



Hôpital général juif
Jewish General Hospital



McGill

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

PAPER OF THE MONTH • JUNE 2019



Cedric Darini, PhD

Post-doctoral Fellow,
Lady Davis Institute



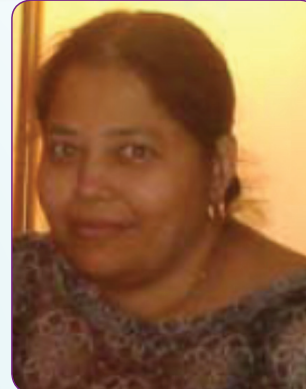
Shuo Wang

Research Associate,
Lady Davis Institute



Nour Ghaddar

PhD Candidate,
McGill University



Jothilatha Krishnamoorthy

Research Technician,
Lady Davis Institute

nature
COMMUNICATIONS

An integrated stress response via PKR suppresses HER2+ cancers and improves trastuzumab therapy

Cedric Darini, Nour Ghaddar, Catherine Chabot, Gloria Assaker, Siham Sabri, Shuo Wang, Jothilatha Krishnamoorthy, Marguerite Buchanan, Adriana Aguilar-Mahecha, Bassam Abdulkarim, Jean Deschenes, Jose Torres, Josie Ursini-Siegel, Mark Basik & Antonis E. Koromilas

This work is a collaborative effort between the labs of Antonis Koromilas, Mark Basik, and Josie Ursini-Siegel at the LDI, and Siham Sabri of McGill. The study identifies a new pathway utilized by the mammary gland epithelial cells to resist the development of HER2+ breast cancer. The pathway is known as the Integrated Stress Response (ISR), which has the capacity to orchestrate a translational and transcriptional reprogramming that determines cell fate in response to different forms of environmental stress, including oncogenic stress. It was found that ISR exhibits anti-tumor effects in HER2+ breast and gastric cancer, whereas its pharmacological activation by a specific class of phosphatase inhibitors increases the efficacy of Trastuzumab or Herceptin, which is the standard treatment for HER2+ breast cancer in the clinic. Equally important, ISR emerges as an independent positive prognostic factor for a better response of HER2+ metastatic breast cancer patients to Trastuzumab-based chemotherapy. These findings reveal the therapeutic potential of the pharmacological activation of ISR for the treatment of HER2+ cancers in combination therapies with Trastuzumab.

doi.org/10.1038/s41467-019-10138-8