Researchers reveal the internal signals cells use to maintain energy

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Lipid kinases produce an active messenger that coordinates communications between peroxisomes and mitochondria--two organelles intimately involved in making and using fuel to support cellular growth. Credit: CI Photos

Scientists at Sanford Burnham Prebys Medical Discovery Institute have

taken a deep dive into a previously overlooked family of proteins and discovered that they are essential to maintaining the energy that cells need to grow and survive. The proteins, known as lipid kinases, produce messengers that help balance cellular metabolism and promote overall health. The findings, published in *Developmental Cell*, provide further support to pursue lipid kinases as promising therapeutic targets for diseases that demand excess energy, such as cancer.

"Cancer cells are hungry—they grow faster than most cell types and need energy to support their aggressive attempts to metastasize," says Brooke Emerling, Ph.D., assistant professor in the Cell and Molecular Biology of Cancer Program at Sanford Burnham Prebys and corresponding author of the study. "Our study is one of the first to look at how PI5P4Ks—lipid kinases with known links to sarcomas and certain types of breast cancer—facilitate communications within the cell and maintain an energy balance to support cell growth."

For years scientists have tried to halt cancer by blocking nutrients from reaching tumor cells. But these attempts have been disappointing because cancer cells are tricky and create back up routes to source food to sustain their growth. Emerling's approach is to find and attack metabolic vulnerabilities within cells, which would deprive them of energy even in an abundance of nutrients and special tactics.

Using a combination of cell lines, imaging technology and mouse tumor models, Emerling's team revealed that PI5P4Ks produce an active messenger that coordinates communications between peroxisomes and mitochondria—two organelles intimately involved in making and using fuel to support cellular growth. In the absence of the messenger, the interplay between the organelles breaks down, mitochondria become overworked, and cells starve and die.

"Mitochondria are the powerhouses of the cell, says Archna Ravi, Ph.D.,

a postdoctoral researcher in Emerling's lab and first author of the paper. "They play an essential role in generating energy to drive cellular function and basically all biological processes. This research supports targeting PI5P4Ks as a cancer treatment strategy because it would deprive tumors of the one thing they can't live without: energy."

Emerling's team previously discovered the essential role of PI5P4K in tumor formation. The new study indicates a role for PI5P4Ks not only in tumor establishment, but for the first time in tumor maintenance.

"We use sarcomas as a tumor model because PI5P4Ks are highly expressed in high grade sarcomas, and their expression correlates with patient survival," says Emerling. "Sarcomas are a rare group of cancers that affect the body's connective tissues, and about half of all cases can be cured, but for the other half, better therapies are desperately needed."

Targeting PI5P4K may also be valuable for other tumor types that have developed profound metabolic alterations to source nutrients, such as triple negative breast cancer. Like sarcomas, triple negative breast cancer therapies remain woefully inadequate.

"Our goal is to develop drugs in the near future that inhibit PI5P4K and test the drugs in mice. If successful, we hope to advance to human clinical trials. I think the future for our research is very bright now," concludes Emerling.

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