The Role of Local Protein Synthesis in Maintaining the Neuromuscular Junction

March 5

Tuesday, 12:30 pm

Billings Building—Rosedale Room

SPEAKER:

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Publications

1. Jones JI, Costa CJ, Cooney C, Goldberg DC, Ponticiello M, Cohen MW, Mellado W, Ma TC, Willis DE. Failure to Upregulate the RNA Binding Protein ZBP After Injury Leads to Impaired Regeneration in a Rodent Model of Diabetic Peripheral Neuropathy. Front Mol Neurosci. 2021;14:728163. doi: 10.3389/fnmol.2021.728163. eCollection 2021. PubMed PMID: 34949989; PubMed Central PMCID: PMC8688773.

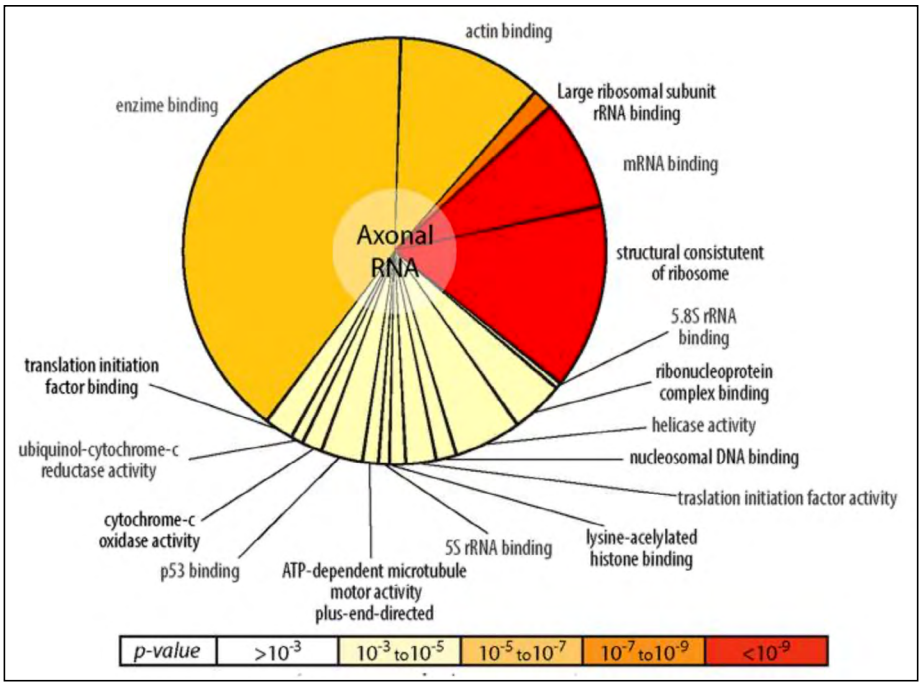
2. Mellado W, Willis DE. Stressing out translation. Science. 2021 Sep 3;373(6559):1089-1090. doi: 10.1126/science.abk3261. Epub 2021 Sep 1. PubMed PMID: 34516848.

3. Gershoni-Emek N, Altman T, Ionescu A, Costa CJ, Gradus-Pery T, Willis DE, Perlson E. Localization of RNAi Machinery to Axonal Branch Points and Growth Cones Is Facilitated by Mitochondria and Is Disrupted in ALS. Front Mol Neurosci. 2018;11:311. doi: 10.3389/fnmol.2018.00311. eCollection 2018. PubMed PMID: 30233312; PubMed Central PMCID: PMC6134038.

4. Rotem N, Magen I, Ionescu A, Gershoni-Emek N, Altman T, Costa CJ, Gradus T, Pasmanik-Chor M, Willis DE, Ben-Dov IZ, Hornstein E, Perlson E. ALS Along the Axons - Expression of Coding and Noncoding RNA Differs in Axons of ALS models. Sci Rep. 2017 Mar 16;7:44500. doi: 10.1038/srep44500. PubMed PMID: 28300211; PubMed Central PMCID: PMC5353576.

Abstract

There is a fundamental gap in our understanding of the molecular mechanisms underlying the normal development of the neuromuscular junction (NMJ). The traditional view where all proteins required for the proper function of the axonal ending are derived from the cell body fails to consider the role of local protein synthesis in the distal axon, which has limited our understanding of the molecular mechanism underlying normal NMJ formation and what drives their loss under pathological conditions. Our long-term goal is to determine the role for local axonal protein synthesis in motor neuron function and uncover the fundamental mechanisms through which local axonal protein synthesis, at the site where the protein is active, contributes to the proper formation and maintenance of NMJs. Our central hypothesis is that reduction in axonal protein synthesis impairs NMJ stability, and that loss of specific locally synthesized proteins is sufficient to disrupt the NMJ. This understanding is essential for unraveling the normal developmental processes that govern NMJ formation and for shedding light on the involvement of dysregulated axonal protein synthesis in neurological disorders where NMJ dysfunction stands as a prominent pathological hallmark. Although much is known about the role of locally available RNAs in synapse formation or in response to axon injury, there is almost no knowledge about the role that motor neuron axonal mRNAs are playing in regard to NMJ establishment and long-term maintenance. Here, I will discuss the mechanisms by which axonal mRNAs are delivered and subsequently translated into proteins, thereby contributing to NMJ formation, and how the loss of local protein synthesis leads to NMJ failure.



Motor neuron axonal transcriptome. Motor neuron transcriptome RNA GO categories. Color is based on significance; the number of genes associated with each category is represented by the size of the pie slice (modified from Rotem et al., 2017).

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