

MOLECULAR REGULATION OF THE PRO-METASTATIC PROTEIN HEF1

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Spread of breast cancer to secondary sites in the body (metastasis) is the overwhelming cause of death, with less than 10% of women with metastatic breast cancer surviving beyond a decade. However, few therapies directly target metastasis, because the mechanisms of metastasis remain poorly understood. The devastating mortality resulting from metastatic disease means there is an urgent need to determine the mechanisms that underlie the development of metastatic disease. Over 65% of breast cancers are estrogen receptor positive and estrogen has emerged as a potential regulator of breast cancer metastasis. We have novel evidence that estrogen can switch on HEF1, a protein that is a recently established metastasis promoting gene in skin cancer, lung cancer and certain brain cancers. Our goal now is to define the molecular pathway that regulates the pro-metastatic function of HEF1 and how this is controlled by estrogen in breast cancer. Central to the migration of metastasizing cancer cells is the formation and turnover of integrin-based cell adhesions to the extra-cellular matrix, known as focal adhesions. We have established that HEF1 is subject to extensive phosphorylation modification and regulates the disassembly of focal adhesions. Our recent data suggest that estrogen signalling in breast cancer cells controls HEF1 phosphorylation via the serine/threonine phosphatase PP2A. As estrogen is key in the development of human breast cancer and the target of important therapeutics for breast cancer, elucidation of this signalling axis will yield important insights into the prognosis and treatment of breast cancer.