Rapamycin effective in mouse model of inherited heart disease and muscular dystrophies

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Rapamycin, an immunosuppressant drug used in a variety of disease indications and under study in aging research labs around the world, improved function and extended survival in mice suffering from a genetic mutation which leads to dilated cardiomyopathy (DCM) and rare muscular dystrophies in humans. There are currently no effective treatment for the diseases, which include Emery-Dreifuss Muscular Dystrophy and Limb-Girdle Muscular Dystrophy. The familial form of DCM often leads to sudden heart failure and death when those affected reach their 40's and 50's.

In research published in the July 25, 2012 online edition of *Science Translational Medicine*, scientists from the Buck Institute and other organizations focused on mutations in the gene LMNA, which produces A-type lamins. Mutations in this gene are associated with at least 13 diseases, with DCM among the most common. DCM accounts for 60 percent of all cardiomyopathy cases. LMNA mutations may account for up to one-third of patients that are diagnosed as having DCM and conduction disease. DCM causes a thinning of the left ventricle and loss of cardiac function.

The study showed that deletion of the LMNA gene led to ramped up activity in the molecular pathway mTOR (mammalian target of rapamycin) and that treatment with rapamycin turns down the abnormal signaling. Senior author Brian K. Kennedy, PhD, President and CEO of the Buck Institute for Research on Aging, says treatment with rapamycin extended mouse lifespan by 60 percent in a relatively rapid onset model of disease.

"What's particularly exciting is that this work offers a therapeutic possibility where there has been none," said Kennedy. "This study, along with others, suggests that clinical trials of rapamycin and its derivatives be initiated for human patients suffering from this form of DCM."

Rapamycin has been shown to extend healthspan in normal mice. It and the mTOR pathway are being intensively studied in aging research laboratories around the world. Kennedy, who came to the Buck Institute from the University of Washington where much of this work was done, said the study first focused on rapamycin in a mouse model of Hutchinson-Gilford Progeria Syndrome, a premature aging disorder that is also based on a mutation in lamin-A. "We found to our surprise that rapamycin is beneficial for DCM instead," he said. "As we investigate and understand the cellular pathways that get disrupted or altered with aging, we will likely be putting our hands on common pathways that become disregulated in various disease states," said Kennedy. "This started out as a study about aging, and it's pointed us toward a specific disease indication, where we might be able to generate a new therapeutic. I am hoping this is the first of many times that this happens."

Provided by Buck Institute for Age Research