Roles for Neuronal Excitability and Bioenergetics in the Regulation of Longevity

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Online Webinar

For Researchers

Speaker:

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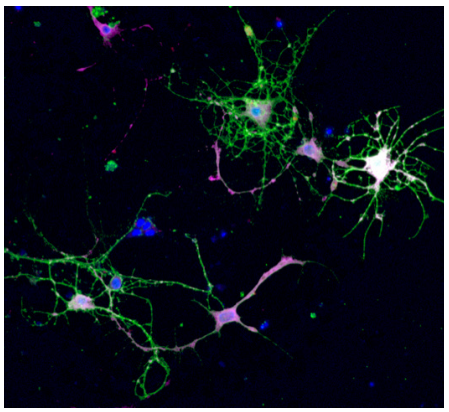
Abstract

Mitochondrial ATP production is a well-known regulator of neuronal excitability. In this talk, I will describe a mechanism by which depolarized neurons elevate the somatic ATP/ADP ratio in *Drosophila* glutamatergic neurons. I will show that depolarization increases phospholipase-Cβ (PLCβ) activity by promoting the association of the enzyme with its phosphoinositide substrate. Augmented PLCβ activity led to greater release of endoplasmic reticulum (ER) Ca^{2+} via the inositol trisphosphate receptor (IP_3R), which in turn, stimulated mitochondrial Ca^{2+} uptake and ATP synthesis.

Expression of a gene encoding an ALS-causing variant of an ER membrane protein, VAPB, decouples mitochondrial ATP production from neuronal activity. Due to a combination of diminished ATP production and elevated ATP consumption — established outcomes in ALS neurons — the levels of ATP in mutant neurons are unable to keep up with the bioenergetic burden of depolarization. The resulting paucity of ATP results in diminished extrusion of cytosolic Ca^{2+}, defects in synaptic vesicle release, and chronic depolarization.

Sustained depolarization of neurons in models of ALS and tauopathy led to untrammeled PLCβ–IP_3R activation, and a dramatic shortening of *Drosophila* lifespan. Investigation of the underlying mechanisms revealed that increased sequestration of Ca^{2+} into endolysosomes was an intermediary in the regulation of lifespan by IP_3Rs. Manipulations that either lowered PLCβ/IP_3R abundance or attenuated endolysosomal Ca^{2+} overload restored animal longevity. Collectively, our findings demonstrate that depolarization-dependent regulation of PLCβ–IP_3R signaling is required for modulation of the ATP/ADP ratio in healthy glutamatergic neurons, whereas hyperactivation of this axis in chronically depolarized glutamatergic neurons shortens animal lifespan by promoting endolysosomal Ca^{2+} overload.



1. Karagas, N.E., Tan, K.L., Bellen, H.J., Venkatachalam, K.*, and Wong, CO.* (2021) **Loss of Activity-Induced Mitochondrial ATP Production Underlies the Synaptic Defects in a *Drosophila* model of ALS.** bioRxiv 2021.12.14.472444. * Corresponding authors. https://doi.org/10.1101/2021.12.14.472444.

2. Jung, J., Liao, H., Coker, S.A., Liang, H., Hancock, J.F., Denicourt, C., and Venkatachalam, K. (2021) **p53 Mitigates the Effects of Oncogenic HRAS in Urothelial Cells via the Repression of MCOLN1.** iScience. 24:10271. PMID: 34222845.

3. Wong, CO.*, Karagas, N.E.*, Jung, J., Wang, Q., Rousseau, M. A., Chao, Y., Insolera, R., Soppina, P., Collins, C.A., Zhou, Y., Hancock, J.F., Zhu, M.X., and Venkatachalam, K. (2021) **Regulation of Longevity by Depolarization-Induced Activation of PLCβ/IP_3R Signaling in Neurons.** Proceedings of the National Academy of Sciences (USA). 118(16): e2004253118. PMID: 33859040. (*, co-first authors).

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