The nuclear pore complex

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Definition : A nuclear pore is a part of a large complex of proteins, known as a nuclear pore complex that spans the nuclear envelope, which is the double membrane surrounding the eukaryotic cell nucleus.

The structure of the nuclear pore complex

Nuclear pore complexes are proteinaceous structures embedded in the double membrane of the nuclear envelope. In order to understand how the NPC functions, it is useful to examine the similarities and differences between NPCs from the yeast *Saccharomyces cerevisiae* and the frog *Xenopus laevis.* The NPC is a large structure with a molecular weight of approximately 125 MDa in vertebrates and 66 MDa in yeast . A vertebrate cell nucleus contains on the order of 2,000 NPCs, whereas the smaller yeast nucleus contains approximately 200. NPCs have eight-fold rotational symmetry through the central axis of the pore and two-fold mirror symmetry through the plane of the nuclear envelope, suggesting assembly as a modular structure, a notion that is supported by structural and biochemical analysis of pore complex assembly *in vitro*.

In addition to their difference in size, yeast NPCs (yNPCs) and vertebrate NPCs (vNPCs) differ in several fundamental structural features. The main mass of the vNPC is contained in a three-part structure that surrounds and supports a central transporter ; the three-layered structure is composed of thin cytoplasmic and nuclear rings that sandwich a central spoke domain. The spoke domain is itself also composed of an inner ring element that surrounds a structure called the central transporter and an outer lumenal ring that interacts with the nuclear membrane; vertical spoke elements connect the cytoplasmic and nuclear thin rings to the central spoke domain. Extending from the cytoplasmic thin ring are eight filaments, each of 2-3 nm in diameter and approximately 50 nm in length. The

nucleoplasmic side of the NPC is comprised of eight 100 nm filaments that join at a smaller ring structure, forming a fish-basket-like structure emanating from the nuclear thin ring .

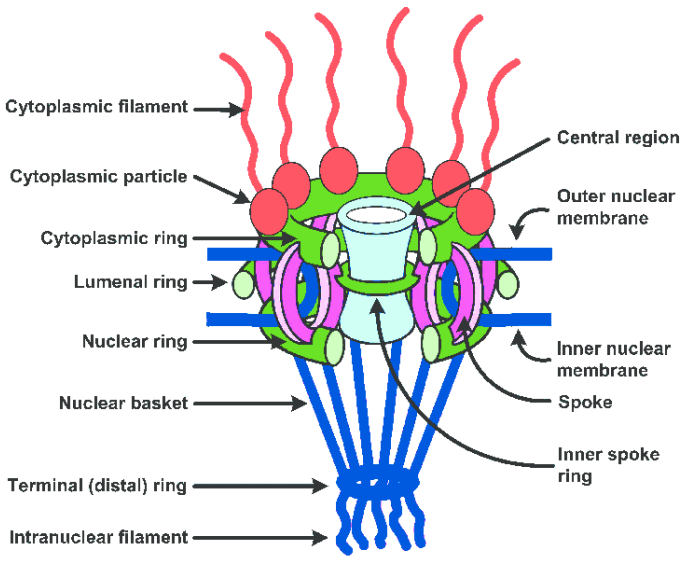

Figure: Structure of NPC

The yNPC is much simpler in structure . Compared to the vNPC, it lacks the cytoplasmic and nuclear thin rings and the lumenal ring of the central spoke domain. Instead, the central transporter is encircled by an inner spoke ring and a membrane-associated ring. Because they lack the outer thin rings, yNPCs also lack parts of the spoke domains that are present in vNPCs. Like vNPCs, yNPCs have filamentous structures emanating from the cytoplasmic and nucleoplasmic faces of the complex, although in yeast these filaments are slightly shorter than in vertebrates . Overall, the yNPC is smaller (96 nm diameter by 35 nm high) than the vNPC (145 nm diameter by 80 nm high), has half the mass of the vNPC and occupies one fifth of the volume.

Transport through the NPC

Permeability studies have demonstrated that the NPC forms a selectively permeable barrier through the nuclear envelope. Inert polymers and small proteins less than 9 nm in diameter

or less than 30-40 kDa in mass can freely diffuse through the NPC . Larger particles traverse the NPC by a facilitated mechanism that is still poorly understood , and the NPC can accommodate the transport of particles as large as 25 nm in diameter. Cryo-electron microscopy images of NPCs indicate that their structure can expand radially to accommodate the passage of larger particles, suggesting that a gating mechanism may be built into the pore . Direct observation of particles in transit through the NPC confirmed that the central transporter structure forms the pathway for macromolecular traffic. Different sites for diffusion channels have been proposed, but no direct observation of diffusion has been made . Although many experiments indicate that the NPC forms an aqueous channel between the nuclear and cytoplasmic compartments, patch-clamp techniques suggest that pore complexes may actually be regulated channels that behave much like ion channels that can open and close .

The bulk of macromolecular traffic through the NPC is mediated by a system of mobile transporter proteins, distinct from the NPC itself, that act together to move molecules between the nuclear and cytoplasmic compartments. The mobile transporters that directly bind molecules to be transported are members of a family of proteins that share common features, the founding member of the family having been importin β, also known as karyopherin β. The mobile transporter proteins all have molecular masses between 90 and 130 kDa, with the bulk of each protein folded into a series of helical HEAT repeats. HEAT repeats are tandemly repeating 40-50 amino-acid motifs that form interactive surfaces in a number of proteins . The transporter HEAT repeats form two domains, an amino-terminal half that binds the small GTPase Ran when it is associated with GTP and a carboxy-terminal half with a cargo-binding domain. It is this domain structure that allows each transporter to function as either an import receptor or an export receptor: export receptors bind their cargoes cooperatively with Ran-GTP, while import receptors release their cargoes when bound to Ran-GTP. Ran is thus the key component that defines compartment identities for transport. The nuclear localization of the Ran guanine-nucleotide exchange factor, RanGEF, is believed to maintain nuclear Ran in a GTP-bound form. A Ran GTPase-activating protein (RanGAP) localized to the cytoplasmic face of the nuclear pore ensures that any Ran in the cytoplasm will be bound to GDP. Other small Ran-binding proteins are

involved in modulating GTP hydrolysis or the transport of Ran from the cytoplasm to the nucleus. The enrichment of RanGTP-binding mobile transporter proteins in the nucleus has also been suggested to contribute to the nuclear abundance of Ran .

A key step in transport is the interaction of the mobile transporter protein with nucleoporins, the structural proteins of the pore complex. These interactions are believed to be the basis for the selective transport of macromolecules through the pore. Many of the nucleoporins involved directly in transport share repeats containing phenylalanine-glycine dipeptides and are known as FG nucleoporins . The FG repeats interact with specific HEAT repeats of the mobile transporter . Although this is a relatively weak interaction, each of the FG nucleoporins contains multiple FG repeats that could provide multiple interaction sites for a transporter. There are at least 22 transporters in human cells.

Which transporters interact with which nucleoporins has been an important question from the beginning. An early model for translocation of proteins through the NPC suggested that the asymmetric arrangement of nucleoporins in the NPC formed an affinity gradient along which a mobile transporter could move by diffusion, with repeated association and dissociation from nucleoporins .