



# Interaction of tumor and stromal cells in pancreatic cancer

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Aberrant cell signaling is a hallmark of cancer. This led to an extensive research and the identification of several oncogene driven signaling pathways (cell-autonomous). However, solid tumors are not only composed of cancer cells but also of normal cells such as fibroblasts, endothelial cells or immune cells. In particular, pancreatic cancer is one of the preeminent examples of a cancer with an excessive stroma reaction. In some cases cancer cells represent only 10% of the entire tumor. It is an ongoing discussion whether this stroma reaction is friend or foe to the hosting organism (1-3). There are many arguments that distinct stroma compartments might contribute to tumor progression but also findings that the stroma might represent a defense mechanism towards tumor cell growth. Undoubtedly there are many cross-talks and communication of tumor cells and its surrounding stroma. Moreover, some authors even suggest that the cancer cells can create its own specific environment which in turn nurses the tumor cells. This idea of a tumor-derived stroma for instance led to the discovery of pancreatic stellate cells, a myofibroblast-like cell type that has a huge influence in the progression of pancreatic cancer (4,5). However the underlying cellular and molecular mechanisms of the critical cross talks within the tumor stroma are rudimentary uncovered.

Undoubtedly, aberrant signaling from the tumor stroma cells influences tumor biology and tumor cell behavior. Since different cell type's process signaling individually the potential of an increased capacity of signal enhancement emerges. This assumption led Christopher Tape and colleagues (6)

to analyze tumor cells and potential feedback loops control reciprocal activation within and by the stromal.

Applying latest advances in proteome labeling allowing a cell specific phosphoproteome and phosphosignaling analyses they assessed cell signaling in the heterocellular system of pancreatic cancer. Using co-cultivation experiments they show a unique non-cell-autonomous communication between stromal cells and tumor cells in a sonic hedgehog dependent manner only when tumor cells harbors an oncogenic *KRAS*<sup>G12D</sup> mutation. They demonstrate a crucial role of MAPK/CDK/CK kinase motif activation in a MEK-ERK dependent manner without involvement of a significant AKT activity. The oncogenic activation of this motive is dependent on the presence and activity of stromal cells using the IGF1R/AXL-network.

Functionally, this reciprocal crosstalk is able to restore mitochondrial proteins in the tumor cells and increases its spare respiratory capacity. Moreover, proteins involved in the DNA replication are upregulate, cell proliferation is increased and tumor cells are protected from apoptosis. Tape and colleagues clearly outline the molecular basis of an intercellular communication system between tumor cells and stromal cells finally resulting in an increased oncogenic capacity of the cancer cell. They prove the involvement of different levels of phosphor-specific activation in both cell types and describe the necessity of three conditions which enables the integrity of this microenvironmental system: an oncogenic stimulus, a non-cell-autonomous signal and a heterotopic cell capable of transducing the signal back to

the initiating cell.

The decryption of two different regulatory levels of the tumor cell proteome, both under the control of oncogenic KRAS clearly underline the complexity of signaling system in the microenvironment of solid tumors. Especially in pancreatic cancer which is characterized by a multitude of different stroma cells the hot spot mutation of *KRAS*<sup>G12D</sup> directly controls complex intracellular signaling networks and adjust this system via activation of distinct stroma cells. The outcome of these regulatory loops might be highly diverse since the reply strongly depends on individual stroma cell characteristics. To which extent these data finally influence therapeutic strategies remains to be validated. However, it is important to point out that the inhibition of single part within a reciprocal system will probably not translate into sufficient pharmacological success in the treatment of pancreatic cancer.

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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