Research identifies 3-D structure of key nuclear pore building block

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The genome of complex organisms is stashed away inside each cell's nucleus, a little like a sovereign shielded from the threatening world outside. The genome cannot govern from its protective chamber, however, without knowing what's going on in the realm beyond and having the ability to project power there. Guarding access to the nuclear chamber is the job of large, intimidating gatekeepers known as nuclear pore complexes (NPCs), which stud the nuclear membrane, filtering all of the biochemical information passing in or out. In new research, scientists have for the first time glimpsed in three dimensions an entire subcomplex of the NPC; it's the key building block of this little understood and evolutionarily ancient structure, an innovation fundamental to the development of nearly all multicellular life on earth.

The findings, by Martin Kampmann, a graduate student in John D. Rockefeller Jr. Professor Günter Blobel's Laboratory of Cell Biology, add details to an unfolding picture of cellular evolution that shows a common architecture for the NPC and the vehicles that transport material between different parts of the cell, called coated vesicles. As early as 1980, Blobel proposed that internal membranes of cells - such as those encompassing the nucleus and vesicles - evolved from folds or invaginations of the outer cell membrane. Rockefeller scientists Brian Chait and Michael Rout suggested in a 2004 paper in PLoS Biology that both the NPC and vesicle coats, which contain similar protein folds, evolved from ancient membrane-coating proteins that stabilized these primordial internal membranes. "So far, it's been unclear how these ancient folds work in the nuclear pore complex", Kampmann says. "Now we can see that the α-solenoid folds form long, flexible arms and hinges that end in the more compact, globular β-propellers. The same architectural principle is found in clathrin, a common component of vesicle coats."

In research to be published online Sunday in *Nature Structural & Molecular Biology,* Kampmann isolated and purified samples of the most fundamental building block of the NPC known as the Nup84 complex, which is composed of seven proteins. The entire NPC - enormous by molecular standards - consists of 30 different kinds of proteins. Focusing on the Nup84 complex, Kampmann used an electron microscope (EM) to take thousands of images of the complex in different states or conformations, which could reflect a role in the expansion and contraction thought to facilitate the passage of various sized molecules through the NPC. By computationally averaging these many different views, he reconstructed the first three-dimensional models of the Nup84 complex. Finally, based on prior work in the Blobel lab using X-ray crystallography to determine the exact atomic structure of individual proteins in the Nup84 complex, he plugged these proteins snugly into the EM structure.

"Because the nuclear pore complex is probably too big and flexible to determine its entire atomic structure by X-ray crystallography, I think this three-dimensional EM approach could be a big help in solving the whole thing," Kampmann says. "It allows us to put the crystal structures that we do have in context." Kampmann is applying the EM approach to other subunits in hopes of fleshing out the overall picture of one of the most mysterious machines in molecular biology. "Martin's data represent an important advance toward piecing together the structure of the NPC," Blobel says.

Given the central role of the nuclear pore complex in the most basic cell processes, defects in its assembly, structure and function can have lethal consequences. Its proteins have been associated with viral infection, primary biliary cirrhosis and cancer. An understanding of how the complex works could lead to treatments for these diseases, and also reveal the evolutionary coup that led to the gene-protecting structure found in every cell more complicated than the simplest single-celled microorganisms: the nucleus.

Source: Rockefeller University (news : web)

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