Jumping over the fence: RNA nuclear export revisited

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The nuclear envelope forms a cocoon that surrounds the cellular genome keeping it out of harm’s way and can be utilized by the cell as a means of functionally regulating chromatin structure and gene expression. At the same time, this double-layered membrane system constitutes a formidable obstacle to the unimpeded flow of genetic information between the genome and the rest of the cell. The nuclear pore has been long considered the sole passageway between nucleus and cytoplasm. A new report challenges this view and proposes a novel mechanism by which RNA transcripts destined for localized translation in highly polarized cell types, cross both inner and outer nuclear envelope membranes and reach the cytoplasm without utilizing the nuclear pore route.

### Compartmentalization Creates Barriers

Although compartmentalization affords eukaryotic cells complex means of functional regulation, it also poses considerable logistical challenges arising by the need to exchange material between separate organelles. The two major cellular compartments are separated by the nuclear envelope (NE), a double membrane system composed of an inner nuclear membrane (INM) facing the nucleoplasm and an outer nuclear envelope (ONM), which faces the cytoplasm and is continuous with the endoplasmic reticulum. While the NE and its associated structures constitute a formidable barrier, protecting the cellular genome against external threats, its presence also poses a significant obstacle to the physiological exchange of information between the genome and the rest of the cell.

In multicellular organisms, the interface between chromatin and the INM is occupied by the nuclear lamina (NL), a 30–100 nm thick, dense protein meshwork, which has an essential role in preserving both the shape and the mechanical properties of the nucleus. The NL is composed of four lamin proteins, which are subdivided in types A and B and collectively belong to the type V intermediate filaments family. The INM-associated type B lamins (i.e., lamin B1 and B2) are the fundamental lamina building blocks, while the nucleus-facing type A lamins (i.e., lamin A and C), have more specialized functions. Besides its scaffolding and protective roles, it is now increasingly clear that the NL represents a hub for the coordinated interaction between macromolecular machineries involved in multiple cellular functions. These include gene regulation, genome organization and repair, as well as mitotic division, nuclear positioning, cytoskeletal remodeling and nucleocytoplasmic transport. Not surprisingly, given its far ranging and pivotal roles, lamina defects have been associated with a variety of human disorders, collectively termed laminopathies, which include muscular dystrophy, cardiomyopathy and progeroid syndrome.

### The Canonical View of Nuclear RNA Export Has Its Difficulties

Given such an apparently inexpugnable fortification, it is not surprising that...
nature has devised specialized pathways to ensure efficient material exchange in and out of the nucleus. Most traffic across the NE and lamina barriers is accomplished through cylindrical macromolecular assemblies termed nuclear pore complexes (NPCs). Among the largest proteinaceous machineries in the cell, these structures are highly selective molecular sieves, controlling the transport of large ribonucleoprotein (RNP) assemblies in and out of the nucleus. While NPCs are highly selective, they are also dynamic: repeated alterations of the lamina network allow NPCs to staple the inner and outer nuclear membranes together. This process is facilitated by the coordination of the INM and ONM, which may be a prerequisite for NE budding. However, while this current unfurling model governing the transport of large nucleo-protein complexes in and out of the nucleus is under investigation, the mechanisms governing the nuclear export of transcripts known as mRNAs are still to be elucidated.

The metazoan NPC consists of a ~325 nm diameter core structure composed of three main rings surrounding a central transport channel. The size of this channel has been inferred from the size of un-deformable artificial cargo as well as from direct measurements and it ranges between ~40 nm near its mid-plane to ~60–70 nm at either end. While much has been learned on the structure and function of the NPCs since their initial observation, one outstanding question has concerned the mechanism by which large ribonucleoprotein (RNP) assemblies gain access to the cytoplasm, when their diameter can be considerably larger than the diameter NPC central transporter. The generally accepted model has been largely based upon observations of Chromatium Balbiani ring mRNP granules (diameter ~50 nm) and of ribosomal large subunits (diameter ~30 nm) export and posits that large RNPs are temporarily rearrested into more elongated structures during nuclear egress and are threaded piecemeal through the NPC central channel. While this current unfurling model governing the transport of large nucleo-protein complexes in and out of the nucleus is under investigation, the mechanisms governing the nuclear export of transcripts known as mRNAs are still to be elucidated. However, while this current unfurling model governing the transport of large nucleo-protein complexes in and out of the nucleus is under investigation, the mechanisms governing the nuclear export of transcripts known as mRNAs are still to be elucidated.

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The Escape Pathway Utilized by Herpes Viruses Bypasses the NPC

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followed by their localized translation.26 Building on this scenario, a lost report by Speese et al.1 challenges the canonical view of RNA export and presents compelling evidence for an alternative pathway that bypasses the NPC altogether.

Studying Wnt signaling in post-synaptic muscle fibers, Budnik and colleagues had previously revealed that a C-terminal fragment of the Wnt-1 receptor (DFz2C) is imported into the nucleus in response to synaptic stimulation, forming discrete peripheral nuclear foci.26-28 In this new study, the authors show that once inside the nucleus, DFz2C localizes in large (i.e., ~200 nm in diameter) electron-dense granules containing bouton-specific mature. RNA transcripts poised for nuclear export. Such granules accumulate on the nuclear face of the NE where they appear to be encased within scaffolds composed of the A-type lamin, laminC (LamC) and to be surrounded by membranes. Interestingly in addition to DFz2C, both laminC and atypical protein kinase C (aPKC) are required for the formation of these granules, and in their absence NMJ development is hampered. The involvement of aPKC suggests that the morphogenesis of the DFz2C/LamC granules requires the reorganization of the lamina and NE structures, as observed during HSV NE budding. Consistent with this conclusion, high-resolution microscopic images indicate that the DFz2C/LamC granules are enveloped by NE invaginations that appear to be continuous with either the INM or the ONM and keep the granular content topologically continuous with either the INM or the ONM.

Nonetheless, their internal structure and molecular composition remains to be established. Presumably they consist of aggregates of mRNPs encodingbouton-specific mRNAs. Nonetheless, their internal structure and molecular composition remains to be established. Presumably they consist of aggregates of mRNPs encodingbouton-specific mRNAs. Nonetheless, their internal structure and molecular composition remains to be established. Presumably they consist of aggregates of mRNPs encodingbouton-specific mRNAs.
Despite these caveats, the prevailing fact remains that the pioneering work recently presented by Speese et al. has shed unexpected light into previously uncharted territory. Their effort will now hopefully be followed up by them and by others and lead to a better understanding of the means by which the two main compartments of the eukaryotic cell can effectively communicate with each other across the NE barrier, especially during active growth and development.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.