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

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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.

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