Review

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Postage for the messenger: designating routes for nuclear mRNA export

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Transcription of mRNA occurs in the nucleus, making the translocation of mRNA across the nuclear envelope (NE) boundary a critical determinant of proper gene expression and cell survival. A major mRNA export route occurs via the NXF1-dependent pathway through the nuclear pore complexes (NPCs) embedded in the NE. However, recent findings have discovered new evidence supporting the existence of multiple mechanisms for crossing the NE, including both NPC-mediated and NE budding-mediated pathways. An analysis of the *trans*-acting factors and *cis* components that define these pathways reveals shared elements as well as mechanistic differences. We review here the current understanding of the mechanisms that characterize each pathway and highlight the determinants that influence mRNA transport fate.

Transport across the NE

Eukaryotic cells are distinguished from their prokaryotic predecessors by the presence of the NE, a double lipid bilayer encasing the heritable genome [1]. In the simplest terms, the NE functions as a physical barrier that separates the contents of the nucleus from those of the cytoplasm. Transcription of mRNA occurs in the nucleus, whereas translation of mRNA into functional protein occurs in the cytoplasm [2,3]. This spatial issue is resolved by mechanisms that efficiently export mRNA across the NE.

An emerging body of work supports the concept that the NE is not simply a static structure that divides subcellular compartments, but rather plays roles in chromatin organization and gene regulation, as recently reviewed in [4]. Structurally, the NE outer nuclear membrane (ONM) is continuous with the endoplasmic reticulum and the inner nuclear membrane (INM). Distinct subsets of integral membrane proteins specifically localize to the ONM and the INM [5]. Physical connections in the NE lumen between ONM- and INM-localized transmembrane proteins maintain the structural integrity of the NE and establish cytoskeleton–chromatin communications [6,7]. In higher eukaryotes, the INM is associated with an essential intermediate filament-based structure called the nuclear lamina [8,9]. Access to the INM requires association with or unraveling of the lamin meshwork. A key process in NE dynamics is the fusion of the ONM and INM to create pores [10]. Nuclear pore complexes (NPCs), large protein assemblies of approximately 60 MDa, are embedded in these pores and serve as selective portals for bidirectional transport [11,12]. Water, sugar, ions, and small molecules diffuse freely through the central NPC channel. By contrast, molecules 5–40 nm in diameter, such as mRNA ribonucleoproteins (mRNPs), rRNA, and proteins, require facilitated transport mechanisms to cross the NPC's selectivity barrier [11,13]. Together, all of these NE components are differentially leveraged in distinct mRNA export pathways.

A long-standing tenet in the field posits that the NPC is the sole route for nucleocytoplasmic transport through the NE. The identification of a novel vesicular, NE budding-mediated mRNA export mechanism has elicited a restructuring of this view [14]. Combined with additional evidence for multiple mRNA export pathways within the NPC, several interesting mechanistic questions are raised: what are the unique features that distinguish these pathways and what are the fates of the associated mRNAs? We discuss here how intrinsic elements of mRNA such as structure, sequence, and length, as well as mRNA-binding proteins/adaptors and transport receptors, effectively serve as postage for the mRNA and dictate which pathways are utilized to cross the NE. We aim to summarize our current understanding of mRNA export pathways and emphasize the outstanding questions yet to be addressed.

Common elements for mRNP trafficking across the NE

Regardless of the transport pathway utilized to cross the NE, the mRNA must be packaged in the nucleus into an mRNP complex. It is well established that assembly of the mRNP is tightly integrated with many aspects of mRNA biogenesis including transcription, processing, and quality surveillance (reviewed in [3,15]). Nascent mRNAs are transcribed in the nucleus by RNA polymerase II (RNAPII). The carboxyl-terminal domain of the largest subunit of RNAPII orchestrates the cotranscriptional loading of accessory factors onto the growing transcript. Dynamic association and disassociation of these accessory protein factors with the mRNA leads to the production of an export-competent mRNP [16]. Proper assembly of an

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mRNP directly impacts the transport of mRNAs and their associated RNA-binding proteins across the NE [15,16].

Multiple common events occur if the mRNP is to be targeted to the NPC for export. First, during mRNP biogenesis, a transport receptor is recruited to the complex. At least four NPC-mediated mRNA export mechanisms have been characterized in higher eukaryotic systems (Figure 1). One of these pathways has been extensively analyzed in *Saccharomyces cerevisiae* (Figure 1D). There are two major transport receptors implicated in two

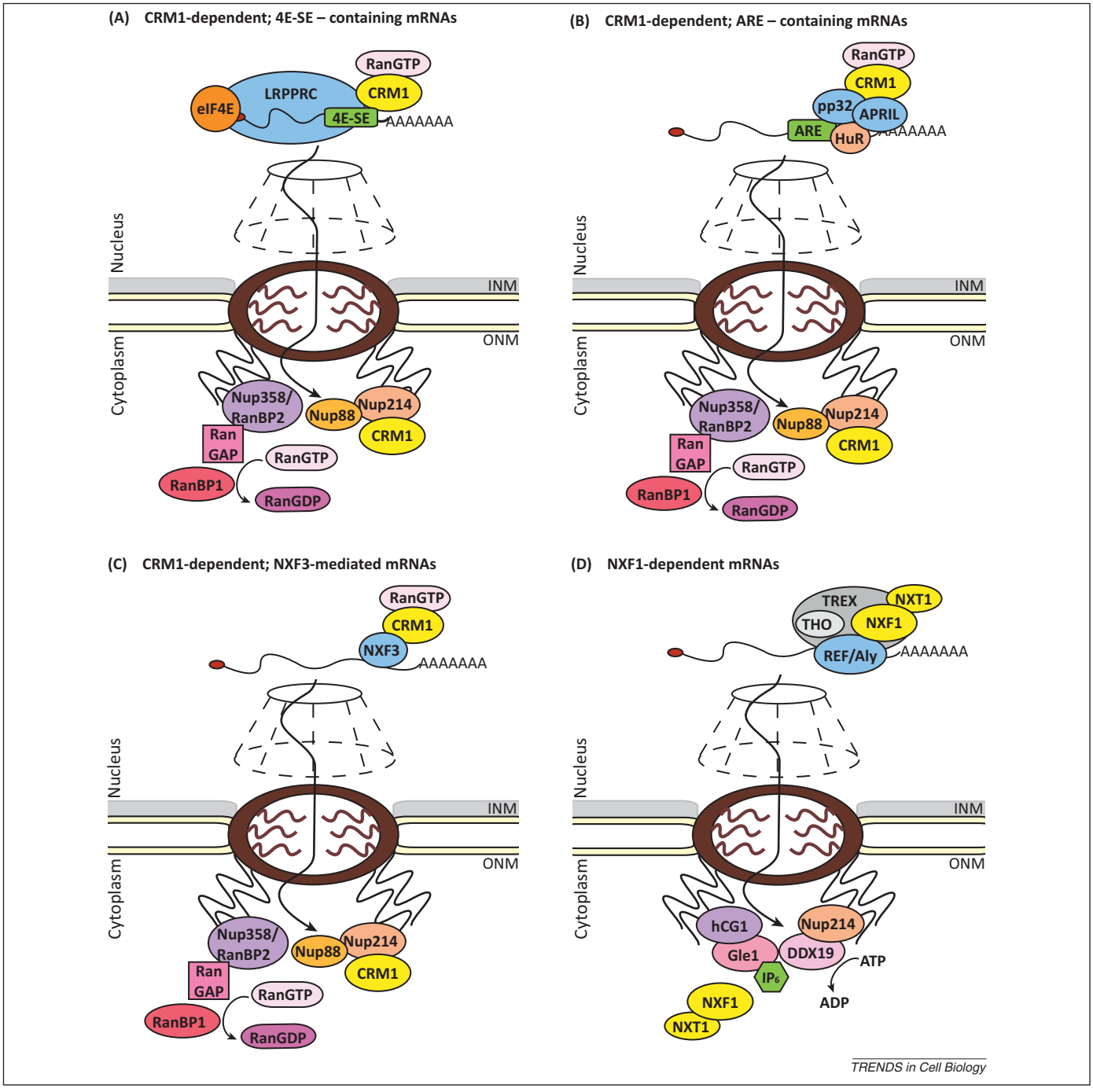

Figure 1. Nuclear pore complex (NPC)-mediated nuclear mRNA export pathways. The major components of the nuclear envelope are the outer nuclear membrane (ONM), inner nuclear membrane (INM), nuclear pore complexes (NPCs), and nuclear lamina (shaded gray). Note that lamins are not present in the unicellular organism *Saccharomyces cerevisiae*. The NPC can be divided into three parts: nuclear basket, central channel lined with phenylalanine–glycine nucleoporins (FG-Nups) (brown wavy lines), and cytoplasmic filaments. Export-competent mRNA ribonucleoproteins (mRNPs) assemble in the nucleus. The fate of these mRNAs is dependent on the factors that bind in the nucleus before export through the NPC. Major nuclear export receptors are indicated in yellow; adaptor proteins for these receptors are indicated in blue. Higher eukaryotic factors are indicated; however, *S. cerevisiae* homologs exist for many of these factors. References are cited in the corresponding text. **(A)** CRM1-mediated mRNA export is RanGTP dependent. Leucine-rich pentatricopeptide repeat protein (LRPPRC) binds eIF4E and the RNA element 4E-SE as part of the eIF4E-dependent CRM1-mediated mRNA export pathway. **(B)** AU-rich element (ARE)-containing mRNAs are bound by the mRNA-binding protein human antigen R (HuR), which recruits CRM1 via the adaptor proteins pp32 and APRIL. **(C)** The tissue-specific factor NXF3 interacts directly with CRM1 and may serve as an adaptor protein for CRM1-mediated mRNA export. **(D)** The major mRNA export receptor NXF1 coupled with its heterodimeric partner NXT1, is required for formation of an export-competent mRNP. REF/Aly serves as an adaptor protein for NXF1. The TREX/THO complex is cotranscriptionally recruited to the mRNP, linking transcription to export. At the cytoplasmic face, NXF1 and NXT1 are remodeled off the mRNP via the concerted action of DDX19, Gle1, and inositol hexakisphosphate (IP_6).