New study explains duality of longevity drug rapamycin

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A Penn- and MIT-led team explained how rapamycin, a drug that extends mouse lifespan, also causes insulin resistance. The researchers showed in an animal model that they could, in principle, separate the effects, which depend on inhibiting two protein complexes, mTORC1 and mTORC2, respectively.

The study suggests that molecules that specifically inhibit mTORC1 may combat age-related diseases without the insulin-resistance side effect, which can predispose people to diabetes.

Senior author Joseph A. Baur, PhD, assistant professor of Physiology, Perelman School of Medicine, University of Pennsylvania, and colleagues at the Whitehead Institute for Biomedical Research and Broad Institute, Massachusetts Institute of Technology, in Cambridge, MA, describe their work in this week's issue of *Science*. Baur is also a member of Penn's Institute for Diabetes, Obesity, and Metabolism.

"The hope is that in the future, we will be able to develop molecules that target mTORC1 specifically, separating out the beneficial effects of rapamycin on aging and disease, and leaving behind the insulin-resistance side effect," says Baur.

"Our results demonstrate that reduced mTORC1 signaling is sufficient to extend lifespan and mTORC2 signaling has profound effects on metabolism," says co-first author Lan Ye, PhD, postdoctoral fellow in the Baur lab. "Our findings indicate that mTORC2 may be an important player in the pathogenesis of type 2 diabetes and metabolic syndrome."

One Compound, Many Effects

Rapamycin extends the lifespan of yeast, flies, and mice and is also an immunosuppressant drug for organ transplants and an anti-cancer drug. It was first discovered as a byproduct of Streptomycin hygroscopicus, a bacterium found in a soil sample from Easter Island, an island also known as Rapa Nui, hence the name. Rapamycin was originally developed as an antifungal agent, but that use was abandoned when it was discovered to have immunosuppressive properties.

The mTOR complexes, for mammalian (or mechanistic) target of rapamycin, are proteins that regulate cell growth, movement, and survival, as well as protein synthesis and transcription. Specifically, there are two mTOR complexes and one mTOR protein. The mTOR protein is the core of both complexes (mTORC1 and mTORC2), which behave differently based on their associated proteins. One or both of the mTOR complexes can be inappropriately activated in certain cancers, and dual-specific inhibitors are being developed as chemotherapeutic agents.

Several theories have been put forward by researchers to explain the observations that patients receiving rapamycin are more prone to developing glucose intolerance, which can lead to diabetes. Chronic treatment with rapamycin impairs glucose metabolism and the correct functioning of insulin in mice, despite extending lifespan. The research team demonstrated that rapamycin disrupts mTORC2 in the mice, and that mTORC2 is required for the insulin-mediated suppression of glucose metabolism in the liver.

On the other hand, they also demonstrated that decreasing mTORC1 signaling was sufficient to extend lifespan independently from changes in glucose metabolism. They used a mouse strain in which mTORC1 activity was decreased and saw that lifespan was extended by 14 percent, yet the animals had normal glucose metabolism and insulin sensitivity.

"Besides developing more specific inhibitors for mTORC1, we remain very interested in

understanding why mTORC1 inhibition extends life in the first place," explains Baur. "We're currently looking at the interactions between mTORC1 and other pathways that influence longevity, as well as its effects on things like free radical generation and protein quality control."

The MIT colleagues on the *Science* paper are co-first author Dudley W. Lamming, PhD, Whitehead Institute, and co-senior author David M. Sabatini, MD, PhD, member of Whitehead Institute, Howard Hughes Medical Institute investigator, and professor of biology at MIT. This study was funded by grants from the American Federation for Aging Research, the National Cancer Institute, and the Bingham Trust, through Penn's Institute on Aging.

More information: "Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity" *Science*, published March 30, 2012

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