Prolyl hydroxylase-2 (PHD2) exerts tumor-suppressive activity in pancreatic cancer.

Pancreatic cancer is one of the most common and poorly treated tumors. In search of new therapeutic approaches, the oxygen sensors prolyl hydroxylases (PHD) are potential targets. PHD2 is considered the key oxygen sensor-regulating hypoxia-inducible factor (HIF). Currently, there is conflicting evidence regarding the exact role of PHD2 in tumorigenesis. The objective of this study was to investigate the role of PHD2 in pancreatic cancer growth and progression. PHD2 expression was analyzed by quantitative real-time polymerase chain reaction analysis and immunohistochemistry in human tissue specimens and cell lines. Knockdown of PHD2 was done by using short-interfering RNAs (siRNAs) specific against PHD2, and PHD2 overexpression was achieved by stable combinational DNA transfection. In vivo, an orthotopic murine model was used. Angiogenic cytokines were assessed with enzyme-linked immunosorbent assays, and invasion was studied with Matrigel assays. PHD2 expression was not altered substantially in cancer tissues and their metastases. Lymph node-negative tissues had higher levels of PHD2 than lymph node-positive tissues. PHD2 was hypoxia-inducible in pancreatic cancer cell lines and regulated cell growth through cyclin D1 down-regulation samples with PHD2 suppression and through p21 up-regulation in samples with PHD2 overexpression. In vivo,
PHD2 caused tumor growth retardation and reduced tumor invasion by inhibiting angiogenesis. This observation was caused by the suppression of angiogenic cytokines and tumor invasion. The current results indicated that PHD2 plays an important role in pancreatic tumorigenesis. In summary, the authors concluded that PHD2 may function as a tumor suppressor gene in pancreatic cancer and, thus, may define a potential target for the treatment of pancreatic cancer.