Targeting c-Myc for the Treatment of Pancreatic Cancer

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Pancreatic cancer is a disease with a high rate of mortality, as it is generally diagnosed in the advanced stages when few effective treatments are available. Given the clinical aggressivity of this disease and the lack of good treatment options, the development of new therapeutic agents is of the upmost importance. c-Myc, a potent oncoprotein that functions as a transcription factor, regulates multiple biological processes, including proliferation, apoptosis, and differentiation. c-Myc is overexpressed in pancreatic cancer; however, mechanisms underlying this frequent overexpression are not clear. Here, we show that c-Myc is aberrantly phosphorylated and stabilized in human pancreatic cancer and that c-Myc expression dramatically accelerates tumorigenesis in a mouse model of pancreatic cancer.

As direct targeting of c-Myc has thus far been difficult, we sought to target the pathways regulating c-Myc transcriptional activity and protein stability. Specifically, we are pursuing inhibition of the Pin1 prolyl isomerase, which we have shown stimulates c-Myc transcriptional activity, and activation of the tumor suppressor PP2A phosphatase, which destabilizes c-Myc. Here, we show that Pin1 is overexpressed in pancreatic cancer and that its knockdown or inhibition reduces tumorigenic potential. We also show that the endogenous PP2A inhibitor, SET, is frequently overexpressed in pancreatic cancer, and knockdown of SET decreases tumorigenic potential. In collaboration with Oncotide Pharmaceuticals, we find that a SET antagonist re-activates PP2A and inhibits c-Myc and other key oncogenic signaling pathways involved in pancreatic cancer. Thus, antagonizing Pin1 or SET could represent an innovative therapeutic approach to target c-Myc in human pancreatic cancer.