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**Jan Jacques Michiels^{1,2}**¹Erasmus University Medical Center, Netherlands²Goodheart Institute, Netherlands**Sticky platelet syndrome and MPN disease burden in JAK2 thrombocythemia and polycythemia vera, and in JAK2, mpl and calr thrombocythemias: Implications for novel non-leukemogenic treatment options in prefibrotic myeloproliferative neoplasms anno 2018**

Hypersensitive (sticky) platelets in JAK2-mutated essential thrombocythemia (ET) and polycythemia vera (PV) with thrombocythemia spontaneously activate at high shear in arterioles, secrete their inflammatory prostaglandin endo-peroxides and induce platelet-mediated arteriolar fibromuscular intimal proliferation. Increased production of prostaglandin endoperoxides E2 and thromboxane A2 released by activated sticky platelets in arterioles account for redness warmth and swelling of erythromelalgia and platelet derived growth factor (PDGF) can readily explain the arteriolar fibromuscular intimal proliferation. The von Willebrand factor (VWF) platelet rich occlusive thrombi in arterioles are the underlying etiopathophysiology of erythromelalgic acrocyanosis, migraine-like transient cerebral attacks (MIAs) and the coronary and abdominal microvascular ischemic events. The irreversible platelet cyclooxygenase inhibition by aspirin cures the erythromelalgia, MIAs and microvascular events, corrects shortened platelet survival to normal, and returns increased plasma levels of beta-TG, platelet factor 4, thrombomodulin and urinary thromboxane B2 excretion to normal in symptomatic JAK2-thrombocythemia patients. *In vivo* activation of sticky platelets and VWF-platelet aggregates account for endothelial cell activation to secrete thrombomodulin and sVCAM followed by occlusion of arterioles by VWF-rich platelet thrombi in patients with erythromelalgic thrombotic thrombocythemia (ETT) in ET and PV patients. ETT is complicated by spontaneous hemorrhagic thrombocythemia (HT) or paradoxical ETT/HT due to acquired von Willebrand disease type 2A at platelet counts above $1000 \times 10^9/L$, which disappear by correction of platelets to normal ($<400 \times 10^9/L$). A new set of International Clinical, Laboratory, Molecular and Pathological (CLMP) criteria for myeloproliferative neoplasms (MPN) define the JAK2^{V617F} trilinear MPNs as a broad continuum of essential thrombocythemia (ET), polycythemia vera (PV), masked PV and post-ET or post-PV myelofibrosis (MF). Normal vs increased erythrocyte counts ($5.8 \times 10^{12}/L$) on top of bone marrow histology separate JAK2^{V617F} ET and prodromal PV from early and classical PV are diagnostic for JAK2^{V617F} trilinear MPN obviating the need of red cell mass measurement. The JAK2^{V617F} trilinear MPNs, JAK2 exon 12 PV, MPL515 thrombocythemia and calreticulin (CALR) thrombocythemia and MF mutually exclude each other. JAK2, MPL and CALR MPN disease burden is best reflected by the degree of anemia, splenomegaly, mutation allele burden, bone marrow cellularity and myelofibrosis. Bone marrow histology of the JAK2^{V617F} trilinear MPNs show variable degrees of erythrocytic (E), megakaryocytic (M), and granulocytic (G) myeloproliferation, peripheral cytoses and splenomegaly related to low intermediate and high JAK2 allele burden. MPL515 thrombocythemia displayed predominantly normocellular megakaryocytic (M) proliferation. CALR thrombocythemia initially presents with megakaryocytic (M) followed by dual granulocytic and megakaryocytic (GM) myelo-proliferation without features of PV. CALR thrombocythemia is featured by dense clustered large immature dysmorphic megakaryocytes with bulky (bulbous) hyperchromatic nuclei, which are never seen in JAK2^{V617F}, JAK2 exon 12 MPN and MPL515 thrombocythemia. Low dose aspirin in thrombocythemia and on top of phlebotomy in PV patients is mandatory for thrombosis reduction and pegylated interferon, hydroxyurea or ruxolitinib for control of MPN burden. Reduction of platelets and leukocytes to normal by pegylated interferon to postpone or eliminate the use of hydroxyurea does reduce and even can eliminate the thrombotic risk and reduce MPN burden in JAK2^{V617F} prodromal PV and in JAK2, CALR and MPL thrombocythemia.

Biography

Jan Jacques Michiels is the Professor of Nature Medicine and Health, Clinical and Molecular Genetics, Blood and Coagulation Research at the University Hospitals Antwerp, Brussels. He is the Editor of *Journal of Hematology & Thromboembolic Diseases*, *World Journal of Hematology* and Editor in Chief of *World Journal of Clinical Cases*.

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