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# Research Roundup

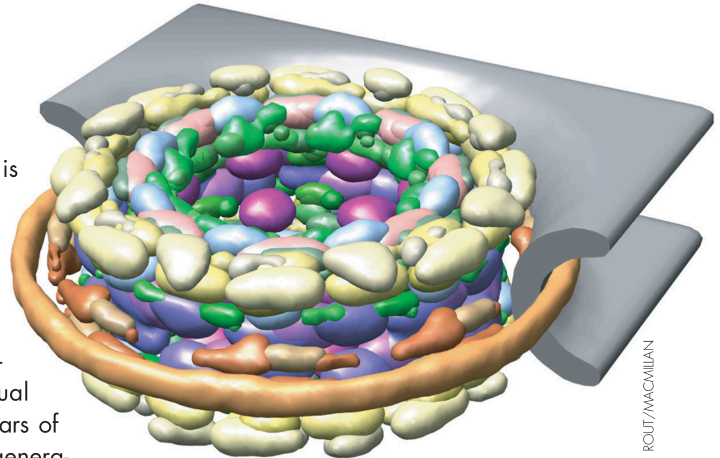
## The NPC, in detail

The nuclear pore complex (NPC) is a huge cylindrical assembly that transports material to and from the nucleus. In a biological tour de force, researchers have determined the positions of all 456 proteins of the NPC, providing structural insights of unprecedented detail. Among other discoveries, Svetlana Dokudovskaya, Liesbeth Veenhoff, Michael Rout, Brian Chait (Rockefeller University, New York, NY), Frank Alber, Andrej Sali (University of California, San Francisco, CA), and colleagues show that the large, complicated NPC is formed by only a few, structurally similar modules, including 16 repeated columns.

The researchers combined data on the size, shape, structure, and neighbors of every NPC protein to create a set of positional probabilities, or "restraints," which were then analyzed and optimized to produce a final structure. Rout compared it in principle to solving a crossword puzzle, in which partial knowledge of one word restrains the possibilities for many others. "If you have tens of thousands of these restraints," he says, "you can pare down until a protein is restrained to a volume of its own size."

Previous characterizations of the NPC structure did not resolve the positions of its individual components. Nine years of work went into the generation and analysis of the data, although future studies of other cell structures should be faster.

The new structure is highly symmetrical. "It's very clear that the underlying architecture of the NPC is modular," says Rout, "and likely arose from several rounds of gene duplication." Each column is paired with an adjacent one of related proteins; the pairs give rise to eight identical spokes that make up the NPC. Gene duplication may also have given rise to the prominent inner and outer rings, which circle within the NPC like concentric belts.

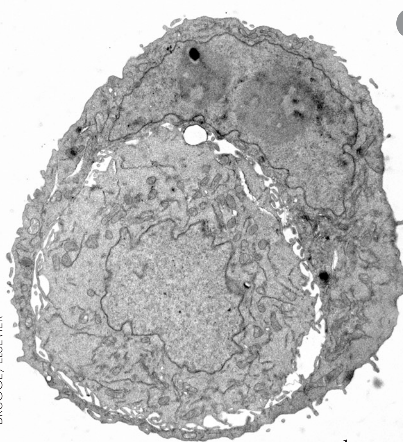

ROUT/MACMILLAN

**The 456 proteins of the nuclear pore complex form 16 central columns and several encircling belts.**

The structure is not the last word on the subject; it gives a protein-level but not atomic-level picture. It also does not include the fine structure of the basket, which projects into the cytoplasm and is believed to aid nuclear transport. The team is now working on solving these structures. JCB

References: Alber, F., et al. 2007. *Nature.* 450:683–694.
Alber, F., et al. 2007. *Nature.* 450:695–701.

## Cells within cells (within cells)


BRUGGE/ELSEVIER

**Within 6 hours of detachment from their substrate, one cell becomes entirely enclosed by another.**

One tumor cell can burrow its way entirely inside another. Now, Michael Overholtzer, Joan Brugge (Harvard Medical School, Boston, MA), and colleagues report that, while its fate is usually met in the host's lysosome, in some cases the burrowing cell can divide or pop back out, or even go along for the ride as the host burrows into yet another cell.

Such "cell-in-cell" structures are common in tumors, but the mechanism of invasion was unknown. By labeling human breast cancer cells with different colors, the authors showed that 25% of cells contained other cells within 12 hours of detachment from their substrate. While apoptosis of one cell can drive phagocytosis by another, blockade of either process did not diminish the rate of invasion.

Invasion was suppressed, however, by stopping actin–myosin II contraction in the internalized cell. "The process requires activity of the invading cell," Brugge says. The group found no evidence that the host initiates the process, and contraction blockade in the host had no effect. Cadherins, which link epithelial cells together, were required and were densest at contacts between the two cells during internalization.

Both cadherins and actin–myosin contraction feature prominently in epithelial compaction, through which multiple layers of attached cells condense into a dense monolayer. The authors suggest that the cell invasion process, which they christened "entosis," may be epithelial compaction gone awry, with the invader tugging so hard it pulls the other cell right around it. The malaria parasite performs a roughly similar trick when invading its host.

Once inside, most cells were degraded by lysosomes, but about 15% were released apparently unharmed. A few divided inside their hosts, and some hosts apparently turned into invaders themselves, giving rise to a cell within a cell within a cell.

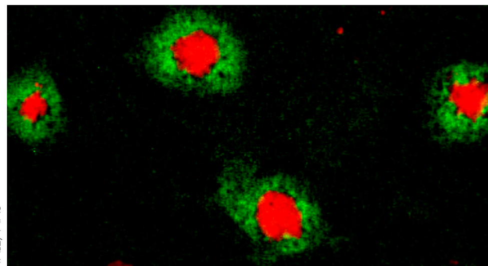
Entosis is not just a novelty of the lab bench: 1–2% of metastatic breast tumor cells contained other cells. Whether entosis promotes tumorigenesis by increasing aneuploidy or inhibits it by killing invasive cells and whether noncancerous cells undergo entosis during development remain to be seen. JCB

Reference: Overholtzer, M., et al. 2007. *Cell.* 131:966–979.

## Building the immunological bull's eye

After an antigen-presenting cell meets a T cell, a bull's eye–shaped immunological synapse is formed, with T cell receptors (TCRs) and their antigen clustered in the center, surrounded by a ring of adhesion molecules that holds the cells together. According to Yoshihisa Kaizuka, Adam Douglass, Ronald Vale (University of California, San Francisco, CA), and colleagues, TCRs and adhesion molecules separate early during synapse formation. They might be further segregated by differential interactions with the T cell's actin cytoskeleton.

The movements of the T cell receptor were previously described, but little was known about the movements of adhesion molecules. Direct imaging of T cells in contact with a flat lipid bilayer containing the right ligands showed that TCRs and adhesion molecules initially clustered at the periphery of the contact zone. Each formed their own microdomains in an actin-dependent process. "This early segregation is probably due to different protein–protein interactions that cause these microdomains to coalesce," Vale says.



VALE/NAS

**Adhesion molecules (green) bound to actin cluster around T cell receptors (red) in the actin-depleted center of an immunological synapse.**

The microdomains were then driven inward by retrograde actin flow. The TCRs traveled farther, to the actin-depleted center of the synapse. Adhesion clusters remained in the actin-rich outer portion, unable to travel further inward. They might be stalled by the dense packing of TCRs already in the center or by their own instability in the absence of actin. Neither set traveled as fast as actin itself, probably because they repeatedly slipped off and reattached to the actin conveyor beneath them. JCB

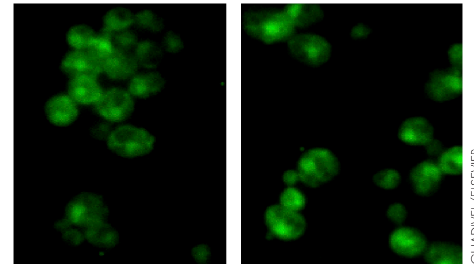
Reference: Kaizuka, Y., et al. 2007. *Proc. Natl. Acad. Sci. USA*. doi:10.1073/pnas.0710258105.

## tRNA's Los is a gain after damage

Shutting down nuclear export of unspliced tRNA keeps cells in G1 during DNA repair, say Ata Ghavidel and colleagues (University of Toronto, Canada).

The authors found that DNA damage caused the nuclear accumulation of tRNAs containing unspliced introns, which are removed in the cytoplasm. This accumulation required the damage-induced signaling molecule Rad53 and correlated with the retention of the main tRNA export receptor, Los1, in the cytoplasm.

Without their exporter, tRNAs were stuck in the nucleus, causing cell cycle arrest in G1 and giving the cell time to repair damage before DNA synthesis. Deleting Rad53 prevented the nuclear tRNA build-up, and damaged cells exited G1 prematurely. Deleting Los1 in these cells restored the G1 arrest.



GHAVIDEL/ELSEVIER

**Unspliced tRNAs (green) accumulate in the nucleus in response to DNA damage (right).**

The G1 stall was not due to decreased cytoplasmic tRNA, which remained in large excess due to its long turnover time. Instead, the stall stemmed from the surplus of nuclear tRNA, which somehow enhanced translation of a stress response factor called Gcn4—a protein that promotes repair and slows the synthesis of G1 cyclins.

"This process couples the nuclear sensing of DNA damage to cytoplasmic protein synthesis," Ghavidel says. "It was an entirely unanticipated mechanism, since tRNA export has traditionally been viewed as constitutive." JCB

Reference: Ghavidel, A., et al. 2007. *Cell*. 131:915–926.

## Lipid + Alzheimer's plaque = problem

Lipids rapidly dissolve Alzheimer's disease plaques into toxic protofibrils, according to Joost Schymkowitz, Frederic Rousseau (Vrije Universiteit Brussel, Belgium), and colleagues.

Insoluble amyloid plaques of the Aβ protein are found throughout the Alzheimer's brain but are thought to be largely inert. By contrast, oligomeric protofibrils—the intermediate between soluble Aβ and insoluble amyloid—are known to be neurotoxic. But once they make plaques, protofibrils were not thought to escape back into toxic form.

Because disturbed lipid metabolism has been implicated in Alzheimer's development, the authors tested the effects of lipids on plaque solubility. When subjected to a variety of naturally occurring lipids, plaques released large amounts of protofibrils that were toxic to neurons in culture. Injecting a mixture of lipids and amyloids into the mouse brain caused memory deficits not seen with either alone. "If the brain harbors a lot of aggregates, it can be a significant reservoir of toxic material," Rousseau says, which may contribute to worsening Alzheimer's disease.

As a silver lining, Rousseau notes, the discovery may make anti-protofibril antibody production much easier, because abundant quantities of protofibrils can be kept in solution for long periods. JCB

Reference: Martins, I.C., et al. 2007. *EMBO J*. doi:10.1038/sj.emboj.7601953.