From Molecule to Movement: Dissecting the Path from Dystonia Mutation to Motor Circuit Dysfunction

October 21

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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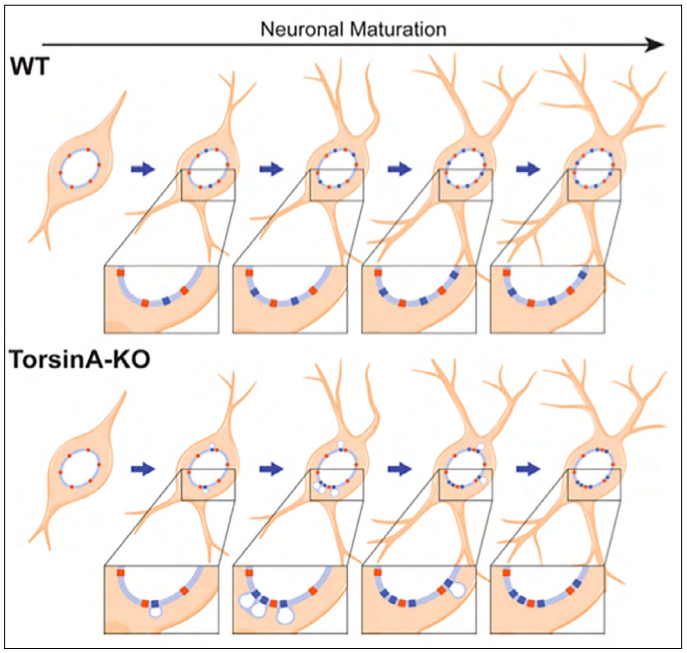
Abstract



Primary dystonia is a movement disorder remarkable for its selective disruption of motor circuits despite the absence of overt neuropathology. Focusing on DYT1 dystonia, the most common inherited form, this talk will explore how a mutation in the TOR1A gene leads to circuit dysfunction during a defined window of brain development. Studies in genetic models reveal that loss of torsinA function impairs neuronal maturation in ways that are only reversible if corrected early in life, highlighting the existence of a critical period for pathogenesis. This developmental vulnerability helps explain the selectivity of the disease and underscores the importance of timing in potential therapeutic approaches. More broadly, the work illustrates how studying rare genetic diseases can uncover general principles of selective vulnerability, circuit development, and the interplay between pathogenesis and pathophysiology in brain disorders.

Publications

1. Kim s, Phan S, Tran HT, Shaw TR, Shahmoradian SH, Ellisman MH, Veatch SL, Barmada SJ, Pappas SS, Dauer WT. *TorsinA is essential for neuronal nuclear pore complex localization and maturation.* Nat Cell Biol. 2024 Sep;26(9):1482-1495. doi: 10.1038/s41556-024-01480-1. Epub 2024 Aug 8. PMID: 39117796.

2. Li J, Levin DS, Pappas SS, Dauer WT: *TorsinA restoration in a mouse model identi ies a critical therapeutic window for DYT1 dystonia.* J Clin Invest 2021 Mar 15; 131(6):e139606. Doi:10.1172/JCI139606.PMID:33529159.

3. Yellajoshyula D, Liang CC, Pappas SS, Penati S, Yang A, Mecano R, Kumaran R, Jou S, Cookson MR, Dauer WT: *The DYT6 Dystonia Protein THAP1 Regulates Myelination within the Oligodendrocyte Lineage.* Dev Cell 42(1): 52-67.e4, 2017. PM28697333/PMC5847273.

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