Nuclear shape-shifters: Lipid and Protein Dynamics at the Nuclear Envelope

Wolfram Antonin (1) and Symeon Siniossoglou (2)

(1) Institute of Biochemistry and Molecular Cell Biology, Medical School, RWTH Aachen University, Aachen, Germany, wantonin@ukaachen.de, ORCID: 0000-0003-4669-379X
(2) Cambridge Institute for Medical Research, University of Cambridge, Cambridge UK, ss560@cam.ac.uk, ORCID: 0000-0001-5424-5466

The nuclear envelope constitutes a selective barrier that segregates chromatin into the nucleus of eukaryotic cells. This property makes the nuclear envelope the defining morphological characteristic of the eukaryotic lineage. For many years, cell biology textbooks painted a rather inert view of the nuclear envelope as a smooth, centrally located, perinuclear circle, busy mediating the bidirectional trafficking of proteins and RNA through nuclear pore complexes. Recent research in the field is now transforming our understanding of the nuclear envelope as a highly dynamic organelle that can undergo extensive local remodeling during physiological processes such as nuclear division or *de novo* nuclear pore biogenesis as well as repairing itself during cell migration or mechanical insults. The seven articles in this special issue tackle different aspects of how membrane lipid metabolism and the regulation of nuclear envelope protein components like lamins and nuclear pore complexes safeguard the homeostasis of the nucleus.

Lamins are intermediate filament proteins that coat the inner nuclear membrane and provide both crucial mechanical support to the nucleus but also help organizing the chromatin [1]. Lamin mutations in humans result in a range of pathologies, including progeria, a disorder causing accelerated ageing. Sears and Roux examine the pathways of lamin recruitment in ruptured nuclei [2]. The authors show that A-type lamins target nuclear envelope ruptures within minutes, by interacting with BAF, another protein enriched at the nuclear envelope. The observation that progeria-associated mutations in the Lamin A or BAF genes inhibit the recruitment of Lamin A protein to the ruptured sites raises the possibility that this could be a contributing factor to the disease.

Changes in nuclear shape are associated with mutations in lamins, aging and many pathologies including cancer. In addition, drastic alterations in nuclear shape take place throughout the physiological life cycle of cells such as during their division or movement. Janssen et al present an in-depth overview of image-based methods for the quantitation of nuclear morphology and nuclear envelope abnormalities [3]. Establishing these quantitative parameters is an essential tool for studies using nuclear morphology as a phenotypic read-out.

An exciting recent finding in the field has been the identification of lipid droplets in the nucleus in a variety of cell types, although their functional significance remain enigmatic [4]. Kumanski et al report the presence of nuclear lipid droplets in cells experiencing DNA replication stress [5]. The authors hypothesize that stalled replication forks, which are known to relocate to the nuclear envelope, may deform the inner nuclear membrane and promote lipid droplet formation at this site.

SMPD4, a sphingomyelinase which converts sphingomyelin into ceramide and phosphocholine, has been linked to congenital microcephaly [6]. This lipid enzyme localizes, different to other sphingomyelinases, at the endoplasmic reticulum and the nuclear envelope and interacts with nuclear pore complex components

[6-7]. Piet et al. now extend these observations by identifying additional nuclear pore complex components by BioID, most prominently Nup35, Nup155 and Aladin [8]. As Nup35 and Nup155 can deform membranes, crucial for nuclear pore complex formation, the authors speculate that SMPD4 supports this action by changing the local membrane curvature by its enzymatic action.

In a review, the same group expands on the idea that lipids and lipid metabolism at the nuclear envelope help shaping the nuclear pore membrane [9]. As some lipids have a cone or anti-cone-like shape it is conceivable that they shape if asymmetrically distributed along the membrane and between the lipid leaflets membranes into a concave or convex form. This could be especially important if lipid enzymes change the overall shape of lipids, in the case of a sphingomyelinase a cylindrical shaped sphingomyelin into a cone-like ceramide, and might thus support dynamic membrane curvature changes, which could be especially relevant during nuclear pore complex formation.

In a comprehensive review Dultz et al provide a topical overview on the architecture of nuclear pore complexes and their life cycle [10]. The review summarizes the current knowledge of how these giant complexes are assembled into the two membrane structure of the nuclear envelope and how these structures are remodeled, repaired and degraded.

Finally, Mitic et al [11] take a closer look Dictyostelium nuclear pore complexes by labeling individual components and following their fate through the cell cycle. The study indicates that some nuclear pore complex proteins leave this huge complex at the beginning of mitosis. Such a partial disassembly of nuclear pore complexes has been described for fungi such as Aspergilllus [12] and is there important to grant spindle components access to the nuclear interior during mitosis while the nuclear envelope remains largely intact.

Funding

WA acknowledges funding by the German Research Foundation [grant number DFG AN377/7-1] and SS by the Biotechnology and Biological Sciences Research Council [grant number BB/T005610/1].

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Burke, B.; Stewart, C. L., The nuclear lamins: flexibility in function. *Nat Rev Mol Cell Biol* **2013,** *14* (1), 13-24.10.1038/nrm3488
2. Sears, R. M.; Roux, K. J., Mechanisms of A-Type Lamin Targeting to Nuclear Ruptures Are Disrupted in LMNA- and BANF1-Associated Progerias. *Cells* **2022,** *11* (5).10.3390/cells11050865
3. Janssen, A. F. J.; Breusegem, S. Y.; Larrieu, D., Current Methods and Pipelines for Image-Based Quantitation of Nuclear Shape and Nuclear Envelope Abnormalities. *Cells* **2022,** *11* (3).10.3390/cells11030347
4. Fujimoto, T., Nuclear lipid droplets - how are they different from their cytoplasmic siblings? *J Cell Sci* **2022,** *135* (5).10.1242/jcs.259253
5. Kumanski, S.; Forey, R.; Cazevieille, C.; Moriel-Carretero, M., Nuclear Lipid Droplet Birth during Replicative Stress. *Cells* **2022,** *11* (9).10.3390/cells11091390

6. Magini, P.; Smits, D. J.; Vandervore, L.; Schot, R.; Columbaro, M.; Kasteleijn, E.; van der Ent, M.; Palombo, F.; Lequin, M. H.; Dremmen, M.; de Wit, M. C. Y.; Severino, M.; Divizia, M. T.; Striano, P.; Ordonez-Herrera, N.; Alhashem, A.; Al Fares, A.; Al Ghamdi, M.; Rolfs, A.; Bauer, P.; Demmers, J.; Verheijen, F. W.; Wilke, M.; van Slegtenhorst, M.; van der Spek, P. J.; Seri, M.; Jansen, A. C.; Stottmann, R. W.; Hufnagel, R. B.; Hopkin, R. J.; Aljeaid, D.; Wiszniewski, W.; Gawlinski, P.; Laure-Kamionowska, M.; Alkuraya, F. S.; Akleh, H.; Stanley, V.; Musaev, D.; Gleeson, J. G.; Zaki, M. S.; Brunetti-Pierri, N.; Cappuccio, G.; Davidov, B.; Basel-Salmon, L.; Bazak, L.; Shahar, N. R.; Bertoli-Avella, A.; Mirzaa, G. M.; Dobyns, W. B.; Pippucci, T.; Fornerod, M.; Mancini, G. M. S., Loss of SMPD4 Causes a Developmental Disorder Characterized by Microcephaly and Congenital Arthrogryposis. *American journal of human genetics* **2019,** *105* (4), 689-705.10.1016/j.ajhg.2019.08.006
7. Cheng, L. C.; Baboo, S.; Lindsay, C.; Brusman, L.; Martinez-Bartolomé, S.; Tapia, O.; Zhang, X.; Yates, J. R., 3rd; Gerace, L., Identification of new transmembrane proteins concentrated at the nuclear envelope using organellar proteomics of mesenchymal cells. *Nucleus* **2019,** *10* (1), 126-143.10.1080/19491034.2019.1618175
8. Piët, A. C. A.; Post, M.; Dekkers, D.; Demmers, J. A. A.; Fornerod, M., Proximity Ligation Mapping of Microcephaly Associated SMPD4 Shows Association with Components of the Nuclear Pore Membrane. *Cells* **2022,** *11* (4).10.3390/cells11040674
9. Peeters, B. W. A.; Piët, A. C. A.; Fornerod, M., Generating Membrane Curvature at the Nuclear Pore: A Lipid Point of View. *Cells* **2022,** *11* (3).10.3390/cells11030469
10. Dultz, E.; Wojtynek, M.; Medalia, O.; Onischenko, E., The Nuclear Pore Complex: Birth, Life, and Death of a Cellular Behemoth. *Cells* **2022,** *11* (9).10.3390/cells11091456
11. Mitic, K.; Grafe, M.; Batsios, P.; Meyer, I., Partial Disassembly of the Nuclear Pore Complex Proteins during Semi-Closed Mitosis in Dictyostelium discoideum. *Cells* **2022,** *11* (3).10.3390/cells11030407
12. De Souza, C. P.; Osmani, A. H.; Hashmi, S. B.; Osmani, S. A., Partial nuclear pore complex disassembly during closed mitosis in Aspergillus nidulans. *Curr Biol* **2004,** *14* (22), 1973-84