

FOOD FOR THOUGHT

SEMINAR SERIES

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1:30 PM – 2:30 PM

Samuel N. Cohen Auditorium
St. Boniface Hospital
Albrechtsen Research Centre
351 Taché Avenue, Winnipeg



NEUROPROTECTIVE FUNCTIONS FOR THE HISTONE DEACETYLASE SIRT6

by

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Neurodegenerative diseases are caused by the loss of neuronal cells. For many years, researchers have been trying to find the causes and possible therapies for the diverse neurodegenerative pathologies. Yet, distinguishing between the causes and the consequences of neurodegeneration is difficult, as all the symptoms and markers get tangled in an array of phenotypes. The most accepted theory of aging is that the accumulation of unrepaired DNA damage is the main cause: As we age, we accumulate DNA lesions, until we reach a threshold of irreparable lesions. The histone deacetylase SIRT6 has been linked to the aging process. SIRT6 knockout mice exhibit an accelerated aging phenotype and die prematurely. SIRT6 promotes DNA repair, but its activity declines with age with a concomitant accumulation of DNA damage. We report that brain-specific SIRT6-deficient mice survive but present behavioral defects with major learning impairments by 4 months of age. Moreover, the brains of these mice show increased signs of DNA damage, cell death, and hyperphosphorylated Tau-a critical mark in several neurodegenerative diseases. Mechanistically, SIRT6 regulates Tau protein stability and phosphorylation through increased activation of the kinase GSK3 α/β . Finally, SIRT6 mRNA and protein levels are reduced in patients with Alzheimer's disease. Taken together, our results suggest that SIRT6 is critical to maintain genomic stability in the brain and that its loss leads to toxic Tau stability and phosphorylation. Therefore, SIRT6 and its downstream signaling could be targeted in Alzheimer's disease and age-related neurodegeneration.



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