Inhibition of basal and mitogen-stimulated pancreatic cancer cell growth by cyclin D1 antisense is associated with loss of tumorigenicity and potentiation of cytotoxicity to cisplatinum.

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Cyclin D1 belongs to a family of protein kinases that have been implicated in cell cycle regulation. Recent studies have demonstrated that elevated cyclin D1 levels correlate with decreased survival in human pancreatic cancer. In this study we expressed in a stable manner a cyclin D1 antisense cDNA construct in PANC-1 human pancreatic cancer cells. Expression of the antisense construct caused a decrease in cyclin D1 mRNA and protein levels and in cyclin D1-associated kinase activity. Antisense expressing clones displayed significantly increased doubling times, decreased anchorage-dependent and -independent basal growth, and complete loss of tumorigenicity in nude mice. EGF, FGF-2, and IGF-I enhanced mitogen-activated protein kinase activity in antisense expressing clones, but failed to stimulate their proliferation. In contrast, all three growth factors were mitogenic in parental cells. Furthermore, the inhibitory effect of cisplatinum on cell proliferation was enhanced markedly in the antisense expressing clones. These findings indicate that cyclin D1 overexpression contributes to abnormal growth and tumorigenicity in human pancreatic cancer and to the resistance of pancreatic cancer to chemotherapeutic agents.

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