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COMMENTARY

Targeting the hypoxia pathway to treat pancreatic cancer

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Abstract: The correlation between hypoxia and pancreatic cancer has long been discussed. Hao's research team made many efforts on revealing the oncogenic function of hypoxic inducible factor-1 (HIF-1) in pancreatic cancer progression and development in recent years. Based on their research, they linked micro-environmental regulation of pancreatic cancer and its clinical significance. Hao's research team suggests it is a promising approach to target HIF-1 for the management of pancreatic cancer progression and invasion.

Keywords: hypoxia, HIF-1, pancreatic cancer

Introduction

Despite continuous progress in combinational treatment and radical surgery techniques, pancreatic ductal adenocarcinoma (PDAC) remains the most lethal tumor, with an average 5-year survival rate below 6%. Two prominent biological characteristics of PDAC, hypoperfusion and desmoplasia, play leading roles in the formation of a hypoxic microenvironment. Hypoxic inducible factor-1 (HIF-1) is a master regulator of cell adaption to hypoxia, and is highly expressed in 88% of pancreatic cancer tissues. Previous studies showed the overexpression of HIF-1 is correlated with poor prognosis, yet the underlying mechanism remains elusive.[1]

During the past several years, Hao's research team[2–7] have focused on understanding the role of HIF-1 in pancreatic cancer and have published much innovative work in this field. They found that HIF-1 G1790A and C1772T single nucleotide polymorphisms appeared more frequently in PDAC, and predicted higher risk for the development of pancreatic cancer. Furthermore, the G1790A single nucleotide polymorphism was associated with expression of HIF-1 protein and tumor progression.[2] Through direct upregulation of its target factors, HIF-1 promoted cell proliferation through cyclophilin A (CypA).[3] In addition, HIF-1 played a crucial role in the perineural invasion and metastasis of pancreatic cancer.[3,4] Fascin is an actin-bundling protein and is overexpressed in pancreatic cancer. HIF-1 directly activated the expression of fascin and mediated PDAC invasion through matrix metalloproteinase-2 (MMP-2).[4] Another actin-bundling protein, LASP-1 (LIM and SH3 protein 1), was also tightly regulated by HIF-1 and promoted metastasis in orthotopic xenograft and immunocompetent mouse models of PDAC.[5] Interestingly, HIF-1 regulated the expression of chemokine (C-X3-C motif) receptor 1 (CX_3CR_1), and CX_3CR_1 activated HIF-1 through the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways. The crosstalk between HIF-1 and CX_3CR_1 mediated perineural invasion[6] and the Warburg effect of PDAC.[7]

The outstanding work of Hao et al has indicated that HIF-1 represents a critical mediator connecting the hypoxic microenvironment and pancreatic cancer cells

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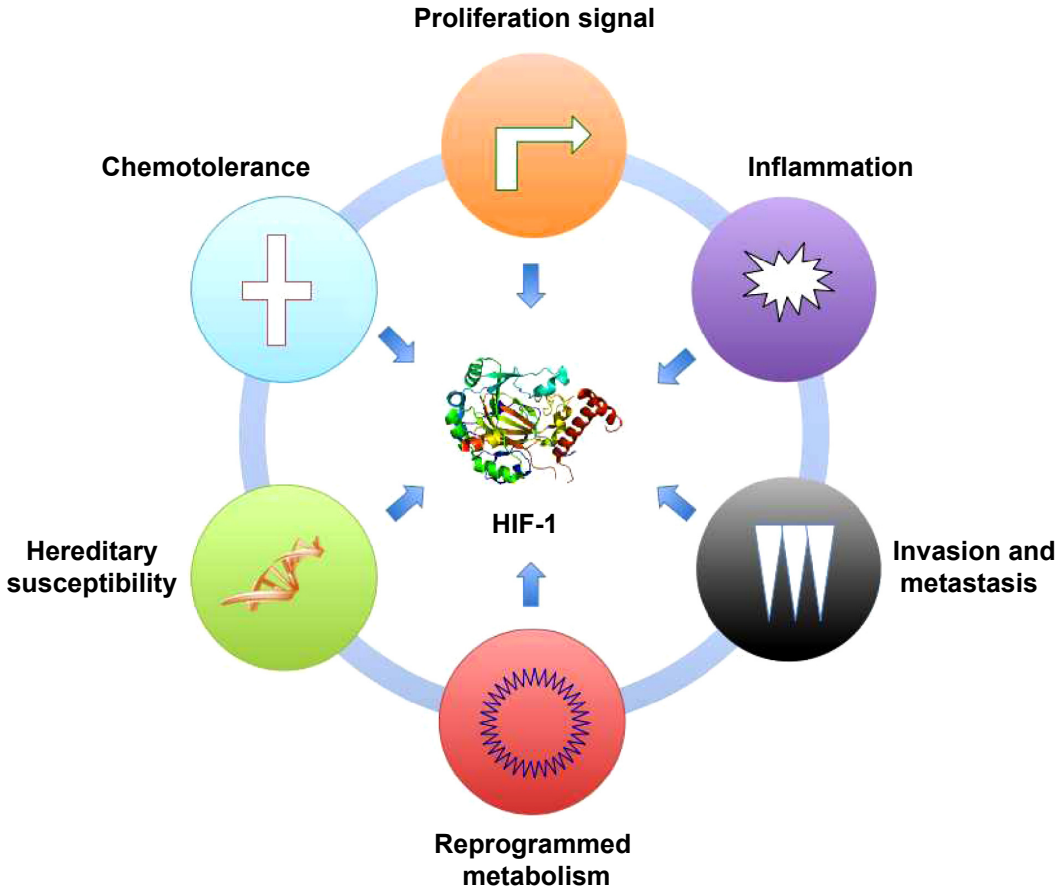

Figure 1 HIF-1 is a central mediator of tumor-related biocharacteristics in pancreatic cancer.
Note: With an indispensable role in transcriptional regulation, HIF-1 is the key factor connecting the hypoxic microenvironment with pancreatic cancer cell tumor specificity.
Abbreviation: HIF-1, hypoxic inducible factor-1.

(Figure 1). These findings suggest a new therapeutic strategy to inhibit pancreatic cancer growth by reprogramming the stroma to alleviate hypoxia, as recently shown in a study of vitamin D.[8] A growing number of reagents have been developed to inhibit HIF-1 activity, including those agents intended for use in clinical trials and US Food and Drug Administration (FDA)-approved drugs. It is reasonable to introduce HIF-1 inhibitors as new candidates for the treatment of pancreatic cancer.

Although HIF-1 is well known to serve as a crucial oncogene, further details of how this transcription factor performs tumor mitogenic and migratory functions remain unknown. Hao's recent work highlighted the experimental and clinical significance of HIF-1 in PDAC, which provides important "bench-to-bedside" clues for utilizing this key transcription factor in the early diagnosis and personalized therapy for PDAC. By further understanding the downstream target genes of HIF-1 and how these are related to the tumorigenic and metastatic phenotype of PDAC, Hao et al take the leading role in functional and mechanistic studies of microenvironmental regulation of hypoxia. Their research findings regarding HIF-1 indicate that the monitoring and management of the hypoxic microenvironment is a promising approach to exploring the aggressive biological nature of PDAC and improving the prognosis of this devastating malignancy.

Disclosure

The authors report no conflicts of interest in this work.

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