Scientists identify sensor that modulates key metabolic pathway

11 March 2016, by Nicole Giese Rura

Only recently have scientists begun to tease apart the molecular links between specific nutrients and mTORC1, a cellular signaling pathway that controls growth and metabolism. Now Whitehead Institute researchers have elucidated how mTORC1 senses the amino acid arginine, which is associated with roles in injury repair, cell division, and immune function.

"We've been chasing these sensors for a long period of time, for more than a decade, and this work finally solves what's been a major puzzle for us," says Whitehead Member David Sabatini. "Knowing arginine's sensor could open the door to therapeutically exploiting the sensor by finding small molecules that can activate or inhibit it and, ultimately, the mTORC1 pathway."

In addition to controlling metabolism and growth, mTORC1 (for mechanistic target of rapamycin complex 1) plays an important role in aging, and its dysfunction has been linked to cancer and diabetes. With a better understanding of how the pathway senses and responds to the presence of nutrients, scientists may be able to decipher how to modulate its activity in response to disease.

In previous work, scientists in the Sabatini lab identified the protein Sestrin2 as the sensor for leucine, another key amino acid affecting the mTORC1 pathway. They also discovered that the lysosomal transmembrane protein SLC38A9 is a putative arginine sensor that is required to activate mTORC1. The lab's latest research, which is described online this week in the journal *Cell*, identifies the previously uncharacterized protein CASTOR1 as a negative regulator of mTORC1 in the presence of low cellular levels of arginine. Together, the arginine and leucine sensors tie mTORC1 to the nutrient levels that control the pathway's activity.

Interestingly, arginine and leucine have parallel mechanisms for regulating mTORC1's activity. When arginine and leucine levels are low, their respective sensors repress mTORC1's activity by binding to the GATOR2 protein complex, a key positive regulator of the mTORC1 pathway. As arginine and leucine levels rise, the amino acids bind to their sensors, thereby disrupting the sensors' interaction with GATOR2 and effectively lifting the brakes from mTORC1.

But this research, which was conducted in human embryonic kidney cells, is only a snapshot of what is happening in a particular type of cell.

"Now that we know the sensors, we have a new handle for looking at how amino acid levels may alter mTORC1 activity in different tissues and developmental contexts," says Lynne Chantranupong, a graduate student in Sabatini's lab and co-author of the *Cell* paper. "This is just a starting point in our understanding of how mTORC1 is regulated."

More information: "The CASTOR proteins are arginine sensors for the mTORC1 pathway" *Cell*, online March 10, 2016.

Provided by Whitehead Institute for Biomedical Research