Mammalian aging process linked to overactive cellular pathway

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Whitehead Institute researchers have linked hyperactivity in the mechanistic target of rapamycin complex 1 (mTORC1) cellular pathway, to reduced ketone production, which is a well-defined physiological trait of aging in mice.

Their results are reported in the December 23 edition of the journal *Nature*.

"This is the first paper that genetically shows that the mTORC1 pathway in mammals affects an aging phenotype," says Whitehead Institute Member David Sabatini. "It provides us with a molecular framework to study an aging-related process in deeper detail."

When we think of aging, sagging skin, dimmed vision, and fragile bones come to mind. But Sabatini's lab is more interested in the cellular changes that occur as organisms age. One cellular pathway, the mTORC1 pathway, is known to coordinate cell growth with nutrient availability and other growth factors. Previous research has shown that when this pathway is inhibited, a variety of animals, including worms, flies, and mice tend to live longer.

Although an increased lifespan suggests that mTORC1 is involved in aging, it fails to clarify mTORC1's precise role in the process. In fact, lifespan is a poor proxy for studying aging, as it is not always a cause of death.

One well-defined trait of aging is a decrease in ketogenesis, or the ability to produce ketones. During sleep or other times of low carbohydrate intake, the liver converts fatty acids to ketones, which are vital sources of energy during fasting, especially for the heart and brain. As animals age, their ability to produce ketones as a response to fasting declines. The cause of this phenomenon remains unknown.

To determine whether mTORC1 mediates ketogenesis in mice, Shomit Sengupta, a former graduate student in Sabatini's lab and first author on the *Nature* paper, studied the effects of induced hyperactivity in the mTORC1 pathway in the livers of fasting mice. He found that while most blood and liver metabolite levels did not change significantly, ketone levels fell.

After establishing that activating the mTORC1 pathway decreases ketogenesis, Sengupta tried to find exactly where mTORC1 was acting. Knowing that peroxisome proliferator-activated receptor alpha (PPAR-alpha) is an activator of liver ketogenesis, Sengupta attempted to jumpstart the process by stimulating PPAR-alpha. Interestingly, ketone levels failed to increase—a clear indication that that mTORC1 was thwarting PPAR-alpha.

"That now places mTORC1 as the master regulator of ketogenesis," says Sengupta, who is now a Research Fellow at Harvard Medical School. "It could be one of many inputs for PPAR alpha – that's unclear right now. But mTORC1 is sufficient and necessary to suppress PPAR-alpha and ketogenesis."

Connecting mTORC1 to the aging-related decline in ketogenesis was the next step. If mTORC1 activation is responsible for lower ketone levels caused by aging, turning on mTORC1 in older mice should not affect their already low ketone levels – it would be like trying to turn off a light switch that is already off. So Sengupta compared the ketone production

of old and young mice during fasting. While turning on the mTORC1 pathway during fasting reduced ketone production in the young mice, the old mice maintained the same, low ketone levels. And when the mTORC1 pathway was turned off in very young mice that were subsequently aged, these older mice did not experience the decline in ketogenesis found in normal mice. Their ketogenesis levels were similar to younger mice, confirming that continual inhibition of the mTORC1 pathway prevented the aging-induced decline in ketone production.

It might follow that suppressing mTORC1 could slow aging, and indeed, some have suggested that the drug rapamycin, an mTOR inhibitor used to treat cancer and to prevent organ transplant rejection, might have anti-aging properties.

"Rapamycin definitely has lots of anti-aging hype," says Sabatini, who is also a professor of biology at MIT and a Howard Hughes Medical Institute (HHMI) investigator. "Having worked with that molecule a lot, I'm not sure I would take it for long periods of time, just for slowing down aging."

Instead Sabatini is focused on a host of more practical questions, including why ketogenesis is suppressed by aging and how aging serves to activate mTORC1.

"We know enough of what's upstream of mTORC1 that I think now we can test different components and ask which one is sort of acting funny in its aged state," says Sabatini.

More information: "mTOR Complex 1 controls fasting-induced ketogenesis and its modulation by aging" *Nature*, December 23, 2010.