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JAK out of the box: MPN-associated JAK2 V617F mutations contribute to aortic aneurysms

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Myeloproliferative neoplasms (MPNs) are clonal disorders of hematopoiesis arising in the hematopoietic stem cell (HSC) compartment and characterized by the excess production of mature myeloid cells (1). The BCR-ABL-negative MPNs include polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). PV is characterized by uncontrolled red blood cell production; ET, by megakaryocytic hyperplasia and elevated platelet counts; and MF, by megakaryocytic hyperplasia and bone marrow fibrosis. The molecular basis of MPNs remained unknown until 2005, when four different groups described a point mutation in the pseudokinase domain of Janus kinase-2 (JAK2), a non-receptor tyrosine kinase, in the majority of MPN patients. The resulting JAK2 V617F mutant protein was found to be constitutively active, leading to hyperactive JAK-STAT signaling downstream of multiple hematopoietic cytokine receptors (2-5).

Although MPNs, particularly PV and ET, are commonly characterized as “indolent” diseases, patients have significantly decreased life expectancies compared to the general population. JAK2 V617F mutations are associated with increased vascular complications, which to date primarily include venous and arterial thrombosis and advanced atherosclerosis (6, 7). Indeed, fatal thrombotic events represent the leading cause of death in JAK2 V617F-positive MPN patients, though the underlying mechanisms remain elusive. Mouse models of JAK2 V617F-driven MPN faithfully recapitulate this phenotype, with lethality primarily attributed to thrombosis (8).

Interestingly, the prevalence of the JAK2 V617F mutation has also been found to be significantly increased in non-MPN patients with coronary artery disease and peripheral artery disease (9, 10), suggesting that the JAK2 V617F mutation may play a role in additional vascular diseases. This observation is supported by the phenomenon of clonal hematopoiesis, in which clonal expansion of hematopoietic cells carrying is associated with significantly increased risk of vascular disorders (11). However, the mechanisms underlying JAK2 V617F-mediated vascular disease remain unclear, and the association of JAK2 V617F with vascular diseases outside of thrombosis, atherosclerosis, CAD and PAD has yet to be studied.

In this issue of Haematologica (12), Yokokawa et al investigate the contribution of bone marrow (BM)-derived JAK2 V617F to the development of aortic aneurysms (AAs), a vascular disease not yet studied in MPN patients. AAs often progress asymptotically and can lead to sudden death, so understanding the mechanisms underlying their onset and associated risk factors is critically important. Here, the authors perform a prevalence study in 39 JAK2 V617F-positive MPN patients, and found that 23% displayed signs of AA. Intriguingly, they find that JAK2 V617F-positive circulating leukocytes demonstrated up-regulation of genes associated with AAs, including matrix metalloproteinase 9 (MMP-9), which plays a well-established role in AAs. This
finding provided the authors’ first insight into the potential mechanism underlying JAK2 V617F-mediated AA.

To further understand the role that hematopoietic-derived JAK2 V617F plays in the development of AAs, the authors turn to a well characterized bone marrow transplantation (BMT) model of JAK2 V617F-driven MPN, in which JAK2 V617F expression is restricted to donor bone marrow cells. Here, the authors utilize mice deficient in apolipoprotein E (ApoE−/−) as recipients, and subject them to continuous infusion of angiotensin II (AngII), a model that has been shown to promote development and expansion of AAs. In their endpoint analysis, the authors compare animals receiving wild type (WT) versus JAK2 V617F-expressing BM cells, and find that, in addition to the expected MPN-like phenotype, JAK2 V617F BMT mice exhibit significantly increased abdominal aorta diameter, indicative of abdominal AAs (AAAs). Moreover, they find that JAK2 V617F expression accelerated the AAA hallmark of arterial extracellular matrix proteolysis as measured by aortic elastic lamina degradation, and led to activation of MMP-9 as well as MMP-2 in the abdominal aorta, both of which are required to produce AAAs. Together, these results suggest that bone marrow-derived JAK2 V617F promotes the development of AAAs.

Digging deeper into the molecular mechanism underlying how JAK2 V617F leads to the development of AAAs, the authors find infiltration of JAK2 V617F-mutant inflammatory cells, including CD68+ macrophages and Ly6B.2+ neutrophils, as well as increased phosphorylation of JAK2 V617F target STAT3, in the abdominal aortas of JAK2 V617F BMT mice receiving AngII. They go on to show that the inflammatory cells are strictly BM-derived, confirming that it is indeed hematopoietic JAK2 V617F causing the development of AAAs in these animals. Finally and most intriguingly, they show that JAK2 V617F BM-derived CD68+ macrophages exhibit significantly increased mRNA expression levels of Mmp2 and Mmp9, both of which could be decreased upon treatment with JAK2 inhibitor ruxolitinib. Additionally, AngII-treated JAK2 V617F BMT mice treated with ruxolitinib experienced decreased incidence of AAAs. These data suggest that JAK2 V617F promotes activation of MMPs in BM-derived inflammatory cells, which leads to AAA development (Figure 1).

Taken together, the results from this study identify a novel vascular disorder associated with JAK2 V617F mutations, provide a direct link between JAK2 V617F and the pathogenesis of AAAs, and offer an additional therapeutic application for FDA-approved JAK2 inhibitors in the prevention of AAA development in JAK2 V617F-positive MPN patients.
References

Figure 1. Hematopoietic JAK2 V617F mutations lead to the development of abdominal aortic aneurysms (AAA). Somatic JAK2 V617F mutations are acquired in the bone marrow at the hematopoietic stem cell (HSC) level. The resulting bone marrow-derived JAK2 V617F-mutated macrophages infiltrate the abdominal aorta, where they demonstrate increased levels of two genes critical for aortic aneurysm formation, matrix metalloproteins 2 and 9 (MMP-2, MMP-9). This expression and the resulting AAA are decreased upon treatment with a JAK inhibitor, ruxolitinib, confirming that the development of AAA is mediated by JAK2 V617F.