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SPOTLIGHT EDITORIAL

Introduction to 'A special spotlight review series on *BCR–ABL*-negative myeloproliferative neoplasms'

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One may ask why *Leukemia* decided to spotlight *BCR–ABL*-negative myeloproliferative neoplasms (MPNs) at this time. The main reason is the spectacular acceleration of scientific discovery in these disorders and the rapid pace of small molecule anti-janus kinases 2 (JAK2) drug development. The fact that polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) can transform to acute myeloid leukemia after a long evolution opens the door to a detailed molecular understanding of the multistep nature of blood cancers.

Equally, the discoveries of JAK2 V617F and of other JAK2 and thrombopoietin receptor mutants in the classic *BCR–ABL*-negative MPNs have raised fascinating questions: is JAK2 V617F the first event in some of the MPNs, and if so, does it play a role in hematopoietic stem cell (HSC) renewal? Must secondary events occur in HSCs harboring the JAK2 V617F mutation as a first event for clonal disease to develop? Or, in contrast, is JAK2 V617F a mutation appearing subsequently to an initial, yet to be discovered genetic or epigenetic event? Arguments for both scenarios exist. The recent description of several subtypes of HSCs opens the possibility that the subtype of HSC where JAK2 V617F appears may influence the disease phenotype. Careful review of all these data is necessary to get facts straight and help clinicians and scientists organize current information into working hypotheses to be tested.

On a more fundamental level this is an exciting time where, once again, disease genetics has facilitated understanding of physiological processes. Due to the concentration of effort on JAK2 signaling and structure, it is expected that a more profound understanding will emerge on how JAKs scaffold to receptors and how normal and mutated JAK2 initiate signaling. That is quite relevant for the signal transduction field, since no structure of a full length JAK exists, nor do we really understand how cytokine receptors' cytosolic domains fold and bind intracellularly to JAK.

Perhaps, most amazing is the rapid progress toward drug development. Not even two years after the first report on JAK2 V617F, several companies have already developed small molecules that are now in testing for treatment of MPNs with JAK2 V617F. The effort was to isolate JAK2 inhibitors that would really be specific for JAK2, avoiding unwanted inhibition of the other three JAKs: JAK1, Tyk2 and JAK3. Taking into account the success of imatinib mesylate in the treatment of chronic myelogenous leukemia and of other malignancies due to activated kinases, the goal is to have a powerful inhibitor of JAK2 that at low concentrations would block the constitutive pathologic signaling of JAK2 V617F, but would not completely block the cytokine-activated JAK2 via receptors. JAK2 is crucial for signaling by erythropoietin, thrombopoietin and several other cytokines, such as interferon gamma. It remains to be seen whether, by simply adjusting the dose, unwanted effects of JAK2 inhibitors, such as anemia, thrombocytopenia or immune defects can be avoided. Ongoing work on the structure and function of JAK2 V617F already suggests that specific JAK2 V617F inhibitors could be obtained in future, and such specific inhibition would be an important step towards specific treatment.

Our spotlight review series covers *BCR–ABL*-negative MPNs from several perspectives including history, disease classification, genetics, signaling, drug development, treatment options and MPN stem cell biology. The question why different activated kinases lead to enhanced differentiation of different mature myeloid lineages, ranging from overproduction of erythroid cells, platelets, granulocytes, eosinophils or mast cells tells us that signaling specificity must exist in blood formation. This puzzle of ascribing pathways to favoring one or the other of the myeloid lineages and the major question of how leukemic/mutated hematopoietic stem cells take over hematopoiesis are now likely to be answered due to the multitude of approaches and availability of high-throughput genomics and proteomics approaches. Progress in this area will certainly impact the search for molecular determinants of other hematological and non-hematological malignancies.

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