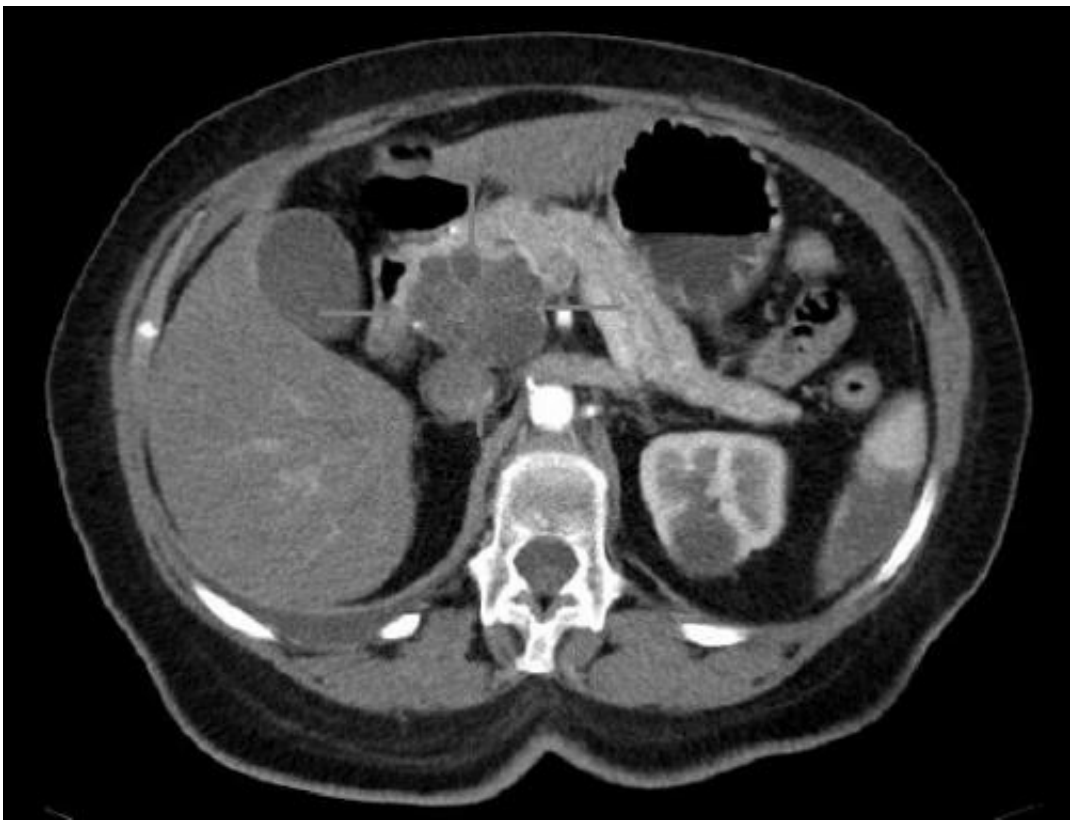
Study reveals why chemotherapy may be compromised in patients with pancreatic cancer

November 11 2015



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

A study at The University of Texas MD Anderson Cancer Center may explain why chemotherapy drugs such as gemcitabine are not effective

for many pancreatic cancer patients, and perhaps point to new approaches to treatment including enhancing gemcitabine's ability to stop tumor growth.

The MD Anderson study in mice suggests that suppressing a cellular plasticity process known as epithelial-to-mesenchymal transition (EMT) in combination with gemcitabine, may boost the drug's effectiveness. Study findings were published in the Nov. 11 online version of *Nature*.

"Diagnosis of pancreatic cancer is associated with poor prognosis despite the availability of current therapies," said Raghu Kalluri, M.D., Ph.D., professor and chair of Cancer Biology, and the study's lead author. "Therefore new treatment strategies are urgently needed."

Kalluri's team looked at EMT, an embryonic cellular plasticity program that is hijacked by cancer cells and is thought to help cancer cells migrate to other organs. Cancer cells spread disease by either dividing (proliferation), or by migrating, allowing them to metastasize. When cancer cells adopt an EMT program to promote their migration, they generally stop dividing. The research findings indicate that EMT leads to arrest of cancer cell proliferation causing impaired sensitivity to chemotherapy, impacting the body's ability to effectively respond to such treatment.

"Gemcitabine works primarily on cancer cells that are dividing or proliferating," said Kalluri. "When cancer cells suspend their proliferation - such as when they launch an EMT program - then anti-proliferation drugs like gemcitabine do not target them well."

"We found that EMT program suppressed drug transporter and concentrative proteins, which inadvertently protected these cancer cells from anti-proliferative drugs such as gemcitabine," added Kalluri. "The correlation of decreased survival of pancreatic cancer patients with an

increased EMT program is likely due to their impaired capacity to respond to chemotherapy, leading to overall poor prognosis and higher incidence of metastasis."

Inhibiting EMT program led to enhanced response of tumors to gemcitabine.

"Collectively, our study offers the opportunity to evaluate the potential of targeting EMT program to enhance efficacy of chemotherapy and likely targeted therapies," said Kalluri.

More information: Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer, *Nature*, DOI: 10.1038/nature16064

Provided by University of Texas M. D. Anderson Cancer Center