The role of PHLPP in pancreatic cancer

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Abstract
Medicine has come a long way in recent years with reliable treatments for many cancers. Pancreatic ductal adenocarcinoma (PDAC) has very few treatment options available. PDAC has a dismal 5 year survival rate of 4% and a median survival span of 6 months from point of diagnosis; with a high rate of chemotherapy and radiation resistance. A better understanding of the molecular events leading to cancer progression is needed in order to improve the treatment and prognosis of PDAC patients. We begin to elucidate the functional importance of PHLPP on suppressing progression and metastasis of PDAC. PHLPP belongs to a novel family of Ser/Thr protein phosphatases. Our previously published studies have demonstrated that PHLPP plays a tumor suppressor role in colon cancer by negatively regulating Akt and inhibiting cell proliferation. To determine the effect of PHLPP on cell migration and invasion, stable cells were generated to knock down or overexpress PHLPP in PDAC cells. The ability of cells to migrate and invade was examined using Transwell assays. We found that increased PHLPP expression significantly reduced the rate of migration and invasion in PDAC cells whereas knockdown of PHLPP had the opposite effect. To begin to elucidate the molecular mechanism underlying PHLPP-mediated inhibition of migration and invasion in PDAC cells, we discovered that the expression level of β4 Integrin was decreased in PHLPP overexpressing cells and increased in PHLPP knockdown cells. The increased expression of β4 Integrin has been shown to promote PDAC development and metastasis, although the mechanism leading to β4 Integrin upregulation is less clear. Interestingly, we found that the expression of β4 Integrin was highly sensitive to PI3K/Akt/mTOR activity in cells in which inhibition of PI3K/Akt/mTOR signaling significantly decreased the expression of β4 Integrin. Moreover, the quantitative real-time RT-PCR analysis revealed that the mRNA expression of β4 Integrin was not altered by changes in PHLPP expression or PI3K/Akt/mTOR activity, thus suggesting a post-transcriptional mechanism. Taken together, these results identify a tumor suppressor role of PHLPP in PDAC. Mechanistically, PHLPP suppresses PDAC cell migration and invasion by negatively controlling β4 Integrin expression through its ability to inhibit PI3K/Akt/mTOR signaling.

Recommended Citation
Pancreatic cancer is the leading cause of cancer-related deaths worldwide due to its aggressive nature (45). For this reason, it is of great importance that we ascertain the interrelations of pancreatic cancer and discover new therapeutics to help combat this devastating disease. HDC, which converts histidine to histamine, has been an important area of study recently due to histamine's known ability to accelerate cancerous cells into cell cycle arrest (45). The exact pathological and physiological role of mast cells and histamine secretion in pancreatic carcinoma is unclear and requires further research. Clinical studies in pancreatic cancer. PHLPP1 and PHLPP2 have a similar domain structure, which includes a putative Ras association domain, a pleckstrin homology domain, a series of leucine-rich repeats, a PP2C phosphatase domain, and a C-terminal PDZ ligand. PHLPP1 has two splice variants, PHLPP1α and PHLPP1β, of which PHLPP1β is larger by approximately 1.5 kilobase pairs. The role of Akt3 is less clear, though it appears to be expressed predominantly in brain. It has been reported that mice lacking Akt3 have small brains.[6]. Phosphorylation of Akt by PDK1 and PDK2[edit]. Investigators have hypothesized that the PHLPP isoforms may play roles in cancer, for several reasons. First, the genetic loci coding for PHLPP1 and 2 are commonly lost in cancer. Cancer. Pancreatic carcinoma is characterized with high biological activity and early involvement of retroperitoneal tissue, lymph nodes, and peripancreatic blood vessels. The majority of pancreatic cancers are diagnosed at an advanced stage. It seems that the management of the splenic vein plays a crucial role during the reconstruction of the SMV/PV confluence [31]. The classical technique of segmental venous resection includes transsection and ligation of the splenic vein.