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The nuclear arsenal of cilia

Colin A. Johnson[1*] & Jarema J. Malicki[2†]

* Lead contact

† Dr. Malicki passed away on 4th January 2019 during the preparation of this manuscript. His obituary has recently been published in the journal *Development* http://dev.biologists.org/content/146/4/dev176677 which describes some of his pioneering work on vertebrate retinogenesis and ciliary function.

[1] Leeds Institute of Medical Research
The University of Leeds
Beckett Street
Leeds, LS9 7TF
United Kingdom

tel: +44 (0)113 343 8443
email: c.johnson@leeds.ac.uk

[2] Bateson Centre &
The Department of Biomedical Science
The University of Sheffield
Western Bank
Sheffield, S10 2TN
United Kingdom

tel: +44 (0)114 222 4638
e-mail: jmalicki@sheffield.ac.uk

Several recent studies have revealed that nuclei and cilia share molecular components implicated in DNA damage response, splicing, gene expression and sub-compartmentalization of the cell. We review evidence that exchange of components between the nucleus and cilia is facilitated by the centrosome, which contributes both to the mitotic apparatus of the nucleus and to cilia structure. Moreover, the centrosome and the pericentriolar material form condensates that share components with stress granules and P-bodies, membrane-less organelles enriched in RNA and RNA-processing proteins. These features may largely explain the origin of similar molecular mechanisms in nuclei and cilia.

Cilia are finger-like protrusions that extend from the surface of most vertebrate cells. Their formation is intimately associated with centrosomes, which consist of two centrioles surrounded by pericentriolar material. Centrioles share with cilia the 9-fold rotational symmetry of microtubule cytoskeleton. The behaviour of both cilia and centrosomes is closely related to the cell cycle. For example, the timing of centriolar duplication and centrosome migration to the cell surface are associated with cell cycle phase: the synthesis of new centrosomes begins during S-phase and they translocate to the cell surface during G1/G0. In the course of migration to the cell surface, centrosomal microtubules extend apically forming the main structural feature of the cilium, the axoneme. During G0, the centrosome remains attached to the cell membrane at the ciliary base and continues providing support for the cilium, thereby acting as the ciliary basal body at this stage (**Figure 1A**). Following re-entry into the cell cycle, the ciliary axoneme is resorbed and the basal body no longer provides structural support for the cilium. It moves away from the cell surface into the cytoplasm, and during mitosis localizes to a spindle pole.

The idea that nucleic acids reside and function in the centrosome, and mediate centriolar duplication, is at least half a century old (reviewed in Marshall and Rosenbaum, 1999). More recently, centrosomes isolated from the oocytes of the surf clam *Spisula solidissima* were found to contain unique RNAs, termed centrosomal RNAs (cnRNA) (Alliegro et al., 2006), although it was feasible that these RNAs were unintentionally carried over into the centrosome preparations. These and other findings have led to the unorthodox propositions that, evolutionarily, centrioles arose from the integration of RNA viruses or bacterial endosymbionts (Chapman et al., 2000; Went, 1977). While such views may be overly speculative, various lines of puzzling evidence continue to link centrosomes and cilia to nucleic acid metabolism and nuclear functions. Here we discuss the recent evidence that ciliary proteins mediate processes in the nucleus such as DNA damage response (DDR) and gene expression. Conversely, proteins commonly thought to

mediate core nuclear functions, such as splicing factors, appear to also function in cilia. Furthermore, the molecular machinery that mediates sub-compartmentalization, and regulates selective trafficking at sub-compartment boundaries, is also shared between nuclei and cilia.

Roles for cilia and centrosomal proteins in DNA damage response

Several recent studies demonstrated that, unexpectedly, some centrosomal proteins re-localize to nuclear foci in response to DDR-inducing genotoxic stress. The best-described example is the centrosomal protein CEP164, which mediates the assembly of distal appendages in the mature mother centriole, initiating subsequent ciliogenesis (Cajanek and Nigg, 2014). For the purposes of definition and clarity, the acronyms and recommended full names of all proteins discussed in the text are listed in **Table 1**, in addition to brief descriptions of their localizations and functions. Interestingly, CEP164 also re-localises to sites of UV-induced DNA damage (Pan and Lee, 2009) and is phosphorylated *in vitro* and *in vivo* by the ataxia telangiectasia-mutated (ATM) and ATM/Rad3-related (ATR) DDR-associated kinases in response to DNA damage induced by UV, replication stress and ionizing radiation (Sivasubramaniam et al., 2008). CEP164 phosphorylation is associated with the establishment of a G2/M damage checkpoint. However, although there is concomitant activation of the checkpoint kinases CHK1 and CHK2 (Pan and Lee, 2009; Sivasubramaniam et al., 2008), it remains unclear if CEP164 phosphorylation is causal in mediating a specific DDR signaling pathway or, indeed, is even required for DDR (Daly et al., 2016).

In addition to CEP164, several other centrosomal/centriolar proteins that mediate ciliogenesis, including CEP290 and SDCCAG8 (also known as NPHP10), can re-localize to nuclei (**Figure 1A**) in response to DNA damage-induced replicative stress (Chaki et al., 2012; Slaats et al., 2015). Furthermore, the core centriolar protein centrin-2 appears to re-localize and directly interact with XPC, the key recognition component of the nucleotide excision repair system, at specific UV-induced DNA repair foci (Nishi et al., 2013; Renaud et al., 2011). These observations suggest the existence of a general mechanism that re-localizes centriolar protein in response to DNA damage. Several other centriolar proteins (CEP131/AZI1, CEP290 and PCM1) are dispersed from the centriolar satellites (but do not appear to re-localize in nuclei) under conditions of DNA damage such as exposure to UV, which promote cilia formation through mechanisms that remain unclear (Villumsen et al., 2013). Similarly, centrosomal protein CEP63 has been identified as an ATM and ATR substrate, with phosphorylation causing dispersion from the centrosome (Smith et al., 2009). Since both the DDR kinases (ATM and ATR) and the checkpoint kinases (CHK1 and CHK2) localize to centrosomes in response to DNA damage

(reviewed in Mullee and Morrison, 2016), it seems likely that other centrosomal proteins are dispersed or re-localized in response to the DDR signaling mediated by these kinases. However, it remains to be determined if centrosomal/centriolar proteins, other than CEP164 and CEP63, are direct substrates of these kinases. How phosphorylation could regulate protein re-localization into different subcellular compartments, and whether re-localization of these proteins this has any direct functional relevance for DDR, also still needs to be determined in mechanistic detail.

Splicing factors, RNA processing and translation at the ciliary apparatus?

Even more puzzling are recent observations that spliceosomal proteins, specifically a group of pre-RNA processing factors (PRPFs) that are expected to localize to nuclei, also localize to the ciliary basal body or the centrosome (**Figure 1A**) and promote ciliogenesis (Wheway et al., 2015). Mutations in several of these PRPFs (PRPF6, PRPF8, and PRPF31), and other PRPFs for which cilia association is less clear (PRPF3, PRPF4 and SNRNP200), cause autosomal dominant forms of retinitis pigmentosa (RP), a comparatively common inherited retinal blindness often associated with ciliary defects (Mordes et al., 2006). All RP-related PRPFs stabilize or mediate the incorporation of the U4/U6.U5 tri-snRNP (small nuclear ribonucleoprotein) subunit into the activated spliceosome, the large RNP complex that catalyses pre-mRNA splicing and produces protein isoform diversity by alternative splicing (Tanackovic et al., 2011). However, spliceosome components other than RP-related PRPFs do not appear to localize to the ciliary basal body (Wheway et al., 2015), implying that PRPFs may have cytoplasmic roles that are spatially restricted to the ciliary apparatus but are unrelated to splicing.

Extra-nuclear ciliary functions of PRPFs are also supported by the dual functions of another splicing factor, polyglutamine-binding protein 1 (PQBP1), in both RNA processing and ciliogenesis. PQBP1, a nuclear protein mutated as a cause of X-linked intellectual disability and neurodegenerative disorders, interacts with many splicing factors (including the U2 snRNP component SF3B1, as well as PRPF6, PRPF8, PRPF19 and PRPF31) and regulates neuronal alternative splicing programmes that are specifically associated with neurite outgrowth (Wang et al., 2013). Interestingly, PQBP1 also localizes at the base of neuronal cilia and is required for ciliogenesis in post-mitotic neurons (Ikeuchi et al., 2013).

Further evidence for cytoplasmic roles of RP-related PRPFs is provided by studies of stress granules, dynamic cytoplasmic structures containing mRNPs stalled during translation initiation (Protter and Parker, 2016). PRPF8 and SNRNP200 (also known as BRR2 or U5-200KD) interact with SND1 (staphylococcal nuclease and tudor domain-containing 1, also

known as p100) (Yang et al., 2007), a major component of stress granules (Shao et al., 2017). By analogy with other splicing factors, such as the serine-arginine (SR) family of RNA binding proteins (Twyffels et al., 2011), the cytoplasmic functions of PRPFs at stress granules and the ciliary base (**Figure 1A**) may include roles in ribostasis (transcriptome homeostasis), specifically the surveillance of unspliced pre-mRNAs and the control of mRNA stability and translation.

In an interesting set of parallel observations, P-bodies (cytoplasmic bodies that participate in mRNA processing and degradation, and share components with stress granules) appear to co-localize with either centrosomes (Aizer et al., 2008) or ciliary basal bodies (Moser et al., 2011) (**Figure 1A**). A recent proteomics study has also identified centrosomal proteins (including CEP192, OFD1, PCM1 and CEP131/AZI1) in P bodies (Youn et al., 2018) (**Figure 1A**). It remains to be seen whether the RNA processing functions of P bodies are spatially restricted to the ciliary apparatus or have any functional role in ciliogenesis. Even more speculative is the possibility that localized protein translation is also associated with the centrosome. Recent work has demonstrated that several translation initiation factors (eIF3B, eIF3G, eIF4A1, eIF4E and eIF4G) localize to the centrosome, and, conversely, the centrosomal protein OFD1 interacts with components of the preinitiation and eIF4 complexes (Iaconis et al., 2017). An attractive function for centrosomal translation would be to facilitate localized "on-demand" translation of ciliary proteins during ciliogenesis, but this hypothesis has still to be tested.

Cilia and nuclear transport: from the unexpected to the predictable?

A striking connection between cilia and the nucleus are similarities between the transport mechanisms that translocate proteins from the cytoplasm into either the nuclear or ciliary compartments. The idea of similarity between the nuclear pore and the base of cilia, the so-called "flagellar pore", was originally inspired by the similarity in the shape and size of the two structures (Rosenbaum and Witman, 2002). One of the first pieces of evidence that nuclear transport mechanisms function in cilia came from observations that a nuclear localization signal (NLS), importin-β2 and a gradient of Ran-GTP mediates the ciliary entry of the kinesin KIF17 (Dishinger et al., 2010). Ran, a small GTPase, is a key mediator of nuclear transport and this study suggested that GTP-bound Ran releases importin cargo in both the nuclear and ciliary compartments (**Figure 2**). Furthermore, nucleoporins (NUPs) were also found at the cilia base (**Figure 1A, Figure 2**) and appeared to co-localize with the centrosomal/centriolar protein, CEP290 (Kee et al., 2012). NUPs are subunits of the nuclear pore, a doughnut-shaped transport channel with 8-fold symmetry that connects the cytoplasm and nucleus (Bui et al., 2013;

Kosinski et al., 2016). The key functional element of the nuclear pore is formed by so-called FG-NUPs, named after intrinsically disordered domains rich in phenylalanine-glycine (FG) repeats. The FG domains project into the centre of the nuclear pore, where they are thought form a stable condensate or hydrogel (**Figure 1B**; see below). The seemingly amorphous tangle of FG domains appears to confer size selectivity of the nuclear pore (reviewed in Schmidt and Görlich, 2016). Although the nuclear pore diameter of 60-80 nm on the outside and 40 nm in the centre is substantially smaller than the 250-300 nm width of the ciliary axoneme (Hezwani and Fahrenkrog, 2017), it is tempting to imagine circular assemblies of nucleoporins at the cilia base that also confer selectivity during ciliary protein transport. Two configurations have been proposed: a single nucleoporin ring that surrounds microtubule doublets at the ciliary base or, alternatively, nine small rings inserted between the Y-shaped links of the ciliary transition zone (Kee and Verhey, 2013).

Analysis of nucleoporin architecture at the cilia base has, however, proved to be challenging and the most significant difficulty in building a model of nucleoporin function at the ciliary base is the lack of sound understanding of where FG-NUPs localize. Unlike some sub-complexes of the nuclear pore (Bui et al., 2013), components of the ciliary transition zone have not been purified and cryoelectron tomography has not yet been successfully performed on structures that contribute to the cilia base. Super-resolution microscopy is perhaps the best route to analyse structures at the base of the ciliary axoneme. Indeed, the application of 4Pi single-molecule localization microscopy revealed that NUP188 localizes to two barrel-shaped cylinders, large enough to encapsulate the basal body and the daughter centriole (del Viso et al., 2016) (**Figure 1A**). This localization is, however, inconsistent with the models discussed above. The picture is complicated further by lack of clarity as to which nucleoporins localize to cilia. Whilst several groups localized cytoplasmic FG (214), outer ring (37, 85), inner ring (35, 188), linker (93), and central FG (62, 98) NUPs to the ciliary base (del Viso et al., 2016; Endicott and Brueckner, 2018; Kee et al., 2012; Takao et al., 2017), others failed to detect some of the same molecules in cilia (Breslow et al., 2013; del Viso et al., 2016). Furthermore, to function as a diffusion barrier, FG domains would most likely project into a transport channel at the ciliary base, but this is inconsistent with the barrel-shaped localizations observed by super-resolution microscopy (del Viso et al., 2016).

However, evidence continues to accumulate that nucleoporins contribute to ciliary transport. In the initial study, interference using an antibody against the FG motifs of NUPs impaired KIF17 transport into cilia (Kee et al., 2012). Subsequently, a more sophisticated assay

that involved clogging of the presumptive ciliary transport entry route by forced dimerization of NUP62, also impaired transport of cytosolic proteins, including KIF17, into the ciliary compartment (Takao et al., 2014). Consistent with this observation, knockdowns of NUP98 and NUP85 increased the permeability of the diffusion barrier that gates entry into the ciliary compartment (Endicott and Brueckner, 2018). In contrast to these studies, ciliary compartment-directed trafficking was unaffected by either cyclohexanediol, a compound that disrupts nuclear pore FG hydrogel (see below), or a truncated form of importin β (Breslow et al., 2013). As both of these methods can be effectively used to manipulate nuclear transport, these observations suggest that nuclear transport machinery functions differently in cilia. Even if FG-NUPs do not form a diffusion barrier, they could still function in other ways. Recent studies have confirmed that importin contributes to the transport of ciliary cargoes GLI2 and KIF17 (Funabashi et al., 2017; Han et al., 2017). As importin interactions with FG-NUPs are well-documented (reviewed in Christie et al., 2016), it seems reasonable that NUPs could function in cilia as importin docking sites. This could facilitate interactions with the ciliary transport machinery rather than contribute to the diffusion barrier.

Why are NUPs and other nuclear transport proteins found at the cilia base? This is perhaps not entirely surprising considering that nuclei and cilia are two cellular sub-compartments that disassemble during cell division, a characteristic not shared by other membrane-bound organelles such as mitochondria, lysosomes or the Golgi apparatus, which may undergo morphological transformations but retain the status of cellular subcompartments during cell division. Disassembly facilitates the exchange of components between the nuclear and ciliary compartments and, moreover, the centrosome functions in both nuclear division and ciliogenesis. As outlined above, during G0, the centrosome migrates to the cell surface and provides the template for ciliary axoneme elongation, whereas during mitosis it interacts first with the nuclear envelope and then with nucleic acids by contributing to mitotic spindle formation. Given its dual role, it is easy to imagine that in the course of evolution the centrosome may have facilitated exchange of functional elements between the nucleus and cilia. This is supported by observations that several nucleoporins localize to centrosomes during mitosis (**Figure 2**), where they appear to have regulatory functions. NUP62, NUP188 and NUP358/RanBP2 all translocate to the centrosome during mitosis and affect mitotic spindle formation (Hashizume et al., 2013a; Hashizume et al., 2013b; Itoh et al., 2013). Depletion of NUP62 results in the appearance of centrosomes containing abnormally shaped supernumerary centrioles associated with the formation of multipolar spindles during cell division (Hashizume et al., 2013b). NUP188, on the other hand, co-localizes with NuMA, a protein that tethers mitotic

spindle microtubules to spindle poles, and its knockdown results in chromosome misalignment (Itoh et al., 2013). Two other nucleoporins, Tpr and Aladin, localize Aurora A kinase to spindle poles during mitosis (Carvalhal et al., 2015; Kobayashi et al., 2015). As NuMA is an Aurora A kinase substrate, these nucleoporins may also contribute to spindle formation by enhancing NuMA activity. Furthermore, in G2 and early in mitosis, NUP358 mediates the association of the centrosome with the nuclear envelope (Splinter et al., 2010).

Other components of the nuclear transport machinery also localize to the centrosome. These include importins, exportins and their regulator Ran, which appears to be tightly associated with the centrosome throughout the cell cycle (reviewed in Lavia, 2016). Together with importins and exportins, which are also targeted to spindle poles, Ran regulates several aspects of centrosome function, including microtubule nucleation by NuMA (Lavia, 2016). In addition to centrosomal functions, Ran, importins and NUPs are key mediators of kinetochore assembly during mitosis (reviewed in Forbes et al., 2015). Since Ran localizes to centrosomes throughout the cell cycle, its presence in the ciliary basal body and cilia is not only unsurprising but to be expected. The same point can be made about NUPs and other nuclear pore components that localize to centrosomes during cell division. In evolutionary terms, the centrosome may therefore provide a bridging mechanism that exchanges functional elements between the ciliary and nuclear compartments. In this context, it is worth noting that some ciliated eukaryotes, for example trypanosomes, undergo closed mitosis in which the nuclear envelope does not break down (Zhou et al., 2014). Further investigations are needed to determine how this affects the sharing of molecular machinery between the nuclear envelope and cilia.

Phase transitions and biomolecular condensates in the nucleus and cilium

A notable common feature that unites molecules with dual roles in the nucleus and cilia is that they invariably contribute to various types of membrane-less organelles (MLOs) (Protter and Parker, 2016; Uversky, 2017), some of which have already been mentioned. MLOs often comprise homogeneous and dynamic supramolecular assemblies of RNA, RNPs and proteins (**Figure 1B**) that form biomolecular condensates within cytoplasmic or nucleoplasmic granules (Uversky, 2017). Stress granules, P bodies, centrosomes and centriolar satellites (small cytoplasmic granules in the pericentrosomal region) can all be classified as cytoplasmic MLOs (**Figure 1C**). Nuclear MLOs are equally diverse and include the nucleolus, Cajal bodies (implicated in snRNP biogenesis), nuclear speckles (pre-mRNA splicing) and paraspeckles (regulation of gene expression). Nuclear pores (**Figure 1C**), although embedded in the nuclear membrane, also share some similarities with MLOs since they abundantly contain disordered FG

domains.

The key characteristic of MLOs is that they contain significant amounts of intrinsically disordered proteins (often interacting with RNA molecules), as well as proteins with both ordered domains and disordered, low complexity regions. Many of the nuclear and ciliary proteins mentioned above seem to share these characteristics, in particular intrinsically disordered and coiled-coil regions. These include: RP-related PRPFs (PRPF6, SNRNP200 and PRPF8) in nuclear speckles; nucleoporins in the nuclear pore; eIF3 and eIF4 in stress granules; and CEP290, centrins and pericentrin in the centrosome/centriolar satellite compartments. The condensation of proteins and RNAs into a biomolecular condensate often leads to the formation of dynamic, liquid-like MLOs that enable the rapid exchange of molecules between the MLO and either the cytoplasm or nucleoplasm (**Figure 1B**). Rapid phase transitions between the dispersed proteins and RNAs, and their condensation into MLOs, have recently emerged as a fundamental and conserved strategy to concentrate specific cellular functions in a small volume. This ensures rapid "on-demand" control of, for example, gene expression (Boulay et al., 2017), signal transduction (Li et al., 2012; Su et al., 2016) and stress responses (Wheeler et al., 2016). RNA often acts as a scaffold for protein binding (Boeynaems et al., 2018; Uversky, 2017), but recent evidence suggests that RNA can both promote and prevent phase transitions, as well as cause aberrant phase transitions suggesting more sophisticated regulatory functions (Maharana et al., 2018).

Some recent evidence has begun to emerge for a direct role of MLOs in mediating ciliogenesis. In an interesting study, so-called "dynein assembly particles" (DynAPs) form in multiciliated cells and appear to concentrate dyneins, their assembly factors, chaperones and components of stress granules (Huizar et al., 2017). However, it remains unclear if DynAPs are directly required for "on demand" ciliogenesis of motile cilia. This study does not examine other possibilities, for example if these particles assemble as an indirect consequence of stress responses. A more convincing example is the pericentriolar material in *C. elegans* embryo, described as a condensate that organizes microtubules through the localized, selective concentration of tubulin (Woodruff et al., 2017). In this system, the coiled-coil protein SPD-5 (Spindle-defective protein 5) appears to be necessary and sufficient for concentrating tubulin and microtubule assembly proteins (such as SPD-2, the orthologue of mammalian centrosomal protein CEP192) thus promoting subsequent formation of microtubule asters (Woodruff et al., 2017). This view of pericentriolar material as an MLO is not necessarily incompatible with earlier work suggesting a more conventional organization into structural domains (Mennella et

al., 2012), since the pericentriolar material that is peripheral to the centriole appears to be organized in a matrix.

Extended coiled-coil interaction motifs, such as those in the Cajal body components SMN and coilin/p80, are implicated in phase transitions of key proteins in several distinct nuclear MLOs (Sleeman et al., 2003). In addition, coiled-coil domains appear to mediate homo- and heterodimerization between splicing factors of the DBHS family, such as SFPQ and NONO, within paraspeckles (Lee et al., 2015). By analogy with nuclear coiled-coil proteins, as well as SPD-5 function, could intra- or intermolecular interactions between centrosomal coiled-coil proteins such as CEP290 mediate phase separation into a condensate with size selective properties at either the centriolar satellites or ciliary transition zone? Such a scenario predicts that a hydrogel at the "ciliary pore" would confer size selectivity during ciliary protein trafficking. This is supported by the similarity of the overall permeability kinetics for both the nuclear and ciliary pores (Lin et al., 2013; Timney et al., 2016).

Summary

The cilium and the nucleus share components of mechanisms involved in DNA damage response, RNA processing, translation, and cellular sub-compartmentalization. This is perhaps not as surprising as it seems at first glance. The cilium and the nucleus cease to exist as subcellular compartments during cell division, which facilitates the intermixing of their contents. Significantly, the centrosome is likely to play a key role in this process since it functions during both ciliogenesis and nuclear division. Whilst the centrosome is an essential structural component at the cilium base and contributes to the ciliary diffusion barrier during quiescence, in the course of mitosis it physically interacts with the components of nuclear pore transport machinery, including NUPs, Ran GTPase and importins. On evolutionary time scales, it is therefore likely to facilitate the exchange of molecular machinery between the nucleus and cilia. Equally important is the fact that the centrosome and surrounding pericentriolar material have characteristics of a membrane-less organelle or sub-compartment that shares and exchanges components with other structures of this type, such as stress granules and P-bodies. This may explain why proteins involved in ribostasis are frequently localized at centrosomes, where they are also likely to acquire new functions. The significance of membrane-less condensates surrounding the centrosome and the ciliary basal body remains largely unknown, and an exciting area of future research will be studies on the dynamic compartmentalization of the cytosol in relation to the cell cycle and cilia-mediated signal transduction.

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References

Aizer, A., Brody, Y., Ler, L.W., Sonenberg, N., Singer, R.H., and Shav-Tal, Y. (2008). The dynamics of mammalian P body transport, assembly, and disassembly in vivo. Mol Biol Cell *19*, 4154-4166.

Alliegro, M.C., Alliegro, M.A., and Palazzo, R.E. (2006). Centrosome-associated RNA in surf clam oocytes. Proceedings of the National Academy of Sciences of the United States of America *103*, 9034-9038.

Boeynaems, S., Alberti, S., Fawzi, N.L., Mittag, T., Polymenidou, M., Rousseau, F., Schymkowitz, J., Shorter, J., Wolozin, B., Van Den Bosch, L.*, et al.* (2018). Protein Phase Separation: A New Phase in Cell Biology. Trends Cell Biol *28*, 420-435.

Boulay, G., Sandoval, G.J., Riggi, N., Iyer, S., Buisson, R., Naigles, B., Awad, M.E., Rengarajan, S., Volorio, A., McBride, M.J.*, et al.* (2017). Cancer-Specific Retargeting of BAF Complexes by a Prion-like Domain. Cell *171*, 163-178 e119.

Breslow, D.K., Koslover, E.F., Seydel, F., Spakowitz, A.J., and Nachury, M.V. (2013). An in vitro assay for entry into cilia reveals unique properties of the soluble diffusion barrier. J Cell Biol *203*, 129-147.

Bui, K.H., von Appen, A., DiGuilio, A.L., Ori, A., Sparks, L., Mackmull, M.-T., Bock, T., Hagen, W., Andrés-Pons, A., Glavy, J.S.*, et al.* (2013). Integrated Structural Analysis of the Human Nuclear Pore Complex Scaffold. Cell *155*, 1233-1243.

Cajanek, L., and Nigg, E.A. (2014). Cep164 triggers ciliogenesis by recruiting Tau tubulin kinase 2 to the mother centriole. PNAS *111*, E2841-2850.

Carvalhal, S., Ribeiro, S.A., Arocena, M., Kasciukovic, T., Temme, A., Koehler, K., Huebner, A., and Griffis, E.R. (2015). The nucleoporin ALADIN regulates Aurora A localization to ensure robust mitotic spindle formation. Mol Biol Cell *26*, 3424-3438.

Chaki, M., Airik, R., Ghosh, A.K., Giles, R.H., Chen, R., Slaats, G.G., Wang, H., Hurd, T.W., Zhou, W., Cluckey, A.*, et al.* (2012). Exome capture reveals ZNF423 and CEP164 mutations, linking renal ciliopathies to DNA damage response signaling. Cell *150*, 533-548.

Chapman, M.J., Dolan, M.F., and Margulis, L. (2000). Centrioles and kinetosomes: form, function, and evolution. Q Rev Biol *75*, 409-429.

Christie, M., Chang, C.-W., Róna, G., Smith, K.M., Stewart, A.G., Takeda, A.A.S., Fontes, M.R.M., Stewart, M., Vértessy, B.G., Forwood, J.K.*, et al.* (2016). Structural Biology and Regulation of Protein Import into the Nucleus. Journal of molecular biology *428*, 2060-2090.

Daly, O.M., Gaboriau, D., Karakaya, K., King, S., Dantas, T.J., Lalor, P., Dockery, P., Kramer, A., and Morrison, C.G. (2016). CEP164-null cells generated by genome editing show a ciliation defect with intact DNA repair capacity. J Cell Sci *129*, 1769-1774.

del Viso, F., Huang, F., Myers, J., Chalfant, M., Zhang, Y., Reza, N., Bewersdorf, J., Lusk, C.P., and Khokha, M.K. (2016). Congenital Heart Disease Genetics Uncovers Context-Dependent Organization and Function of Nucleoporins at Cilia. Dev Cell, 1-16.

Dishinger, J.F., Kee, H.L., Jenkins, P.M., Fan, S., Hurd, T.W., Hammond, J.W., Truong, Y.N.-T., Margolis, B., Martens, J.R., and Verhey, K.J. (2010). Ciliary entry of the kinesin-2 motor KIF17 is regulated by importin-β2 and RanGTP. Nature Cell Bio *12*, 703-710.

Endicott, S.J., and Brueckner, M. (2018). NUP98 Sets the Size-Exclusion Diffusion Limit through the Ciliary Base. Curr Biol *28*, 1643-1650.e1643.

Forbes, D.J., Travesa, A., Nord, M.S., and Bernis, C. (2015). Nuclear transport factors: global regulation of mitosis. Curr Opin Cell Biol *35*, 78-90.

Funabashi, T., Katoh, Y., Michisaka, S., Terada, M., Sugawa, M., and Nakayama, K. (2017). Ciliary entry of KIF17 is dependent on its binding to the IFT-B complex via IFT46-IFT56 as well as on its nuclear localization signal. Mol Biol Cell *28*, 624-633.

Han, Y., Xiong, Y., Shi, X., Wu, J., Zhao, Y., and Jiang, J. (2017). Regulation of Gli ciliary localization and Hedgehog signaling by the PY-NLS/karyopherin-β2 nuclear import system. PLoS biology *15*, e2002063.

Hashizume, C., Kobayashi, A., and Wong, R.W. (2013a). Down-modulation of nucleoporin RanBP2/Nup358 impaired chromosomal alignment and induced mitotic catastrophe. Cell death and differentiation *4*, e854.

Hashizume, C., Moyori, A., Kobayashi, A., Yamakoshi, N., Endo, A., and Wong, R.W. (2013b). Nucleoporin Nup62 maintains centrosome homeostasis. Cell cycle (Georgetown, Tex) *12*, 3804-3816.

Hezwani, M., and Fahrenkrog, B. (2017). The functional versatility of the nuclear pore complex proteins. Semin Cell Dev Biol *68*, 2-9.

Huizar RL, Lee C, Boulgakov AA, Horani A, Tu F, Marcotte EM, Brody SL, Wallingford JB. A liquid-like organelle at the root of motile ciliopathy. Elife *7*, e38497.

Iaconis, D., Monti, M., Renda, M., van Koppen, A., Tammaro, R., Chiaravalli, M., Cozzolino, F., Pignata, P., Crina, C., Pucci, P.*, et al.* (2017). The centrosomal OFD1 protein interacts with the translation machinery and regulates the synthesis of specific targets. Sci Rep *7*, 1224.

Ikeuchi, Y., de la Torre-Ubieta, L., Matsuda, T., Steen, H., Okazawa, H., and Bonni, A. (2013). The XLID protein PQBP1 and the GTPase Dynamin 2 define a signaling link that orchestrates ciliary morphogenesis in postmitotic neurons. Cell reports *4*, 879-889.

Itoh, G., Sugino, S., Ikeda, M., Mizuguchi, M., Kanno, S.-i., Amin, M.A., Iemura, K., Yasui, A., Hirota, T., and Tanaka, K. (2013). Nucleoporin Nup188 is required for chromosome alignment in mitosis. Cancer Science *104*, 871-879.

Kee, H.L., Dishinger, J.F., Blasius, T.L., Liu, C.J., Margolis, B., and Verhey, K.J. (2012). A size-exclusion permeability barrier and nucleoporins characterize a ciliary pore complex that regulates transport into cilia. Nature Cell Bio *14*, 431-437.

Kee, H.L., and Verhey, K.J. (2013). Molecular connections between nuclear and ciliary import processes. Cilia *2*, 11.

Kobayashi, A., Hashizume, C., Dowaki, T., and Wong, R.W. (2015). Therapeutic potential of mitotic interaction between the nucleoporin Tpr and aurora kinase A. Cell cycle (Georgetown, Tex) *14*, 1447-1458.

Kosinski, J., Mosalaganti, S., von Appen, A., Teimer, R., DiGuilio, A.L., Wan, W., Bui, K.H., Hagen, W.J.H., Briggs, J.A.G., Glavy, J.S.*, et al.* (2016). Molecular architecture of the inner ring scaffold of the human nuclear pore complex. Science *352*, 363-365.

Lavia, P. (2016). The GTPase RAN regulates multiple steps of the centrosome life cycle. Chromosome research : an international journal on the molecular, supramolecular and evolutionary aspects of chromosome biology *24*, 53-65.

Lee, M., Sadowska, A., Bekere, I., Ho, D., Gully, B.S., Lu, Y., Iyer, K.S., Trewhella, J., Fox, A.H., and Bond, C.S. (2015). The structure of human SFPQ reveals a coiled-coil mediated polymer essential for functional aggregation in gene regulation. Nucleic Acids Res *43*, 3826-3840.

Li, P., Banjade, S., Cheng, H.C., Kim, S., Chen, B., Guo, L., Llaguno, M., Hollingsworth, J.V., King, D.S., Banani, S.F.*, et al.* (2012). Phase transitions in the assembly of multivalent signalling proteins. Nature *483*, 336-340.

Lin, Y.C., Niewiadomski, P., Lin, B., Nakamura, H., Phua, S.C., Jiao, J., Levchenko, A., Inoue, T., Rohatgi, R., and Inoue, T. (2013). Chemically inducible diffusion trap at cilia reveals molecular sieve-like barrier. Nat Chem Biol *9*, 437-443.

Maharana, S., Wang, J., Papadopoulos, D.K., Richter, D., Pozniakovsky, A., Poser, I., Bickle, M., Rizk, S., Guillén-Boixet, J., Franzmann, T.M.*, et al.* (2018). RNA buffers the phase separation behavior of prion-like RNA binding proteins. Science (New York, NY) *360*, 918-921.

Marshall, W.F., and Rosenbaum, J.L. (1999). Are there nucleic acids in the centrosome? In Current Topics in Developmental Biology, R.E. Palazzo, and G.P. Schatten, eds. (Academic Press), pp. 187-205.

Mennella, V., Keszthelyi, B., McDonald, K.L., Chhun, B., Kan, F., Rogers, G.C., Huang, B., and Agard, D.A. (2012). Subdiffraction-resolution fluorescence microscopy reveals a domain of the centrosome critical for pericentriolar material organization. Nature Cell Bio *14*, 1159-1168.

Mordes, D., Luo, X., Kar, A., Kuo, D., Xu, L., Fushimi, K., Yu, G., Sternberg, P., Jr., and Wu, J.Y. (2006). Pre-mRNA splicing and retinitis pigmentosa. Mol Vis *12*, 1259-1271.

Moser, J.J., Fritzler, M.J., and Rattner, J.B. (2011). Repression of GW/P body components and the RNAi microprocessor impacts primary ciliogenesis in human astrocytes. BMC Cell Biol *12*, 37.

Mullee, L.I., and Morrison, C.G. (2016). Centrosomes in the DNA damage response--the hub outside the centre. Chromosome res *24*, 35-51.

Nishi, R., Sakai, W., Tone, D., Hanaoka, F., and Sugasawa, K. (2013). Structure-function analysis of the EF-hand protein centrin-2 for its intracellular localization and nucleotide excision repair. Nucleic Acids Res *41*, 6917-6929.

Pan, Y.R., and Lee, E.Y. (2009). UV-dependent interaction between Cep164 and XPA mediates localization of Cep164 at sites of DNA damage and UV sensitivity. Cell cycle *8*, 655-664.

Protter, D.S., and Parker, R. (2016). Principles and Properties of Stress Granules. Trends Cell Biol *26*, 668-679.

Renaud, E., Miccoli, L., Zacal, N., Biard, D.S., Craescu, C.T., Rainbow, A.J., and Angulo, J.F. (2011). Differential contribution of XPC, RAD23A, RAD23B and CENTRIN 2 to the UV-response in human cells. DNA Repair (Amst) *10*, 835-847.

Rosenbaum, J.L., and Witman, G.B. (2002). Intraflagellar transport. Nature reviews Molecular cell biology *3*, 813-825.

Schmidt, H.B., and Görlich, D. (2016). Transport Selectivity of Nuclear Pores, Phase Separation, and Membraneless Organelles. Trends Biochem Sci *41*, 46-61.

Shao, J., Gao, F., Zhang, B., Zhao, M., Zhou, Y., He, J., Ren, L., Yao, Z., Yang, J., Su, C.*, et al.* (2017). Aggregation of SND1 in Stress Granules is Associated with the Microtubule Cytoskeleton During Heat Shock Stimulus. Anat Rec (Hoboken) *300*, 2192-2199.

Sivasubramaniam, S., Sun, X., Pan, Y.R., Wang, S., and Lee, E.Y. (2008). Cep164 is a mediator protein required for the maintenance of genomic stability through modulation of MDC1, RPA, and CHK1. Genes Dev *22*, 587-600.

Slaats, G.G., Saldivar, J.C., Bacal, J., Zeman, M.K., Kile, A.C., Hynes, A.M., Srivastava, S., Nazmutdinova, J., den Ouden, K., Zagers, M.S.*, et al.* (2015). DNA replication stress underlies renal phenotypes in CEP290-associated Joubert syndrome. J Clin Invest *125*, 3657-3666.

Sleeman, J.E., Trinkle-Mulcahy, L., Prescott, A.R., Ogg, S.C., and Lamond, A.I. (2003). Cajal body proteins SMN and Coilin show differential dynamic behaviour in vivo. J Cell Sci *116*, 2039-2050.

Smith, E., Dejsuphong, D., Balestrini, A., Hampel, M., Lenz, C., Takeda, S., Vindigni, A., and Costanzo, V. (2009). An ATM- and ATR-dependent checkpoint inactivates spindle assembly by targeting CEP63. Nature Cell Bio *11*, 278-285.

Splinter, D., Tanenbaum, M.E., Lindqvist, A., Jaarsma, D., Flotho, A., Yu, K.L., Grigoriev, I., Engelsma, D., Haasdijk, E.D., Keijzer, N.*, et al.* (2010). Bicaudal D2, Dynein, and Kinesin-1 Associate with Nuclear Pore Complexes and Regulate Centrosome and Nuclear Positioning during Mitotic Entry. PLoS biology *8*, e1000350.

Su, X., Ditlev, J.A., Hui, E., Xing, W., Banjade, S., Okrut, J., King, D.S., Taunton, J., Rosen, M.K., and Vale, R.D. (2016). Phase separation of signaling molecules promotes T cell receptor signal transduction. Science *352*, 595-599.

Takao, D., Dishinger, J.F., Kee, H.L., Pinskey, J.M., Allen, B.L., and Verhey, K.J. (2014). An Assay for Clogging the Ciliary Pore Complex Distinguishes Mechanisms of Cytosolic and Membrane Protein Entry. Curr Biol *24*, 2288-2294.

Takao, D., Wang, L., Boss, A., and Verhey, K.J. (2017). Protein Interaction Analysis Provides a Map of the Spatial and Temporal Organization of the Ciliary Gating Zone. Curr Biol, 1-15.

Tanackovic, G., Ransijn, A., Thibault, P., Abou Elela, S., Klinck, R., Berson, E.L., Chabot, B., and Rivolta, C. (2011). PRPF mutations are associated with generalized defects in spliceosome formation and pre-mRNA splicing in patients with retinitis pigmentosa. Hum Mol Genet *20*, 2116-2130.

Timney, B.L., Raveh, B., Mironska, R., Trivedi, J.M., Kim, S.J., Russel, D., Wente, S.R., Sali, A., and Rout, M.P. (2016). Simple rules for passive diffusion through the nuclear pore complex. J Cell Biol *215*, 57-76.

Twyffels, L., Gueydan, C., and Kruys, V. (2011). Shuttling SR proteins: more than splicing factors. FEBS J *278*, 3246-3255.

Uversky, V.N. (2017). Intrinsically disordered proteins in overcrowded milieu: Membrane-less organelles, phase separation, and intrinsic disorder. Curr Opin Struct Biol *44*, 18-30.

Villumsen, B.H., Danielsen, J.R., Povlsen, L., Sylvestersen, K.B., Merdes, A., Beli, P., Yang, Y.G., Choudhary, C., Nielsen, M.L., Mailand, N.*, et al.* (2013). A new cellular stress response that triggers centriolar satellite reorganization and ciliogenesis. EMBO J *32*, 3029-3040.

Wang, Q., Moore, M.J., Adelmant, G., Marto, J.A., and Silver, P.A. (2013). PQBP1, a factor linked to intellectual disability, affects alternative splicing associated with neurite outgrowth. Genes Dev *27*, 615-626.

Went, H.A. (1977). Can a reverse transcriptase by involved in centriole duplication? Journal of theoretical biology *68*, 95-100.

Wheeler, J.R., Matheny, T., Jain, S., Abrisch, R., and Parker, R. (2016). Distinct stages in stress granule assembly and disassembly. Elife *5*.

Wheway, G., Schmidts, M., Mans, D.A., Szymanska, K., Nguyen, T.-M.T., Racher, H., Phelps, I.G., Toedt, G., Kennedy, J., Wunderlich, K.A., *et al.* (2015). An siRNA-based functional genomics screen for the identification of regulators of ciliogenesis and ciliopathy genes. Nature Cell Bio.

Woodruff, J.B., Ferreira Gomes, B., Widlund, P.O., Mahamid, J., Honigmann, A., and Hyman, A.A. (2017). The Centrosome Is a Selective Condensate that Nucleates Microtubules by Concentrating Tubulin. Cell *169*, 1066-1077 e1010.

Yang, J., Valineva, T., Hong, J., Bu, T., Yao, Z., Jensen, O.N., Frilander, M.J., and Silvennoinen, O. (2007). Transcriptional co-activator protein p100 interacts with snRNP proteins and facilitates the assembly of the spliceosome. Nucleic Acids Res *35*, 4485-4494.

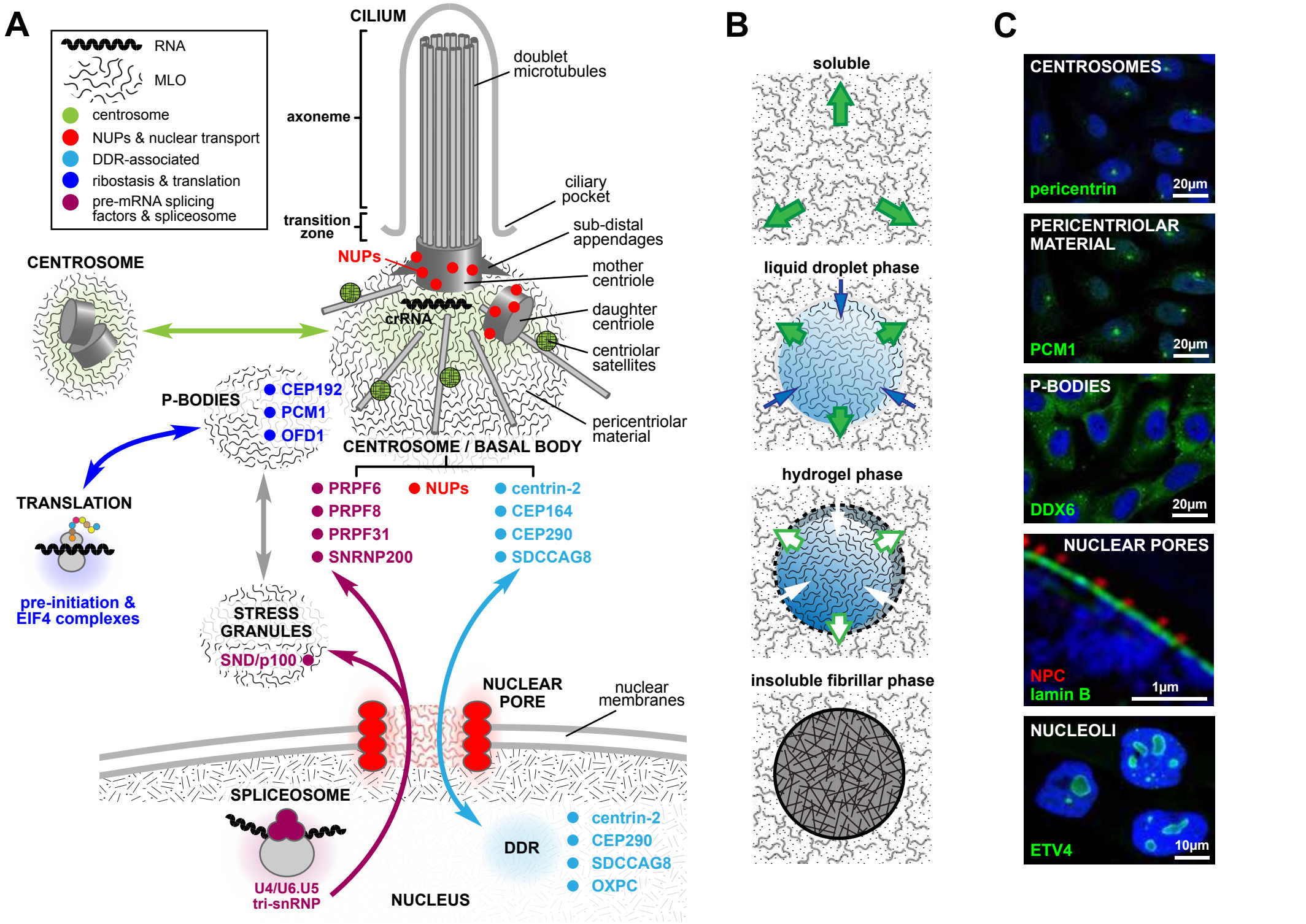
Youn, J.Y., Dunham, W.H., Hong, S.J., Knight, J.D.R., Bashkurov, M., Chen, G.I., Bagci, H., Rathod, B., MacLeod, G., Eng, S.W.M., *et al.* (2018). High-Density Proximity Mapping Reveals the Subcellular Organization of mRNA-Associated Granules and Bodies. Mol Cell *69*, 517-532 e511.

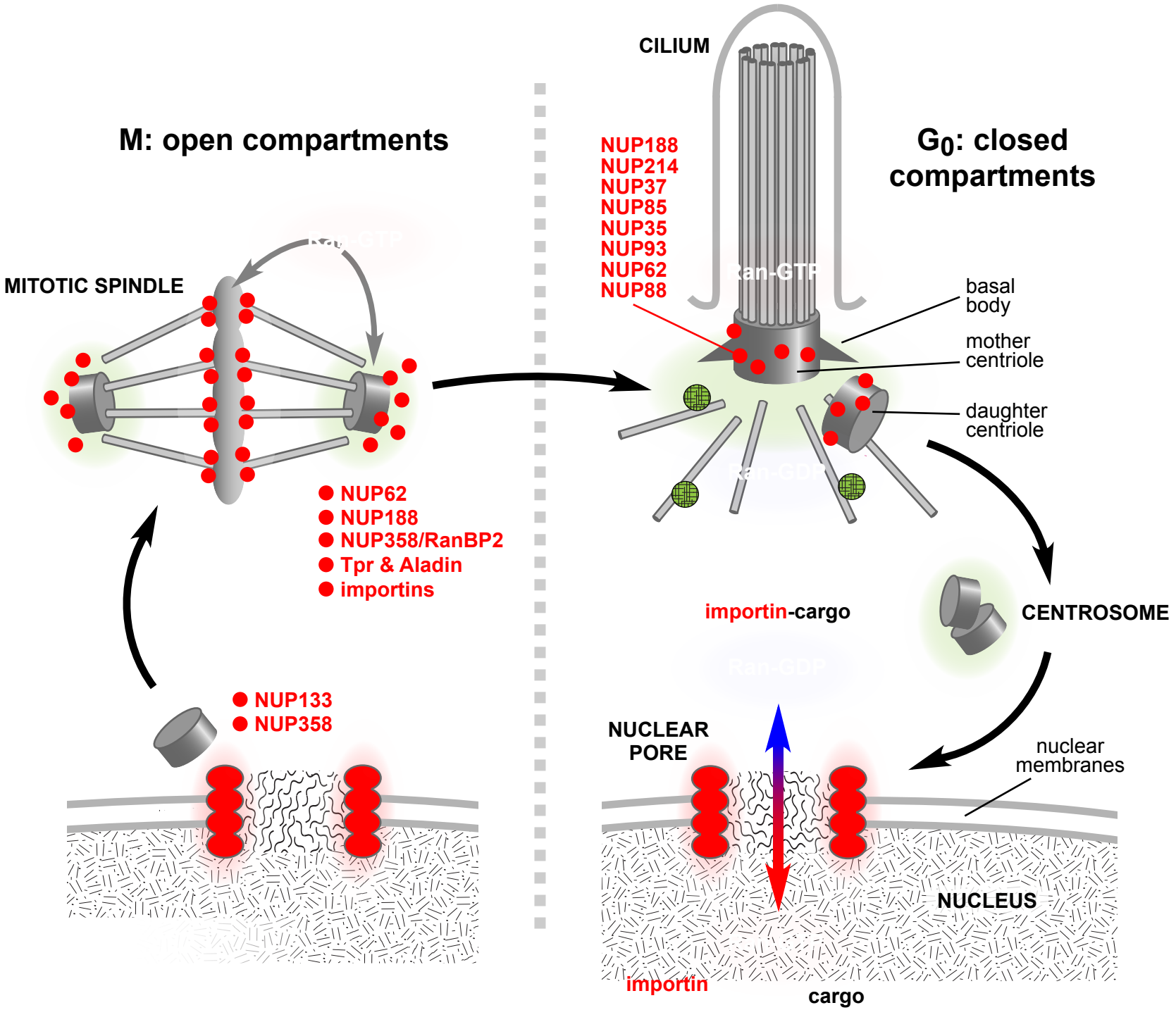
Zhou, Q., Hu, H., and Li, Z. (2014). New Insights into the Molecular Mechanisms of Mitosis and Cytokinesis in Trypanosomes. In (Elsevier), pp. 127-166.

Figure Legends

Figure 1. Membrane-less organelles mediate the exchange of proteins and functions between the ciliary and nuclear compartments. (A) Schematic of protein exchange between the cytoplasmic (top) and nuclear (bottom) compartments, and between colour-coded organelles or functions, indicated by coloured arrows. P-bodies co-localize with either centrosomes or ciliary basal bodies (green), and interact and exchange material with stress granules (grey double-headed arrow). Membrane-less organelles, or hydrogel conferring size selectivity within the nuclear pore (red), are indicated by oval tangled mesh structures. Abbreviations: crRNA, centrosomal RNA; DDR, DNA damage response; MLO, membrane-less organelle. **(B)** Examples of intracellular protein phases. Top panel: soluble molecules (for example, protein and RNA) diffuse freely and are dispersed in the cytoplasm or nucleoplasm, indicated by the long green arrows. Middle panels: specific proteins with intrinsically disordered domains can undergo liquid-liquid phase transitions to form a concentrated droplet-like state (pale blue sphere containing tangled mesh). In a liquid droplet, the molecules within the phase can still diffuse (short green arrows) and exchange with soluble molecules outside of the droplet. In a hydrogel (dark blue sphere), both diffusion and exchange are much slower (white arrows). Bottom panel: under pathogenic conditions, condensates can form insoluble fibrillar structures with loss of dynamic behaviour of all molecules. Fibrils are indicated by cross-hatched short lines. **(C)** Examples of membrane-less organelles discussed in the main text, stained for the indicated marker proteins and visualized by immunofluorescence confocal, or 3D structured illumination microscopy for nuclear pores and nuclear envelope (NPC in red, lamin B in green; image courtesy of Lothar Schermelleh). All other images were obtained from the Human Protein Atlas (www.proteinatlas.org).

Figure 2. Nucleoporins and other components of nuclear transport machinery are associated with the centrosome throughout the cell cycle. Left panels: in early mitosis, the centrosome migrates to the nuclear envelope, a process facilitated by the nucleoporins, NUP358/RanBP2 and NUP133. Later, during mitosis after the nuclear envelope breaks down, NUPs contribute to a variety of functions in the mitotic spindle, both at the centrosome and kinetochores. Right panels: in G0 of the cell cycle, entry into the ciliary and nuclear compartments is thought to be selectively facilitated, in part, by Ran GTPase, importins and NUPs.


A
RNA
MLO
centrosome
NUPs & nuclear transport
DDR-associated
ribostasis & translation
pre-mRNA splicing factors & spliceosome
CILIUM
doublet microtubules
axoneme
transition zone
ciliary pocket
sub-distal appendages
mother centriole
daughter centriole
centriolar satellites
pericentriolar material
NUPs
crRNA
CENTROSOME
P-BODIES
CEP192
PCM1
OFD1
CENTROSOME / BASAL BODY
TRANSLATION
pre-initiation & EIF4 complexes
PRPF6
PRPF8
PRPF31
SNRNP200
NUPs
centrin-2
CEP164
CEP290
SDCCAG8
STRESS GRANULES
SND/p100
NUCLEAR PORE
nuclear membranes
SPLICEOSOME
U4/U6.U5 tri-snRNP
DDR
centrin-2
CEP290
SDCCAG8
OXPC
NUCLEUS
B
soluble
liquid droplet phase
hydrogel phase
insoluble fibrillar phase
C
CENTROSOMES
pericentrin
20μm
PERICENTRIOLAR MATERIAL
PCM1
20μm
P-BODIES
DDX6
20μm
NUCLEAR PORES
NPC
lamin B
1μm
NUCLEOLI
ETV4
10μm


M: open compartments
G0: closed compartments
CILIUM
NUP188
NUP214
NUP37
NUP85
NUP35
NUP93
NUP62
NUP88
basal body
mother centriole
daughter centriole
MITOTIC SPINDLE
NUP62
NUP188
NUP358/RanBP2
Tpr & Aladin
importins
importin-cargo
CENTROSOME
NUP133
NUP358
NUCLEAR PORE
nuclear membranes
NUCLEUS
importin
cargo

protein	name	function
Aladin	aladin WD repeat nucleoporin	component of nuclear pore complex; WD-repeat protein regulating nucleocytoplasmic transport
ATM	ataxia telangiectasia-mutated serine/threonine kinase	master regulator of cell cycle checkpoint signaling pathways; required for DNA damage responses and genome stability
ATR	ATM/Rad3-related serine/threonine kinase	master regulator of cell cycle checkpoint signaling pathways; required for fragile site stability and centrosome duplication
Aurora A kinase	alias: AURKA, Aurora A	cell cycle-regulated serine/threonine kinase; required for mitotic spindle assembly and centrosome duplication/separation
centrin-2	alias: CETN2, caltractin	MTOC function, centriole duplication and correct spindle formation, component of the XPC complex during nucleotide excision repair
CEP63	centrosomal protein 63	centriole replication and spindle assembly, DNA damage checkpoint during G2/M transition of mitotic cell cycle
CEP131	centrosomal protein 131, alias: AZI1	Component of centriolar satellites; regulation of G2/M transition of mitotic cell cycle, Centrosome maturation, Cilium Assembly
CEP164	centrosomal protein 164	centriole distal appendage-specific protein involved in microtubule organization, DNA damage response, and chromosome segregation
CEP192	centrosomal protein 192	regulator of pericentriolar material recruitment, centrosome maturation and centriole duplication
CEP290	centrosomal protein 290	localizes to the centrosome, cilium and centriolar satellites; required for cilium assembly, G2/M transition of mitotic cell cycle
CHK1	checkpoint kinase 1, alias: CHEK1	serine/threonine kinase required for checkpoint mediated cell cycle arrest in response to DNA damage
CHK2	checkpoint kinase 2, alias: CHEK2	serine/threonine kinase required for checkpoint mediated cell cycle arrest in response to DNA damage
coilin	alias: p80	component of nuclear Cajal bodies involved in the modification and assembly of nucleoplasmic snRNPs
eIF3	eukaryotic translation initiation factor 3 complex	complex required for initiation of protein synthesis; associates with the 40S ribosome to form the 43S pre-initiation complex
eIF4	eukaryotic translation initiation factor 4 complex	complex involved in cap recognition required for mRNA binding to the ribosome
GLI2	glioma-associated oncogene family zinc finger 2	transcription regulator of the Sonic hedgehog signaling pathway
importin-β2	alias: karyopherin subunit beta 1	binds to nuclear localisation signals at the nuclear pore complex, mediating nucleocytoplasmic protein import
KIF17	kinesin family member 17	plus-end-directed ATP-dependent microtubule motor activity, intraciliary transport involved in cilium assembly
NONO	non-POU domain-containing octamer-binding protein	RNA-binding nuclear protein involved in transcriptional regulation and pre-mRNA splicing
NuMA	nuclear mitotic apparatus protein 1	structural component of the nuclear matrix, interacts with microtubules and regulates mitotic spindle formation
NUP35	nucleoporin 35	inner ring component of the nuclear pore complex
NUP37	nucleoporin 37	outer ring component of the nuclear pore complex, required for normal kinetochore-microtubule interaction and mitosis
NUP62	nucleoporin 62	central component of the nuclear pore complex, associates with importins during nucleocytoplasmic transport
NUP85	nucleoporin 85	outer ring component required for nuclear pore complex assembly and maintenance, RNA export and mitotic spindle assembly
NUP93	nucleoporin 93	linker component required for assembly and maintenance of the nuclear pore complex
NUP98	nucleoporin 98	central component of the nuclear pore complex; mediates nuclear import, nuclear export and mitotic progression
NUP188	nucleoporin 188	inner ring component forming a scaffold for the central channel of the nuclear pore complex
NUP214	nucleoporin 214	cytoplasmic nucleoporin involved in nucleocytoplasmic receptor-mediated import across the nuclear pore complex
NUP358	nucleoporin 358, alias: RAN binding protein 2	nucleoporin implicated in the Ran-GTPase cycle, component of the nuclear export pathway
OFD1	oral-facial-digital syndrome 1 protein	component of centrioles and centriolar satellites required for ciliogenesis
PCM1	pericentriolar material 1	component of centriolar satellites, required for protein localisation and anchoring of microtubules to centrosomes
pericentrin	alias: PCNT	component of the pericentriolar material, organizes microtubule arrays during mitosis and meiosis at the centrosome
PQBP1	polyglutamine-binding protein 1	nuclear protein involved pre-mRNA splicing, transcription regulation and cytoplasmic stress granule assembly
PRPF3	pre-mRNA processing factor 3	U4 component of the U4/U6-U5 tri-snRNP complex required for spliceosome assembly; mutations cause RP type 18
PRPF4	pre-mRNA processing factor 4	component of the U4/U6-U5 tri-snRNP complex required for spliceosome assembly
PRPF6	pre-mRNA processing factor 6	component of the U4/U6-U5 tri-snRNP complex involved in pre-mRNA splicing; mutations cause RP type 60
PRPF8	pre-mRNA processing factor 8	U5 component of the U4/U6-U5 tri-snRNP complex; positions U2, U5 and U6 snRNAs at splice sites; mutations cause RP type 13
PRPF19	pre-mRNA processing factor 19	ubiquitin-protein ligase that stabilizes the U4/U5/U6 tri-snRNP spliceosomal complex
PRPF31	pre-mRNA processing factor 31	U4 component of the U4/U6-U5 tri-snRNP complex required for spliceosome assembly; mutations cause RP type 11
RAN	Ras-related nuclear protein	small GTP binding protein required for nucleocytoplasmic transport through the nuclear pore complex
SFPQ	splicing factor, proline- and glutamine-rich	pre-mRNA splicing factor required for early spliceosome formation, forming a heteromer with NONO
SMN	survival of motor neuron 1	component of the SMN complex required for assembly of snRNPs
TPR	translocated promoter region protein	forms intranuclear filaments that interact with nuclear pore complexes, mediating nucleocytoplasmic export of mRNAs and proteins
SDCCAG8	serologically defined colon cancer antigen 8, alias: NPHP10	centrosomal protein required for MTOC organisation, G2/M transition of mitotic cell cycle and interphase microtubule organization
SF3B1	splicing factor 3b subunit 1	component of the splicing factor 3b protein complex, contributing to U2 snRNP formation
SND1	staphylococcal nuclease and tudor domain-containing 1	transcriptional co-activator, regulates mRNAs involved in G1-to-S phase transition
SNRNP200	small nuclear ribonucleoprotein U5 subunit 200, alias: BRR2	RNA helicase component of the U5 snRNP and U4/U6-U5 tri-snRNP complexes; mutations cause RP type 33
XPC	XPC subunit, DNA damage recognition and repair factor	component of XPC (xeroderma pigmentosum complementation group C) complex; mediates early steps of nucleotide excision repair

Table 1. Summary of proteins discussed in the text, listing their localizations and functions. Abbreviations: MTOC, microtubule organizing center; RP, retinitis pigmentosum; snRNAs, small nuclear RNAs; snRNPs, small nuclear ribonucleoproteins