Dietary restriction

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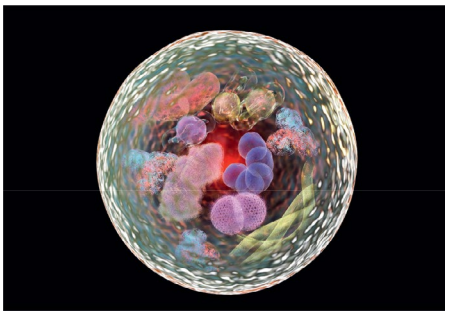
Spermidine controls autophagy during fasting



Caloric restriction and intermittent fasting have autophagy-enhancing geroprotective effects in various model organisms. Similarly, administering the natural polyamine spermidine can extend the lifespan and healthspan of model organisms in an autophagy-dependent way. However, it was unclear whether the effects of caloric restriction and fasting require spermidine. A study by Sebastian Hofer and colleagues now delves into the relationship between fasting, spermidine levels and autophagy, and shows that spermidine-induced autophagy is important for the lifespan and healthspan benefits of fasting.

This study began when, during another project, the researchers made an intriguing observation while analyzing metabolomics data from human cohorts.

"We were surprised – and genuinely excited – when we saw increased spermidine levels in blood metabolomics of fasting humans," says Frank Madeo, co-corresponding author of the study. "Initially, this made no sense to us as the amino acid precursors for polyamine synthesis – arginine and methionine – were down, and we began systematically analyzing polyamine content in fasting cells and organisms."

In yeast, flies, mice and human cells, the researchers meticulously quantified changes in polyamine levels (specifically, spermidine) during nutrient starvation and fasting. They revealed a consistent increase in spermidine levels across species during these paradigms. This elevation in spermidine was linked to enhanced autophagic flux, a cellular process that declines with age and is associated with various age-related diseases.

In yeast and worms, genetic or pharmacological inhibition of spermidine synthesis impaired the beneficial effects of fasting on autophagy and longevity. Conversely, supplementation with spermidine could rescue these effects, which underscores the pivotal role of spermidine in mediating the life-extending benefits of fasting.

"Up to this paper, we always thought of spermidine supplementation as a possibility to correct age-associated declines in polyamine content, which contributes to a loss of proteostatic homeostasis, especially autophagic capacity," notes first author of the study, Sebastian Hofer. "Discovering this cell-intrinsic role of spermidine for enhanced autophagic flux upon starvation periods has been quite a surprise to us. Polyamine synthesis seems to act as a gatekeeper for full autophagic activity."

Future directions will probably further explore the molecular mechanisms that link nutrient sensing, spermidine, autophagy and longevity.

"There are really so many interesting paths forward", adds Hofer. "We are already working on translating more of our cellular experiments to rodent experiments. We will now test other putative geroprotective interventions in mice and study their dependence and effect on polyamines. Another thing that we get asked a lot, obviously, is whether the health-improving effects of fasting can be boosted with additional spermidine intake. Exciting times ahead."

The results presented by Hofer et al. are compelling and demonstrate that fasting-induced spermidine elevation is crucial for the activation of autophagy and the extension of lifespan in model organisms. Furthermore, the study highlights the conservation of these mechanisms across species.

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