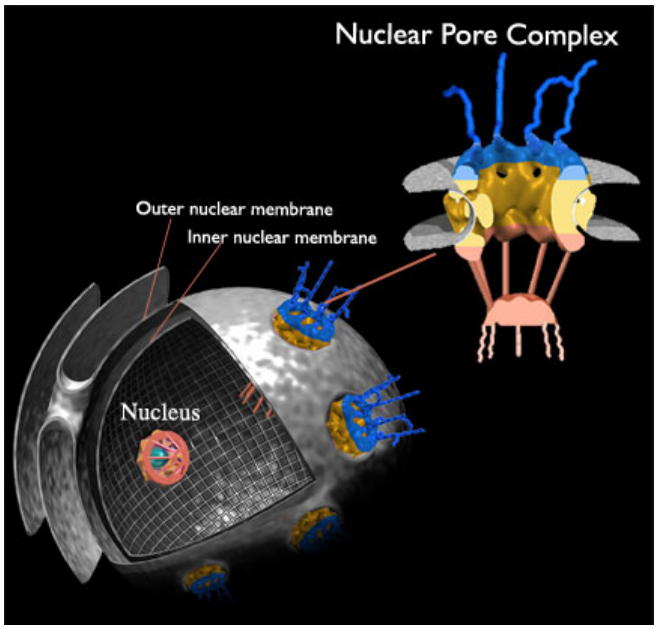
The Nuclear Pore Complex – A Nanoscale Gateway to the Nucleus

As the sole points of passage between the nucleus and the cytoplasm for large biological molecules, nuclear pore complexes (NPCs) form gateways that regulate the import and export of cargo to the nucleus. Many oncogenic and developmental defects are directly associated with alterations in nucleocytoplasmic transport. Dr. Michael Rout and colleagues at The Rockefeller University in New York are interested in understanding how the NPC mediates transport and in gaining a better understanding of the nature of these defects. Using a variety of techniques and yeast as a model system, they are studying the structure of the NPC and relating this to its sites of interactions and reactions with soluble nuclear transport factors. They hope to gain a better understanding of the role the NPC plays in nuclear regulation and maintenance.

A full understanding of how the NPC mediates transport requires a comprehensive inventory of the molecular components of the NPC, knowledge of how each component contributes to the overall structure of this large molecular translocation machine and information on the interactions its proteins make with components of the soluble phase. Dr. Rout and his colleagues have catalogued the components of the yeast NPC and determined that it is composed of 456 constituent proteins of ~30 distinct types. NPCs show a broad degree of compositional and structural conservation among all eukaryotes studied. Morphological studies show that NPCs are doughnut-shaped structures, consisting of eight spokes arranged radially around a central channel that serves as the conduit for macromolecular transport. Each NPC spans the nuclear envelope through a pore by the fusion of the inner and outer nuclear envelope membranes. Numerous filamentous structures project from the NPC into the cytoplasm and nucleoplasmin.



Schematic of the Nuclear Pore Complex

The Nuclear Pore Complex is a proteinaceous assembly of approximately 50 MDa that selectively transports cargoes across the nuclear envelope. It is an octagonally symmetric cylindrical structure around the axis of transport with planar symmetry through the nuclear envelope. The yeast NPC has been well characterized and is thought to contain 456 proteins of 30 distinct types.. The diameter of the entire yeast NPC is ~98nm; the central channel is ~38 nm and the height of the structured portion is ~37nm. The inner channel of the NPC is lined with specialized proteins that form the selective barrier for transport.

Based on their detailed knowledge of NPC structure and mode of action, Dr. Rout and colleagues are now designing *engineered* NPCs that mimic the transport selectivity of those found in nature. Although passive diffusion through the central lumen occurs in a size-dependent manner, selective transport of factors and their cargo-bound complexes is regulated by transient binding to the specialized proteins that line the interior of the lumen. Dr. Rout and his colleagues have designed a functionalized membrane that incorporates all the features of a nanoscale filter to achieve efficient passage of the correct proteins. Cargo that does not contain the correct signals to bind the proteins on the lining of the lumen are inhibited from passing through the NPC. Dr. Rout and colleagues have successfully shown that their artificial system faithfully reproduces key features of trafficking through the NPC, including transport-factor-mediated cargo import.

References

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