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Excess nutrient signals in cells lead to premature aging in animals, study shows

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Cells are signaled to have nutrients in excess, and this leads to malfunction and inflammation in organs such as the pancreas, the liver and the kidneys. The finding, by CNIO researchers and published in *Nature Aging*, suggests that an intervention on the inflammation alone can relieve symptoms and increase survival.

The research has been conducted on animal models, but comparing their molecular processes with blood samples from people in their 70s indicates that results can be extrapolated to human aging.

The reality of a population that is aging at an accelerated rate makes it a priority to understand what happens in the body over time, on a molecular scale. The mTOR protein complex is known to be involved in many processes, as a key agent in multiple functions of the body and especially in metabolism.

The new paper finds, in animal models, that when mTOR activity is just slightly increased, aging sets in earlier on, and the lifetime of animals can be shortened by up to 20%.

Given the central role of mTOR in metabolism, this research provides some clues to understand why aging-related diseases appear or worsen in people with a high body mass index, an indicator related to obesity and inflammation. It also sheds light on why calorie restriction—a type of diet associated with increased longevity in animals—can promote healthy aging, as certain genes activated by limiting nutrient intake interact with mTOR.

In addition, the study introduces a new research tool created "to study the relationship between nutrient increase and the aging of different organs," says lead author Alejo Efeyan, head of the Metabolism and Cell Signaling Group at the National Cancer Research Center (CNIO).

Premature aging in animals that 'believe' to be eating more than they do

The activity of the mTOR protein complex is regulated according to the amount of nutrients available in the cell. The authors of this study devised a system to "trick" mTOR, and thus regulate its activity at will in animal models.

The inside of cells is a continuous coming and going of chemical signals,

which are transmitted thanks to proteins (of course, the cells also communicate with each other, through intercellular signaling). The mTOR protein complex is a key agent in the large cellular communication highway involved in harnessing energy: cell metabolism. We also know that mTOR influences longevity, although we do not yet fully understand how.

To manipulate the activity of mTOR at will, the CNIO team focused not on mTOR itself, but on the protein that should send the signal indicating the amount of nutrients available in the cell. The researchers genetically modified this protein to get it to "lie" and signal to mTOR that there are more nutrients in the cell than there actually are.

Thus, the chemical signal pathway of mTOR is activated as if the animals are eating more, although in reality their diet does not vary.

When animals with this protein, which tricks mTOR, reach maturity, the functioning of the cells begins to fail and characteristic symptoms of aging are detected: the skin becomes thinner, and damage occurs in the pancreas, liver, kidneys and other organs.

Immune system cells come to repair them but are overwhelmed by the amount of damage. They accumulate and, instead of repairing, trigger inflammation that further increases problems in those organs.

The result of this vicious circle is that the lifespan of these animals in which mTOR is working harder than normal is shortened by 20%, which on the human scale would be equivalent to about 16 years.

The study sought to cut this circle by blocking the immune response that causes inflammation. Damage in the organs then improved enough to gain what in humans would be a few years of life.

For this reason, the authors state that acting on chronic inflammation is "a potential therapeutic measure that controls deterioration of health," says first author Ortega-Molina

Results can also apply to humans

What happens when acting on the information that mTOR receives, simulating an excess of nutrients, is reminiscent of a change that occurs during natural aging. The CNIO group compared its model to colonies of naturally aging mice, both its own and those belonging to the National Institute on Aging (NIA).

For example, the activity of lysosomes, which are the organelles with which the cell removes and recycles its waste, is reduced in both naturally aged and genetically modified animals. "When there is an excess of nutrients it makes sense that the cell shuts down the recycling activity of lysosomes, because this recycling operates especially when there are no nutrients," Efeyan says.

This decrease in lysosomal activity also occurs in human aging, as verified by the group from the University of Valencia when contrasting blood samples from young people and septuagenarians.

Beyond this paper, Efeyan believes that this new animal model offers "ample fertile ground to ask more questions about how nutrient increase, or their signaling, facilitates processes in the different organs that allow us to understand their aging in particular. Or, for example, investigate the relationship with neurodegenerative diseases, because there is some inflammation in the central nervous system. It's a tool that many more people can use."

More information: A mild increase in nutrient signaling to mTORC1 in mice leads to parenchymal damage, myeloid inflammation and

shortened lifespan, *Nature Aging* (2024). DOI: 10.1038/s43587-024-00635-x

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