JAK2 and Endothelial Function: New Options for Anti-Thrombotic Therapies

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The activation of Janus kinases (JAKs) is a crucial enzymatic step in the signal transduction of many growth factors and cytokines. Four members, JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) have been identified and they all are well-known due to their function in the haematopoietic and immune system. Their profound involvement in the regulation of the immune response made JAKs to be attractive drug targets for inflammatory disorders such as rheumatoid arthritis and cancers of the immune system such as multiple myeloma. Genetic alterations of JAKs were described for all four JAKs and associated with human diseases. While inherited loss of function mutations in JAK3 and TYK2 were found in severe combined immune deficiency and atopic dermatitis, respectively, somatic gain of function mutations in JAK1, JAK2 and JAK3 resulted in myeloproliferative neoplasms (MPNs) and leukaemia/lymphomas. For example, generation of fusion proteins consisting of JAK2 and TEL, breakpoint cluster region (BCR) or pericentriolar material-1 were described in chronic myeloid leukaemia, acute myeloid leukaemia or acute lymphoblastic leukaemia. In addition, the point mutation JAK2V617F gained fame after it was identified as the major driving force in non-BCR-ABL1 MPNs in particular in polycythaemia vera, essential thrombocythaemia and primary myelofibrosis. The JAK2V617F mutation can also be found, but much less frequent, in the hypereosinophilic syndrome, chronic or juvenile myelomonocytic leukaemia, acute myeloid leukaemia and refractory anaemia with ringed sideroblasts (for review see Haan et al.).

So far, it was common belief that the acquired somatic JAK2V617F mutation affects mainly haematopoietic stem cells, multi-potent progenitor cells, cells from the lymphoid lineage and some differentiated cells like granulocytes. However, several recent studies reported occurrence of the JAK2V617F mutation in endothelial cells (ECs) of patients with MPN and Budd–Chiari syndrome. In fact, thromboembolic events represent a major cause of morbidity and mortality during the chronic phase of MPN patients, before the onset of the accelerated phase with evolution to myelofibrosis or acute leukaemia. Thrombotic manifestations in MPN patients are affecting unusual sites like the portal vein or splanchnic veins. Indeed, splanchnic vein thrombosis affects 0.9 to 5% of the patients with polycythaemia vera and 3 to 10% of the patients with essential thrombocythaemia. Vice versa, approximately 40 and 30% of Budd–Chiari syndrome or portal vein thrombosis patients, respectively, have underlying MPNs.

Although the thrombotic risk in the MPN patients can be associated with an increased haematocrit, leucocytosis or platelet dysfunction, it is so far unknown what makes MPN patients to be prone to thromboembolic events. Since ECs are critically involved in the regulation of vascular structure, cellular adhesion, vascular tone and thromboresistance, it may be very well possible that the JAK2V617F mutation in ECs of an MPN patient predisposes him to thrombosis.

Indeed, this problem was tackled by Guadall et al and the outcome of their studies is described in an article of the current issue of Thrombosis and Haemostasis. To address this problem, the authors used isogenic JAK2V617F and JAK2 wild-type (WT) induced pluripotent stem (iPS) cells from an MPN patient and redirected these iPS cells towards the endothelial lineage. Tube formation assays in matrigel and nitric oxide formation as characteristic parameters of ECs first revealed that the iPS cells can be differentiated towards the endothelial lineage and that no principal difference between the cells from the two genotypes was detectable. However, the authors detected a gain of function in JAK2V617F cells when compared with the WT cells; this became visible by increased levels of phosphorylated JAK2 and signal transducer and activator of transcription 3 (STAT3). These findings resemble the enhanced intra-cellular JAK2/STAT3 signalling as observed in JAK2V617F haematopoietic cells. Moreover, the authors observed an increased proliferation in the cells with the JAK2V617F mutation when compared with WT ECs.
Next, the authors were able to link the observed findings to an activated status of ECs that is prone to thrombotic events by looking at the formation of Weibel–Palade bodies and expression of von Willebrand factor (vWF) and P-selectin (CD62P). All these parameters, numbers and fluorescence intensity of Weibel–Palade bodies as well as expression of vWF and P-selectin were significantly higher and also accompanied by accumulation of P-selectin at the cell surface in JAK2V617F cells when compared with WT cells.

To characterize the consequences of JAK2V617F expression in the ECs further, the authors obtained the respective transcriptomic profile of these cells. The authors found 428 genes being differentially expressed (259 up- and 169 down-regulated) in JAK2V617F versus WT cells. Importantly, a gene set enrichment analysis showed that various over-expressed genes were highly related to pro-inflammatory and pro-adhesive properties, to extracellular matrix regulation, and to generation of glycoproteins, processes that are also involved in venous stenosis and thrombosis. In particular, the induction of a pro-thrombotic phenotype of the JAK2V617F cells was underlined by the over-expression of the interleukin (IL)-33 receptor; IL-33 is known to induce JAK2V617F cells was underlined by the over-expression of JAK2 activation factors such as thrombopoietin, or ribonucleic acid transcription, they and even more their growth of megakaryocytes, which results in higher production of cytokines, leukocytosis and thrombocytosis and thereby improves the clinical status as well as prolongs survival of patients with myelofibrosis.

References

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