Primary Thrombophilia XVI: A Look at the Genotype of the Sticky Platelet Syndrome Phenotype

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Abstract
The sticky platelet syndrome (SPS) was described by Mammen in 1983. Since then, scientists in several countries have identified the condition and published cases or series of patients, thus enabling the description of the prevalence of the inherited condition, its salient clinical features, and the treatment of the disease. The diagnosis of the SPS phenotype requires fresh blood samples and special equipment which is not available in all coagulation laboratories. In the era of molecular biology, up to now it has not been possible to define a clear association of the SPS phenotype with a specific molecular marker. Some molecular changes which have been described in platelet proteins in some persons with the phenotype of the SPS are here discussed. Nowadays, the SPS phenotype may be considered as a risk factor for thrombosis and most cases of the SPS developing vaso-occlusive episodes are the result of its coexistence with other thrombosis-prone conditions, some of the inherited and some of them acquired, thus leading to the concept of multifactorial thrombophilia. Ignoring all these evidence-based concepts is inappropriate, same as stating that the SPS is a nonentity simply because not all laboratories are endowed with adequate equipment to support the diagnosis.

Keywords
platelets, hyperaggregability, thrombosis, thrombophilia

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Introduction
Platelets were first described by the Italian pathologist Giulio Bizzozero in 1882 when he defined these cells as the third morphological element of blood. These small, anucleate cells travel as discoid fragments in the circulation, with an average circulating life span of 8 to 9 days. The development of this cell line is the paragon of an elegant and finely orchestrated series of cellular processes known as megakaryocytogenesis and thrombopoiesis. Megakaryocyte maturation hinges on nuclear duplication without cell division, resulting in giant cells. Cytoplasmic organelles are then organized into domains representing nascent platelets, demarcated by a network of invaginated plasma membranes; fragmentation of the megakaryocyte cytoplasm into individual platelets results from the shear forces of circulating blood, perhaps largely in the pulmonary circulation. Thrombopoietin is the dominant hormone controlling megakaryocyte development, but many cytokines and hormones also play a role, including interleukins 3, 6, and 11.

Platelets are unique in their structural assembly, and although they lack a nucleus, they contain several mitochondria. Their phospholipid bilayer plasma membrane is the site of expression of many thrombosis-prone conditions. The SPS phenotype may be considered as a risk factor for thrombosis and most cases of the SPS developing vaso-occlusive episodes are the result of its coexistence with other thrombosis-prone conditions, some of the inherited and some of them acquired, thus leading to the concept of multifactorial thrombophilia. Ignoring all these evidence-based concepts is inappropriate, same as stating that the SPS is a nonentity simply because not all laboratories are endowed with adequate equipment to support the diagnosis.

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of various surface receptors and lipid rafts that actively participate in many signaling pathways and intracellular trafficking. Platelet reactivity can be heavily influenced by biologically active markers such as CD36, CD41, CD42a, CD42b, and CD61. These include some active surface receptors and platelet secretory products. Platelets tend to alter the expression and signaling of these markers in different disease circumstances, and potentially compromising their prognoses, while also providing a broad field to explore disease progression. To date, we are still missing sufficient information on the physiological role of blood platelets, so an open field is available to clinicians and researchers to analyze and develop innovative findings, particularly in terms of aggregation and in the so-called sticky platelet syndrome (SPS).

A Brief Overview on Platelet Function

Platelets require many integrins and receptors to fulfill their functions. If a vessel is injured, the platelet’s proximity to the endothelial wall allows it to reach the subendothelial extracellular matrix exposed after injury, via cell-surface glycoprotein (GP) VI and integrin α2β1, as well as by binding of the von Willebrand factor (vWF) to the platelet’s surface GP Ib-IX-V complex. All these events are initiated by different signal pathways that have been discovered, activation of adenosine diphosphate (ADP) and ATP receptors, GP VI collagen receptor, and GP Ib-IX-V. Inhibitory, activator, and negative feedback signals have been described. Inhibitory signals allow platelets to remain in an inactivated state. Nitric oxide (NO) and prostacyclin 12 (PGI2) are the main vasoactive activator hormones. NO activates guanylyl cyclase and prostacyclin (PGI2) that in turn, activate cGMP-dependent Protein kinase G, and decrease intracellular calcium thus inducing cAMP production. Activation signals are responsible for platelet aggregation and thrombus formation; the process begins with adhesion receptor-mediated platelet activation, followed by signal-induced activation of G-protein-coupled receptors. Negative feedback signals regulate and control both inhibitory and excitatory signals.

Platelets play a primordial role in the mechanisms of hemostasis and thrombosis through aggregation and adhesion to the damaged vascular endothelium. This step requires the interaction between environmental factors and other platelets, triggering a complex process on the surface of the platelet membrane via specific receptors. Finally, the activation of platelets is strictly dependent on the interaction between the external and internal environment of the cell, and is mediated through membrane receptors; in terms of platelet adhesion, the most interesting receptors due to their critical roles, are the GP on the membrane surface, which are listed from the largest to the smallest size as I through IX. These GP belong to the integrin family and are α/β heterodimeric protein complexes. The most abundant platelet-specific integrin receptor on the surface of platelets is the IIb/IIIa (αIIb/β3) receptor, responsible for the binding of platelets to fibrinogen, collagen, prothrombin, vWF, thrombospondin, and vitronectin; its activity is one of the main promoters of platelet aggregation.

In addition, primary hemostasis relies on platelet adhesion, activation, secretion, and aggregation. The initial stimulus that initiates platelet adhesion is injury to the endothelium that consequently, mainly exposes collagen fibers and vWF; the interaction of platelets with these substrates provides the surface for platelet adhesion and serves as a key point for platelet activation. The binding of platelet surface receptors with their ligands activates various biochemical intracellular signaling pathways through second messengers, such as tyrosine kinase, calcium, phospholipase C, phosphoinositol-3-kinase, and cyclic AMP, among others. These lead to 4 essential changes in platelets:

- Modification of the actin cytoskeleton, whereby the originally discoid shape of the platelet changes into a sphere with long membrane projections.
- Membrane phospholipase A2 activity is stimulated by increased calcium concentrations within the platelets, which leads to the release of arachidonic acid (AA) from membrane phospholipids. Cyclooxygenase-1 converts AA to prostaglandin H2, an intermediate product that is further metabolized by thromboxane synthase into TXA2.
- Release of the content of both alpha (integral membrane proteins, coagulants, anticoagulants, fibrinolytic proteins, adhesion proteins) and dense intracellular platelet granules (cations, phosphates, bioactive amines, and nucleotides) into the canalicular system.
- Increased expression of GP IIb/IIIa on the platelet membrane, which allows its binding to soluble fibrinogen and promotes further platelet aggregation.

In summary, platelet aggregation is regulated primarily by the binding of GP IIb/IIIa to fibrinogen, and to a lesser extent, vWF, and fibronectin. Both molecules simultaneously act as a bridge between several platelets. This platelet–fibrinogen–platelet junction activates the platelet to initiate the clot aggregation process.

Some Molecular Features of the Platelet Function

Many efforts have been made to explore the impact of micro ribonucleic acids (miRNAs) on the expression of genes directed to fine-tune and decrease noise in protein expression, and in proteins that are active in the physiology and pathophysiology of platelets. Platelets contain many miRNAs, but few studies have established a connection between individual platelet miRNAs and platelet function. To date, specific functions of most miRNAs within platelets remain unexplored. Over the past several years, many reports have suggested that platelet miRNAs are biologically and clinically relevant: (i) they are tools to understand platelet physiology and MK gene expression; (ii) they are potential regulators of platelet RNA and
protein expression; and (iii) they are a source of circulating miRNAs.21

The first human platelet miRNA profiling was reported as part of a study testing the differential expression of miRNA in patients with polycythemia vera and established that miR-26b was significantly increased in these cases. Platelet reactivity is another disorder in which miR-96 was shown to down-regulate vesicle-associated membrane protein 8 mRNA expression and protein levels.22 miR-21 has recently been shown to attenuate platelet release of transforming growth factor β-1, a master regulator of fibrosis.23 Follow-up studies have varied considerably in terms of the most common miRNAs in platelets, miR-223-3p has been described as the most abundant platelet miRNA in numerous studies suggesting that it plays a role in disease. In previous reports, Elgheznawy et al24 found that miR-223 is decreased in diabetic subjects, while Stratz et al25 reported the opposite in patients with type 2 diabetes. In other studies, mice that are deficient in miR-223 exhibited shorter bleeding times, larger FeCl3-induced thrombi, greater sensitivity to low doses of thrombin, and impaired clot retraction; another report referred that platelet miR-223 expression appears to be decreased in subjects with increased on-clopidogrel activity.21

These are only a few examples of what represent new opportunities for future research. Table 1 summarizes the top 10 expressed miRNAs in mouse megakaryocytes and their precursors referred in several studies.26 These miRNAs open the door to progressively acquire new insights into the relationship between disease and platelet physiology.

### Salient Features of the SPS Phenotype

The SPS phenotype is a qualitative platelet disorder with familial occurrence (an autosomal dominant trait affecting both genders), defined by increased in vitro platelet aggregation after the addition of very low concentrations of ADP and/or epinephrine (EPI).27 This disorder remains multifactorial and predisposes to, rather than causes, thrombosis and often remains silent until a second insult to the coagulation system or vasculature occurs.28 Since thrombosis is a complex disorder involving the interaction between many different types of genes with environmental factors, and these processes culminate in the development and coexistence of more than 1 thrombosis-prone conditions (which can be inherited and some of them acquired), the term of multifactorial thrombophilia may be used.29

There is no characteristic clinical pattern to the SPS. Although clinical findings are very similar to those typically seen in patients with any other hereditary or secondary thrombophilia.30 Some authors have described that arterial thrombosis is the most common clinical manifestation of the syndrome. These observations have led to constant research on SPS since its discovery in 1983, in an attempt to weave a biologically plausible mechanism explaining the complexities of this pathological entity (Table 2).31 According to Bick et al, the SPS may be considered as a frequent cause of unexplained arterial thrombosis.32 Beside these reports, SPS is remarked as a risk factor to the development of venous or arterial thrombosis, migraine, graft-versus-host disease (GVHD), and pregnancy complications, particularly in states of physiological stress that exacerbate the risk of developing a thrombotic episode. However, not all patients with SPS are symptomatic or develop thrombotic complications.50

The exact prevalence of SPS is unknown due to the lack of studies focused on exploring the presence of this entity. Only a few countries have published studies on this syndrome, including Mexico, where it represents the second most frequent inherited thrombophilic condition identified in Mexican mestizos.51 SPS has been identified and published worldwide: A total of 1783 patients have been published from different parts of the world between 1988 and 2019 and informed that cases have increased in the last 10 years, most of them have been identified in Slovakia, the United States, Mexico, Germany, and Russia.48

### Overview of the Diagnosis of SPS

There has been extensive discussion over the years of whether SPS is a real entity due to the fact that there are multiple transient or persistent acquired factors which may induce a hyperreactive platelet phenotype. To establish a diagnosis of hereditary SPS, one must prove that the platelet hyperreactivity persists over time and that another family member expresses the same phenotype. Another controversial factor is the fact that the concentrations of agonists used have not been fully standardized, nor is the percent of platelet aggregation which is considered positive. The usual percent of platelet aggregation which is considered normal at full concentrations of agonist is greater than 60%. If this cutoff is reduced, or if the agonists are not sufficiently diluted, then a higher percentage of individuals will be considered to have hyperreactive platelets.52

The most widely used method in order to prove platelet hyper-aggregability is that described by Mammen (diagnostic criteria are described in Table 3).38 And according to the aggregation pattern, 3 types of the syndrome can be identified. Type II is the most common (hyperaggregability to EPI alone), followed by type I

### Table 1. Top miRNAs Expressed in Mice.

| Rank | CMPs    | MEP        | Megakaryocytes |
|------|---------|------------|---------------|
| 1    | miR-720 | miR-720    | miR-720       |
| 2    | miR-16  | miR-142-3p | miR-142-3p    |
| 3    | miR-142-3p | miR-16   | miR-16        |
| 4    | miR-30b | let-7      | miR-223       |
| 5    | miR-706 | miR-709    | miR-98        |
| 6    | miR-136 | miR-19b    | miR-18a       |
| 7    | miR-98  | miR-106a   | miR-709       |
| 8    | miR-18a | miR-19a    | miR-15b       |
| 9    | miR-15a | miR-15b    | miR-706       |
| 10   | miR-19b | miR-25     | miR-19b       |

**Abbreviations:** MEP, megakaryocyte–erythroid progenitors; CMPs, common myeloid progenitors.

**Source:** Ref.26
Table 2. Most Relevant Published Studies on Platelet Function and SPS (Adapted from Ref31).

| Year   | Study                                                        |
|--------|--------------------------------------------------------------|
| 1873   | Bizzozero and Osler: Platelets as separate components of blood were recognized in pioneering studies. |
| 1880   | The first quantitative and qualitative platelet disorders were described.32 |
| 1900-1910 | Hayem and Duke: The role of platelets in hemostasis was further demonstrated in several clinical studies. |
| 1962   | Born and O’Brienin: Introduction of turbidimetric platelet aggregometry.33,34 |
| 1978   | Ten Cate et al: Described platelet aggregation in a cohort of 50 patients with transient ischemic attack (TIA) or cerebral infarction. They proposed a possible platelet defect as the cause of these events.35 |
| 1979   | Weiss et al: Publication of the first treaty on the prothrombotic qualitative platelet disorder.36 |
| 1980   | Mûhtfeld et al: Described 22 patients with transient ischemic attack (TIA), all showing on repeated testing, an increase in platelet adhesion and/or aggregation; they suggested that this platelet hyperaggregability could be the underlying cause of TIA in those individuals. |
| 1983   | Holiday et al: The first recognition of SPS as a distinct disorder of hemostasis, at the 9th International Conference on Stroke and Cerebral Circulation in Arizona.37 |
| 1984   | Mammen: Published a case report of a 24-year-old woman that suffered an acute MI while pregnant. There were no identifiable risk factors or disease.38 |
| 1988   | Mammen et al: Published the first large series of patients with the sticky platelet syndrome (SPS). |
| 1995   | Mammen et al: Summed up their 10-year experience with this most probably inherited platelet defect characterized by increased platelet aggregability with ADP and/or EPI.39 |
| 1996   | Mammen et al: In studies including over 200 patients, they identified 2 types of patients: one with the classic hyperaggregability of platelets to ADP and epinephrine, now referred to as type I, and the other, with hyperaggregability only with epinephrine, type II.39 |
| 1997   | Berg-Dammer et al: In a case report of 2 patients in Germany with cerebrovascular thromboses, therapy with low-dose aspirin normalized the hyperaggregable platelet state.40 |
| 1998   | -Chittoor et al: Reported the case of a 30-year-old woman who initially suffered thrombosis of the superior sagittal sinus manifested as sudden visual disturbances. -Bick: Was among the first to describe SPS in patients with venous thrombosis.41 |
| 1999   | Andersen: Reported her experience with 195 prospectively screened patients with arterial, venous, or mixed thromboses.42 |
| XXI century | Chaturvedi and Dzieczkowski: The first to describe the occurrence of SPS in association with other inherited thrombophilic disorders in the same individual.43 |
| 2004   | Lewerenz et al: SPS as a cause of cutaneous changes. |
| 2007   | Mûhtfeld et al: SPS as a cause of graft dysfunction (kidney). |
| 2010   | Kubisz et al and Ruiz Argüelles et al: SNP’s of PLT proteins studied in SPS. |
| 2013   | Ruiz Argüelles et al: The first prospective study on the treatment of SPS. |
| 2017   | Sokol et al: Recommendations for the standardization of aggregometry, SPS diagnostic criteria.44 |
| 2019   | Peter Kubisz et al: Sticky Platelet Syndrome: 35 Years of Growing Evidence.45 |
| 2019   | Yagmur et al: Demonstration of the clinical and diagnostic relevance of platelet hyperaggregability in women with infertility and a history of miscarriage, in a study conducted in Germany.46 |
| 2019   | Garcia-Navarrete YI et al: Antithrombotic treatment of sticky platelet syndrome worldwide.47 |
| 2020   | Vallejo-Villalobos et al: Primary Thrombophilia XIV: Worldwide Identification of the Sticky Platelet Syndrome.48 |
| 2020   | Vadelova L et al: Possible association of miR-96 in patients with SPS and pregnancy complications.49 |

(hyperaggregability to ADP and EPI), whereas type III (hyperaggregability to ADP alone) is infrequent.53 (see Figure 1).54

SPS and Current Management

Treatment of SPS relies on attenuate the abnormal platelet hyperaggregability with antiplatelet drugs. In most cases, acetylsalicylic acid (ASA) appears to be an adequate option but there are situations in which other antiplatelet drugs are needed.47 Patients that are allergic or intolerant to aspirin can be managed with clopidogrel, and in cases in which platelet hyperreactivity persists over an established time period, the combination of ASA and clopidogrel at the usual doses appears to provide good results. For example, in a study published in 2015 which analyzed the results of treatment in 55 patients with SPS

Table 3. Diagnostic Criteria for SPS.

| Laboratory Classification: |
|---------------------------|
| • Type I: Hyperaggregability with EPI and with ADP |
| • Type II: Hyperaggregability with EPI only |
| • Type III: Hyperaggregability with ADP only |

Suggestive of diagnosis: Hyperaggregability with only 1 reagent and only 1 concentration, and a history of thrombosis Firm diagnosis:43 History of thrombosis plus:

1. Platelet hyperaggregability with 2 concentrations and 2 different reagents
2. Hyperaggregability at 1 concentration with 2 different reagents
3. Abnormalities with a single concentration and with 1 reagent on 2 occasions

Abbreviations: SPS, sticky platelet syndrome; EPI, epinephrine; ADP, adenosine diphosphate.

Source: Ref.33
followed for a median of 129 months, the authors found that after the administration of antiplatelet drugs, particularly ASA platelet hyperreactivity in patients with the SPS phenotype could be reverted, leading to a substantial decrease in the rate of rethrombosis. All 55 patients included in the study had at least 1 episode of thrombosis before starting treatment, but once administered, rethrombosis episodes decreased to 3.6% at 129 months.55

New Molecular Insights and Their Relationship with Other Conditions

After more than 30 years of research, the definition of the SPS requires an update since this syndrome has a multifactorial etiology in which genetic and environmental factors may play an active role.33 Table 4 shows the most common genes associated to the condition.56 The genetic origin proposed for some authors as we previously mentioned, relies on the mutations on the membrane GPs, mainly the GP6 gene mutation which encodes GPVI: a crucial platelet membrane GP important for an adequate platelet activation, adhesion, and aggregation.57,58

In a recent study, there was found an increased frequency of major haplotype TTGTGA and 2 minor haplotypes CGATAA and

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**Table 4. Genes Related to the Sticky Platelet Syndrome**

| Symbol | Description                                  |
|--------|----------------------------------------------|
| GP6    | Glycoprotein VI Platelet                      |
| GAS6   | Growth Arrest Specific 6                      |
| F5     | Coagulation Factor V                           |
| ITGB3  | Integrin Subunit Beta 3                        |
| PEAR1  | Platelet Endothelial Aggregation Receptor 1   |
| SERPINC1 | Serpin Family C Member 1                      |
| SERPIN E1 | Serpin Family E Member 1                      |

Malacards.org. (referred on May 6, 2021). Available at: https://www.malacards.org/card/sticky_platelet_syndrome.
and TTGTGG of GP6 gene in patients with SPS, they also observed that the allele G of a single nucleotide polymorphism (SNP) rs12610286 and major haplotype TTGTGA were significantly increased in patients with SPS type I and stroke. Kotuščić et al. found in a case-control study an increased occurrence of SNPs 1613662 and 1654419 in patients with SPS and history of deep venous thrombosis (DVT). Also, the risk of developing DVT in patients with SPS is related with the presence of other risk factors, including some gene polymorphisms. On the other hand, Sokol et al found that ADRA2A allele (rs1800545) might be an independent risk factor, and that PEAR1 alleles (rs12041331 and rs12566888) might be an independent protective factors for DVT in patients with SPS type II. Kotuščić et al. found in a case-control study an increased occurrence of SNPs 1613662 and 1654419 in patients with SPS and history of deep venous thrombosis (DVT). Also, the risk of developing DVT in patients with SPS is related with the presence of other risk factors, including some gene polymorphisms. On the other hand, Sokol et al found that ADRA2A allele (rs1800545) might be an independent risk factor, and that PEAR1 alleles (rs12041331 and rs12566888) might be an independent protective factors for DVT in patients with SPS type II.60 In a case-control study SNPs 1671153, 1613662, and 1654419 were more frequent in patients with SPS and pregnancy loss according to Sokol et al.61 On the other hand, Vadelova et al. found a considerably increased expression of platelet miR-96 in patients with SPS and pregnancy complications, while miR-223 and miR-126 were not correlated with miscarriages.

In the SPS, there are only a few studies regarding the role of m-RNA in the physiopathology of this condition, most of them related with chronic degenerative diseases and infertility. Diabetes mellitus (DM) is associated with a hypercoagulable state, specifically, signaling pathways in the platelets of diabetic patients are dysregulated, leading to platelet hyperactivation and an increased risk of microcapillary embolization. In a state of hyperglycemia, platelets are more prone to aggregation through nonenzymatic glycation of platelet membrane proteins and consequently increased expression of certain GPs (Ib-IX, IIb/IIIa) and receptors necessary for platelet function. As is well known, DM is related to overexpression of inflammatory cytokines, which may stimulate endothelial expression of factor VIII and vWF, as well as increase vascular cell adhesion molecules, endothelin-1 and E-selectin, and decrease the production of NO and prostacyclin, all contributing to endothelial cell injury and a prothrombotic state. Considering SPS as a state of platelet hyperaggregability, many questions have arisen on its possible role in the complex pathogenesis of diabetic microvascular complications. Hence, different authors have questioned whether DM patients with an early onset of chronic complications should be screened for the presence of the SPS. Several studies have shown that individuals with DM have increased platelet activation, and that this could potentially be explained by an abnormality in miRNA, such as the previously described miR-223, miR-26b, and miR-126 leading to dysregulation in platelet function.46

Recent investigations have centered on the relationship between the presence of the SPS and infertility and/or miscarriage. Pregnancy is well known to represent a hypercoagulable state which predisposes to the development of thrombi and secondarily, to pregnancy complications and miscarriage. In one of our previous prospective study, we analyzed 108 thrombophilic women and found a relative risk of 2.66 of having a miscarriage in female patients with SPS in comparison with healthy females. Some studies support our data and have shown that recurrent miscarriage and infertility could be related in patients with undiagnosed SPS. Yagmur et al. studied 208 patients with infertility for 11 years, and found that 33.2% of the patients with SPS had a history of miscarriage. These observations are interesting since a molecular mechanism could be related to that clinical outcome.
Closing Remarks

As a result of our interest in the SPS, we have been able to learn several pieces of information on the SPS which are summarized in Table 5.

The genetic and molecular influence within the pathogenesis of SPS must be a trigger to adopt newer molecular tests to perform new investigations capable of demonstrating the role of new miRNA in the physiopathology of the SPS, and the activation of platelet aggregation. Moreover, and considering the molecular basis of the pathogenesis in SPS in which miR-26b, miR-223, and miR-126 regulated genes play an important role; we could take them as key targets to create new antiplatelet drug therapies in SPS and other hyper aggregation states.

The importance of these studies and the need of further studies lies not only in the establishment of new biomarkers but also in the creation of new therapies and an adequate approach as well as evaluate the possible impact of SPS in other important and frequent conditions.

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