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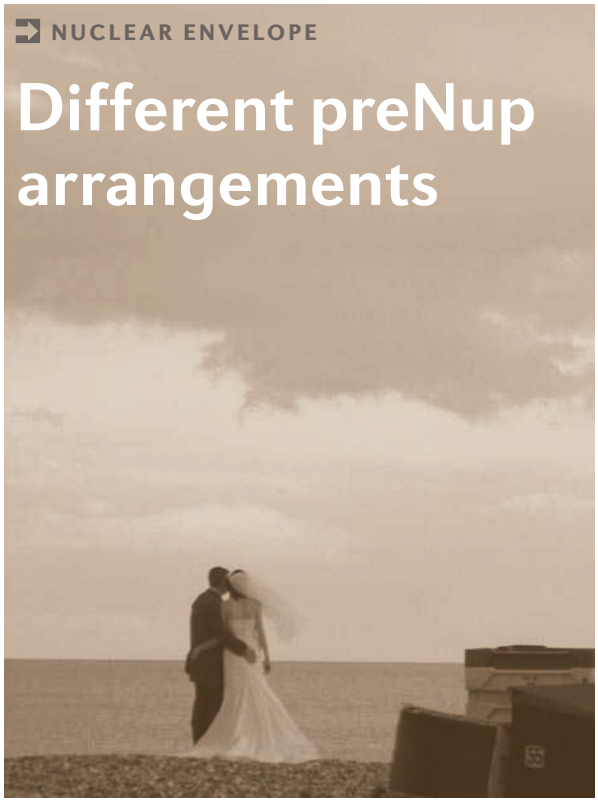
NUCLEAR ENVELOPE

Different preNup arrangements



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> the cell cycle determines which Nup is involved in NPC formation

Nuclear pore complexes (NPCs), comprising many nucleoporins (Nups), are embedded in the nuclear envelope and function as nucleus–cytoplasm channels. NPC assembly in metazoans occurs during two different cell cycle phases. At the end of mitosis, NPCs assemble in a reforming nuclear envelope, and in interphase they form in a growing intact nuclear envelope. Doucet *et al.* now show that the cell cycle determines which Nup is involved in NPC formation: post-mitotic NPC assembly requires the Nup ELYS, whereas interphase NPC assembly requires the transmembrane Nup POM121 and a membrane curvature sensor domain of NUP133.

Using RNA interference, the authors show that NPCs still form in the absence of ELYS or POM121, albeit at reduced levels, and that knockdown of both Nups has an additive inhibitory effect. As ELYS recruits the NUP107–160 complex (an essential NPC component, comprising nine Nups) to post-mitotic chromatin, the ELYS-independent NPC formation probably occurs during interphase. Indeed, ELYS knockdown reduced the number of NPCs in G1 phase of the cell cycle but did not affect NPC doubling in interphase. Furthermore, cytosolic ELYS depletion in a *Xenopus* egg extract system inhibited NPC formation in a reforming but not an intact nuclear envelope. Thus, ELYS is dispensable for interphase NPC formation but is required to recruit NUP107–160 to post-mitotic (and therefore accessible) chromatin.

By contrast, POM121 knockdown did not affect G1 NPCs but inhibited NPC assembly in interphase. POM121 was found to have a working nuclear localization signal (NLS) that is required for its function, as POM121-depleted cells rescued with a POM121 NLS mutant still showed a block in interphase NPC assembly. In addition, POM121 knockdown prevented the recruitment of NUP107 to the nuclear envelope, suggesting that POM121 precedes NUP107–160 in NPC assembly during interphase. Indeed, POM121 was shown to be involved in the formation of a prepore in intact nuclear envelopes at the sites of NPC formation.

The fusion of the inner and outer nuclear membranes, which is required for the formation of a channel across the double membrane nuclear envelope, results in membrane curvature. This might be detected by the membrane curvature sensor domain (known as ALPS) of NUP133, a component of the NUP107–160 complex. NUP133 with a mutated ALPS domain mislocalized to the cytoplasm (where it colocalized with NUP107) and showed reduced NPC incorporation in interphase but not after mitosis. Furthermore, NUP133-depleted cells rescued with the NUP133 mutant had defective NPC assembly during interphase and increased numbers of NPC formation sites that contained POM121 without NUP133. This confirms that POM121 precedes NUP107–160 recruitment in interphase NPC assembly and that a functional membrane curvature sensor is required for NUP107–160 recruitment to new pore sites in interphase.

Therefore, interphase and post-mitotic NPC assembly are mechanistically distinct and accommodate the differences in nuclear envelope topology at these cell cycle stages. As ELYS, NUP133 and POM121 are conserved among metazoans, it will be interesting to see whether these distinct mechanisms occur in all species that undergo open mitosis.

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ORIGINAL RESEARCH PAPER Doucet, C. M. *et al.* Cell cycle-dependent differences in nuclear pore complex assembly in metazoa. *Cell* **141**, 1030–1041 (2010)
FURTHER READING Strambio-De-Castillia, C, Niepel, M. & Rout, M. P. The nuclear pore complex: bridging nuclear transport and gene regulation. *Nature Rev. Mol. Cell Biol.* **11**, 490–501 (2010)