Commentary

Inflammation exerts a nonrandom risk in the acquisition and progression of the MPN: Insights from a Mendelian randomization study

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The chronic myeloproliferative neoplasms (MPN) are blood stem cell disorders characterized by somatic mutations that activate the JAK-STAT signaling pathway \cite{1}. The activating mutation JAK2V617F is present in nearly 100\% of polycythemia vera (PV), and in 60\% of primary myelofibrosis (PMF) and essential thrombocytosis (ET) patients. Despite the same mutation, these entities vary with regard to age at onset, gender distribution, and natural history, suggesting that host and environmental factors are significant disease modifiers of both disease acquisition and disease evolution. The MPN are characterized clinically by genomic instability, high thrombosis rates and high levels of inflammatory cytokines, all of which may be causal or consequential to activated JAK-STAT signaling \cite{2}. Clonal hematopoiesis (CH) is defined as an expansion of blood stem cell clones that bear advantageous somatic mutations. JAK2V617F is not only the most common mutation in the MPN, it is the fifth most common lesion in CH\cite{3}. While the JAK2V617F positive MPN are considered rare diseases, CH, and particularly JAK2V617F CH occurs at relatively common rates in the ageing population \cite{4,5}. JAK2V617F CH can remain latent without evidence of an MPN, or can clonally expand and progress to an MPN. CH carriers, and in particular JAK2V617F CH carriers, similar to MPN patients, are at increased risk of developing blood cancers, cardiovascular disease and venous thromboses. These risks are hypothesized to be due to CH lesion-specific perturbations of inflammatory signaling \cite{6}.

To test the role of inflammation as causal or consequential to the development of JAK2V617F CH or MPN, Pedersen et al analyzed 107,969 individuals from the Copenhagen Population Study using a Mendelian randomization approach \cite{7}. The Copenhagen Population study provides an unprecedented MPN research opportunity for three reasons. First, its large size and extensive phenotyping allows well controlled studies of genetic variation. Second, the robust Danish Patient Registry allows MPN diagnosis tracking during long term follow up. Third, 49,143 individuals from this study population had already been examined for JAK2V617F CH using a highly sensitive assay \cite{4}. The authors selected the variant IL6R rs4537545 as this is in high linkage disequilibrium with the variant IL6R rs2228145, which is a functional variant that leads to decreased number of interleukin-6 receptors in the cellular membrane and thereby suppresses interleukin-6 downstream inflammatory signaling; the authors evaluated the former as the marker of the functional variant.

This study first showed that the IL6R rs4537545 variant did in fact result in lower levels of C-reactive protein concentration, in a gene dosage dependent manner. Next, they demonstrated that age- and sex-adjusted risk of acquiring any MPN was 40\% lower among carriers of the loss of function IL6R rs4537545, even when controlled for age, gender and smoking status. This relative risk reduction was even more prominent when examined in the JAK2V617F CH sub cohort. Then, when stratified by age, BMI, gender and smoking status, the IL6R rs4537545 variant was more protective in individuals with JAK2V617F CH, in males, in older individuals, in PV and MF patients, and in individuals without a cancer history. Interestingly, the protection was more prominent for PV and MF consistent with the increased levels of inflammation that have been described in MF, and also the higher prevalence and burden of JAK2V617F CH in PV \cite{2}. The findings that protection was more prominent in males, in older individuals and in those without a cancer history, suggests that in these contexts, inflammation and ageing risks run together (“inflammaging”) and are especially active at promoting disease risk in vulnerable populations.

Persistent low grade inflammation in the HSC compartment leads to ROS accumulation, DNA damage, and the acquisition and expansion of mutations in hematopoietic stem cells. MPN and CH are chronic neoplastic diseases characterized by accumulation and clonal expansion of somatic mutations, which in turn exacerbate ROS and DNA damage \cite{8,9}. The data presented in this population-based study, despite limitations such as population stratification and the possibility of horizontal pleiotropy, suggest that germline variants that regulate inflammatory signaling can modify the risk of JAK2V617F CH, and...
MPN development and progression. Finally, these results support that targeting interleukin-6 signaling could be a promising therapeutic approach for patients with MPN to reduce risk of progression, and also may be a strategy to lower CH rates in the general population. Our worldwide population is ageing, and the insights provided by this study will be applicable to many contexts beyond blood diseases, where the effects of inflammation are particularly damaging [10].

Author contributions

TK, HK and ARM drafted and edited the commentary. SC and LMSR contributed comments and edited the commentary.

Declaration Competing of Interest

The authors have no conflicts of interest to disclose

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