

## Medical Therapy for Advanced Pancreatic Cancer: Work in Progress

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Drug resistance of pancreatic cancer cells is a well-known phenomenon that occurs mainly as a result of active survival mechanisms sometimes associated with the non efficacious delivery of drugs due to the fibrosis which is the major constituent of pancreatic ductal adenocarcinoma [1, 2, 3]. Furthermore, it is well known that organ functions - normally at a pH of approximately 7.4 - are strongly affected by the disruption of pH homeostasis; this is due to the fact that the organs contain a large number of enzymes with pH sensitive catalytic activity. In contrast, the extracellular pH decreases to below 6.5 in the central regions of solid tumors because of the accumulation of lactate, and this phenomenon is due to poor vascularization [4, 5] associated with an increase in tumor specific aerobic glycolysis combined with impaired mitochondrial oxidative phosphorylation [6]. The diminished pH within the tumor is an additional cause of chemotherapy resistance for pancreatic tumors. Finally, other local pancreatic substances may participate in the spread of the tumors. For example, the local renin angiotensin system (RAS) promotes angiogenesis and proliferation via vascular endothelial growth factor expression or epidermal growth factor receptor expression [7, 8]. The synergistic inhibition of tumor growth has been demonstrated in experimental animals by combining the administration of gemcitabine and losartan which are able to cause vascular endothelial growth factor suppression [9] and induce apoptosis of pancreatic cancer cells by the inhibition of RAS [10, 11]. Therefore, it is necessary to develop alternative strategies and novel therapeutics for the effective treatment of advanced pancreatic

cancer - which constitutes the major part of the currently diagnosed pancreatic ductal carcinomas [12] - and three papers recently published on these topics are of particular interest.

The first one is the paper of Singh *et al.* [13] who evaluated the effect of pancreatic cancer cells treated with gemcitabine in the presence of CXCL12, a chemokine receptor expressed in a variety of malignancies and extensively studied for its role in cancer pathogenesis. They found that the pancreatic cancer cells exhibited reduced cytotoxicity in the presence of CXCL12 as compared to the cells treated with drug alone. Thus, CXCL12 induced the activation of focal adhesion kinase (FAK) extracellular regulated MAP kinase (ERK) and Akt signalling pathways, enhanced the transcriptional activities of b-catenin and NF-kappa B, and expression of survival proteins. AMD3100, an antagonist of CXCR4, arrested CXCL12-induced pancreatic cancer cell growth and drug resistance. This suggests that future clinical trials designed for treating patients with pancreatic cancer might benefit from targeting this signaling axis alone or in combination with chemotherapy.

The second paper of particular interest is that of Fukamachi *et al.* [14]. These authors tested the effect of external acidic pH on the efficacy of 24 chemical compounds including molecular-targeted inhibitors and anti-tumor reagents in human cancer cells. For example, they found that lovastatin showed no cytotoxicity in pancreatic carcinoma cells at concentrations up to 10  $\mu$ M and a pH of approximately 7.4, while lovastatin at a concentration of 10  $\mu$ M decreased the survival of these cells to below 40% at acidic pH. What do these findings mean when translated into clinical practice? They suggest that screening tests under acidic conditions are required in order to better define the current therapeutic lines of treatment and to develop new chemotherapeutic reagents.

The third and last paper reports the epidemiological findings of Nakai *et al.* [15] who retrospectively explored the impact of angiotensin I-converting enzyme inhibitors (ACEIs) and angiotensin II type-1

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receptor blockers (ARBs) in a cohort of 155 patients with pancreatic cancer who were receiving gemcitabine monotherapy. They found that ACEIs/ARBs in combination with gemcitabine might improve clinical outcomes in patients with advanced pancreatic cancer. Even if the study is retrospective and based on a low number of patients, we think that, based on the large scale use of these drugs in clinical practice, prospective trials are needed to test this fascinating hypothesis.

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**Conflict of interest** None

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