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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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Refractory GERD treatment

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About 30-40 % of GERD patients fail to respond to conventional treatments (standard or double dose of proton-pump inhibitors (PPI), prokinetics, low dose antidepressants) and, despite the efforts of the pharmaceutical companies to rule out new drugs beneficially affecting reflux pathophysiology, their management give rise to a major medical problem. However, there are preclinical and preliminary clinical evidences on the usage of newer, both pharmacological and non-pharmacological, remedies in refractory GERD management. These remedies need an accurate updated reviewing work in order to give to the physician a clear snapshot of "where are we now" in GERD management (describing refractory GERD definition and differential diagnosis, and the issues arising from conventional therapies) and "what we will do" about the most promising treatments for refractory GERD. This last issue is crucial because will condition the attention of physician towards some of newer remedies for this subset of patients, in synergy with the pharmaceutical industry. T.A.R.G.I.D. is the largest gastrointestinal translational laboratory across Europe that is a world referral center for the study of gastrointestinal motility, in general and of the GERD pathophysiology and treatment, in particular. According to my previous PhD program experience in and the actual collaboration with TARGID I will talk about: GERD definition and its physiopathology, refractory GERD definition and its pathophysiology issues, diagnostic flow-chart (including definition of overlap diseases and refractory GERD misdiagnosis (e.g. functional dyspepsia)), evidence-based therapeutic flow-chart including both pharmacological (older and newer PPI types and dosage, prokinetics, drugs affecting lower esophageal sphincter functioning) and non-pharmacological treatments (laparoscopic, endoscopic antireflux surgery), newer development directions in refractory GERD management.

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