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Study reveals key molecular link in major cell growth pathway

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A team of scientists led by Whitehead Institute has uncovered a surprising molecular link that connects how cells regulate growth with how they sense and make available the nutrients required for growth. Their work, which involves a critical cellular growth pathway known as mTOR, sheds light on a key aspect of cells' metabolism that involves tiny cellular compartments, called lysosomes, and harnesses a sophisticated technology for probing their biochemical content. The researchers' findings also implicate a new protein, SLC38A9, as a potential drug target in pancreatic cancer. Their study appears in the October 19th issue of the journal *Cell*.

"SLC38A9 is a really elegant protein that ties together two critical functions: activating a key pathway that controls cell growth and releasing the substrates, namely amino acids, needed for that growth," says senior author David Sabatini, a Member of Whitehead Institute, a professor of biology at Massachusetts Institute of Technology, and investigator with the Howard Hughes Medical Institute. "This was a totally unexpected finding, one that has important implications for human diseases, including pancreatic cancer."

Amino acids are one of the basic building blocks of life. When strung together in different combinations, they make a stunning array of proteins that carry out a variety of biological functions. Amino acids typically accumulate in two locations within cells: either freely floating within the cellular milieu or sequestered inside the lysosomes. For the last decade, Sabatini and his laboratory have studied the mechanisms by

which cells sense the levels of amino acids at these sites and translate that information into subsequent go/no-go decisions about growth.

About three years ago, Sabatini and his colleagues, as well as other scientists, discovered SLC38A9, a protein embedded within the outer surface of lysosomes. Although its function was not entirely clear at the time, the researchers suspected it worked as a kind of sensor by reading out the levels of amino acids within lysosomes (specifically the amino acid arginine) and then activating downstream signals for growth.

To clarify how SLC38A9 works, the researchers, including the study's first authors Gregory Wyant and Monther Abu-Remaileh, eliminated or "knocked out" its function in cells. Since they hypothesized that it worked passively as an amino acid detector, they did not expect to see major changes in the levels of amino acids inside the lysosomes. But that is precisely what they found—especially for the so-called essential amino acids, which cannot be synthesized by the human body and therefore must be acquired from food. When SLC38A9 function was absent, the levels of these essential amino acids in lysosomes went up. And when Wyant and his colleagues boosted the protein's function to higher than normal levels, they observed the opposite effect.

"These were some big clues that SLC38A9 was doing more than we imagined, and they suggested that SLC38A9 could transport amino acids out of the lysosome," says Wyant, a graduate student in Sabatini's laboratory. The researchers confirmed this suspicions in follow-up experiments, which revealed that SLC38A9 is necessary for these essential amino acids, such as leucine, exit from lysosomes.

The amino acids needed to fuel cell growth are often recycled from intact proteins. That includes proteins found inside cells (through a process called autophagy), as well as those found outside (known as macropinocytosis). Both of these recycling streams converge on the

lysosome, and, as Sabatini's team discovered, depend on SLC38A9 activity.

Pancreatic cancer cells are known to be highly dependent on the flow of amino acids from the lysosome. When the researchers knocked out SLC38A9 function in these cells, either in human cell lines or mouse models, tumor growth was significantly reduced. In contrast, normal cells appeared to be unaffected.

"Our results suggest that an inhibitor of SLC38A9 may provide a way to specifically target pancreatic cancer cells," says Sabatini.

Yet before such therapeutic possibilities can be explored, additional research on SLC38A9 is needed, including three-dimensional studies of the protein as well as a deeper understanding of its regulation. These will help the researchers develop a more complete picture of its molecular abilities—an important stepping-stone toward developing drugs that can disable it.

A key capability that underlies the new *Cell* study is the technical wherewithal to peer into lysosomes and analyze their biochemical makeup. These structures make up only a tiny fraction of the overall volume of a cell—just 2 percent—and their content is highly dynamic. Abu-Remaileh and Wyant pioneered a strategy for rapidly isolating lysosomes and detecting the metabolites within them.

"We would not have discovered the majority of these findings without this method," said Abu-Remaileh, a postdoctoral fellow in Sabatini's laboratory. "It is allowing us to address some really important and longstanding questions about the biology of lysosomes."

More information: Wyant G, Abu-Remaileh M, et al. "mTORC1 activator SLC38A9 is required to efflux essential amino acids from

lysosomes and use protein as a nutrient." *Cell* DOI: 10.1016/j.cell.2017.09.046