Genetic causes of myeloproliferative diseases: stratification of patients and new therapeutic targets

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Myeloproliferative neoplasms (MPN) are characterized by clonal overproduction of terminally differentiated myeloid cells, increased risk of thrombosis, bleeding and leukemic transformation. Both acquired and constitutional genetic alterations contribute to the MPN pathogenesis. An overview of genomic data generated over the past decade using SNP microarray analysis and exome sequencing will be provided. The genetic defects associated with MPN are classified into the following categories: 1) germline genetic predispositions, 2) disease initiating mutations (JAK2, MPL, CALR) and 3) mutations driving disease progression. The germline genetic predispositions include a variety of factors with weak and strong effect that predispose carriers to acquisition of somatic mutations that initiate MPN. The disease initiating mutations are targeting the JAK/STAT signaling pathway. Three genes (JAK2, CALR, MPL) are mutated in a mutually exclusive manner in more than 95% of MPN cases. JAK2 mutations are present most frequently in all three MPN subtypes while the less frequent CALR and MPL mutations are present only in primary myelofibrosis and essential thrombocythemia and have not been seen in polycythemia vera. JAK2, CALR, and MPL induce overlapping phenotypes but also influence the clinical course specifically. A fraction of MPN patients that are negative for the common JAK2, CALR, and MPL mutations often carry unusual JAK2 and MPL mutations. The last group of mutations associated with disease progression is the most diverse. Both somatic point mutations and chromosomal aberrations are identified that strongly influence leukemic transformation and in each patient both types of defects are often detected in complex mono- or bi-clonal hierarchies. At the leukemic stage, each patient seems to be a unique transformation event and patient stratification at this stage of the disease will be challenging. The clinical utility of somatic mutations will be discussed focusing on their predictive power and monitoring of minimal residual disease. Emerging new therapeutic targets and treatment strategies will be summarized.