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Mechanistic finding may help deal with side effects of lifespan-extending drug rapamycin

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Rapamycin, an FDA-approved drug, extends lifespan in mice up to 30%, making it of major interest to researchers intent on slowing the aging process in humans in order to extend healthspan, the healthy years of life. But long term use of rapamycin, approved for use in several disease indications, has side effects - raising questions about its use to prevent the chronic diseases of aging. In a study, now published online in *Aging Cell*, researchers at the Buck Institute have discovered new insights into how rapamycin inhibits the nutrient signaling pathway mTOR (mechanistic target of rapamycin) - a finding that could provide a way to avoid or eliminate side effects of the drug.

mTOR is a complex pathway that plays a vital role in regulating cellular and organismal growth. Rapamycin, which inhibits mTOR activity, has varied effects on its two multi-protein complexes, mTORC1 and mTORC2. Many of the negative metabolic side effects of rapamycin, reported in both human clinic trials and mouse studies, have been attributed to inhibition of mTORC2.

While rapamycin acutely and directly inhibits mTORC1, the protein complex linked to longevity, only chronic administration of the drug inhibits mTORC2, which is linked to the side effects. Buck Institute researchers in the Kennedy lab have discovered that it's the relative expression of FK506 binding proteins (primarily FKBP12 and FKBP51) that determine the extent of the rapamycin-induced inhibition of mTORC2. Brian Kennedy, PhD, Buck President and CEO and senior scientist on the study says the finding is important for those working to

get rapamycin and its analogs into human clinical trials. "The work gives us insights into how we might alter rapamycin in order to get the mTORC1 specificity needed to get the longevity effects with reduced side effects," he said. "The findings also suggest that we could develop treatments based on the activity of the FK506 binding proteins."

Buck postdoctoral fellow Katherine H. Schreiber, PhD, led the research team. She first discovered that cell lines that are responsive to mTORC2 inhibition by rapamycin contain high levels of FKBP12 and low levels of FKBP51. Manipulating the levels of FKBP12 and FKBP51 changed their responsiveness to rapamycin, indicating that these proteins are key players in the cellular response to rapamycin. In addition, there was a striking difference in the expression level of FKBPs across mouse tissues that correlated with their responsiveness to mTORC2 inhibition by rapamycin. Tissues that are highly responsive to mTORC2 inhibition by rapamycin, including the heart, have high levels of FKBP12, whereas insensitive tissues such as the kidney have very low levels of FKBP12."We need to understand more about these binding proteins - why is there a lot in some tissues and not in others," said Schreiber. "This would give us some insights as to where these mTORC2 side effects come from and give us options for selectively dealing with them."

Kennedy says the study provides the basic science that pharmaceutical studies can build on. "Our hope is that this work facilitates the development of therapies that can be tested in humans," he said. "There is no longer any doubt about the efficacy of rapamycin in mouse studies - both in extending lifespan and healthspan. This study is part of our effort to move this work into humans as quickly and as safely as possible."

More information: Rapamycin-mediated mTORC2 inhibition is determined by the relative expression of FK506 binding proteins, *Aging*

Cell, 2015. onlinelibrary.wiley.com/doi/10 … 1111/acel.12313/full