Dissecting the NUP107 complex
Multiple components and even more functions

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The nuclear pore complex (NPC) is a fascinating structure whose functional relevance and complexity attract significant interest. Within the NPC, several different subcomplexes interact with each other to form a highly conserved and stable structure. One of these subcomplexes is the NUP107 complex, constituted by 7–9 members. A wide variety of functions have been ascribed to the NUP107 complex, ranging from NPC assembly to mRNA export to cell differentiation. Recently, genetic dissection of the NUP107 complex has provided novel insight to the assembly of the complex and has, moreover, revealed an unexpected connection with the mitotic spindle assembly checkpoint protein MAD1.

The structure of the NPC is defined by the presence of different modules: a cylindrical central scaffold that forms the channel, cytoplasmic filaments and the nuclear basket. The central scaffold has an 8-fold symmetry along the vertical axis and forms five coaxial rings: a membrane ring, two adjacent inner rings and two outer rings facing the nucleus and the cytoplasm, respectively. Nups containing transmembrane domains are responsible for anchoring the NPC to the NM and interact with structural nups in the central scaffold, whereas nups with phenylalanine-glycine (FG) repeats occupy the central channel to maintain a selective permeability barrier. Finally, the nuclear basket and cytoplasmic fibrils are formed by nups that contribute to specific nuclear import and export processes.

In recent years, an increased interest for the NPC has arisen since nups, apart from their role in nucleocytoplasmic transport, have been involved in many other cellular processes such as regulation of gene expression, epigenetic and heterochromatin regulation, DNA repair, and mitotic spindle formation. Here, we discuss the latest discoveries on one of the most studied subcomplexes of the NPC, the NUP107 complex.

**The NUP107 Complex: Structure and Function During Interphase**

The NUP107 complex [Nup107 in Saccharomyces cerevisiae; despite high degree of conservation of most nups, different gene names are applied to almost each organism, but for simplicity we will predominantly use human nomenclature...
Finally, structural work from the Blobel laboratory has led to a fence-like model in which 32 copies of the NUP107 complex assemble into four horizontal rings connected to transmembrane nups on the outside and adaptor and channel nups on the inside. The two latter models both place the NUP107 complex in a head-to-tail orientation, which is compatible with recent mutational analyses demonstrating that NUP133 can localize to NPCs independently of NUP107 (see below). Moreover, applying polarized fluorescence microscopy to determine the orientation of nups in living cells also supported the idea that the NUP107 complex is parallel to the NE plane. However, further studies are needed before a final conclusion can be reached on the position of the NUP107 complex.

The NUP107 complex is a key player early in NPC biogenesis both in interphase and mitosis. EM and cryo-electron tomography have provided important insight into NPC architecture, but the resolution has not been sufficient to unequivocally place the Y-shaped NUP107 complex within the NPC. Instead, several groups have used alternative methods, which has led to different working models. Based on structural similarity between several NUP107 complex members and components of COPII vesicle coats Schwartz and colleagues suggested that 16 copies of the NUP107 complex are arranged orthogonally to the plane of the NE in a lattice with the short arms of the Ys facing toward each other, possible bridged by NUP93 complexes. Rout and coworkers proposed based on a computational approach that the NUP107 complex is oriented parallel to the plane of the NE, forming two outer rings, each consisting of eight copies of the complex, and separated by inner rings.

Figure 1. Structure and location of the NUP107 complex. (A) Schematic representation of the NPC. Nups forming the cytoplasmic fibrils, the central scaffold and the nuclear basket are depicted. In colors are highlighted the components of the five coaxial rings of the central scaffold. (B) Structure of the NUP107 complex. Location of NUP37 and NUP43 within the Y shaped structure is unknown although a possible physical interaction between NUP43 and NUP107 has been suggested. Due to the stable interaction of ELYS with the NUP107 complex, its enrichment at NPCs and kinetochores, and its critical role in recruiting the NUP107 complex to these structures, ELYS protein could be considered a tenth member of the NUP107 complex. (C) Localization of NUP107 in C. elegans early embryos. In interphase, the NUP107 complex accumulates at the NE as part of the NPC whereas during mitosis NUP107 associates with kinetochores. Overlay images show the NUP107 complex in red, tubulin in green and DNA in blue.
and mitosis (Table 2). During interphase when the NMs enclose the nucleus, the recruitment of nups to form novel NPCs represents a challenge. However, the discovery that the NUP107 complex shares structural similarity with COPII vesicle coats and the observation that some of its members (NUP133, SEH1 and SEC13) have domains that may act to stabilize the curvature of the NMs in the pore, suggest that the NUP107 complex may act in interphase NPC assembly during or immediately after fusion of the outer and inner NMs.

In *S. cerevisiae*, most members of the NUP107 complex are not critical for growth at normal temperature, but deletions become lethal in combination with other nup mutations or under stress conditions (Table 1). In vertebrates, inhibition of any of the NUP107 complex members frequently leads to the dissociation of the entire complex, which has been an obstacle to a detailed molecular understanding of how the complex functions. A noteworthy exception was the identification of a NUP133 allele, which causes embryonic lethality at day 9.5–10.5 of mouse embryonic development, but without affecting localization of other nups including NUP107 complex members. Interestingly, expression of NUP133 was found to be restricted to specific tissues and developmental stages, further arguing that NUP133 is not required for general NPC function. Moreover, a recent study

### Table 1. NUP107 complex members in selected organisms

| Human | Drosophila melanogaster | Caenorhabditis elegans | Saccharomyces cerevisiae | Schizosaccharomyces pombe | Aspergillus nidulans | Ustilago maydis | Arabidopsis thaliana |
|-------|-------------------------|------------------------|-------------------------|---------------------------|---------------------|-----------------|---------------------|
| NUP37 | CG11875                 | -                      | Nup37                   | Nup37                     | -                   | -               | -                   |
| NUP45 | Nup43                   | -                      | NPP-23                  | -                         | -                   | -               | -                   |
| NUP55 | Nup55                   | NPP-21                 | Nup85                   | Nup85                     | NUP85               | -               | -                   |
| NUP96 | Nup96                   | NPP-32                 | Nup107                  | Nup107                    | NPP-40              | Nup84          | NUP107              |
| NUP107| Nup107                  | NPP-41                 | Npp120                  | Nup120                    | Nup120              | Nup120         | NUP160              |
| NUP133| Nup133                  | NPP-13                 | Nup133                  | Nup133                    | NPP-13              | Nup133         | NUP133              |
| NUP160| Nup160                  | NPP-16                 | Nup160                  | Nup160                    | NPP-16              | Nup160         | NUP160              |
| SEH1  | Nup44A                  | NPP-18                 | Seht1                   | Seht1                     | Seht1               | Seht1          | SEH1                |
| SEC13 | Sec13*                  | NPP-20                 | Sec13*                  | Sec13*                    | Sec13*              | Sec13*         | Sec13*              |

Curated protein names as they appear in model organism repositories are indicated when possible. For simplicity, human nomenclature is used throughout the text. Asterisks indicate that genetic disruption has a severe impact on organismal survival; mutational analysis has still not been reported for most genes.

### Table 2. Overview of functions ascribed to the NUP107 complex

| Function | Organism (NUP107 complex component and reference) |
|----------|--------------------------------------------------|
| NPC biogenesis and organization | Vertebrates (NUP107 complex20,22; C. elegans, NUP96, NUP16010, NUP107, NUP133, NUP16021, N. pombe, NUP133, NUP16022); S. cerevisiae (NUP85, NUP96, NUP107, NUP133, NUP16023, S. pombe [NUP133, NUP16024]); |
| mRNA export | Vertebrates (NUP96, NUP133, NUP16025, S. cerevisiae [NUP85, NUP107, NUP133, NUP16026, S. pombe [NUP133, NUP16027]); S. cerevisiae [NUP107, NUP133, NUP16028]); |
| Gene activation | D. melanogaster (SECH1) |
| Transcriptional elongation | S. cerevisiae (NUP107, NUP133, NUP16029); S. pombe (NUP133, NUP16030); |
| Membrane stabilization | Vertebrates (NUP133, S. cerevisiae, NUP160, SEH1, SEC13, A. nidulans [NUP107, NUP133, NUP16031]); |
| Kinetochore function | Vertebrates (NUP133, SEH1, NUP107 complex32, C. elegans [NUP10733]); |
| MAD1 localization | C. elegans (NUP10734); |
| Centrosome attachment | Vertebrate (NUP133) |
| Telomere anchoring and silencing | S. cerevisiae (NUP96, NUP107, NUP133, NUP16035); |
| DNA repair | S. cerevisiae (NUP107, NUP133, NUP16036); |
| Immunity | Vertebrate (NUP9637, A. thaliana [NUP96, NUP160, SEH138]); |
| Neural differentiation | Vertebrate (NUP133); |
| Hybrid inviability | D. melanogaster [NUP16039]; |
| Cold stress tolerance | A. thaliana [NUP16040]; |

See text for details.
in the nematode *Caenorhabditis elegans* has shown that also the NUP107 protein is dispensable for assembly of the NUP107 complex and its anchoring to other nups.37 In *C. elegans* NUP107 null embryos, the members of the NUP107 complex, with the exception of NUP43 that was partially displaced, localized properly at the NPC during interphase.53 This provided the first test of the localization of NUP43 in the Y structure and it also supported the idea that NUP133 can be anchored to the NPC through interaction with other nups apart from NUP107. Importantly, other nups not forming part of the NUP107 complex were also localized correctly in *C. elegans* embryos lacking NUP107.54-57 Demonstrating that the requirement for the NUP107 complex in both interphase and post-mitotic NPC assembly58-60 is independent of NUP107 protein. Concordantly, an exhaustive analysis of the effect of truncations of individual subunits of the NUP107 complex in *S. cerevisiae* showed that both NUP133 and NUP160 can be assembled into the NPC independently of their interactions with the rest of the NUP107 complex subunits.60-61 Also, the study identified the three tips of the Y as the critical regions for connection of the NUP107 complex with the NPC and demonstrates that in particular the short arms of the Y are important for cell fitness. These data contrast with the observation that human NUP133 fused to GFP required the NUP107 interaction to be assembled into the NPC.62 However, the addition of a GFP molecule to different components of the NUP107-160 complex has in several cases altered their interaction with other nups.63-65 This implies that future analyses are required to confirm whether endogenous human NUP133 resembles its yeast and nematode counterparts or depends on direct interaction with NUP107 for NPC targeting. Constituents of the NUP107 complex are stably associated with NPCs in interphase, suggesting they are part of the NPC structural scaffold.66-68 Although in yeast, components of the NUP107 complex interact with the RAN GTPase machinery, nuclear import and export of molecules mediated by the RAN-GTP gradient seem to work properly in NUP107 complex mutants.69-71 In contrast, the export of mRNAs is severely affected in cells lacking one or several NUP107 complex members.72-75 While most studies have focused on bulk mRNA export, NUP96-deficient mouse cells appear to have specific defects in nuclear export of immune-related mRNAs (Table 2).76 Unlike the export of most other molecules, mRNA export does not depend on a RAN-GTP gradient driven by the ATPase activity of the helicase DDX19/Dhp5 that localizes to the cytoplasmic fibrils of the NPC.77 In *S. cerevisiae*, NUP85 binds directly the mRNA adaptor NXf1/Mex67 and mutations that prevent this interaction inhibit specifically export of mRNA but not export of tRNA or ribosomal subunits.78 The precise role of the NUP107 complex in mRNA export is still unknown but could be to facilitate the interaction of NXf1/Mex67 with FG-repeat nups lining the transport channel during translocation through the NPC or to stimulate mRNA release into the cytoplasm.79 An unexpected interaction with Centrin 2 (CETN2), which mainly has been investigated in the context of centrosome function, in both human and *Xenopus laevis* also points to a role of the NUP107 complex in mRNA export: In vitro binding assays and co-immunoprecipitation experiments revealed that Centrin 2 binds to NUP160 and perturbation of Centrin 2 expression leads to nuclear accumulation of mRNA.80 The role of the NUP107 complex in gene expression is not restricted to nuclear-cytoplasmic transport (Table 2). Recent studies have shown that the NPC can facilitate genome organization, interacting with both heterochromatin and euchromatin. Genome-wide analyses in yeasts and flies have shown that many nups are associated with highly transcribed, developmental and stress-induced genes.81-83 In this context, *S. cerevisiae* NUP107 and NUP133 mutants have transcription elongation defects in vitro, probably as an indirect effect of the coupling between transcription and mRNA export.84 Intriguingly, studies in *Drosophila melanogaster* have demonstrated that some mobile nups (NUP50, NUP62 and NUP98) and SEC13 from the NUP107 complex can affect transcription in the nuclear interior.85-87 Unlike in yeast, regulation of transcription by nups in the nuclear interior does not affect transcription elongation and SEC13 associates with active genes away from the nuclear envelope (NE) before the recruitment of RNA polymerase II.88 Despite the role of the NUP107 complex in gene activation, genome-wide analysis in *S. cerevisiae* showed that members of the complex were coregulated with the silent HMR locus and telomeres to the nuclear periphery.89-91 Anchoring to the NE is required not only for silencing but also for efficient DNA damage repair at subtelomeric regions.92-94 Although DNA repair can occur away from the nuclear periphery, the NUP107 complex interacts with components of both the DNA repair and SUMO pathways and recruits sumoylation enzymes to the NE, thereby potentiated repair of persistent double strand breaks and collapsed replication forks.95,96

**Mitotic Functions of Nups**

In addition to the well-established role of NPCs in nuclear-cytoplasmic transport, growing evidence show that the NUP107 complex as well as other nups also have important functions during mitosis.97-99 At least four connections have been established between nups and the cell division machinery: (1) control of centrosome positioning; (2) binding of nups to kinetochores; (3) control of spindle assembly checkpoint (SAC) protein localization and (4) regulation of anaphase onset. Accurate chromatin segregation by the mitotic spindle is pivotal to cell and organismal survival and rely on several surveillance mechanisms and partially redundant pathways. When metazoan cells enter mitosis the NE breaks down and microtubules emanating from the centrosomes capture the condensing chromosomes to form stable attachments at kinetochores (K-fibers).99-101 Prior to NE breakdown the duplicated centrosomes separate along the NE to opposite sides of the nucleus in a dynein-dependent manner.99 Attachment of centrosomes to the NE requires specific outer and inner NM proteins harboring KASH and SUN domains, respectively.102

![Image](https://example.com/image.png)
In addition, a recent study of the dynein adaptor Bicaudal D2 (BICD2) identified RANBP2/NUP358 as a novel regulator of centrosome-NE interaction in HeLa cells.\(^5\) RANBP2 was found to recruit C. elegans Bic-CaD2 (BICD2) identified in centrosome positioning to serve as a binding site for BICD2.\(^2\) An alternative centrosome positioning pathway involving nups was identified through an analysis of NUP133 and CENP-F in HeLa cells.\(^5\) CENP-F accumulates at the NE at G2/M transition (thus slightly later than BICD2) through an interaction with the N-terminus of NUP133. Knockdown of NUP133 in HeLa cells prevented NE localization of CENP-F, which in turn is responsible for targeting dynein to the nuclear periphery in prophase. Depletion of either NUP133 or CENP-F produced a similar centrosome detachment phenotype in prophase. Presumably due to centrosome mis-positioning, mitotic spindle morphology was initially aberrant, but functional spindles were eventually assembled and chromosome segregation occurred normally.\(^5\) Centrosome positioning is determinant for mitotic spindle orientation and hence the plane of cytokinesis. An RNAi screen of oocyte-enriched genes revealed that several nups (NUP54, NUP62, NUP93 and NUP205) are required for proper spindle orientation in C. elegans embryos.\(^6\) An RNAi screen of C. elegans cell lines showed no defect in inter-kinetochore distance and found similar ~40% less NDC80 complex protein in SEH1-depleted cells.\(^7\) Nevertheless, it is remarkable that localization of the NUP107 complex on one hand and CENP-F and the NDC80 complex on the other is interdependent. Another indication that nups are important for proper kinetochore structure comes from cold treatment studies. Defective kinetochore function can be detected by the lack of cold-stable K-fibers. In two studies, depletion of either RANBP2 or SEH1 from HeLa cells caused a dramatic decrease in quantity of cold-stable microtubules, and inter-kinetochore distance was reduced by 50% in cells treated with SEH1 siRNAs, suggesting that the NUP107 complex is required for proper tension-generating kinetochore-microtubule attachments.\(^8\) However, a similar study using SEH1 siRNAs to interfere with the NUP107 complex reported at modest (6%) decrease in inter-kinetochore distance and found similar density of cold-stable K-fibers as in control cells.\(^9\) Instead, SEH1-depleted cells had ~40–80% less AURKB/Aurora B associated with metaphase chromosomes.\(^9\) C. elegans NUP107 null embryos likewise show no defect in inter-kinetochore distance, and Aurora B recruitment is reduced by 34% (see below).\(^9\) In addition to serve as binding platforms for microtubules emanating from centrosomes, kinetochore nups can also function as sites for microtubule nucleation. Combined nocodazole and cold treatment revealed...
that the NUP107 and γ-TuRC complexes are required at kinetochores for efficient microtubule re-growth.19 Moreover, the NUP107 complex was found to be responsible for recruiting the γ-TuRC complex to kinetochores. In agreement with these findings, depletion of the NUP107 complex from X. laevis embryos leads to formation of abnormal spindles in vitro,20 however, robust mitotic spindles are still formed in SEH1 siRNA-treated human cells and C. elegans null embryos.21,22 Errors in kinetochore-microtubule attachment occur even during normal cell division but are detected and corrected by the spindle assembly checkpoint (SAC) during mitotic phase (Fig. 2A).23-27 In interphase, SAC proteins MAD1 and MAD2 localize at NPCs in interphase. Throughout the eukaryotic cell cycle, MAD1 and MAD2 localize at NPCs. At least four nups (NUP35, NUP153, NUP153 and TPR) are implicated in recruiting MAD1. (B) During mitosis, the NUP107 complex accumulates at kinetochores where it interacts with CENP-F, the NDC80 complex, ELYS, RANBP2, and the γ-TuRC complex. Depletion of NUP107 affects kinetochore function and reduces AURKB/Aurora B recruitment. MAD1, which detects unattached kinetochores, accumulates on mitotic chromatin in the absence of NUP107. TPR localizes to the mitotic spindle matrix and is important for proper MAD1 function. Chromatin is shown in blue; centrosomes and microtubules in pink. See text for details.

Figure 2. Interaction of the NUP107 complex with cell division components. (A) In interphase, SAC proteins MAD1 and MAD2 localize at NPCs. At least four nups (NUP35, NUP153, NUP153 and TPR) are implicated in recruiting MAD1. (B) During mitosis, the NUP107 complex accumulates at kinetochores where it interacts with CENP-F, the NDC80 complex, ELYS, RANBP2, and the γ-TuRC complex. Depletion of NUP107 affects kinetochore function and reduces AURKB/Aurora B recruitment. MAD1, which detects unattached kinetochores, accumulates on mitotic chromatin in the absence of NUP107. TPR localizes to the mitotic spindle matrix and is important for proper MAD1 function. Chromatin is shown in blue; centrosomes and microtubules in pink. See text for details.
This opens the possibility that at least in C. elegans and humans MAD1 and NUP107 may translocate together from NPCs to kinetochores at mitosis onset. Although NUP107 is not required for MAD1 accumulation at unattached kinetochores, NUP107 may influence the dynamics or activities of MAD1. In support of this, C. elegans NUP107 null embryos are more sensitive to cellular stress, such as cyclin B3 depletion or hypoxia, which normally are detected by the SAC.27 We also note that MAD1 has recently been reported to function in K-fiber formation independently of MAD2,28 suggesting that NUP107 could regulate MAD1 in processes not directly related to the SAC.

When correct bipolar attachment of all kinetochores is achieved, CDC20 is released from SAC proteins and together with EZR1/CDH1 activates the anaphase promoting complex/cyclosome APC/C.29 APC/C induces separation of sister chromatids through degradation of cyclin B and Securin. Interestingly, also this step of mitosis is being regulated by nups since NUP98 and RAE1 can form a complex with APC/C, thereby inhibiting degradation of securin.30 As consequence, mice with reduced levels of NUP98 and RAE1 suffer from aneuploidy.

Conclusion and Future Outlook

Careful genetic manipulations are instrumental to unravel the precise function of individual nups and dissection of the NUP107 complex has yielded insight into the assembly of this crucial NPC subunit. Thus, depletion of individual members, including NUP107 and NUP133, has demonstrated that NPC assembly and function is surprisingly robust against perturbations. However, further analyses are required before we completely understand the molecular details of the NUP107 complex and its contributions to NPC function. In particular, it is important to keep in mind that the configuration of the NUP107 complex may differ between tissues and developmental stages, which add another layer of complexity.

The intriguing discovery of the NUP107 complex at kinetochores is now well-established, but the functional implications remain to be characterized in depth. Interactions with kinetochore components have been described, but certain ambiguity exists. Determination of the kinetochore targeting mechanism for the NUP107 complex is incomplete and requires further interaction studies with bona fide kinetochrome proteins as well as other kinetochrome nups, such as ELYS and RANBP3. Finally, the novel link between the NUP107 complex and SAC protein MAD1 deserves to be explored, including in other organisms.

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