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Pancreatic adenocarcinoma and its microenvironment: Models and pharmacological targeting

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Among cancers in critical clinical needs, pancreatic ductal adenocarcinoma (PDAC) is the most intractable. Patients are frequently diagnosed too late to be eligible for surgical resection. Chemotherapy (gemcitabine) has provided almost no survival benefit. There is an urgent need to understand the pathobiology of its premalignant stages and the mechanisms for cancer cell chemoresistance. The KRAS gene is mutated in most PDAC. Pancreatic expression in mice of the Kras oncoprotein efficiently initiates carcinogenesis but not progression to cancer, which necessitates other inputs. Phosphoinositide 3-Kinase (PI3K) activation is required for Kras-induced PDAC initiation and maintenance. Strikingly, somatostatin sst2 receptor loss of gene (SSTR2) expression is observed in most PDAC and inhibits PI3K when re-expressed in cancer cells. We showed that sstr2 monoallelic loss in mice is per se sufficient to activate the PI3K/AKT pathway and, when combined with mutated Kras, to enhance the occurrence of premalignant lesions that rapidly progress to malignancy and metastase to lymph nodes. Additionally, we showed that sst2 expression is progressively lost in mutated Kras-initiated lesions that spontaneously progress to cancer, this expression loss involving PI3K activity. We propose that sst2 expression loss and consequent relief of the physiological brake limiting PI3K/AKT amplifies Kras-driven pathways thus fostering pancreatic carcinogenesis. PDAC is extremely stroma-rich. Cancer-associated fibroblasts (CAFs) secrete proteins that promote cancer cell chemoresistance. We demonstrated that CAF secretome-triggered chemoresistance is abolished upon inhibition of the protein synthesis PI3K/mTOR regulatory pathway which we found highly activated in primary cultures of CAFs, isolated from human PDAC resections. CAFs selectively express the sst1 somatostatin receptor. The SOM230 analogue (Pasireotide) activates the sst1 receptor and inhibits the PI3K/mTOR pathway and the synthesis of secreted proteins. Consequently, tumour growth and chemoresistance in nude mice xenografted with pancreatic cancer cells and CAFs are reduced when chemotherapy (gemcitabine) is combined with SOM230 treatment.

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The Nrf2 mediated antioxidant defense against oxidative stress in BxPC-3 pancreatic cancer cell line and targets for therapeutic intervention

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In the present investigation the proteomic analysis of oxidatively stressed BxPC3 human pancreatic cancer cells have shown the elevated level of a6b4 integrin, caveolin-1, K-RAS, EGFR, annexin A4 and annexin A11 as compared to HPDE control. The high throughput proteomic and bioinformatic analysis by protein center and ingenuity pathway analysis have shown the altered integrin signaling pathway and MAPK pathway in pancreatic ductal adenocarcinoma cell line. Further, the activation of NRF2 transcriptional factor in BxPC-3 exposed to extreme oxidative stress shows that it may bind to the DNA at the location of the hARE (human antioxidant response element) which is the master regulator of the total antioxidant system. It seems likely that upon exposure of cells to oxidative stress, Nrf2 is phosphorylated in response to protein kinase C, phosphatidylinositol 3-kinase and MAP kinase pathways. After phosphorylation, Nrf2 translocates to the nucleus, binds AREs and transactivates detoxifying enzymes and antioxidant enzymes, such as glutathione S-transferase, and superoxide dismutases and as a result cancer cells are able to mount antioxidative defense and have the ability to adapt oxidative stress. The pathway analysis has also demonstrated that at least seven signal transduction cascades were induced by ECM interaction with integrin heterodimers, which may trigger aberrant signaling which could lead to pancreatic cancer adenocarcinoma. The data have clearly shown the activation of INT-ILK-PT3K-ILKAP-AKT and Cav-GRB2-SOS-cRas-Raf-MEK cascades. Specially, the caveolin-1 seems to be important therapeutic target for the treatment of pancreatic cancer adenocarcinoma and could be used as prognostic biomarker.

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