Diagnostic utility of aberrant methylation of tissue factor pathway inhibitor 2 in pure pancreatic juice for pancreatic carcinoma.

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The tissue factor pathway inhibitor 2 (TFPI-2) is a Kunitz-type serine proteinase inhibitor. Recently, the aberrant methylation of TFPI-2 was detected frequently in pancreatic carcinoma (PCa) tissues but not in normal pancreatic tissues. We analyzed the aberrant methylation of TFPI-2 in the pure pancreatic juice (PPJ) aspirated endoscopically from patients with various pancreatic diseases. Using the highly sensitive methylation-specific polymerase chain reaction (MSP) and quantitative MSP (Q-MSP) assay, we investigated the aberrant methylation of TFPI-2 in nine human PCa cell lines and in the PPJ from patients with PCa, intraductal papillary mucinous neoplasms (IPMN) and chronic pancreatitis (CP). The incidence of aberrant TFPI-2 methylation was seven (77.8%) of nine PCa cell lines by Q-MSP. In cell lines, the expression of TFPI-2 mRNA by quantitative reverse transcription-polymerase chain reaction showed an inverse correlation to the aberrant methylation of TFPI-2. The incidence of aberrant TFPI-2 methylation in the PPJ was 21 (58.3%) of 36 PCa patients, three (17.6%) of 17 IPMN and one (4.8%) of 21 CP by MSP assay. Using a suitable cut-off value of 2.5 according to the receiver operating characteristic curve, the incidence of aberrant TFPI-2 methylation in the PPJ by real-time MSP was 18 (62.1%) of 29 PCa patients, one (5.1%) of 17 IPMN and three (14.3%) of 21 CP, respectively. The incidence of quantitative TFPI-2 hypermethylation in the PPJ with PCa was significantly higher than that with IPMN ($P < 0.001$) or CP ($P < 0.001$). Moreover, the aberrant methylation rate of TFPI-2 in the PPJ was 100%, as observed (6/6) in the PCa patients with liver metastasis, and 86.7% (26/30) in stages IVa + IVb of PCa by Q-MSP assay. These results suggest that promoter methylation of TFPI-2 in the PPJ may be a useful marker in the diagnosis and progression of PCa using an endoscopically feasible approach.