Regulation of Mitochondrial Function and Motor Neuron Degeneration in SMA

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Contact information of lead PI
Country

USA

Title of project or programme

Regulation of Mitochondrial Function and Motor Neuron Degeneration in SMA

Source of funding information

NIH (NINDS)

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01/09/2015

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4

The project/programme is most relevant to:

Spinal muscular atrophy (SMA)

Keywords

Spinal Muscular Atrophy, motor neuron degeneration, HDAC5 gene, Cyclin-Dependent Kinase 5, Mitochondria

Research Abstract

? DESCRIPTION (provided by applicant): Regulation of Mitochondrial Function and Motor

Neuron Degeneration in SMA. Spinal muscular atrophy (SMA), the leading genetic cause of infant mortality, is characterized by the degeneration of spinal motor neurons. Although the genetic mutations that lead to SMA have been mapped to the Survival Motor Neuron 1 (SMN1) gene, mechanisms underlying spinal motor neuron degeneration remain largely unknown. Currently, there is no effective treatment for SMA despite ongoing clinical trials. This proposal aims to investigate a novel mechanism regulating mitochondrial functions, and how dysregulation of this mechanism leads to mitochondrial oxidative stress and motor neuron degeneration in SMA. Findings from these studies will have broad implications for understanding neurodegenerative disorders and for developing therapeutic strategies. Using two SMA mouse models and human SMA patient spinal cord samples, we have found that the kinase activity of cyclin-dependent kinase 5 (Cdk5) and its phosphorylation of histone deacetylase 5 (HDAC5) on serine 279 (S279) is significantly increased in motor neurons affected by SMA, leading to increased cytoplasmic localization of HDAC5. We have also observed that HDCA5 deacetylates mitochondrial outer membrane-binding protein Miro, which regulates mitochondrial movement and clearance. Furthermore, we made novel findings that mitochondrial oxidative stress was dramatically increased while mitochondrial movement was reduced in SMA motor neurons. In this proposal, we plan to use a combination of mouse genetic, cell biological and biochemical approaches to investigate how Cdk5-mediated phosphorylation of HDAC5 S279 regulates mitochondrial function and how dysregulation of this mechanism leads mitochondrial oxidative stress and motor neuron degeneration in SMA. Specifically, we will 1) characterize the effects of HDAC5-mediated deacetylation on Miro functions; 2) elucidate the mechanisms by which mitochondrial functions are dysregulated in SMA; 3) investigate the role of Cdk5 signaling pathway in SMA pathogenesis in vivo. Findings from the proposed research will provide insights into mechanisms regulating mitochondrial function, oxidative stress and motor neuron degeneration in SMA. These studies will facilitate the development of new therapeutic strategies for SMA and other neurodegenerative disorders.

Lay Summary

PUBLIC HEALTH RELEVANCE: Spinal muscular atrophy (SMA) is the leading genetic cause of infant mortality, affecting approximately one in every six thousand live births. This proposal aims to explore a novel mechanism regulating mitochondrial functions, and how dysregulation of this mechanism leads mitochondrial oxidative stress and motor neuron degeneration in SMA. These studies will facilitate the development of new therapeutic approaches for SMA and other neurodegenerative disorders.

Further information available at:

Types:
Investments > €500k

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United States of America

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Spinal muscular atrophy (SMA)

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