Molecular Basis of Neurodegeneration in a Mouse Model of Polr3-related Disease

January 23, 2024

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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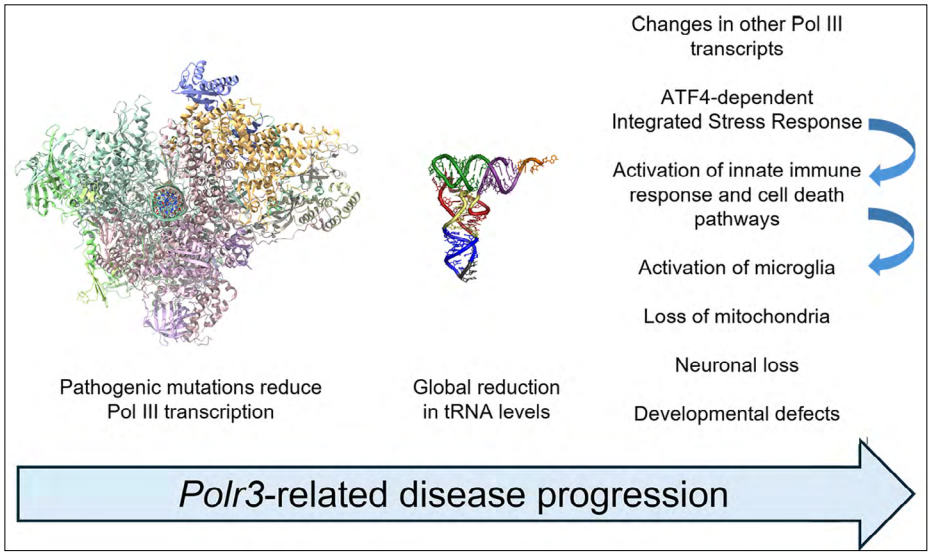
Abstract

RNA polymerase (Pol) III is a ubiquitously-expressed 17 subunit enzyme responsible for the synthesis of abundant small non-coding RNAs that function in protein synthesis and secretion, pre-mRNA splicing, and other important cellular processes. Despite the essential function of the enzyme, pathogenic mutations in multiple subunits cause a spectrum of neurodegenerative diseases. These Polr3-related disorders include a prevalent form of leukodystrophy with hypomyelination, hypodontia and hypogonadotropic hypogonadism (4H leukodystrophy) as distinguishing features along with cerebellar atrophy, myopia and short stature. Disease mechanisms are poorly understood and no treatment options are available. Recently developed mouse models of Polr3-related disease exhibit phenotypes consistent with the clinical features seen in patients and have provided important insights into the cellular and molecular bases of neurodegeneration. I will present our findings and discuss hypotheses concerning disease pathogenesis and the largely selective effects of Polr3 mutations on the central nervous system.



Publications:

Metabolic programming a lean phenotype by deregulation of RNA polymerase III. Willis IM, Moir RD, Hernandez N. Proc Natl Acad Sci U S A. 2018 Nov 27;115(48):12182-12187. doi: 10.1073/pnas.1815590115.

Defective myelination in an RNA polymerase III mutant leukodystrophic mouse. Merheb E, Cui MH, DuBois JC, Branch CA, Gulinello M, Shafit-Zagardo B, Moir RD, Willis IM. Proc Natl Acad Sci U S A. 2021 Oct 5;118(40):e2024378118. doi: 10.1073/pnas.2024378118.

Molecular basis of neurodegeneration in a mouse model of Polr3-related disease. Moir RD, Merheb E, Chitu V, Stanley ER, Willis IM. bioRxiv 2023 https://biorxiv.org/cgi/content/short/2023.12.12.571310v1

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