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Dr.sc. hum

Identification and functional characterisation of novel therapeutic targets for the treatment of pancreatic cancer

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Pancreatic cancer is a fast-growing cancer and is the fourth leading cause of cancer death across the globe. The rate of diagnosis is almost similar to the rate of mortality because in majority of patients, tumor is discovered in the late stages when it has spread throughout the pancreas. This aggressive behavior of pancreatic cancer give raises to resistance to conventional treatment approaches such as radiation, surgery, chemotherapy or combination of them. Therefore, there is an urgent need for development of novel diagnostic and treatment strategies for early detection and treatment of this cancer. Targeted therapies using specific small inhibitor molecules have shown successful results treatment of different types of solid tumors. Accordingly, investigation to find appropriate targets based on gene mutations or important pathways involved in the development of pancreatic cancer seems a promising approach. The purpose of this study was to identify novel factors with important roles for survival of pancreatic cancers cells leading to the identification of novel targets for therapeutic intervention. In this thesis, gene expression profiling data from pancreatic ductal adenocarcinoma and normal tissue samples was employed to identify the most significant pathways that are deregulated in pancreatic cancer. We identified relationship between ER stress (related to calcium signaling) and *DRD2* (as a modulator and important therapeutic target of dopaminergic synapse) in the superfamily of GPCRs. Pharmacologically blocking or genetic silencing of this receptor resulted in cell growth inhibition in cancer cells. Interestingly, our data demonstrated that cell-growth inhibitory function of DRD2-antagonist Pimozide on pancreatic cancer cells is considerably stronger than on normal fibroblast cells. DRD2 was identified as cAMP effector that negatively regulates calcium homeostasis in the cytosol of pancreatic cancer cells leading to regulation of apoptosis-inducing ER stress, and was involved in regulation of cell migration. Furthermore, we found that combination of a DRD2

antagonist and gemcitabine potentiate sensitization of resistant pancreatic cancer cells to chemotherapy. In summary, our findings show that targeting DRD2-cAMP-ER stress axis in pancreatic cancer cells can be a novel strategy to improve treatment efficiency by retarding resistance development and reducing side effects in patients with cancer. Detection of DRD2 protein in pancreatic duct cells in tumor lesions whereas low or negative detection of this protein in duct cells of healthy pancreatic tissue samples supports the appropriateness of this molecule as a therapeutic target against pancreatic cancer.