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Nup62: A novel regulator of centrosome integrity and function

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Nucleoporins are the constituents of the nuclear pore complex (NPC), the large transport channel that regulates molecular trafficking across the nuclear envelope. Each mammalian NPC is an ~60–125 MDa multiprotein assembly built from multiple copies of ~30 different nucleoporins.[1] In addition to their role in nucleocytoplasmic transport, the NPC and its components have been implicated in a variety of other cellular processes, ranging from gene expression regulation to cytoskeleton organization. Importantly, some of these roles have been attributed to nucleoporins located outside of the NPC, indicating that they can function independently of this structure.

In higher eukaryotes, the nuclear envelope breaks down during prometaphase, causing NPCs to disassemble into nucleoporin subcomplexes. These complexes are then reused to build NPCs in the newly formed nuclear envelopes. But a growing body of evidence indicates that nucleoporins do not just sit in the mitotic cytoplasm waiting to be reassembled into NPCs; in fact, they act as critical regulators of a number of mitotic events that ensure high-fidelity chromosome segregation, and thereby prevent aneuploidy. These include formation of a bipolar mitotic spindle; establishment of stable kinetochore-microtubule attachments; kinetochore assembly; timely chromosome segregation; and correct localization of spindle assembly checkpoint proteins.[1] Although depletion or overexpression of a number of nucleoporins causes multipolar spindles,[2-4] a phenotype frequently associated with supernumerary centrosomes, whether nucleoporins actively participate in centrosome biogenesis was unknown. Now, work from the Wong group highlights a critical role for nucleoporin Nup62 in this process.[5]

The centrosome is a cytoplasmic, nonmembranous organelle composed of 2 orthogonally arranged barrel-shaped structures, the centrioles, each encircled by 9 triplet microtubules and an electron-dense matrix in which the centrioles are embedded, termed pericentriolar material (PCM).[6] As the major microtubule-organizing center in animal cells, the centrosome nucleates and anchors the interphase and mitotic microtubule arrays. The centrosome also contributes to cytokinesis and subsequent cell cycle progression, as well as to spindle positioning.[6] Centrosomes divide once per cell cycle, in a mechanism that is intimately connected to centriole duplication. A G_1 cell typically contains one pair of centrioles, which duplicate in S phase giving rise to 2 pairs. The 2 pairs of centrioles remain together through G_2, where they recruit additional PCM proteins in a process called centrosome maturation. During prophase, they start migrating to opposite poles to assemble the mitotic spindle.

Using an siRNA-mediated approach to reduce Nup62 expression in HeLa cells, Hashizume and Moyori observed a significant increase in the number of multinucleated cells, which was associated with a cell cycle arrest at the G_2/M phase and increased cell death.[5] Electron microscopy analysis of Nup62-depleted cells showed normal NPC morphology, leading the authors to propose an NPC-independent role for this nucleoporin in cell cycle regulation. Strikingly, Nup62-depleted interphase cells displayed aberrant centrosomes, consisting of 3 centrioles, instead of the pair characteristic of normal cells, suggesting centriole duplication defects. Moreover, Nup62 depletion induced centrosome amplification, multipolar spindle formation, improper spindle orientation, and alterations in microtubule polymerization.[5] But how does Nup62 regulate centrosome homeostasis? The authors found that Nup62 localized to centrosomes/spindle poles via its C-terminal domain, where it associated with the centrosomal proteins gamma-tubulin and hSAS-6, and that its depletion caused mislocalization of several centrosomal components. This suggests that Nup62 is involved in the recruitment of critical proteins to the centrosome. Altogether, these results provide the first compelling evidence for a nucleoporin as a key regulator of centrosome biogenesis and maturation.[5]

An important task for the future is to define the detailed molecular mechanism through which Nup62 exerts these effects. As suggested by the authors, Nup62 may be acting through its interacting partner SAS-6, a protein required for centrosome duplication.[7] It will also be interesting to determine if other members of the Nup62 complex (Nup45, Nup54, and Nup58) are centrosomal and/or involved in regulating centrosome homeostasis. In *C. elegans,* spindle orientation defects were found after depletion of the Nup62 complex homologs,[8] suggesting that these proteins play mitotic roles. Finally, supernumerary centrosomes and multipolar spindles may also arise from perturbations of microtubule dynamics, and it would be exciting to investigate whether Nup62 is involved in this process.

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