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Clinical and molecular effects of order of acquired mutations in myeloproliferative neoplasms

Cancers arise and evolve from the accumulation of somatic mutations. With the addition of each mutation, tumor subclones are selected for biologic attributes that increase growth and proliferation potential. However, the authors hypothesized that it may not only be the presence of the mutations that affects these attributes but also the order in which the mutations arise, since their interactions and resulting environment likely play a key role in the development of subsequent genetic events and the tumor's neoplastic behavior. Myeloproliferative disorders are an ideal system in which to examine this hypothesis because these disorders represent an early stage of neoplasia that is not accessible in many solid tumors and because it is possible to isolate single hematopoietic stem and progenitor cells from circulating blood and culture them to directly compare subclonal populations from a single patient. This study identified 24 patients that had *JAK2* V617F and *TET2* mutations. Individual hematopoietic cells from these patients were isolated and cultured, and the resulting subclones were genotyped for *JAK2* and *TET2* mutation status. By examining the population of subclones, the order in which these two mutations occurred could be determined. The investigators could then compare the *JAK2*-first patients to the *TET2*-first patients for differences in clinical characteristics as well as gene expression and mutation status of other genes associated with myeloid neoplasms. The order in which the mutations were acquired was found to result in many significant differences. The *JAK2*-first patients presented at a younger age than the *TET2*-first patients, were more likely to present with polycythemia vera than essential thrombocythemia and with thrombotic events, and had increased sensitivity to *JAK2* inhibitors. Furthermore, the types of immature progenitor cells seen by subcloning were affected by which mutation was first—there were more myeloid progenitors in *TET2*-first patients and more erythrocyte and megakaryocyte progenitors in *JAK2*-first patients. By comparing the subcloned cell populations within patients, it was discovered that neoplastic stem cells from *TET2*-first patients were more likely to expand and give rise to hematopoietic stem and progenitor cells, whereas those from *JAK2*-first patients proliferated and differentiated, resulting in increased megakaryocytic and erythroid cells. It was also shown that many of the genes that are up- or downregulated when a *JAK2* mutation is acquired are regulated differently after a *TET2* mutation has already occurred, suggesting that *TET2* mutations alter the cellular milieu and prevent *JAK2* mutations from affecting certain genes. Overall, this work demonstrates that the order in which *JAK2* and *TET2* mutations are acquired affects clinical, cellular, and molecular features. These effects likely occur as a result of mutation order affecting the cellular environment, the expression and regulation of other genes and pathways, and the epigenetic program of hematopoietic stem cells and progenitor cells. These findings likely can be extrapolated to many other tumorigenesis mechanisms and have strong implications for selecting targeted molecular treatments.

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