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CD95 signaling in pancreatic cancer

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To our current knowledge, most pancreatic cancers arise from premalignant lesions within the pancreatic duct epithelia. The resulting pancreatic ductal adenocarcinomas are characterized by their death rate that roughly equals their incidence rate. The dismal prognosis of pancreatic cancer is mainly caused by late-stage cancer diagnosis as well as our currently limited therapies. Based on a better understanding of underlying molecular changes will enable development of new therapeutic strategies.

Activation of the CD95L/CD95 signaling cascade has long been regarded as an irrevocable trigger for programmed cell death (apoptosis). However, recent studies have demonstrated that CD95 is capable of activating a large number of non-apoptotic signal transduction pathways, too. Based on these findings, CD95 has been shown to play a pro-tumorigenic role in glioblastoma multiforme (GBM) as well as in many other solid tumors.

The current work is the first study to demonstrate the tumor promoting effects of CD95 in pancreatic cancer. For this reason, three different cell lines were used as model systems for pancreatic cancer: PANC1, an established human pancreatic cancer cell line, Panc 02, an established murine pancreatic cell line and PanD24, a cell line that was isolated from primary human pancreatic cancer which possesses cancer stem cell-like characteristics. While both cell lines were resistant to CD95-mediated apoptosis, stimulation with the CD95 ligand led to increased invasion, adhesion and cell cycle progress. As a molecular basis for these findings, activation of both the PI3K and MAPK pathway could be identified. Moreover, further analysis revealed that SCK, a SH2 domain-containing molecule, can serve as a binding partner for the CD95 receptor, coupling it to the PI3K and MAPK signaling pathways. These *in vitro* data could be confirmed in a next series of *in vivo* experiments, where treatment with APG101, a new CD95L-inhibitor resulted in abrogation of the pro-tumorigenic effects of CD95 in a mouse model of pancreatic cancer.

Moreover, the results presented in this work demonstrate a potential effect of CD95 on MDSCs (myeloid-derived suppressor cells): In slowly growing mouse pancreatic cancers, CD95L-dependent depletion of MDSCs resulted in a higher tumor incidence rate yet simultaneous

reduction of tumor size. Taken together, these data suggest that inhibition of CD95 signaling might be a promising novel therapeutic rationale in pancreatic cancer.