GENETIC AND BIOLOGICAL MARKERS IN MPNs: HOW HAVE THEY INFLUENCED CLINICAL PRACTICE?

Professor Radek Skoda

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Biography

Professor Radek C. Skoda is an internationally recognized expert in the molecular pathogenesis of myeloproliferative neoplasms (MPNs). He is a Professor of Molecular Medicine and chair of the Department of Biomedicine at the University of Basel and the University Hospital Basel in Switzerland. He has been elected Member of the Swiss Academy of Medical Sciences. He is an MD with training in internal medicine and haematology. As a postdoctoral fellow he trained in the Department of Genetics at Harvard Medical School in Boston, MA (with Prof. Philip Leder). His research interests are focused on the molecular pathogenesis of MPNs and genetic analyses of familial MPNs.

Professor Skoda's laboratory in Basel discovered, together with three other laboratories, the *JAK2* V617F mutation as a highly recurrent somatic mutation in MPNs. His laboratory also showed that *JAK2* V617F can be preceded by other gene mutations and that *JAK2* V617F positive MPN patients transforming to acute leukemia may exhibit Acute Myeloid Leukemia (AML) that is negative for *JAK2* V617F. More recently, his laboratory used next generation sequencing to determine the mutational profiles in a cohort of MPN patients and found that the number of somatic mutations negatively correlated with prognosis. His laboratory also developed a mouse model of MPNs and showed that the phenotype (essential thrombocythemia or polycythemia vera) correlated with the expression levels of the mutant *JAK2* V617F and more recently that MPN disease can be initiated from single hematopoietic stem cells expressing *JAK2* V617F as the only genetic alteration. His laboratory is currently studying the influence of individual signaling components on the *JAK2* V617F induced phenotype and found that loss of STAT1 decreases megakaryopoiesis and favors erythropoiesis, whereas loss of STAT3 enhances thrombocytosis and shortens survival. In addition, professor Skoda's laboratory also described the first familial mutations in the thrombopoietin gene causing hereditary thrombocytosis.

Professor Skoda has received several awards including the Ham Wasserman Lecture Award of the American Society of Haematology (2007), the research prize of the Cloetta-Foundation (2005), and the Ellermann Prize for Haematology (1999) and has authored several influential articles and reviews on the molecular basis of myeloproliferative neoplasms. He has also presented in educational and scientific sessions at ASH and EHA.

ABSTRACT

The link between genetic and biological markers in prognosis of myeloproliferative neoplasms (MPNs) is irrefutably proven. The association between mutations and various disease phenotypes has been demonstrated over the past few years with examples such as *JAK2* V617F associated with higher platelet counts and consequently higher risk of thrombosis. The pathogenesis of thrombosis is multifactorial and can also be seen through biochemical changes in the cell membrane causing the aggregation of platelets, leukocytes and red blood cells in blood vessels. Driver and somatic mutations can lead to abnormal expression of inflammatory biomarkers corresponding to the increased risk of thrombotic complications in MPNs. The intricacies of these various connections are still being researched and will help eventually in reducing the risk of thrombotic complications in these diseases.

References:

- Tefferi A, *et al. Leukem.* 2014;28:1472-7.
- Carobbio A, *et al. Blood.* 2011;117:5857-5859.
- Landolfi R, *et al. Haematologica.* 2011;96:183-186.

Conflict of interest:

- NOVARTIS
- SANOFI
- SHIRE

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Professor
Stefan N. Constantinescu

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Biography

Professor Stefan N. Constantinescu is a recognised expert in signalling by cytokine receptors and the JAK-STAT pathway in hematopoiesis. He is a Member of the Ludwig Institute for Cancer Research and a Professor at the University Catholic of Louvain's de Duve Institute, where he is Head of Cell Signalling Program. He was elected to Membership at the Royal Academy of Medicine of Belgium. His background is MD, PhD followed by postdoctoral training in molecular cell biology at the Whitehead Institute for Biomedical Research at Massachusetts Institute of Technology, Cambridge, MA (with Prof. Harvey F. Lodish).

Studies performed in Professor Constantinescu's laboratory in Brussels identified the dimeric structure, active orientation and conformational requirements for activation of cytokine receptors such as those for erythropoietin (EpoR) and thrombopoietin (TpoR, c-Mpl) in association with JAK2. In collaboration with Prof. William Vainchenker at Institut Gustave Roussy, Villejuif, France, he contributed to the discovery of *JAK2* V617F and to the elucidation of its oncogenic mechanism in myeloproliferative neoplasms. He identified the first constitutive active oncogenic mutants of *JAK1* (*JAK1* V658F) and *TYK2* (V678F). Work on cytokine receptor juxtamembrane domains in the laboratory of Professor Constantinescu led to the identification of thrombopoietin receptor (TpoR) W515A/L/KR activating mutations, which were subsequently found by several teams in *JAK2* V617F-negative myelofibrosis and essential thrombocythemia patients. More recently, the group identified a pocket in *JAK2* V617F pseudokinase domain that could be targeted by small molecules for specific inhibition of mutant and not wild type JAK2, and described specific gene regulation induced constitutive active STAT5 and not by physiologically activated STAT5 by cytokines, which is highly relevant for progression of myeloproliferative neoplasms. His group also focuses on how calreticulin mutants induce pathologic signalling that is causative in myeloproliferative neoplasms. In the past 10 years Professor Constantinescu has authored several influential reviews on the molecular basis of myeloproliferative neoplasms and has presented educational sessions at ASH and EHA.

ABSTRACT

Understanding the genomic landscape of myeloproliferative neoplasms (MPNs) first started in 2005 with the discovery of the *JAK2* (Janus Kinase 2) V617F mutation. This was closely followed with the discovery of the *MPL* (receptor for thrombopoietin) mutations at W515 and recently the *CALR* (calreticulin) mutations. These three classes of mutations have been identified as phenotypic driver mutations in MPNs with *JAK2* V617F consisting of more than 95 percent prevalence in polycythemia vera (PV). Research surrounding the *CALR* mutations has been the centre of attention due to their prevalence in essential thrombocythaemia (ET) and apparent mutual exclusivity from the *JAK2* and *MPL* mutations. The groups of professors Kralovics and Green contributed to defining the presence and initial role of *CALR* in ET and primary myelofibrosis (PMF). The most prevalent *CALR* mutations, a 52 bp deletion (type 1) and a 5 bp insertion (type 2), are preferentially associated with myelofibrosis and ET, respectively. *JAK2*, *MPL* and *CALR* mutations can be part of a wider range of genetic markers such as loss of function mutations in *ASXL1, EZH2, DNMT3A* and *TET2* that contribute to clonal dominance and disease burden in MPN disease subtypes. It is certain that the diagnostic approach to MPNs requires the inclusion of the mutational status of these driver mutations and this will undoubtedly have an impact on how we manage our patients in the future.

References:

- Klampfl T, *et al. N Engl J Med.* 2013;369:2379-90.
- Nangalia, *et al. N Engl J Med.* 2013;369:2391-405.
- Tefferi A, *et al. Nat Rev Clin Oncol.* 2014;11:125-6.
- Cazzola M, *et al. Blood.* 2014;123:3714-9.
- Cabagnols X, *et al. Leukemia.* 2015;29:249-52.

Conflict of interest:

- SANOFI
- AMGEN
- SHIRE
- DARFA PHARMA
- PERSONAL GENETICS
- TEVA