


---

**Clinical Observations**

Comment on Landgren et al, page 2199

**MPDs: it’s all in the family**

Jerry L. Spivak | Johns Hopkins University School of Medicine

Dameshek was wrong. In this issue of Blood, in a landmark epidemiologic study, Landgren and colleagues demonstrate that first-degree relatives (parents, siblings, and offspring) of Swedish myeloproliferative disorder (MPD) patients have a 5- to 7-fold increased risk of developing an MPD.

Once thought to be rare and mainly reportable as such, a Polycythemia Vera Study Group (PVSG) analysis of 652 polycythemia vera (PV) patients found 5 with similarly affected parents, suggesting the possibility of familial PV. Gilbert was the first to challenge the perception that MPDs in general were random in occurrence and that familial MPD was rare. From the literature and a survey of MPD patients, she was able to collect 42 families in which an MPD occurred in up to 3 generations, and in 50% of the pedigrees more than one type of MPD was represented. In a more recent survey of 438 MPD patients, 35 families with at least 2 affected members were identified, a prevalence of 7.6%, and the frequencies were similar for PV (8.7%), essential thrombocythemia (ET, at 5.9%), and primary myelofibrosis (PMF, at 8.2%). In this study, more than 2 generations were involved in 60% of the pedigrees, while 60% had a single MPD phenotype with PV in the majority. In the largest report to date, involving 174 patients in 72 families, similar observations were made.

Landgren and colleagues took a different approach. They exploited the interlocking Swedish healthcare and population databases, for which every resident is assigned a unique registration number. In this way, between 1958 and 2005, they were able to collect data on 11,039 MPD patients (6217 PV, 2838 ET, 1172 PMF, and 812 MPD not otherwise specified) with 24,577 first-degree relatives, and 43,550 matched controls with 99,542 first-degree relatives, giving their observations substantial statistical power. Not only was there an increased risk of acquiring an MPD among the first-degree relatives, but the risk also did not differ for a particular MPD, although the low number of PMF patients made the predictions for it less reliable. Furthermore, the risk among the first-degree relatives of patients with a particular MPD was not restricted to that MPD. Among the first-degree relatives, a higher risk was also observed for siblings, suggesting the possibility of recessive inheritance, although most smaller studies support an autosomal-dominant inheritance with variable penetrance. 4, 6 Importantly, in keeping with the female predominance in PV and ET, there was a higher risk for female relatives and the relatives of female probands compared with their male counterparts. In contrast to a smaller study, 4 no evidence was found for anticipation, although anticipation has been a feature of other familial hematologic neoplasms. There was no increased risk among the first-degree relatives for acute myeloid leukemia or myelodysplastic syndrome, but there was a borderline risk for chronic myeloid leukemia (CML) and a significantly increased risk for chronic lymphocytic leukemia (CLL), malignant melanoma, and brain cancer.

What conclusions can be drawn from this study? First, since a relatively genetically homogenous population was studied, the observations may not be totally applicable to other population groups. For example, in the United States, the age of MPD onset is lower, particularly in women with PV or ET. Second, given the high risk for an MPD in first-degree relatives, the term sporadic should be applied cautiously when a new MPD patient is encountered. In this regard, the familial MPDs are clinically similar to their sporadic counterparts with the exception that the frequency of JAK2 V617F expression is reduced in familial PV. 4, 3 Third, Dameshek was actually partially correct. While a higher risk for acquisition of a hematologic malignancy is seen in families in which there is a hematologic malignancy, acquisition of the same type of malignancy at such a high frequency is unusual, supporting the contention that PV, ET, and PMF have a common genetic basis. In this regard, the risk for acquiring CLL as well as CML should probably be considered as part of the general tendency for familial aggregation of hematologic malignancies and not specific to the MPD, particularly since CML is rarely familial. Fourth, the increase in ET prevalence, which coincided in part with a switch by Swedish hematologists from using the PVSG diagnostic criteria to the World Health Organization (WHO) MPD diagnostic criteria, probably reflects the unacceptable insensitivity of the WHO diagnostic criteria for recognizing PV. This is unfortunate, because PV is the ultimate phenotypic expression of the JAK2 V617F mutation. Finally, the data of Landgren and colleagues serve to remind us that in MPDs, phenotype is driven as much and possibly more by as-yet-undefined genetic influences as it is by those that have been defined.

Conflict-of-interest disclosure: The author declares no competing financial interests.

**References**

1. Dameshek W. Physiopathology and course of polycythemia vera as related to therapy. JAMA. 1950;142:790-797.


4. Rumi E, Passamonti F, Della Porta MG, et al. Familial chronic myeloproliferative disorders: clinical phenotype...
Comment on Pluskota et al, page 2327

Microparticles facilitate neutrophil/platelet crosstalk

Robert K. Andrews and Michael C. Berndt
Monash University; University College Cork

In this issue of Blood, Pluskota and colleagues reveal a new prothrombotic pathway initiated by neutrophil-derived microparticles through the interaction of the leukocyte integrin Mac-1 (αMβ2) on microparticles with its counterreceptor on platelets, GPIbα, the major ligand-binding subunit of the GPIb-IX-V complex (see figure). These findings have broad implications for the pathogenesis, monitoring, and/or future therapy of inflammatory/thrombotic disease.

All inflammatory/thrombotic vascular cells (leukocytes, platelets, endothelial cells) generate microparticles, small membrane-bound vesicles budded off from the parent cell that generally reflect that cell’s surface-receptor profile. Microparticles are not just by-products of cellular activation or apoptosis, but are functional and modulate the activity of other cells. They also represent potentially selective biomarkers of diseases involving cellular perturbation. One important role for leukocyte-derived microparticles is to deliver clot-promoting tissue factor rapidly to a developing thrombus. In this case, P-selectin glycoprotein ligand-1 (PSGL-1) on the microparticle targets activated platelets by binding platelet P-selectin. Activated platelets are also strongly procoagulant due to increased exposure of phosphatidyl serine, the expression of coagulation factor-binding receptors, the secretion of polyphosphates, and through glycoprotein (GP) Ibα, which acts as a molecular scaffold localizing coagulation factors such as high-molecular-weight kininogen, factors XI and XII, and thrombin. Interestingly, the present findings indicate that leukocyte-derived microparticles play another potential role in thrombus development by acting as a novel platelet agonist targeting GPIbα. This provides a potential explanation of how chronic inflammation can perpetuate a prothrombotic phenotype.

Pluskota and colleagues show that microparticles derived from activated neutrophils express functional Mac-1 and act as platelet agonists by virtue of Mac-1 binding platelet GPIbα. GPIbα is a constitutively expressed platelet-adhesion receptor that initiates thrombus formation at arterial shear rates by binding von Willebrand factor (VWF) or other ligands. Engagement of GPIbα by Mac-1–bearing microparticles leads to phosphorylation of the signaling protein Akt, which is an intermediary in GPIbα-dependent signaling downstream of phosphatidylinositol (PI) 3-kinase activation, and upstream of surface expression of P-selectin and activation of αIIbβ3 (which binds fibrinogen and VWF and mediates
MPDs: it's all in the family

Jerry L. Spivak