

REVIEW

Nuclear pore proteins and the control of genome functions

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Nuclear pore complexes (NPCs) are composed of several copies of ~30 different proteins called nucleoporins (Nups). NPCs penetrate the nuclear envelope (NE) and regulate the nucleocytoplasmic trafficking of macromolecules. Beyond this vital role, NPC components influence genome functions in a transport-independent manner. Nups play an evolutionarily conserved role in gene expression regulation that, in metazoans, extends into the nuclear interior. Additionally, in proliferative cells, Nups play a crucial role in genome integrity maintenance and mitotic progression. Here we discuss genome-related functions of Nups and their impact on essential DNA metabolism processes such as transcription, chromosome duplication, and segregation.

Eukaryotic chromosomes are enclosed by the double-lipid bilayer of the nuclear envelope (NE), which is perforated at multiple sites by nuclear pore complexes (NPCs). NPCs are large protein structures mediating macromolecular trafficking between the nuclear and cytoplasmic compartments. Each NPC is composed of multiple copies of ~30 different subunits, called nucleoporins (Nups), arranged in octagonal rotational symmetry around the central transport channel. In vertebrates, this molecular assembly has a molecular weight of ~120 MDa and can be structurally divided into a core scaffold formed by the Nup93/Nup205 complex and two rings composed of the Nup107/Nup160 complex flanking the former in the vertical plane (Fig. 1; D'Angelo and Hetzer 2008; Hoelz et al. 2011). Attached to the inner side of this structure are the so-called FG-Nups, which contain natively unfolded phenylalanine-glycine (FG) domains such as the Nup62 complex, establish the selective permeability barrier, and regulate receptor-mediated translocation through the NPC (Wente and Rout 2010; Grossman et al. 2012). Somewhat surprising for a membrane-embedded complex, there are only three known transmembrane Nups (Pom121, Ndc1, and Gp210), which link the NPC to the NE (Fig. 1). The nuclear pore is completed by peripheral filamentous protein complexes that extend into the cytoplasm and nucleoplasm, referred to as the cytoplasmic filaments and nuclear basket, respectively (D'Angelo and Hetzer 2008; Hoelz et al. 2011).

Cytoplasmic filaments are mainly formed by Nup358/RanBP2, Nup214, and Nup88, while the nuclear basket is composed of Nup153 and Tpr (Fig. 1; for Nup orthologs, see Rothballer and Kutay 2012).

The selective access of regulatory factors into the nucleus and export of specific RNA molecules mediated by the NPC is required for the accurate progression of most major cellular processes. However, our perception of the NPC components is rapidly evolving, as accumulating evidence indicates that they can also directly impact DNA metabolism by genome-related functions (Liang and Hetzer 2011). Among these, one of the most remarkable and well-conserved roles of Nups is to associate with specific target genes to regulate their transcriptional activity (Casolari et al. 2004; Taddei et al. 2006; Capelson et al. 2010; Kalverda and Fornerod 2010; Vaquerizas et al. 2010; Liang et al. 2013; Pascual-Garcia and Capelson 2014). Importantly, these gene regulatory functions are not limited to NE-embedded NPCs in metazoans, as peripheral Nups can perform the same tasks in the nuclear interior (Capelson et al. 2010; Kalverda et al. 2010). Although initial reports mainly highlighted the function of Nups in transcriptional activation, recent evidence supports NPC components as general transcriptional regulators associated with both transcriptionally permissive and repressive activities.

It is still uncertain how NPC components could modulate gene expression, but it has been proposed that Nups might mediate this function by influencing the chromatin landscape. Indeed, the NE, as the largest physical scaffold of the nucleus, has been historically suggested to influence the nonrandom organization of the eukaryotic chromosomes and thus their functions (Akhtar and Gasser 2007; Mekhail and Moazed 2010; Van de Vosse et al. 2011). High-resolution images of the nuclear structure of different mammalian cell types revealed that the NE is underlain by the nuclear lamina, an intermediate filament structure that generally associates with heterochromatin, interrupted by decondensed euchromatin patches under the NPCs (Belmont et al. 1993; Schermelleh et al. 2008).

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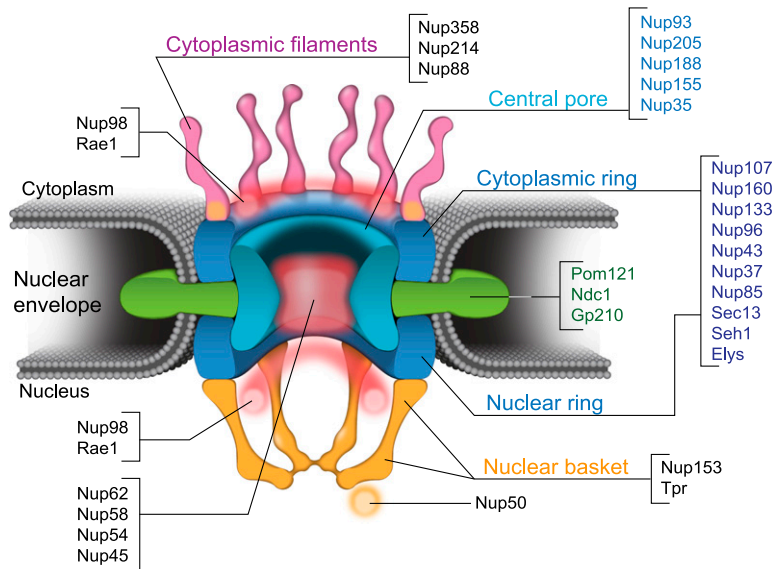


Figure 1. NPC structure and molecular composition. Representation and predicted molecular composition of the vertebrate NPC. For the corresponding orthologs in other model organisms, see Rothballer and Kutay (2012). The NPC core scaffold and its components are represented in dark blue and light blue, the transmembrane subunits are shown in green, the cytoplasmic structures are represented in magenta, and the basket is shown in orange. Peripheral Nups showing higher mobility by FRAP, and other approaches are depicted in black.

These observations suggested that NPC components might influence chromosome compartmentalization, chromatin structure, or chromatin organization, generating differentially regulated regions.

NPC number and structure are coordinated with cell cycle progression, suggesting that Nups might play additional roles in genome propagation and maintenance in proliferating cells. The most dramatic structural change of the metazoan NPC takes place at the onset of mitosis, when individual Nups become heavily phosphorylated, and NPCs are disassembled (Hetzer 2010; Doye 2011; Laurell and Kutay 2011). Subsequently, NPC subunits relocate to mitotic substructures, primarily the kinetochores, and many of them display mitotic-specific functions in spindle assembly or anaphase onset, for example (Wozniak et al. 2010). During mitotic exit, NPCs reassemble into the reforming NE, and their number is roughly doubled during interphase (Doucet et al. 2010). In particular, NPC components also influence the dynamics of S phase and contribute to genome integrity maintenance, avoiding the accumulation of DNA lesions (Loeillet et al. 2005; Nagai et al. 2008; Bermejo et al. 2011). Here we review recent literature highlighting functions of Nups in transcriptional regulation and chromatin organization, genome duplication and preservation, and chromosome segregation.

Gene expression regulation by NPC components

Transcriptional regulation in yeast

The association of NPCs with decondensed, presumably active, chromatin regions was initially interpreted as a mechanism to couple transcription of active genes with mRNA export, the so called “gene gating” hypothesis (Blobel 1985). According to this idea, gene tethering to the NPCs would result in mRNA nuclear export and influence mRNA production as well. Anchoring of active genes to the NPCs has been shown for a large number of

yeast genes. Some of the best-characterized examples are inducible genes, whose expression can be stimulated by environmental changes, and their activation correlates with subnuclear relocalization. For instance, temperature or nutrient shifts induce the expression of genes such as *HSP104*, *HXK1*, *INO1*, *SUC2*, or the *GAL* genes, among others, which are specifically activated and recruited to the NPC (Brickner and Walter 2004; Casolari et al. 2004; Cabal et al. 2006; Dieppois et al. 2006; Taddei et al. 2006; Sarma et al. 2007; Light et al. 2010). Tethering to the NPC is thought to provide optimal transcriptional activity of these genes and can be facilitated by several NPC substructures, primarily the basket components, and assisted by the transcriptional activator SAGA and the mRNA export machinery (Rodriguez-Navarro et al. 2004; Cabal et al. 2006; Taddei et al. 2006; Light et al. 2010; Dieppois and Stutz 2010; García-Oliver et al. 2012). Experiments using Nup2 fused to micrococcal nuclease indicated that Nups tend to bind the promoter regions of inducible genes, suggesting that Nup-promoter interactions might represent an early event in the transcriptional activation of a subset of genes such as the *GAL* genes (Schmid et al. 2006). The recruitment of inducible genes to the NPC also relies on the presence of specific DNA elements within the promoter region, called gene recruitment sequences (GRSs). Genes that associate with Nup2, Mlp1, Mlp2, Nup60, or Nup116 show enrichment of GRSs at their promoters (Ahmed et al. 2010; Light et al. 2010). To date, three different classes of GRSs have been identified as necessary and sufficient to regulate association with the NPC. Mutating the GRSs present in the promoter area of the inducible *INO1* or *TSA2* genes blocks their interaction with the NPC, and, when artificially inserted in typically nucleoplasmic loci, GRS-containing regions can relocate them to the NPC (Ahmed and Brickner 2010; Ahmed et al. 2010; Light et al. 2010). Interestingly, this mechanism might be conserved in other species, as GRS-mediated targeting to the NPC was also observed in *Schizosaccharomyces pombe* (Ahmed et al. 2010), and the *HSP-16.2*

promoter seems sufficient to anchor chromatin at the nuclear periphery in *Caenorhabditis elegans* (Rohner et al. 2013), although more precise technical approaches will be necessary to determine whether particular DNA motifs could mediate Nup association with chromatin in multicellular organisms.

The role of NPCs in transcriptional regulation does not seem to be restricted to inducible genes but extends to constitutively active genes. Identification of Nup-binding sites throughout the genome by chromatin immunoprecipitation (ChIP) coupled to DNA microarray analysis (ChIP-chip) suggested that NPC basket components Nup2, Nup60, and Mlp1/2 along with scaffold components Nic96 and Nup116 occupy regions with high transcriptional activity (Casolari et al. 2004, 2005). Even if some of these NPC–chromatin interactions might require further validation by imaging, highly expressed ribosomal and glycolysis-related genes are associated to the NPC, and Nup2 was detected to bind the promoter of constitutively active genes (Casolari et al. 2004, 2005; Schmid et al. 2006; Yoshida et al. 2010; Van de Vosse et al. 2013). Altogether, these observations indicate that NPC tethering correlates with transcriptional activity (Fig. 2).

Association of NPC components with genes may result in negative regulation of transcriptional activity as well, extending the role of Nups as multifaceted players in gene expression control. In *Saccharomyces cerevisiae*, subtelomeric regions and silent mating type loci represent repressed regions. The ability of Nups to influence the efficient silencing and localization of these regions remains under debate and requires further clarification (Galy et al. 2000; Feuerbach et al. 2002; Hediger and Gasser 2002; Hediger et al. 2002; Gartenberg et al. 2004; Therizols et al. 2006; Ruben et al. 2011; Van de Vosse

et al. 2013). However, recent reports have proposed that a subset of scaffold components, including Nup133, Nup84, and Nup170, might participate in the efficient silencing of subtelomeric regions (Therizols et al. 2006; Van de Vosse et al. 2013). Negative gene regulation has also been observed for the ribosomal protein genes (which appear to be associated with the yeast NPC core components, and down-regulation of Nup170 increases the expression of these genes [Yoshida et al. 2010; Van de Vosse et al. 2013]) as well as inducible genes (as binding of *GAL1* to Nup1 down-regulates its transcriptional activity [Green et al. 2012], and Nup120 and Nup133 were reported to facilitate *SUC2* repression [Sarma et al. 2011]). Therefore, NPC components can promote transcriptional repression as well and, as such, could be considered focal points for transcriptional regulation (Fig. 2).

Gene expression regulation in metazoans

While in yeast most, if not all, gene–Nup interactions occur at the NE, the situation is more complex in metazoans, where Nups are not spatially restricted to the NPC but can interact with the genome at sites that are not associated with the NE. Fluorescence recovery after photobleaching (FRAP) experiments in mammalian cells show strikingly different residence times of Nups at the NPC (Rabut et al. 2004). On the one hand, NPC core components are extremely stable, with residence times of several hours at the nuclear pore (Rabut et al. 2004) and even up to months or years in post-mitotic cells, as shown by protein turnover analyses (Fig. 1; Savas et al. 2012; Toyama et al. 2013). In contrast, most peripheral Nups show dynamic association with the NPC, with residence times ranging from seconds to minutes (Fig. 1; Rabut et al.

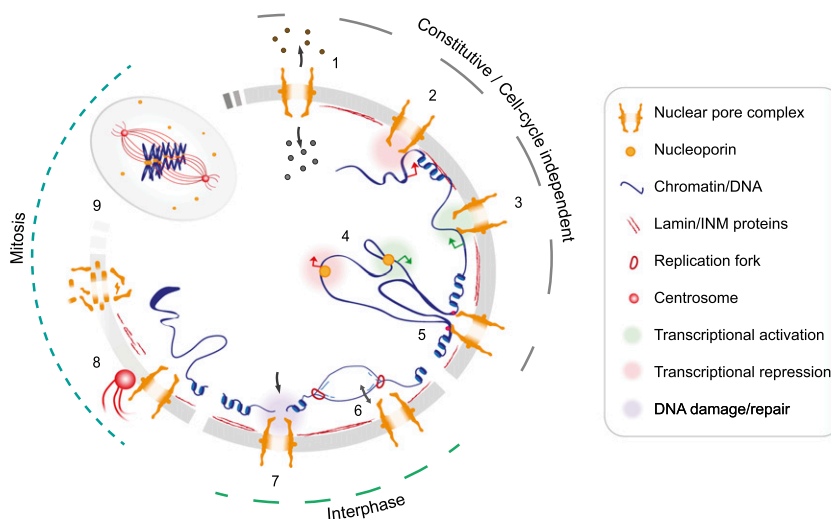


Figure 2. How NPC components affect genome functions. Proposed roles for NPC components in eukaryotic cells regardless of the cell cycle activity (constitutive roles/cell cycle-independent) reported in cycling cells (interphase) and during mitosis (mitosis). (1) NPCs mediate nucleocytoplasmic transport in every eukaryotic nucleus. (2–4) Nups have been proposed to participate in transcriptional regulation, promoting either transcriptional activation (green circles) or repression (red circles) independently of the proliferative status of the cell. Gene expression regulation by Nups takes place mainly at the NE-embedded NPC in yeast (2,3), while in metazoans (4), a subset of mobile Nups (see also Fig. 1) can relocate to the nuclear interior to perform the same gene regulatory functions. (5) In both compartments, Nups might influence chromatin structure or organization of the tethered regions in collaboration with

other factors (pink circles). (6) In proliferating cells, NPC–chromatin contacts must be regulated (arrow) during S phase to avoid replication fork collapse. (7) NPC components might facilitate the repair of a subset of persistent DNA lesions recruited to the NPC vicinity in yeast. (8) In organisms with open mitosis, NPC components assist NE breakdown and centrosome migration. (9) After NPC disassembles, some NPC components accumulate at the kinetochores, while other remain dispersed throughout the mitotic cell. By ensuring the localization and function of key mitotic components, Nups promote accurate spindle assembly, mitotic progression, and faithful chromosome segregation.

2004). The observed mobility of peripheral Nups is consistent with their ability to function away from the NPC as soluble regulatory modules. Interestingly, the mobility of Nups like Nup153, Nup98, or Nup50 is connected to RNA polymerase II (Pol II)-mediated transcriptional activity, indicating that off-pore Nups might actively participate in transcriptional regulation (Griffis et al. 2002; Buchwalter et al. 2014). Experimental support for this hypothesis was provided in *Drosophila*, where several Nups, such as Nup98, Nup50, Sec13, and Nup62, were found to bind specific chromatin regions in the nuclear interior (Capelson et al. 2010; Kalverda et al. 2010). In particular, DNA adenine methyltransferase identification (DamID), ChIP, and immunohistochemical approaches showed that these mobile Nups interact with transcriptionally active chromatin regions in the nuclear interior (Capelson et al. 2010; Kalverda et al. 2010). Depletion or overexpression of Nup98, for instance, deregulates the expression of hundreds of genes in the nuclear interior and at the NPC without altering their subnuclear localization (Capelson et al. 2010; Kalverda et al. 2010). Additionally, ChIP–chip analyses in *Drosophila* showed that nuclear basket components Nup153 and Mtor/Tpr associate with actively expressed regions enriched of transcriptionally permissive chromatin marks such as acetylated H3K16 and high RNA Pol II occupancy (Vaquerizas et al. 2010). Silencing of basket Nups deregulates, negatively, the expression of thousands of genes throughout the nucleus (Vaquerizas et al. 2010).

Moreover, indicative of the multidimensional relationship between Nups and gene expression regulation, metazoan Nups are also related to transcriptional silencing. For example, Nup88 associates with transcriptionally inactive regions in the nuclear interior of *Drosophila* salivary gland cells (Capelson et al. 2010). Based on the only study performed in human cells, ChIP–chip experiments suggested that Nup93–chromatin interactions might be enriched at repressive marks such as H3K27me3 or H3K9me3 in HeLa S3 cells (Brown et al. 2008). However, direct association with heterochromatin should be carefully interpreted, as this study used double cross-linking. This is particularly important in this case, as metazoan NPCs are usually devoid of heterochromatin (Schermelleh et al. 2008). Nevertheless, consistent with a functional role of Nups negatively regulating transcriptional activity, the Nup93 ortholog in *C. elegans*, NPP-13, was found in the proximity of tRNA genes, and its depletion increased the expression of these genes (Ikegami and Lieb 2013). Altogether, these observations support an evolutionarily conserved role of Nups in global gene expression regulation independently of the subnuclear localization of the transcriptional event and overcoming the restricted access of chromatin regions to the NPC in multicellular organisms (Fig. 2).

It is still unknown how Nups are recruited to intranuclear sites and whether Nup–chromatin interactions at the NPC or off-NPC might lead to differential transcriptional regulation events. However, it is possible that Nups could play specialized functions in these two

different scenarios. For example, while a mutant form of *Drosophila* Nup98 restricted to the nucleoplasmic space shows preferential binding for actively transcribed genes, NPC-bound Nup98 does not (Kalverda et al. 2010). This suggests that, at least in some cases, Nup-mediated gene regulation may be uncoupled from the NPC in metazoans. In differentiating human cells, Nup98 participates in gene activation at the NPC, and fully active genes are then released to the nuclear interior, where intranuclear Nups maintain their transcriptional levels (Liang et al. 2013). Thus, both pools of Nup98 might be essential for optimal gene expression regulation but potentially display different activities. Interestingly, Nup98, Nup62, and Nup50 were shown to co-occupy the same subset of genes in the nuclear interior in *Drosophila*, suggesting potential physical and functional interactions among Nups to regulate gene expression away from the NPC environment (Kalverda et al. 2010). Although continued work will be required to obtain a detailed understanding of Nup functions on-pore and off-pore, the potential role of Nups as fundamental and versatile regulators of gene expression in metazoans is already evident.

Critical gene regulatory functions of Nups are also supported by their association with diseases and cell type-specific NPC composition observed in multicellular organisms (Olsson et al. 2004; Gomez-Cavazos and Hetzer 2012). Mutations in Nups are responsible for a number of developmental disorders and cancer, including cases of acute myeloid leukemia (AML). The latter is caused by oncogenic fusions of Nup98 to a number of different DNA-binding proteins (Franks and Hetzer 2013). Interestingly, these fusion proteins retain the Nup98 FG domain, which can act as a strong regulator of gene transcription (Kasper et al. 1999; Bai et al. 2006). In addition, cardiac dysfunction has been linked to mutations in human Nup155 (Zhang et al. 2008). As mentioned above, Nup98, Nup62, Nup50, or Sec13 target genes identified in *Drosophila* embryonic cells and salivary glands are enriched for developmental regulators and developmentally induced genes (Capelson et al. 2010; Kalverda et al. 2010). Interestingly, Nup98 target genes in human cells change during differentiation, likely influencing specific transcriptional programs as cell identity evolves (Liang et al. 2013). Last, down-regulation of Nup50 or Gp210 abolishes the differentiation of mouse myoblasts to myotubes (D'Angelo et al. 2012; Buchwalter et al. 2014). In conclusion, considering the plasticity of Nup-mediated transcriptional control, it might be anticipated that Nups play a pivotal role in differentiation and development.

Mechanisms underlying gene expression regulation by Nups

The molecular mechanisms underlying Nup-mediated gene regulation are not well understood. Nevertheless, several studies indicate that NPC components might impact gene expression regulation by controlling the chromatin structure and accessibility of transcription factors. It has been proposed that NPCs could serve as

functional hubs formed in specific chromatin loci to locally enrich the enzymatic machinery required for the multistep process leading to epigenetic reformatting and optimal transcriptional regulation of their targets. For example, transcriptional activation at the NPC involves the conserved interaction of nuclear basket components with the histone acetyltransferase SAGA, RNA export factors, and the yeast SUMO protease Ulp1 (the yeast ortholog of SENP1 and SENP2) (Rodríguez-Navarro et al. 2004; Chow et al. 2012; García-Oliver et al. 2012; Texari et al. 2013; Umlauf et al. 2013). Disruption of Ulp1 activity at the NPC or the interactions established among the NPC, SAGA, and RNA export complexes impedes the association of *GAL*-inducible genes with the NPC in *S. cerevisiae* and delocalizes the *HSP70* gene in *Drosophila* or the *HSP-16.2* locus in *C. elegans* away from the NE (Rodríguez-Navarro et al. 2004; Cabal et al. 2006; Kurshakova et al. 2007; Luthra et al. 2007; Rohner et al. 2013; Texari et al. 2013). It has been proposed that desumoylation events mediated by Ulp1 would be prerequisite for tethering and activation of inducible genes such as *GAL1* (Texari et al. 2013). Derepressed genes would subsequently be recognized by chromatin modifiers like SAGA or other transcriptional regulators, leading to their transcriptional activation. Indeed, NPC basket components and the histone acetyltransferase SAGA co-occupy the same regions within the target genes to stimulate transcriptional activity. Nups may use a similar mechanism to promote transcriptional silencing. In relation to inducible genes, NPC components interact with the repressor Mig1, and deletion of Nup120 or Nup133 impedes the association of Mig1 with the *SUC2* promoter (Sarma et al. 2011). In addition, the interaction of the RNAi machinery with chromatin at the NPC promotes silencing of stress-inducible genes in *S. pombe* (Woolcock et al. 2012). Last, Nup170 has been proposed to promote gene silencing and chromatin remodeling of subtelomeric regions by facilitating the function or targeting of the chromatin remodeler RSC and the Sir4 silencer (part of the SIR complex) in yeast (Van de Vosse et al. 2013). Hypothetically, similar features could be envisioned for the intranuclear Nup-bound genes, where dynamic Nups might target specific chromatin remodelers reported to interact with them, like CBP/p300 or the MSL complex (Kasper et al. 1999; Mendjan et al. 2006).

Transcriptional regulation by NPC components through chromatin structure control is also reflected by the role of Nups in transcriptional memory. Association of Nup100 in yeast or its human ortholog, Nup98, with gene promoters like *INO1* or the interferon γ -inducible *HLA-DRA*, respectively, keeps them poised for subsequent activation events through chromatin structure alterations, including H2A.Z deposition and H3K4me2 (Brickner et al. 2007; Ahmed et al. 2010; Light et al. 2010, 2013). Interestingly, *INO1* is retained at the NPC upon activation through another specific DNA sequence called memory recruitment sequence (MRS), while Nup98 interacts with *HLA-DRA* in the nucleoplasm, suggesting a conserved function of Nups in the regulation of chromatin structure and transcriptional memory

maintenance regardless of their subnuclear localization (Light et al. 2013).

The control exerted over chromatin by NPC components to regulate gene expression further extends to higher-order chromatin organization. One form of three-dimensional (3D) chromatin architecture is gene looping, which represents another mechanism for gene expression regulation and transcriptional memory maintenance (O'Sullivan et al. 2004; Lainé et al. 2009; Tan-Wong et al. 2009, 2012). NPC basket component Mlp1 binds the promoter and 3' end regions of the inducible gene *HXX1*, suggesting the formation of a loop (Tan-Wong et al. 2009). Chromosome conformation capture (3C) analyses demonstrated that Mlp1 is required for the maintenance of the looping of this gene, which is functionally important for its rapid transcriptional reactivation (Tan-Wong et al. 2009). Interestingly, ChIP-chip experiments of yeast Nups described the association of many 3' ends to the NPC, suggesting a potentially more extensive role of the NPC components in the 5'–3' gene looping and the stabilization of *cis*-chromatin interactions (Casolari et al. 2004). In addition, yeast genes present in different chromosomes but sharing the same GRS can cluster around the same area at the NPC upon activation (Brickner et al. 2012). This association is facilitated by Nup2 and mediated by specific transcription factors such as Put3, indicative of the contribution of NPCs to *trans*-chromatin interactions.

It has been proposed that the impact of Nups on chromatin structure and organization could originate from their role as chromatin boundary elements, defining active and silent regions. Several NPC components, and particularly Nup2, were identified to display boundary activity in yeast, isolating reporter regions from heterochromatin spreading (Ishii et al. 2002; Dilworth et al. 2005). This function might be conserved at the vertebrate NPC, as NPC–chromatin interactions are enriched in the insulator Su(hw) along the *Drosophila* genome (Kalverda and Fornerod 2010). In human cells, the chromatin-binding sites of the stable Nup93 show positive correlation with CTCF insulator sites, a major organizer of the human genome (Phillips and Corces 2009), in the presence of histone deacetylase inhibitor TSA (Brown et al. 2008). In addition, a role of the NPC components as chromatin boundaries has been suggested to explain the characteristic compartmentalization of the chromosomes at the nuclear periphery observed by high-resolution microscopy, where NPCs represent “heterochromatin exclusion areas” (Belmont et al. 1993; Schermelleh et al. 2008). Consistently, silencing the basket component Tpr is sufficient to allow the spreading of heterochromatin throughout the nuclear periphery in human cells (Krull et al. 2010). Altogether, these observations support a structural role for NPC components in 3D organization of the genome (Fig. 2).

In a tentative model of Nup-mediated gene regulation, Nups might impose boundaries along the chromosomes in association with other scaffolding proteins, thus compartmentalizing chromatin regions. Isolation of specific zones would favor specific chromatin interactions, bringing regulatory elements together that might be stabilized

by NPC components. The ability of Nups to interact with various chromatin regulators would expose the tethered regions to the activity of specific enzymes, depending on the desired transcriptional outcome, and thus generating “repressive” and “permissive” transcriptional environments through the nucleus (Fig. 2).

DNA replication and genome integrity maintenance

Faithful replication of the genetic material during S phase is essential to ensure the integrity of the genome. The DNA replication program follows a strict temporal and spatial organization where replication origins located throughout the nuclear interior are fired early during S phase, whereas late-firing replication origins tend to accumulate at the nuclear periphery (Natsume and Tanaka 2010). Chromatin tethering and transcriptional activity taking place at the NPC-tethered regions represent a barrier to the passage of the replication fork and would increase the topological tension during DNA replication (Bermejo et al. 2011; Helmrich et al. 2013). To relieve this stress, the S-phase checkpoint machinery of *S. cerevisiae*, orchestrated by Mec1 and Rad53 kinases, phosphorylates Nups such as the nuclear basket component Mlp1 (Bermejo et al. 2011). Modification of this Nup would detach tethered chromatin regions from the NPC, alleviating the topological tension preventing fork collapse (Fig. 2). Deletion of Nup1 shows similar alleviation in this study, and other NPC components such as Nup153 or Nup98 have also been identified as potential targets of the vertebrate S-phase checkpoint proteins ATR/Chk1 (Matsuoka et al. 2007; Bermejo et al. 2011; Blasius et al. 2011), suggestive of a more elaborate regulation of the NPC–chromatin contacts during DNA replication. After replication fork passage, these regions should reanchor to the NPC and resume their optimal transcriptional activity. Supporting this idea, studies following the subnuclear localization of inducible genes during the yeast cell cycle show that the peripheral localization observed for these regions during G1 is prevented during S phase, when they are released into the nuclear interior, and are again anchored to the NPC in G2 in a process regulated by CDK1 phosphorylation of Nup1 (Brickner and Brickner 2011). Therefore, dynamic post-translational modifications of the NPC structure must be coordinated with cell cycle progression for accurate genome metabolism and integrity preservation.

Recent evidence links DNA replication proteins to the NPC. In *Xenopus* egg extracts, Elys/Mel-28, which is part of the Nup107/Nup160 complex, interacts with the MCM2–7 complex, the main component of the eukaryotic replicative helicase (Gillespie et al. 2007). This observation led the investigators to propose a potential functional coordination between NE assembly and replication origin licensing during nuclear reorganization in this organism (Gillespie et al. 2007). This interaction appears conserved in vertebrates. A mutation of the zebrafish *ELYS* gene reduces Mcm2 chromatin levels and sensitizes tissue progenitors to replication stress, suggesting a potential role for this Nup in the activity

of dormant replication origins (Davuluri et al. 2008; Gao et al. 2011). Although functional links between NPC components and replication origin licensing or firing are unclear, the observations reported above and the strong relationship between chromatin architecture, transcriptional activity, and DNA replication reported (Chakraborty et al. 2011; Smith and Aladjem 2014; Therizols et al. 2014) make it tempting to speculate that NPC-mediated chromatin organization might affect the licensing or activity of at least a subset of replication origins present in the nuclear periphery.

DNA damage signaling and repair machineries play a fundamental role in preventing the accumulation of DNA lesions. A series of Nup mutants in yeast and metazoan cells show accumulation of DNA damage and hypersensitivity to DNA-damaging agents, suggesting their potential involvement in DNA damage response or repair pathways (Galy et al. 2000; Loeillet et al. 2005; De Souza et al. 2006; Palancade et al. 2007; Davuluri et al. 2008; Paulsen et al. 2009; Gao et al. 2011). A role of NPC components orchestrating these responses has been inferred from the particular spatial relocalization to the NE of persistent DNA lesions and collapsed replication forks in *S. cerevisiae* (Therizols et al. 2006; Nagai et al. 2008; Oza et al. 2009; Horigome et al. 2014). The recruitment to the NPC in particular depends on the core Nup84 complex and the checkpoint kinases Mec1 and Tel1 (Nagai et al. 2008). Interestingly, down-regulation of several subunits of the Nup107/Nup160 complex, the vertebrate ortholog of the yeast Nup84 complex, generates the accumulation of spontaneous DNA damage in human cells (Paulsen et al. 2009). Mechanistically, concentration of the SUMO machinery at the NPC could modulate proper ubiquitination levels of intervening factors and facilitate repair (Palancade et al. 2007; Nagai et al. 2008; Dou et al. 2011). Thus, the yeast NPC can also accommodate a favorable environment for DNA repair, preventing genome instability. While a subset of persistent DNA lesions relocate to the NE in the yeast nucleus, this particular behavior has not been observed in mammalian cells (Soutoglou and Misteli 2007; Nagai et al. 2010). Therefore, it will be interesting to determine whether any mobile Nup could be recruited to intranuclear damaged regions to facilitate their repair. Overall, NPC components seem to play a fundamental role in genome integrity maintenance as targets of DNA damage response pathways and even in facilitating DNA repair (Fig. 2).

The role of Nups in chromosome segregation

Early mitotic stages

Accurate segregation of sister chromatids during mitosis is critical to prevent genomic lesions and avoid the deleterious consequences of aneuploidy formation in the daughter cells (Siegel and Amon 2012). As an early stage to successfully execute mitosis, centrosomes migrate to opposite sides of the nucleus during prophase using the NE and NPCs as a sliding platform. Assisting the centrosomes in their relocation, the cytoplasmic

peripheral NPC component Nup358 helps centrosome anchoring by its association with the molecular motors dynein and kinesin through the adaptor protein Bicaudal D2, which localizes at the NPC during G2 (Fig. 2; Cai et al. 2001; Payne et al. 2003; Splinter et al. 2010). More centrally located as part of the Nup107/160 complex, Nup133 also contributes to centrosome tethering, providing anchoring to the dynein/dynactin complex independently of the Nup358–Bicaudal D2-mediated pathway (Bolhy et al. 2011). In addition, silencing of the transport channel component Nup62 results in aberrant centrosome conformation with defective maturation and mitotic malfunction (Hashizume et al. 2013b).

In metazoans, nuclear compartmentalization is lost during NE breakdown (NEBD), which occurs at the prophase–prometaphase transition (Hetzer 2010). This dramatic cell remodeling process must occur in a tightly organized way to avoid fatal errors and allow proper mitotic progression. During NEBD, NPCs are rapidly disassembled in a stepwise manner (Dultz et al. 2008; Laurell and Kutay 2011). Although little is known about how this process takes place at the molecular level, it is thought to be connected to the characteristic hyperphosphorylation of NPC components during mitosis. Supporting this idea, post-translational modification of the GLFG repeats of Nup98 (one of the first Nups released from the NPC during prophase) (Lénárt et al. 2003; Dultz et al. 2008), mainly by CDK1 and NIMA-related kinases, is required for efficient NPC disassembly and NEBD kinetics (Laurell et al. 2011). Subsequently, phosphorylation-defective Nup98 mutants display delayed NPC disassembly and loss of compartmentalization (Laurell et al. 2011). Similarly, hyperphosphorylation of the transmembrane component Gp210 in *C. elegans*, likely by Cyclin B/Cdc2, contributes to efficient NPC disassembly and NEBD (Galy et al. 2008). In addition, Nup358 and Nup153 directly assist NEBD progression, likely by recruiting the membrane remodeler COPI coatamer complex through their zinc finger domains (Liu et al. 2003; Prunuske et al. 2006). Even if these observations implicate NPC components in NEBD orchestration, further studies would be required to clarify the events triggered by post-translational modification of NPC components in NPC disassembly, NEBD, and further mitotic events.

Spindle assembly and anaphase onset

Upon NEBD, microtubules emanating from the centrosomes bind the kinetochores aligning the chromosomes along the equatorial plate of the cell. Completion of spindle formation is monitored by the spindle assembly checkpoint (SAC), which holds anaphase onset (Musacchio and Salmon 2007). After complete disassembly of the NPC, subcomplexes such as the Nup107/160 relocate to the kinetochore, where it has been proposed to develop new functions in chromosome congression and normal spindle assembly (Belgareh et al. 2001; Loiodice et al. 2004; Zuccolo et al. 2007). Supporting this idea, *Xenopus* egg extracts depleted of the Nup107/160 complex show unattached sperm chromosomes, and depletion of Seh1

or Nup107 leads to impaired chromosome alignment and mitotic delay in human cells (Orjalo et al. 2006; Zuccolo et al. 2007; Platani et al. 2009; Mishra et al. 2010). Consistently, Elys/Mel-28 was identified as a dual Nup/kinetochore protein, and its depletion leads to severe defects in spindle assembly and chromosome segregation as well (Fernandez and Piano 2006; Galy et al. 2006; Rasala et al. 2006). At the molecular level, Nup107/Nup160 components and Elys were shown to recruit the microtubule nucleator γ -tubulin ring complex (γ TuRC) to unattached kinetochores to drive microtubule nucleation (Mishra et al. 2010; Yokoyama et al. 2014). All of the Nups of this complex could cooperate to promote proper spindle assembly, although it has also been proposed to be a predominant role for Elys (Yokoyama et al. 2014). In addition, the Nup107/Nup160 complex might also regulate mitotic progression by controlling the spatial positioning of the chromosome passenger complex (CPC) (Platani et al. 2009). Composed of the kinase Aurora B, INCENP, Borealin, and Survivin, the localization of the mitotic regulator CPC is tightly regulated: It accumulates at the centromeres during early mitosis and relocates to the spindle mid-zone after anaphase onset and the mid-body during cytokinesis, displaying essential functions at all stages (Carmena et al. 2012). Interestingly, silencing Seh1 or Elys leads to impaired Aurora B localization, resulting in defective chromosome segregation (Platani et al. 2009; Clever et al. 2012).

A fraction of Nup358 also relocates from NPCs to kinetochores and spindle microtubules during early mitosis to play an active role in the regulation of the stability of kinetochore–microtubule interactions. This was inferred from the loss-of-function experiments in Nup358-depleted cells resulting in the appearance of unaligned chromosomes, multipolar spindles, and mitotic catastrophe (Joseph et al. 2004; Hashizume et al. 2013a). In addition, Nup358, which is a large multidomain protein that includes SUMO E3 ligase activity (Pichler et al. 2002), is also required for progression into anaphase, as it sumoylates the topoisomerase TopoIIa, promoting its targeting to the centromeres, where it is required to release the topological links during anaphase onset (Dawlaty et al. 2008). Indicative of the crucial role of Nup358 in faithful chromosome segregation, reduced levels of Nup358 lead to the appearance of aneuploidy and tumor development in mice (Dawlaty et al. 2008).

An intriguing interplay between the mitotic machinery and NPC components is the conserved interaction established between the Mad1/Mad2 complex (a terminal transducer of the SAC) and the basket Nups Tpr and Nup153 (Campbell et al. 2001; Lee et al. 2008; Lince-Faria et al. 2009; Schweizer et al. 2013; Rodriguez-Bravo et al. 2014). Mad1 and Mad2 can be detected at the NPC during interphase, and while both Tpr and Nup153 seem important for subnuclear Mad2 localization, Mad1 localization mainly depends on Tpr (Rodriguez-Bravo et al. 2014). In particular, phosphorylation of Tpr by CDK1 might regulate this interaction (Rajanala et al. 2014). Upon NEBD, Mad1 and Mad2 are recruited to the unattached kinetochores by the upstream SAC compo-

nents, while Tpr and Nup153 enrichment is not evident at any particular mitotic substructure in most cell types. Thus, whether their interaction persists during mitosis is controversial, and alternative explanations have been proposed to explain why perturbed levels of NPC basket components affect the activity of the SAC, leading to mitotic defects (Schweizer et al. 2013; Rodriguez-Bravo et al. 2014). The interaction of Mad1 and Mad2 with the basket components during interphase might influence the mitotic surveillance checkpoint in the subsequent mitosis. According to this idea, the Mad1/Tpr interaction at the NPC promotes activation of Mad2, leading to Cdc20 neutralization. Accumulation of this signal during interphase would inhibit the interaction of Cdc20 with the anaphase-promoting complex (APC/C) after NEBD and during the early stages of mitosis, preventing mitotic failure (Rodriguez-Bravo et al. 2014). Alternatively, Tpr might contribute to SAC robustness and proper spindle orientation by affecting Mad2 stability and localization at unaligned kinetochores in different organisms (De Souza et al. 2009; Lince-Faria et al. 2009; Schweizer et al. 2013). Supporting a specific role of Tpr at the kinetochores, FRAP and imaging experiments in *Drosophila* and *Aspergillus nidulans* showed a specific accumulation of Tpr orthologs (Mtor/Mlp1) surrounding the spindle microtubules rather than randomly distributed throughout the mitotic cell (De Souza et al. 2009; Lince-Faria et al. 2009). Regarding Nup153, it has been proposed to display different roles during mitotic progression (Mackay et al. 2009), and unbalanced levels of this protein influence SAC activity by affecting Mad1 localization and phosphorylation status, consequently leading to mitotic aberrancies (Lussi et al. 2010).

The Nup Rael and its partner at the NPC, Nup98, appear redistributed throughout the cell in mitosis. However, Rael is crucial for normal mitotic progression and stabilization of microtubules at the kinetochore, and perturbed levels of this Nup lead to chromosome segregation and SAC defects (Babu et al. 2003; Blower et al. 2005). This is not surprising, considering its extensive homology with SAC component Bub3 (Babu et al. 2003) and the reported interactions with the checkpoint kinase Bub1, the spindle assembly factor NuMA (nuclear mitotic apparatus), and microtubules (Wang et al. 2001; Babu et al. 2003; Wong et al. 2006). Nup98 also facilitates bipolar spindle formation in *Xenopus*, interacting with microtubules and antagonizing MCAK (mitotic centromere-associated kinesin) activity, a microtubule depolymerizing enzyme (Cross and Powers 2011). In addition, Nup98 and Rael regulate APC/Cdh1 activity during prometaphase/metaphase, ensuring timely securin degradation and preventing premature cohesin cleavage and therefore precocious sister chromatid separation (Jeganathan et al. 2005). Importantly, the role of Rael/Nup98—ensuring the assembly of a normal spindle and timely anaphase onset—might partially contribute to the prevention of genome segregation defects and malignant transformation observed in Nup98-associated mutations (Salsi et al. 2014).

Telophase, NE reformation, and cytokinesis

By late anaphase, Nups start to be recruited to the chromosomes driving NPC and NE reassembly (Doucet et al. 2010; Mackay and Ullman 2011). Simultaneously, the central spindle is compacted into the midbody, eventually leading to abscission. The coordination of the mitotic exit network with NE reassembly is far from being fully characterized at the molecular level. However, it is noteworthy that reduced levels of NPC components such as Nup153, Elys, and Nup107/Nup160 complex members generate an accumulation of cells with unresolved midbodies (Rasala et al. 2006; Mackay et al. 2009; Platani et al. 2009). One possible explanation of this phenomenon is that Nups could influence the mitotic exit, which to a large extent involves massive dephosphorylation of mitotic kinase targets. Supporting the latter, the coordinated activity of several protein phosphatases is required to recycle the nuclear components after mitosis. Nup153 and Nup50 interact with the protein phosphatase PP1 and its targeting subunit, Repo-Man (Moorhead et al. 2008; Vagnarelli et al. 2011), suggesting that they might influence proper PP1 localization and/or activity affecting the dephosphorylation cascades.

In summary, Nups show essential transport-independent functions during mitosis, and disruption of their activities results in a collection of mitotic aberrations. NPC components impact several mitotic stages but seem to mainly concentrate their efforts around the kinetochores during prometaphase to stabilize their interactions with the microtubules by controlling the spatial localization and activity of specific components, ensuring normal spindle assembly and anaphase onset (Fig. 2).

Conclusions and perspectives

In their capacity to form macromolecular transport channels in the NE, regulation of nucleocytoplasmic transport is a critical function of Nups (Fig. 2). Molecular trafficking affects virtually every process in the cell, and, consequently, any observation made in the presence of unbalanced levels of NPC components or Nup mutant forms should be carefully interpreted. However, increasing evidence suggests additional roles of Nups affecting fundamental genome functions, some of which are likely to be independent of nuclear transport (Fig. 2). In eukaryotic cells, NPC components can associate with specific genes and regulate their expression. In yeast, this function might be restricted to the NE-embedded NPC, and chromatin regions would relocate to the nuclear periphery, while in multicellular organisms, this function has apparently extended throughout the nucleus, as mobile Nups can detach from the NPC and relocate to intranuclear regions as well (Fig. 2). While the recruitment of specific genes to the NPC is at least partially understood, the mechanisms underlying the recruitment of Nups to intranuclear regions are still uncharacterized. Theoretically, mobile Nups could recognize and bind specific DNA sequences (Ahmed and

Brickner 2010), particular epigenetic marks, or specific chromatin remodelers. Comprehensive characterization of intranuclear and NE-associated NPC–chromatin interactions will be required to better understand the transport-independent functions of Nups. Additionally, it would also clarify whether mobile Nups collaborate in the nuclear interior to regulate transcriptional activity, mimicking the regulation exerted at the NPC, as inferred from the observations made in *Drosophila* nuclei reporting the co-occupation of several mobile Nups at specific genes (Kalverda et al. 2010).

Nup-mediated gene expression regulation might likely be caused by the role of NPC components in chromatin structure and organization (Fig. 2). However, further evidence directly linking Nups to genome architecture and chromatin structure is essential for determining their precise roles, especially in multicellular organisms. It will be particularly interesting to study the molecular connections between the NPC components and the reorganizing chromosomes during nuclear reformation after mitosis. Tethering of specific chromatin regions by NPC components during late anaphase might potentially represent an early event in the non-random organization of the interphase chromosomes, thus linking mitotic Nup–genome interactions to nuclear function.

In proliferating cells, Nups have been shown to play a central role in the preservation of genome integrity, influencing replication fork progression, DNA repair, and accurate chromosome segregation (Fig. 2). First, the observations regarding the post-translational modification of NPC components to allow fork passage during S phase indicate the relevance of a precise and dynamic regulation of NPC–chromatin contacts, which would likely affect different DNA metabolic processes and Nup functions (Regot et al. 2013). Second, the recruitment of persistent DNA lesions to the NPCs reported in yeast might be reflective of the ability of Nups to gather particular loci and enzymatic machineries together, as shown for transcriptional regulation, potentially facilitating DNA repair. Interestingly, NPC-associated chromatin in human cells is repaired in a different way compared with the lamin-associated regions (Lemaître et al. 2014). However, while transport-dependent roles of Nups in DNA repair are being uncovered (Lemaître et al. 2012; Moudry et al. 2012), transport-independent involvement of Nups in DNA repair in vertebrates remains undefined. Last, indicative of the potential roles of the off-pore Nups, an increasing number of NPC components has been shown to display mitotic-specific roles, ensuring accurate chromosome segregation. Again, one general interpretation of these observations is that Nups seem to form a platform to coordinate the action of specific enzymes with their targets. How Nups adapt their functions during mitosis and whether their phosphorylation by mitotic kinases is linked to that adaptation remain to be explored. Nevertheless, accurate regulation of Nup levels and functions seems crucial to avoid the accumulation of DNA lesions and aneuploidy and likely prevent malignant transformation.

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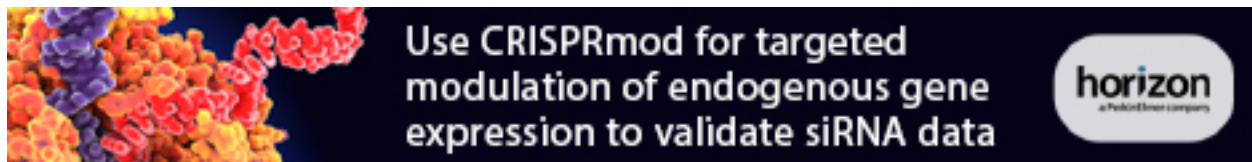
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