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## Five (un)easy pieces: the MYH9-related giant platelet syndromes

The pace in defining the molecular basis of megakaryocyte/platelet development and function continues to accelerate. This is readily apparent from the growing list of recognized critical cytokines, their receptors and downstream pathways and transcription factors.[1-4] It should be foreseen that the resources and data provided by the Human Genome Project applied to the study of inherited platelet defects will not only quicken this pace but should also lead to novel and sometimes unexpected insights.

A classic example of the potential power of these hereditary diseases in understanding platelet function is provided by the rare autosomal dominant Bernard-Soulier syndrome (BSS; MIM 231200). It can be said that the pre-Human Genome Project molecular analysis of this giant platelet syndrome, first described over 50 years ago,[5] helped to firmly establish the importance of the GPIb-V-IX complex. In this issue of *Haematologica*, DiPumpo *et al.*[6] present results which begin to explore the pathogenic mechanisms underlying an interesting family of giant platelet disorders in which the genetic defect has only recently been determined. Seemingly, the GPIb-V-IX complex is becoming established as a common pathway.

Until two years ago, the five autosomal dominant giant-platelet disorders, May-Hegglin anomaly (MHA; MIM 155100), and Sebastian (SBS; MIM 605249), Fechtner (FTNS; MIM 153640), Epstein (EPS; MIM 153650) and Alport-like syndromes with macrothrombocytopenia (APSM; MIM 153650) were categorized as unrelated disorders of unknown etiologies. Interestingly, and despite their broad phenotypic spectrum, overlapping clinical and morphologic features suggested a possible genetic link. MHA, SBS, and FTNS uniquely possess characteristic paracrystalline leukocyte inclusions (Döhle-like bodies). These pale blue staining cytoplasmic inclusions were first noted by May almost 100 years ago.[7] FTNS is distinguished by the additional clinical features of high-tone sensorineural deafness, cataracts, and nephritis. APSM is similar to FTNS except that Döhle-like inclusions have not been described and it is distinguished from the classical X-linked form of Alport syndrome in that COL4A5 gene mutations are not present. Finally, EPS is similar to both FTNS and APSM, except that cataracts and leukocyte inclusions have not been described.

Recently, we and others have mapped the genetic defect underlying all five of these syndromes to chromosome 22q11-13[8-11] and established that all are caused by mutations in the non-muscle myosin heavy chain IIA gene.[12-15] Hence, MHA, SBS, FTNS, EPS, and APSM represent a class of allelic disorders with phenotypic diversity and we have proposed the name myosin heavy chain 9 syndrome to encompass them.[14]

MYH9 is expressed in many different tissues, including platelets, leukocytes, kidney, and cochlea, is part of a hexameric enzyme complex, which binds actin, has ATPase activity, and is required for motor activity.[16] The genetic studies suggest that mutations in MYH9 are involved in the pathogenesis of macrothrombocytopenia, bleeding, deafness, cataracts, and nephritis. Obviously, therefore, MYH9 must also play a role in the normal development and maintenance of these cells, processes and structures.

How then is this balance maintained? Most likely, the understanding of the pathogenic mechanisms will be driven by biochemical extension of the genetic findings. A possible biological basis to the bleeding defect in MHA and SBS has now been described. DiPumpo *et al.*,[6] present novel findings suggesting a linkage between MYH9 mutations and an alteration in platelet surface expression of the GPIb-V-IX complex. Specifically, following size fractionation of platelets from genetically defined MHA and SBS affected subjects, the authors demonstrated that 7/8 individuals had decreased

levels of surface complex expression. These results were most notable in large-sized platelet subpopulations. The implication is that the bleeding tendency in these disorders is secondary to abnormal *in vivo* platelet-vessel wall and platelet-platelet interactions caused by decreased levels of GPIb-V-IX. An interesting finding given the necessary interconnection between cytoskeletal components and membrane proteins. This suggested mechanism deserves to be explored in the future.

These interesting observations represent the first extension to exploring the altered downstream pathways which lead to bleeding dysfunction in the MYH9-related disorders. The shared pathway with BSS of decreased GPIb-V-IX complex seems to satisfy one question. However, these results do not explain the macrothrombocytopenia shared between all these disorders, including BSS. Therefore, as with any good result, more questions have arisen in this puzzle. Clearly, the challenges ahead are exciting.

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## Imatinib: can one outwit chronic myeloid leukemia?

Imatinib mesylate (IM), or STI571, or Glivec, is a landmark medicine of which both the pharmaceutical industry and the hematology community can be justly proud. Indeed, it illustrates one of the few cases in which the precise knowledge of the molecular basis of a neoplastic condition has led to a deliberate search for a chemical that would target the crucial molecule, in this case the ABL protein tyrosine kinase (PTK). Within less than 20 years since the cloning of the BCR-ABL fusion gene,[1] we now have the results of highly significant clinical trials,[2,3] and a drug available in the pharmacy that can be prescribed to patients when appropriate. In this issue of Haematologica Marin *et al.* provide an authoritative review on the clinical use of IM in patients with chronic myeloid leukemia (CML).[4]

The analogy between chemotherapeutic agents that recognize a target specific to abnormal somatic cells and antibiotics that recognize a target specific to bacterial cells is evident. Since the introduction of penicillin or streptomycin, it took only a few years to observe that bacteria could *become resistant* to these agents. It took only a few more years to realize that this phenomenon was not due to some sort of adaptive process, but to selection by the antibiotic of bacterial mutants that already existed before exposure to the antibiotic itself.[5] In the case of IM, the initial clinical description has