Researchers identify novel anti-aging targets

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Caenorhabditis elegans. Credit: Wikipedia

A recent study published in *Nature* has reported two conserved epigenetic regulators as novel anti-aging targets. The research, by scientists from Dr. Cai Shiqing's Lab at the Center for Excellence in Brain Science and Intelligence Technology, Institute of Neuroscience of the Chinese Academy of Sciences (CAS), and Dr. Jiang Lubing's team at

Institut Pasteur, Shanghai of CAS, identified conserved negative regulators of healthy aging by using multiple modalities and systems, thus providing insights into how to achieve healthy aging.

Aging is associated with progressive decline in physiological functions over time and is a major risk factor for a number of chronic diseases, such as Alzheimer's disease, cancer, and diabetes. Over the past decades, the understanding of longevity regulation has progressed greatly, and a number of longevity pathways conserved from yeast to mammals have been delineated.

However, increasing longevity is not often accompanied by an extended healthspan, despite global increases in life expectancy. Thus, how to achieve healthy aging (i.e., an extension of healthspan) is one of the most important and challenging heath issues nowadays. Despite its extreme importance, the biological mechanisms underlying healthy aging, as defined by the preservation of normal behavioral capabilities, remains to be elucidated.

Previous studies from Dr. Cai's lab have revealed that behavioral performance in aged animals can be improved by increasing neurotransmitters. They also showed that variation in levels of neurotransmitters may contribute to different rates of age-related decline among individuals.

In the current study, the researchers used the animal models *C. elegans* and mouse, along with human datasets to identify novel anti-aging targets and unravel a mechanism for regulating cognitive aging. *C. elegans* is a tiny free-living nematode, about 1 mm in length. Due to its short lifespan and clear genetic background, *C. elegans* has been widely used in aging research.

To identify aging modulators, the researchers performed a genome-wide

RNAi screen for genes that regulate behavioral deterioration in aging *C. elegans*. They identified 59 genes that potentially regulate the rate of age-related behavioral deterioration. By constructing a co-expression network of these screening hits, they found that a neuronal epigenetic reader BAZ-2 and a neuronal histone 3 lysine 9 (H3K9) methyltransferase SET-6 appeared as a key node in the network. Deletion of baz-2 and set-6 prevented age-related deterioration in the worm's food-induced behavior, food intake, and male virility.

By analyzing published databases, the researchers found that the expression levels of their human homologues BAZ2B and EHMT1 increase with age in human brains, and positively correlate with Alzheimer's disease (AD) progression. Strikingly, ablation of Baz2b, the mouse ortholog of baz-2, attenuated age-dependent body weight gain and prevented cognitive decline in aging mice. Their findings suggest that BAZ2B and EHMT1 are key aging modulators and appear to be novel anti-aging targets.

In addition, the researchers demonstrated that these epigenetic modulators repressed the expression of nuclear genes encoding mitochondrial proteins by occupying the promoter regions and hence reduced mitochondrial function, a mechanism conserved in mouse brain tissues. Deletion of baz-2/BAZ2B and set-6/EHMT1 delayed the aging process by improving mitochondrial function.

Mitochondrial dysfunction has been implicated in the pathogenesis of Alzheimer's disease (AD). By analyzing gene expression in the brains of AD patients, they found that the expression levels of BAZ2B and EHMT1 negatively correlate with the expression of key mitochondrial function-related genes, suggesting that BAZ2B and EHMT1 can regulate mitochondrial function in aging human brains.

The researchers in this study performed a genome-wide RNAi screen

and provided the first view of genes that modulate behavioral aging. They showed that two conserved epigenetic factors modulate the aging of the nervous system by regulating mitochondrial function. This newly discovered epigenetic regulation of mitochondrial function is critical for achieving healthy aging of the brain. Given the reversible nature of epigenetic regulation, BAZ2B and EHMT1 emerge as promising drug targets for combating behavioral and cognitive aging.

More information: Two conserved epigenetic regulators prevent healthy ageing, *Nature* (2020). DOI: 10.1038/s41586-020-2037-y , nature.com/articles/s41586-020-2037-y

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