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Emerging role of inhibitory regulators of the JAK/STAT pathway in myeloproliferative neoplasms pathogenesis

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Abstract

Myeloproliferative neoplasms (MPN) are clonal hematopoietic stem cell disorders characterized by deregulated proliferation of one or more myeloid lineages, notably due to independence from normal cytokine regulation. They classically include: Polycythemia vera (PV), Essential thrombocythemia (ET), Primary myelofibrosis (PMF) with an estimate incidence of 5/100,000 people. A major advance in the pathogenesis of these disorders was the discovery of an identical gain-of-function acquired mutation in Janus kinase 2 (JAK2) tyrosine kinase, *JAK2*V617F in MPN patients. Later, other mutations relevant to disease pathogenesis with varying frequency, typically targeting genes involved in signaling, epigenetic deregulation and leukemic transformation were identified, suggesting that MPNs are complex diseases, probably resulting from the combination of several genetic events.

The *JAK2*V617F mutation is the first therapeutic target to down regulate this activated signaling pathway, with a number of clinical trials currently under investigation for tyrosine kinase inhibitors. However, the benefits of this therapy limit to a salutary effect on constitutional symptoms and splenomegaly for PV and ET patients, while there is no curable treatment for PMF.

Therefore, the identification of key signaling molecules directly and specifically targeting JAK/STAT cascade is a decisive point in MPN treatment. In this respect, the important role of inhibitory regulators of this pathway, notably the LNK protein, in MPN pathogenesis has been recently highlighted with the generation of murine models and the identification of novel mutations in these inhibitory proteins in MPN subtypes. These findings strongly suggest the use of these regulatory molecules in the development of targeted therapies in MPNs.

Biography

Dr. Laura Velazquez obtained her PhD degree at the Pasteur Institute in France, followed by her postdoctoral training at the Samuel Lunenfeld Research Institute at Mount Sinai Hospital in Toronto. Back to Paris, she obtained an “Avenir” group at Inserm and her appointment to CNRS in 2003. She is actually group leader of the myeloproliferative disorders team at the research Unit U978 Inserm/Université Paris 13. Lately, Dr. Velazquez’ main research interest is the study of the LNK adaptor protein in hematopoietic diseases, notably in MPNs, where she has several international publications. She is referenced in Who’s Who in the World 2011 and 2012and Who’s Who in Health and Medicine 2012.She is member of several editorial boards of international journals.