

SPOTLIGHT

How to unravel a basket: NPC reorganization during meiosis

Annemiek C. Veldsink¹ and Liesbeth M. Veenhoff¹

While our understanding of the nuclear pore complex (NPC) structure is progressing spectacularly, the organizational principles of its nuclear basket remain elusive. In this issue, King et al. (2022. *J. Cell Biol.* <https://doi.org/10.1083/jcb.202204039>) provide new insights into the mechanisms that govern nuclear basket reorganization during meiosis.

The nuclear pore complex (NPC) is one of the largest protein complexes in eukaryotic cells, and recent advances have solved its structure in great detail. However, the organizational principles of two NPC domains have remained enigmatic: the central channel, made up by intrinsically disordered FG-nucleoporins (FG-Nups), and the nuclear basket, composed of the five nucleoporins Nup60, Nup2, Nup1, Mlp1, and Mlp2 (Fig. 1).

Multiple studies highlight that the NPC architecture on the nuclear side is modular and dynamic (2, 3 and references therein). Basket nucleoporins are among the most frequently exchanged nucleoporins and posttranslational modifications like SUMOylation, ubiquitylation, and acetylation can promote dissociation of individual basket nucleoporins from the NPC. In fact, at any point in time, a significant fraction of NPCs does not contain all five basket nucleoporins. Absence or displacement of basket proteins is characteristic for certain yeast NPC subpopulations, including nucleolar NPCs, NPCs that tether heterochromatin or extrachromosomal DNA circles, and newly assembled NPCs. However, how the dynamic association of basket nucleoporins with the NPC is regulated in time is far from understood.

In this issue, King et al. (1) explore the dynamics of the nuclear basket during yeast meiosis. The authors follow up on their earlier observation that the yeast nuclear basket proteins detach from the NPC core

upon meiotic entry (4). During meiosis, the NPC core proteins are sequestered to the Gametogenesis Uninherited Nuclear Compartment (GUNC) where they are ultimately degraded, while the basket nucleoporins return to the nascent gametes. To gain insight into the mechanisms that regulate basket detachment and inheritance, the authors followed the localization of various nucleoporins with high resolution and live-cell imaging experiments. Intriguingly, the meiotic relocalization of nuclear basket proteins follows a two-step mechanism in which the basket proteins do not exhibit uniform behavior (Fig. 1). In meiosis I, the nuclear basket proteins Nup60 and Nup2 transiently detach from the NPC core and return to the nuclear periphery at the end of meiosis I. Interestingly, only some of the nuclear basket proteins displayed this behavior, as the basket proteins Mlp1 and Nup1 showed respectively no or minor relocalization in this timeframe. In meiosis II, in line with previous work from the same group (4), all basket nucleoporins detach from the periphery and return to the gamete nuclei. Thus, the individual basket nucleoporins are subject to distinct regulatory events in meiosis I and II.

The precise timing of Nup60 and Nup2 detachment in meiosis I suggested that meiotic basket remodeling may be regulated by cell cycle kinases. Using several kinase mutants that stall meiotic progression, King et al. show that the polo-like kinase Cdc5 drives the

detachment of Nup60 from the NPC. In particular, by employing an unbiased SWAT-MS proteomics approach, the authors mapped Cdc5-dependent phosphorylation sites across the proteome and attribute Nup60/Nup2 detachment to Cdc5-dependent phosphorylation of several phosphosites in the N-terminus of Nup60. Phosphorylation of these residues, which overlap with a region that mediates the binding of Nup60 to the NPC core (5), functions as a molecular switch for releasing Nup60 and Nup2 from the NPC.

The N-terminus of Nup60 also contains an amphipathic helix that directly interacts with the inner nuclear membrane (5). Since Nup60 and Nup2 reattached to the nuclear envelope at the end of meiosis I, the authors hypothesized that this amphipathic helix may become important for its relocalization to the nuclear periphery. Nup60 mutants that either lack the amphipathic helix or fail to bind the membrane due to a point mutation displayed similar meiotic detachment as endogenous Nup60, but failed to reattach to the nuclear envelope after meiosis I. Consequently, all nuclear basket subunits, but not nucleoporins from the NPC core, mislocalized in gametes. In line with Nup60 serving as an important linker protein in the basket (6), the N-terminal region of Nup60 thus plays a crucial role in both unraveling and reconstructing the nuclear basket after meiosis.

Since King et al. show that the non-uniform regulation of individual basket

¹European Research Institute for the Biology of Ageing, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.

Correspondence to Liesbeth M. Veenhoff: lm.veenhoff@rug.nl.

© 2023 Veldsink and Veenhoff. This article is distributed under the terms of an Attribution–Noncommercial–Share Alike–No Mirror Sites license for the first six months after the publication date (see <http://www.rupress.org/terms/>). After six months it is available under a Creative Commons License (Attribution–Noncommercial–Share Alike 4.0 International license, as described at <https://creativecommons.org/licenses/by-nc-sa/4.0/>).

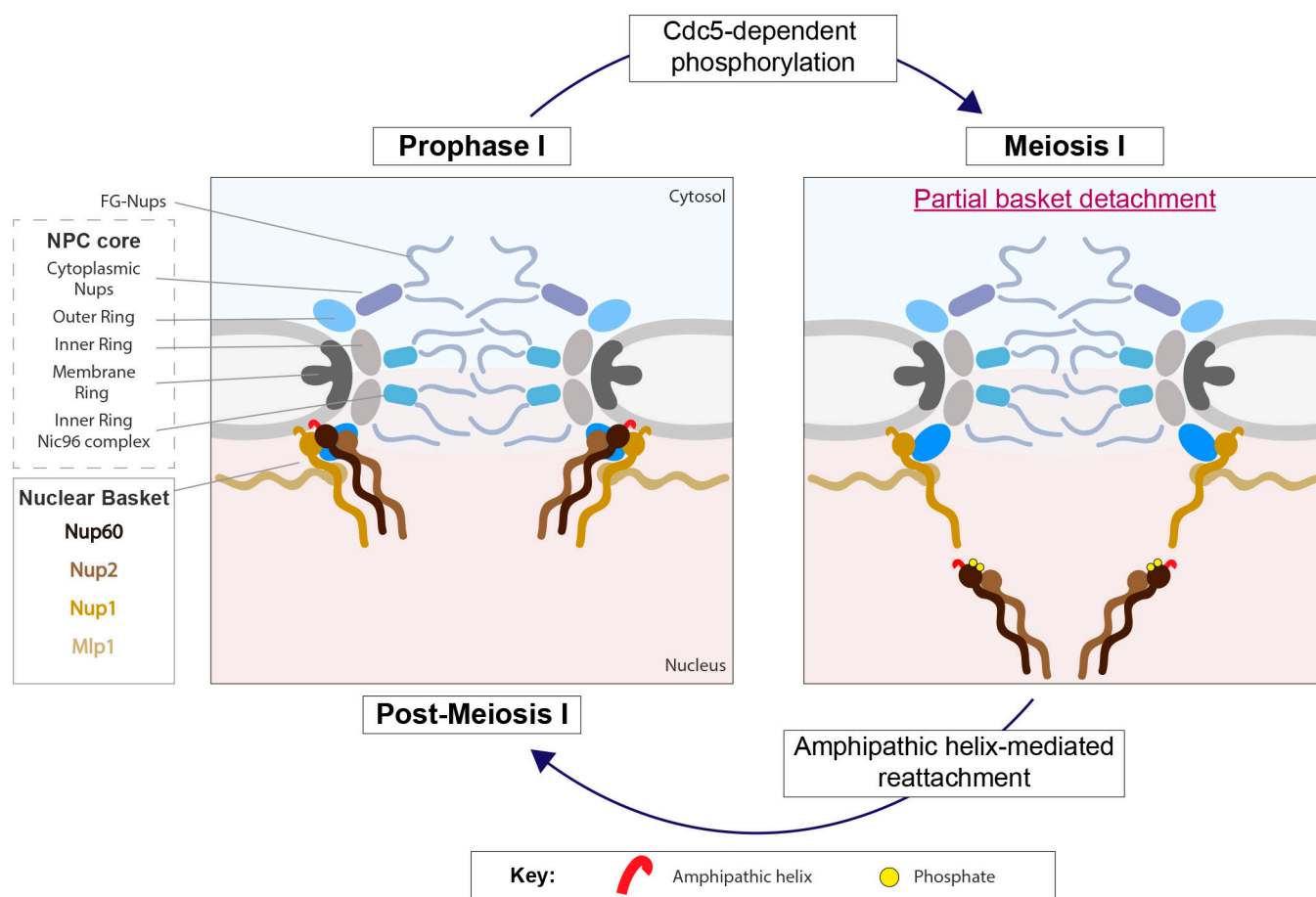


Figure 1. **Remodeling of the NPC's nuclear basket structure in meiosis I as proposed by King et al (1).** In prophase I, all basket proteins (depicted in brown) are attached to the NPC core (depicted in blue/gray). Meiotic activation of the polo-like kinase Cdc5 drives phosphorylation of the N-terminus of Nup60 (yellow dots), which causes detachment of Nup60 and Nup2 but not Nup1 and Mlp1. Nup60 and Nup2 reattach to the nuclear periphery at the end of meiosis I, through a process that is driven by an amphipathic helix in Nup60 (depicted in red). Mlp2 is not included in this model.

nucleoporins is conserved in fission yeast meiosis, it raises the question why only part of the basket transiently detaches from the NPC. One may speculate that releasing part of the basket may allow attachment of other nuclear structures, driving NPC specialization toward scaffolding functions, or, it may be needed to detach NPCs from nuclear envelope-anchored structures such as chromatin. A more comprehensive phenotyping of the Nup60 mutants that are unable to detach or reattach, as developed in this study, may provide answers. Another equally intriguing question is why basket nucleoporins, but not core NPC components, are inherited by the gametes. Due to their dynamic nature, the basket nucleoporins are likely the youngest part of the NPC and may therefore be less prone to damage than the long-lived nucleoporins from the NPC scaffold or the aggregation-prone FG-Nups in the NPC central channel. Hence a mechanism for their clearance during the rejuvenating meiotic process may

not have evolved. Alternatively, the inheritance of baskets may serve a function, for example in nuclear envelope reorganization or, as also mentioned by the authors, as a cue for NPC reassembly.

The behavior of Nup60 during meiosis shows interesting parallels with replicative aging yeast cells: Nup60 is displaced from those NPCs that scaffold age-related extra-chromosomal DNA circles (7), Nup60 protein levels decline in aging (8), and mutants that lack Nup60 age more rapidly (7). Finding causal relationships in ageing research is often difficult, but a comparison of NPC structures in replicative aging and meiosis, using similar elegant strategies as used by King et al. and possibly complemented with biochemical studies, could be helpful. Altogether, the work by King et al. inspires future studies to better understand how basket composition relates to specific NPC functions in meiosis and other

biological contexts in which the basket is partially assembled.

Acknowledgments

The authors declare no competing financial interests.

References

1. King, G.A., et al. 2022. *J. Cell Biol.* <https://doi.org/10.1083/jcb.202204039>
2. Dultz, E., et al. 2022. *Cells.* <https://doi.org/10.3390/cells1091456>
3. Fernandez-Martinez, J., and M.P. Rout. 2021. *Trends Biochem. Sci.* <https://doi.org/10.1016/j.tibs.2021.01.003>
4. King, G.A., et al. 2019. *Elife.* <https://doi.org/10.7554/eLife.47156>
5. Mészáros, N., et al. 2015. *Dev. Cell.* <https://doi.org/10.1016/j.devcel.2015.02.017>
6. Cibulka, J., et al. 2022. *Sci. Adv.* <https://doi.org/10.1126/sciadv.abl6863>
7. Meinema, A.C., et al. 2022. *Elife.* <https://doi.org/10.7554/eLife.71196>
8. Rempel, I.L., et al. 2019. *Elife.* <https://doi.org/10.7554/eLife.48186>