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## **TFF1 Is Overexpressed Early in Pancreatic Cancer and Stimulates Cancer Cell Invasion and Stromal Cell Growth and Migration**

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**Background:** Our previous microarray analysis indicated that TFF1 is overexpressed in human pancreatic cancer when compared with normal and pancreatitis tissues. In this study, we examined the role of TFF1 in cancer and the surrounding stromal cells.

**Methods:** TFF1 expression in pancreatic adenocarcinoma tissues and cell lines was analyzed using microarray, quantitative real-time polymerase chain reaction (QRT-PCR), and immunohistochemistry. The effects of recombinant TFF1 on cell proliferation and invasion of the pancreatic cancer cell lines BxPC3 and Mpanc96 were analyzed using MTS and Matrigel-coated invasion chambers. Immortalized human pancreatic stellate cells (stromal cells) were analyzed for TFF1 expression; TFF1 effect on cell growth and migration was also analyzed.

**Results:** Microarray analysis indicated a 178-fold increase in TFF1 expression in pancreatic cancer tissues when compared to normal pancreas tissues, and this difference was confirmed by QRT-PCR. Immunohistochemistry showed early expression of TFF1 in pre-neoplastic lesions (5/6 PanIN1; 6/6 PanIN2, and 5/6 PanIN3) as well as in highly invasive tumors (60%). In contrast, pancreatic cancer cells and stromal cells expressed very low to no TFF1 in vitro; however, TFF1 expression was induced when they were implanted orthotopically into nude mice. In vitro assays indicated that exogenous TFF1 increased cancer cell invasion in a dose-dependent manner (0 nM  $0.17\pm 0.02$ , 1 nM  $0.20\pm 0.01$ , 10 nM  $1.12\pm 0.05^*$ , 100 nM  $1.550\pm 0.06^*$ ,  $*P<.05$ , n=3). However, TFF1 had no effect on cancer cell proliferation. In contrast, it increased the growth and migration of HPCS cells (human pancreatic stellate cells) in a dose-dependent manner (growth: 0 nM  $0.57\pm 0.01$ , 1 nM  $0.62\pm 0.01$ , 10 nM  $0.86\pm 0.07^*$ , 100 nM  $1.04\pm 0.09^*$ ,  $*P<.05$ , n=3; migration: 0 nM  $0.28\pm 0.02$ , 1 nM  $0.37\pm 0.02$ , 10 nM  $0.44\pm 0.01^*$ , 100 nM  $0.74\pm 0.03^*$ ,  $*P<.05$ , n=3)

**Conclusions:** These data suggest that interactions within the tumor microenvironment stimulate cancer cell expression of TFF1, which increases the invasiveness of pancreatic cancer cells and the growth of stromal cells.