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How cells sense nutrients and fuel cancer cell growth

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In cancer, genes turn on and off at the wrong times, proteins aren't folded properly, and cellular growth and proliferation get out of control. Even a cancer cell's metabolism goes haywire, as it loses the ability to appropriately sense nutrients and use them to generate energy. One particular piece of cellular machinery that is known to malfunction in a number of cancers is a group of proteins called mTORC1. This master control center coordinates many cellular functions by sensing external signals such as nutrients and growth factors and telling cells how to respond.

Now, in a paper published October 7 in *Molecular Cell*, scientists at Sanford-Burnham Medical Research Institute (Sanford-Burnham) have identified a new member of the mTORC1 team—a protein called p62—that is crucial to the cell's response to dietary amino acids. This finding provides new information about mTORC1 and its role in cellular metabolism in both normal cells and cancer cells. What's more, it provides scientists with a new therapeutic target for cancers in which mTORC1 malfunctions.

"We think of p62 as a signaling hub—it has several domains that can bind many different proteins to regulate important cellular function like growth and survival. Levels of p62 are also elevated in many cancers," said Maria Diaz-Meco, Ph.D., professor in Sanford-Burnham's NCI-designated Cancer Center and senior author of the study. "In this study, we looked for new p62 binding partners and found that p62 interacts with components of the well-known mTORC1 complex."

The amino acids a person consumes (in a high-protein diet, for example) set off a cellular chain reaction that involves mTORC1, but only some of the players in this string of events are fully understood. This study fills in some of the gaps by showing that amino acids trigger p62 to bind a protein called raptor. In turn, p62 and raptor join the mTORC1 complex. Once these and other proteins are assembled in the lysosome (a cellular compartment where enzymes are stored), mTORC1 is activated.

One common way of determining a protein's function is to see what happens in cells that don't have it. When the team generated mice and cells that lack p62, they observed that mTORC1 no longer responded to amino acids. In other words, p62 is required for mTORC1 activation by amino acids. Moreover, it was only amino acid stimulation that required p62. Even without it, mTORC1 was still activated by other signals, such as insulin and growth factors.

"The study helps connects the dots between amino acids in the diet and downstream cellular processes like protein synthesis and cellular growth. It also shows us just how important cellular location is in the mTORC1 pathway—if the complex isn't located in the lysosome, it doesn't get activated," said Dr. Diaz-Meco. "Now we want to fill in more blanks until every step in this pathway is completely understood. This information will allow us to better understand cellular metabolism and its link to human diseases such as cancer."

This finding is the result of a long-time collaboration with the laboratory of another Sanford-Burnham professor, Jorge Moscat, Ph.D. The laboratories of Dr. Diaz-Meco and Dr. Moscat have been unraveling the roles and functions of p62 since they first discovered it in 1998, as part of a complex network of proteins that play critical roles in the control of obesity and inflammation in cancer. These investigators believe that this network is a fertile ground for new therapeutic targets for obesity and type 2 diabetes, as well as cancer. Projects underway in their labs are

aimed at pharmacologically targeting p62 and related proteins to generate new medicines for these diseases. This particular study, now published in Molecular Cell, also involved contributions from two other Sanford-Burnham faculty members, Angeles Duran, Ph.D. and Malene Hansen, Ph.D.

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