Silencing of GRP94 expression promotes apoptosis in pancreatic cancer cells.

Abstract:
As a molecular chaperone, GRP94 is the most abundant glycoprotein in the endoplasmic reticulum, playing an important role in maintaining cellular homeostasis. Here, we investigated the expression and the role of GRP94 in regulating cell growth and apoptosis in pancreatic cancer cells. GRP94 mRNA levels were analyzed by QRT-PCR. Immunohistochemistry was performed to localize GRP94 in tissues of the normal pancreas (n=20), chronic pancreatitis (n=20) and pancreatic ductal adenocarcinoma (n=44). Silencing of GRP94 expression was carried out by transfection with specific siRNA oligonucleotides. Apoptosis was induced by treatment with actinomycin D. Compared to normal pancreatic tissues, median mRNA levels of GRP94 were 1.5- and 3.7-fold (p<0.05) lower in chronic pancreatitis and pancreatic cancer tissues, respectively. GRP94 protein was strongly expressed in normal acinar cells and moderately expressed in normal ductal cells. GRP94 expression was lost in 48% of the cancer cases. Moderate or strong staining in cancer cells was observed in 32 and 20% of pancreatic cancer tissues, respectively. Silencing GRP94 by siRNA increased apoptosis of pancreatic cancer cells in vitro. Patients with higher than the median expression have a tendency for a worsened survival. When the small number of patients with the highest expression (n=3) were compared with the rest of the group (n=41), the
survival difference was significantly worse (5 vs. 18 months, respectively, \( p=0.006 \)). Down-regulation of GRP94 decreases apoptosis resistance in pancreatic cancer cells. Clinically, patients with high GRP94 expression show a tendency for a worsened survival.