Pancreatic Stellate Cells and Pancreatic Carcinoma: An Unholy Alliance

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The importance of the stromal compartment in the development, proliferation, invasion, metastasis and resistance of epithelial cancers has increasingly been recognized in recent decades [1, 2]. This stromal reaction is found in many carcinomas, e.g. in breast, prostate, colon, ovarian and pancreatic cancer. It is made up of stromal cells, endothelial cells, immune cells and extracellular matrix proteins. Moreover, the ECM proteins in the stroma act as a reservoir for growth factors released either by tumor or stromal cells, thus enabling autocrine and paracrine stimulation of the cells within the tumor mass. In this respect, groundbreaking work in solid tumors was done by Mina Bissell with breast carcinoma as her model system [3]. Recently, Vonlaufen et al. have contributed a review on the relationship between activated pancreatic stellate cells (PSCs) and pancreatic ductal adenocarcinoma cells which is worth reading [4]. Vonlaufen et al., with their own study [5] and those of some other groups (see their review), convincingly demonstrate a reciprocal influence of both non-epithelial and epithelial constituents of pancreatic carcinoma which works to their mutual benefit. Thus, the coinjection of PSC and pancreatic tumor cells enhances tumor growth and metastasis. In In vitro and animal models, PSCs increase tumor cell proliferation and decrease basal and induced apoptosis of pancreatic tumor cells. On the other hand, pancreatic tumor cells activate PSCs, recruit them to their vicinity and stimulate their proliferation. This review clearly exemplifies the specialized milieu in which both cell types grow to their mutual benefit, thus forming one of the deadliest tumors we know.

Based on our own experience, we would like to point out a few additional issues which may add to this excellent review. In view of the histopathological appearance of typical ductal adenocarcinomas of the pancreas, we asked whether the carcinoma cells themselves contribute to the de novo production of matrix proteins in the context of such a stromal-rich tumor; and this was indeed the case [6, 7]. Thus, one of the questions raised in Vonlaufen’s review can be answered. The driving force behind the stimulation, both in vitro and in vivo, is TGF-beta1; transfection of TGF-beta1 in a tumor cell line not expressing TGF-beta1 and not capable of stroma-induction will result in a significant desmoplasia [8]. This underscores once again the pivotal role of this growth factor in the development and progression of pancreatic ductal adenocarcinoma since it is already expressed in the preneoplastic lesions, i.e. PanIN1 [9]. Since PanIN1

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Abbreviations
PSC: pancreatic stellate cell

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Figure 1. Immunocytochemistry for collagen I (COL I) and fibronectin (FN) in a normal pancreas and PanIN 1B. The PanIN lesion was K-ras positive (mutated, data not shown).
already typically possess, for the most part, K-\textit{ras} mutations [10], we could also demonstrate the beginning of matrix expression in such lesions (Figure 1). Furthermore, immortalized pancreatic duct cells [11] already pick up the expression of matrix proteins on the RNA [12] and protein level (Figure 2). Therefore, the epithelial tumor cell expressing TGF-beta1 is the driving force; the underlying cause for the TGF-beta1 expression which ultimately kicks off the induction of desmoplasia is the activation of K-\textit{ras}, as part of the epithelial-to-mesenchymal transition [13].

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**References**