'Promiscuous' protein interactions found in the nuclear pore complex

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(PhysOrg.com) -- The NPC is the only way in or out of a cell's nucleus. It plays a key role in cellular metabolism and signaling, and any malfunction in these pores can have lethal consequences. Now new research reveals further insights into the design of this evolutionarily ancient and little-understood transport machinery. The findings suggest that the nuclear pore complex takes on different formations to carry out its function.

In higher organisms, cells are very selective about what passes in and out of their nuclei, where the genes reside. This selectivity helps protect the DNA and is the job of machines that stud the envelope of the nucleus, called nuclear pore complexes. These gatekeepers have proved largely inscrutable to researchers over the years, despite their conspicuously large size (they are made of 30 different proteins, or nucleoporins), but bit by bit, scientists are learning how these machines work.

Now a new study reveals the molecular structure of the largest piece of the molecule-trafficking complex to be captured by x-ray crystallography to date. Researchers have also shown that one member of the three-protein structure interacts promiscuously with two nucleoporins as do other proteins in the nuclear pore, supporting a model of a flexible complex that can rearrange itself into different formations. The work suggests an important design feature of this transport organelle, an ancient evolutionary innovation fundamental to the development of multicellular life on Earth.

The research, performed by Vivien Nagy, a visiting graduate student, André Hoelz, a research associate, and colleagues in Rockefeller University's Laboratory of Cell Biology, uncovered the molecular structure of three interacting proteins that form the centerpiece of the Nup84 complex — an important structural component of the nuclear pore complex. The Nup84 complex is a Y-shaped heptamer — a molecule composed of seven units — that was recently imaged in three dimensions by Martin Kampmann, also a member of the lab headed by Günter Blobel, John D. Rockefeller Jr. Professor and an investigator at the Howard Hughes Medical Institute.

In experiments to be published online in the *Proceedings of the National Academy of Sciences*, Nagy, Hoelz and colleagues provide the molecular specifics of the only piece of the Nup84 complex that remained unknown, furthering the structural characterization of this building module. They also describe competing interactions within the Nup84 complex and discuss the possibility of binding promiscuity as a common feature in the nuclear pore complex. These findings suggest that more than one assemblage of its elements may be necessary for the function of the nuclear pore complex — to import and export macromolecules including ribosomes and messenger RNA.

"Now that we realize that promiscuity may be a major factor in the nuclear pore complex — that the nucleoporins have different ways of interacting with each other — the complex is no longer just a three-dimensional jigsaw puzzle," Hoelz says. "Now we have to place these structures into a fourth dimension and find out when they adopt these different shapes. We're trying to take snapshots, static pictures, and turn them into a movie. It will require a lot more pictures, a lot more structures, before we understand the function and dynamics of this intricate transport organelle."

More information: *Proceedings of the National Academy of Sciences*

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