Hôpital général juif
Jewish General Hospital

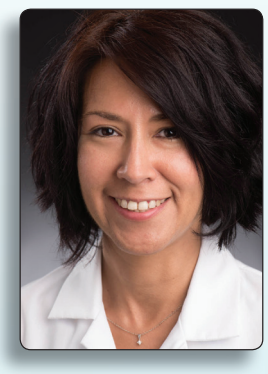
McGill

Institut Lady Davis de recherches médicales | Lady Davis Institute for Medical Research

PAPER OF THE MONTH • APRIL 2018

Wilson Miller, MD, PhD

Associate Director for Clinical Research, Lady Davis Institute
Director, Clinical Research Unit, Jewish General Hospital
Clinical Lead, Rossy Cancer Network
James McGill Professor, Departments of Medicine and Oncology, McGill University



Sonia del Rincón, PhD

Assistant Professor, Department of Oncology, McGill University

Yao Zhan, PhD

Experimental Medicine, McGill University

William Yang, MSc

Experimental Medicine, McGill Medicine

JCI The Journal of Clinical Investigation

MNK1/2 inhibition limits oncogenicity and metastasis of KIT-mutant melanoma

Yao Zhan, Jun Guo, William Yang, Christophe Goncalves, Tomasz Rzymski, Agnieszka Dreas, Eliza Żyłkiewicz, Maciej Mikulski, Krzysztof Brzózka, Aniela Golas, Yan Kong, Meng Ma, Fan Huang, Bonnie Huor, Qianyu Guo, Sabrina Daniela da Silva, Jose Torres, Yutian Cai, Ivan Topisirovic, Jie Su, Krikor Bijian, Moulay A. Alaoui-Jamali, Sidong Huang, Fabrice Journe, Ghanem E. Ghanem, Wilson H. Miller Jr., and Sonia V. del Rincón

The acral/mucosal subtype of melanoma – a rare form of melanoma – is not very responsive to targeted therapies. This hard-to-treat tumor type is often characterized by a mutation in the *KIT* gene that encodes for a cell surface signaling receptor. The MNK1/2-eIF4E axis, residing downstream of KIT, was a previously unexplored pathway holding potential for treatment. When mutated, KIT doesn't require binding of an external factor; it is always in the 'ON' position and this causes oncogenic signaling. This paper shows that the brakes could be placed on KIT signaling, by blocking the MNK1/2-eIF4E axis. This axis facilitates downstream synthesis of proteins that have long been associated with cancer.

To this point, the MNK1/2 targets had not been fully explored. The authors propose that MNK1/2 inhibitors could be effective in a molecularly defined cohort of melanoma patients with KIT aberrations, which currently represents a pressing therapeutic challenge. An inhibitor of MNK1/2 has been tested in an animal model of *KIT*-driven metastasis. While it doesn't destroy the melanoma, it was shown to slow its growth and reduce its invasive and metastatic properties. There are clinical trials underway using MNK inhibitors in combination with immunotherapies on different cancers. This is promising because immunotherapies have produced complications due to their toxicity, whereas the MNK inhibitors are not toxic.

DOI: 10.1172/JCI91258