. Its deficiency in patients with the Quebec platelet disorder is probably responsible for the defect in platelet factor V, which is likely to be degraded by abnormally regulated platelet proteases.

**Jacobsen or Paris–Trousseau syndrome** This is a rare syndrome that is associated with a mild hemorrhagic diathesis and is characterized by congenital thrombocytopenia, normal platelet life span, and increased number of narrow megakaryocytes, many of which present with signs of abnormal maturation and intramedullary lysis. A fraction of the circulating platelets have giant α-granules, which are unable to release their content upon platelet stimulation with thrombin. A deletion of the distal part of one chromosome 11 (del [11]q23.3qter) was found in the affected patients [83,84].

**Abnormalities of the α- and δ- granules (α,δ- storage pool deficiency)** α,δ-storage pool deficiency is characterized by deficiencies of both α- and δ-granules [85,86]. The clinical picture and the platelet aggregation abnormalities are similar to those of patients with δ-SPD.

**Abnormalities of the signal-transduction pathways** Congenital abnormalities of the arachidonate/thromboxane A₂ pathway, involving the liberation of arachidonic acid from membrane phospholipids, defects of cyclooxygenase or thromboxane synthetase are associated with platelet function defects and mild bleeding (reviewed in [1]). Other congenital abnormalities of the platelet signal-transduction pathways that have been described involve G-proteins (Gζ deficiency) [87], the phosphatidylinositol metabolism (partial selective PLC-α2 isozyme deficiency) [88], and defects in pleckstrin phosphorylation [89], which have been recently reviewed by Rao et al. [3].

Three patients were recently described, with a polymorphism of the gene encoding the extra-large stimulatory G-protein α-subunit (XLSα), associated with hyperresponsiveness of platelet, Gζ-enhanced intraplatelet cAMP generation and a bleeding syndrome [90]. The functional polymorphism in these patients involves the imprinted region of the XLS2gene, a phenomenon not described previously for platelet disorders but already known for defects expressing phenotypically in other tissues.

**Abnormalities of membrane phospholipids**

**Scott syndrome** This is a rare bleeding disorder associated with the maintenance of the asymmetry of the lipid bilayer in the membranes of blood cells, including platelets [91], leading to reduced thrombin generation and defective wound healing. The cause of the defect is still unclear [4].

**Stormorken syndrome** Resting platelets from patients with this syndrome display a full procoagulant activity [92]. Therefore, compared with the Scott syndrome, this condition represents the other side of the coin, yet surprisingly it is also associated with a bleeding tendency. Platelets respond normally to all agonists, with the exception of collagen.

**Miscellaneous abnormalities 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 [93]. The term was later used to indicate the platelet secretion defects not associated with platelet granule deficiencies or abnormalities of the arachidonate pathway [50,51] or, generally, all the abnormalities of platelet function associated with defects of signal transduction [94]. With the progression of our knowledge in platelet pathophysiology, this heterogeneous group, which includes the majority of patients with congenital disorders of platelet function [94], will become progressively smaller, losing those patients with better defined biochemical abnormalities responsible for their platelet secretion defect. For example, patients with heterozygous P2Y₁₂ deficiency were once included in this group of disorders until their biochemical abnormality was identified [50,51,61].

**Other platelet abnormalities**

Spontaneous platelet aggregation and decreased responses to thrombin are observed in patients with Montreal platelet syndrome, a rare and poorly characterized congenital thrombocytopenia with large platelets [95].

Platelet function abnormalities have been reported in osteogenesis imperfecta, Ehlers–Danlos syndrome, Marfan’s syndrome, hexokinase deficiency and glucose-6-phosphate deficiency [3].

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