AB075. P047. Human pancreatic stellate cells secreted fibronectin promote chemoresistance to gemcitabine in PDAC

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Abstract: The pancreatic stellate cell (PSC) is the primary cell type of the desmoplastic stroma of pancreatic ductal adenocarcinoma (PDAC). A prominent characteristic of PDAC that contributes to its malignant features is the presence of a dense stroma which is composed of various extracellular matrix (ECM) proteins such as fibronectin (FN) and collagens. PSCs interact with cancer cells and influence the progression of the disease through a complex network of signaling molecules involving ECM proteins. Gemcitabine remains a cornerstone of PDAC treatment in all stages of the disease despite suboptimal clinical effects partly linked to the development of chemoresistance within weeks of treatment initiation. We investigated PSC populations isolated from different human PDACs and examined the effects of PSC-conditioned medium (PSC-CM) on the chemosensitivity of different commercial human pancreatic cancer cell lines: AsPC-1, BxPC-3, Capan-2, HPAF-II, Mia PaCa-2, Panc-1 and SW-1990. The PSC-CM induced varying degree of resistance to cytotoxic activities of gemcitabine among the cancer cell lines examined. Secretome analysis of PSC-CM identified 5,245 peptides corresponding to 687 different proteins (532 of them with more than one peptide), including several ECM-related proteins with the highest number of peptides observed for FN. A FN inhibitor, synthetic Arg-Gly-Asp-Ser (RGDS) peptide, blocked the development of PSC-CM induced chemoresistance in cancer cells, suggesting that the use of FN blocking agents in addition to the gemcitabine-based chemotherapy could counteract chemoresistance and provide better clinical outcomes.

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