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NUCLEAR TRANSPORT

A new way out

The exit of proteins and mRNAs from the nucleus has long been thought to occur by only one route, through the nuclear pore complex (NPC). The finding that large ribonucleoprotein particles (RNPs) can also be exported by budding of the nuclear envelope suggests that this may not always be the case.

Budnik and colleagues made this discovery while studying the mechanisms of WNT signalling during *Drosophila melanogaster* synapse development. The WNT homologue Wingless is required for synapse differentiation and regulates this by binding to the *D. melanogaster* Wingless receptor Frizzled 2 (DFz2); this triggers DFz2 internalization and cleavage of its carboxyl terminus to produce a DFz2C fragment that is imported into the nucleus. The authors previously observed that DFz2C forms large foci in the nucleus and so set out to determine the nature, and fate, of these foci.

Using fluorescence microscopy, they showed that DFz2C foci colocalize with a lattice of the A-type lamin LAMC at the inner nuclear membrane, and that both DFz2C and LAMC mutually depend on each other for this localization. Mutations in human A-type lamins result in muscular dystrophies; consistent with this, the authors found that expression of a disease-associated LAMC mutant impaired the formation of the DFz2C foci. Moreover, depletion of LAMC resulted in defects in synapse differentiation that were similar to the defects observed when DFz2C import is inhibited.

This suggested that the nuclear lamina might be important for normal WNT signalling during synapse development. To understand why, the researchers tracked the fate of DFz2C foci. They saw that most DFz2C foci were surrounded by invaginations of the nuclear envelope but did not colocalize with NPCs. Electron microscopy analysis showed that DFz2C foci are electron-dense granules that localize in the perinuclear space, bound by the inner nuclear membrane, and are also present in the cytoplasm close to nuclear envelope evaginations. This led the authors to propose that DFz2C foci might be released into the cytosol by budding of the nuclear envelope.

Could DFz2C foci contain cargo that is functionally relevant for synapse differentiation? The authors observed that DFz2C foci contain RNAs, and live-imaging studies revealed that some RNA-containing granules exit the nucleus. Importantly, mRNA encoding PAR6 (partitioning defective 6), which is a component of the atypical protein kinase C (aPKC)–Bazooka (BAZ) complex, was present in the DFz2C foci and also localized at the developing synapse in a LAMC-dependent manner. aPKC and BAZ were also present in DFz2C foci and were important for synapse differentiation. Thus, DFz2C foci may have a direct role in transporting mRNAs to the synapse for local translation downstream of DFz2C nuclear import.

The mechanism by which these RNPs exit the nucleus is reminiscent of that used by herpes virus during the release of viral capsids. Although the virus was thought to hijack a membrane disassembly mechanism, this work suggests that it may instead be subverting an endogenous pathway for nuclear exit of large RNPs. There are initial indications that this may be a conserved pathway that is used for widespread functions. Certainly, this calls for a reconsideration of whether the NPC is the only portal for nuclear exit, and the reasons why specific lamin mutations result in muscular dystrophy.

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ORIGINAL RESEARCH PAPER Speese, S. D. *et al.* Nuclear envelope budding enables large ribonucleoprotein particle export during synaptic Wnt signaling. *Cell* **149**, 832–846 (2012)