Diverse pathways to longevity in mammals uncovered

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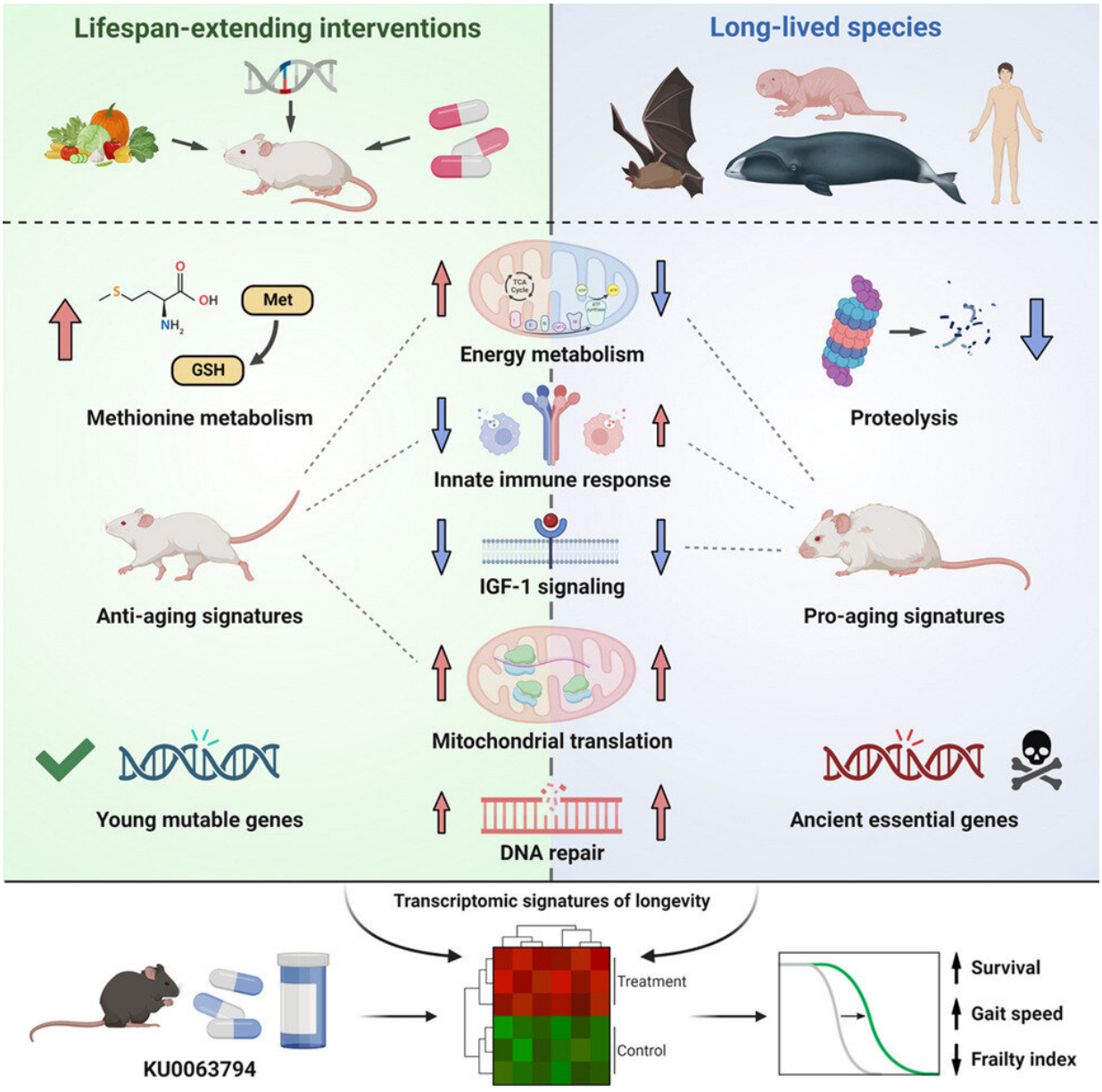

Graphical abstract. Credit: *Cell* (2023). DOI: 10.1016/j.cell.2023.05.002

Researchers from Brigham and Women's Hospital, a founding member of the Mass General Brigham healthcare system, have discovered gene expression signatures of longevity across 41 mammalian species and compared them with biomarkers of lifespan-extending interventions and mammalian aging. This work revealed distinct and universal molecular mechanisms of longevity and provided new ways to identify lifespan-extending interventions. Results are published in *Cell*.

"There are multiple mechanisms for longevity, some of which can be induced by simple interventions, while others have developed through evolution over millions of years," said first author Alexander Tyshkovskiy, Ph.D., of the Division of Genetics. "We believe that if we truly want to extend human lifespan, we should target molecular mechanisms that not only drive extended lifespan in short-lived mammals, like mice, but are also conserved in species with very long lives."

Mammals exhibit substantial variation in longevity across species, with large animals typically living longer. However, there are exceptions to this rule. Lifespan within species is also malleable. Dozens of interventions have been shown to extend the lifespan of mice, such as growth hormone receptor knockout, rapamycin, and calorie restriction.

However, intraspecies lifespan is usually negatively correlated with size. Smaller organisms of the same species tend to live longer, as demonstrated by higher average lifespan of small dog breeds and dwarf mice. This suggests that the mechanisms associated with longer lifespan can be different across and within species. However, to date, comprehensive comparison of various molecular features of longevity

has been lacking.

"This study revealed the great diversity of mechanisms that control lifespan within and across species," said Vadim Gladyshev, Professor of Medicine, the corresponding author in this study, in whose lab at the Brigham this study was conducted. "It also provided new molecular tools for aging research and exposed the untapped potential for identifying new ways to extend lifespan and healthspan."

In this work, the researchers used high-throughput techniques to identify genes whose activity is associated with maximum lifespan of mammalian species in multiple organs, including liver, kidney and brain. Similar mechanisms of long-lived mammals were observed across tissues, such as upregulation of DNA repair and downregulation of insulin signaling and energy metabolism.

Comparison of these signatures with the effects induced by established lifespan-extending interventions in mice revealed that there are multiple distinct molecular strategies of lifespan regulation within and across species. For example, long-lived species like whales tend to exhibit "upregulation" or higher expression of genes involved in certain branches of the innate immune response, which may be an adaptive mechanism to decrease the amount of damaged or precancerous cells accumulating with age.

In contrast, established lifespan-extending interventions in mice tend to downregulate these genes, reducing chronic inflammation and its detrimental effect in old mice.

However, the researchers also found that certain molecular mechanisms were associated with increased longevity in both long-lived species and mice with extended lifespan. One such mechanism was the downregulation of insulin-like growth factor 1 (IGF-1), a signaling

molecule involved in cell growth, glucose, and lipid metabolism.

While activity of IGF-1 is well known to affect lifespan, the researchers were surprised to observe a consistent pattern across many organs and species. Similarly, they found longevity to be reliably associated with the upregulation of genes that control protein synthesis in mitochondria, organelles that produce energy to fuel various cellular processes.

To examine the interplay between molecular mechanisms of longevity and aging, the authors conducted a meta-analysis of 92 publicly available datasets corresponding to aging-associated gene expression profiles of three species, including mice, rats, and humans. Interestingly, age-related changes of gene expression turned out to be similar across different organs and species.

Besides, they were counteracted by lifespan-extending interventions, such as calorie restriction, rapamycin and certain genetic manipulations. However, surprisingly, features of long-lived mammals showed a positive correlation with aging signatures. This suggests that not all age-related changes in the organism are detrimental, which is further supported by the case of IGF-1, downregulated not only in long-lived mammals but also in aged animals.

These and other findings described in the article indicate that while some molecular mechanisms of longevity are universal for the naked mole rat and calorie restricted mice, others exhibit fundamental differences. The authors propose that molecular changes induced by simple lifespan-extending interventions in mice but not in long-lived mammalian species, such as the inhibition of certain innate immune response pathways, represent partially effective strategies that promote longevity by regulating the organism's response to damage already accumulated with age.

While reducing immune reactions may benefit aging organisms with developed chronic inflammation, an activated immune response in early life may provide additional advantages by slowing down the accumulation of damaged cells and delaying the onset of chronic inflammation. In contrast, common biomarkers of longevity, such as enhanced mitochondrial function and suppression of IGF-1 activity, likely reflect fundamental mechanisms that protect against the accumulation of primary age-related damage.

Supporting this hypothesis, compounds targeting inflammatory response successfully improved survival of cells from short-lived species like mice and rats but showed reduced efficacy in cells from long -lived species. On the other hand, compounds that affected insulin signaling and mitochondrial translation exhibited similar survival improvements for cells from both short-lived and long-lived species.

Finally, the researchers examined if the discovered longevity biomarkers can be practically applied to identify novel lifespan-extending interventions in mammals. In a pilot screen, they used publicly available database to find chemical compounds that induce gene expression changes associated with longevity in human cells. They also subjected mice to these compounds for 1 month, examining gene expression profiles of the drugs in mouse liver and kidney after this treatment.

The researchers selected one of the compounds, mTOR inhibitor KU0063794, that showed strong positive association with the signatures of longevity both across and within species, and treated old mice with this drug. The compound indeed extended remaining lifespan and improved physical activity of the animals. This indicates that molecular biomarkers of long-lived animals can streamline the process of identifying new longevity interventions. Currently, the researchers are testing other candidate compounds predicted with their screening platform.

"Molecular data can significantly facilitate the search for new medications and interventions that promote longevity," Tyshkovskiy said. "Conducting longevity studies for drugs require substantial investments of time and financial resources. Using molecular screening methods, we can save valuable time and funds, identifying promising candidates for further investigation."

More information: Alexander Tyshkovskiy et al, Distinct longevity mechanisms across and within species and their association with aging, *Cell* (2023). DOI: 10.1016/j.cell.2023.05.002

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