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On the Nuclear Pore Complex and Its Roles in Nucleo-Cytoskeletal Coupling and Mechanobiology

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Abstract—The nuclear pore complex (NPC) is primarily recognized for its function as the gateway for nucleocytoplasmic traffic, regulating biochemical exchange between the cytoplasm and the nucleoplasm. On the other hand, the LINC complex, comprised of SUN-domain and KASH-domain proteins, is typically credited as the main physical bridge across the nuclear envelope. However, recent evidence suggests that the NPC is also directly engaged with the cytoskeletal elements and the nucleoskeleton, and as such provides a direct physical association between the nucleus and the cytoskeleton. Moreover, by controlling the transport of inner nuclear membrane proteins, including components of the LINC complex, the NPC plays additional roles in physically connecting the cytoskeleton and the nucleus. This review examines the NPC's direct and indirect contributions to nucleo-cytoskeletal coupling and mechanobiology.

Keywords—Nuclear pore complex, SUN, KASH, LINC, Mechanotransduction, Nuclear envelope.

INTRODUCTION

The nuclear envelope (NE) divides the interior of the eukaryotic cells into two physically separated regions, namely the cytoplasm and the nucleoplasm. Although a double-layered NE separates these two compartments, they are chemically and physically linked *via* two different protein complexes residing at the NE, namely the nuclear pore complex (NPC) and the LINC (linker of the nucleoskeleton and the cytoskeleton). The NPC acts as the exclusive gateway for macromolecular transport between the cytoplasm and the nucleoplasm, while the LINC complex is generally known as the physical linkage between the interior of the nucleus and the cytoskeleton.

The NPC is a large macromolecular complex composed of specific proteins called nucleoporins (Nups). More than 30 different types of Nups assemble into an eightfolded symmetric structure.[97] The central channel of the NPC is sandwiched between the cytoplasmic and nuclear rings. Eight filaments project from the cytoplasmic ring into the cytoplasm and eight filaments emanate from the nuclear ring and form a basket-like structure, known as the nuclear basket[44] (Fig. 1). The distinctive property of the NPC is the fast yet selective nature of transport it facilitates. Each NPC is capable of handling ~1000 translocations per second.[74] While the NPC allows free passage of small molecules and ions (up to 40 kDa), larger molecules (diameters of up to 40 nm) require binding to specific types of proteins called transporters, e.g. karyopherins (Kaps), to be actively transported.[81,40] Some of the Nups possess intrinsically disordered regions that line the inner face of the NPC.[16] These Nups are rich in phenylalanine-glycine repeats, therefore called FG Nups, and are suggested to play the chief role in active transport of cargos through the NPC *via* formation of weak interactions with transporters. While various computational and experimental studies have explored the transport through the NPC,[1,3,27,48,51,54,66,72,73,76,87,99] the underlying mechanism of this process remains elusive.

Although NPCs are primarily known for their role as the gateway for 'chemical' exchange between the nucleoplasm and the cytoplasm, they are also directly and indirectly involved in the 'physical' linkage between the cytoskeleton and the nucleoskeleton in various cellular processes. Since the biochemical aspect of NPC function has been widely discussed and reviewed previously, we focus here specifically on the role of the NPC as a physical bridge between the

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nucleus and the cytoskeleton. First, the direct associations of NPCs with the nucleoskeleton and the cytoskeleton are discussed. Subsequently, we review the interactions between components of the NPC with the NE and how the NPC induces curvature into the NE and is assembled and integrated into it. The role of NPCs in actively transporting the inner nuclear membrane (INM) proteins, specifically components of the LINC complex, into the nucleus is then examined, which suggests an indirect role for the NPC in establishing the physical link between the nucleoskeleton and the cytoskeleton by regulating transport of INM proteins.

ASSOCIATIONS OF NPCs WITH THE NUCLEOSKELETON

Nuclear Lamina is Structurally Coupled to the NPC

Nuclear lamina is a network of lamin filaments and lamin-binding proteins located near the inner nuclear membrane (INM).[39] Lamins are type V intermediate filament proteins that can be categorized into two major types—A and B. Lamins are responsible for a wide variety of vital functions such as supporting the integrity of the nuclear membrane, NPC positioning, DNA replication, RNA transcription, nuclear and chromatin organization, cell cycle regulation and cell development, differentiation, migration, and apoptosis.[23,31,35,43] The lamina network is suggested to act as a "molecular shock absorber" due to its extensibility and limited compressibility.[13] Nuclear lamina is structurally coupled to the NPC forming a network that inhibits independent movement of NPCs with respect to each other[14] (Fig. 1). This connection is mediated by different types of nucleoporins. For example, Nup53 is tightly associated with the nuclear membrane and lamina and interacts with lamin B. Furthermore, it is suggested that Nup53 is positioned near the pore membrane and lamina where it anchors a subcomplex Nup93, Nup155 and Nup205.[38] The NPC is also associated with the nuclear lamina through Nup153; depletion of Nup153 in Hela cells causes defective nuclear lamina organization. Nup153-depleted cells exhibit lobes and membrane invaginations in the nuclei.[100] Moreover, Nup153 has multiple binding sites for lamin types A and B, facilitating the interaction of both N-terminus and C-terminus of Nup153 with lamins. Mutations in lamin A (specifically in the Ig-fold domain) affect Nup153 binding, suggesting a role for Nup153 in lamin-associated diseases, i.e. laminopathies.[2] Lamins also prevent the aggregation of the NPCs on the NE in specific stages of the cell cycle (late G2 and prophase). NPCs are attached to dynein motor protein through Nup358 (discussed in "NPC Components Associate with Microtubules and Motor Proteins at Different Stages of the Cell Cycle" section) and the movement of dynein on microtubules toward centrosome leads to clustering of the NPCs in the absence of lamins. NPCs are anchored to lamins, and lamins resist the force applied by dynein to the NPCs and therefore regulate positioning of the NPCs.[32]

Chromatin

Nuclear periphery was previously thought to have no more than a repressive influence on gene expression. However, studies have shown that NPCs and genes are physically associated.[49] The physical interaction between the NPC and genes, which is mediated through physical adaptor proteins such as SAGA and TREX-2[49] (for a comprehensive review, see Köhler and Hurt[49]) can regulate levels of transcription, increase the efficiency of mRNA processing and export, affect chromatin structure, transcription and interchromosomal clustering of genes within the nucleus.[49,64,82] Moreover, some nuclear basket proteins such as Mlp1, Nup2 and Nup60 are involved in the interaction between genes and the NPC.[9,59,80]

Euchromatin is a lightly packed form of chromatin, which is often under active transcription. Heterochromatin, on the other hand, is a tightly packed form of chromatin, which is not transcribed. Heterochromatins are located adjacent to the NE and nuclear lamina, but are gapped with heterochromatin free zones that are associated with the NPCs. This association is mediated by nuclear basket protein Tpr. RNAi mediated depletion of Tpr leads to occurrence of heterochromatin all over the NE with even the NPCs being covered by heterochromatin.[50] Hence, heterochromatin, which includes strongly repressed genes, localize near the nuclear lamina, while euchromatin localizes near the NPC,[5,46,79] Genes in the euchromatin have different levels of expression and nuclear pore proteins interact with both highly and poorly expressed parts of the genome. Different categories of Nups correlate with different levels of gene expression.[83] Some of the Nups have the ability to leave the nuclear pore and diffuse into the nucleoplasm for transcription.[42] Nups such as Nup60, Nup98, Nup50, Nup62 and Sec13 are found to bind specific regions of chromatin in the nuclear interior,[8,46] Studies have shown that in higher eukaryotes, nucleoporins inside the nucleoplasm mainly interact with highly transcribed genes. On the other hand, poorly expressed genes interact with NPC-tethered Nups.[46,83,53] As an example, Nup98 is one of the Nups that can leave the NPC

and has at least two pools: NPC-bound and nucleoplasmic.[68,30] Studies on Drosophila have shown that nucleoplasmic Nup98 localizes to promoters of genes that are substantial in processes such as development, and knockdown of this Nup results in suppression of these genes. These observations imply that Nup98 has a key role as a transcription factor in Drosophila.[8,25,46] Therefore, cells might be able to regulate transcription by controlling levels of nucleoplasmic Nup98.[25]

LINC Complexes

NPCs are additionally linked to the nucleoskeleton through close associations with elements of the LINC complex.[56] LINC complexes are composed of inner and outer nuclear membrane proteins that interact in the perinuclear space (PNS). SUN (Sad1p/UNC (uncoordinated)-84) domain containing proteins, which are anchored to the inner nuclear membrane, interact with KASH (Klarsicht, ANC1 and Syne Homology)

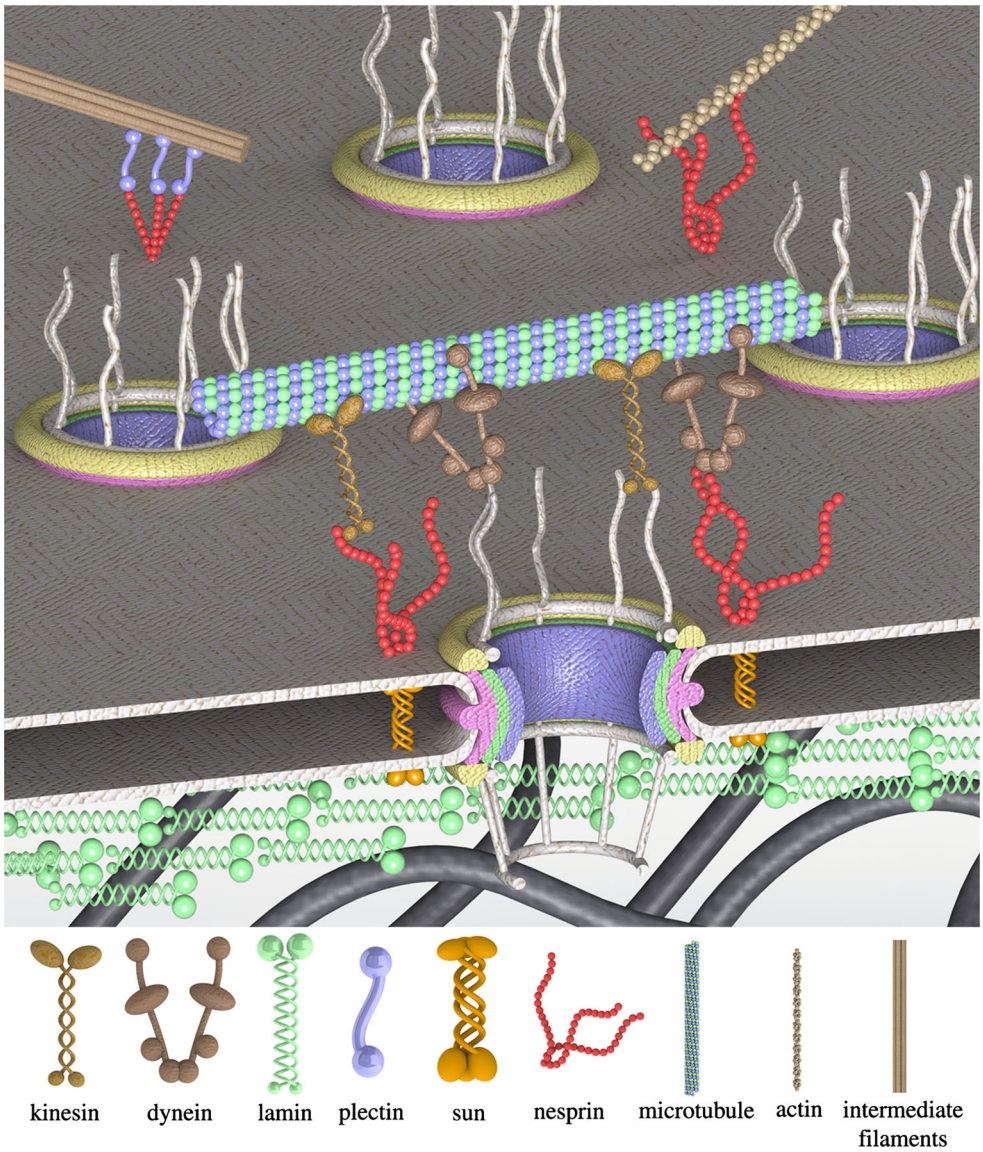

FIGURE 1. A 3-D schematic representation of the nuclear pore complex (NPC) embedded in the nuclear envelope (NE) along with its interactions with the nuckleoskeleton and the cytoskeleton. The scaffold of the central channel of the NPC is made up of three layers of nucleoporins (Nups) shown in magenta, green, and pink (disordered regions of the FG Nups that fill the inner part of the NPC are not shown). Cytoplasmic filaments of NPCs associate with microtubule filaments in the cytoplasm through kinesin and dynein motor proteins (shown on the front NPC). Similarly, linker of the nuckeloskeleton and the cytoskeleton (LINC) complexes interact with cytoskeletal filaments, including microtubules (shown on front LINCs), actins, and intermediate filaments (shown on LINC complexes in the back), through nesprins and plectins. Moreover, in the nucleoplasm, NPCs interact with nuclear lamina and chromatin.

domain proteins, which are anchored to the outer nuclear membrane (Fig. 1). Through the interactions of SUN proteins with lamins and chromatin, and the interaction of KASH domain proteins with microtubules, actin filaments and intermediate filaments, a direct physical linkage is formed between the nucleoskeleton and the cytoskeleton.[41,56,57,77,84,96] Due to its interactions with Nup153, the LINC complex protein SUN1 is suggested to play a role in NPC-lamina interactions.[24,52,56] Another nucleoporin, POM121 is also known to directly but transiently interact with LINC complex protein SUN1 to initiate NPC assembly.[89]

ASSOCIATION OF NPCs WITH THE CYTOSKELETON

NPC Components Associate with Microtubules and Motor Proteins at Different Stages of the Cell Cycle

Nups play different roles in association with various cytoskeletal elements, both in interphase and mitosis. The recruitment of Nup358, also known as RanBP2, to kinetochores during metaphase is essential for proper attachment of microtubules to kinetochores. Moreover, Nup358 is shown to interact with interphase microtubules through its N-terminal region (BPN) and regulate microtubule organization and cell migration.[45] Immunoprecipitation studies have shown that human Nup358 directly interacts with adenomatous polyposis coli (APC), which plays a role in microtubule reorganization, cell polarity, and migration.[67] In addition, with the aid of kinesin-2, Nup358 regulates the localization of APC to the cell cortex, a process that is independent of the nucleocytoplasmic transport. Therefore Nup358 is recognized as a localizer of kinesin-2 and APC to the microtubule ends in proximity of the cell cortex, which regulates the dynamics of microtubules and cell polarity.[67] Nup358 is also found to directly interact with BICD2 (mammalian homologue of the Drosophila Bicaudal D, which is an adapter protein between dynein motor and its cargos) in G2 phase of the cell cycle. BICD2, in turn, regulates centrosome and nuclear positioning prior to mitotic entry through regulation of dynenin and kinesin-1[86] (Fig. 1).

Nups are also proposed to promote the attachment of microtubules and kinetochores as well as nucleation/stabilization of microtubules during mitosis.[70] For instance, Nup358, Mlp1, and Nup107-160 subcomplex relocalize to kinetochores[15,70,78] Moreover, NPC is indirectly involved in mitosis checkpoints by recruiting Mad1/Mad2 to contribute to assembly of spindle checkpoint.[75] Mad1 is anchored to the membrane by Mlp1/Tpr[15] and is required for Mad2 localization.[75] Nup153 is also suggested to be involved in localization of Mad1.[58] In the case of defective microtubule-kinetochore attachment, these two proteins (Mad1/Mad2) inhibit metaphase to anaphase transition.[28]

These observations highlight the role of the NPC as a physical link to the cytoskeleton. These linkages could help regulate various cellular functionalities such as NPC distribution on the NE, as discussed earlier.

NPCs may Indirectly Associate with the Actin Cytoskeleton and Intermediate Filaments Through Their Association with LINC Complexes

To the best of our knowledge, there is no evidence on a direct interaction between NPC components and cytoplasmic actin filaments. However, a reorganization of the actin cytoskeleton upon depletion of Nup153 suggests some direct or indirect association of NPCs with actins.[10,100] A likely candidate for this association is through LINC complexes. As previously mentioned, components of LINC directly interact with actin filaments through KASH domain proteins (Fig. 1). KASH domain proteins Nesprin 1 and 2 directly bind to actin *via* their calponin homology actin binding domains.[12,57,85] Although completely speculative at this point, if SUN1 proteins can bind simultaneously with KASH proteins while associated with NUP153,[56] they can provide a direct link between the NPC and various elements of the cytoskeleton. As a result, NPCs may indirectly experience forces from actin and intermediate filaments, which may have implications in nucleocytoplasmic transport. Indeed, the SUN1-Nup153 interaction has shown to be an integral component of mammalian mRNA export. However, it remains unclear whether this interaction depends upon the direct linkage of SUN proteins with elements of the cytoskeleton.

INTERACTIONS OF NPCs WITH THE NE

The process of NPC assembly into the NE is rather complicated, involving different types of Nups. Inducing curvature into the NE, directly interacting with the NE, or interacting with transmembrane proteins, different types of Nups cooperate to form the solid yet flexible structure of the NPC. Although there are some controversies in the field on specific details of this process as well as whether the structure of the NPC is rigid or flexible,[11,48,88] the overall procedure is studied by various research groups. Here, we briefly outline some of the key observations about how NPCs assemble and integrate into the NE.

NPC Assembly into the NE: Post-Mitotic Versus Interphase Assembly

The central channel of the NPC is made up of three functionally distinct layers of Nups, namely the FG repeat layer, the scaffold layer (also called the adapter proteins layer), and the membrane layer,[17,44,55] (Fig. 2). NPCs assemble *via* different pathways at two different stages of the cell cycle. Some NPCs assemble at the end of mitosis, when the NE and NPCs assemble concomitantly, while the rest of the NPCs are assembled during interphase and integrated into the sealed NE.[19] Several nucleoporins are identified as major regulators of NPC formation and assembly. In this section, we introduce the main role players, i.e. different Nups, involved in this process.

Independent of other proteins, Nup53 can directly interact with the nuclear membrane.[94] It is shown that the RNA recognition motif domain, a substantial domain for functionality of Nup53 in NPC assembly, is necessary for the interaction of Nup53 with membranes. Nup53 has two membrane binding domains, one at the N-terminal domain and the other at the C-terminal domain, both of which require the middle RNA recognition motif domain.[94] The RNA recognition motif is primarily responsible for dimerization of Nup53.[34] Since this motif is required for Nup53 interaction with the NE, it is suggested that dimerization is also required for its interaction with membranes. Although either of the two binding sites is sufficient for NPC assembly at the end of mitosis, the membrane binding site at the C-terminus is specifically required for NPC assembly during interphase.[94] On the other hand, in both yeast and metazoa, Nup53 interacts with transmembrane protein Ndc1, which is an essential interaction for NPC formation and assembly[22,37,61,69,92]; the N-terminal transmembrane domain of Ndc1 is necessary and sufficient for this interaction. The two observations, i.e. direct interaction of Nup53 with the NE versus the interaction of Nup53 with Ndc1, seem contradictory at the first glance. However, the interaction between Nup53 and Ndc1 is believed to counteract or fine-tune the membrane deformation capability of Nup53 for a proper NPC assembly.[22] Alternatively, it is suggested that these two functionally redundant interactions offer different modes of association between the NPC and the membrane.[94]

Nuclear basket protein Nup153 is essential for interphasic NPC assembly but not for post-mitotic assembly (Fig. 2). Through an amphipathic helix located at the N-terminus, Nup153 directly binds to the inner nuclear membrane, and, in turn, facilitates recruitment of the Nup107-160 complex (also known as the Y-complex), which is critical for NPC assembly.[93] POM121, a transmembrane nucleoporin, is also found to be critical in integration of the Nup107/160 complex into assembly sites during interphase.[20] Conversely, ELYS is shown to be crucial for NPC assembly at the end of mitosis but not during interphase. ELYS is a nucleoporin that facilitates the recruitment of the Nup107/160 complex to chromatin.[20]

Nup155 is another nucleoporin that is suggested to be essential for membrane fusion and NPC assembly in both nematodes and vertebrates[26] (Fig. 2). After the identification of early steps in NPC assembly that in-

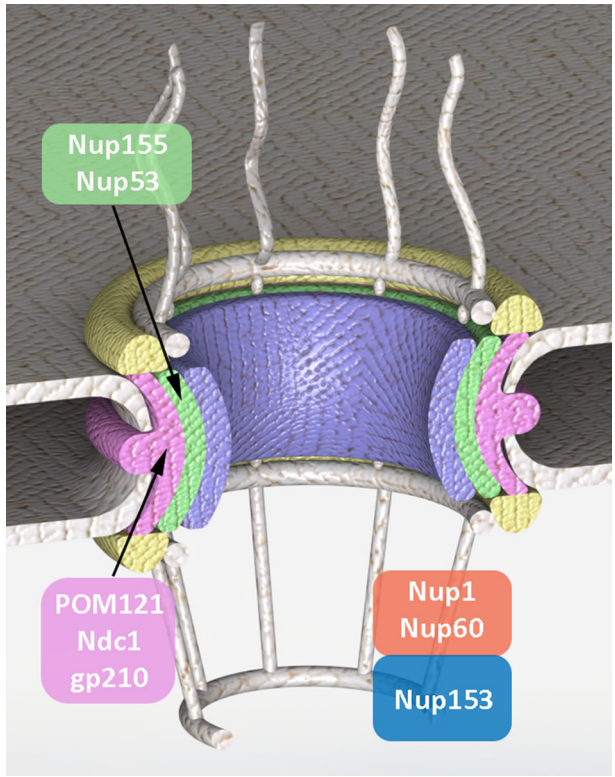

FIGURE 2. A closer view of the NPC scaffold. NPC has three distinct parts, namely the central channel, the cytoplasmic filaments, which emanate into the cytoplasm, and the nuclear basket. The central channel of the NPC is comprised of three layers of nucleoporins (Nups), namely the FG repeat layer (magenta), the scaffold layer (also called adapter proteins layer) (green), and the membrane layer (pink).[17,55] The FG layer is the innermost layer of the structure, where FG Nups, i.e. Nups rich in phenylalanine-glycine repeats, fill the inner part of the pore and facilitate transport of cargos. The scaffold layer is in between the other two layers and involves Nups such as Nup53 and Nup155, which play substantial roles in NPC formation and assembly. The membrane layer is the third layer, which primarily consists of transmembrane proteins including POM121, Ndc1, and gp210. Some of the nuclear basket proteins, including Nup1 and Nup60 from yeast (labeled in the red box) and Nup153 from mammals (labeled in the blue box), are also suggested to be involved in NPC assembly into the NE. Moreover, a specific complex of Nups, referred to as the coat Nup complex (CNC), forms an outer ring that is symmetrically located on the cytoplasmic and nuclear faces (shown in yellow).[55] Only the Nups that are discussed in this review are shown.

volve Nup107-160 complex as well as POM121[4,36,95] *in vivo* and *in vitro* studies demonstrated that Nup155 is subsequently recruited to these proteins and is required for NPC assembly.[26]

Role of Transmembrane Proteins in NPC Assembly

Nuclear pore proteins gp210,[29,98] and POM121[33] have been identified to play a role in anchoring of the NPC to the membrane (Fig. 2). Most of the structure of protein gp210 is localized inside the perinuclear space, while the small tail is exposed outside of the membrane.[98] Study of the exposed tail revealed that gp210 has an early role in NPC formation.[21] POM121 is also necessary for NE formation and NPC assembly *in vitro*.[4] On the other hand, while initial studies identified gp210 as an essential factor for NPC assembly, later studies argued any role for gp210 in this process. In line with this, while NPC assembly begins early in NE formation, gp210 is recruited to the membrane relatively late.[4]

Nucleoporins Induce Curvature into the NE

Recent *in vitro* and *in vivo* experiments revealed a direct interaction among nuclear basket proteins, namely Nup1 and Nup60, with the inner nuclear membrane[63] (Fig. 2). Specific conserved domains of yeast Nup1 and Nup60 are shown to interact with nuclear membrane and induce membrane curvature. Amphipathic helices are commonly known to induce membrane curvature.[62] Bipartite motifs consisting of an amphipathic helix accompanied by an alpha-helical region are suggested to facilitate this curvature induction by combining both hydrophobic insertion and scaffolding mechanisms.[63] This mechanism is supported by various observations including *in vitro* bending of membranes by Nup1 and Nup60 and *in vivo* reshaping of the nuclear membrane at high levels of Nup1. In addition, it was previously observed that Nup60 has some affinity to phospholipid bilayers, lending more support to the role of Nup60 in inducing membrane curvature.[71]

The putative viewpoint on the formation and assembly of the NPC depicts a rather complicated procedure involving several Nups and transmembrane proteins. One interesting aspect of such a complex structure could be associated with the hypothesis that NPCs could change their diameter based on cargo concentration inside the pore, i.e. demand for transport.[48] However, this hypothesis has been debated.[11,88] Ultimately, the association of all the involved proteins as well as protein complexes lead to formation of an octagonal structure with eight identical spokes. Theoretical studies have suggested that this eightfold symmetry maximizes the bending stiffness of each of the eight individual spokes, facilitating transport through the nuclear pore.[97]

INDIRECT CONTRIBUTION OF THE NPC IN ESTABLISHING THE LINKAGE BETWEEN THE CYTOSKELETON AND THE NUCLEOSKELETON

Proper localization of inner nuclear membrane proteins to the NE depends on their active transport through the NPC into the nucleus. Depletion of karyopherins importin-α and importin-β has been shown to disrupt the localization of Heh1 and Heh2 to the inner nuclear membrane.[47] Lamin B receptor (LBR) is also found to bind Ran[60] and importins[7] and its translocation depends on the Ran function.[101] Some of the LINC complex components also follow the same process. In *C. elegans*, localization of the SUN protein UNC-84 to the inner nuclear membrane is suggested to require active transport through the NPC to be able to appropriately localize to the inner nuclear membrane and form the LINC complex.[90] SUN2 is also found to possess a classical nuclear localization signal, as well as a perinuclear domain, that contribute to the localization of this protein to the inner nuclear membrane *via* transport through the NPC.[91] Therefore, these observations suggest an indirect role for NPC to regulate the formation of a physical bridge between the cytoskeleton and the nucleoskeleton in eukaryotic cells.

CONCLUSION

The NPC is widely known for its chief role as the exclusive gateway for controlling the bidirectional traffic into and out of the nucleus. However, evidence on the interactions between the NPC components with the NE, cytoskeletal elements and the nucloskeleton suggests another essential role for the NPC as a physical linker between these important cellular components. One could therefore speculate that transport through the NPC is associated with cytoskeletal or nucleoskeletal signals, which are, in turn, partly regulated by extracellular cues. NPCs contribute to the regulation of gene expression by controlling transport of cargos, including mRNAs. This is further supported by recent evidence on the role of SUN1, which is suggested to interact with nucleoporins in mRNA export.[52] On the other hand, NPCs are subjected to NE tensions. LINC complexes, which are embedded in the NE, are linked to both the cytoskeleton and the nucleoskeleton, and also interact with NPC components.[56,52] Therefore, either directly or indirectly

through the NE or LINC complexes, NPCs are exposed to cytoskeletal and nucleoskeletal signals.[6] Moreover, NPCs interact with elements of the nucleoskeleton and the cytoskeleton to mediate vital processes such as cytoskeletal organization, cell motility, and gene expression,[8,10,18,100] further lending support to the potential role of the NPC in mechanotransduction.[65] Nonetheless, few studies have examined the functional implications of NPCs as a physical linkage between the two compartments of the cell and their contribution to the regulation of nucleo-cytoskeletal coupling and mechanobiology. Further studies are required to evaluate the credibility of these hypotheses and their implications in various cellular functions.

CONFLICTS OF INTEREST

M. Soheilypour, M. Peyro, Z. Jahed and M. R. K. Mofrad declare that they have no conflicts of interest.

ETHICAL STANDARDS

No human studies were carried out by the authors for this article. No animal studies were carried out by the authors for this article.

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