The role of nuclear pores in gene regulation, development and disease

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Nuclear-pore complexes (NPCs) are large protein channels that span the nuclear envelope (NE), which is a double membrane that encloses the nuclear genome of eukaryotes. Each of the typically 2,000–4,000 pores in the NE of vertebrate cells is composed of multiple copies of 30 different proteins known as nucleoporins. The evolutionarily conserved NPC proteins have the well-characterized function of mediating the transport of molecules between the nucleoplasm and the cytoplasm. Mutations in nucleoporins are often linked to specific developmental defects and disease, and the resulting phenotypes are usually interpreted as the consequences of perturbed nuclear transport activity. However, recent evidence suggests that NPCs have additional functions in chromatin organization and gene regulation, some of which might be independent of nuclear transport. Here, we review the transport-dependent and transport-independent roles of NPCs in the regulation of nuclear function and gene expression.

Keywords: chromatin; gene regulation; nuclear-pore complex; nucleoporin; transcription

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See Glossary for abbreviations used in this article.

Introduction

The transport of macromolecules between the nucleus and the cytoplasm of eukaryotic cells is mediated exclusively through the nuclear-pore complexes (NPCs), which are large multiprotein channels that span the double-lipid bilayer of the nuclear envelope (NE; D'Angelo & Hetzer, 2008; Fahrenkrog *et al.*, 2004). The selective transport of proteins, RNA and ribonucleoproteins across the NE is a highly regulated process that involves signal-dependent interactions of cargo molecules with transport receptors (Gorlich, 1997). These cargo–receptor complexes bind to proteins of the nuclear-pore channel, which, together with other crucial factors such as the Ran GTPase system, mediate active and directional transport (Weis, 2002; Terry *et al.*, 2007). Each NPC is composed of multiple copies of approximately 30 nucleoporins (Nups; Cronshaw *et al.*, 2002). Given

their role as exclusive nucleocytoplasmic transport channels, it is not surprising that mutations in multiple Nups have been linked to cellular and developmental defects, as well as to several human diseases. The surprising fact is the observed specificity of these phenotypes, which are often manifested in specific cell types and in particular molecular pathways (Table 1; Meier & Brkljacic, 2009). These findings imply that individual pore components might act as crucial regulators of gene expression during differentiation and signal transduction.

By controlling the access of transcription factors or the export of specific messenger RNA (mRNA) molecules, the NPCs have a crucial transport-dependent role in gene expression. Alterations in pore function or composition can result in the subcellular mislocalization of regulatory factors and, therefore, a misregulation of cellular growth and identity (Cronshaw & Matunis, 2004). However, in addition to the well-established transport function of the NPC, the nuclear pore has been proposed to exert a more direct role in gene expression through physical interactions of Nups with the nuclear genome (Akhtar & Gasser, 2007; Brown *et al.*, 2008). Such interactions have been proposed to contribute to chromatin organization inside the nucleus and to the transcriptional status of genes that physically associate with pore components. Therefore, to understand the tissue-specific roles of Nups and the regulatory nature of the NPC, it is important to consider both transport-dependent and transport-independent mechanisms.

The dynamic and stable structures of the NPC

The NPC is one of the largest macromolecules in the cell; it has a molecular mass of 60–90 MDa (Rout *et al.*, 2000) and exhibits an eightfold-symmetrical structure that forms a transport channel across the NE (D'Angelo & Hetzer, 2008; Weis, 2007; Lim & Fahrenkrog, 2006). The roughly 30 different Nups that compose the pore can be grouped into at least three categories (Fig 1A). The scaffold Nups form the core of the NPC and are assembled into two large multiprotein subcomplexes: Nup107–160 and Nup93–205 (Alber *et al.*, 2007). Recent structural studies suggest that these scaffold Nups are similar to clathrin and COPII vesicle coats, which has led to the hypothesis that both classes of proteins share common ancestors (Alber *et al.*, 2007; Debler *et al.*, 2008; Devos *et al.*, 2004). The scaffold Nups might be tethered to the NE by the transmembrane Nups POM121, NDC1 and gp210, which constitute the second class of NPC components (Hetzer *et al.*, 2005). The third group are the peripheral

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Table 1 | Tissue-specific roles of metazoan nucleoporins

Metazoan nucleoporins (<i>Saccharomyces cerevisiae</i> homologue)	Tissue-specific disorder or developmental aspect	Nature of nucleoporin mutation	References
Human Nup155 (Nup157, Nup170)	AF, which is a cardiac disorder characterized by clinical arrhythmia	Homozygous missense R391H in humans; large truncation (leaving 271/1,391 amino acids) in mouse model	Zhang <i>et al</i> , 2008
<i>Drosophila</i> Nup154 (Nup157, Nup170)	Male and female gametogenesis, various steps of oogenesis and spermatogenesis	P-element insertion in the 5' region of the gene, resulting in reduced expression (hypomorph)	Gigliotti <i>et al</i> , 1998; Grimaldi <i>et al</i> , 2007
Human Nup98, mouse Nup98 (Nup145N, Nup116)	Acute myeloid leukaemia (and other haematological malignancies); haematopoietic stem-cell proliferation	Multiple genomic translocations, which result in fusion of Nup98 fragment, including FG repeats, to another gene	Nakamura <i>et al</i> , 1996; Slape & Aplan, 2004; Takeda <i>et al</i> , 2006
Mouse Nup96 (Nup145C)	Immune-system function, interferon response, B-cell and T-cell proliferation	Genetic knockout by an inserted early stop codon	Faria <i>et al</i> , 2006
Human Nup214 (Nup159)	T-cell acute lymphoblastic leukaemia	Genomic translocations, which fuse Nup214/CAN fragment to another gene	Graux <i>et al</i> , 2004; Saito <i>et al</i> , 2004
<i>Drosophila</i> Nup88/mbo (Nup82)	Trachea, central nervous system, imaginal discs of larvae; immune response	Genetic null by removal of 5'-coding sequences	Uv <i>et al</i> , 2000
Human Nup62 (Nsp1)	Primary biliary cirrhosis (autoimmune liver degeneration)	Autoimmune antigen	Wesierska-Gadek <i>et al</i> , 2007
Human Nup62 (Nsp1)	Autosomal recessive infantile bilateral striatal necrosis (degeneration of the basal ganglia)	Homozygous missense Q391P mutation	Basel-Vanagaite <i>et al</i> , 2006
Human Gp210 (–)	Primary biliary cirrhosis (autoimmune liver degeneration)	Autoimmune antigen	Tartakovsky & Worman, 1995
Human Nup358/RanBP2 (–)	Familial cases of infection-triggered acute necrotizing encephalopathy	Heterozygous missense mutation T585M	Neilson <i>et al</i> , 2009
Mouse Nup133 (Nup133)	Neural stem/progenitor cell differentiation	Functional null mutation owing to truncation/stop codon	Lupu <i>et al</i> , 2008
Human Aladin (–)	Triple A syndrome (adrenal insufficiency, absence of tear secretion and achalasia)	Various nonsense, frameshift and missense mutations	Cronshaw & Matunis, 2003
Zebrafish ELYS/Flo (–)	Proliferating progenitor cells in developing retina and intestine	Truncated protein owing to early stop codon and lower expression levels	Davuluri <i>et al</i> , 2008; de Jong-Curtain <i>et al</i> , 2008

AF, atrial fibrillation; CAN, Nup214/CAN; ELYS, embryonic large molecule derived from yolk sac; Flo, flotie lotte; Gp210, glycoprotein of 210 kDa; mbo, members only; Nup, nucleoporin; RanBP2, Ran-binding protein 2.

Nups, which associate with the NPC scaffold, and have crucial roles in mediating the selectivity and permeability of the nuclear pore. A large proportion of the peripheral Nups is constituted by FG repeat-containing Nups. These FG-repeat motifs fill the central channel of the nuclear pore, thereby precluding the entry of molecules that are more than 40 kDa (Weis, 2007). In addition, FG Nups provide low-affinity binding sites for multiple transport receptors (Wente, 2000), thereby mediating the passage of transport receptors and their cargos, and functioning as a selective permeability barrier (for further information on the various models of NPC selectivity see D'Angelo & Hetzer, 2008; Frey & Gorlich, 2007; Rout *et al*, 2003; Weis, 2007). Other peripheral components of the NPC include the nuclear proteins Tpr, Nup153 and Nup50, and the predominantly cytoplasmic Nup88, Nup214 and Nup358. These distal Nups, which protrude as filaments from the NE-embedded core (Beck *et al*, 2007), have been implicated in the initiating steps of export and import, respectively.

One unique characteristic of NPC organization, which might be crucial for understanding nuclear-pore function, was revealed by fluorescence-recovery after photobleaching (FRAP) analysis in living cells (Rabut *et al*, 2004). Monitoring the dissociation rates of GFP-tagged Nups in cultured cells showed that the NE localization of the scaffold nuclear-pore components remains stable over many hours, which is consistent with their role as structural nuclear-pore components. By contrast, the nuclear-pore association of many peripheral Nups—such as Nup153 and Nup98—is highly dynamic, with residence times of seconds rather than hours (Daigle *et al*, 2001; Rabut *et al*, 2004). Although these results need to be interpreted with some caution because they were obtained with tagged proteins, they raise the interesting question of whether the dynamic behaviour of peripheral Nups is crucial for transport or whether they are engaged in a different set of nuclear functions that might involve shuttling between the nuclear periphery and other intranuclear locations. The Nups that have been identified as the most dynamic in this assay—including

Nup153, Nup50 and Nup98—also happen to be components or associated factors of the nuclear basket (see glossary; Stoffler *et al*, 2003). Interestingly, the dynamic movement of Nup98 and Nup153—which can bind to mRNA-export factors (Pritchard *et al*, 1999) and RNA (Ball *et al*, 2007), respectively—has been shown to depend on active transcription (Griffis *et al*, 2004). Therefore, it is plausible that the high mobility of nuclear basket Nups might reflect their involvement in transcription or in the delivery of mRNA to the nuclear pore.

In a recent study, the unique molecular organization of Nups was correlated to their expression status in dividing versus terminally differentiated cells (D'Angelo *et al*, 2009). Comparing expression levels revealed that both dynamic and stable Nups are transcribed in proliferating cells, whereas only the stable scaffold Nups are sharply downregulated when cells exit the cell cycle. Furthermore, the core structures of nuclear pores were shown not to turn over during the entire lifespan of non-dividing cells. The lack of a replacement mechanism for NPC scaffold components comes at a cost for long-lived post-mitotic cells such as mammalian brain neurons that can persist for the whole life of an organism. An age-dependent deterioration of the NPC was observed that resulted in a breakdown of the nuclear-permeability barrier, leading to aberrant nuclear accumulation of the cytoplasmic protein tubulin (D'Angelo *et al*, 2009).

The NPC in tissue-specific development and disease

Given the indispensable role of the NPC in cellular function and the highly conserved nature of its components, tissue-specific requirements for Nups might seem surprising. Nonetheless, many reports have shown the involvement of both stable and dynamic Nups in particular aspects of development and in specific human pathologies (Table 1). As a compelling example, a recent study has isolated a mutation in human NUP155—a component of the scaffold NUP93–205 complex—that underlies atrial fibrillation (AF), which is an inherited form of clinical arrhythmia that can lead to sudden cardiac death (Zhang *et al*, 2008). Although homozygous mice carrying the knockout *Nup155* allele die around the time of mid-embryogenesis, the heterozygous animals show an AF phenotype. This suggests that a reduction in the levels of NUP155 or its mistargeting, such as that found in the naturally isolated allele of *Nup155*, results in a tissue-specific disorder. Interestingly, the fly homologue of NUP155, Nup154, has also been shown to have a tissue-specific role, although it seems to be important for the function of a different organ; in *Drosophila*, Nup154 has crucial roles in gametogenesis, affecting egg-chamber development in females and meiotic progression in both sexes (Gigliotti *et al*, 1998; Grimaldi *et al*, 2007).

Perhaps the best-studied examples of Nup alterations that underlie specific human disorders are the identified translocations of the *NUP98* and *NUP214* genes, which result in fusions of the Nups to transcriptional and signalling regulators, and have been characterized as mutations leading to several types of leukaemia (Nakamura *et al*, 1996; Saito *et al*, 2004; Slape & Aplan, 2004). The oncogenic fusion of NUP98 to the transcription factor HOXA9 results in acute myelogenous leukaemia and has been shown to induce the aberrant expression of HOXA9 target genes, beyond the effects of the overexpression of HOXA9 alone, and to block the differentiation of human hematopoietic cells (Ghannam *et al*, 2004; Takeda *et al*, 2006). The fusion of NUP98 to PHD-finger proteins has also been shown to produce similar effects and to lock target genes into an aberrantly active state, resulting in leukaemic transformation (Wang *et al*, 2009). These findings agree with the idea

Fig 1 | Nuclear pores and chromatin organization. (A) Schematic illustration of the NPC. The three different classes of Nups and their relative locations within the NPC are shown. (B) Electron micrograph image of a mammalian nucleus, illustrating the positioning of the NE against darkly stained condensed heterochromatin, and of the nuclear pores (arrowheads) against the lighter stained open euchromatin. Reproduced with permission from <http://synapses.clm.utexas.edu> (J. Spacek). Gp210, glycoprotein of 210 kDa; hCG1, candidate gene 1; INM, inner nuclear membrane; Ndc1, nuclear division cycle 1; NE, nuclear envelope; NPC, nuclear-pore complex; Nup, nucleoporin; ONM, outer nuclear membrane; Pom121, pore membrane protein of 121 kDa; Rae1, RNA export 1; Sec13, secretory mutant 13; Seh1, Sec13 homologue; Tpr, translocated promoter region.

that the normal function of NUP98 might include the regulation of gene expression. The fusion between NUP214 and the tyrosine kinase ABL1 is present in a significant portion of acute lymphoblastic leukaemia cases. Recent data suggest that localization of NUP214/ABL1 to the NPC and its interaction with other Nups are required to induce transformation (De Keersmaecker *et al*, 2008). It remains to be tested whether changes in nuclear-pore composition and consequently altered function are crucial events in the pathogenesis of haematopoietic malignancies.

A Transport-dependent regulation

B Transport-independent regulation

Fig 2 | Models of transport-dependent and transport-independent mechanisms of gene regulation by the nuclear-pore complex. The NPC consists of stable core components (dark blue) and peripheral Nups (red), which are often dynamic. **(A)** Transport-dependent regulation might involve interactions between cell type-specific TFs (green) and a specific NPC component, between an IMP (gray) that carries a TF (orange) and a specific FG Nup, or between a given mRNA and a particular Nup. **(B)** Transport-independent regulation might involve chromatin tethering to the NPC (nucleosomes are shown as gray discs), or the recruitment of active genes (Pol II is shown in green) to the NPC through interactions with SAGA/Sus1 (gray), mRNA or the associated mRNA export and processing machinery (light blue). Alternatively, dynamic Nups (red) could shuttle away from the nuclear pore and interact with active genes, mRNA or mRNA export/processing machinery inside the nucleus. IMP, import receptor; mRNA, messenger RNA; NPC, nuclear-pore complex; Nup, nucleoporin; Pol II, RNA polymerase II; SAGA, Spt-Ada-Gcn5-Acetyltransferase; Sus1, suc synthase 1; TF, transcription factor.

Interestingly, both the dynamic Nup98 and the stable Nup96—which are products of the same gene but are auto-proteolytically cleaved into two polypeptides (Fontoura *et al*, 1999)—also have a crucial role in the function of the immune system and are upregulated by interferons in response to viral infections (Enninga *et al*, 2002). A heterozygous mutation in Nup96 has been shown to affect the expression of interferon-regulated genes and to disrupt the normal function of macrophages, and B and T lymphocytes, with no detectable gross pathological abnormalities in other organs (Faria *et al*, 2006). Moreover, the role of Nup96 in the immune response seems to be evolutionarily conserved, as NUP96 in *Arabidopsis thaliana* has also been shown to be required for the basal defence and resistance responses mediated by plant immune sensors (Zhang & Li, 2005).

The cell-type specificity of the roles of Nups has similarly been observed in development and differentiation (Table 1). For example, mouse NUP133—a component of the stable NUP107–160 subcomplex—was recently shown to have a role in embryonic development of the neural lineage, such that NUP133-null neural progenitors could not efficiently produce terminally differentiated neurons (Lupu *et al*, 2008). Furthermore, a mutation in the zebrafish ELYS—a Nup that closely associates with the same subcomplex—was reported to inhibit normal development and proliferation of the retina and the intestine (Davuluri *et al*, 2008; de Jong-Curtain *et al*, 2008). Mutations in several plant Nups have been reported to cause diverse developmental defects, which seem to be comparatively mild and

relatively specific (Meier & Brkljacic, 2009). One such example is a mutant allele of the nuclear basket Nup Tpr/NUA, which affects the flowering time, seed production and leaf morphology of *A. thaliana* (Xu *et al*, 2007).

One of the most interesting questions regarding the regulatory functions of the NPC is whether various cell types have different nuclear-pore compositions. Cell type-specific expression of Nups has been documented for the dynamic nuclear-pore proteins NUP50 and GP210 in mice (Olsson *et al*, 2004; Smitherman *et al*, 2000). Similarly, the expression of Nup88/*mbo*, as well as its mutant phenotype, seems to be tissue specific in *Drosophila* (Uv *et al*, 2000). Gamete formation and spermatogenesis, in particular, seem to rely on transport-mediated developmental regulation (Hogarth *et al*, 2005). In addition to the fly Nup154, mammalian NUP BS-63, which is homologous to Nup358, is expressed specifically in spermatids and human sperm (Cai *et al*, 2002). Although the molecular basis of most of these disparate cases of tissue-specific roles of Nups is not yet characterized, the potential mechanisms can be grouped into transport-dependent and transport-independent gene regulation, as discussed below.

Transport-dependent gene regulation by Nups

There are several mechanisms by which a tissue-specific transport function of the NPC can be achieved. It can occur through the selective transport of a specific protein such as the import or export of a particular transcription factor, or through the regulated export of a crucial RNA (Fig 2). These mechanisms can be achieved either

by expressing tissue-specific transport receptors or by changing the relative composition of NPCs. In support of the former idea, transport receptors seem to have differential affinities for different FG domains, suggesting that a particular FG Nup will probably interact with only a subset of transport receptors (Damelin & Silver, 2000; Pyhtila & Rexach, 2003; Strawn *et al*, 2004). An example of the latter is the nuclear accumulation of Dorsal (a transcription factor with roles in development and immune response), which has been shown to depend specifically on Nup88/*mbo* (Uv *et al*, 2000). Although *mbo* mutants do not show defects in general NLS-mediated protein import or mRNA export, they fail to accumulate Dorsal in the nuclei and, consequently, to activate the immune response properly. Interestingly, Nup88 was proposed to regulate the location of the nuclear export receptor CRM1, which becomes mislocalized to the nucleus in *mbo* mutants and seems to drive the aberrant export of Dorsal (Roth *et al*, 2003). In addition, the same group proposed that variations in levels of the Nup214–Nup88 complex at the pore change the amount of NPC-bound CRM1, thereby influencing the relative strength and duration of NF- κ B-signalling responses (Xylourgidis *et al*, 2006).

A role in the export of particular mRNAs has been reported for NUP96 in mammalian macrophages (Faria *et al*, 2006). The lower levels of NUP96 in *Nup96^{+/-}* mice seem to disrupt the nuclear export of a subclass of immune-related transcripts, probably contributing to the reduced levels of some of the proteins that they encode. Interestingly, the same *Nup96^{+/-}* condition is reported to affect the cell cycle-dependent nucleocytoplasmic distribution of several mRNAs in T cells (Chakraborty *et al*, 2008). In contrast to the nuclear accumulation observed in macrophages, most of the tested mRNAs were seen to accumulate aberrantly in the cytoplasm of *Nup96^{+/-}* T cells, suggesting that NUP96 can facilitate or inhibit specific mRNA export, perhaps depending on the cell type, cell-cycle stage or type of mRNA.

Several mutants of plant Nups show an accumulation of mRNA in the nucleus (Meier & Brkljacic, 2009), although none has been linked to a particular mRNA subset that would help to explain the relatively specific developmental problems that they induce. Intriguingly, the levels of three specific miRNAs are significantly reduced in a *Tpr/NUA* mutant of *Arabidopsis* (Jacob *et al*, 2007). As miRNAs are known to be involved in many aspects of development, the link between Nups and miRNA metabolism could be crucial to understanding the tissue-specific roles of nuclear-pore components.

Despite the examples described above, it is often difficult to envision how transport specificity can be achieved through different nuclear-pore compositions, as each pore must establish interactions with various molecules simultaneously. Although the involvement of FG Nups in specific transport events can be based on their proposed affinities for particular transport receptors (Weis, 2007), it is more challenging to explain these types of tissue-specific behaviour for components of the NPC core. One possibility is that an altered nuclear-pore number or altered transport rate can have distinct effects on different tissues. Early studies reported markedly altered transport rates and nuclear-pore permeability in cells of varying cell division and differentiation states (Feldherr & Akin, 1990). A recent study on the role of zebrafish ELYS might provide an example of the developmental consequences of the reduction of nuclear-pore number (de Jong-Curtain *et al*, 2008). *Flo*—a mutant of ELYS, which is thought to be required for nuclear-pore assembly—caused

Glossary

ABL1	v-abl Abelson murine leukaemia viral oncogene homologue 1
CBP	CREB-binding protein
ChIP	chromatin immunoprecipitation
COPII	coat protein complex II
CRM1	chromosome region maintenance 1, also known as exportin 1
Dosage compensation	an epigenetic process by which gene expression from the single male X and two females Xs is equalized between the sexes; in <i>Drosophila</i> , this involves a twofold increase in transcription from the male X
ELYS	embryonic large molecule derived from yolk sac, a nucleoporin
FG Nup	nucleoporin with conserved phenylalanine glycine repeat motifs that can be of the FG, GLFG (L for leucine) or FXFG (X for any amino acid) type
<i>Flo</i>	flotte lotte
GAL	galactosidase
gp120	glycoprotein of 120 kDa, a transmembrane nucleoporin
HOX	homeobox
Mex67	mRNA export
<i>mbo</i>	members only
miRNA	microRNA, a type of non-coding RNA molecule with roles in regulation of development and growth
Mlp1	myosin-like protein 1, a homologue of translocated promoter region
MNase	micrococcal nuclease, an enzyme that can cleave DNA; when fused to a protein of interest, it can be used to map the binding sites of the protein using the cleavage pattern of the genome
Mtor	megator
NDC1	nuclear division cycle 1, a transmembrane nucleoporin
NF- κ B	nuclear factor- κ B
NLS	nuclear-localization signal
NSD1	nuclear receptor binding SET domain protein 1
<i>NUA</i>	nuclear pore anchor
Nuclear basket	a structural element of the nuclear pore, created by the nuclear filaments attached to the core of the nuclear-pore complex and joined in a distal ring
PHD	plant homeodomain
POM121	pore membrane protein of 121 kDa, a transmembrane nucleoporin
Prp20	pheromone-response pathway protein 20, also known as RanGEF or RCC1
Ran	ras-related nuclear protein
SAGA	Spt-Ada-Gcn5-Acetyltransferase
Sus1	suc synthase 1
THO	suppressor of the transcriptional defect of hyperrecombination protein 1
<i>Tpr</i>	by overexpression, a complex of proteins involved in messenger ribonucleoprotein biogenesis
	translocated promoter region, a nucleoporin of the nuclear basket of the nuclear-pore complex

tissue-specific defects, most markedly during the development of the intestinal epithelium. It could be that the number of nuclear pores is considerably reduced in the highly proliferating intestine of the

Flo mutant, as without correct nuclear-pore insertion, every cell division dilutes the total number further. In more slowly proliferating tissues, the nuclear-pore number is less severely affected and cells develop normally. Although this maybe true, the cell-proliferation rate does not seem to be a consistent distinguishing factor for the tissues that Nup mutations have been described to alter. The phenotypes of Nup alleles suggest that alternative roles of the NPC might have to be considered to explain the full range of the regulatory functions of the nuclear pore.

Transport-independent gene regulation by Nups

The proposed involvement of the nuclear pore in chromatin organization and transcriptional regulation might also explain the tissue-specific roles of nuclear-pore components. High-resolution images of mammalian nuclei distinctly show the non-random association of decondensed chromatin with nuclear pores (Fig 1B), suggesting a relationship between NPCs and active genes. One can envision that it would be advantageous for a cell to co-regulate the two endpoints of nuclear gene expression—that is, the production of mRNA and its eventual exit into the cytoplasm. According to this idea—known as the gene-gating hypothesis—nuclear pores are able to specifically interact with, and perhaps regulate, active sites in the genome (Blobel, 1985). Several lines of experimental evidence, mainly obtained in yeast, have provided support for the gene-gating hypothesis, showing a connection between the NPC and transcriptional activation.

The reported interaction between the yeast nuclear basket component Nup2, which is a homologue of Nup153, and the promoters of active genes—known as the Nup-PI phenomenon—indicates that nuclear pores can interact with active genes during the initial steps of transcription (Schmid *et al*, 2006). In this regard, enhancing the association of an inducible gene with the NPC was shown to boost its transcript levels (Taddei *et al*, 2006). Furthermore, a genome-wide ChIP analysis in *Saccharomyces cerevisiae* showed that a subset of Nups, including the nuclear basket components Mlp1 (which is a homologue of Tpr), Nup2 and Nup60, often occupy regions of highly transcribed genes (Casolari *et al*, 2004). A recent study of *Drosophila* dosage compensation (see glossary) showed that Nup153 and Mtor/Tpr are necessary for the twofold hypertranscription of the male X (Mendjan *et al*, 2006), implicating NPC components in the establishment of active chromatin and suggesting that metazoans could similarly use the NPC for the epigenetic regulation of their gene-expression programmes. Furthermore, mammalian NUP98 has been reported to interact physically with histone acetyltransferase CBP/p300 (Kasper *et al*, 1999). This interaction seems to be highly relevant to the cancer-associated roles of NUP98, as an oncogenic fusion of NUP98 to NSD1 histone methyltransferase was shown to produce aberrant activation, hyperacetylation and recruitment of p300 to Hox-A genes in leukaemogenesis (Wang *et al*, 2007).

What mediates the interaction between active genes and the NPC? Sus1—a member of the mRNA-export complex that interacts physically with the NPC component Nup1—was shown to associate with the histone acetyltransferase complex SAGA, which is involved directly in transcriptional activation (Rodriguez-Navarro *et al*, 2004). In addition, the recruitment of active GAL genes to the nuclear periphery was shown to depend on Sus1 and other SAGA components (Cabal *et al*, 2006; Luthra *et al*, 2007), which is perhaps the strongest evidence in support of the gene-gating hypothesis. The mRNA-export

receptor Mex67 was shown to contribute to the association of active genes with the nuclear periphery (Dieppl *et al*, 2006). The mRNA molecule could itself be another ‘physical glue’ for the proposed Nup-active gene association. However, although Nup153—which is the homologue of Nup1, Nup2 and Nup60—can physically bind to RNA (Ball *et al*, 2007), and the chromatin association of Mlp1 was found to be RNase sensitive (Casolari *et al*, 2005), no specific RNA-based interactions have been identified so far. Two new interesting candidates have recently been implicated in the association between transcribing genes and NPCs: some components of the exosome seem to mediate the post-transcriptional tethering of GAL genes to the NE (Vodala *et al*, 2008), and the THO complex seems to link 3'-end RNA processing to nuclear-pore association (Rougemaille *et al*, 2008).

Interestingly, the sites of NPC interactions with chromatin, which were identified by the ChIP approach in yeast, were preferentially located in the 3' ends of active genes (Casolari *et al*, 2004). This is in contrast to the observed Nup-PI phenomenon, which was discovered by mapping the MNase–Nup2 fusion, and was found to involve Nup binding to the promoter and 5' regions (Schmid *et al*, 2006). One explanation for this apparent contradiction would be the presence of both gene ends at the NPC through interactions with different Nups, resulting in DNA looping. It has been suggested that such chromatin looping at the NPC could establish active chromatin domains, into which protein factors involved in activation are clustered (Akhtar & Gasser, 2007; Menon *et al*, 2005).

By contrast, the high-resolution images of the nucleus (Fig 1B) suggest another potential function of the NPC. Heterochromatin seems to be interspersed by pores in a highly periodic manner, and it seems plausible that the NPC would have a role in setting up this organization by acting as a boundary between condensed and decondensed regions. Boundary elements are generally defined by their ability to prevent communication between active and silent chromatin, which they are thought to do by physically partitioning the chromatin fibre (Burgess-Beusse *et al*, 2002; Gerasimova *et al*, 1995). Examples of this type of involvement have been reported for the NPC: yeast Nup2, Nup60 and Prp20/RanGEF were identified in a screen for chromatin-boundary activities that can prevent the spreading of repressing factors into neighbouring genes (Ishii *et al*, 2002). In addition, Prp20-bound histones show a pattern of histone modifications typical for both heterochromatin and euchromatin, implying that Prp20, which can interact with Nup2, could establish a chromatin boundary at the NPC (Dilworth *et al*, 2005). Interestingly, the yeast genome ChIP studies discussed above correlated the binding of Prp20 to non-transcribing genes (Casolari *et al*, 2004), supporting the idea that the Nup-associated boundary activity could be an additional function of the NPC, separable from its involvement in transcriptional activation. Intriguingly, the only characterization of a genome-wide binding pattern of a metazoan Nup performed so far showed an enrichment of repressive heterochromatic histone marks (Brown *et al*, 2008). ChIP analysis of Nup93 showed that its binding sites correlate with regions of high trimethylation of H3K9, H4K20 and H3K27, although the results were obtained from a different cell type than that used for the analysis of genome-wide histone modifications, and therefore should be interpreted with caution. Nonetheless, they support the involvement of nuclear pores in tethering non-active chromatin regions for the purposes of genome organization.

During mitosis in higher eukaryotes, the NE and the nuclear pores break down and reform around newly segregated chromatin (D'Angelo & Hetzer, 2008). Mitotic propagation of cell-specific chromatin architecture is intimately linked to this reassembly; yet, how post-mitotic nuclear reformation around chromatin translates into interphase chromatin organization is unknown. Studies in *Xenopus* cell-free systems showed that the Nup107–160 complex, ELYS, Nup153 and Nup358 are recruited to chromatin early in the post-mitotic reassembly independently of nuclear membranes (Franz *et al*, 2007; Rasala *et al*, 2006; Walther *et al*, 2003). The association of Nups with chromatin represents one of the initial events in nuclear reorganization, suggesting that they could be involved in the propagation of chromatin organization through mitosis and, therefore, in epigenetic memory. An interesting role in epigenetic memory has been proposed for the yeast NPC, in which a long-term association of an inducible gene with the nuclear pore was reported to occur for several cell generations after the initial activation in yeast (Brickner *et al*, 2007). Although yeasts undergo closed mitosis and do not need to reform their NE, a role of the NPC in positional or epigenetic memory remains an intriguing possibility.

There might be two distinct types of mechanism by which the NPC regulates gene expression in a transport-independent manner (Fig 2). One is the physical association of the stable NE-embedded nuclear-pore structure with the chromatin fibre, which could have a role in tethering a chromatin boundary or in the general establishment of the three-dimensional organization of chromatin inside the nucleus. As the core of the NPC does not turn over during the entire lifespan of a cell (D'Angelo *et al*, 2009), this extreme stability makes the core components of the NPC ideal candidates for establishing long-term transcription programmes. We hypothesize that the highly stable central core of the nuclear pore can be viewed as a scaffold for nuclear architecture and could be used as a basis for epigenetic memory in differentiated cells. By contrast, a subset of NPC components seems to have a role in transcriptional activation or in coordinating the processes of transcription and mRNA processing and export. In this sense, the mechanism would not be entirely transport independent, as the overall purpose of this interaction might be to achieve the efficient or regulated transport of mRNA. The NE-embedded NPC could accommodate the recruitment of crucial machinery or the DNA looping necessary to establish an active chromatin domain. Interestingly, the Nups that have been implicated in transcriptional activation, including Nup153/Nup1/Nup2/Nup60 and Nup98, are also highly dynamic (Rabut *et al*, 2004). An intriguing possibility is that the dynamic behaviour of these Nups underlies their role in transcriptional activation. Dynamic Nups could move away from the nuclear pore to interact with transcribing genes or with mRNA and associated machinery inside the nucleus—that is, not at NE contact sites; this idea is supported by the reported transcription-dependent mobility of Nup153 and Nup98 (Griffis *et al*, 2004). The classification of these dynamic proteins as Nups might not fully reflect their functional diversity as, in addition to transport, they could also have roles in transcriptional gene regulation. The nuclear pore might sequester and/or use these proteins until signals alter their distribution to fulfil their additional roles away from the nuclear pore. This view of the NPC as a chromatin-interacting regulatory entity could provide an explanation of how tissue-specific functions of NPC components are achieved.

Sidebar A | In need of answers

- (i) Do nuclear pores have different nucleoporin (Nup) composition in various cell types? Which Nups are expressed in particular tissues and/or at specific developmental times?
- (ii) Is the deterioration of the permeability function of the nuclear-pore complexes a general mechanism for ageing in long-lived post-mitotic cells?
- (iii) Are transcribing loci recruited to the nuclear pores in metazoan cells, similar to that observed in yeast? Do certain metazoan Nups interact preferentially with transcribing genes versus heterochromatic loci?
- (iv) What is the function of the dynamic behaviour of some peripheral Nups? Does it have a role in transport or in a pore-independent transcription-dependent nuclear process?
- (v) What role do alterations in nuclear-pore composition and Nup expression have in leukaemogenesis, and do other cancers involve perturbations of nuclear pore function?

Conclusions

Our knowledge of the nuclear pore has expanded significantly for more than 50 years, since its initial identification as the exclusive transport channel between the nucleoplasm and the cytoplasm. The cell and tissue-specific transport events and regulatory roles of the NPC, in the context of normal and abnormal cell physiology, now await elucidation (Sidebar A). Evidence is emerging from studies in yeast, plants and animals that NPC composition varies among cell types, stages of the cell cycle and developmental stages. Furthermore, a new picture is emerging in which the NPC is active in chromatin organization and gene regulation in a transport-independent manner. On the one hand, the immobile and stable nature of the NPC core could provide a scaffold for tethering and partitioning the chromatin template; on the other hand, highly dynamic nuclear-pore components can move to non-peripheral locations inside the nucleus, where they might be similarly involved in transcriptional regulation. It is likely that at least some of the uncovered tissue-specific roles of Nups originate from these genome-organizing functions of the NPC, which is a idea that awaits further exploration.

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