Inflammation in del(20q): a MST opportunity?

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Comment on Stoner et al, page 1730

In this issue of Blood, Stoner et al identify aberrant activation of inflammatory signaling pathways as a result of the Hippo kinase, MST1, loss in myeloid malignancies with deletion of chromosome 20q.1

Chromosomal aberrations are a common feature of many cancer subtypes. Recurring cytogenetic abnormalities that are found specifically in particular cancers may provide important information about disease pathogenesis and identify a path toward treatment susceptibility.2 Deletions in the long arm of chromosome 20, or del(20q), is a common cytogenetic finding in patients with blood cancers, particularly myelodysplasia, myeloproliferative neoplasm (MPN), and acute leukemia. Interestingly, when found in patients with myelodysplasia (MDS), it is associated with a relatively favorable prognosis3 and contrasts with the adverse prognostic effect of other cytogenetic abnormalities such as monosomy of chromosome 7 or chromosome 3p abnormalities. In MPN, cytogenetic abnormalities are associated with more advanced disease, and del(20q) is the most common chromosomal aberration in primary and post-polycythemic myelofibrosis.4 Mapping of the commonly deleted region of chromosome 20q has identified a number of candidate genes that may contribute to myeloproliferative neoplasm with haploinsufficient expression.5

In the accompanying manuscript, Stoner et al examined gene expression changes from patients with del(20q) MDS and found that many of the downregulated genes were located on del(20q). In particular, STK4, encoding the Hippo kinase MST1, was downregulated in MDS with del(20q) and myelofibrosis. Functionally, deletion of STK3 and STK4 Hippo kinases in normal hematopoietic cells induced an MDS-like state characterized by thrombocytopenia, enlarged platelets, and myeloid skewing. These effects were also seen at the level of hematopoietic stem cells, as evidenced by loss of hematopoietic stem cell fitness and engraftment. This was dependent on gene dosage, with the most pronounced findings in homozygous deletion. Furthermore, retroviral expression of human JAK2V617F cooperated with STK3/4 haploinsufficiency to increase the rate of myelofibrosis and disease progression. Again, these findings reflect the association of del(20q) and other chromosomal changes with progression of MPN from early stage disease, such as polycythemia vera, to advanced myelofibrosis.

Mechanistically, the progression to myelofibrosis was associated with inflammatory cytokines, in particular increased expression of interleukin 6 (IL-6), IL-1β, IL-15, and MMP-3. Using pathway analysis of gene expression studies, they were able to show that this mutant JAK2V617F and STK3/4 haploinsufficient context had activated regulators of innate immune signaling and inflammatory regulators associated with activation of the NF-κB pathway. To understand how MST1 loss might lead to NF-κB activation, the authors concentrated on the described interaction between MST1 and IRAK1 and confirmed this finding, while also showing that MST1 expression was able to suppress IRAK-TRAF6 mediated activation of NF-κB signaling and downstream inflammatory pathways. This identifies a novel treatment pathway through the inhibition of upstream mediators IRAK1/4.
NF-κB signaling and that this suppression was dependent on the kinase activity of MST1.

Activation of the NF-κB pathway has been found in other models of secondary myelofibrosis, and targeting this pathway has some efficacy in preventing the progression of disease. Therefore, to translate these findings, the authors used an IRAK1/4 inhibitor in the Jak2V617F, Stk3/4 haplinsufficient mouse model of myelofibrosis. This proinflammatory signaling that characterized the myeloblastic phenotype was inhibited by the IRAK1/4 inhibitor in vivo, providing a logical path to clinical translation that may benefit patients with advanced MPN and increased inflammatory signaling (see figure).

Altogether, Stoner et al provide a compelling argument for a functional role of MST1 loss in the pathogenesis of myeloid malignancies, leading to dysregulated inflammatory signaling and progression to advanced disease. A number of questions still remain, such as identifying the best way of dampening down inflammatory signaling in these diseases and why del(20q) leads to a relatively favorable prognosis compared with other cytogenetic abnormalities. This work builds on a recurrent theme that identifies pathologival activation of inflammation and immune pathways in myeloid blood cancers and provides hope that these findings may be leveraged to design new treatments for our patients with these diseases.

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THROMBOSIS AND HEMOSTASIS

Comment on Shao et al, page 1745

Low FV beneficial in FV/FVIII deficiency?

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In this issue of Blood, Shao and colleagues demonstrate that the low factor V (FV) levels in patients with combined deficiency of FV and FVIII (F5F8D) may in fact be beneficial for the patients and ameliorate their bleeding tendency.

This report adds to the growing list of observations that FV not only is procoagulant but also that it works as an anticoagulant. The paper brings new understanding of the basic pathology of F5F8D and also lays the foundation for a change in the treatment strategy of the disease.

Blood coagulation is initiated by vascular damage, which exposes tissue factor (TF) to the circulating coagulation proteins. This initiates a series of proteolytic reactions that result in the formation of thrombin and a fibrin clot. Factor VIIa (FVIIa) bound to TF activates factors IX and X (FIX and FX), which team up with their respective activated cofactors, factor VIIa and Va (FVIIa and FVa) (see figure). FXaFVa activates prothrombin to generate the initial thrombin. Feedback from this reaction activates the system by converting the procofactors FVIII and FV to their active forms, and the system can now proceed at maximum speed.

The role of FIIaFVIIa is to provide amplification by generating more FXa. The cofactors FVa and FVIIa are crucial as the enzymes FIXa and FXa have low intrinsic activities. This is illustrated by the severe bleeding phenotype affecting individuals with hemophilia A, due to defective or absent FVIII. In contrast, it has been puzzling that patients with FV deficiency generally have a mild bleeding phenotype. Patients with combined FVIII and FV deficiency also have a mild bleeding phenotype, and the report by Shao and colleagues provides a possible explanation by demonstrating that the low FV levels are associated with efficient thrombin generation. Reconstitution of FV to normal levels results in anticoagulation and decreased thrombin generation. This illustrates the importance of the anticoagulant functions of FV.

To date, 2 anticoagulant properties of FV have been identified (see figure). The discovery of activated protein C (APC) resistance, caused by the FVLeiden mutation, as a major risk factor for venous thrombosis led to the identification of FV as an APC cofactor functioning in synergy with the anticoagulant protein S in the degradation of FVIII in the FIXaFVIIa complex. Loss of the APC cofactor activity due to the FVLeiden mutation is one of the mechanisms that generates a hypercoagulable state. The second anticoagulant function of FV is related to its interaction with full-length tissue factor pathway inhibitor (TFPIa). TFPIa, which regulates both the FVIIaTF complex and FXa, circulates bound to FV. As a consequence, individuals with FV deficiency have low TFPIa and therefore defective anticoagulation, which may be the explanation for the mild bleeding phenotype in FV deficiency.

FV serves not only as a carrier of TFPIa in circulation but also as a synergistic TFPIa cofactor together with protein S in the inhibition of FXa. A minor splice isofom of FV, denoted FV-Short, which is particularly efficient as...