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SOD1 Oxidation in Biological Aging

NEUROSCIENCE GRAND ROUNDS

Date: Friday, February 24, 2023
Apotex Lecture Hall 050

SPEAKER

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BIO

Dr. Jiming Kong received his MD and PhD degrees in China. He did post-doctoral trainings in University of Massachusetts Medical Centre and University of Manitoba. He is currently a professor at the Department of Human Anatomy and Cell Science, University of Manitoba. Dr. Kong has research interests in ageing and age-related neurodegenerative diseases. He is also interested in myelination in the central nervous system.

RESEARCH

Background: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease. There is no cure currently. The discovery that mutations in the gene SOD1 are a cause of ALS marks a breakthrough for the search of effective treatments for ALS. SOD1 is an antioxidant that is highly expressed in motor neurons. Human SOD1 is prone to aberrant modifications. Familial ALS-linked SOD1 variants are particularly susceptible to aberrant modifications. Once modified, SOD1 undergoes conformational changes and becomes misfolded. This study aims to determine the effect of selective removal of misfolded SOD1 on the pathogenesis of ALS.

Methods: Based on chaperone-mediated protein degradation pathway, we designed a fusion peptide named CT4, and tested its efficiency in knocking down intracellularly misfolded SOD1 and its efficacy in modifying pathogenesis ofALS.

Results: Expression of a plasmid carrying the CT4 sequence in human HEK cells resulted in robust removal of misfolded SOD1 induced by serum deprivation. Co-transfection of the CT4 and the human SOD1 G93A plasmids at various ratios in rat PC12 cells demonstrated a dose-dependent knockdown efficiency on G93A, which could be further increased when misfolding of SOD1 was enhanced by serum deprivation. Application of the full length CT4 peptide to primary cultures of neurons expressing the G93A variant of human SOD1 revealed a time-course of the degradation of misfolded SOD1; misfolded SOD1 started to decrease by 2 h after the application of CT4 and disappeared by 7 h. Intravenous administration of the CT4 peptide at 10 mg/kg to the G93A mice at the age of 4 months old induced reduction of human SOD1 in spinal cord tissue by 68% in 24 h and 54% in 48 h. Intraperitoneal administration of the CT4 peptide starting from 60 days of age significantly delayed the onset of ALS and prolonged the lifespan of the G93A mice. Conclusions: The CT4 peptide directs degradation of misfolded SOD1 in high efficiency and specificity. Selective removal of misfolded SOD1 significantly delays the onset of ALS, demonstrating that misfolded SOD1 is the toxic form of SOD1 that causes motor neuron death. The study provides a proof of concept that selective removal of misfolded SOD1 is a promising treatment for ALS.

OBJECTIVES

1. Posttranslational modification of SOD1 plays a role in ageing and age-related neurodegenerative diseases.

2. Selective removal of misfolded SOD1 is a promising treatment for ALS.

3. SOD1 oxidation accelerates celluar senescence in neural stem cells; Knockdown oxidized SOD1 increases proliferation and stemness of neural stem cells.

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