Nuclear pore complexes (NPCs) are best known for their central role in controlling the molecular trafficking between the cytoplasm and the nucleus. NPCs are assembled from about 30 different proteins and a growing body of evidence suggests that these nucleoporins are not only acting in the context of NPCs, but also in the nucleoplasm and cytoplasm. In this context it is well accepted that a set of nucleoporins are important regulators of a variety of mitotic processes, including kinetochore assembly, spindle checkpoint control and cytokinesis, whereas others associate with chromatin and administer gene expression. However, the functional importance of nucleoporins go far beyond these roles and this review will provide an overview of the latest insights into the versatility of metazoan nucleoporins with an emphasis on their roles in cell migration, cellular signaling and tissue-specific activities.

Introduction

Nuclear pore complexes (NPCs) span the inner and outer nuclear membrane of the nuclear envelope (NE) and master all macromolecular exchange between the cytoplasm and the nucleus of interphase eukaryotic cells. NPCs are large multi-protein complexes that are composed of ~30 different proteins (nucleoporins) or Nups, which are typically organized in repetitively arranged subcomplexes to form the NPC. NPCs exhibit 8-fold rotational symmetry and as a result nucleoporins are found in copy numbers of eight per NPC or multiple thereof. In total about 500 individual proteins form the NPC. The principle structural organization of the NPC is evolutionary conserved and has been determined by distinct electron microscopy (EM) approaches mainly in Xenopus laevis oocyte nuclei, but also, for example, in yeast, amphibians, plants and humans. Overall NPCs have a roughly tripartite architecture: a central framework (also called central pore membrane. In metazoans, this group comprises gp210, Ndc1 and POM121 (Fig. 1B). The second group of nucleoporins contains β-helical solenoid and β-propeller fold motifs and locates more toward the central channel of the NPC. This group of nucleoporins, which includes the Nup107-160 complex as well as the Nup93 complex, is crucial for the formation of the NPC scaffold. The third group comprises nucleoporins characterized by the presence of repetitive phenylalanine-glycine (FG) motifs (spanned by hydrophilic linkers) and/or by coiled-coil motifs, which are typically engaged in nucleocytoplasmic transport. This third group can be further subdivided into nucleoporins of the cytoplasmic filaments, such as Nup95 and Nup214, nucleoporins of the central channel, such as Nup98 and the Nup62 complex, and the nuclear basket nucleoporins Nap55, Nup50 and Tpr (Fig. 1B)

Besides being important structural elements of the NPC and fundamental for general nucleocytoplasmic transport, nucleoporins often exhibit an enormously dynamic character due to which they are either directly or indirectly engaged in a variety of other cellular processes, both in interphase and mitotic cells. Several recent review articles have addressed the role of nucleoporins in mitotic and gene expression control, and we will focus here on the dynamic character of nucleoporins and their functions in distinct cellular signaling pathways, cell migration and differentiation. Nucleoporin function in these processes occurs often in a tissue-specific manner and only become evident from studies using animal models.

Nucleoporin Dynamics, Dynamic Nucleoporins

NPCs have been assumed to be rather static of nature, in contrast to the highly mobile cargoes and transport receptors that traverse...
the NPC during nucleocytoplasmic transport events. In fact, in mammalian cells, the NPC as a whole appears stably anchored to the NE\textsuperscript{21,22}. Single NPCs only move in arrays in response to changes in nuclear shape during the cell cycle but show no independent movement within the plane of the NE\textsuperscript{22}. In contrast to the whole NPC, individual nucleoporins can be very dynamic. The turnover of nucleoporins at NPCs range from seconds to days, both in dividing and non-dividing cells\textsuperscript{21,23}. In this context especially the so-called scaffold nucleoporins, such as the Nup107-160 complex (Fig. 1B), are very stably associated with the NPC and long-lived with basically no turnover during the cell cycle, whereas, for example, the nuclear basket proteins Nup153

Figure 1. Nuclear pore complex (NPC) architecture and nucleoporin localization in the NPC. (A) Cross-sections along embedded nuclear envelopes of Xenopus oocyte nuclei allow side views of NPCs visualized by transmission electron microscopy. Shown are an NPC in a slightly worm’s-eye view (left) and a schematic representation of the main structural components of the NPC (right). (B) Nucleoporins can be subdivided into different subgroups depending on their structural motifs and localization: transmembrane nucleoporins (white), scaffold nucleoporins (green), nucleoporins of the cytoplasmic filaments and the cytoplasmic ring (rose), central channel nucleoporins (blue) and nuclear basket and nuclear ring nucleoporins (yellow). Nup153 indicated at the nuclear ring and the distal ring refer to the respective anchoring sites of its N terminus and zinc-finger domain.
and Nup98 (Fig. 1B) are characterized by their highly dynamic behavior.21-23 Nup153 and Nup50 both play important roles in facilitated nucleocytoplasmic transport. Nup153 is known to be key for nuclear protein import as well as most RNA export pathways and to interact with virtually every nuclear transport receptor studied.24 Nup153 dynamically associates with the NPC and its exchange at NPCs is inhibited when RNA polymerases I or II are blocked.25 Fluorescence recovery after photobleaching (FRAP) experiments revealed a two-step recovery of GFP-Nup153 at NPCs in both HeLa and NRK cells with an overall recovery rate of 1/2 41 sec.26-30 Beyond Nup153 as a whole, its FG-repeat domain further increases Nup153’s dynamic nature.24-26 Nup153 is organized in three domains and immuno-EM studies have revealed their complex topology in the NPC, with the N-terminal and zinc-finger domain anchoring Nup153 to the NPC (Fig. 1B).28-30 The C-terminal FG-repeat domain of Nup153 in contrast is highly flexible and dynamic within the NPC,26,28 a feature that was also observed for the FG-repeat domains of Nup214, Nup98 and Nup62.21,23 Consistent with their role in facilitated nucleocytoplasmic transport, the spatial distribution of FG-repeat domains alters in a transport- and energy-dependent manner.26-28

Nup50 (also known as Nup60) enhances nucleocytoplasmic transport by acting as cofactor for importin β-mediated nuclear protein import.30 Nup50 has binding sites for importin α, importin β and RanGTP, and shuttles between the nucleus and the cytoplasm together with nuclear import complexes.36 A similar dynamic behavior has been described for Nup214 and Nup60p, the yeast orthologs of Nup50.37 Analogous to the role of Nup50 in importin β-mediated nuclear import, Nup98 appears to act as mobile cofactor for CRM1-mediated nuclear export.30 Nup98 is anchored to the center of the NPC and likely the major constituent of the NPC’s permeability barrier.39,40-42 Nup98 dynamically associates with the NPC in a transcription-dependent manner,25,43 and it binds directly to CRM1 in a RanGTP-dependent manner. Exogenously expressed GFP-Nup98 sequesters endogenous CRM1 from the nucleoplasm and NE to Nup98-intranuclear dots (so-called GLFG bodies44), which results in the inhibition of nuclear export of the Ran-binding protein RanBP1.30

### Nucleoporins and Cell Migration

A dynamic character of nucleoporins appears not only important for nucleocytoplasmic transport, but also for cell migration. Three nucleoporins, Nup62, Nup153 and Nup358, appear of importance in this context (Table 1). Nup62 belongs to the group of FG nucleoporins and is part of the Nup62 complex (Fig. 1B). The Nup62 complex further includes Nup58, its splice-variant Nup45 as well as Nup54/55 and it is located toward the central pore of the NPC.22 Nucleoporins of the Nup62 complex have medium turnover rates at the NPC.22 In Jarkt cells infected by human immunodeficiency virus (HIV)-1, however, Nup62 translocates into the cytoplasm in association with the viral RNA and the HIV proteins Rev and Gag.43 Hence, Nup62 apparently leaves the NPCs as part of the growing HIV-1 vRNA-RNP complex.50 Moreover, in HeLa and activated human erythroleukemia cells, Nup62 was found to cycle between the plasma membrane and the perinuclear recycling compartment, which appears crucial for cell migration.44-46 The recruitment of Nup62 (and its complex partners) to the plasma membrane and to membrane ruffles is mediated by Exo70, a component of the exocyst complex. Depleting Nup62 significantly impairs cell motility due to disruption of the Nup62-Exo70 complex at the leading edge of the cell.47

### Table 1. Table summarizing nucleoporin functions in cell migration, cell signaling as well as tissue specific functions

| Nucleoporins | Model | Function | Transport dependent | Binding partners | Refs. |
|-------------|-------|----------|---------------------|-----------------|-------|
| Nup133      | Mice  | Neuronal differentiation | -                  | 25,43           | 92    |
| Nup62       | Human cell lines | Cell migration | -                  | Exo70           | 48    |
| Nup153      | Human cell lines | Cell migration | -                  | Smad2           | 52    |
|             | Human cell lines | TGF-β signaling | +                  | Smad2, Smad3, Smad4 | 84, 85 |
| Nup214      | Human cell lines | TGF-β signaling | +                  | Smad2           | 84    |
|             | Human cell lines | cAMP signaling | -                  | Epac1           | 86    |
| Nup96       | Nkp153+/−; mice | Immune system, IFN signaling | ?                  | 102            |
|             | Nkp153+/−; mice | Immune system, IFN signaling | ?                  | 102            |
| Drosophila  | CNS, retinal neurons | Neurogenesis | ?                  | 72             |
| Mice Nup358+/− | CNS, retinal neurons | Neurogenesis | ?                  | 72             |
| Nkp153      | Mice Nup153+/−; | Heart (Atrial myocytes) | +                  | Exo70           | 100   |
|             | Heart (Ventricular cardiomyocytes) | Exo70 | +                  | HDAC4           | 103   |
| Nkp155      | Heart (Ventricular cardiomyocytes) | Exo70 | +                  | HDAC4           | 103   |
| Mice Nup133+/− | Neuroan differentiation | -          |                  | 92             |
| KIF5B, KIF8C | Human cell lines | Cell migration | -                  | Exo70           | 48    |
| Nup98       | Human cell lines | Cell migration | -                  | Smad2, Smad3, Smad4 | 84, 85 |

Color code according to the localization of nucleoporins within the NPC and according to Figure 1: scaffold nucleoporins (green), nucleoporins of the cytoplasmic filaments and the cytoplasmic ring (blue), central channel nucleoporins (blue) and nuclear basket and nuclear ring nucleoporins (yellow).
As outlined above, the C-terminal FG domain of Nup153 was found to be highly dynamic within the NPC in NRK cells and Xenopus oocyte nuclei, while in a heterokaryon assay Nup153 was found to shuttle very slowly, suggesting that it rarely moves sufficiently far out of the NPC toward the cytoplasm. This notion has recently been challenged as Nup153 was detected in the cytoplasm of oligodendrocyte precursor cells derived from patients with multiple sclerosis (MS). The functional relevance of this observation has remained elusive, but might have an impact on the inefficient differentiation of the oligodendrocytes seen in MS. Furthermore, Nup153 accumulates at the vegetal tip of actin bundles emanating from germinal vesicles of the sea pineapple Halocynthia roretzi during their breakdown in meiosis. A link between Nup153 and the actin cytoskeleton is further supported by the finding that depletion of Nup153 from HeLa and human breast cancer MDA231 cells led to reorganization of the actin cytoskeleton and impaired lamellipodia formation, which coincided with defects in cell migration and reduced wound-healing rates.

A third nucleoporin linked to cell migration is Nup358, the largest vertebrate nucleoporin, also known as RanBP2. Nup358 is a multi-domain nucleoporin (Fig. 2) that localizes to the cytoplasmic filaments of the NPC and it is involved in a multitude of cellular processes (Fig. 2 and Table 1), that range from more general functions in nucleocytoplasmic transport, mitosis, and cellular signaling due to its E3 SUMO ligase activity to tissue-specific functions particularly in neurons and muscle cells. Moreover, Nup358 interacts with interphase microtubules (MTs) through its N-terminal, leucine-rich domain and overexpression of this MT-targeting domain in CHO cells increased MT bundling and stability, whereas depletion of Nup358 led to a decrease in polarized cell migration and stable MTs. Endogenous Nup358 and a GFP-fusion of Nup358's N-terminal domain were found in the cytoplasm and to co-localize with MTs at cell extensions. The recruitment of Nup358 to MTs appears to depend on the adenomatous polyposis coli (APC) protein, a MT plus-end binding tumor-suppressor protein. APC exhibits several MT-binding domains and, through its middle region, APC interacts with both MTs and Nup358. Ectopic expression of this middle region is sufficient to recruit Nup358 to MT plus ends, and binding of Nup358 to APC as well as the MT-motor kinesin-2 are important for APC's localization at the cell cortex. Interestingly, in migrating neurons and rat embryonic fibroblasts, APC was found to associate with Nup153 at the nuclear membrane. The APC-Nup153 complex appears to serve as anchoring site for MTs emanating from the centrosome. Whether or not the APC-Nup153 interaction is important for cell migration has not been analyzed specifically, but the APC-Nup358 as well as the APC-Nup153 interaction are important for centrosome reorientation during migration after wound-scratching, suggesting that Nup153 acts in cell migration via both the actin cytoskeleton and MTs.

Nucleoporins and Cellular Signaling

Due to their central location at the transit routes between the cytoplasm and the cell nucleus, nucleoporins often act as scaffold for proteins being involved in cellular signaling, as seen in transforming growth factor β (TGF-β) and cyclic AMP signaling, as well as DNA damage response. TGF-β cytokines critically regulate a variety of developmental processes and cell homeostasis by an evolutionary conserved mechanism involving Smad transcription factors, which upon phosphorylation translocate into the nucleus.
While neither the depletion of Nup358 or of Nup153 impairs as a theme by which cellular signaling is further regulated. This

Epac1 functions in cellular processes by cAMP. In a yeast two-hybrid screen using Epac1 as bait, extracellular matrix adhesion, and its activity is directly regulated ranging from exocytosis to cell-cell-junction formation and cell-

Nup93 is important for their recruitment to the nuclear peri-

Sec13 and Nup93 appear specifically involved in Mad nuclear import in Drosophila. All together this suggests that nucleoporins control Smad/Mad nuclear import, directly and/or indirectly, and consequently TGF-β signal transduction and developmental processes.

Nucleus Volume 3 Issue 2

Tissue-Specific Nucleoporin Functions

Thus far little is known about tissue-specific expression pattern and activity of nucleoporins. In particular, mice models and studies in Drosophila, however, have recently provided some interesting novel insights in this respect. In Drosophila retinal neurons, Nup358 acts as a chaperone for red-green opsin, to which it binds via its Ran-binding domain (RBD) and cyclophilin-like domain (Fig. 2). Similarly, Nup358 interacts with red-green opsin in human and bovine cells but not with closely related blue-cone or rod opsin. In mice, Nup358 acts as a chaperone for the mitochondrial metallo-chaperone Cox11. The association of Nup358 with Cox11 is mediated by Nup358’s leucine-rich domain (Fig. 2). Both proteins co-purify from retinal extracts and co-localize to mitochondria in several classes of neurons, including photoreceptor neurons and neurons of the central nervous system (CNS). Furthermore, Nup358 is able to suppress the inhibitory activity of Cox11 over hexokinase 1 (HKI), the major regulator of glycolysis. Haploinsufficiency in Nup358 causes a pronounced decrease of HKI and ATP levels in the CNS. This decrease in HKI and ATP levels coincides with defects in glucose clearance and the electrophysiological response of photoreceptors and postreceptorial neurons, as well as the delocalization of mitochondria in the photoreceptor neurons. Nup358 is highly expressed in these retinal neurons and found in the cytoplasm along with RanGTP. Furthermore, Nup358 associates with kinesin KIF5B and KIF5C in the cytoplasm via its leucine-binding domain (Fig. 2; KBD), which binds leucine-rich heptad repeats in the

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C-terminal coiled-coil domain of the kinesin heavy chain in a RanGTP-dependent manner. In the presence of MTs and ATP, binding of Nup358 enhances the low intrinsic ATPase activity of KIF5B, which in addition to the KBD also requires the RBD2 and RBD3 of Nup358. Inhibition of the interaction between Nup358 and the KIF5s leads to perinuclear clustering of mitochondria, deficits in the mitochondria membrane potential as well as cell shrinkage, pinpointing to a kinesin-dependent role of Nup358 in mitochondria transport and function. In aged mice, haploinsufficiency of Nup358 protects neurons against light-induced oxidative stress. Prolonged light exposure is a determinant factor in inducing neurodegeneration of photoreceptors by apoptosis. Upon light-elicited stress, aged Nup358+/− mice have suppressed apoptosis and reduced membrane dysgenesis in central retina regions as compared with wild type mice. Mechanistically the neuroprotective function of Nup358 is not understood, but reduced levels of Nup358 coincide with reduced levels of free fatty acids, which might be of benefit for compensating the increase in light-elicited oxidative stress in central retina regions. Insufficiency in Nup358 furthermore causes upregulation of the orphan transmembrane tyrosine kinase receptor EkbB2 and suppression of ubiquitylation in response to light stress, which may also contribute to apoptosis suppression in central retina regions of Nup358−/− mice. Together these studies have revealed a determinant role for Nup358 in glucose, energy and lipid homeostasis in neurons of the CNS and the retina, and implicate Nup358 (and its binding partners) as key player in neuropathic and neurodegenerative diseases.

Hypomorphic mutant alleles of Nup154 affect female and male fertility in Drosophila (see above). Mutations in Nup155, the human homolog of Nup154, are associated with atrial fibrillation (AF), the most common form of sustained clinical arrhythmia. While homozygous Nup155−/− mice die during embryonic development, heterozygous Nup155+/− mice show an AF phenotype. The AF-related mutation in Nup155 in human and the reduction of Nup155 in mice are associated both with inhibition of Hsp70 mRNA export and nuclear import of Hsp70 protein. The heterozygous mice have no overt structural abnormalities in their heart and skeletal muscle, but atrial myocytes showed significantly shortened action potential duration as seen in AF. The importance of Nup155 for normal cardiac function is further supported by studies in rat. Here Nup155 was identified as HDAC4-interacting protein in ventricular cardiomyocytes from neonatal rats, which appears important for sarcomere formation and myocyte growth. HDAC4-target genes control cardiac growth and truncated mutants of Nup155 that fail to bind HDAC4 suppressed HDAC4-induced gene expression as well as chromatin association of HDAC4, suggesting that Nup155-mediated localization of HDAC4 is required for HDAC4’s effect on gene expression in cardiomyocytes.

Heterozygous Nup96−/− mice show selective alterations of the immune system with decreased expression of IFN-regulated gene products, impaired antigen presentation and impaired T cell proliferation upon immunization. Moreover, Nup96−/− mice and cells derived from these mice are highly susceptible to viral infection, indicating that Nup96 is not only regulated by interferons, but actively participates in interferon-mediated immune response. Together these studies show that animal models are prerequisite to unravel tissue-specific functions of nucleoporins and that nucleoporins can influence pathways and processes beyond primary anticipations.

**Nucleoporins and Differentiation**

In an in situ muscle differentiation system using mouse C2C12 cells, Nup358 was implicated in myogenesis. Depletion of Nup358 in myoblasts suppressed myotube formation without affecting cell viability. This study further revealed that a general change in expression levels of nucleoporins during skeletal muscle differentiation, indicating that NPCs undergo a remodeling process during differentiation. In mice, a null allele of Nup133, a component of the Nup107-160 complex (Fig. 1), is disrupting terminal differentiation of neurons. In the mouse embryo, Nup133 expression levels vary in between tissues, developmental stages and axial positions within the same tissue. Nup133-deficient epiblasts and embryonic stem cells maintain features of pluripotency and differentiate inefficiently along the neural lineage, whereas NPC assembly in the mouse embryonic tissue is not affected, suggesting that in mice Nup133 may modulate NPC activity rather than acting as a core structural component in NPC assembly. The underlying molecular mechanisms that lead to defects in muscle and neuronal differentiation in the absence of Nup358 and Nup133, respectively, remain to be elucidated.

**Conclusions**

Recent progress has shed light on the role of nucleoporins beyond general nucleocytoplasmic transport: The versatility of nucleoporins makes them integral players not only in mitotic events and gene expression control, but also genome maintenance, cell migration and cellular signaling. Thereby they are acting from their location within the NPC or, as for example Nup358, Nup153 and Nup62, in the cytoplasm (Fig. 3). Their multi-functional properties further implicate nucleoporins in tissue-specific cascades, which, for example, control glucose, energy and lipid homeostasis and cellular differentiation. Future studies will doubtlessly address in more detail the molecular mechanisms that allow nucleoporins to act this many-sided and it will be exciting to see what other surprises go along with that.

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Figure 3. Nucleoporins and their localizations outside the NPC. Nup358, Nup153 and Nup2 have been detected in the cytoplasm, frequently associated with cytoskeletal elements. Their roles in the cytoplasm appear tissue-specific. The color-code used for the nucleoporins corresponds to the one used in Figure 1 and Table 1. Within the NPC, Nup358 localizes to the cytoplasmic filaments (rose), Nup62 is one of the central channel nucleoporins (blue), and Nup153 is a component of the nuclear basket (yellow).

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