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NEUROMETABOLIC DISEASE

Treating mitochondrial diseases with mTOR inhibitors—a potential treatment for Leigh syndrome?

Inhibition of the mechanistic target of rapamycin (mTOR) signalling pathway slows ageing in model organisms. Using a mouse model, researchers from the University of Washington in Seattle now show that mTOR inhibition might also slow the progession of Leigh syndrome, a mitochondrial disease. Every year in the USA, Leigh syndrome affects 1 in 40,000 newborn babies who develop a complex neuropathy and do not live past 6 or 7 years of age.

> “...inhibition of mTOR suppresses mitochondrial disease...”

The new study, published in *Science,* builds on previous work in yeast, which showed that mitochondrial defects could be rescued by inhibiting mTOR signalling—an evolutionarily conserved mechanism for sensing nutrient levels in the cell and thereby regulating growth. “Inhibition of mTOR is important for lifespan and healthspan extension in response to calorie restriction,” explains Matt Kaeberlein, who led the study.

The team reasoned that if mTOR inhibition can alleviate a mitochondrial defect in yeast, then why not in a higher organism. The researchers used the *Ndufs4*-knockout mouse, which has defects in the assembly of complex 1 in the mitochondrial electron transport chain, leading to a neurodegenerative phenotype that mimics Leigh syndrome. By treating the *Ndufs4*$^{-/-}$ mice daily with rapamycin, an mTOR inhibitor, the group was able to extend lifespan from a median of 50 days to 114 days (P <0.0001). Importantly, rapamycin-treated mice did not develop the distinctive neurological lesions, characterized by astrocyte activation and glial marker reactivity, which were seen in mice treated with a vehicle control.

“The most significant finding is that inhibition of mTOR suppresses mitochondrial disease,” says Kaeberlein. “Although we don’t know for sure if mTOR inhibition will alleviate mitochondrial disease in humans, I think it’s likely that the mechanisms are conserved.”

The team now plans to elucidate the genes and tissues specifically involved in this effect, and to identify biomarkers to monitor disease progression. Unfortunately, rapamycin can lead to immunosupression, hyperlipidaemia and impaired wound healing. Consequently, Kaeberlein and his team plan to test different inhibitors of mTOR signalling in their mouse model. As Kaeberlein concludes,“other inhibitors of mTOR might pave the way towards therapies for patients without the side effects of chronic rapamycin treatment.”

Tim Geach

Original article Johnson, S. C. *et al.* mTOR inhibition alleviates mitochondrial disease in a mouse model of Leigh syndrome. *Science* doi:10.1126/science.1244360