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PANCREAS NEWS

Pancreatic Stellate Cells and Pancreatic Carcinoma: An Unholy Alliance

Johannes-Matthias Löhr[1,2], Ralf Jesenofsky[2]

[1]CLINTEC, Department of Surgical Gastroenterology, Karolinska Institute. Stockholm, Sweden.
[2]Clinical Cooperation Unit Molecular Gastroenterology, German Cancer Resaerch Center. Heidelberg, Germany

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

Correspondence Johannes-Matthias Löhr
Karolinska Institute, CLINTEC K53, Hälsovägen 11, SE-141 86, Stockholm, Sweden
Phone +46-8.5858.9591; Fax: +46-8.5858.2340
E-mail: matthias.lohr@ki.se

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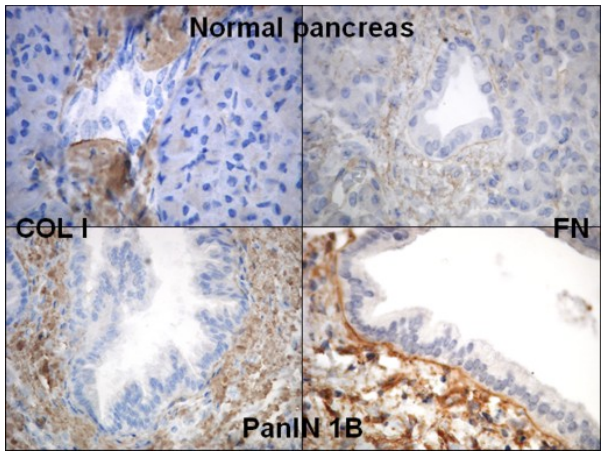

Figure 1. Immunocytochemistry for collagen I (COL I) and fibronectin (FN) in a normal pancreas and PanIN 1B. The PanIN lesion was K-*ras* positive (mutated, data not shown).

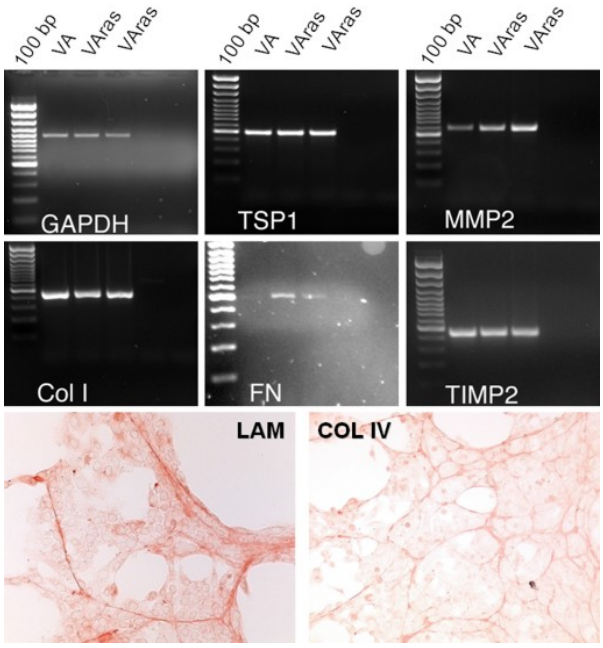

Figure 2. Immortalised (VA) and further *ras*-transfected bovine pancreatic duct cells. RT-PCR (upper) and immuncytochemistry (lower) for collagen type I (COL I), collagen type IV (COL IV), laminin (LAM), fibronectin (FN), MMP2, TIMP2, and TSP1.
GADPH: control. Analysis of the molecules was subject to the availability of bovine sequences and cross-reacting antibodies [12, 13].

already typically possess, for the most part, K-*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-*ras*, as part of the epithelial-to-mesenchymal transition [13].

Conflict of interest The authors have no potential conflict of interest

References

1. Liotta LA. Tumor invasion and metastases: role of the extracellular matrix: Rhoads Memorial Award lecture. Cancer Res 1986; 46:1-7. [PMID 2998604]

2. Strobel ES, Strobel HG, Bross KJ, Winterhalter B, Fiebig HH, Schildge JU, Löhr GW. Effects of human bone marrow stroma on the growth of human tumor cells. Cancer Res 1989; 49:1001-7. [PMID 2912545]

3. Bissell MJ, Weaver VM, Lelievre SA, Wang F, Petersen OW, Schmeichel KL. Tissue structure, nuclear organization, and gene expression in normal and malignant breast. Cancer Res 1999; 59 (7 Suppl.):1757-63s. [PMID 10197593]

4. Vonlaufen A, Phillips PA, Xu Z, Goldstein D, Pirola RC, Wilson JS, Apte MV. Pancreatic stellate cells and pancreatic cancer cells: an unholy alliance. Cancer Res 2008; 68:7707-10. [PMID 18829522]

5. Vonlaufen A, Joshi S, Qu C, Phillips PA, Xu Z, Parker NR, et al. Pancreatic stellate cells: partners in crime with pancreatic cancer cells. Cancer Res 2008; 68:2085-93. [PMID 18381413]

6. Löhr M, Trautmann B, Göttler M, Peters S, Zauner I, Maillet B, Klöppel G. Human ductal adenocarcinomas of the pancreas express extracellular matrix proteins. Br J Cancer 1994; 69:144-51. [PMID 8286197]

7. Löhr M, Trautmann B, Gottler M, Peters S, Zauner I, Maier A, et al. Expression and function of receptors for extracellular matrix proteins in human ductal adenocarcinomas of the pancreas. Pancreas 1996; 12:248-59. [PMID 8830331]

8. Löhr M, Schmidt C, Ringel J, Kluth M, Müller P, Nizze H, Jesenofsky R. Transforming growth factor-beta1 induces desmoplasia in an experimental model of human pancreatic carcinoma. Cancer Res 2001; 61:550-5. [PMID 11212248]

9. Ito D, Fujimoto K, Doi R, Koizumi M, Toyoda E, Mori T, et al. Chronic exposure of transforming growth factor beta 1 confers a more aggressive tumor phenotype through downregulation of p21(WAF1/CIP1) in conditionally immortalized pancreatic epithelial cells. Surgery 2004; 136:364-74. [PMID 15300203]

10. Kern S, Hruban R, Hollingsworth MA, Brand R, Adrian TE, Jaffee E, Tempero MA. A white paper: the product of a pancreas cancer think tank. Cancer Res 2001; 61:4923-32. [PMID 11406572]

11. Löhr M, Müller P, Zauner I, Schmidt C, Trautmann B, Thevenod F, et al. Immortalized bovine pancreatic duct cells become tumorigenic after transfection with mutant k-ras. Virchows Arch 2001; 438:581-90. [PMID 11469690]

12. Jesenofsky R, Zubakov D, Faissner R, Ringel J, Hoheisel JD, Lösel R, et al. Genes and proteins differentially expressed during in vitro malignant transformation of bovine pancreatic duct cells. Neoplasia 2007; 9:136-46. [PMID 17356710]

13. Fensterer H, Giehl K, Buchholz M, Ellenrieder V, Buck A, Kestler HA, et al. Expression profiling of the influence of RAS mutants on the TGFB1-induced phenotype of the pancreatic cancer cell line PANC-1. Genes Chromosomes Cancer 2004; 39:224-35. [PMID 14732924]