A new therapeutic intervention for patients with pancreatic ductal adenocarcinoma

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A research team from China investigated the expression of toll-like receptor (TLR) 4, nuclear factor-kB (NF-kB) p65 and hypoxiainducible transcription factor 1a (HIF-1a) in pancreatic ductal adenocarcinoma (PDAC) and their clinical significance. Their results demonstrated that TLR4, NF-kB p65 and HIF-1a are overexpressed in PDAC, TLR4 may be partly involved in up-regulating HIF-1a, and both synergestically promote development of PDAC.

Pancreatic ductal adenocarcinoma (PDAC) is a highly malignant digestive tumor with a very poor prognosis. Hypoxia-inducible transcription factor-1α (HIF-1α) is involved in malignant progression in many solid tumors, including PDAC, upregulation of HIF-1α accelerates PDAC progression, but the exact regulatory mechanisms of HIF-1αin PDAC has not been unequivocally addressed. Recently, an increasing number of studies reported that toll-like receptors (TLRs) were upregulated in epithelial malignancies and involved in tumor progression, but whether TLRs, such as TLR4, is expressed on PDAC cells remains unknown. In immune-related cells, TLR signal pathway may induce expression of HIF-1α, but it is also still unclear whether there exists some association between TLR4 and HIF-1α in tumor microenviroment, such as PDAC.

A research article to be published on June 21, 2010 in the *World Journal of Gastroenterology* addresses this question. The research team led by He-Shui Wu, MD, from Department of Pancreatic Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and

Technology, Wuhan, used real time polymerase chain reaction and immunohistochemistry, to detect TLR4, NF-κB p65 and HIF-1α expression in 65 cases of PDAC tissues and 38 cases of corresponding adjacent tissues.

Their study revealed that TLR4, NF-κB p65 and HIF-1α were overexpressed in PDAC. The expression of TLR4 and HIF-1α was associated with tumor size, lymph node metastasis, venous invasion and pathological stage. Furthermore, the expression of TLR4 was positively correlated with expression of HIF-1α. Thus, TLR4 may be a novel marker for the progression and prognosis of PDAC, and may provide a new strategy for therapeutic intervention in the treatment of patients with PDAC in the future.

Based on these results and previous reports, the authors speculated that active TLR4 signal pathway may be partly involved in up-regulating HIF-1α in PDAC tumor microenviroment via NF-κB pathway, and promoted progression of PDAC. These results demonstrated a new view of molecules involved in regulatory mechanism of HIF-1α and thus may provide new therapeutic targets for PDAC.

More information: Zhang JJ, Wu HS, Wang L, Tian Y, Zhang JH, Wu HL. Expression and significance of TLR4 and HIF-1α in pancreatic ductal adenocarcinoma. World J Gastroenterol 2010; 16(23): 2881-2888. www.wjgnet.com/1007-9327/full/v16/i23/2881.htm

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