Breakthrough in how pancreatic cancer cells ingest nutrients points to new drug target

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In a landmark cancer study published online in *Nature*, researchers at NYU School of Medicine have unraveled a longstanding mystery about how pancreatic tumor cells feed themselves, opening up new therapeutic possibilities for a notoriously lethal disease with few treatment options. Pancreatic cancer kills nearly 38,000 Americans annually, making it a leading cause of cancer death. The life expectancy for most people diagnosed with it is less than a year.

Now new research reveals a possible chink in the armor of this recalcitrant disease. Many cancers, including pancreatic, lung, and colon cancer, feature a mutated protein known as Ras that plays a central role in a complex molecular chain of events that drives cancer cell growth and proliferation. It is well known that Ras cancer cells have special nutrient requirements to grow and survive. But how Ras cells cope to actually meet their extraordinary nutrient requirements has been poorly understood—until now. In the study, led by Cosimo Commisso, a postdoctoral fellow in the Department of Biochemistry and Molecular Pharmacology at NYU School of Medicine, show for the first time how Ras cancer cells exploit a process called macropinocytosis to swallow up the protein albumin, which cells then harvest for amino acids essential for growth.

"A big mystery is how certain tumors meet their excessive nutrient demands ," says Dr. Commisso, whose work is funded in part by the Pancreatic Cancer Action Network. "We believe they accomplish this by macropinocytosis."

The findings suggest that Ras cancer cells are particularly dependent on macropinocytosis for growth and survival. When the researchers used a chemical to block the uptake of albumin via macropinocytosis in mice with pancreatic tumors, the tumors stopped growing and in some cases even shrank. Moreover, pancreatic cancer cells in mice featured more macropinosomes—the vesicles that transport nutrients deep into a cell—than normal mouse cells.

The discovery of a "protein eating" mechanism unique to some cancer cells sets the stage for drugs that could block the engulfing process without causing collateral damage to healthy cells and suggests new ways to ferry chemotherapeutic cargo into the heart of cancer cells.

"This work offers up a completely different way to target cancer metabolism," says lead principal investigator of the study Dafna Bar-Sagi, PhD, senior vice president and vice dean for Science, chief scientific officer and professor, Department of Biochemistry and Molecular Pharmacology, NYU Langone Medical Center, who first identified macropinocytosis in Ras-transformed cancer cells. "It's exciting to think that we can cause the demise of some cancer cells simply by blocking this nutrient delivery process."

Crucial to the team's findings is the work of Matthew G. Vander Heiden, assistant professor of biology at the David H. Koch Institute for Integrative Cancer Research at MIT and Christian Metallo, assistant professor of bioengineering at the University of California at San Diego, who characterized how Ras cells derive energy from the constituent amino acids released after protein engulfment.

Other key contributors include Craig B. Thompson, president and CEO of the Memorial Sloan-Kettering Cancer Center and Joshua D. Rabinowitz, professor of chemistry at the Lewis Sigler Institute for Integrative Genomics at Princeton University.