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Proline-rich tyrosine kinase 2 and its phosphorylated form pY881 are novel prognostic markers for non-small cell lung cancer progression and patients' overall survival

Bo-hua Kuang[1], **Meng-qing Zhang**[1], **Li-hua Xu**[2], **Li-juan Hu**[3], **Hong-bo Wang**[1], **Wei-feng Zhao**[4], **Yong Du**[1] and **Xing Zhang**[1]
[1]Sun Yat-sen University Cancer Center, China
[2]The First Affiliated Hospital of Guangzhou Medical College, China
[3]Affiliated Tumor Hospital of Guangzhou Medical College, China
[4]Henan Provincial People's Hospital, China

Background: Our previous study revealed that proline-rich tyrosine kinase 2 (Pyk2) is implicated inboth anchorage-independent growth and anoikis resistance in lung cancercells. This study aims to explore the expression and clinical significance of Pyk2 and its phosphorylated formsin non-small cell lung cancer (NSCLC).

Methods: The mRNA and protein levels of Pyk2 or cancer stem cell (CSC) markers were either examined by RT-PCR or Western blotting. An immunohistochemistry (IHC) assay was conducted to analyze the expression of Pyk2 and its phosphorylated formsin 128 NSCLC cases.

Results: The levels of Pyk2 mRNA, total protein, and its phophorylated forms (pY402andpY881) were higher in lung cancer lesions thanin the paired noncancerous tissues. The IHC analysis showed the levels of the Pyk2 and Pyk2 [pY881] proteins were highly expressed in 70 (54.7%)and 77 (60.2%) cases, respectively. Both Pyk2 and Pyk2[pY881] were independent prognostic factors for NSCLC patients, and had a potentially predictive role in NSCLC drug treatment. The gain and loss study of Pyk2 function revealed that Pyk2 could up-regulate CSC marker expression and enhance the transforming ability of NSCLC cells.

Conclusion: Pyk2 and phosphorylated Pyk2[pY881] are potential prognostic factors and therapeutic targets for NSCLC.

Hypoxia induces VEGF-C expression in metastatic tumor cells via a HIF-1α-independent translation-mediated mechanism

Barbara Garmy-Susini
INSERM, France

Various tumors metastasize via lymph vessels and lymph nodes to distant organs. Even though tumors are hypoxic, the mechanisms of how hypoxia regulates lymphangiogenesis remain poorly characterized. Here, we show that hypoxia reduced VEGF-C transcription and cap-dependent translation by upregulation of hypo-phosphorylated 4E-binding protein 1 (4E-BP1). However, initiation of VEGF-C translation was induced by hypoxia through an internal ribosome entry site (IRES)-dependent mechanism. IRES-dependent VEGF-C translation was independent of HIF-1α signaling. Notably, the VEGF-C IRES activity was higher in metastasizing tumor cells in lymph nodes than in primary tumors, likely because lymph vessels in these lymph nodes were severely hypoxic. Overall, this transcription-independent but translation-dependent upregulation of VEGF-C in hypoxia stimulates lymphangiogenesis in tumors and lymph nodes, and may contribute to lymphatic metastasis.

Biography

Barbara Garmy-Susini is a member of the Scientific Advisory Committees for the French Society of Angiogenesis. She has developed an expertise in the field of lymphatic and started the first laboratory at the INSERM institute (French National Institute of Health) entirely dedicated to the study of lymphatic function.