Pore Relations: Nuclear Pore Complexes and Nucleocytoplasmic Exchange

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Introduction

One of the main characteristics distinguishing eukaryotes from prokaryotes is that eukaryotes compartmentalize many life processes within membrane bound organelles. The most obvious of these is the nucleus, bounded by a double-membraned nuclear envelope (NE). The NE thus acts as a barrier separating the nucleoplasm from the cytoplasm. An efficient, regulated and continuous exchange system between the nucleoplasm and cytoplasm is therefore necessary to maintain the structures of the nucleus and the communication between the genetic material and the rest of the cell. The sole mediators of this exchange are the nuclear pore complexes (NPCs), large proteinaceous assemblies embedded within reflexed pores of the NE membranes (Davis, 1995). While small molecules (such as nucleotides, water and ions) can freely diffuse across the NPCs, macromolecules such as proteins and ribonucleoprotein (RNP) particles are actively transported in a highly regulated and selective manner. Transport through the NPC requires specific soluble factors which recognize transport substrates in either the nucleoplasm or cytoplasm and mediate their transport by docking them to specific components of the NPC (Mattaj and Englmeier, 1998). In order to understand how transport works, we must first catalog the soluble transport factors and NPC components, and then study the details of how they interact.

Despite interesting differences in detail, NPCs from all eukaryotes studied appear to share a common architecture (Davis, 1995; Yang, et al., 1998) (Figure 1). The NPC is comprised of a cylindrical core and a filamentous periphery, and has an octagonal rotational symmetry around its cylindrical axis. The core contains a tubular structure (termed the central transporter) surrounded radially by eight spokes interconnected by rings. The core is mirror symmetric in the plane of the NE, and contains both the anchor for the nuclear membrane and the gate for entry to and exit from the nucleus (in the form of the central transporter). Peripheral filaments bristle from the core, projecting into the nucleoplasm and cytoplasm. They appear asymmetric in the plane of the NE; while the cytoplasmic filaments spread like a coronet from the cytoplasmic side of the NPC, the nuclear filaments connect at their far ends to form a structure resembling a fish trap or basket.
Nucleoporins, the Building Blocks of the NPC

The conserved NPC architecture is reflected by the homology between NPC components from different organisms. A variety of techniques have identified numerous NPC component proteins (termed nucleoporins, or NUPs) in several eukaryotes, from yeast to mammals. The amenability of yeast to biochemical and genetic analyses has allowed researchers to use this model organism to identify what may be the entire complement of protein components for the NPC (Doye and Hurt, 1997; Fabre and Hurt, 1997) (our unpublished data). Of course, given the dynamic nature of NPCs and their interactions with soluble factors, it is not always clear what constitutes a NUP. As we shall see, there are NPC components that may reversibly associate with the NPC, and some which are actually found mainly associated with other organelles, and are thus not considered NUPs. Nevertheless some order can be maintained by invoking an operational definition, such that a NUP is considered to be a protein that is mainly associated in a stable fashion with the octagonally symmetric body of the NPC.

While original estimates suggested that the NPC may be composed of as many as 100-200 nucleoporins (Forbes, 1992; Rout and Wente, 1994), it now seems that no more than 30 different proteins are needed to build a yeast NPC (Doye and Hurt, 1997; Fabre and Hurt, 1997) (our unpublished data). However, the mass of the NPC is in the range of 50 MD (yeast) to over 100 MD (vertebrates) (Reichelt, et al., 1990; Yang, et al., 1998). So if, for example, the yeast NPC has only 30 or so proteins, compared to a 4 MD ribosome, made of ~80 proteins, how is this mass achieved? It seems the answer is in the symmetry. The octagonal and mirror symmetries of the NPC allows nucleoporins to be present in 8, 16, or even 32 copies, unlike ribosomal proteins, which almost without exception, are only present in one copy per ribosome. Furthermore, nucleoporins can be as large as 350 kD, and for example in yeast, have an average MW of ~100 kD, compared with the ~25 kD average MW of a ribosomal protein. Hence, in the NPC, 30 different NUPs of average ~100 kD, each present in 16 copies, would sum to 50 MD (whereas 80 different ~25 kD ribosomal proteins present each at only one copy makes the expected ~2 MD, with the remaining 2 MD supplied by the rRNA).

By localizing NUPs to particular structures and combining this information with data from physical interactions between NUPs, a structural map of the NPC is beginning to emerge (Davis, 1995; Fabre and Hurt, 1997). Nucleoporins can be divided into three overlapping classes: membrane proteins, core components, and components of the peripheral filaments. Pore
membrane proteins span the lipid bilayer and because of their strategic location within the pore, they are presumed to be involved in anchoring the NPC within the NE. Unlike other nucleoporins, to date, there is no obvious homology between membrane proteins of yeast and metazoans. This may be partly due to the fact that yeast do not breakdown the NE and NPCs during mitosis, whereas metazoans have to rebuild an NPC after each cell division. The NPC core is made of several proteins whose size and abundance allows them to contribute a significant amount of the NPC’s mass. Interestingly, only one third of the yeast nucleoporins are essential, likely reflecting the multiple contacts each NUP makes with its numerous neighbors (Fabre and Hurt, 1997). This creates a complex structural framework that is not disrupted by the loss of a single component. As might be expected by the symmetry of the core, most proteins localized within this region seem to be symmetrically disposed on both the cytoplasmic and nucleoplasmic sides (our unpublished data). The central transporter lies within the core structure and is also symmetric, as are its components (such as the vertebrate p62/p58/p54 complex found at both ends of the central transporter (Grote, et al., 1995; Guan, et al., 1995), and the similarly located homologous yeast NSP1/NUP57/NUP49 complex (Doye and Hurt, 1997; Fahrenkrog, et al., 1998). Moving away from this central region of the NPC, the structure becomes asymmetric, and some NUPs found distal to the NPC core are found on only one or the other side of the NPC (such as the yeast cytoplasmic NUP159 (Kraemer, et al., 1995) or the vertebrate nuclear NUP153 (Sukegawa and Blobel, 1993)).

**Building an NPC**

Before an NPC can function, it must first be made, and presumably some of the NUPs have a role in NPC assembly. At least in yeast, NPCs appear to be continuously assembled throughout the cell cycle (Winey, et al., 1997). As leaving a gaping hole in the NE would generally be considered to be a bad thing for a cell, the NPC must punch a hole through both membranes of the NE and insert itself in such a way that neither the nucleoplasm nor the lumen of the ER (which is continuous with the NE) leak during this process. Rather than slowly constructing elaborate sealed precursors, it appears that NPCs form by an extremely rapid process without any obvious intermediates. This “sleight-of-hand” approach may involve the almost simultaneous formation of a correctly sized NE pore, and the insertion of prefabricated subcomplexes which mature into a functional NPC (Bastos, et al., 1995; Davis, 1995). This must
be a highly cooperative process, perhaps triggered by local fusion of the inner and outer membranes. In many metazoans, the NE is reversibly disassembled during mitosis, such that they also undergo a round of NPC assembly at telophase. Although it is not clear that the processes of mitotic NPC reassembly are the same as those at interphase, it is presumed that they share similar mechanisms. As a result, mitotic NPC reassembly has been the system of choice to study NPC biogenesis. NPCs probably assemble from the membrane pore proteins inwards (Gant, et al., 1998). The morphology of the mitotic NPC reassembly intermediates suggests an ordered hierarchical assembly (Bastos, et al., 1995; Gant, et al., 1998). The inner and outer membranes of the NE first fuse locally to form a small pore, which rapidly becomes filled with rings and spokes. This is then followed by the addition of more peripheral rings, and the peripheral filaments.

At least in some cases, NPC components exist as preassembled subcomplexes in the cytoplasm (Forbes, 1992; Bastos, et al., 1995; Davis, 1995; Macaulay, et al., 1995), suggesting that the rapidity of NPC assembly owes a lot to its construction from a relatively small number of prefabricated parts. In fact, we might speculate that the main function of some nucleoporins is to direct NPC assembly. Gp210, for example, would be such a candidate, perhaps required for mitotic reassembly of NPCs; it is conspicuously absent from yeast, which do not disassemble their nuclei at any point in the cell cycle. In addition, non-NUP proteins may be recruited from other parts of the cell to help during assembly, before becoming incorporated into the NPC. This role has been suggested for SEC13, a protein normally found in COPII vesicles trafficking between the ER and Golgi complex, but which was also found in a complex with numerous NUPs (Siniossoglou, et al., 1996; Fontoura, et al., 1999). As most SEC13 is associated with the ER and its vesicles rather than the NPCs, it is an example of an NPC component that is not a nucleoporin. Its function in forming coats around vesicles may be borrowed to help stabilize the reflexed membrane of the nascent nuclear pore, or recruit other proteins to promote fusion during NPC assembly, thus explaining its dual localization (Siniossoglou, et al., 1996)

**Association of the NPC with Adjacent Structures**

The NPC can not be considered as an isolated structure, as it interacts with components of its surroundings, including the NE, the nucleoplasm and the cytoplasm. As the whole NPC can move rapidly in the plane of the nuclear envelope (Belgareh and Doye, 1997; Bucci and Wente,
1997), these interactions are labile. Such multiple interactions are reflected in individual NUPs. For example, NUP153 has different domains which bind transport factors from the nucleoplasm and cytoplasm, attach it to the NPC, and connect the NPC to the adjacent filamentous nuclear structures (Enarson, et al., 1998; Shah, et al., 1998). Interactions with the filamentous nuclear lamina, which runs in a layer beneath and parallel with the NE, are probably important for maintaining the normal spacing of metazoan NPCs, as disruptions of the lamina can lead to abnormal NPC distributions (Lenz-Bohme, et al., 1997). Another set of filamentous proteins associated with NPCs is the Tpr family. Though not nucleoporins, the Tpr homologues extend from the tip of the nuclear basket to form a network that interconnects adjacent NPCs and extends a considerable distance into the nucleoplasm (Cordes, et al., 1997; Strambio-de-Castillia, et al., 1999). Indeed, this family represents perhaps the best candidates yet for major components of the nucleoskeleton (the nuclear analog of the cytoskeleton). Because removal of the yeast Tpr homologues decreases the efficiency of nucleocytoplasmic transport, and interactions between Tpr and transport factors have been found in vitro, it has been proposed that these proteins act as “tracks” to guide the movement of nucleocytoplasmic transport between the NPC and deep within the nuclear interior (Cordes, et al., 1997; Bangs, et al., 1998; Shah, et al., 1998).

The Mechanism of Transport

Obviously the main function of the NPC, once assembled, is to mediate nucleocytoplasmic exchange; both the passive diffusion of small molecules, and active bi-directional macromolecular transport. Indeed, the assembled membrane and core structures can, in one sense, be considered a framework providing the correct positioning of the nucleoporins that mediate transport. Transport cargoes are generally recognized first by transport factors in the nucleoplasm or cytoplasm. The transport factor-cargo complex then docks to the peripheral filaments before translocating through the central transporter, to be released on the other side of the NPC (Mattaj and Englmeier, 1998). The components of nucleocytoplasmic transport can therefore be separated into two classes: a stationary phase, consisting of components of the NPC, and a mobile phase of transport factors. Many of these transporters are part of a structurally-related family of proteins collectively termed karyopherins or KAPs (Mattaj and Englmeier, 1998; Wozniak, et al., 1998). Individual members of the family have numerous
alternative names (for example importin, transportin, exportin) as discussed by Wente et al. in this issue.

In the soluble phase, the directionality of transport is determined by where karyopherins load and release their cargo, which in turn, has been shown to be dependent on their interaction with the small Ras-like GTPase Ran. As Ran is maintained in its GTP-bound form in the nucleus and in its GDP-bound form in the cytoplasm, karyopherins can sense their location through Ran, and either bind or release their cargoes appropriately (see Figure 2 and legend for details). As the hydrolysis of GTP by Ran releases energy, it seems that Ran not only confers the direction of transport but also powers it (Mattaj and Englmeier, 1998).

Although we have referred to the NPC as the stationary phase of transport, it is clear that NPCs are in fact very dynamic, and large morphological changes have been observed during transport. One of the most striking examples of this must be the opening of the nuclear basket to accommodate large RNP particles as they unwind through the central transporter (Kiseleva, et al., 1996). Another example is the central transporter itself, whose structure has been studied at high resolution and found to exist in a number of different conformations. It seems that the central transporter represents the “transport gate.” In its “resting” conformation, it has a central hole of ~9 nm which prevents the passive diffusion of large molecules across the NPC while permitting the free diffusion of small molecules. However, during the active transport of macromolecules, the central transporter appears to dilate to allow the passage of the transporting materials through it (Akey, 1990). Indeed, the tube of the central transporter presents a significant hindrance to the free exchange of macromolecules across the NPC. Thus, diffusion through the constricted central transporter is an entropically unfavorable process for macromolecules, which therefore tend to be excluded from this region (Feldherr and Akin, 1997).

However, analysis of the NPC components has provided a big clue as to how this barrier may be overcome, and thus how transport through the NPC may occur. Almost half of the known NPC components contain binding sites for numerous transport factors. Large numbers of these binding sites are strategically positioned throughout the NPC: from its cytoplasmic tip, through the central transporter to its nuclear tail, and beyond. Most, if not all, of these are distributed along filamentous structures. The best studied karyopherin binding sites are the peptide (Phe-Gly) repeat motifs present in nearly half of the known nucleoporins (Doye and Hurt, 1997; Fabre and Hurt, 1997). In one NUP these repeats have been shown directly to form
filaments (Buss, et al., 1994), and numerous other repeat motif containing nucleoporins have been localized to filamentous NPC structures (Bastos, et al., 1995; Fahrenkrog, et al., 1998). Although there is only minimum amino acid sequence conservation in the repeat motifs between presumed homologues from different species (Rout and Wente, 1994; Doye and Hurt, 1997; Fabre and Hurt, 1997), there may be a high degree of functional conservation as the position of these homologues within the NPC is well conserved (e.g., NSP1/NUP57/NUP49 compared with p62/p58/p54, above). The Brownian motion of these putative filamentous proteins could help to exclude the nonspecific diffusion of large molecules across the central tube by a process termed "entropic exclusion" (Brown and Hoh, 1997). In this way, they may contribute to the NPC's apparent resting diameter of ~9 nm. On the other hand, these NUPs contain an abundance of binding sites, surrounding the narrow central tube, which would provide a means to recruit transport factor-cargo complexes to the mouth of the central tube. This would, by contrast, promote the specific diffusion of transport factor-cargo complexes through the central tube, between the binding sites found on both the nuclear and cytoplasmic sides of the NPC (Figure 3). The NPC would thus effectively be a "virtual gate" - as proteins that bind the NPC would pass the diffusion barrier of the central channel much more freely than those that do not, gating selectivity would be achieved without necessarily invoking a gate composed of any moving parts. The observed dilation in the NPC may be a consequence of cargo movement.

Taken together, it would seem that NPC-mediated nucleocytoplasmic transport is based on essentially three steps (Figure 3). The first is that the reversible binding of transport factors to the large number of NPC binding sites would encourage the free diffusion of transport factor-cargo complexes between both faces of the NPC. This is then followed by a second step, in which the transport factor-cargo complexes would move preferentially to asymmetric binding sites on the same side of the NPC as their ultimate destination. The particular Ran-bound state of the karyopherin would determine the direction of this step. Thus importers, not bound to Ran, would have their highest affinity for the docking sites on the peripheral nuclear basket. This is consistent with the observed accumulation of a Ran-binding deficient karyopherin mutant on the nuclear side of the NPC (Gorlich, et al., 1996). Similarly Ran-bound export factors would preferentially jump to binding sites on the peripheral cytoplasmic filaments; for example, while the export factor CRM1 binds to several repeat containing nucleoporins, when complexed to Ran-GTP it binds preferentially to the cytoplasmic NUP214 (Kehlenbach, et al., 1999). The
third step involves either Ran-GTP binding or GTP hydrolysis (depending on the direction of transport), which leads to displacement of the cargo from the carrier and the carrier from the NPC (Mattaj and Englmeier, 1998; Wozniak, et al., 1998). This, being essentially irreversible, terminates the transport reaction and ensures the overall directionality of transport. It can readily be seen from Figure 3 how import factors may now be recycled out of the nucleus, in a manner analogous to the transport of export factors without cargo. Similarly, recycling of export factors may be analogous to cargo-less import. The energy driving nucleocytoplasmic transport may therefore be provided by the hydrolysis of Ran-bound GTP during each transport and recycling round.

Although the NPC contains an abundance of repeats, and different karyopherins can recognize the same NUP, different karyopherins have strong preferences for particular repeat motif classes. In one case it has been shown that a particular karyopherin (KAP121) appears to utilize a particular repeat-containing docking site within NUP53. KAP121 is the only karyopherin detected in association with NUP53, and accumulation of KAP121 at the NPC is specifically reduced in the absence of NUP53 (Marelli, et al., 1998). It therefore seems that one reason for the large number of repeat motif nucleoporins is to mediate separate pathways across the NPC for different kinds of karyopherins, reducing competition between these pathways at the NPC and creating a potential for differential control (Rout and Wente, 1994; Marelli, et al., 1998; Wozniak, et al., 1998). As deletion of KAP121 is lethal, but the deletion of its favored docking site is not (Marelli, et al., 1998), another important principle seems to be that these pathways are not totally separate; they can overlap if necessary, with each karyopherin therefore having a choice of more or less favored pathways across the NPC.

The many different classes of repeat motifs may also reflect the fact that there may be nuclear transport factors other than karyopherins, and they also use them as NPC docking sites. Thus the TAP/p15 complex (MEX67/MTR2 in yeast), which is implicated in RNA export, binds specifically to NUP repeat motifs during its passage across the NPC (Gruter, et al., 1998; Katahira, et al., 1999). Similarly NTF2, which is suggested to mediate Ran exchange between the nucleoplasm and cytoplasm but also seems involved in a number of other processes, binds reversibly to repeat motif domains (Nehrbass and Blobel, 1996; Mattaj and Englmeier, 1998; Ribbeck, et al., 1998). Finally, different classes of repeat motif NUPs may be bound at different stages of transport. In particular, while the symmetrically localized NUPs are docked in the
initial stages of transport, the terminal reaction of each transport cycle occurs on one of the distal asymmetrical repeat motif NUPs (Mattaj and Englmeier, 1998; Kehlenbach, et al., 1999). It may be that the particular order of the binding sites within the NPC helps correctly guide or channel the transport factors as they cross the NPC.

In addition to repeat motifs, additional binding sites exist within nucleoporins. For example, binding sites for the energy-providing protein Ran abound in vertebrate nucleoporins, both in the form of the conserved Ran binding domain and in the more recently characterized Ran-binding zinc finger motifs (Wu, et al., 1995; Mattaj and Englmeier, 1998; Nakielny, et al., 1999; Yaseen and Blobel, 1999). This may serve to increase the concentration of Ran at the NPC and hence improve the efficiency of the transport termination steps. They may also be involved in mediating an exchange of Ran across the NPC, and in maintaining the correct balance of Ran GDP in the cytoplasm and Ran GTP in the nucleoplasm. This latter possibility is supported by the presence of RanGAP1 binding sites (the protein which maintains the GDP form of Ran) on the cytoplasmic filaments of vertebrate NPCs (Mattaj and Englmeier, 1998) (see also Figure 2). Similarly, mRNP41 (RAE1 or GLE2 in yeasts) which is also implicated in RNA export, cycles on and off a unique binding site (Murphy, et al., 1996). The GLE2 binding domain is essential, but autonomous, as it can be moved from one nucleoporin to another (Bailer, et al., 1998). The list of binding sites may not end there; NUP358, the current record holder for the number and variety of such binding sites, contains: a coiled-coil domain (anchoring it to the NPC), four Ran Binding Domains, a zinc finger region (also for binding Ran), numerous FG repeats (for binding karyopherins, NTF2 and the like), two RanGAP1 binding repeats, and a cyclophilin A (prolyl isomerase) homology domain (Wu, et al., 1995).

Perspectives

Over the past few years, there have been tremendous advances in our understanding of the molecular mechanisms of nuclear transport. Most of our new understanding has focused on the soluble transport factors, so the challenge now is to determine how these factors interface with the NPC to mediate directional transport. Although we have presented a model for how transport may occur through the NPC, based on our current knowledge, it is important to realize that this simple scheme is speculative and leaves many questions unanswered. In particular, does Ran have a role within the NPC, in addition to the terminal reactions? What is the role of Ran
binding sites within specific nucleoporins? (Not to mention the plethora of other binding sites on proteins like NUP358). How does the NPC change its conformation during transport? How many contacts do cargo/carrier complexes make during transport and how do these translate into directional movement through the NPC? An important step towards answering these questions will be to complete a map of NUPs in the NPC, and to determine the proteins they contact both temporally and spatially during transport and NPC biogenesis.

Another rapidly expanding area of research is that of nucleocytoplasmic transport regulation. Although in most cases this is achieved by controlling the affinity of a transport substrate for its transport factor (Mattaj and Englmeier, 1998), intriguing evidence is emerging that nucleoporins are also regulated. The yeast nucleoporin NUP53 is specifically phosphorylated during mitosis (Marelli, et al., 1998). This correlates with a decrease in the binding of the NPC to KAP121, which prefers NUP53 as a docking site. Thus, it appears that phosphorylation is used to control the affinity of a NUP’s docking site for its transport factors. It has also been shown that many of the repeat motif NUPs are modified by O-linked glycosylations (Bastos, et al., 1995; Davis, 1995), although the reasons for this are still unclear.

Studies on the function of the NPC, and the roles of individual NUPs in regulated nuclear transport, NPC assembly, gene expression and the maintenance cellular structure are all expected to be very fruitful areas of future research, neatly complementing the parallel work on the interaction between transport factors and substrates.
Summary

- Nuclear pore complexes are the sole sites of exchange between the nucleus and cytoplasm.
- A large family of transport factors carry cargo between the nucleus and cytoplasm through the NPC.
- The NPC is a huge symmetric octagonal structure comprised of dozens of nucleoporins.
- Nucleoporins make many contacts with surrounding structures including the nuclear envelope, the cytoplasm and nuclear interior.
- A subset of nucleoporins contain a repeated peptide motifs which serve as docking sites for transport factors.
- The directionality of transport is determined by the transport factor, and its interactions with the small GTPase Ran and nucleoporins.
- Very little is known about how the NPC mediates transport, NPC assembly and the NPC’s role in regulating transport, but these areas of research are beginning to emerge.

Our data, cited as "our unpublished data", is now published in: M.P.Rout, J.D.Aitchison, A.Suprapto, K.Hjertaas, Y.Zhao and B.T.Chait. : "The yeast nuclear pore complex: composition, architecture and mechanism." *J. Cell Biol. 148, 635-651 (2000)*. We are grateful to Colin Dingwall and Rick Wozniak for critical reading of the manuscript, and to Beth Hatton for excellent secretarial assistance. M.P.R. is supported by the Rita Allen Foundation and the Irma Hirschl Trust and J.D.A by the Medical Research Council of Canada and Alberta Heritage Foundation for Medical Research.
Figure Legends

Figure 1.
Structure of the nuclear pore complex. Each NPC is a large proteinaceous assembly composed of a symmetrical cylindrical core, made of eight spokes surrounding a hollow central transporter. Each spoke is composed of several struts and attached to its neighbors by coaxial rings to form the spoke-ring complex. The NPC is embedded in the nuclear envelope, and a considerable portion of each spoke traverses the pore membrane and resides in the NE lumen. Peripheral elements include eight cytoplasmic particles and filaments and nuclear filaments which form a basket-like structure attached distally to elements of the nucleoskeleton.

Figure 2.
Directional transport is controlled by the interaction of karyopherins with Ran-GTP, nucleoporins and substrates. Importers release their substrates when they interact with Ran-GTP, while exporters bind Ran-GTP in order to bind their substrates. On the other hand, if Ran hydrolyses its GTP to GDP, importers can now bind their cargo, whereas exporters release theirs (Mattaj and Englmeier, 1998; Moore, 1998). In the nucleus, Ran is maintained in its GTP-bound state by the nuclear-restricted GTP exchange factor RCC1 (Moore, 1998) while the localization of the Ran GTPase activating protein to the cytoplasm and the cytoplasmic filaments of the NPC (Matunis, et al., 1996; Mahajan, et al., 1997), ensures that cytoplasmic Ran hydrolyses its GTP and so is maintained in its GDP-bound form. By so compartmentalizing the modulators of Ran, the cell maintains a gradient of Ran-GTP across the nuclear envelope. Thus substrates to be imported bind to their transport factors in the cytoplasm in the presence of Ran-GDP, but when this complex meets Ran-GTP in the nucleoplasm, the switch is pulled; Ran-GTP binds to the transporter, changing its conformation causing cargo release. In contrast, as an export complex reaches the cytoplasm, Ran GAP stimulates GTP hydrolysis and the cargo is released (Fig. 2). Ran is the only known energy utilizing transport factor, and so the energy driving all nucleocytoplasmic transport may come from this gradient of RanGTP (Moore, 1998).

Figure 3.
A model for nuclear import and export through the NPC. Karyopherins pick up their cargo in either the nucleus or cytoplasm, and bind to the NPC by interacting reversibly with (repeat-containing) NUPs (Step 1). Directional movement is ensured by movement to higher affinity terminal docking sites on the NPC side opposite that from which the karyopherins started (Step 2), followed by Ran-mediated release at these sites (Step 3). See text for details.
References

Apologies to those whose original work could not be cited due to space limitations; readers are encouraged to refer to the original publications.


