The emerging role of SIRT6 in the mitochondrial regulation

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Introduction and study design

Motivation

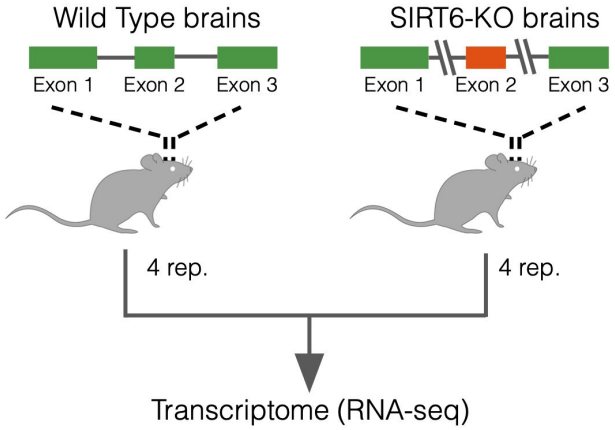
SIRT6 functions as a histone deacetylase and mono-ADP-ribosylase, acting as a regulator of genomic stability, DNA repair, telomere maintenance and cellular metabolism in the brain. While it has clear roles in protection against aging-associated diseases, the molecular mechanisms underlying SIRT6 impact on mitochondrial function in the brain are still poorly understood.

Research objective

To address this question, we examined the SIRT6-induced changes in mitochondrial activity by comparing transcriptomic profiles of brain-specific SIRT6 knockout mice (brSIRT6-KO) and wild-type mice (WT).

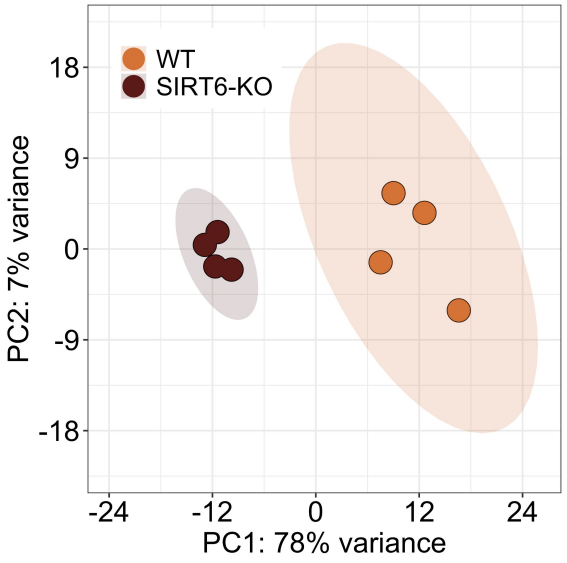
Study design

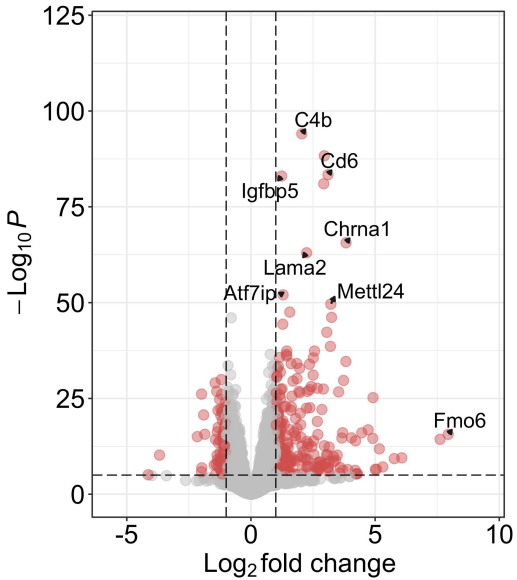
To generate RNA-seq, we utilized two groups of mice that were WT (4 replicates) and KO (4 replicates) for SIRT6.

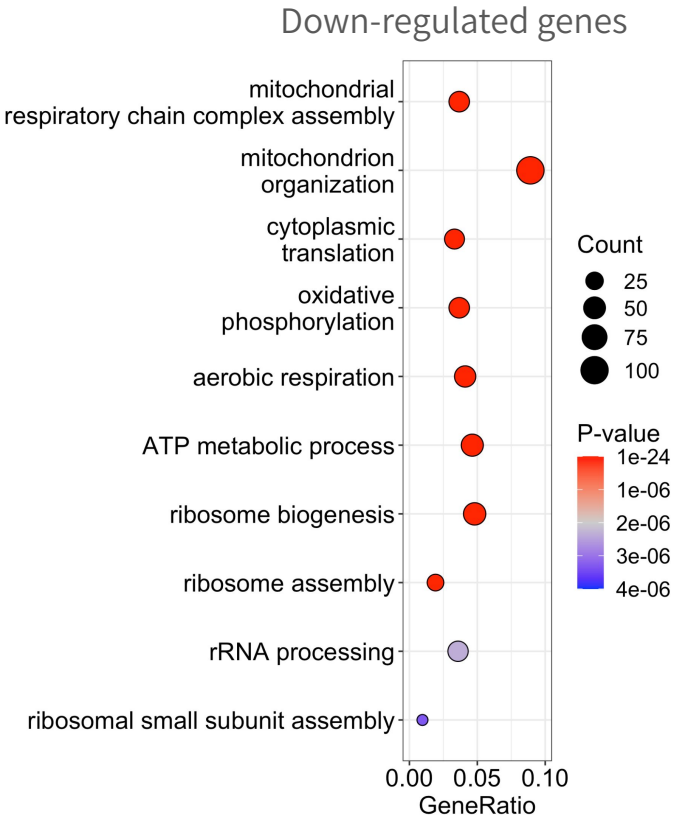


SIRT6 controls expression of mitochondria-related genes

To study the effect of the lack of SIRT6 at the transcriptional level, we performed differential gene expression (DGE) analysis for WT vs SIRT6-KO and found a total of 2870 differentially expressed (DE) genes. GO analysis of down-regulated genes revealed enriched terms associated with essential mitochondrial processes.

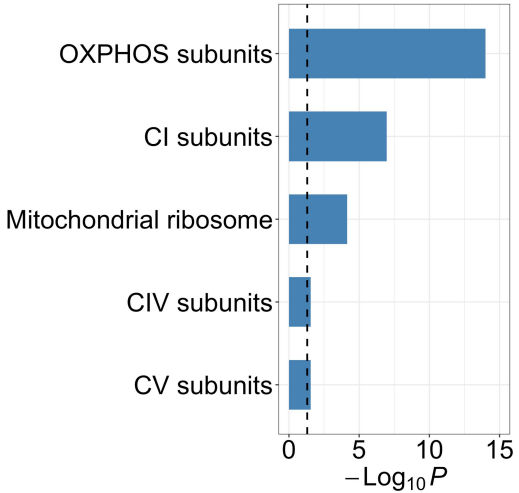


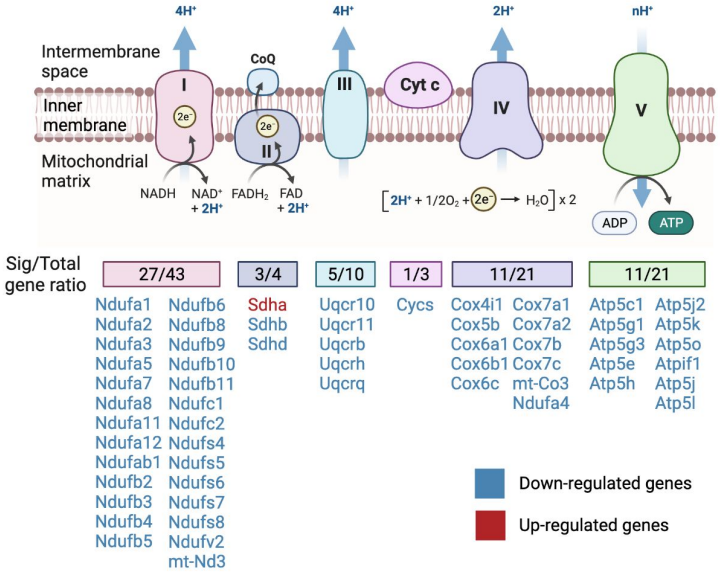


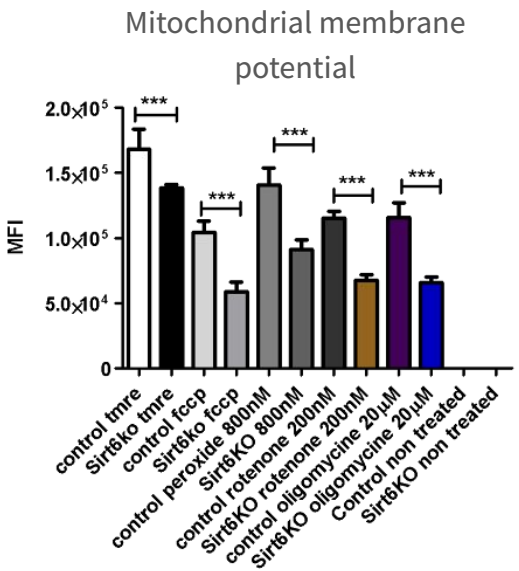


SIRT6 deficiency leads to impaired OXPHOS

We found that the deficiency of SIRT6 results in transcriptional downregulation of mitochondrial genes predominantly involved in regulation of oxidative phosphorylation (OXPHOS) complexes, including Complex I, IV, and V. In line with this result, mitochondria showed reduced membrane potential in SIRT6-KO compared to control in both untreated and treated with OXPHOS complex inhibitors SH-SY5Y cells.

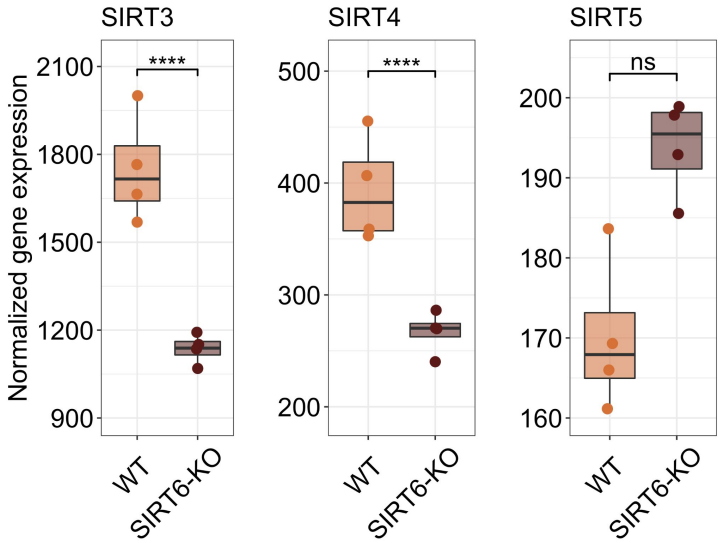


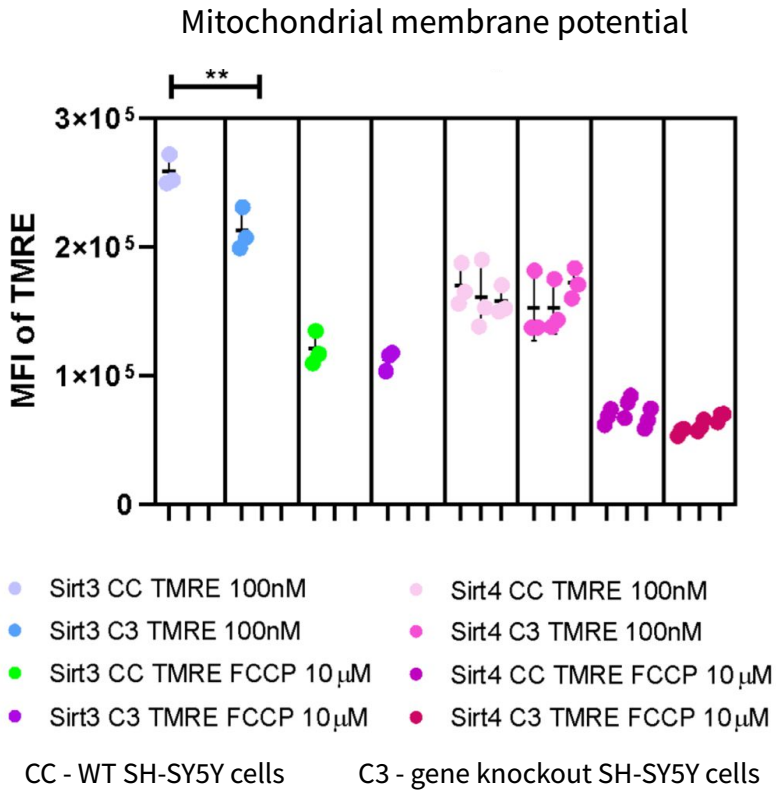




SIRT6-SIRT3 axis promotes OXPHOS in the brain

SIRT6 deficiency also leads to down-regulation of SIRT3 and SIRT4 that are localized in mitochondria and regulate several OXPHOS-related genes. As in the case of SIRT6-KO, SIRT3-deficient cells demonstrate reduced mitochondrial membrane potential compared to control SH-SY5Y cells.

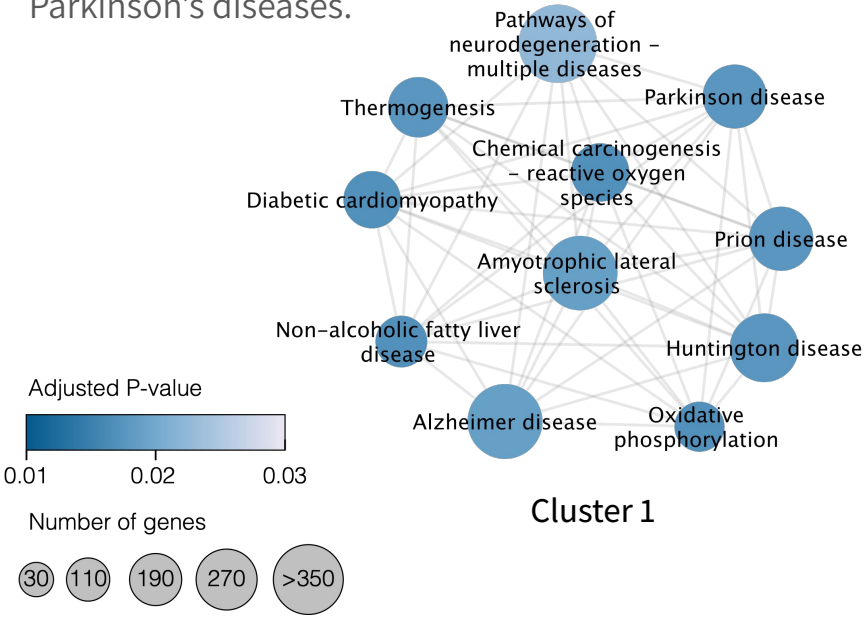




Neuroprotective activity of SIRT6

GSEA analysis

Gene Set Enrichment analysis revealed a number of significantly affected pathways associated with neurodegenerative disorders, including Alzheimer's and Parkinson's diseases.



Cluster 1

Proposed model

Given the clear role of SIRT6 in mitochondrial regulation, we proposed the following model of neuroprotective SIRT6 functions: