

KIT/D816V induces SRC-mediated tyrosine phosphorylation of MITF and altered transcription program in melanoma

Bengt Phung¹, Julhash U. Kazi¹, Alicia Lundby², Kristin Bergsteinsdottir³, Jianmin Sun¹, Colin R. Goding⁴, Göran Jönsson⁵, Jesper V. Olsen², Eiríkur Steingrímsson³, and Lars Rönnstrand¹

¹Div. of Translational Cancer Research, Dept of Laboratory Medicine, Lund University, Lund, Sweden

²NNF Center for Protein Research, University of Copenhagen, Copenhagen, Denmark

³Department of Biochemistry and Molecular Biology, University of Iceland, Reykjavik, Iceland

⁴Ludwig Institute for Cancer Research, University of Oxford, Oxford, United Kingdom

⁵Melanoma Genomics, Div. of Oncology and Pathology, Dept. of Clin. Sciences, Lund, Sweden.

Abstract

The oncogenic D816V mutation of the KIT receptor is well characterized in systemic mastocytosis and acute myeloid leukemia. Although KIT^{D816V} has been found in melanoma, its function and involvement in this malignancy is not understood. Here we show that KIT^{D816V} induces tyrosine phosphorylation of the microphthalmia-associated transcription factor (MITF) through a triple protein complex formation between KIT, MITF and SRC family kinases. In turn, phosphorylated MITF activates target genes that are involved in melanoma proliferation, cell cycle progression, suppression of senescence, survival and invasion. By blocking the triple protein complex formation, thus preventing MITF phosphorylation, the cells become hypersensitive to SRC inhibitors. We have therefore delineated the mechanism behind the oncogenic effects of KIT^{D816V} in melanoma and provide a rationale for testing SRC family kinase inhibitors to treat KIT^{D816V}-transformed melanomas.