Pancreatic cancer is one of the most aggressive tumors of the digestive tract. The locally advanced stage of the disease at the time of diagnosis and early recurrence after curative resection makes pancreatic cancer the fourth leading cause of cancer-related deaths in the Western world [1,2]. Thus, the prognosis of pancreatic cancer is extremely poor with a 5-year-survival rate of less than 5% when all stages are combined [2]. Absence of early symptoms leading to late diagnosis, the highly aggressive nature of the tumor with rapid metastasis to and invasion of lymph nodes, liver, intra- and extrapancreatic nerve structures are the main characteristics of this malignancy. Increased trans-differentiation from an epithelial cellular structure to a more mesenchymal phenotype is also an important molecular aspect. This particularly involves an increased migratory and invasive potential which is a "prerequisite" for invasion and distant metastasis. Perineural invasion (PNI) is a prominent and general feature of pancreatic cancer, known as an important prognostic factor since it causes retropancreatic tumor extension and therefore precludes curative resection [3]. Furthermore perineural invasion has a strong impact on local recurrence after curative tumor resection.

YPEL1 is a previously classified human protein which belongs to YPEL family. YPEL1 demonstrates a striking degree of conservation between species but has no known biochemical function nor can any function be inferred due to a lack of homology with any other characterized genes [4]. It appears to be a ubiquitous intracellular protein with a potential to bind zinc and a capacity to interact with itself [5]. Recently we have identified YPEL1 as potentially involved in perineural invasion of pancreatic cancer [6]. One of the genes which were found to be deregulated in perineural invasive cells was YPEL1. In this study we sought to analyze endogenous expression of YPEL1 in 9 cultured pancreatic cancer cell lines. Quantitative real time PCR demonstrated moderate to low expression of this gene in all cell lines (Figure 1). Highest levels of YPEL1 expression was observed in Panc-1 cells (88.0±11.0 copies/10,000 copies cpb) whereas lowest expression was detected in Colo357 pancreatic cancer cells (4.3±0.3 copies/10,000 copies cpb). We also performed hypoxic treatment of Capan2 cells; however these experiments did not reveal induction or repression of YPEL1 expression by hypoxia in these cancer cells.

Results and discussion. Recently we have developed an ex-vivo perineural invasion model for pancreatic cancer and described the consensus transcriptome signature of perineural invasion [6]. One of the genes which were found to be deregulated in perineural invasive cells was YPEL1. In this study we sought to analyze endogenous expression of YPEL1 in 9 cultured pancreatic cancer cell lines. Quantitative real time PCR demonstrated moderate to low expression of this gene in all cell lines (Figure 1). Highest levels of YPEL1 expression was observed in Panc-1 cells (88.0±11.0 copies/10,000 copies cpb) whereas lowest expression was detected in Colo357 pancreatic cancer cells (4.3±0.3 copies/10,000 copies cpb). We also performed hypoxic treatment of Capan2 cells; however these experiments did not reveal induction or repression of YPEL1 expression by hypoxia in these cancer cells (Figure 1).

Next we analyzed the expression of YPEL1 mRNA in pancreatic bulk tissues. 19 normal pancreas (organ donor), 19 chronic pancreatitis and 31 pancreatic ductal adenocarcinoma tissue samples were used for this experiment. Quantitative PCR revealed significantly downregulated expression of YPEL1 in human pancreatic cancer tissues compared to normal pancreatic tissues (Figure 2, p<0.05). Previous studies have demonstrated a role of YPEL1 in
the regulation of mesenchymal to epithelial-like transition [4]. It is well known that pancreatic cancer cells lose their epithelial morphology and gain more mesenchymal characteristics during malignant transformation [8]. It is difficult to say whether reduced expression of YPEL1 in pancreatic cancer (Figure 2) has a key regulatory role in this process; however, downregulation of YPEL1 appears to be due to the loss of epithelial morphology of these tumors. We studied the survival of pancreatic cancer patients depending on YPEL1 tissue expression. The median YPEL1 value in pancreatic cancer patients was taken as a cut-off to compare patients with high/low YPEL1 mRNA levels using the Kaplan-Meier method. Interestingly higher YPEL1 mRNA levels indicated a tendency for a worsened prognosis for patients (Figure 3). Thus, the median survival in the high YPEL1 group was 13 months versus 16 months in the YPEL1 low group. However this difference did not reach statistically significance (p=0.17).

YPEL1 is localized at centrosomal part of nuclei [9] and is conserved between humans, mice and birds. Over-expression of this protein in fibroblasts alters vimentin and actin cytoskeletal components [4], thus changing the morphogenetic behavior towards an epithelial-like phenotype. One of the important events of normal and malignant morphogenesis is the regulation of a cellular phenotype between a mesenchymal, motile cell type, and an epithelial, sessile cell type. Therefore YPEL1 might be an important factor during the development and malignant transformation of tissues. Further studies are required to better assess the role of human YPEL1 in pancreatic cancer pathogenesis.

REFERENCES

SUMMARY

EXPRESSION OF YPEL1 IN PANCREATIC CANCER CELL LINES AND TISSUES

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YPEL1 is a nuclear protein that is suggested to be involved in mesenchymal to epithelial-like transition during tissue development. Recently we have identified YPEL1 as a gene whose expression is deregulation in perineural invasive pancreatic cancer cells. In this study we assessed the expression of YPEL1 in normal and diseased pancreatic tissues and pancreatic cancer cell lines. Quantitative real time polymerase chain reaction was used to analyze the expression of YPEL1 mRNA in nine cultured pancreatic cancer cell lines and pancreatic bulk tissues of the normal pancreas (n=19), chronic pancreatitis (n=19) and pancreatic adenocarcinoma tissues (n=31). Quantitative real time polymerase chain reaction analysis revealed a significant down-regulation of YPEL1 mRNA expression in pancreatic adenocarcinoma tissues compared to normal tissues (54.1±5.2 vs. 85.8±14.1 copies/10,000 copies cpb) and low expression of this gene indicated a tendency for better survival of pancreatic cancer patients (16 vs. 13 months; p=0.17). Expression of YPEL1 mRNA was present in all tested pancreatic cancer cell lines with comparably low to moderate expression levels of 4.3 – 88.0 copies/10,000 copies cpb. Reduced expression of YPEL1 in pancreatic cancer might be related to perineural invasion, and prognosis. YPEL1 might be an important factor during the development and malignant transformation of tissues. Further studies are required to better assess the role of human YPEL1 in pancreatic cancer pathogenesis.

Key words: pancreatic cancer, Yippee-like 1, YPEL.