Medication against schizophrenia inhibits pancreatic cancer

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Cancer of the pancreas is an extremely aggressive disease with a dismal prognosis. The number of cases that is newly diagnosed with this type of cancer each year is almost the same as the one of people who succumb to it. While advances in prevention, early detection and treatment have led to a drop in mortality rates in most other cancer types, a growing number of people in Germany and world-wide develop pancreatic cancer and die from it.

"The tumors do not cause any signs or symptoms for a long time and are therefore diagnosed late," says Jörg Hoheisel from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg. "In addition, the tumor biology is very aggressive, i.e., the cancer starts spreading metastases early on. And to make things worse, pancreatic cancer rapidly develops resistance against available chemotherapy drugs."

Therefore, scientists are making great efforts to identify novel molecular targets that can be attacked to fight pancreatic cancer. Hoheisel and his colleagues from Heidelberg, Tübingen, Liverpool, Verona, Toronto and Montreal undertook a large-scale analysis of gene activities in 195 pancreatic cancer cases. "We leveraged quantitative and computational biology approaches that we have established in order to identify genes that may play a central role in several pancreatic cancer-relevant signaling pathways among almost 3,000 genes that exhibited abnormally high or low activities" said Riazalhosseini of McGill University who co-led the study with Hoheisel., In this way, they identified the dopamine

receptor DRD2. The DRD2 gene was significantly more active in cancer cells than in healthy pancreatic cells, and the levels of DRD2 receptor protein found in the cancer cells were four times the normal.

Blocking the dopamine receptor inhibits cancer growth

The dopamine receptor mediates the effect of the dopamine neurotransmitter in the brain. Dopamine is an important brain chemical that increases motivation and drive. How can a receptor protein that is known to clinicians primarily for its role in schizophrenia and psychotic disorders influence the malignant characteristics of cancer cells? The researchers pursued this question in pancreatic cancer cell lines in which they had turned off the DRD2 gene. They observed that these cells in fact grew more slowly and formed smaller tumors when transferred to mice.

DRD2 is a key molecule in many psychotic diseases and is therefore targeted by numerous psychopharmaceutical agents. Drugs that block the function of DRD2 ("dopamine antagonists") have been available since the 1950s. Among them is the antipsychotic pimozide. Using this substance, the investigators collaborating with Hoheisel succeeded in substantially slowing down the growth and impeding the mobility of pancreatic cancer cell lines.

The researchers transferred human pancreatic cancer cells to mice and allowed them to grow into tumors. After treating the animals with another dopamine antagonist - haloperidol, a medication that is often prescribed to treat schizophrenia - they developed smaller tumors and, more importantly, fewer metastases than untreated animals.

"We do not know yet whether haloperidol or related medications have

the same effect in pancreatic cancer patients as they have in tumor cells and mice," Hoheisel said. He added as an interesting observation that schizophrenia patients, who are treated mostly with dopamine antagonists, have a lower rate of solid tumors on the whole than the general population. It is therefore possible that the cancer-inhibiting effect might not be restricted to the pancreas.

The DKFZ researchers now plan to examine in a study with pancreatic cancer patients whether drugs from the group of dopamine antagonists have a favorable effect on the course of the disease. For this, they will continue collaborating closely with Markus W. Büchler from Heidelberg University Hospital and the colleagues at McGill University in Montreal with the goal of treating pancreatic cancer patients. "We are very lucky to have come across established medications. This should make the required and laborious safety examinations easier," said Hoheisel.

Dopamine receptor protects cancer cells from biochemical stress

The DKFZ researchers additionally wanted to gain an understanding of the molecular mechanisms by which the dopamine receptor drives cancer growth. Normally, DRD2 prevents cells from experiencing biochemical stress via a crucial intracellular signaling molecule called cAMP. After blocking DRD2, the rapidly dividing cancer cells are particularly exposed to this kind of stress. This leads to a breakdown of the cell division cycle and then to cell self-destruction (apoptosis).

The investigators found higher-than-normal activity of the DRD2 gene already in chronic pancreatitis, which is considered to be a precancerous stage of pancreatic cancer. Other authors have also described increased activity levels of the DRD2 gene in cancer stem cells. Hoheisel and colleagues therefore think that this alteration occurs at a very early stage

of cancer development.

More information: Pouria Jandaghi et al, Expression of DRD2 is Increased in Human Pancreatic Ductal Adenocarcinoma and Inhibitors Slow Tumor Growth in Mice, *Gastroenterology* (2016). DOI: 10.1053/j.gastro.2016.08.040

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