Scientists discover new component of key growth-regulating signaling pathway

June 14 2011

(PhysOrg.com) -- Researchers in the lab of Whitehead Institute Member David Sabatini have identified a new substrate of the mammalian target of rapamycin (mTOR) kinase, called Grb10, by using a two-pronged approach of mass spectrometry and kinase specificity profiling.

“These results show that mTOR participates in most key cellular processes, consisting with its established role in common diseases like diabetes, cancer, and neurodegeneration” says Sabatini, who is also a Howard Hughes Medical Institute (HHMI) investigator and a professor of biology at MIT.

The research is published in the June 10 issue of *Science*.

The Grb10 protein was known to interact with insulin receptors and to inhibit the ability of cells to respond to insulin. By identifying the relationship between Grb10 and mTOR, Peggy Hsu, a former graduate student in the Sabatini lab and first author of the Science paper, was able to show that Grb10 is important for mTOR to inhibit signaling downstream of extracellular growth factors like insulin. This provides researchers with a more detailed understanding of the function of mTOR, especially in the context of cancer, and opens up new areas for mTOR research.

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The role of mTOR in nutrient sensing and regulation of cell growth has been conserved from yeast to worms, flies, and mice. In humans, it is also important in overall organismal nutrient metabolism and organism size; dysregulation of mTOR has been linked to diabetes and some cancers. Despite its biological and medical importance—drugs that inhibit mTOR are used to treat certain cancers and to suppress the immune system to prevent transplant rejections—little is actually known about the substrates that mTOR targets or the precise manner in which it affects multiple cellular processes.

Hsu, who is now finishing her medical degree at Harvard Medical School, says that until recently, the search for mTOR substrates has been non-systematic and hamstrung by rapamycin's limited inhibition of mTOR. With the advent of new mTOR inhibitors that target mTOR directly, including the inhibitor Torin1 that Hsu used in her work, researchers are now able to get a more complete picture of what mTOR regulates.

According to Hsu, use of these new mTOR inhibitors in conjuction with mass spectrometry and the kinase specificity profiling method will transform both future and current mTOR research.

"I think this will open up different areas of potential exploration," says Hsu, who worked closely with the labs of Michael Yaffe at MIT and Jarrod Marto at Harvard Medical School. "I hope this work allows other reseachers to make a connection very quickly by looking through our data, and to basically say, 'Aha! I thought mTOR would be involved in process X. And now maybe I have a way to study it.' "

More information: "The mTOR-Regulated Phosphoproteome Reveals a Mechanism of mTORC1-Mediated Inhibition of Growth Factor

Signaling" *Science*, June 10, 2011

Provided by Whitehead Institute for Biomedical Research