The *JAK2* gene as a protagonist in chronic myeloproliferative neoplasms

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The identification of the association of a *JAK2* gene mutation with chronic myeloproliferative neoplasms (cMPN) negative for BCR-ABL[1,2] has allowed significant advances in the understanding of this group of hematologic diseases. The *JAK2* gene, located on chromosome 9p24, encodes the JAK2 protein which is a cytoplasmic tyrosine kinase that plays an important role in the signal transduction of various hematopoietic growth factors. The JAK2V617F mutation results in the substitution of the amino acid valine for phenylalanine in the pseudokinase domain (JH2) causing constitutive activation of the kinase domain (JH1) and hypersensitivity to protein growth factors.

Among the BCR-ABL negative cMPN cases, the JAK2617F mutation occurs at a frequency of 96% in polycythemia vera (PV), and 50% of essential thrombocythemia (ET) and chronic idiopathic myelofibrosis (MF) patients[2]. The association of this mutation with BCR-ABL negative cMPN has contributed to improve the diagnosis, classification and treatment of patients, in particular in respect to PV. Tefferi and Pardanani[3] suggested that an investigation of the JAK2V617F mutation in the peripheral blood should be integrated into the initial assessment of patients with suspected diagnosis of PV and of those of thrombocytosis of unknown cause, with thrombotic complications, including cerebral or abdominal thrombosis, and other clinical manifestations of myeloproliferative diseases.

Other less frequent mutations were also found in the *JAK2* gene in JAK2V617F-negative PV patients, as well as in other myeloproliferative neoplasms. Several studies report deletions, point mutations and duplications[4] mainly affecting the seven highly conserved amino acid residues (F537-F547) in the JAK2 protein. PV patients positive for these mutations are often heterozygous for the mutation and are characterized by the predominance of myelopoesis, serum erythropoietin levels below normal and lower age at diagnosis[3-5]. The clinical evolution of these patients is similar to JAK2V617F-positive PV patients[5].

The V617F mutation of the *JAK2* gene triggers three clinical manifestations and there is evidence that genetic and additional epigenetic events contribute to the pathogenesis[6]. In addition, other genes, such as the *MPL*, *TET2* and *ASXL1* genes, may also be mutated with the accumulation of mutations possibly explaining the different phenotypes observed in MPN.

The *MPL* gene, located on chromosome 1p34, encodes the thrombopoietin receptor (cMPL). Its expression is important for growth and survival of megakaryocytes. Some mutations in this gene result in gain of function and have been associated with thrombocytosis, splenomegaly, myelofibrosis and an increased risk of thrombosis[7]. Mutations in the transmembrane domain of cMPL were observed in nine patients negative for the JAK2V617F mutation (MPLW515L and MPLW515K); mutations were also detected in JAK2V617F-positive patients.

The *TET2* (4q24) gene has many mutations (frameshift, missense, nonsense) that are observed in JAK2V617F cMPN-positive (17%) and JAK2V617F-negative patients (7%), with mutational frequencies of approximately 16% in PV, 5% in ET, 17% in MF, 14% in post-PV MF, 14% in post-TE MF and 17% in blast-phase MPN[8]. The main function of the TET2 protein is the conversion of 5-methyl-cytosine to 5-hydroxymethyl cytosine; it eventually affects the epigenetic regulation of transcription.

The *ASXL1* gene maps to chromosome 20q11.1 and belongs to the enhancer of trithorax and polycomb gene family. The function of this gene is believed to include dual activator/suppressor activity toward transcription and includes repression of retinoic acid receptor-mediated transcription. Mutations in this gene are associated with myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CML)[9]. In a recent study of 300 patients with a spectrum of non-MPN myeloid malignancies, *ASXL1* gene mutations were found in 62 patients (~21%): ~7% in MDS without excess blasts, 11-17% in MDS with ring sideroblasts, 31% in MDS with excess blasts, 23% in post-MDS acute myeloid leukemia (AML), 33% in CML and 30% in primary AML. It was observed that mutations of the *ASXL1* gene occur in MPNs in both chronic and blast phases. In a study of 64 patients with ET (n = 35), MF (n = 11), PV (n = 10), blast-phase MPN (n = 5) and unclassifiable MPNs (n = 3), mutations of this gene in heterozygosis were identified in five JAK2V617F-negative

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patients (~ 8%; 3 MF, 1 ET and 1 blast-phase ET)[10].

There are other reports in the literature associating gene mutations to BCR-ABL-negative cMPN. The knowledge about genotype-phenotype interaction could elucidate the molecular mechanisms and contribute to improvements in diagnosis, in the status and in the treatment of patients with ET, MF and PV.

References

1. Levine RL, Wadleigh M, Cools J, Ebert BL, Wernig G, Huntly BJ, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell. 2005;7(4):387-97.
2. Spivak JL, Silver RT. The revised World Health Organization diagnostic criteria for polycythemia vera, essential thrombocytosis, and primary myelofibrosis: an alternative proposal. Blood. 2008;112(2):231-9.
3. Tefferi A, Pardanani A. Evaluation of "increased" hemoglobin in the JAK2 mutations era: a diagnostic algorithm based on genetic tests. Mayo Clin Proc. 2007;82(5):599-604.
4. Kjaer L, Westman M, Hasselbalch Riley C, Høgdall E, Weis Bjerrum O, Hasselbalch H. A highly sensitive quantitative real-time PCR assay for determination of mutant JAK2 exon 12 allele burden. PLoS One. 2012;7(3):e33100.
5. Passamonti F, Elena C, Schnittger S, Skoda RC, Green AR, Girodon F, et al. Molecular and clinical features of the myeloproliferative neoplasm associated with JAK2 exon 12 mutations. Blood. 2009;117(10):2813-6.
6. Chauffaille ML. Neoplasias mieloproliferativas: revisão dos critérios diagnósticos e dos aspectos clínicos. Rev. Bras. Hematol. Hemoter. 2010;32(4):308-16.
7. Teofili L, Giona F, Torti L, Cenci T, Ricerca BM, Rumi C, et al. Hereditary thrombocytosis caused by MPLSer505Asn is associated with a high thrombotic risk, splenomegaly and progression to bone marrow fibrosis. Haematologica. 2010;95(1):65-70.
8. Tefferi A, Lim KH, Abdel-Wahab O, Lasho TL, Patel J, Patnaik MM, et al. Detection of mutant TET2 in myeloid malignancies other than myeloproliferative neoplasms: CMML, MDS, MDS/MPN and AML. Leukemia. 2009;23(7):1343-5.
9. Lee SW, Cho YS, Na JM, Park UH, Kang M, Kim EJ, et al. ASXL1 represses retinoic acid receptor-mediated transcription through associating with HP1 and LSD1. J Biol Chem. 2010;285(1):18-29.
10. Carbuccia N, Murati A, Trouplin V, Brecqueville M, Adélaïde J, Rey J, et al. Mutations of ASXL1 gene in myeloproliferative neoplasms. Leukemia. 2009;23(11): 2183-6.

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