Medical Xpress

Study finds how diabetes drug metformin inhibits progression of pancreatic cancer

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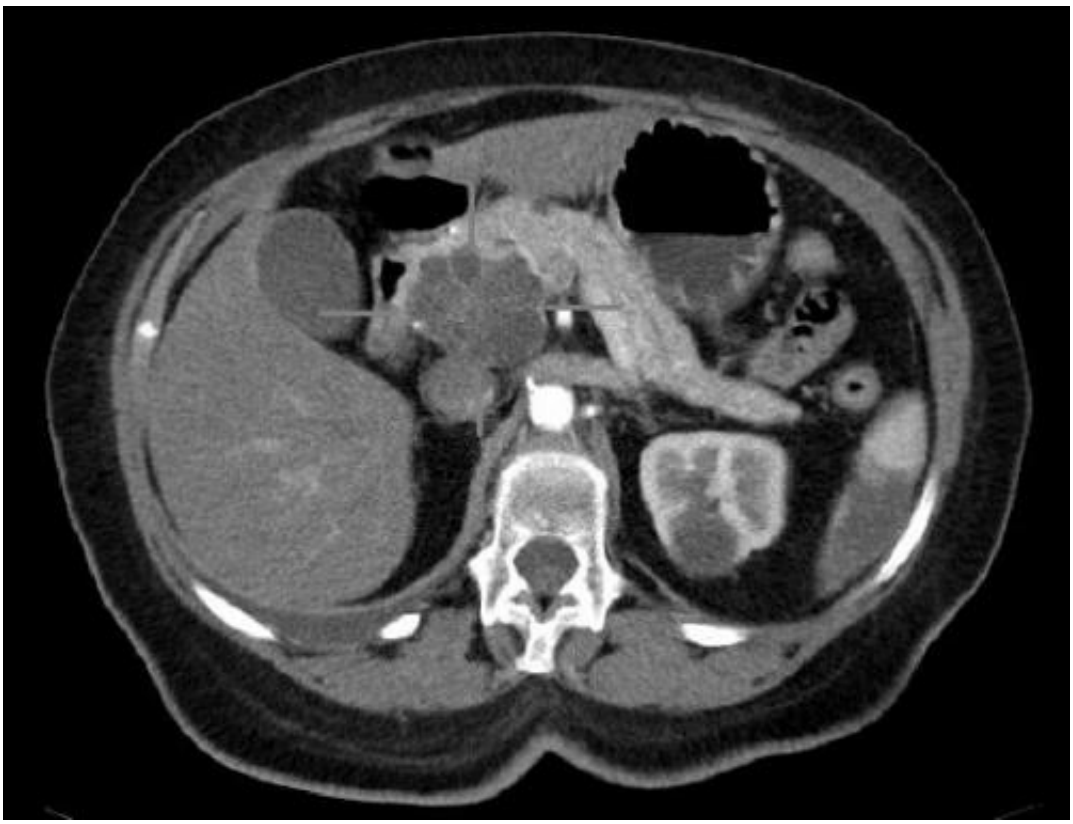

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Massachusetts General Hospital (MGH) investigators may have uncovered a novel mechanism behind the ability of the diabetes drug metformin to inhibit the progression of pancreatic cancer. In their report

that has been published in the open access journal *PLOS One*, the research team describes finding that metformin decreases the inflammation and fibrosis characteristic of the most common form of pancreatic cancer. Their findings in cellular and animal models and in patient tumor samples also indicate that this beneficial effect may be most prevalent in overweight and obese patients.

"We found that metformin alleviates desmoplasia - an accumulation of dense connective tissue and tumor-associated immune cells that is a hallmark of pancreatic cancer - by inhibiting the activation of the pancreatic stellate cells that produce the extracellular matrix and by reprogramming immune cells to reduce inflammation," says Dai Fukumura, MD, PhD, of the Steele Laboratory of Tumor Biology in the MGH Department of Radiation Oncology, the study's co-senior author. "We also found these effects only evident in tumors from overweight or obese individuals, who appear to have tumors with increased fibrosis."

The study focused on pancreatic ductal adenocarcinoma, the most common form of pancreatic cancer, which accounts for almost 40,000 cancer death in the U.S. ever year. Half of those diagnosed with this form of pancreatic cancer are overweight or obese, and up to 80 percent have type 2 diabetes or are insulin resistant. Diabetic patients taking metformin - a commonly used generic medication for type 2 diabetes - are known to have a reduced risk of developing pancreatic cancer; and among patients who develop the tumor, those taking the drug may have a reduced risk of death. But prior to the current study the mechanism of metformin's action against pancreatic cancer was unclear, and no potential biomarkers of response to metformin had been reported.

The researchers first found that levels of hyaluronan, a component of the extracellular matrix, were 30 percent lower in tumor samples from overweight or obese patients who were taking metformin to treat diabetes than in those who did not take the drug. In an obese animal

model of pancreatic cancer, those that received metformin had reduced expression of both hyaluronan and collagen-1 and fewer activated pancreatic stellate cells (PSCs). Studies in cultured cells identified the signaling pathway by which metformin reduces the production of hyaluronan and collagen-1 by PSCs and also prevents the recruitment of tumor-associated macrophages, which increase the inflammatory environment.

In obese mouse models, the researchers found that metformin treatment reduced levels of tumor-associated macrophages by 60 percent and reduced expression of genes involved in remodeling the extracellular matrix of tumor tissue. The tumors of animals treated with metformin also had reductions in a metastasis-associated change in cellular characteristics called epithelial to mesenchymal transition (EMT) and in the overall level of metastasis. These tumor-related effects of metformin appear to be independent of the drug's effects on metabolic pathways involved in glucose metabolism and body weight.

"Nearly 200 clinical trials are currently underway investigating the effect of metformin on tumors in both diabetic and non-diabetic patients," say co-senior author Rakesh K. Jain, PhD, director of the Steele Laboratory. "Understanding the mechanism behind metformin's effects on pancreatic and other cancers may help us identify biomarkers - such as patient body weight and increased tumor fibrosis - that can identify the patients for whom metformin treatment would be most beneficial." Fukumura is an associate professor of Radiation Oncology, and Jain is the Cook Professor of Tumor Biology at Harvard Medical School. Later this year Jain will be among nine recipients of the 2016 National Medal of Science.

More information: Joao Incio et al. Metformin Reduces Desmoplasia in Pancreatic Cancer by Reprogramming Stellate Cells and Tumor-Associated Macrophages, *PLOS ONE* (2015). DOI:

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