Examining SIRT6 regulation as a key component of aging

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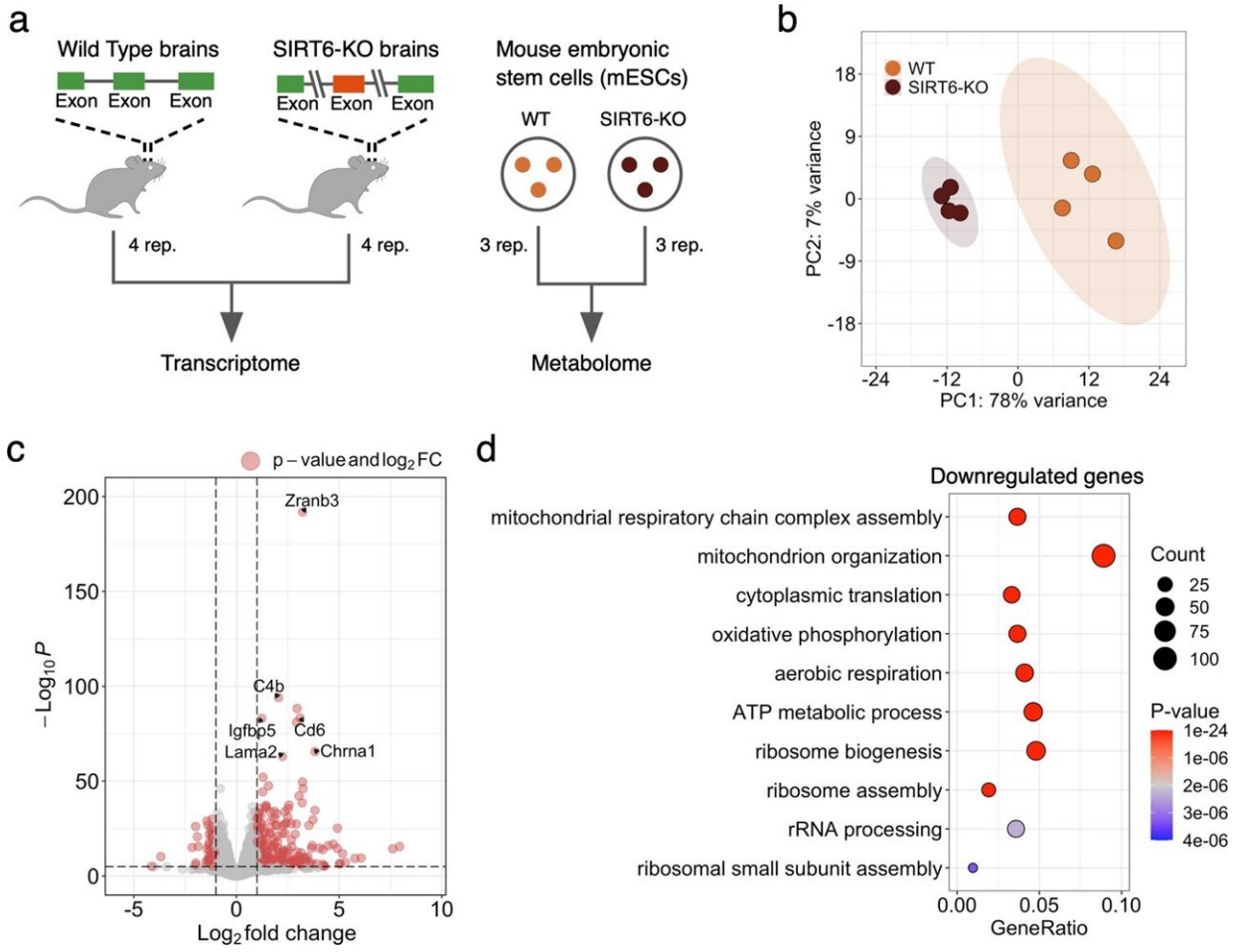

SIRT6 regulates gene expression levels. **a** Schematic illustration of the experimental design used in this study. Transcriptome profiles were collected from Wild Type (WT) and SIRT6-knockout (brSIRT6-KO) mouse brain samples. WT and brSIRT6-KO SH-SY5Y metabolomic profiles were complemented with metabolomics data on mouse embryonic stem cells. **b**

Principal Component Analysis (PCA) plot showing separation between WT (orange) and brSIRT6-KO (brown) samples. Orange and brown ovals represent confidence ellipses of WT and brSIRT6-KO groups. **c** The volcano plot showing up- and downregulated differentially expressed genes in brSIRT6-KO mice compared to WT mice. Red dots indicate significantly changed genes, and gray dots represent insignificant genes. **d** GO analysis showing the top 10 enriched biological processes for downregulated genes. Each circle corresponds to the enriched GO term and varies in size according to the number of significant genes belonging to this term. The gene ratio represents the number of DE genes belonging to the enrichment categories divided by the total number of genes per category. Credit: *Cell Death & Disease* (2023). DOI: 10.1038/s41419-022-05542-w

Anti-aging creams, shakes, exercises, you name it, you can read about it online. However, what does science have to say about aging? Ben-Gurion University of the Negev life sciences researcher Dr. Debra Toiber has uncovered what seems to be a key preventive measure of DNA breakdown, which many believe causes aging and neurodegenerative diseases. Dr. Toiber has been focused on a protein called SIRT6, and she has discovered that it seems to have remarkable properties. Its absence seems to downgrade DNA repair significantly.

In a new paper just published in *Cell Death and Disease*, Dr. Toiber and her international colleagues have found that SIRT6 is a key regulator of mitochondrial function in the brain.

"Mitochondrial dysfunction is one of the hallmarks of aging and one of the main characteristics of multiple neurodegenerative diseases. Many defects are observed in the mitochondria's efficiency during aging; however, what initiates these events is unclear," explains Dr. Toiber.

"We found that SIRT6 keeps mitochondria functioning through the

transcription regulation of mitochondrial genes," she says.

Using transcriptomics, metabolomics, and molecular assays, she and her team observed that in the absence of SIRT6 in the brain, nuclear expressed mitochondrial genes are down-regulated, the number of mitochondria per cell decays, there is an increase in Reactive Oxygen Species (ROS) production, and the mitochondrial membrane potential is impaired, causing major metabolic changes.

This effect is partially the result of SIRT6 regulating the expression of the mitochondrial Sirtuins 3 and 4. Importantly, re-introducing SIRT3 and 4 can rescue the membrane potential capacity. Particularly in the brain, during neurodegeneration, mitochondria lose the ability to generate enough Adenosine Tri phosphate (ATP), generate toxic ROS, and impair the production of important metabolites for brain functioning.

"Our results show parallel changes in mitochondrial gene expression induced by the lack of SIRT6 in the brain to the changes observed in aging, Alzheimer's disease, Parkinson's disease, and ALS, suggesting that SIRT6 decay in the brain is the driver of these changes," Dr. Toiber says.

More information: Dmitrii Smirnov et al, SIRT6 is a key regulator of mitochondrial function in the brain, *Cell Death & Disease* (2023). DOI: 10.1038/s41419-022-05542-w

Provided by Ben-Gurion University of the Negev