Research reveals novel transport mechanism for large ribonucleoproteins

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The movement of genetic materials, such as RNA and ribosomes, from the nucleus to the cytoplasm is a critical component in a cell's ability to make the proteins necessary for essential biological functions. Until now, it was believed the nuclear pore complex was the sole pathway between the cell nucleus and cytoplasm for these materials. New evidence published in *Cell* by Vivian Budnik, PhD, Melissa J. Moore, PhD, and colleagues at the University of Massachusetts Medical School, reveals a novel budding mechanism, similar to the process used by some viruses, capable of exporting large ribonucleoprotein particles from the nucleus to the cytoplasm.

"The findings in this paper fundamentally change our understanding of mRNA export from the nucleus," said Moore, the Eleanor Eustis Farrington Chair in Cancer Research, Howard Hughes Medical Institute Investigator and professor of biochemistry & molecular pharmacology. "In addition to the canonical pathway of mRNA export going through the nuclear pore complex, we now know that large RNA transport granules can be assembled in the cell nucleus and exported via a budding mechanism previously thought to only be used by the herpes virus."

This study has helped to unravel how RNAs support the development of the post-synaptic apparatus, said Budnik, professor of neurobiology. "It provides new evidence about communication between the nucleus and cytoplasm that have implications for diseases that affect the nuclear envelope such as muscular dystrophies and herpes-type infections such as shingles."

Found along the surface of the nuclear envelope, nuclear pores are small openings that allow certain molecules, such as messenger RNA, transfer RNA and ribosomes, to be transported across this physical barrier that separates a cell's nucleus and DNA from its cytoplasm. Once in the cytoplasm, these genetic materials are the factories and blueprints used by the cell to create proteins. In some cells, these RNAs are bound together in large clusters known as transport granules, which are carried to precise locations within a cell to synthetize specific proteins needed at that site.

"When we look at these transport granules to scale, we see that they're too large to pass through the nuclear pore complex," said Moore. "An open question has been, where are these transport granules first assembled? And if it's in the nucleus, how do they make their way to the cytoplasm?"

Working to understand how synapses develop and communicate with neighboring muscle cells, Budnik discovered a new method whereby these large granules, in the form of ribonucleoprotein (RNP) particles, were transported across the nuclear envelope. Specifically, Budnik and colleagues were investigating how the Wnt/wingless (Wg) protein secreted by the motor neuron initiates a reaction involving the DFrizzled2 (DFz2) receptor on the nearby muscle cell. This interaction between Wg and DFz2 eventually leads a portion of the DFz2 into the muscle cell nucleus where it accumulates around large RNP granules containing messenger RNAs. Once they reach their final destination in the muscle cell cytoplasm, these RNAs are responsible for making the synaptic proteins critical to increasing the size of the junction between motor neuron and muscle cell.

It was while investigating this process that Budnik and colleagues witnessed these large granules exiting the muscle cell's nucleus in an unusual manner. "What was so surprising," said Sean D. Speese, PhD,

former postdoctoral fellow in the Budnik lab and currently research assistant professor at Oregon Health and Sciences University, "was that the nuclear DFz2-large-RNPs utilized a novel mechanism for exiting the nucleus, which appeared independent of the nuclear pores and resembled the egress of herpes-type viruses from the nuclear envelope."

During infection, herpes virus particles are assembled in the nucleus. But they are much too large to exit through the nuclear pores. Instead, they bud through the double membranes of the nuclear envelope. To exit the nucleus, the protein shell surrounding the virus disrupts the lamina, a fibrous component located beneath the inner nuclear membrane which, among other properties, anchors the nuclear pore complexes to the nuclear membranes. This allows the virus to bud into the space between the inner and the outer nuclear membrane, becoming enveloped by the inner nuclear membrane. Fusion of this coat with the outer nuclear membrane then allows the virus to be released into the cytoplasm.

"Similarly, we found that DFz2C-RNPs used the same mechanism and viral machinery to reach the cytoplasm," said Speese. Once inside the muscle cell nucleus, the DFz2C RNPs recruit proteins, such as kinase C, to disrupt the lamins, which allows them to bud into the inner nuclear membrane. "In both cases, this process was dependent on an A-type lamina protein, which in humans is associated with a number of muscular dystrophies and early aging syndromes when mutated," said Speese.

Collectively, these discoveries have significant ramifications on our understanding of multiple biological questions including RNA transport, synapse development and the herpes virus, which causes chicken pox and shingles and Epstein–Barr virus, which causes mononucleosis.

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