Leibniz Institute on Aging – Fritz Lipmann Institute

Press release

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Faster aging due to stress

African mole-rats possess very remarkable characteristics for aging research. They almost never develop cancer, are largely healthy even in old age, and are extremely long-lived compared to other rodents. Some mole-rat species even age differently depending on their status in the colony: if they are sexually active, they live almost twice as long as their conspecifics. Researchers at the Leibniz Institute on Aging - Fritz Lipmann Institute (FLI) in Jena and the University of Duisburg-Essen have investigated which status-specific changes underlie this life-extending phenomenon. They found that mole-rats workers of the genus *Fukomys* are under constant stress and therefore age prematurely.

Jena/Essen. African mole-rats (*Bathyergidae*) are a family of rodent species that live in large underground colonies. In this study mole-rats of the genus *Fukomys* were examined that are close but hairy relatives of the better known naked mole-rats (*Heterocephalus glaber*). Like these, *Fukomys* mole-rats have very interesting characteristics for aging research: they almost never develop cancer, are still largely healthy in old age, and are extremely long-lived for their small body size. Because larger and heavier mammal species usually live longer than smaller species. With a life expectancy of more than 20 years, mouse- or rat-sized mole-rats live many times older than one would be expect based on their weight. They are also extremely long-lived compared to their close relatives, which often only live a few years.

Furthermore, these mole-rat species are eusocial mammals that, like ants and bees, live in a kind of "caste system" with a single pair at the top of a colony (breeding pair, royal caste) and their progeny from multiple litters (non-breeder, so called workers). In contrast, the workers must forgo their own reproduction in favor of the royal caste. Interestingly, breeders reach the age of 20 years or more in captivity, whereas non-breeders usually die before their tenth birth date. This divergence of survival probabilities between breeders and non-breeders is found in all *Fukomys* species studied so far, irrespective of sex. Researchers from the Leibniz Institute on Aging - Fritz Lipmann Institute (FLI) in Jena, together with colleagues from the University of Duisburg-Essen and University Hospital Essen, have investigated this phenomenon in more detail. The study was recently published in the renowned journal "eLife".

Life expectancy increases after advancement to royal caste

"In eusocial mole-rats, only the pair at the top of the colony normally reproduces. It is responsible for reproduction and the continuity of the colony," reports Dr. Arne Sahm of FLI and lead author of the study. The other animals in the colony do not reproduce, but they are not infertile either. When they leave the colony, they can also reproduce and start their own colony. This strategy helps to avoid incest within the family of origin. This also means that workers within their home colony generally cannot ascend to the royal caste. However, the life-extending ascent to the "reproductive caste" can be successfully simulated in laboratory experiments when an animal is mated with an opposite-sex specimen from another colony. The initiated change from non-breeder to breeder status apparently marks the beginning of a slow-down in the aging process.

Status-specific changes in gene expression

Since they are the same species and caste ascension is possible in principle, a different genetic configuration can be excluded as an explanation for the divergent aging rates. "In previous work, we were also able to show that the workers hardly differ from the reproductively active animals in terms of their diet and activities, with the sole exception of sexual activity," adds Dr. Philip Dammann of the University of Duisburg-Essen.

"We therefore suspected that the same genome is apparently interpreted differently in the royal caste members. With the ascent of the caste, a switch is turned on, in a way, that regulates the genes differently," says Dr. Arne Sahm, explaining the hypothesis. To test this hypothesis, the research team from Jena and Duisburg-Essen examined more than 600 samples from different organs and tissues of two *Fukomys* species (*F. mechowii* and *F. micklemi*) of the royal caste and of age-matched workers for status-specific changes in gene expression. The aim was both to identify genes and signaling pathways associated with status-dependent longevity and to compare these findings with those already known from shorter-lived species.

Dilemma of different results for short- and long-lived model organisms

For most organs and tissues, the scientists found only minor differences in gene expression between the castes. They found stronger changes especially in tissues responsible for hormone production (e.g., thyroid and adrenal gland). One significant difference concerned anabolism, i.e. the build-up of endogenous substances such as proteins. This was significantly more pronounced in the royal caste. "This is an extremely interesting finding, because it is in direct contrast to many findings from research on short-lived model organisms," explains Steve Hoffmann, research group leader at FLI and professor of computational biology at Friedrich Schiller University in Jena. It is known from research on nematodes, fruit flies and mice that life expectancy increases when anabolic metabolism is inhibited.

"Until today, it is still largely unclear to what extent the findings obtained on short-lived organisms can also be applied to long-lived species, such as humans," Prof. Steve Hoffmann emphasizes. "On the contrary, our results show that they cannot always be transferred one-to-one to longer-lived species. Comparative approaches with short- and long-lived species could be one way to circumvent this dilemma. In the case of the mole-rats, for example, comparison within a species is possible."

Permanent stress leads to premature aging

Another important change affected the synthesis of steroid hormones. While in the royal caste mainly those genes were upregulated that are responsible for the production of sex hormones (which was also to be expected, because the animals became sexually active), in the workers mainly genes responsible for the production of steroid hormones (glucocorticoids) were read out. These glucocorticoids, also called stress hormones, have an influence on metabolism, water and electrolyte balance, the cardiovascular system and the nervous system. They also have anti-inflammatory and immunosuppressive effects by weakening the body's immune responses.

"This is an indication that the workers are under constant stress and thus age earlier," emphasizes Dr. Sahm. A number of features that are triggered by chronic stress also occur in such mole-rats. In humans and many other mammals, a prolonged abundance of

glucocorticoids leads to Cushing's syndrome, which increases susceptibility to disease and results in an increase in body fat and significant weight gain. This was also observed in the *Fukomys* species: In the experiment, workers gained on average twice as much weight as members of the royal caste.

New model for stress-induced aging?

The research team is now looking for possibilities to what extent the accelerated aging of *Fukomys* mole-rats induced by permanent stress is suitable as a model to study the effects of stress and stress-induced aging in humans. There is already evidence that people who suffer from traumatic stress, chronic stress or stress caused by low social status also age faster.

Publication

Increased longevity due to sexual activity in mole-rats is associated with transcriptional changes in the HPA stress axis. Sahm A, Platzer M, Koch P, Henning Y, Bens M, Groth M, Burda H, Begall S, Ting S, Goetz M, Van Daele P, Staniszewska M, Klose JM, Costa PF, Hoffmann S, Szafranski K, Dammann P. Elife. 2021, 10, e57843. doi: 10.7554/eLife.57843, https://elifesciences.org/articles/57843

Picture

Breeding status determines the pace of aging in gray mole rats (*Fukomys mechowii*). A 9 year old female from the worker caste with clear signs of aging (left) next to her 6 year older mother from the royal caste (right), which looks much fitter. The photos were taken on the same day (M. Schmitt).

(Source: https://www.researchgate.net/figure/Breeding-status-determines-the-pace-of-aging-in-Fukomys-mechowii-Left-An-unusually-old_fig6_51089448; doi:10.1371/journal.pone.0018757.g003)

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Background information

The **Leibniz Institute on Aging – Fritz Lipmann Institute (FLI)** – upon its inauguration in 2004 – was the first German research organization dedicated to research on the process of aging. More than 350 employees from around 40 nations explore the molecular mechanisms underlying aging processes and age-associated diseases. For more information, please visit www.leibniz-fli.de.

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