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The expression of Prolyl Hydroxylase 1, 2 , 3 and Their Effects on Tumor Growth in Pancreatic Cancer

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Recently, the role of tumor hypoxia has become a major focus in cancer research since it influences both local and systemic tumor growth. Hypoxia inducible factor (HIF) is a transcriptional regulator that play a key role in many aspects of oxygen homeostasis. The heterodimeric HIF complex is regulated by proteolysis of its alpha-subunits, following oxygen dependent hydroxylation of specific prolyl residues. Three HIF prolyl hydrolxylases, PHD 1, 2 ,3 have been identified that have the potential to catalyze this reaction. Analysis of PHDs in pancreatic tissues and cell lines revealed a significant difference for each isform between normal and cancer tissues. In normal pancreas , PHD1 and PHD2 was expressed at a higher level than PHD3, localised at acini, islet cells, endothelial cells of the blood vessels and ductal cells. However, in pancreatic cancer PHD3 was singificantly elevated, and PHD2 showed a decreased levels compared with normal pancreatic tissues. Both PHD2 and PHD3 expression was decreased in poorly differentiated grade 3 tumors, compared with grade 2 tumors. Genomic overexpresssion of PHD2 and PHD3 by stable transfection into Miapaca2 and Panc1 pancreatic cancer cells resulted in a decrease of VEGF secretion under hypoxia, and inhibition of tumor growth in vivo, whereas silencing of PHD2 using siRNA technique resulted in a increase of VEGF secretion under normoxia. The results of the present study indicate that PHDs play an important role in the pathophysiology of pancreatic cancer , and that use of gene-transfer approaches is a potential therapeutic intervention strategy for the treatment of pancreatic cancer through degradation of HIF-1α targeted by prolyl hydroxylases.