The use of low intensity ultrasounds as a novel therapeutic tool in pancreatic cancer.

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Purpose: Pancreatic tumors are resistant to many therapies due to the presence of a desmoplastic stroma that inhibits the entry of chemotherapy drugs. Therefore, a strategy that modulates the stroma could be a potential therapeutic option. Studies have shown effects on cell proliferation, migration and cytokines with of Low Intensity Ultrasounds (LIUS). The use of LIUS as a novel, non-invasive tool to modulate the stroma was investigated in pancreatic cancer models.

Materials and methods: Pancreatic tumor cell lines, Panc-1 and MiaPaCa and the fibroblast cell line BJ-hTERT were exposed to LIUS (1035kHz and 10V) twice per day over a 3 day period. Cellular proliferation, viability and vitality were assessed. Furthermore, mRNA expression of epithelial (EpCAM, CK and MUC1), mesenchymal (SNAIL and ZEB) and angiogenesis (VEGF) markers were assessed in tumor cells and classic activation markers were assessed in fibroblasts (a-SMA, FAP and FSP) via qPCR. Cell migration in response to LIUS was also assessed via a wound healing assay using the PAULA microscope.

Results: Small differences were observed in tumor cell viability after exposure to LIUS, whereas a reduction in cell vitality was observed, particularly in MiaPaCa cells. Furthermore, an increase in the expression of the epithelial marker EpCAM was observed in tumors cells and a reduced expression of the tumor marker MUC1 was observed in Panc-1 cells. There

was a small but significant decrease in overall VEGF expression. Modest differences were also observed in the viability of BJ-hTERT fibroblasts after exposure to LIUS and there was a significant reduction in the expression of the fibroblast activation factor FAP. Furthermore, there was a reduction in the migration capacity of Panc-1 cells, both with and without stimulation with TFGB. The migration capacity of BJ-hTERT was also inhibited after exposure to LIUS.

Conclusions: The effects of LIUS on cell proliferation, viability and gene expression are small and may not be biologically relevant. However, the effects of LIUS on cell migration are more profound, particularly in fibroblast cells. Low Intensity Ultrasounds (LIUS) could be a complementary tool in the treatment of pancreatic cancer that targets the stroma and inhibits tumor dissemination.