Nuclear Pore Complex Dysfunction in Dystonia Pathogenesis: Nucleoporins in the Spotlight

Hot Topic article on: Prophet SM, Rampello AJ, Niescier RF, et al. *Atypical nuclear envelope condensates linked to neurological disorders reveal nucleoporin-directed chaperone activities*. Nat Cell Biol 2022.

Advances in genetic profiling have led to the discovery of a number of molecular defects involved in the development of dystonia.[1] Despite the progress in this field, relationships between the associated disease pathways remain difficult to understand, and no consensus on unifying driver molecules has been reached.[1] Dysfunction of torsinA induced by a recurrent mutation in *TOR1A* has been identified as the first monogenic cause of dystonia,[1] but the pathogenesis of clinical manifestations is still incompletely understood. In an article published in the *Nature* series, Prophet and colleagues[2] now provide fascinating insights into the roles of nuclear pore complexes (NPCs) and a subset of its components, the phenylalanine-glycine-rich region-containing nucleoporins (FG-NUPs), in the etiology of *TOR1A*-related dystonia. NPCs are cylindrical channels in the nuclear envelope, controlling bidirectional exchange of biomolecules, and built from about 30 different nucleoporins.[3] The highly conserved group of FG-NUPs (NUP98, NUP54, NUP62, and others) line the interior of NPCs, forming a permeability barrier, and thus represent key mediators of nucleocytoplasmic transport.[3] By studying virally derived model proteins tied to nuclear transport, comparative mass spectrometry–based proteomics data, and microscopic ultrastructural changes in torsinA knock-out cell lines and primary mouse neurons, Prophet and colleagues[2] reveal two main mechanisms contributing to cellular pathology in the context of torsinA dysfunction. First, the authors highlight the formation of abnormal "bleb"-like herniations containing nonfunctional FG-NUPs at the nuclear envelope of affected cells, resulting in NPC-biogenesis deficits.[2,3] Second, they demonstrate that FG-NUP-enriched condensates in "blebs" result in sequestration of protein quality-control network components such as HSP40/HSP70 chaperones, triggering a cascade of proteotoxic stress.[2] Both pathological effects observed in relation to mutant torsinA implicate FG-NUP perturbation in the genesis of early-onset dystonic movements, most likely via mechanisms of impaired nucleocytoplasmic shuttling, compromised intracellular proteostasis, or a combination thereof.[2] Prophet and colleagues[2] also propose that the transient nature of "blebs" with enrichment of FG-NUPs can explain the window of vulnerability associated with penetrance of *TOR1A*-related dystonia (developmental period until about 30 years), depending on how effectively cells can cope with nuclear-transport defects and proteotoxicity.

In support of a wider role for FG-NUPs in dystonia pathogenesis, a particular member of this protein family has been most recently linked to a new hereditary form of the disease: bi-allelic variants of *NUP54* were shown to underlie early-onset dystonia with striatal lesions[4]; affected individuals presented generalized progressive dystonia, whereas their cells exhibited profound reductions in NUP54 and other FG-NUP levels indicative of NPC dysfunction.[4]

The cumulative evidence, considered together with the previously established association between dystonia and further FG-NUPs such as NUP62,[5] suggests that these proteins should be added to the list of molecules that may have broader mechanistic implications across different dystonia subtypes and patient groups. A better understanding of the genetic and molecular basis of FG-NUP involvement in dystonia pathophysiology may help in developing more efficacious treatments.

Alessio Di Fonzo, MD, PhD,[1]
Michael Zech, MD[2,3*]
[1]*Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy*
[2]*Institute of Neurogenomics, Helmholtz Zentrum München, Munich, Germany*
[3]*Institute of Human Genetics, School of Medicine, Technical University of Munich, Munich, Germany*

Data Availability Statement

Data available on request from the authors.

Alessio Di Fonzo, MD, PhD,[1]
Michael Zech, MD[2,3*]
[1]*Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy*
[2]*Institute of Neurogenomics, Helmholtz Zentrum München, Munich, Germany*
[3]*Institute of Human Genetics, School of Medicine, Technical University of Munich, Munich, Germany*

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***Correspondence to:** Privatdozent (PD) Dr. Michael Zech, Institute of Neurogenomics, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH), Ingolstädter Landstraße 1, 85764 Neuherberg, Munich, Germany; E-mail: michael.zech@mri.tum.de

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Author Roles

A.F.: concept and design, editing of the text.
M.Z.: concept and design, data analysis, drafting and revising of the text.

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