Not all organs age alike

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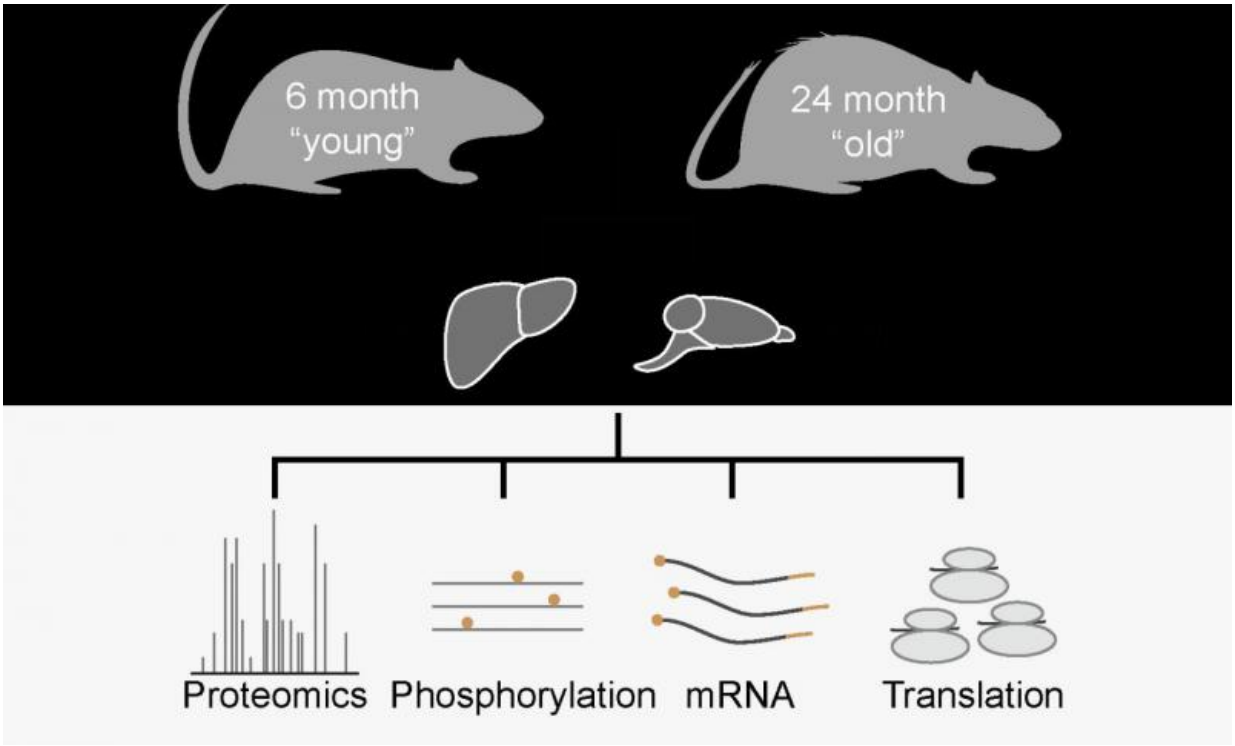


Credit: Ori and Toyama et al./*Cell Systems* 2015

Aging is typically thought of as the gradual decline of the whole body, but new research shows that age affects organs in strikingly different ways. A study published September 17 in *Cell Systems* provides the first comprehensive view of how cellular proteins age in different organs, revealing major differences between the liver and brain in young and old rats. The findings suggest that how an organ ages may depend on its

unique cellular properties and its physiological function in the body.

"Changes that occur in aging can be diverse and difficult to pin down, and looking simply at one parameter might result in not seeing the whole picture," says co-first author Brandon Toyama of the Salk Institute for Biological Studies. However, harnessing the power of several state-of-the-art technologies has let the group see age-dependent changes that could not be seen before. The result, according to Toyama, is "a rich resource that should stimulate the generation of new experimentally testable hypotheses, leading to a better understanding of aging on the organism level."

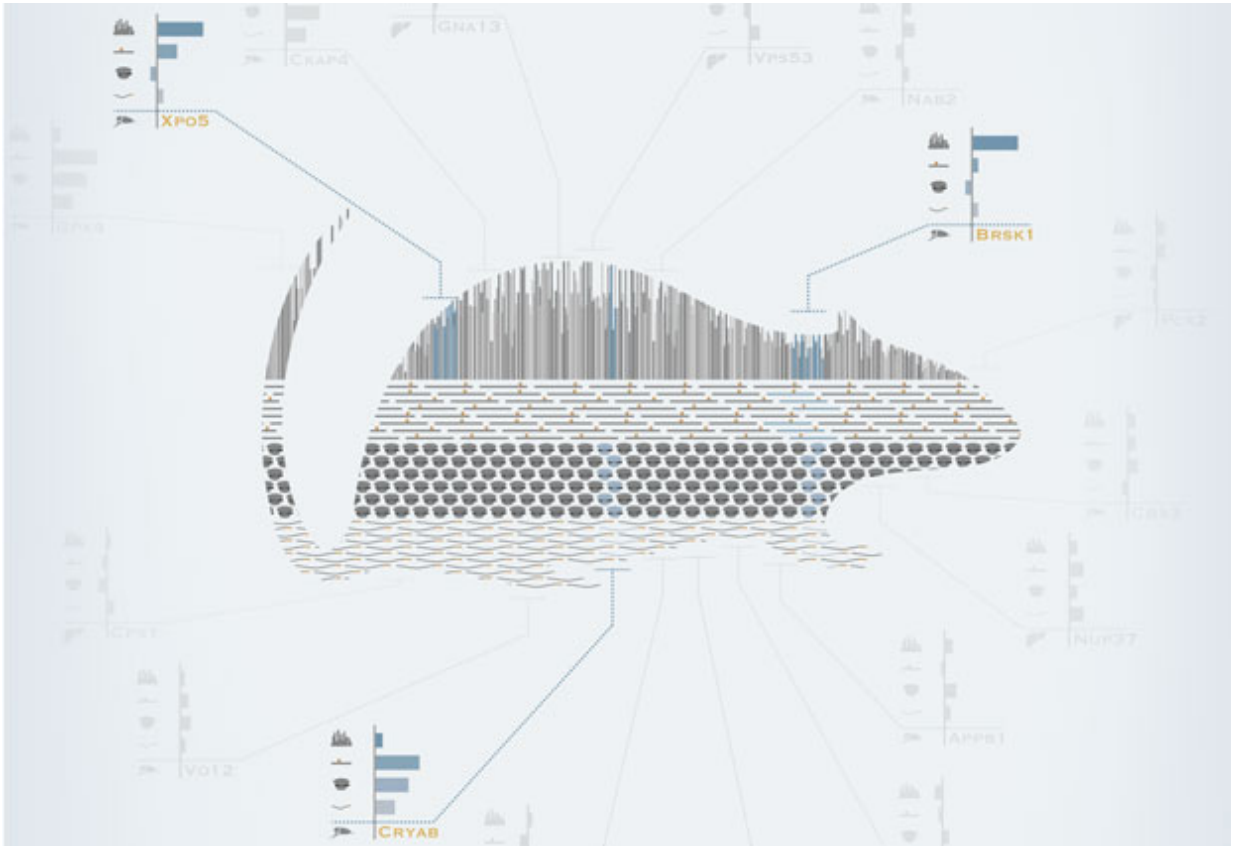
Aging causes the progressive deterioration in the function of organs, as well as the functions of cells and proteins within them. Past studies have shown that the activity level of genes also changes with age, with most genes showing similar changes in expression across organs. However, a recent large-scale study showed that the vast majority of proteins across different organs don't change in abundance during aging. These findings have left it unclear how aging affects cellular proteins and whether age-related changes that affect proteins differ across organs.

To answer these questions, Toyama, co-first author Alessandro Ori of the European Molecular Biology Laboratory (EMBL), and senior authors Nicholas Ingolia of the University of California, Berkeley, Martin Hetzer of the Salk Institute, and Martin Beck of EMBL took an integrated "omics" approach instead of focusing on one isolated aspect of gene expression as in past studies. The combination of genomics and proteomics allowed them to simultaneously analyze changes in transcription, translation, protein levels, alternative splicing, and protein phosphorylation to gain a comprehensive and quantitative view of protein differences in the liver and brain of young and old rats.

They identified 468 differences in protein abundance between young

and old animals, mainly due to changes in protein synthesis. Another set of 130 proteins showed age-related changes in their location within cells, phosphorylation state, or splice form—changes expected to affect the activity level or function of the proteins. "Our work significantly expands the list of proteins that are affected by chronological age in mammals," Beck says. "In most cases, individual datasets would not have been sufficient to extrapolate these networks, highlighting the complexity of the effects of chronological age on the proteome and the benefits of our integrative approach."

Strikingly, most of these age-related protein differences were specific to one organ. The protein aging patterns seem to relate to the organ's specific cellular properties or function. Because cells in the liver are frequently replaced throughout adulthood, this organ has ample opportunity to replenish its proteins. By contrast, most neurons in the adult brain are non-dividing cells that must survive for an organism's entire lifetime, so the longer-lived proteins in the brain are more vulnerable to the accumulation of damage and loss of function over time.



The scientists combined data from a variety of techniques to better understand how rats -- and humans -- age. Credit: Brandon Toyama

As a result, a larger fraction of proteins was affected by aging in the brain compared to the liver. In the brain, aging altered proteins involved in neuronal plasticity and memory formation, whereas several metabolic networks were altered in the liver. "Our study showed that organs have different aging mechanisms and that aging is largely driven by changes in protein production and turnover," Hetzer says. "Based on our findings, we would define aging as an organ-specific deterioration of the cellular proteome."

In future studies, the researchers will analyze other organs such as the

heart to further examine the general and organ-specific effects of aging and investigate how and why these changes are occurring. "We expect these organs to have specific aging signatures, like the brain and liver," Hetzer says. "An interesting open question is whether one organ can affect the aging of another organ, that is, is aging sensed at the organismal level? Answering this question would give us a more comprehensive understanding of the aging process and how it relates to disease."

The researchers will also study how aging differs across individuals to determine the role of genetic variability. "This research may shed new light on the molecular mechanisms underlying age-related diseases, enabling the identification of risk factors to predict which individuals are most susceptible based on their genetic makeup," Beck says. "In the end, a better understanding of the molecular mechanisms of aging could lead to the development of novel therapies to prevent or treat a range of age-related diseases."

More information: *Cell Systems*, Ori and Toyama et al: "Integrated Transcriptome and Proteome Analyses Reveal Organ-Specific Proteome Deterioration in Old Rats" dx.doi.org/10.1016/j.cels.2015.08.012

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