Antiaging biochemical mechanism found in mouse, bat and naked mole rat cells

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Naked mole rat. Credit: Jan Zwilling, IZW

Aging is an inevitable part of life, yet some species are aging very differently than others, even than very similar ones.

For example, naked mole rats, east African rodents of a size comparable to moles or mice, show a strongly delayed process of aging and live up to 30 years. Scientists from Russia, Germany and Switzerland have now confirmed a mechanism in mouse, bat and naked mole rat cells—a "mild depolarization" of the inner mitochondrial membrane—that is linked to aging: Mild depolarization regulates the creation of mitochondrial reactive oxygen species (mROS) in cells and is therefore a mechanism of the anti-aging program. In mice, this mechanism falls apart at the age of one year, while in naked mole rats, this does not occur until around 20 years. This newly confirmed mechanism is described in detail in a paper published in the *Proceedings of the National Academy of Sciences*.

Mitochondrial reactive oxygen species (mROS) such as hydrogen peroxide are byproducts of cell respiration and, in higher doses, associated with diseases and aging processes. There are mechanisms at the inner and outer mitochondrial membranes that regulate mROS production. the key function of cell respiration is energy production in the form of adenosine triphosphate (ATP) through coupling of mitochondrial respiratory chain complexes with ATP synthase.

Mitochondrial intermembrane space enzymes (hexokinases I + II and creatine kinase) have now been confirmed to slightly lower the membrane potential of the inner mitochondrial membrane (mild depolarization). This means that the differences in the electric load between the inner and the outer space of the mitochondria are lowered, and the energy production through ATP synthesis is reduced to some extent. At the same time, this leads to the cessation of mROS production. "The proof of this effect is implying that mild depolarization is a mechanism of the anti-aging program, effectively slowing down aging processes in the cell," says senior author Vladimir Skulachev (Lomonosov Moscow State University).

The research team was able to show that both biochemical mechanisms

do not operate in the same intensity and efficiency in different species and tissues and at different ages: The researchers examined the hexokinases I + II and creatine kinase mechanisms in various tissues (lung, kidney, brain, skeletal muscles, heart, and others) in mice,naked mole rats, and Seba's short-tailed bats.

They found interesting differences: Mild depolarization significantly starts decreasing after one year of age in mice with negligible levels after 24 months in skeletal muscles, diaphragm, heart, brain, and spleen. In lung and kidney tissue, mild depolarization decreases to a lesser extent with aging.

"The crumbling of the anti-aging program in the cells starts after only a third of the average lifespan in mice, while the naked mole rats and Seba's short-tailed bats maintain mild depolarization and hence the suppression of mROS production up to high ages," explain co-authors Thomas Hildebrandt and Susanne Holtze from the Leibniz Institute for Zoo and Wildlife Research (Leibniz-IZW). "This contributes to the extraordinary longevity of these species."

These biochemical mechanisms explain how the aging and the anti-aging programs within cells function and are regulated. However, it has not yet been determined where and how these processes are activated and controlled. "The master biological clock has not yet been identified," says lead author Mikhail Vyssokikh (Lomonosov Moscow State University). "We suspect it to be located in the suprachiasmatic nucleus of the hypothalamus, which is responsible for the circadian and seasonal rhythms."

This question and some other yet unknown components of the aging and anti-aging programs will be targets of high interest for future gerontological investigations.

More information: Mikhail Y. Vyssokikh et al. Mild depolarization of the inner mitochondrial membrane is a crucial component of an anti-aging program, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.1916414117

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