FEBS Letters

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EDITORIAL

Biomedical implications of nuclear transport

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A defining feature of eukaryotes is the nucleus, where most of the genetic information resides and is safeguarded within the confines of the nuclear envelope (NE). While this barrier serves to protect the genome and separate transcription from translation, the need to facilitate transport across the NE itself represents a challenge [1]. Nuclear pore complexes (NPCs) support bidirectional transport between the nucleus and cytoplasm and, together with other NE constituents, play critical roles in genome organization, gene expression and nucleocytoplasmic trafficking [2]. As a result, perturbations in the homeostasis of NPC or NE biology are implicated in a range of pathological states, such as neurodegenerative or movement disorders, ageing, cancer, acute necrotizing encephalopathy (ANE) and viral infection [2]. Furthermore, variations in the composition and organization of the NPC are now known to occur between evolutionary lineages with likely significant connections with divergent requirements [3]. Here, in the first of two collections devoted to the NPC and associated nuclear components, we have assembled a selection of articles with novel perspectives on biomedical implications of NPC biology and nucleocytoplasmic trafficking. Together, these articles explore some of the latest findings and insights into the role of NPCs in essential biological pathways, and the assembly of these fascinating molecular structures.

Firstly, Padilla-Mejia and Field [4] address fundamental concepts of NPC and NE structure and composition throughout eukaryotic evolution. In particular, they discuss trypanosomes, protozoa with novel nuclear components that have evolved to meet the specific demands of trypanosome biology. By examining the nuclear lamina and NPC in trypanosomes, Padilla-Mejia and Field emphasize lineage-specific and conserved aspects of nuclear organization. This exploration is not only scientifically intriguing but also relevant for understanding the mechanisms exploited by these parasitic protozoa in immune evasion and life cycle progression and how they cause disease. Desgraupes *et al.* [5] pursue this by

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doi: 10.1002/1873-3468.14752

focusing on a nucleoporin that appeared in metazoans and underwent genomic rearrangements during ape evolution. RANBP2/Nup358 is a cytoplasmic filament nucleoporin and E3 SUMO ligase involved in various cellular processes, which are discussed in depth in the first part of the review. Authors then explore how the dysregulation or mutation of RANBP2 contributes to human pathologies, thus highlighting its importance to human evolution and health.

Next, Kuiper *et al.* [6] delve into NPC assembly, emphasizing the need for careful control over the condensation of phenylalanine-glycine (FG) repeat nucleoporins, which constitute the permeability barrier. Defects in NPC assembly or homeostasis are associated with movement disorders, amyotrophic lateral sclerosis (ALS) and senescence. Recent progress in understanding NPC assembly and its connection to human disorders are discussed, illuminating spatial and temporal control mechanisms required for orderly NPC assembly. In a related area, Cristi *et al.* [7] dissect the critical role of NPCs in maintaining the equilibrium between the nucleus and cytoplasm, elucidating their involvement in neurodegenerative disease pathogenesis. In particular, the importance of the ESCRT-III pathway for NE maintenance and repair, and in preserving functional NPCs, is emphasized. Authors thus highlight how the selective reduction of specific nucleoporins can lead to neurodegenerative pathology. Through a comprehensive description of surveillance pathways that safeguard NPC biogenesis and assembly, we gain a deeper understanding of the pathological cascade leading to diseases such as ALS, frontotemporal dementia (FTD) and Huntington's disease (HD).

Ferreira continues with the topic of NPC assembly and focuses on phase separations during nucleocytoplasmic transport and their impact on proteostasis in the context of neurodegenerative diseases [8]. Specifically, Ferreira addresses how impairments to nucleocytoplasmic transport contribute to dysregulation in cellular partitioning and lead to the formation of protein aggregates—a hallmark of multiple neurodegenerative diseases. A particular focus on RANBP2 is introduced by dissecting its role in the survival of photoreceptor and motor neurons under homeostatic and pathophysiological conditions. Ferreira concludes by highlighting current clinical needs and potential therapeutics targeting neurotoxic aggregates.

Finally, Fichtman and Harel [9] guide us on a journey through the history of microscopy imaging, from the first lenses to modern electron microscopy (EM). By providing a magnified view of individual NPCs, authors showcase recent advances in field emission scanning EM. They then argue that this technique offers a topographic surface perspective, complementing the three-dimensional models derived from other imaging methods, and which may become an important tool in understanding the manner in which NPC structural variability can lead to pathology, which is absent from other imaging approaches.

We anticipate that this FEBS Letters collection will help readers unravel the complexities of nucleocytoplasmic transport and nuclear pore complex assembly, by offering a comprehensive overview of their roles in health, disease and evolution. The articles here represent a mosaic of research, combining cellular and molecular insights with technological advancements. We invite readers to embark on this journey with us and explore the frontiers of cell biology, where the nucleus and its gatekeepers hold the keys to understanding many aspects of the complexity of life.

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