Extracellular matrix and matrix-processing cells in pathophysiology of pancreatic cancer

Unlike other types of cancer, pancreatic cancer (PC) is associated with tissue 'scarring' and inflammation – the hallmarks of so called desmoplastic reaction. In pancreatic tumors, products of the reactive/regenerative processes that drive desmoplasia yield the cell-free components of a specific microenvironment (here: the nearest cell vicinity) that can account up to 80% of the tumor mass. Deposition of protein fibers in the tumor stroma (or the matrix, which is a mixture of water and proteins) forms a physical barrier between the normal pancreatic cells and cancer. Therefore, mutant cells that are 'hidden' by the matrix can easier escape the immune system of the tumor host. The stroma also poses serious problems in the effective drug targeting to the cancer cells. All these contribute significantly to a very poor success rate in pancreatic cancer treatment, limiting the 5-year survival rate to 9%. This means that out of 400,000 patients diagnosed each year with PC, within 60 months 376,000 people will die.

The current dogma says that the 'scar' helps the tumor to grow. However, the matrix that accumulates gradually in the tumor and encapsulates cancer cells, initially is a natural body defense mechanism against the disease! At the early stages of cancer development, production of the stroma protects the pancreas from a contact with mutant cells and rapid cancer spread in the pancreatic tissue. The pancreas is a very important gland that precisely regulates sugar homeostasis in the body as well as releases digestive enzymes that break the foods in the processes of digestion. This organ produces large amounts of fluids released either to the bloodstream, in order to regulate sugar level, or to the gut, wherein pancreatic juice aids the digestion. The 'spongy' pancreas each day produces up to 1 L volume of pancreatic juice, and the flow of the juice through the organ exerts appropriate physiological fluid pressure. However, growth of solid pancreatic cancer could locally increase this normal mechanical stress since the tumor tissue is stiffer than the pancreas itself. Also, production of the matrix components could further add to the local tissue stiffness. Specialist cells that produce and process the stroma are pancreatic fibroblasts, similar to the skin cells that aid the processes of the wound healing in response to the injury. Analogically, pancreatic fibroblast can also form a 'scar' tissue. The scientists had attempted to completely remove certain pancreatic fibroblasts from pancreatic tumors in order to improve drug penetration to cancer cells.

Unexpectedly, complete killing of pancreatic fibroblast did not improve the survival! Instead, even more aggressive tumors were grown. These tumors depleted of the activated fibroblast, rapidly killed the tumor hosts. Importantly, these findings were published independently by two groups of the scientists who demonstrated the importance of better understanding of the interactions between cancer cells and fibroblasts in pancreatic cancer, since this is a lot more complex process than historically thought. Preliminary data presented in this grant proposal demonstrate that it is rather the matrix normalization than its complete elimination, that should be attempted in order to successfully cure pancreatic cancer and improve patient survival.

Only very recently the mechanical characteristics (low/high stiffness, fluid pressure, and others) of tissues was put into the spotlight, highlighting the importance of the physical signals from the local environment - the mechanical cues: pressure, strain or stress. However, we have not yet answered questions how the processes of fibroblast activation, including the changes in cell signaling, cell metabolism, cell stiffness and stiffness of cell's nearest surrounding, affect the tumor formation and growth. The proposed research program will be carried out by a newly established research group lead by a scientist with over nine years of the postdoctoral experience (50% abroad) in pancreatic diseases. We aim to investigate the biology of pancreatic cancer and explain how stiffness of the matrix modifies fibroblast activation and changes the stroma. Application of the gel substrates of different stiffness will allow us to investigate how mechanical stress influences the potential of cancer cells to spread and grow the distant metastases, also after chemotherapy. The flow of fluid will be applied to the cells in order to mimic the conditions that cancer cell must overcome in the bloodstream to survive and grow a metastasis in a new organ. Finally, series of experiments will test how the presence of mechanical stress affects tumor growth in the animal models. These studies will analyze the differences in tumor structure in their relation to the stress applied to cancer cells prior the injection to the tumor hosts.

These experiments will help us better understand the mechanobiology of pancreatic cancer in order to improve the therapy of this deadly disease.