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Deep Insight Section

The nuclear pore complex becomes alive: new insights into its dynamics and involvement in different cellular processes

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Abstract

In this review we summarize the structure and function of the nuclear pore complex (NPC). Special emphasis is put on recent findings which reveal the NPC as a dynamic structure in the context of cellular events like nucleocytoplasmic transport, cell division and differentiation, stress response and apoptosis. Evidence for the involvement of nucleoporins in transcription and oncogenesis is discussed, and evolutionary strategies developed by viruses to cross the nuclear envelope are presented.

Running title: NPC becomes alive

Keywords: nucleus; nuclear pore complex; nucleocytoplasmic transport; nuclear assembly; apoptosis; rheumatoid arthritis; primary biliary cirrhosis (PBC); systemic lupus erythematosus; cancer

1. Introduction

Eukaryotic cells in interphase are characterized by distinct nuclear and cytoplasmic compartments separated by the nuclear envelope (NE), a double membrane that is continuous with the endoplasmic reticulum (ER). Nuclear pore complexes (NPCs) are large supramolecular assemblies embedded in the NE and they provide the sole gateways for molecular trafficking between the cytoplasm and nucleus of interphase eukaryotic cells. They allow passive diffusion of ions and small molecules, and facilitate receptor-mediated transport of signal bearing cargoes, such as proteins, RNAs and ribonucleoprotein (RNP) particles (Görlich and Kutay, 1999; Conti and Izaurralde, 2001; Macara, 2001; Fried and Kutay, 2003). A consensus model of the 3D architecture of the NPC has evolved from
extensive electron microscopy (EM) and tomography studies in both yeast and higher eukaryotes (Unwin and Milligan, 1982; Hinshaw et al., 1992; Akey and Radermacher, 1993; Yang et al., 1998; Stoffler et al., 2003; Beck et al., 2004). Accordingly, the NPC consists of an eightfold symmetric central framework. The cytoplasmic ring moiety of the central framework is decorated with eight cytoplasmic filaments, whereas the nuclear ring moiety is topped with eight tenuous filaments that join distally into a massive distal ring and thereby form a distinct nuclear basket (**Fig. 1**). The overall 3D model of the NPC is conserved from yeast to higher eukaryotes, except for variations in linear dimensions among species (Fahrenkrog et al., 1998; Cohen et al., 2002; Stoffler et al., 2003).

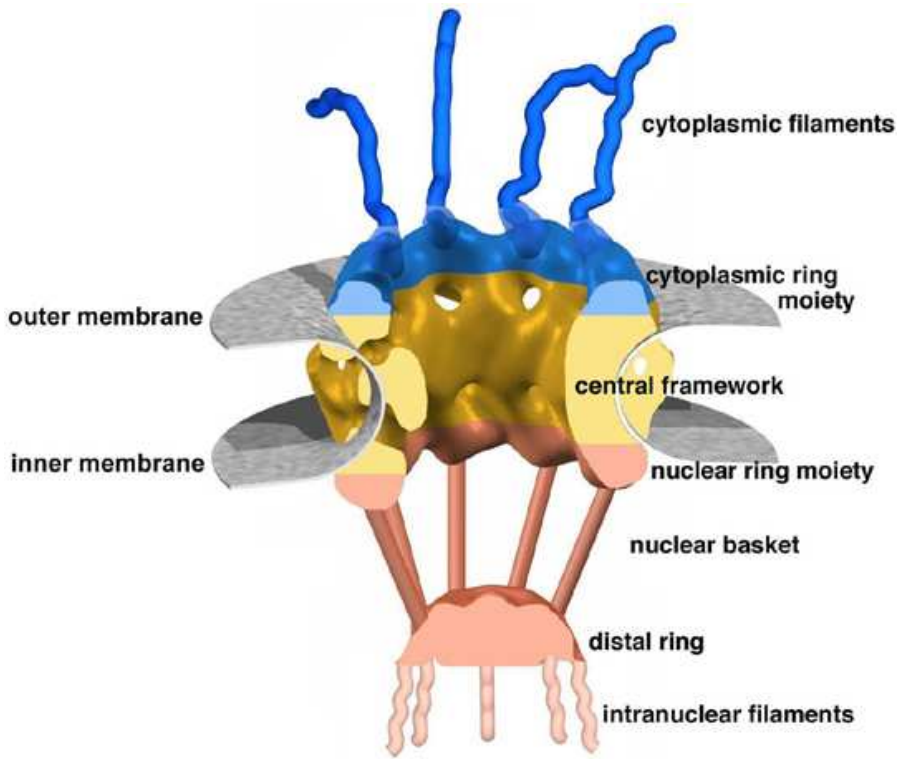

Figure 1: 3D consensus model of the NPC.
The main structural components of the NPC include the central framework embedded in NE membrane, the cytoplasmic ring moiety and cytoplasmic filaments, the nuclear ring moiety and the nuclear basket. Figure was modelled with a visual programming environment (ViPEr) at the Scripps Research Institute (http://www.scripps.edu).
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2. Nucleoporins: the Molecular Components of the Nuclear Pore Complex

Based on their molecular mass of ~125 MDa (Reichelt et al., 1990) and the high degree of 822 symmetry of their central framework, it is assumed that both vertebrate and yeast NPCs are composed of multiple copies of ~30 different proteins, called nucleoporins (Nups) (Panté and Aebi, 1996; Stoffler et al., 1999; Fahrenkrog and Aebi, 2002). Up to date, ~30 yeast (**Table 1**) and ~26 vertebrate (**Table 2**) nucleoporins have been identified and characterized (Rout et al., 2000; Cronshaw et al., 2002).

Table 1: Saccharomyces cerevisiae nucleoporins

Name	Homologues	Motifs	Location	Properties and function
Snl1p (18 kDa)	−	transmembrane	NE and ER	stabilizing role in NPC structure and function
Sec13p (32 kDa)	Sec13	WD	cytoplasmic and nuclear periphery of the central pore	member of Nup84 complex; vesicular transport from ER to Golgi
Ylr018p/Pom34p	−	transmembrane	cytoplasmic and nuclear face of the NPC core	anchors NPC to the NE
Yrb2p/Nup36p	*h* RanBP3	FXFG Ran binding	unknown	Ran binding protein
Seh1p (39kDa)	Seh1	WD	cytoplasmic and nuclear periphery of the central pore	member of Nup84 complex; vesicular transport from ER to Golgi
Gle2p (40 kDa)	*Sp* Rae1p	−	cytoplasmic and nuclear periphery of the central pore	role in mRNA export
Rip1p (42 kDa)/ Nup42p	*h* Rip1/Rab	FG	cytoplasmic filaments; nuclear basket; nucleus	essential for export of heat shock RNA

Nup2 p (78 kDa)	Nup50	FXFG coiled coil Ran binding	nuclear; NPC	role in Srp1p/Kap60p export pathway
Nup49p	*r* Nup58/Nup45 *Sp* Nup49	GLFG coiled coil	cytoplasmic and nuclear periphery of the central pore	role in protein import and RNA export
Nup53p	*X* MP44	FG coiled coil	cytoplasmic and nuclear face of the NPC core	role in import of ribosomal proteins; phosphorylated during mitosis
Nup57p	*r* Nup54 *Sp* Nup57	GLFG coiled coil	cytoplasmic and nuclear periphery of the central pore	role in protein import and RNA export
Nup59p	*X* MP44	FG coiled coil	cytoplasmic and nuclear face of the NPC core	member of Nup170 complex;
Nup60p	−	FXF Ran binding	nuclear basket	tethering of Nup2 to the NPC
Gle1p (62 kDa)	*h* Gle1	NES	cytoplasmic filaments; cytoplasm	role in mRNA export
Npl4 (64 kDa)	−	degenerated repeat motifs: GSXS, GSSX, GSXF, GFXS	unknown	role in protein import, RNA export and biogenesis
Ndc1 (74 kDa)	*Sp* Cut11p	transmembrane	NPC; SPB	required for proper SPB duplication; NPC assembly?
Nup82p	Nup88	coiled coil	cytoplasmic periphery of the central pore	docking site for Nsp1-Nup159 complex; role in RNA export
Nup84p [a]	*r* Nup107	−	cytoplasmic filaments and nuclear periphery of the NPC	member of Nup84 complex; role in RNA export
Nup85p	Nup85	−	cytoplasmic and nuclear periphery of the NPC	member of Nup84 complex
Nsp1p [b] (86 kDa)	*r*, *h*, *X* Nup62	FXFG coiled coil	cytoplasmic and nuclear periphery of the central pore; nuclear basket	member of Nsp1 complex; C-terminal domain essential; role in protein import in complex with Nup82, Nic96, Nup159
Nic96p	*r*, *h*, *X* Nup93 *Sp* Npp106	coiled coil	cytoplasmic and nuclear periphery of the central pore; nuclear basket	anchors Nsp1complex into the NPC; N-terminal domain essential; role in NPC assembly; role in mRNA export
Nup100p	*r*, *h*, *X* Nup98	GLFG	biased towards cytoplasmic face of the NPC	role in nuclear protein import and mRNA export; interaction with Kap95p and Mex67p
Nup116p	*r*, *h*, *X* Nup98	GLFG	biased towards cytoplasmic face of the NPC	C-terminus necessary for targeting and association with the NPC; role in mRNA export; recycling of Kap95p
Nup120p	Nup160	−	cytoplasmic and nuclear face of the NPC core	member of Nup84 complex; role in mRNA export
Nup1p (133 kDa)	C-terminus of Nup153	FXFG	nuclear basket	role in nuclear protein import, mRNA export and NPC morphology
Nup133p	Nup133	−	cytoplasmic and nuclear face of the NPC core	role in mRNA export, and NPC morphology
Nup145p	*r*, *h*, *X* Nup98	GLFG	C-terminus at the cytoplasmic filaments; N-terminus at the nuclear basket	*In vivo* cleavage; C-terminal domain is part of Nup84 complex and essential for mRNA export and NPC morphology
POM152	−	transmembrane	cytoplasmic and nuclear face of the NPC core	anchors NPC to the NE
Nup157p	*r* Nup155, *D* Nup154	−	cytoplasmic and nuclear face of the NPC core	member of Nup170 complex; NPC core protein

Nup159p	Nup214	FG coiled coil	cytoplasmic periphery of the central pore	in complex with Nsp1p-Nup82p; C-terminus essential; N-terminus involved in mRNA export
Nup170p[c]	*r* Nup155	−	cytoplasmic and nuclear face of the NPC core	member of Nup170 complex; NPC core protein
Nup188p	Nup188	−	cytoplasmic and nuclear face of the NPC core	member of Nup170 complex; NPC core protein
Nup192p	*r*, *h* Nup205	−	cytoplasmic and nuclear face of the NPC core; nuclear basket filaments	Necessary for assembly of Nup49p, Nup57p, Nup82p, and Nic96 into the NPC
Mlp1p/Mlp2p	*D*, *X*, *r*, *h*, Tpr	coiled coil P/F-rich region	nuclear basket and intranuclear filaments	C-terminal of Mlp1p responsible for nuclear localization; Mlp1p prevents export of unspliced mRNAs protein import; tethering of telomers to the NPC

[a]Nup84 complex: C-Nup145, Nup120, Nup85, Nup84, Sec13p, Seh1p
[b]Nsp1 complex: Nsp1, Nup49, Nup57, Nic96
[c]Nup170 complex: Nup188, Nup170, Nup157, Nup59
Abbreviations: D, *Drosophila melanogaster*; h, human; r, rat; Sp, *Saccharomyces pombe*; SPB, spindle pole body; X, Xenopus
For more details see references: Stoffler et al. (1999); Rout et al. (2000); Fahrenkrog et al. (2001).

Table 2: Vertebrate nucleoporins

Name	**Homologues**	**Motifs**	**Location**	**Properties and function**
Nup37	−	WD	−	member of Nup107-160 complex
Seh1	*Sc* Seh1	WD	cytoplasmic and nuclear periphery of the central pore	member of Nup107-160 complex
Sec13	*Sc* Sec13	WD	cytoplasmic and nuclear periphery of the central pore	member of Nup107-160 complex; interacts with Nup96
RAE1	*Sc* Gle2p	WD	nucleoplasmic face of NPC	in complex with Nup98 contributes to nuclear export of mRNAs
Nup45	*Sc* Nup49p	FG coiled coil	cytoplasmic and nuclear periphery of the central pore	generated by alternative splicing of Nup58; member of Nup62 complex; role in nuclear protein import
Nup50	*Sc* Nup2	FG, Ran binding	nucleoplasmic face of the NPC	in complex with Nup153
Nup54	*Sc* Nup57p	FG, PA coiled coil	cytoplasmic and nuclear periphery of the central pore	member of Nup62 complex; role in nuclear protein import
ALADIN	−	WD	cytoplasmic side of the NE (immunofluorescence data)	triple A syndrome
Nup58	*Sc* Nup49p	FG, PA coiled coil	cytoplasmic and nuclear periphery of the central pore	member of Nup62 complex; role in nuclear protein import
Nup62[a]	*Sc* Nsp1p, *Hv* Nup62	FXFG coiled coil	cytoplasmic and nuclear periphery of the central pore; nuclear basket	member of Nup62 complex; role in nuclear protein import; PBC autoantibodies, in complex with CAN/Nup214
PBC68	−	−	nucleoplasmic face of NPC	colocalizes to mitotic spindle; involved in PBC
Nup85	*Sc* Nup85	−	central pore	member of Nup107-160 complex;
Nup88	*r* Nup84	coiled coil	cytoplasmic face of the NPC	C-terminal domain contains CAN/Nup214 binding site; upregulated in some tumors; in complex with CAN/Nup214
Nup93	*Sc* Nic96p, *Sp* Npp106	coiled coil	nuclear periphery of the central pore; nuclear basket	role in NPC assembly; in complex with Nup205/Nup188 and Nup62 complex
Nup96	*Sc* C-Nup145p	−	nucleoplasmic face of the	member of Nup107-160 complex; generated by autoproteolytic in vivo

			NPC	cleavage of a Nup98-Nup96 precursor; in complex with Nup98 and Nup153
Nup98	*Sc* Nup100p, Nup116p, and N-Nup145p	FXFG, GLFG, FG	cytoplasmic periphery of the central pore; nuclear basket and nucleus	role in export of snRNAs, 5S RNA, rRNA, and mRNA, but not tRNA; role in import and export of HIV proteins; role im AMLs; in complex with RAE1 and Nup7 complex
Nup107[b]	*Sc* Nup84p	leucine zipper	cytoplasmic and nuclear periphery of the central pore	member of Nup107-160 complex; in complex with Nup98 and Nup153
POM121	−	FXFG, transmembrane	NPC core	anchors NPC to the NE; N-terminal domain required for nuclear targeting, N-terminal and transmembrane domain required for NPC targeting; in complex with gp210
Nup133	*Sc* Nup133	−	cytoplasmic and nuclear periphery of the central pore	member of Nup107-160 complex; in complex with Nup98 and Nup153
Nup153	*Sc* Nup1p	FXFG, 4 (in *Xenopus* 5) Zn-fingers	nuclear basket	termination site for nuclear protein import; N-terminus contains targeting and assembly information; C-terminus highly mobile; in complex with Nup107-160 complex
Nup155	*D* Nup154p, *Sc* Nup157p, and Nup170p	−	cytoplasmic and nuclear face of the NPC	role in mRNA export (interaction with Gle1p)
Nup160	*Sc* Nup120	−	cytoplasmic and nuclear periphery of the central pore	member of Nup107-160 complex; in complex with Nup98 and Nup153
Nup188	*Sc* Nup188	−	−	in complex with Nup205/Nup93
gp210	−	transmembrane	lumen of the NE	anchors NPC to the NE; related to autoimmune diseases; PCB autoantibodies; in complex with POM121
Nup205	*Sc* Nup192	leucine zipper	−	in complex with Nup188/Nup93
CAN/Nup214	Nup159	FXFG, FG leucine zipper	cytoplasmic periphery of the central pore	role in nuclear protein import, mRNA export and cell cycle; involved in AMLs; in complex with Nup88 and Nup62
Tpr (265 kDa)	*Sc* Mlp1p, *Sc* Mlp2p	coiled coil, leucine zipper	nuclear basket	C-terminus essential for nuclear import; N-terminus required for NPC association; possible role in mRNA export or recycling of transport factors; appears in oncogenic fusions with the oncogenes *met*, *trk*, and *raf*
RanBP2/Nup358	−	Ran binding, FXFG, FG, 8 Zn-fingers	cytoplasmic filaments	nucleocytoplsmic transport

[a]Nup62 complex: Nup62, Nup58, Nup54, Nup45
[b]Nup107-160 complex: Nup160, Nup133, Nup107, Nup96, Nup85, Nup43, Nup37, Sec13, Seh1
Abbreviations: D, *Drosophila melanogaster*; Hv, *Hydra vulgaris*; r, rat; Sc, *Saccharomyces cerevisiae*; Sp, *Saccaromyces pombe*; AMLs, acute myeloid leukemias; PBC, primary biliary cirrhosis
For more details se references: Stoffler et al. (1999); Fahrenkrog and Aebi (2002); Cronshaw et al. (2002).

Many nucleoporins contain characteristic distinct domains of phenylalanine-glycine (FG) containing repeats. These repeat motifs are not required for targeting nucleoporins to the NPC but they play an important role in interactions between nucleoporins and soluble transport receptors (**Table 1** and **2**) (Rexach and Blobel, 1995). Recent experiments analyzing the role of FG repeats for nucleocytoplasmic transport have shown that the asymmetric localized FG repeats are dispensable, whereas certain symmetric ones are crucial for nucleocytoplasmic transport and cell viability (Strawn et al., 2004; Zeitler and Weis, 2004). *In vitro* pulldown assays employing *Xenopus* egg extracts, isolated rat liver nuclei or lysates from yeast nuclei demonstrate specific interactions between nucleoporins and the transport factors importin α,

importin β and RanGTP (Iovine and Wente, 1997; Shah et al., 1998; Shah and Forbes, 1998; Marelli et al., 1998; Stochaj et al., 1998; Seedorf et al., 1999). FG repeats might function as docking sites for transport receptor molecules which in turn, interact with cargo. Additionally, the FG repeats might not only function as docking sites but also as parking sites to keep receptor-cargo complexes in a waiting position at the NPC for later subsequent passage through the central pore.

Precise localization of the nucleoporins in the NPC is essential for understanding their functions in nucleocytoplasmic transport and in NPC assembly at the molecular level. Immunolocalization of nucleoporins using immunogold EM has shown that most nucleoporins are symmetrically localized at both the cytoplasmic and nuclear periphery of the NPC and only few of them being located asymmetrically to either the cytoplasmic or nuclear periphery in both yeast and vertebrate NPC (Panté et al., 1994; Fahrenkrog et al., 1998; Rout et al., 2000; Fahrenkrog and Aebi, 2002; Cronshaw et al., 2002). Interestingly, many nucleoporins are organized into distinct subcomplexes within the NPC structure (Finlay et al., 1991; Panté et al., 1994; Belgareh et al., 2001; Walther et al., 2003). Some of these subcomplexes like the Nup107-160 complex and the Nup62 complex even stay intact during mitosis and might represent elementar building blocks of the NPC.

Despite the conserved structural features of NPCs among different species as yeast and vertebrates there have been some reports about cell-type specific expression of certain nucleoporins (Wang et al., 1994; Hu and Gerace, 1998; Nothwang et al., 1998; Cai et al., 2002; Coy et al., 2002; Olsson et al., 2004). For example, RanBP2L1, and POMFIL1 represent cell-type specific expressed proteins with homology to the nucleoporins RanBP2/Nup358 and POM121 which are coded by different genes (Wang et al., 1994; Nothwang et al., 1998; Cai et al., 2002; Coy et al., 2002). In contrast, the differentially expressed nucleoporins Nup45 and Nup58, both constituents of the Nup62 NPC subcomplex, seem to be generated by alternative splicing from the same gene (Hu and Gerace, 1998). The most recent report concerns the restricted expression of the transmembrane nucleoporin gp210: the mRNA as well as the expressed protein seem to be specific for cultured embryonic stem cells and certain polarized epithelial cells, whereas no expression could be detected in several cultured cell lines of fibroblastic and epithelial origin (Olsson et al., 2004). This result is of special importance since there seem to be only two transmembrane nucleoporins, gp210 and POM121, to anchor the entire 125 MDa NPC to the nuclear envelope, pointing towards a crucial role for POM121 in the architectural design of this multiprotein assembly.

3. Nuclear pore complex: static versus dynamic structure

3.1. Nucleoporin domain flexibility and nucleoporin turnover at the NPC

Contrary to the assumption that the NPC is a rather static structure, a number of recent studies have provided evidence that some of the nucleoporins are mobile within the NPC. For example, it has been shown that the vertebrate nucleoporin Nup98, originally localized to the nuclear basket (Radu et al., 1995), can also be found on the cytoplasmic face of the NPC (Griffis et al., 2003). Nup98 can dynamically associate with the nuclear pore and shuttle between the NPC and intranuclear bodies and additionally between the nucleus and the cytoplasm in a transcription-dependent manner (Zolotukhin and Felber, 1999; Griffis et al., 2002 and 2004). Because Nup98 plays a role in RNA export (Powers et al., 1997), its mobility proposes that Nup98 might associate with RNA close to its transcription site and then further accompany the processed RNA through the NPC into the cytoplasm.

Nup153 plays a role in the import of proteins into the nucleus as well as in the export of RNAs and proteins into the cytoplasm (Bastos et al., 1996; Shah and Forbes, 1998). Nup153 associated with export cargo shuttles between the nuclear and cytoplasmic faces of the NPC (Nakielny et al., 1999). Initially the vertebrate Nup153 had been localized to the distal ring of the nuclear basket (Panté et al., 1994) and close to or at the nuclear ring of the NPC (Walther et al., 2001). Immunogold EM with domain-specific antibodies against Nup153, in combination with recombinantly expressed epitope-tagged Nup153 in the *Xenopus* oocytes, has revealed a domain-specific topology within the NPC (Fahrenkrog et al., 2002). Nup153 seems to be anchored through its N-terminal domain to the nuclear ring moiety and its central Zn-finger domain to the distal ring of the NPC. By contrast, the C-terminal domain which harbors ~40 FG repeats (about 700 amino acids), appears to be highly mobile, as it has been localized throughout the nuclear basket and even at the cytoplasmic periphery of the central pore of the NPC (**Fig. 2**; Fahrenkrog et al. (2002 and 2004); Fahrenkrog and Aebi (2003)). In their native state FG-repeats are unfolded and highly unstructured (Bayliss et al., 2000; Allen et al., 2002; Denning et al., 2002 and 2003) so that the C-terminal domain of Nup153 could extend up to ~200 nm if completely stretched out, meaning that the C-terminal domain can reach all the way from the distal ring of the nuclear basket through the central pore into the cytoplasmic periphery of the NPC. This high mobility and structural flexibility of the FG repeats which act as binding/docking sites for cargo complexes might significantly increase the efficiency of cargo translocation through the NPC.

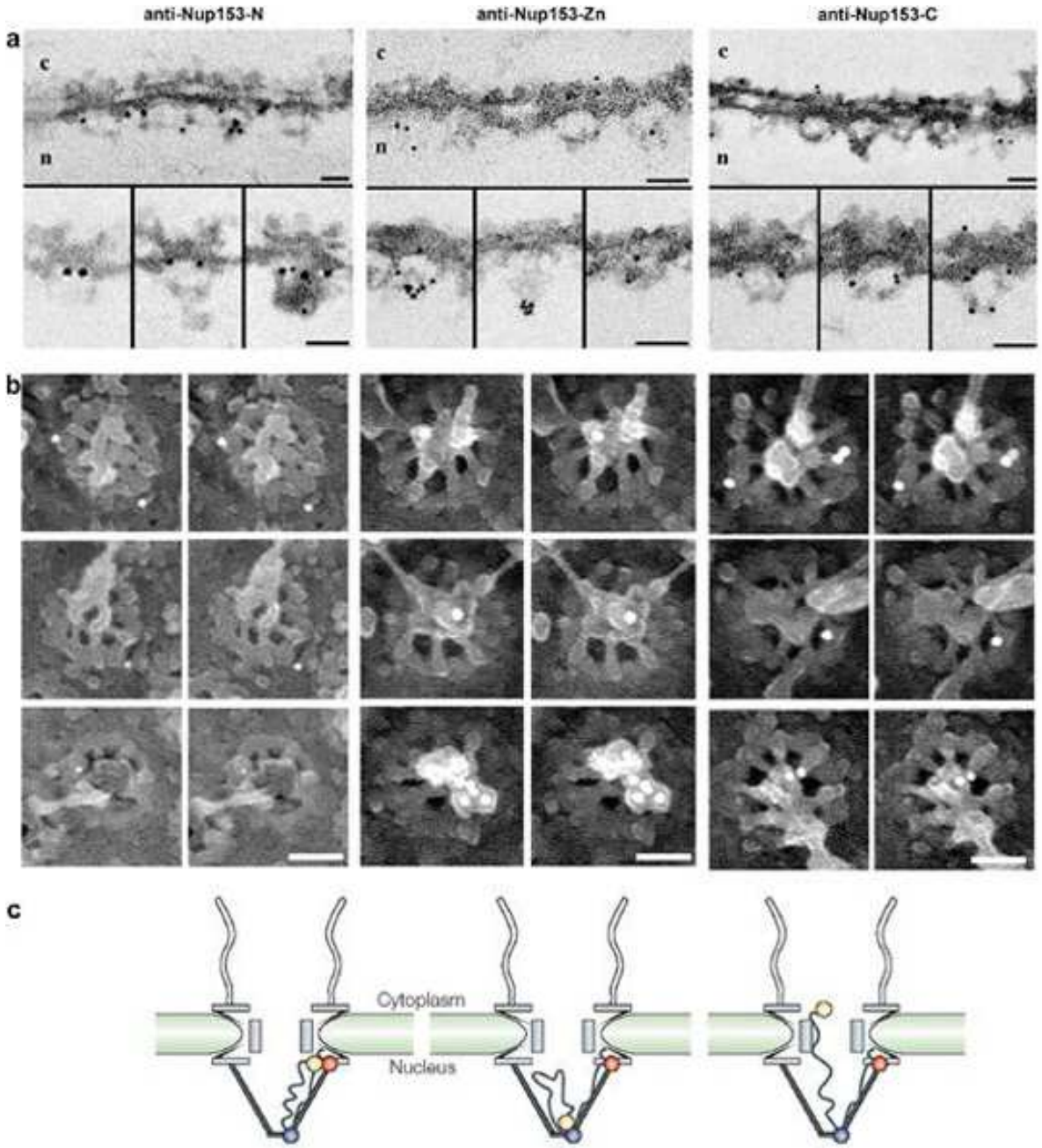

Figure 2: Localization of the N-terminal, Zn-finger, and C-terminal domain of Nup153 in the 3D architecture of the NPC.
Isolated *Xenopus* nuclei were preimmunolabeled with the respective anti-Nup153-domain antibody directly conjugated to 8-nm colloidal gold and prepared for EM by Epon embedding and thin-sectioning (a) and by quick-freeze/freeze-drying/rotary metal-shadowing (b).
(a) Shown are a crosssectioned NE stretch with labeled NPCs, together with a gallery of selected examples of gold-labeled NPC in cross sections. c, cytoplasm; n, nucleus. Scale bars: 100 nm
(b) Stereo images of selected examples of the nuclear face of *Xenopus* oocyte NPCs labeled with colloidal gold-tagged domain-specific anti-Nup153 antibodies. Scale bars: 50 nm.
(c) Schematic representation of the epitope distribution using domain-specific antibodies against Nup153 and epitope-tagged His–Nup153–myc that had been incorporated into *Xenopus* NPCs. The N-terminal (red) and Zn-finger (blue) domains of Nup153 have a stationary location at the nuclear ring moiety and the distal ring, respectively. The C-terminal, FG-repeat domain (yellow) of Nup153 is highly flexible and mobile and can be mapped to the nuclear ring moiety (left), the distal ring (middle) and even the cytoplasmic periphery (right) of the central pore.

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In addition to this structural flexibility, the association of Nup153 with the NPC exhibits remarkable dynamics: fluorescence recovery after photobleaching (FRAP) experiments have demonstrated that on average Nup153 stays associated with the NPC for no longer than about 40 seconds (Daigle et al., 2001; Griffis et al., 2004; for an overview of the turn over times of individual Nups at the NPC see Rabut et al., 2004a). This is interesting since Nup153 has been documented to be crucial for the formation of structurally intact NPCs. If nuclear envelopes are assembled *in vitro* from meiotic *Xenopus laevis* egg extracts depletion of Nup153 from this extract abolishes the incorporation of Tpr, Nup93 and Nup98 into the NPCs (Walther et al., 2001). In an attempt to combine these two findings into a model, two distinct Nup153 pools have been proposed to co-exist at the NPC: a stably associated one which has an architectural function, and a dynamic one exhibiting a high turnover rate (Griffis et al., 2004). Further investigations revealed that similar to Nup98, the mobility of Nup153 is also governed by transcriptional activity, in a way that transcription decreases the dissociation rate from the NPC by a factor of 10 so that a considerable amount of either protein does not exchange any more, i.e. stably associated with the NPC (Griffis et al., 2004). Dissection of Nup98 and Nup153 demonstrated that RNA polymerase I and RNA polymerase II exert distinct effects on the mobility of these two nucleoporins via distinct domains within the two proteins. As might be expected, these domains are the respective NPC interacting domains that have been described previously (Griffis et al., 2004). However, as yet nothing is known about the mediators of this transcription-dependent mobility nor about the exact molecular modifications of Nup98 and Nup153 that are responsible for their mobile behaviour.

3.2. Mitosis, cellular stress and apoptosis

Another aspect of NPC dynamics is revealed by the fact that the NE of higher eukaryotes disintegrates and NPCs disassemble into distinct subcomplexes during mitosis. Although the functional significance of this mitotic disassembly of NPCs is not known, the molecular mechanism leading to this phenomenon appears to be governed by the phosphorylation/dephosphorylation of nucleoporins as has been shown for the transmembrane nucleoporin gp210, as well as for Nup62, Nup153, CAN/Nup214 and RanBP2/Nup358 (Macaulay et al., 1995; Favreau et al., 1996). Examples of nucleoporin subcomplexes that stay intact during mitosis are the Nup107-160 subcomplex, the Nup62 complex, and the CAN/Nup88 subcomplex (Macaulay et al., 1995; Bodoor et al., 1999; Matsuoka et al., 1999; Belgareh et al., 2001). Towards the end of anaphase, NPCs sequentially reassemble around chromatin, and while one would expect this process to be initiated by transmembrane nucleoporins, there are also indications that the association of the Nup107-160 complex with chromatin might be the first step in the reassembly of the NPC after mitosis (**Fig. 3**; Walther et al. (2003); see also Bodoor et al. (1999)). In the near future the use of defined biochemical fractions or even recombinantly expressed nucleoporins in combination with *in vitro* assembly reactions and ultrastructural analysis by TEM and SEM will yield further insights into the distinct assembly steps that eventually yield functional NPCs (Finlay et al., 1991; Walther et al., 2001, 2002 and 2003; Liu et al., 2003).

In addition to this reassembly after mitosis, a second mechanism for the *de novo* formation of NPCs in pre-existing nuclear membranes must take place in lower eukaryotes that go through closed mitosis and therefore never disassemble their NEs. Furthermore, morphometric analysis and FRAP experiments on cells cultured from higher eukaryotes demonstrate that NPCs can also assemble into preformed NEs (Maul et al., 1972; Winey et al., 1997; Daigle et al., 2001). Hence, here we have the interesting situation that two distinct molecular events lead to the formation the same large supramolecular assembly (see also Rabut et al., 2004b).

Late Anaphase	**Telophase**		**Telo/G1**
Nup153	Nup62 complex	CAN/Nup214	gp210
Nup107-160 complex		Nup84	Tpr
Pom121			

Figure 3: Schematic representation of the appearance of nucleoporins at the nuclear periphery towards the end of mitosis.
The diagram summarizes results from immunofluorescence staining and GFP-labeling experiments. (accoding to Bodoor et al., 1999; Daigle et al., 2001; Walther et al., 2003). The Nup62 complex consists of the nucleoporins Nup62, Nup58, Nup54 and Nup45 with cell type specific variations (Hu et al., 1996). The Nup107-160 complex is a huge NPC subcomplex which accounts for nearly one third of the NPCs total mass and is assembled from at least nine different proteins Nup160 (hNup120), Nup133, Nup107, Nup96, Nup85 (Nup75), Nup43, Nup37, Seh1 and Sec13 (Loïodice et al., 2004).

Finally, it should be mentioned that NPCs and nucleoporins might play a more active role in the progression of mitosis than believed earlier. To this end, it has been shown that the giant nucleoporin RanBP2/Nup358 plays an important role in mitotic progression and that the RanGAP1-RanBP2 complex is essential for microtubule-kinetochore interactions during mitosis (Salina et al., 2003; Joseph et al., 2004). Moreover, the Nup107-160 complex localizes in part to kinetochores during mitosis, and depletion of some members of the homologous complexes in yeast and *C. elegans* leads to defects in cell division (Galy et al., 2003; Baï et al., 2004; Loïodice et al., 2004).

As mentioned above, yeasts and other lower eukaryotes undergo a closed mitosis so that their NEs and NPCs stay intact during this process. Recently however, it could be shown that even in these cells NPCs exhibit cell cycle-dependent dynamics. For example, the yeast nucleoporin Nup53p is associated with Nup170p during interphase but following changes at the onset of mitosis it becomes associated with another nucleoporin, Nic96p (Makhnevych et al., 2003). This change presumably leads to the exposure of a binding site for the transport factor Kap121p, which after association with Nic96p, prematurely releases its cargo and thereby prevents efficient nuclear import. Hence, this is a good example how physiological changes in nuclear transport activity can be regulated at the level of NPC architecture. Stress-induced structural reorganization of NPCs in yeast cells and the proteolytic breakdown of certain nucleoporins during apoptosis in higher eukaryotes are further examples of dynamic NPC modifications (Ferrando-May et al., 2001; Shulga and Goldfarb, 2003; Kihlmark et al., 2004; Loïodice et al., 2004). In yeast, for example, an increase in NPC permeability is observed under certain stress situations such as high concentrations of aliphatic alcohols, the presence of deoxyglucose, or during chilling of the yeast cultures (Shulga and Goldfarb, 2003). If yeast cells depleted of the nucleoporin Nup170p are treated with increasing concentrations of certain alcohols, dissociation of several other nucleoporins, both centrally and peripherally located ones, is observed. Whilst no dissociation of any nucleoporin was observed in wild-type cells, the above mentioned results still may be taken as an indicator for rearrangements occurring in NPC architecture following stress treatment of the yeast cells (Shulga and Goldfarb, 2003).

One hallmark of apoptotic cells is the condensation of their chromatin followed by the fragmentation of their DNA. Recent studies investigated the question of a possible link between these apoptotic features and changes in the structure and function of NPCs (Ferrando-May et al., 2001; Kihlmark et al., 2004; Loïodice et al., 2004).

During apoptosis nucleoporins are sequentially cleaved, amongst the first ones being the transmembrane nucleoporin POM121 and RanBP2/Nup358, followed by Nup153, Nup62 and the NE-associated lamins. Concomitant with these later steps clustering of the NPCs is observed, while an increased permeability of the nucleus, the redistribution of nuclear transport factors and the nuclear accumulation of mRNAs are hallmarks of earlier stages of apoptosis (Ferrando-May et al., 2001; Kihlmark et al., 2004; Loïodice et al., 2004). To date, the debate is still on whether these observed changes in NPC architecture and nuclear transport are causally linked to the later apoptotic program occurring in the nucleus.

4. Nucleocytoplasmic transport

Whereas ions and small molecules move in and out of the nucleus by passive diffusion, transport of proteins, RNAs, ribonucleoprotein particles (RNPs), and ribosomal subunits is an energy-dependent and receptor-mediated process. Because many excellent reviews about nucleocytoplasmic transport have been published in the last few years (c.f. Corbett and Silver, 1997; Mattaj and Englmeier, 1998; Görlich and Kutay, 1999; Kaffman and O'Shea, 1999; Conti and Izaurralde, 2001; Komeili and O'Shea, 2001; Macara, 2001; Weis, 2002; Quimby and Dasso, 2003; Fried and Kutay, 2003; Johnson et al., 2004; Xu and Massagué, 2004), we describe here only the best characterized classical receptor-mediated nucleocytoplasmic transport (**Fig. 4a**). Accordingly, cargo to be transported in or out of the nucleus harbors a nuclear localization signal (NLS) for nuclear import or a nuclear export signal (NES) for nuclear export. NLS and NES are recognized by soluble transport receptors known as importins and exportins, also called karyopherins. These receptors facilitate transport through the NPC by interaction with FG repeats that many nucleoporins harbor. The key regulator of the directionality of nucleocytoplasmic transport is Ran, a member of the Ras-related GTPase superfamily, by switching between its GDP- and GTP-bound form. The nucleotide exchange factor, RanGEF (or RCCI) is bound to DNA and facilitates RanGTP formation in the nucleus, whereas the GTPase activating protein, RanGAP, that is excluded from the nucleus, assures depletion of the cytoplasm of RanGTP in combination with Ran binding protein RanBP1 and RanBP2. Hence, interaction of Ran with its compartmentalized regulatory proteins RanGEF and RanGAP generates a gradient across the NE with a high RanGTP concentration in the nucleus and a low level in the cytoplasm, and vice versa for RanGDP

(**Fig. 4b**).

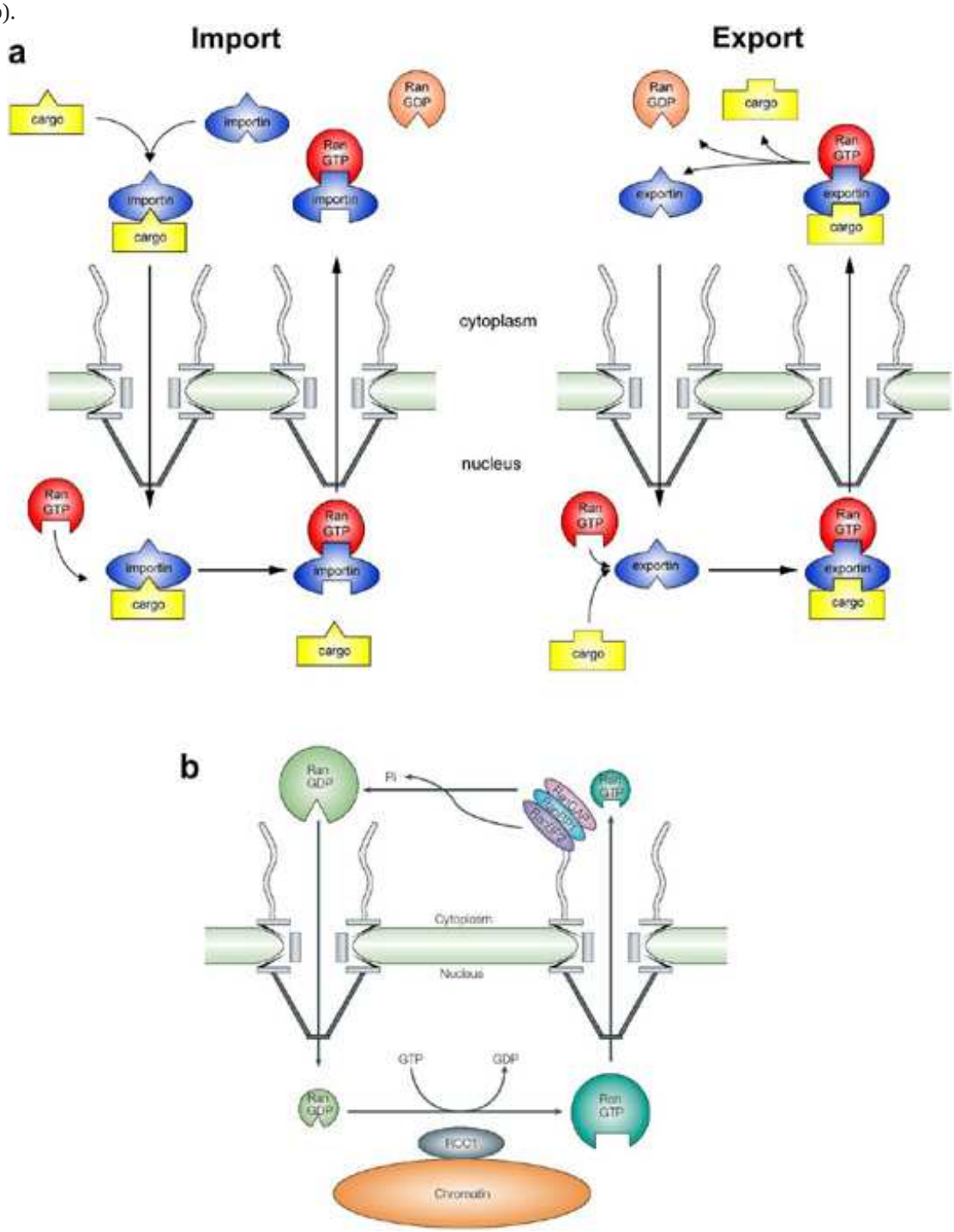


Figure 4: Scheme of import (left) and export (right) of proteins (a) and control of the nucleocytoplasmic transport by Ran (b).
(a) In the cytoplasm an importin binds to cargo molecules containing a nuclear localization signal and mediate interactions with the NPC to translocate the complex into the nucleus. Nuclear RanGTP binds to the importin and induces cargo release from the complex. The importin–RanGTP complex is then recycled to the cytoplasm, where RanGTP is displaced from the importin by RanBP1 and/or RanBP2 and subsequently hydrolyzed by RanGAP. In the case of export, cargo with a nuclear export signal binds to an exportin induced by RanGTP in the nucleus and the trimeric complex is then translocated through the NPC to the cytoplasm, where RanGTP is removed from the complex by GTP hydrolysis and the exportin dissociates from the cargo. The exportin recycles back to the nucleus and is ready for the next round of the export cycle.
(b) Directionality of the nucleocytoplasmic transport by the RanGTPase system. Chromatin-bound RCC1 is the nucleotide exchange factor for Ran (RanGEF) and promotes exchange from RanGDP to RanGTP. This results in a high concentration of RanGTP in the nucleus. After translocation of importin-RanGTP complex back to the cytoplasm, RanGTP becomes hydrolyzed by cooperation of RanGTP-binding proteins (RanBP1 and RanBP2) and Ran GTPase-activating protein (RanGAP). This prevents the accumulation of RanGTP and results in its low concentration in the cytoplasm.

5. NPCs and diseases

NPCs via the nucleoporins have been implicated in several malignancies such as leukemias and others cancers, as well as in certain autoimmune diseases. Furthermore, as gateways between the cytoplasm and the nucleus they also play a pivotal role in viral infections.

Several autoimmune diseases are caused by autoantibodies recognizing nuclear antigens resulting in such divers illnesses as systemic lupus erythematosus, rheumatoid arthritis and primary biliary cirrhosis (PBC). Anti-NPC autoantibodies identified so far react with the nucleoporins Nup62, Nup153, Tpr, Nup358/RanBP2 and the transmembrane nucleoporin gp210 (reviewed in Nesher et al., 2001; Enarson et al., 2004). The epitopes of several of these antibodies have been mapped but the exact mode of action is unknown. Often, these anti-nucleoporin antibodies co-exist with other autoantibodies so that their relevance for disease progression is unclear. Interestingly, anti-gp210 autoantibodies are often found in PBC which are negative for anti-mitochondrial antibodies which gives them a potential diagnostic relevance. In addition, these antibodies are often associated with more severe forms of the disease thus also being a possible prognostic marker.

Nucleoporins are involved in several cases of acute myeloid leukemia and a few other hematological malignancies as well as rare cases of other tumors (**Table 3**) (Cronshaw and Matunis, 2004). For Nup88, its overexpression is associated with malignant tumors (Gould et al., 2000 and 2002; Emterling et al., 2003; Agudo et al., 2004), whereas in most other cases the role of Nups in tumorigenesis stems from chromosomal rearrangements that result in oncogenic fusion proteins.

With the exception of the RanBP2/Nup358-ALK fusion protein which localizes to the NPC, in all other known examples the oncogenic fusion protein does not involve the NPC-interacting domain(s) of the nucleoporin and thus is no longer associated with the NPC. The most common oncogenic fusions involve a segment of the gene encoding the FG-repeat domain of the nucleoporin Nup98 which, in turn, becomes linked to genes of the homeobox family of transcription factors. It was found that the Nup98 derived FG-repeat segments of the resulting oncogene interact with the transcriptional coactivators CBP (CREB binding protein) and p300 thereby leading to increased gene transcription (Kasper et al., 1999).

Interestingly, FG-repeat segments of two other nucleoporins, Nup153 and CAN/Nup214, could substitute for the Nup98 segment in the oncogenic fusion protein (Kasper et al., 1999). It will be interesting to see if there is a link between this observed transactivation activity and the previously mentioned transcription-dependent mobility of Nup98 within the nucleus and at the NPC. Similarly, leukemias involving CAN/Nup214 chromosomal translocations, the FG-repeat domain of this nucleoporin gets fused to the DNA-binding proteins SET and DEK (von Lindern et al., 1992a and 1992b). In the case of chromosomal rearrangements involving the nucleoporin Tpr, the N-terminal coiled-coil domain of this protein is fused to the protein kinases MET, RAF and TRK and thereby yielding oncogenic dimerization of these kinases (Hays and Watowich, 2003).

Significant progress has been achieved in recent years in the elucidation of the mechanisms that viruses use to deliver their genetic material to the nucleus for replication (**Fig. 5**; reviewed in Greber and Fassati (2003) and Gustin (2003)). After fusion at the plasma membrane or endocytotic uptake the virus particles are in the cytoplasm where they encounter different fates. The problem for entry of the genetic material into the nuclear compartment is the limited diameter of the NPC. Recent experiments employing protein covered colloidal gold particles showed that objects up to 39 nm diameter are able to travers the NPC (Panté and Kann, 2002). Thus smaller viruses like the parvovirus MVM (minute virus of mouse, 25 nm capsid diameter) or HBV (hepatitis B virus, 32-36 nm capsid diameter) are able to cross the NPC without the need for capsid disassembly. *In vivo* in the case of HBV, however, passage through the NPC is facilitated by the phosphorylation of HBV capsids during maturation which makes nuclear localization signals accessible for the nuclear transport receptors importin-α and -β (Rabe et al., 2003). After passage through the central pore of the NPC virus particles then reach the nuclear basket where immature capsids are apparently trapped, whereas capsid protein and DNA from matured viruses are released into the nucleoplasm (**Fig. 5a** and **6**; Rabe et al. (2003)).

In contrast to the situation for HBV, herpes simplex virus (HSV, 125 nm capsid diameter) or adenovirus particles (90 nm diameter) in the cytoplasm are too large to travers the NPC. In a first step these virus particles dock at the cytoplasmic side of the NPC. This docking of HSV particles at the NPC is dependent on the presence of importin-β, whereas adenovirus capsids directly associate with the cytoplasmically localized nucleoporin CAN/Nup214 (Wisnivesky et al., 1999; Ojala et al., 2000; Trotman et al., 2001). HSV then releases its DNA through the NPC into the nucleoplasm, whereas adenovirus particles first trap cytosolic factors like Hsc70, together with histone H1 and transport factors which are necessary for the subsequent capsid disassembly prior to viral DNA-translocation into the nucleus (**Fig. 5b** and **c**; Trotman et al. (2001)).

Table 3: Oncogenic nucleoporin chromosal rearrangements

Rearrangement	Nucleoporin/partner gene	Partner gene features	Disease
t(7;11)(p15;p15)	*NUP98/HOXA9*	Homeodomain	AML, CML, MDS, MDS/AML
t(2;11)(q31;p15)	*NUP98/HOXD13*	Homeodomain	AML, MDS/AML
t(1;11)(q23;p15)	*NUP98/PMX1*	Homeodomain	MDS/AML
t(7;11)(p15;p15)	*NUP98/HOXA11*	Homeodomain	CML, AML
t(11;12)(p15;q13)	*NUP98/HOXC11*	Homeodomain	AML
t(7;11)(p15;p15)	*NUP98/HOXA13*	Homeodomain	AML
t(2;11)(q31;p15)	*NUP98/HOXD11*	Homeodomain	AML
t(11;12)(p15;q13)	*NUP98/HOXC13*	Homeodomain	AML
inv11(p15;q22)	*NUP98/DDX10*	RNA helicase	AML, MDS/AML
t(11;20)(p15;q11)	*NUP98/TOP1*	DNA topoisomerase	AML, MDS/AML
t(4;11)(q21;p15)	*NUP98/RAP1GDS1*	Nucleotide exchange factor	T-ALL
t(9;11)(p22;p15)	*NUP98/LEDGF*	Transcription factors	AML
t(5;11)(q35;p15)	*NUP98/NSD1*	SET domain	AML
t(8;11)(p11.2;p15)	*NUP98/NSD3*	SET domain	AML
t(6;9)(p23;q34)	*NUP214/DEK*	DNA binding	AML, MDS
t(9;9)(q34;q34)	*NUP214/SET*	Nuclear, DNA associated (?)	AML
t(1;7)(q25;q21-31)	*TPR/MET*	Protein kinase	Osteosarcoma
Tpr/RAF	*TPR/RAF*	Protein kinase	Adenocarcinoma, fibroblastoma
Inv(1q)	*TPR/TRK*	Protein kinase	Papillary thyroid carcinoma
t(2;2)(p23;q13)	*NUP358/ALK*	Protein kinase	IMT

Summary of oncogenic chromosomal rearrangements involving nucleoporin genes. Given are the involved nucleoporin genes and the fusion partner as well as its function and the resulting disease. Most known examples of chromosomal rearrangements involve the nucleoporin Nup98, others the nucleoporins CAN/Nup214, Tpr and RanBP2/Nup358. For references on the individual oncogenes see Cronshaw and Matunis (2004).

Abbreviations: AML, acute myeloid leukemia; CML, chronic myeloid leukemia; IMT, inflammatory myofibroblastic tumor; MDS, myelodysplastic syndrome; SET,Su(var)3-9, enhancer-of-zeste, trithorax; T-ALL, T-cell acute lymphoblastic leukemia.

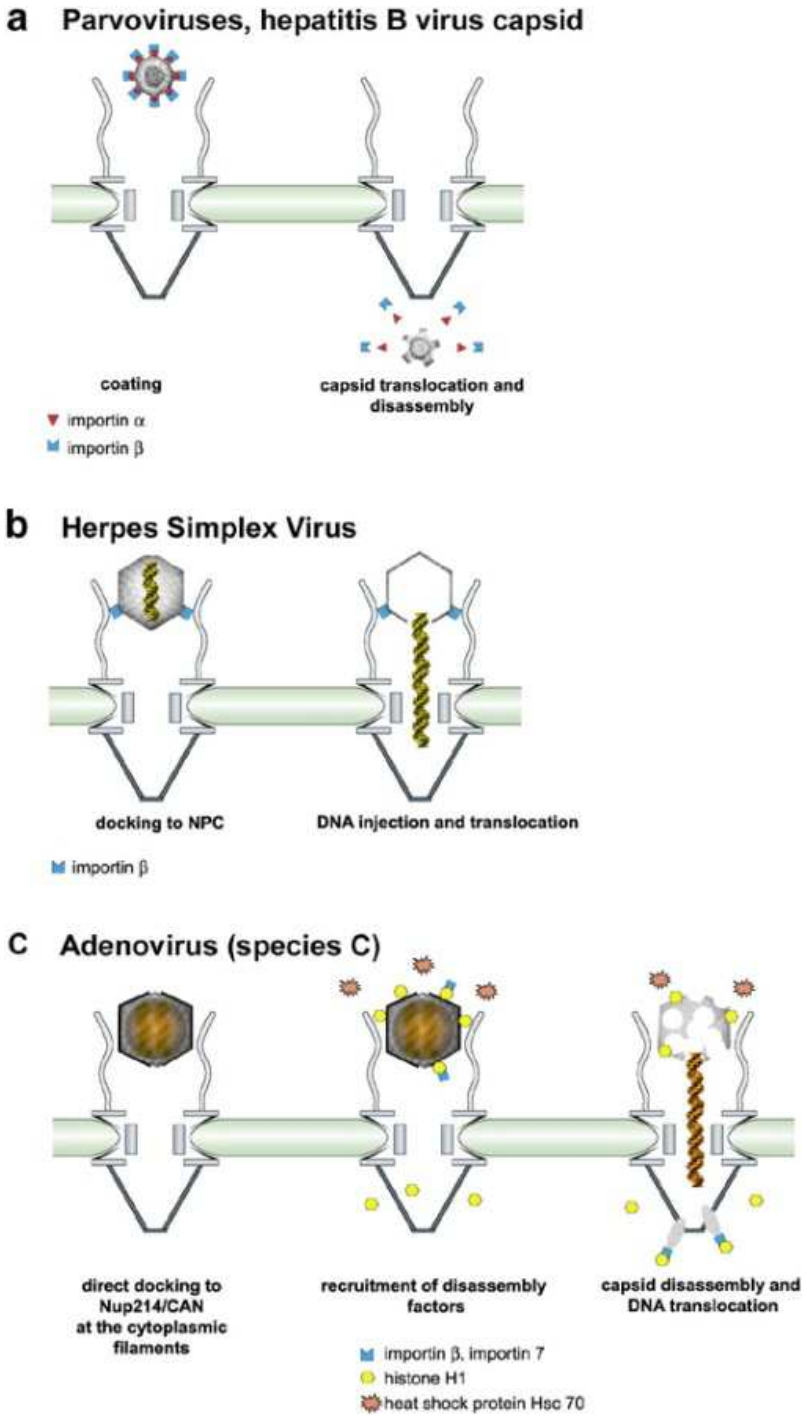


Figure 5: Schematic representation of different strategies for nuclear import of viral genomes.
Cytosolic capsids mediate the nuclear import of the viral genomes by at least three different mechanisms: (a) importin α- and β-mediated nuclear import of whole capsids; (b) importin β- mediated docking at the NPC and DNA injection into the nucleus, and (c) direct docking and disassembly at the NPC.
(a) Parvoviruses and HBV have a diameter close to the physical opening of the central pore of the NPC. In the cytoplasm, capsids undergo conformational changes leading to exposure of the NLSs and subsequent interaction with importins. The small capsid size allows the translocation of whole viral capsids through the NPC into the nucleus where the capsids are disassembled by a still unknown mechanism.
(b) Tegument-free capsid of the HSV docks at cytoplasmic filaments of the NPC via importin β. Capsids are not completely disassembled, but partially opened and the linear double-strand DNA genome is injected to the nucleus.
(c) Partially uncoated and fiberless capsids of adenoviruses are delivered to the NPC where they directly dock to the FG repeats of Nup214/CAN at the cytoplasmic filaments of the NPC. Subsequently series of disassembly factors are activated which facilitate capsid disassembly and are required for import of the viral DNA-protein core.

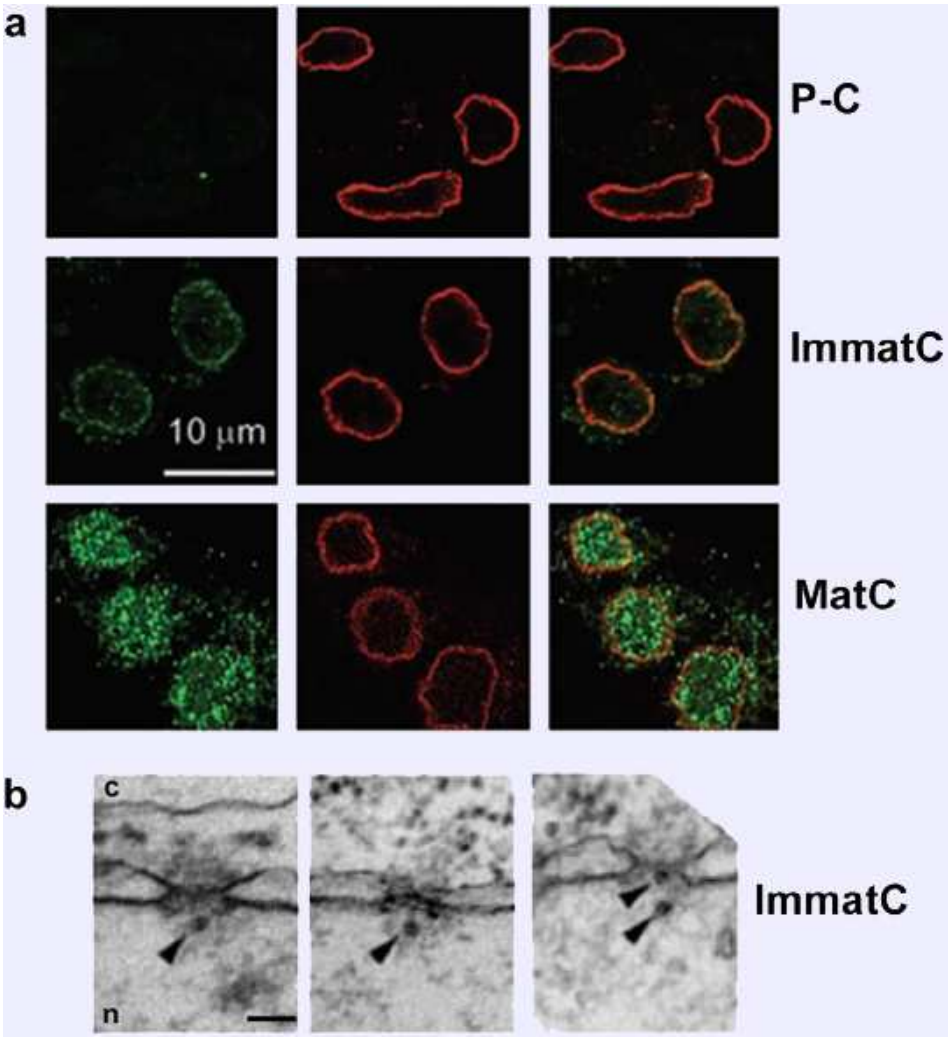


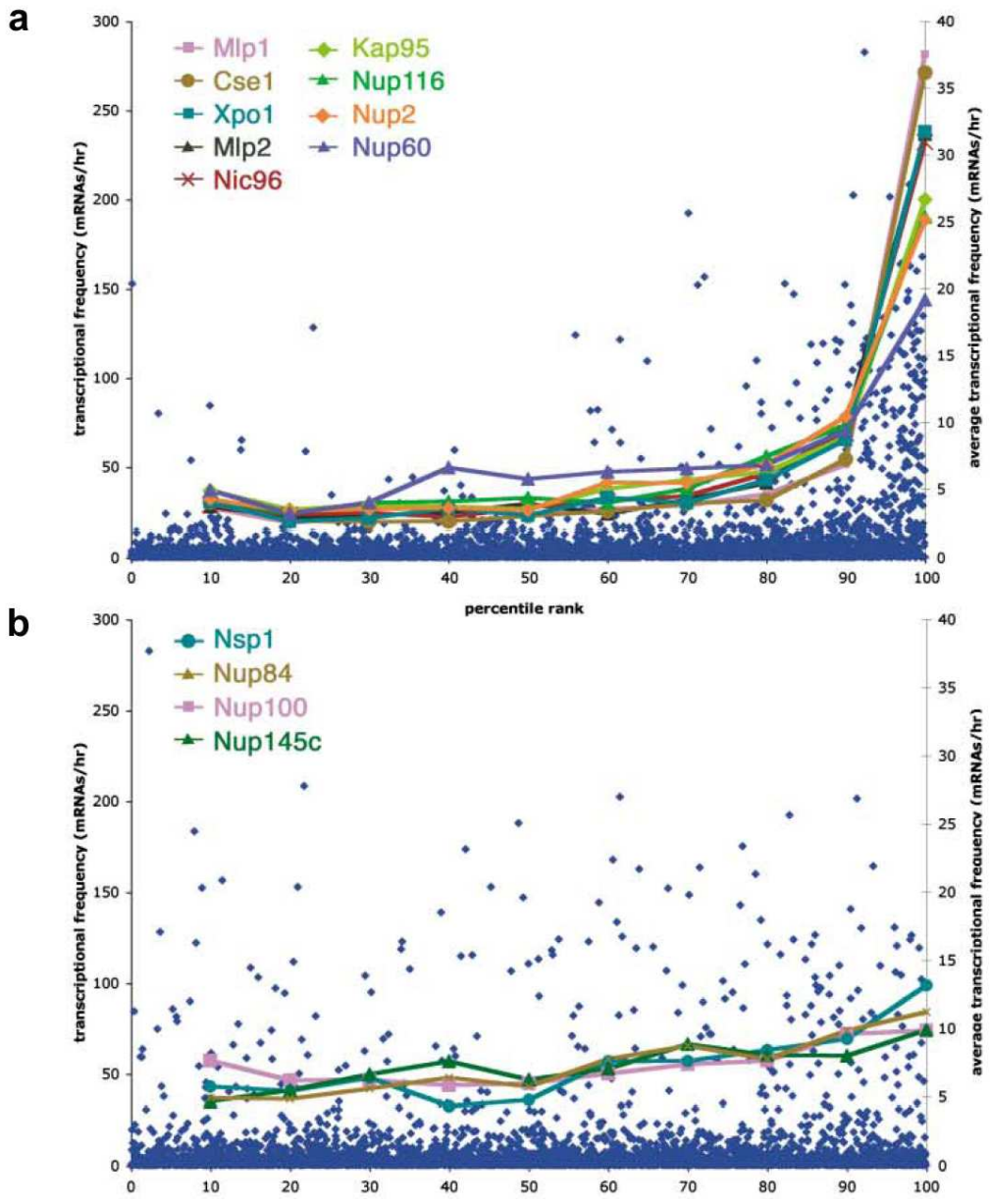
Figure 6: Maturation-dependent nuclear entry of HBV capsids.
(a) Localization of hepatitis B capsids in digitonin-permeabilized HuH-7cells by confocal laser scanning microscopy after immunofluorescence labeling. Capsids (green, *Left*) and NPCs (red, *Center*) were stained by indirect immunofluorescence. Merged images are shown in the last column *(Right)*. Recombinant capsids, devoid of viral polymerase (P-C) do not bind to cellular structures, immature capsids (ImmatC) show nuclear binding, whereas mature capsids (MatC) generate intranuclear capsids. Scale bar: 10 µm.
(b) Views of nuclear envelope cross sections with adjacent cytoplasm (c) and nucleoplasm (n) from a *Xenopus laevis* oocyte that has been microinjected with ImmatC. Arrowheads point to capsids associated with the nuclear face of the NPC. Scale bar: 100 nm.
"Fig was modified and reprinted from *Proc. Natl. Acad. Sci. U.S.A.* **100**, Rabe et al.: Nuclear import of hepatitis B virus capsids and release of the viral genome, 9849-9854, © (2003), with permission from National Academy of Sciences, U.S.A."

Certain RNA viruses like picornaviruses (e.g. poliovirus or rhinovirus) and rhabdoviruses replicate in the cytoplasm of host cells and thus do not have to cross the NE. However also in cells infected with these viruses, NPC structure and nucleocytplasmic transport are often severely disturbed (Gustin, 2003). It has been shown that the infection of cells with polioviruses or rhinoviruses results in the cytoplasmic accumulation of certain nuclear proteins like La, Sam68 or nucleolin which then interact with the viral RNA and might aid in their replication. This is achieved by inhibiting active nucleocytoplasmic transport via the proteolytic degradation of nucleoporins like Nup62 and CAN/Nup214 (and possibly others as well) (Gustin and Sarnow, 2001 and 2002). Another strategy is used by the vesicular stomatitis virus (VSV). Its most abundant virion component, the M protein, causes cell rounding, inhibits transcription and also blocks nuclear export of U snRNAs, rRNAs and mRNAs as well as snRNP and classical nuclear import. As one cellular protein interacting with M protein the nucleoporin Nup98 could be identified which binds transport receptors and has been shown to be crucial for nuclear export of mRNAs (von Kobbe et al., 2000). Interestingly during antiviral response via interferon signaling Nup98 gets upregulated and this upregulation releases the M protein induced mRNA export block (Enninga et al., 2002).

6. Nucleoporins and transcriptional control

Already by 1985 a "gene-gating" hypothesis was proposed (Blobel, 1985) suggesting an interaction of the NPC with genes as a means of transcriptional regulation. In recent years experimental evidence for such interactions arised from studies in yeast. In this context, the interaction of telomeric chromatin with the NPC, especially Nup145C, Nup60p, Mlp1p and Mlp2p result in transcriptional silencing (Feuerbach et al., 2002), whereas tethering of chromosomes to the nucleoporin Nup2p lead to a block in heterochromatin spreading, i.e. Nup2p exhibits chromatin boundary activity, thus leading to gene activation (Ishii et al., 2002). In the most recent report genes interacting with several nucleoporins and transport factors were identified (Casolari et al., 2004). This was achieved by chromatin immunoprecipitation using certain nucleoporins and transport factors as baits and analysis of the precipitated gene sequences by microarray hybridization analysis (Casolari et al., 2004). It turned out that more frequently transcribed genes were clearly associated with certain nucleoporins (amongst others Mlp1p, Mlp2p, Nup2p and Nup60p) and transport factors, whereas the RanGEF Prp20p was found to interact mainly with infrequently transcribed genes (**Fig. 7**). Future *in vivo* chromosomal painting and nucleoporin labeling studies together with high resolution light microscopy under gene inducing conditions will clarify the significance of these observations.

In this review we have described the involvement of the NPC in various physiological events and hope to leave the reader with a dynamic impression of that complex and fascinating structure.



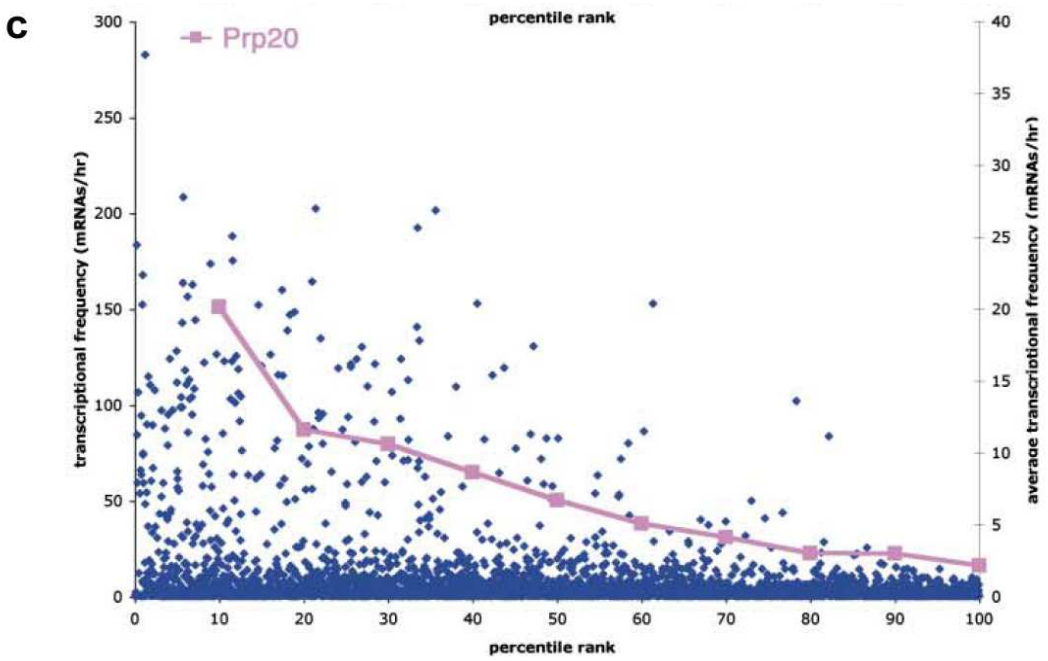


Figure 7: Correlation between genome occupancy and transcriptional frequency.
The interaction of several nucleoporins and transport factors with genomic sequences was analyzed by chromatin immunoprecipitation followed by microarray-anlysis of the bound sequences in comparison to whole-cell extract signals. Each blue diamond indicates an individual spot on the microarray (i.e. an individual gene) where the position on the x-axis is determined by the ratio (bound copies of a gene):(copies of a gene in the whole cell culture extract) and the position on the y-axis gives the experimentally determined transcriptional frequency for that gene (see Damelin and Silver (2002), Casolari et al. (2004) and references therein). (a) diamonds represent individual genes interacting with Nic96p whereas the the coloured curves give the overall binding trends for the indicated nucleoporins and transport factors. (b) diamonds represent individual genes interacting with Nup100p whereas the the coloured curves give the overall trends for the indicated nucleoporins. (c) diamonds represent individual genes interacting with the RanGDP exchange factor Prp20, the general trend is represented by the purple curve.
"Fig was modified and reprinted from *Cell* **117**, Casolari et al.: Genome-wide localization of the nuclear transport machinery couples transcriptional status and nuclear organization, 427-439, © (2004), with permission from Elsevier".

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