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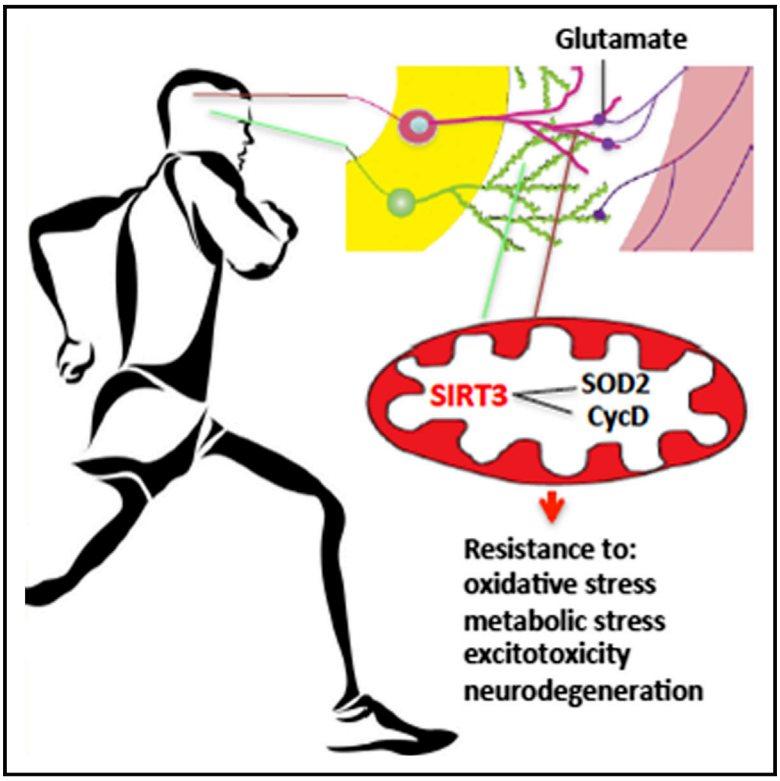
Mitochondrial SIRT3 Mediates Adaptive Responses of Neurons to Exercise and Metabolic and Excitatory Challenges

Graphical Abstract



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In Brief

Cheng et al. find that neurons lacking the mitochondrial deacetylase SIRT3 are more vulnerable to dysfunction and degeneration in mouse models of epilepsy and Huntington's disease. Exercise and synaptic activity induce hippocampal SIRT3 expression to modulate mitochondrial protein acetylation and bolster neuronal resistance to oxidative stress and apoptosis.

Highlights

- Exercise and glutamatergic signaling induce SIRT3 expression in cortical neurons
- SIRT3 deacetylates SOD2 and cyclophilin D in neuronal mitochondria
- SIRT3 prevents neuronal death in mouse models of epilepsy and Huntington's disease
- SIRT3 mediates adaptive responses of neurons to excitotoxic and metabolic stress

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Mitochondrial SIRT3 Mediates Adaptive Responses of Neurons to Exercise and Metabolic and Excitatory Challenges

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SUMMARY

The impact of mitochondrial protein acetylation status on neuronal function and vulnerability to neurological disorders is unknown. Here we show that the mitochondrial protein deacetylase SIRT3 mediates adaptive responses of neurons to bioenergetic, oxidative, and excitatory stress. Cortical neurons lacking SIRT3 exhibit heightened sensitivity to glutamate-induced calcium overload and excitotoxicity and oxidative and mitochondrial stress; AAV-mediated *Sirt3* gene delivery restores neuronal stress resistance. In models relevant to Huntington's disease and epilepsy, *Sirt3*$^{-/-}$ mice exhibit increased vulnerability of striatal and hippocampal neurons, respectively. SIRT3 deficiency results in hyperacetylation of several mitochondrial proteins, including superoxide dismutase 2 and cyclophilin D. Running wheel exercise increases the expression of *Sirt3* in hippocampal neurons, which is mediated by excitatory glutamatergic neurotransmission and is essential for mitochondrial protein acetylation homeostasis and the neuroprotective effects of running. Our findings suggest that SIRT3 plays pivotal roles in adaptive responses of neurons to physiological challenges and resistance to degeneration.

INTRODUCTION

Glutamate, the major excitatory neurotransmitter in the vertebrate brain, triggers membrane depolarization, influx of Na^+ and Ca^{2+}, and increased mitochondrial oxidative phosphorylation and superoxide production in neurons (Mattson et al., 2008). Neurons normally recover rapidly from excitation by restoring the transmembrane ion gradients, replenishing energy substrates, and removing reactive oxygen species (ROS). This recovery depends critically on properly functioning mitochondria that generate ATP and buffer Ca^{2+} transients. However, in pathological conditions where neurons are excited excessively (epilepsy), deprived of oxygen and glucose (stroke and cardiac arrest), or suffer more insidious metabolic and oxidative stress (Alzheimer's, Parkinson's, and Huntington's diseases), mitochondria fail to counteract the stress and neurons therefore degenerate and die (Mattson, 2003).

When transiently exposed to mild to moderate levels of metabolic, oxidative, and excitatory stress, neurons respond adaptively by engaging signaling pathways that bolster their bioenergetics, antioxidant defenses, and abilities to prevent and repair molecular damage (Mattson, 2008). For example, exposure of neurons to a low level of glutamate can protect them from being killed by a higher level of glutamate, and intermittent exercise and fasting can counteract neurodegenerative disease processes in animal models of Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), epilepsy, and stroke (Mattson, 2012; Zigmond and Smeyne, 2014). Evidence supports the involvement of several underlying mechanisms including upregulation of neurotrophic factors, DNA repair enzymes, protein chaperones, and autophagy (Mattson, 2012). Mitochondria might play several roles in adaptive responses of neurons to excitatory, metabolic, and oxidative stress (Mattson et al., 2008). For example, manganese superoxide dismutase (SOD2) is an essential antioxidant enzyme that serves as the first line of defense against the superoxide free radicals generated by the electron transport chain. SOD2 can protect neurons against degeneration in experimental models of neurodegenerative disorders (Keller et al., 1998; Andreassen et al., 2001). While mitochondria are crucial for neuronal stress resistance, they are also the organelle that mediates apoptosis, a form of programmed cell death implicated in many acute and chronic neurodegenerative conditions (Mattson, 2000). Excessive DNA damage, Ca^{2+} overload, and oxidative stress causes the association of cyclophilin D with mitochondrial membrane permeability transition pores (PTPs), which triggers opening of the PTP, through which cytochrome C passes into the cytosol where it