Another Piece of the Myeloproliferative Neoplasms Puzzle
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Myeloproliferative neoplasms are clonal hematopoietic disorders that manifest as expansion of one or more myeloid lineages. The most common myeloproliferative neoplasms are chronic myeloid leukemia (CML), polycythemia vera, essential thrombocytopenia, and primary myelofibrosis. Whereas the genetic basis for CML has been known for more than 30 years, the specific genetic events that contribute to the pathogenesis of polycythemia vera, essential thrombocytemia, and primary myelofibrosis remained unknown until 2005.

Our first insight into the molecular cause of these disorders came when the somatic JAK2 V617F mutation\(^1-4\) was identified in the majority of patients with polycythemia vera and in a subset of patients with essential thrombocytemia and primary myelofibrosis. Subsequent studies identified JAK2 exon 12 mutations in patients with JAK2 V617F–negative polycythemia vera\(^5\) and mutations in the gene encoding thrombopoietin receptor (MPL) in a subset of patients with JAK2 V617F–negative essential thrombocytemia and primary myelofibrosis.\(^6\) In each case, expression of these mutations led to increased JAK-STAT signaling and expression of these mutant disease alleles in mice led to a myeloproliferative disease phenotype. These data suggest that mutations that activate the JAK2 pathway are a common pathogenetic event in myeloproliferative neoplasms. These discoveries led to the clinical development of JAK inhibitors, which are now approved for patients with primary myelofibrosis.\(^7\)

Recent studies have identified additional novel mutations in patients with myeloproliferative and other myeloid neoplasms.\(^8,9\) However, these recently identified mutations are observed both in patients with mutated JAK2 or MPL and in those without these mutations; they are also seen in other myeloid cancers, including myelodysplastic syndromes and acute myeloid leukemia. As such, it was not known which specific mutations occurred in patients with myeloproliferative neoplasms without JAK2 or MPL mutations, nor was it known whether there were recurrent acquired mutations that activate the JAK2 pathway in this substantial subset of patients.

Two studies in the Journal now solve this puzzle and identify mutations in a specific gene in the majority of patients with myeloproliferative neoplasms who have nonmutated JAK2 or MPL. In the studies by Klampfl et al.\(^10\) and Nangalia et al.,\(^11\) investigators performed exome sequencing of paired myeloproliferative neoplasms and normal DNA to identify recurrent mutations in the gene encoding calreticulin (CALR) in the majority of patients with nonmutated JAK2 or MPL. Klampfl et al. performed exome sequencing on samples obtained from 6 such patients and identified acquired insertion and deletion CALR mutations in all 6 patients. In contrast, Nangalia et al. performed exome sequencing on samples from 151 patients with myeloproliferative neoplasms; this provided an unprecedented view of the mutational landscape in these cancers and allowed the authors to identify CALR mutations in all 6 patients. They then performed targeted sequencing of a large cohort of patients with myeloproliferative neoplasms and other myeloid cancers. In contrast, Nangalia et al. performed exome sequencing on samples from 151 patients with myeloproliferative neoplasms; this provided an unprecedented view of the mutational landscape in these cancers and allowed the authors to identify CALR mutations in patients with essential thrombocytemia or primary myelofibrosis without JAK2 or MPL mutations.
Although the two studies used different approaches to identify the CALR mutations, the findings from these two studies provide strong genetic evidence that CALR mutations have an important role in the pathogenesis of these disorders. First, CALR mutations are exclusively seen in patients with essential thrombocythemia or primary myelofibrosis without JAK2 or MPL mutations and are never observed in patients with polycythemia vera or in patients with JAK2 or MPL mutations. Second, the mutations occur in a specific C-terminal region of CALR and always generate a frameshift mutation. Third, CALR mutations are observed in purified stem or progenitor cells from patients with myeloproliferative neoplasms and remain stable during disease evolution. Taken together, these genetic data suggest that CALR mutations represent a novel driver event that occurs early in pathogenesis and has a functional role similar to that of JAK2 or MPL mutations during the development of myeloproliferative neoplasms.

Despite these critical observations, many questions remain regarding the role of CALR mutations in the pathogenesis of myeloproliferative neoplasms and in the relevance of CALR mutations to therapeutic response. Previous studies have suggested that CALR can regulate STAT signaling pathways, and Klampfl et al. found that expression of mutant (but not non-mutant) CALR can activate STAT signaling in hematopoietic cells. The mutations in CALR that were observed in patients with myeloproliferative neoplasms lead to the expression of a protein that lacks an endoplasmic reticulum targeting sequence; it is not clear how this results in increased STAT signaling or how the CALR mutations lead to a clonal advantage in hematopoietic cells. Additional studies are needed to dissect the functional relevance of CALR mutations. However, the genetic data in these two studies provide critical insight into the role of CALR mutations in the development of myeloproliferative neoplasms and suggest an important role for CALR mutations in altering JAK-STAT signaling.

As has been the case in many genetic diseases and in other human cancers, exome sequencing has led to an important new insight into the genetic basis of myeloproliferative neoplasms. There remain important unanswered questions regarding the genetic basis of these tumors, including how a single point mutation in JAK2 can contribute to the pathogenesis of three related, but clinically distinct, myeloid neoplasms. Most important, Klampfl et al. and Nangalia et al. fill a gap in our knowledge by identifying the most common mutation in patients without JAK2 or MPL mutations and allow us to better appreciate the genetic complexity of the different myeloproliferative syndromes.

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