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Autor(en) des Beitrags: Erkan, M; Reiser-Erkan, C; Michalski, CW; Kong, B; Esposito, I; Friess, H; Kleeff, J

Titel des Beitrags: The impact of the activated stroma on pancreatic ductal adenocarcinoma biology and therapy resistance.

Abstract: Around 95% of patients diagnosed with pancreatic cancer will die of their disease within 5 years, three quarters within a year. The major hurdle in improving prognosis is the lack of a therapeutic time window. Early cancerous lesions are far beneath our threshold of detection. Therefore, at the time of diagnosis even early (T1) tumors can be metastatic and resistant to conventional treatments. Several therapies targeting epithelial tumor cells—all showing impressive results in vitro and in animal experiments—have failed to show relevant effects in clinical trials. This discrepancy between experimental data and clinical reality results mostly from the inefficiency of our current experimental setups in recreating the tumor microenvironment. Forming more than 80% of the tumor mass, the fibrotic stroma of pancreatic ductal adenocarcinoma is not a passive scaffold for the malignant cells but an active player in carcinogenesis. This component is mostly missing in the xeno-/allograft- mouse models. Although tumors are bigger if stellate cells are co-implanted, due to the disproportionate cancer/stromal cell ratio and—possibly—too rapid tumor growth, the stromal reaction is much smaller than in human pancreatic cancer. One the other hand, desmoplasia is present only in some of the genetically engineered mouse models. Clinically, stromal activity of the pancreatic ductal adenocarcinoma has as great an impact on patient
prognosis as the lymph node status of the tumor. The exact molecular mechanisms behind this observation remain obscure. However, one possible fundamental biologic explanation could be that selective pressure applied by the stroma leads to the evolution of cancer cells. Consequently, somatic evolution of invasive cancer could be viewed as a sequence of phenotypical adaptations to this barrier, highlighting the importance of the fibrotic tumor microenvironment in the behavior of pancreatic cancer. In this review, the interaction of the epithelial tumor cells with the stroma in humans and in various animal models is scrutinized, and novel therapeutic options for uncoupling cancer-stroma interactions are discussed.