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Pancreatic cancer is one of the most lethal of human malignancies, and potent therapeutic options are lacking. Inhibition of cell cycle progression through pharmacological blockade of cyclin-dependent kinases (CDK) has been suggested as a potential treatment option for human cancers with deregulated cell cycle control. Dinaciclib (SCH727965) is a novel small molecule multi-CDK inhibitor with low nanomolar potency against CDK1, CDK2, CDK5 and CDK9 that has shown favorable toxicity and efficacy in preliminary mouse experiments, and has been well tolerated in Phase I clinical trials. In the current study, the therapeutic efficacy of SCH727965 on human pancreatic cancer cells was tested using in vitro and in vivo model systems. Treatment with SCH727965 significantly reduced in vitro cell growth, motility and colony formation in soft agar of MIAPaCa-2 and Pa20C cells. These phenotypic changes were accompanied by marked reduction of phosphorylation of Retinoblastoma (Rb) and reduced activation of RalA. Single agent therapy with SCH727965 (40 mg/kg i.p. twice weekly) for 4 weeks significantly reduced subcutaneous tumor growth in 10/10 (100%) of tested low-passage human pancreatic cancer xenografts. Treatment of low passage pancreatic cancer xenografts with a combination of SCH727965 and gemcitabine was significantly more effective than either agent alone. Gene Set Enrichment Analysis identified overrepresentation of the Notch and Transforming Growth Factor-β (TGF-β) signaling pathways in the xenografts least responsive to SCH727965 treatment. Treatment with the cyclin-dependent kinase inhibitor SCH727965 alone or in combination is a highly promising novel experimental therapeutic strategy against pancreatic cancer.