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Mechanisms help pancreatic cancer cells avert starvation

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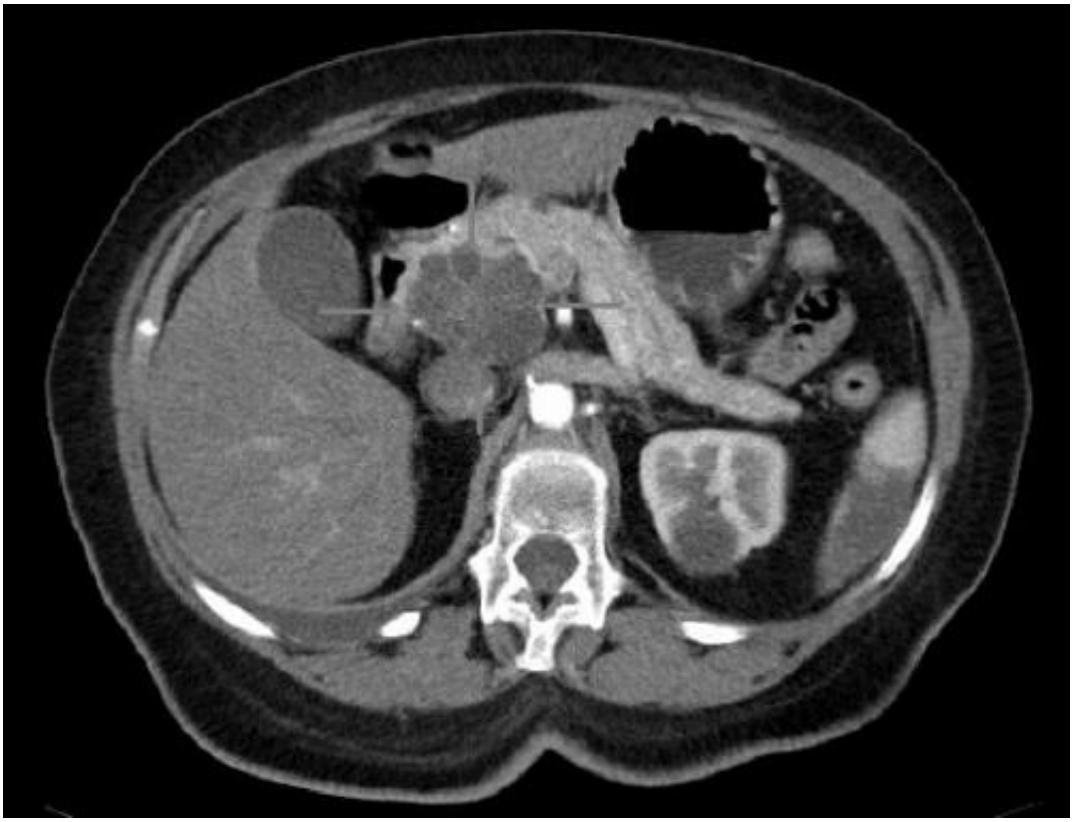

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

A new study reveals the mechanism that helps pancreatic cancer cells avoid starvation within dense tumors by hijacking a process that pulls nutrients in from their surroundings.

Led by researchers at NYU Grossman School of Medicine, the study explains how changes in the gene RAS—known to encourage the abnormal growth seen in 90 percent of pancreatic cancer patients—also accelerate a process that supplies the building blocks required for that growth.

Called macropinocytosis, the process engulfs proteins and fats, which can be broken down into amino acids and metabolites used to build new proteins, DNA strands, and cell membranes. Cancer cells cannot multiply without these resources on hand, say the study authors.

Published online December 11 in the journal *Nature*, the new work identifies the key molecular steps that are marshalled by the cancer cells to boost micropinocytosis.

"We found a mechanism related to nutrient supply that we believe could be used to deny RAS mutant tumor cells of a key survival mechanism," says first study author Craig Ramirez, Ph.D., a postdoctoral fellow in the Department of Biochemistry and Molecular Pharmacology at NYU School of Medicine.

Theater of Operations

Specifically, the research team found that RAS mutations further activate the protein SLC4A7, which enables the protein called bicarbonate-dependent soluble adenylate cyclase to activate the enzyme protein kinase A. This in turn was found to change the location of a protein called v-ATPase.

By shifting where v-ATPase operates from the depths of cells to areas near their outer membranes, the reaction positions the enzyme to deliver the cholesterol needed by RAC1 to attach to cell membranes, the researchers say. Build-up of v-ATPase near outer membranes, and the

related positioning of Rac1, enable membranes to temporarily bulge, roll over on themselves, and form nutrient-engulfing pockets (vesicles) during macropinocytosis.

In cell culture studies, treatment of mutant RAS cells with the SLC4 family inhibitor S0859 led to a significant reduction in RAS-dependent v- ATPase localization to outer membranes, as well as to the inhibition of micropinocytosis.

Furthermore, analysis of molecular data from human pancreatic ductal adenocarcinoma (PDAC) tissue revealed that the gene for SLC4A7 is expressed four-fold higher in tumors than in normal nearby pancreatic tissue.

The study team also showed that silencing the gene for SLC4A7 in pancreatic cancer cells slowed down or shrunk tumors in mice. After 14 days, 62 percent of tumors with silenced SLC4A7 showed reduced growth in mice compared with tumors with the active gene, and 31 percent of tumors showed shrinkage.

"We are now searching for drug candidates that might inhibit the action of SLC4A7 or v-ATPase as potential future treatments that block macropinocytosis," says study senior author Dafna Bar-Sagi, Ph.D., senior vice president, vice dean for science, and chief scientific officer at NYU Langone Health. "Both of these proteins are in principle good targets because they're linked to cancer growth and operate near the cancer cell surfaces, where a drug delivered through the bloodstream could reach them."

More information: Craig Ramirez et al. Plasma membrane V-ATPase controls oncogenic RAS-induced macropinocytosis, *Nature* (2019). DOI: 10.1038/s41586-019-1831-x

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