Using the Oxytosis/Ferroptosis Pathway to Understand and Treat Age-Related Neurodegenerative Diseases

April 8

Tuesday, 12:30 pm

Billings Building

Rosedale Room

SPEAKER:

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Host: Rajiv R. Ratan, M.D., Ph.D.

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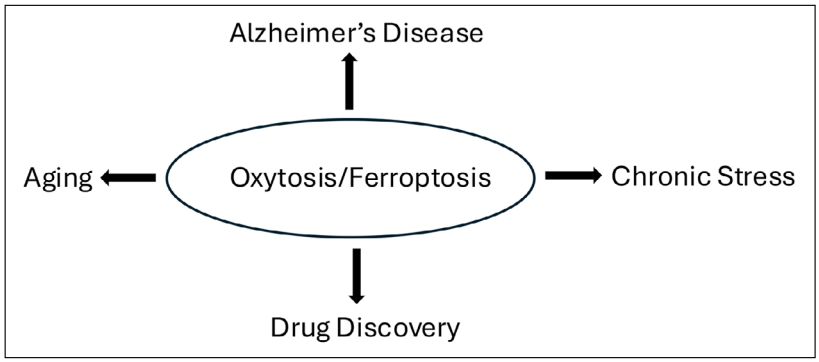
Abstract

A major focus of the research in my lab centers around the oxytosis/ferroptosis pathway and its role in age-related neurodegenerative diseases. This cell death pathway was first characterized by my lab and others beginning in the early 1990's and named oxytosis but was rediscovered by the cancer field in 2012 and (re-) named ferroptosis. Not only have we been interested in understanding the critical proteins and metabolites that are involved in this pathway but we have also used it as our primary screen for identifying novel drug candidates for the treatment of Alzheimer's and potentially other age-related neurodegenerative diseases. This is because oxytosis/ferroptosis has emerged as a degenerative mechanism that re-capitulates many of the changes that occur in the aging brain and therefore could play a key role in AD development and progression. It should be noted that while mammalian cultured cells die rapidly following the induction of oxytosis/ferroptosis, this is likely not be the case in vivo. Oxytosis/ferroptosis follows a series of steps that, in vivo, could take place over an extended time period there by leading to a slow degeneration of basic neuronal functions prior to any cell death. In the context of age-related neurodegenerative diseases, this would translate into oxytosis/ferroptosis taking place as a chronic process rather than an acute event, and its inhibition being relevant throughout the course of disease progression and not only at its point of initiation. Using the oxytosis/ferroptosis pathway to screen for novel neuroprotective compounds, we have identified several potential drug candidates that act by a variety of distinct mechanisms to block activation of this pathway. In animal studies, not only do these compounds prevent cognitive impairment but they also counteract other physiological risk factors associated with dementia including aging itself. Moreover, we have also used these compounds in a chemical biology approach to better understand the role of the oxytosis/ferroptosis pathway in both aging and neurodegenerative diseases.



Publications

1. Dafre, A. L., Zahid, S., Probst, J. J., Currais, A., Yu, J., Schubert, D. and Maher, P. *CMS121: a novel approach to mitigate aging-related obesity and metabolic dysfunction.* Aging 16:4980-4999, 2024.

2. Liang, Z., Candib, A., Soriano-Castell, D., Fischer, W., Finley, K. and Maher, P. *Fragment-based drug discovery and biological evaluation of novel cannabinoid-based inhibitors ofoxytosis/ferroptosis for neurological disorders.* Redox. Biol. 72:103138, 2024.

3. Currais, A., Raschke, W. and Maher, P. *CMS121, a novel drug candidate for the treatment of Alzheimer's disease and age-related dementia.* J. Alzheimer's Disease, 101:S179-S192, 2024.

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