Researchers map new metabolic pathway involved in cell growth

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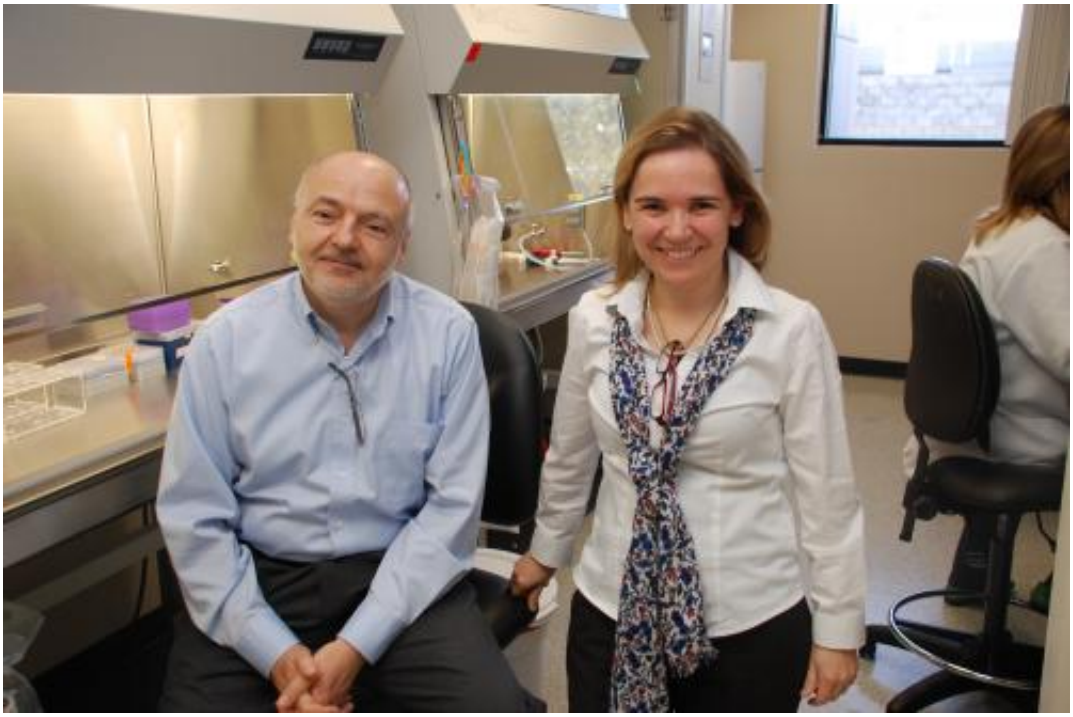

Shown here are Drs. Diaz-Meco and Moscat in their lab. Credit: Sanford-Burnham Medical Research Institute

Deciphering the body's complex molecular pathways that lead to disease when they malfunction is highly challenging. Researchers at Sanford-Burnham Medical Research Institute now have a more complete picture of one particular pathway that can lead to cancer and diabetes. In the study published by *Molecular Cell*, the scientists uncovered how a protein

called p62 has a cascade affect in regulating cell growth in response to the presence of nutrients such as amino acids and glucose. Disrupting this chain may offer a new approach to treating disease.

The protein p62 interacts with another protein called TRAF6 to activate a protein complex called mTORC1. In fact, researchers have found that mTORC1, also known as mammalian target of rapamycin complex 1, is highly activated in cancer cells. The pathway that controls mTORC1 activation is also important for metabolic homeostasis (i.e., stability). When the pathway malfunctions, metabolic disorders such as diabetes can result and tumors can progress.

About a year ago, Maria Diaz-Meco, Ph.D., Jorge Moscat, Ph.D., and their colleagues had identified that p62 is an important player in this complex pathway. But they didn't know how. Their new study shows that p62 activates mTORC1 through TRAF6.

"The mTORC1 pathway is a major complex important not only for cancer but also for metabolic homeostasis," said Diaz-Meco. "For that reason, it's very important to unravel the mechanism that controls how mTORC1 responds to the different signals."

"mTORC1 responds to many growth signals," she added, "but the specific mechanisms that channel the activation of mTORC1 by nutrients such as amino acids and glucose are still not completely understood. Our goal was to discern the specific mechanisms that regulate this important pathway."

The researchers found that TRAF6 plays a role in activating mTORC1 by molecularly modifying it in a process called ubiquitination. TRAF6, meanwhile, itself becomes activated in the presence of amino acids. "When you have a diet high in meat, the concentration of amino acids in your blood increases, and that's a way to activate this pathway," Moscat

said. This can have tremendous implications not only for diabetes, but also for cancer-cell proliferation, which needs a constant supply of nutrients to grow.

More work is needed to fully understand the pathway, but the researchers next plan is to find ways to disrupt the interaction between p62 and TRAF6, with the ultimate goal of inactivating mTORC1 and therefore controlling cancer progression. "Because mTORC1 is a highly important protein that regulates growth, therapies aimed at blocking mTORC1 activation may offer a new approach to treating disease," Diaz-Meco said.

Provided by Sanford-Burnham Medical Research Institute