Fas and Fas-ligand expression in human pancreatic cancer.

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OBJECTIVE: To investigate Fas and FasL expression in pancreatic tissues and cultured pancreatic cancer cell lines, and to assess the ability of anti-Fas antibodies to induce apoptosis. SUMMARY BACKGROUND DATA: Activation of the Fas receptor by Fas-ligand (FasL) results in apoptosis, and dysregulation of this pathway may contribute to abnormal cell proliferation. METHODS: Northern blotting and immunohistochemistry were used to compare Fas and FasL expression in normal and cancerous tissues. DNA 3'-OH end labeling was used to detect apoptotic cells. The effects of Fas activation on cell growth and signaling pathways were investigated in culture. RESULTS: Pancreatic cancers exhibited increased Fas RNA levels, whereas FasL mRNA levels were similar in both groups. Despite the colocalization of Fas and FasL in the cancer cells, an apoptotic signal was present in approximately 10% of these cells in only 2 of 16 cancer samples. Fas and FasL were coexpressed in all four cell lines, whereas Fas-associated phosphatase 1 was below the level of detection in all cell lines. Only COLO-357 cells underwent apoptosis after Fas activation. Apoptosis was associated with enhanced activation of jun kinase (JNK) and p38 mitogen-activated protein kinase (MAPK). In the presence of actinomycin D, Fas antibody also induced apoptosis in the other three cell lines. CONCLUSIONS: These results suggest that pancreatic cancer cells are resistant to Fas-mediated apoptosis by mechanisms excluding receptor downregulation or Fas-associated phosphatase upregulation and raise the possibility that Fas-mediated apoptosis may be dependent on the activation of the JNK/p38 MAPK pathway in these cells.

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