# mRNA nuclear export at a glance

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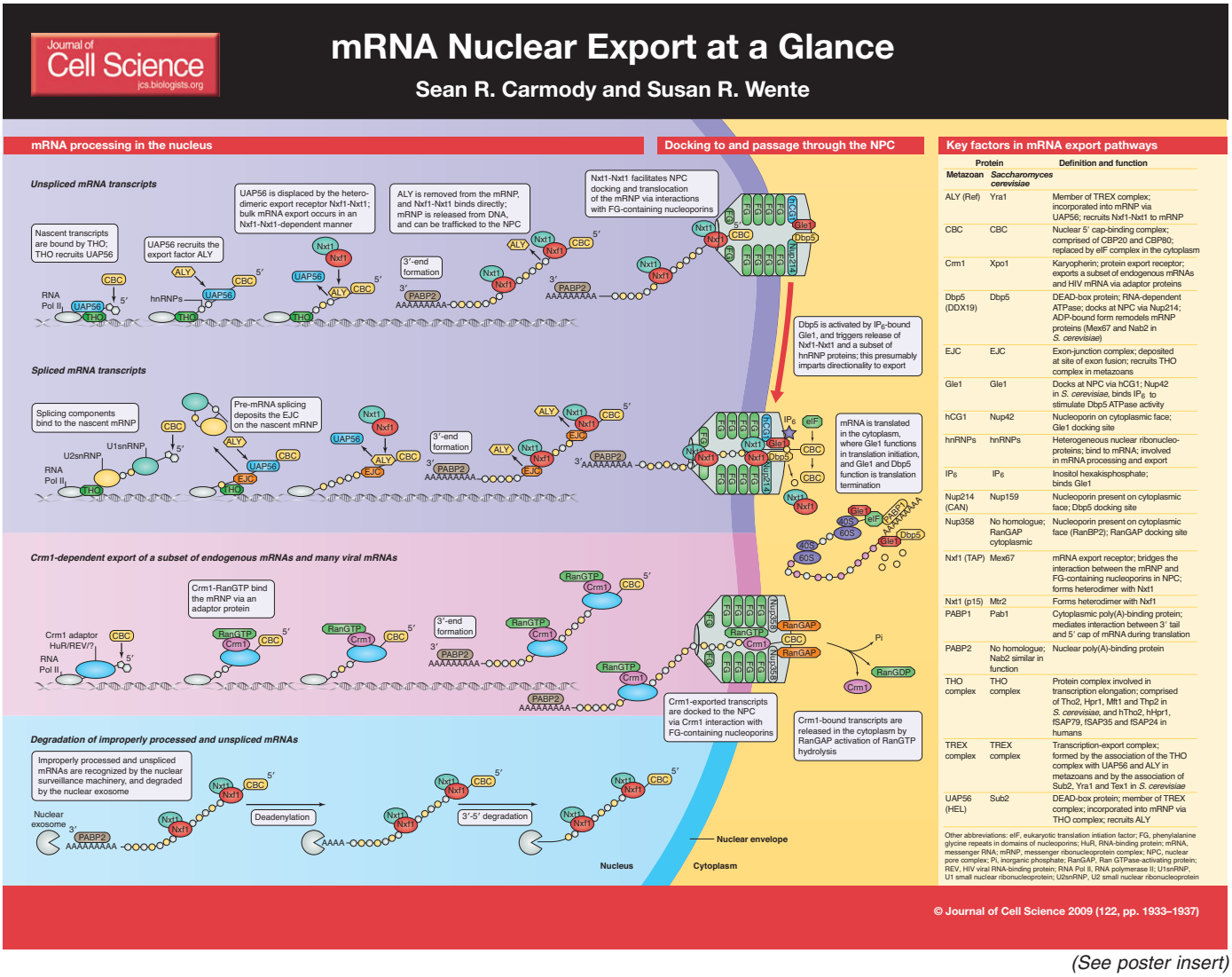
Eukaryotic gene expression is controlled by multiple mechanisms, and its regulation is central for physiological responses to extracellular and intracellular signals. An essential step in this process involves the movement of mRNA transcripts from the site of synthesis in the nucleus to the cytoplasm, where they can be translated into proteins. The nuclear export of mRNA transcripts can be broken down into distinct stages: first, pre-mRNA is transcribed in the nucleus, where it is processed and packaged into messenger ribonucleoprotein (mRNP) complexes; second, the mRNPs are targeted to and translocate through nuclear pore complexes (NPCs) that are embedded in the nuclear envelope; and third, the mRNPs are directionally released into the cytoplasm for translation. Recent work has revealed that there is extensive mechanistic coupling between each of these steps (Kohler and Hurt, 2007). Moreover, it has been shown that perturbations in the factors that are essential for mRNA nuclear export have surprising links to different disease states. In this article and its accompanying poster, we provide an overview of the mRNA nuclear export pathway.

## Early mRNA processing events: assembly of mRNPs

The formation of an export-competent mRNP begins at transcription. During transcriptional elongation, the nascent mRNA transcript is bound by a number of factors, some of which are part of the family of heterogeneous nuclear ribonucleoproteins (hnRNPs). hnRNPs are highly abundant nuclear RNA-binding proteins that are essential for various steps in the mRNA life cycle, including packaging, export and translation. There are ~30 different hnRNPs in humans, and about ten in *Saccharomyces cerevisiae* (Dreyfuss et al., 2002). Although some of these proteins have minimal sequence conservation from yeast to humans, several core functions are conserved. For example, human cells harbor a nuclear poly(A)-binding protein, PABP2 (Dreyfuss et al., 2002), and a cytoplasmic poly(A)-binding






*(See poster insert)*

protein, PABP1 (Burd et al., 1991). In *S. cerevisiae*, Pab1 is a homologue of human PABP1 (Caponigro and Parker, 1995) but the nuclear poly(A)-binding protein, Nab2, is not structurally similar to human PABP2 (Anderson et al., 1993). Different hnRNP proteins associate with the mRNP at distinct steps in the export pathway (Dreyfuss et al., 2002). Notably, some hnRNPs harbor nuclear-retention signals and are removed prior to the export of the mRNP, whereas others are retained during export and released in the cytoplasm, and then are shuttled back into the nucleus.

## Key steps in mRNA processing

There are four main processing events that occur during the formation of a mature mRNA transcript: 5′ capping, splicing, 3′-end cleavage and polyadenylation. Each of these modifications impacts export in two ways. First, if an mRNA is not properly processed, it will not be exported and instead will be targeted for degradation. Second, the processing events serve as triggers to recruit protein factors that are necessary for export.

The first change that a nascent pre-mRNA transcript undergoes is 5′ capping. When a transcript reaches about 20-30 nucleotides in length, a 7-methylguanosine cap is added to the 5′ end, which protects the nascent pre-mRNA from degradation (Shatkin and Manley, 2000). In microinjected *Xenopus* oocytes, uncapped mRNA is either poorly exported from the nucleus, or not exported at all (Cheng et al., 2006). The 5′ cap is bound by the cap-binding complex (CBC; composed of the proteins CBP20 and CBP80) (Izaurralde et al., 1995). Next, a transcript undergoes splicing, and a set of proteins is simultaneously deposited at the site of exon fusion. These proteins are defined as the exon-junction complex (EJC). Capping and splicing are both important for the recruitment of the transcription-export (TREX) complex (Cheng et al., 2006; Masuda et al., 2005). The TREX complex is highly conserved and is essential for mRNA export. It consists of the THO complex (which is made up of several components; see poster and table) and a set of export factors that include Sub2 (an ATP-dependent DEAD-box RNA helicase), Yra1 and Tex1 in *S. cerevisiae* and UAP56 (also known as HEL) and ALY (also known as REF) in human cells (Masuda et al., 2005; Piruat and Aguilera, 1998; Strasser et al., 2002). In *S. cerevisiae*, the THO complex associates with the nascent mRNA during transcription, and participates in both transcription elongation and mRNA export. Yeast strains that have mutations in the genes that encode any of the four THO-complex members have defects in mRNA export and transcription elongation and show an accumulation of transcripts in foci at or near their sites of transcription (Jimeno et al., 2002; Strasser et al., 2002). Once it is associated with the mRNA, the THO complex then recruits the remaining TREX-complex components (Strasser et al., 2002). Interestingly, in higher eukaryotes, the TREX complex is poorly recruited to transcripts that lack either the 5′ cap or the EJC, indicating that its mechanism of recruitment is linked to splicing and/or capping and not to transcription (Cheng et al., 2006; Zhou et al., 2000).

The final pre-mRNA processing events are 3′-end cleavage and polyadenylation. A polyadenylation site is recognized in the 3′-untranslated region (UTR), resulting in pre-mRNA cleavage immediately downstream. The poly(A) tail is added by a poly(A) polymerase and bound by a poly(A)-binding protein (Proudfoot, 2004). Notably, studies of Sub2 or THO-complex mutants have demonstrated that the 3′ end of genes is a site for the assembly of novel protein-DNA complexes that include NPC components (Rougemaille et al., 2008). This suggests that THO and Sub2 act at a step after 3′-end processing.

## Recruitment of mRNA export factors, nuclear quality control and targeting to the NPC

The trafficking of most cargos that move between the nucleus and the cytoplasm involves karyopherin-mediated receptors, and transport directionality is determined by a gradient of the GTP-bound state of the small GTPase Ran (Madrid and Weis, 2006). In this regard, mRNA export is atypical in that it occurs by a mechanism that is distinct from that of proteins, tRNA or microRNA. Bulk mRNA is exported via the non-karyopherin heterodimer of Nxf1 (metazoan; also known as TAP; Mex67 in *S. cerevisiae*) and Nxt1 (metazoan; also known as p15; Mtr2 in *S. cerevisiae*), and does not rely on the RanGTP gradient (Herold et al., 2000; Segref et al., 1997). The Nxf1-Nxt1 heterodimer is recruited to the mRNP via the TREX component ALY. Early work in *S. cerevisiae* showed that Mex67-Mtr2 and Sub2 bind to the same domain in Yra1. As such, Sub2 could recruit Yra1 to the mRNP and then be displaced by Mex67-Mtr2 (Strasser and Hurt, 2001). Furthermore, recent work in vertebrates shows that the binding of the Yra1 homologue, ALY, to mRNA is stimulated by the presence of the ATP-bound form of the Sub2 homologue UAP56. This binding increases the ATPase activity of UAP56 (Taniguchi and Ohno, 2008). Moreover, Nxf1 binds mRNA-associated ALY, forming a ternary complex, and the RNA-binding affinity of Nxf1 is increased in the presence of ALY. Cells that express an altered form of Nxf1 that binds to ALY but not to mRNA have defective mRNA nuclear export (Hautbergue et al., 2008). Taken together, these data suggest a model whereby ATP-bound UAP56 (*S. cerevisiae* Sub2) recruits ALY (*S. cerevisiae* Yra1) to the mRNP. ATP hydrolysis by UAP56 triggers the transfer of the mRNA to ALY. Next, Nxf1-Nxt1 (*S. cerevisiae* Mex67-Mtr2) binds to ALY, which causes another transfer event and results in an mRNP with bound export receptor. It is unknown how many receptors must bind a single mRNA for efficient export to occur.

Notably, whereas bulk mRNA export occurs via the Nxf1 pathway, a subset of endogenous transcripts is exported via the karyopherin Crm1 (Xpo1 in *S. cerevisiae*). Crm1 also mediates the export of unspliced, or partially spliced, HIV mRNA via a virally encoded adaptor protein, Rev (Cullen, 2003; Fischer et al., 1995). Crm1 is not an RNA-binding protein, and thus must use an adaptor for the export of endogenous mRNAs, as it does for HIV transcripts. Some possible adaptors have been reported, including HuR for the export of *Cd83* and *Fos* mRNAs, and eukaryotic translation initiation factor 4E (eIF4e) for *cyclin D1* mRNA in human cells (Brennan et al., 2000; Culjkovic et al., 2006; Prechtel et al., 2006). However, adaptors for other potential Crm1-exported transcripts have yet to be discovered.

Therefore, correct nuclear processing and recruitment of an export factor targets an mRNA for export from the nucleus. However, if a transcript is not properly processed, it can be recognized by the nuclear surveillance machinery, retained in the nucleus and degraded by the nuclear

exosome. This has been documented in elegant studies of mutants that are defective in mRNA splicing, export and polyadenylation (Brodsky and Silver, 2000; Hilleren et al., 2001; Lei and Silver, 2002; Libri et al., 2002; Zenklusen et al., 2002).

## Docking to and passage through the NPC

Following completion of proper nuclear processing and the recruitment of an export receptor, an mRNP is considered to be export competent. This export-competent mRNP is specifically targeted to the NPC via its export receptor. For some transcribed genes, the positioning of the respective chromatin region near the NPC might facilitate export by physically linking the processes (reviewed by Akhtar and Gasser, 2007). Such a mechanism is described in an early gene-gating model (Blobel, 1985).

The export receptor docks at the NPC by interacting with a discrete class of NPC proteins known as the FG-Nups, which have been thus designated based on the presence of distinct domains containing multiple repeats of the amino acids phenylalanine (F) and glycine (G), separated by characteristic spacer sequences (Alber et al., 2007; Denning et al., 2003). Specific subtypes of FG repeats include FxFG and GLFG (L, leucine). Approximately one third of the 30 proteins that make up the NPC are FG-Nups. These assemble into peripheral substructures on the cytoplasmic and nuclear NPC faces and throughout the NPC central channel (Alber et al., 2007). Both the karyopherin receptors and Nxf1-Nxt1 mRNA export receptor directly bind to the FG repeats in domains that are distinct from their respective cargo or mRNP-binding domains (reviewed by Stewart, 2007). Thus, the export receptor serves to bridge the interaction of the mRNP and the NPC.

Binding of the export receptor to the FG-Nups is required for NPC docking and translocation of the mRNP. Studies of the Balbiani ring mRNP in *Chironomus tentans* showed that the 5′ end of the mRNP docks first to the NPC nuclear face, with extrusion through the NPC proceeding with the 5′ end leading (Visa et al., 1996). Whether this ‘5′ first’ mechanism is utilized by smaller mRNPs is unknown [the Balbiani ring mRNP measures ~50 nm in diameter (Mehlin et al., 1992)]. The binding of transport receptors to the FG-Nups is thought to mediate the movement of the mRNP through the NPC by some type of facilitated diffusion mechanism (Weis, 2007). It is commonly agreed that the FG-Nups themselves do not provide directionality to translocation. Interestingly, however, work has revealed that a specific subset of the FG-Nups is required for Mex67-Mtr2-mediated mRNA export in *S. cerevisiae* (Terry and Wente, 2007). Crucial FG-Nup-binding sites for mRNA export are found on the nucleoplasmic face and in the central channel of the NPC. Moreover, Mex67-Mtr2 apparently utilizes a set of FG-Nups that are distinct from those used by several key karyopherins. Notably, the docking of transcripts that are exported in a Crm1-dependent manner is mediated by the interaction between Crm1 and FG-Nups.

## Release into the cytoplasm and links to translation

The final step of mRNP translocation through the NPC involves directional release into the cytoplasm. Because mRNA export mediated by Nxf1-Nxt1 is not dependent on the RanGTP gradient, an alternative mechanism must determine directionality. Recent work in *S. cerevisiae* provides compelling evidence that the directionality of cytoplasmic release is determined by the function of two conserved, essential mRNA export factors, Dbp5 and Gle1, and soluble inositol hexakisphosphate ($IP_6$) (Alcazar-Roman et al., 2006; Weirich et al., 2006). Dbp5 is an RNA-dependent ATPase of the DEAD-box protein family, and binds to the NPC cytoplasmic face by interacting with the NPC protein Nup214 (also known as CAN; Nup159 in *S. cerevisiae*) (Schmitt et al., 1999; Snay-Hodge et al., 1998; Tseng et al., 1998; Weirich et al., 2004). Gle1 specifically binds to $IP_6$ and docks to a neighboring NPC protein hCG1 (Nup42 in *S. cerevisiae*) (Alcazar-Roman et al., 2006; Kendirgi et al., 2005; Murphy and Wente, 1996; Strahm et al., 1999). As an mRNP reaches the cytoplasmic side of the NPC, it associates with Gle1 and Dbp5. It is possible that Dbp5 is also co-transcriptionally recruited to the mRNP (Zhao et al., 2002). $IP_6$-bound Gle1 stimulates the ATPase activity of Dbp5, thereby converting Dbp5 from an ATP- to ADP-bound state (Tran et al., 2007). It is thought that a conformational change induced by the Dbp5-ATP to Dbp5-ADP switch triggers the removal of a subset of proteins from the mRNP, including the export receptor Mex67 and the poly(A)-binding protein Nab2 (von Moeller et al., 2009). This changes the protein composition of the mRNP (Lund and Guthrie, 2005; Tran and Wente, 2006; Tran et al., 2007). As such, spatially controlled remodeling of the mRNP being exported confers the export directionality with removal of the export receptor. The number of Dbp5 ATP hydrolysis cycles that occur per mRNP transported, and the specificity mechanism for selective remodeling, are unknown. In contrast to mRNA export mediated by Nxt1-Nxf1 (Mex67-Mtr2), the release of Crm1-bound transcripts into the cytoplasm occurs with the hydrolysis of RanGTP.

The proteins that are removed by Dbp5 are recycled via import into the nucleus for another round of mRNA export. In addition, as the mRNP enters the cytoplasm, specific cytoplasmic mRNA-binding proteins are incorporated. Studies of Balbiani ring mRNP export find that the binding of cytoplasmic factors occurs immediately with entry of the 5′ end of the transcript into the cytoplasm; the CBC is replaced with eIF4e, ribosomes bind and translation begins before the entire mRNP has been extruded from the NPC (Daneholt, 2001). Interestingly, Dbp5, Gle1 and $IP_6$ also have roles in translation (Bolger et al., 2008; Gross et al., 2007). Assembly of the termination complex on the mRNA might require Gle1-$IP_6$-dependent stimulation of Dbp5, and Gle1 also has a distinct role in translation initiation. These links to translation further show the inherent connections between steps in gene expression.

## Links to disease and development

Based on the essential roles of mRNA export in proper gene expression, an increasing number of connections to human disease and development are being discovered. Distinct pathophysiological states are correlated with defective mRNA export mechanisms. This includes perturbations resulting from mutations in genes encoding export factors or mRNA-binding proteins, from mutations in genes that cause inhibition of proper export of their own transcripts, and from downregulation or hijacking of the endogenous mRNA export machinery by viruses to allow specific viral gene

expression. Examples of each are discussed below.

Recent work shows that LCCS1, a fetal motor neuron disease, is linked to mutations in human *GLE1* (Nousiainen et al., 2008). The molecular mechanism for the Gle1 defect and the basis for the neuron-specific defects await analysis. In addition, the fragile X mental retardation protein, FMRP, interacts with an Nxf1 homologue, Nxf2, and destabilizes *Nxf1* mRNA in neurons, presumably leading to a decrease in the protein levels of this mRNA export factor (Zhang et al., 2007). Such downregulation of the mRNA export receptor Nxf1 could potentially alter the pool of exported transcripts if Nxf1 and Nxf2 target different subsets of mRNAs, or if the two proteins export some transcripts more efficiently than others. Mutations of genes encoding specific export factors have also been shown to play a role in vertebrate development. Nxf2 is required for cardiac development in zebrafish (Huang et al., 2005), although the precise mechanism for this cardiac-specific phenotype is not fully known. Another disease that is associated with aberrant mRNA export is osteogenesis imperfecta type I (OI) (Hurt and Silver, 2008). In patients with OI, the mutation of one of the two genes encoding collagen, *COL1A1* or *COL1A2*, results in bone fragility. Whereas multiple mutations in the coding region of collagen genes are linked to OI, a specific splice-site mutation in one cohort of patients has been reported to result in defective splicing and nuclear retention of collagen mRNA, thus lowering collagen expression (Johnson et al., 2000; Stover et al., 1993). Taken together, these data support the idea that defects in the mRNA nuclear export pathway can have direct consequences on human health and development.

Nucleocytoplasmic transport and mRNA nuclear export are essential for the proliferation of viruses that depend on nuclear replication (Fontoura et al., 2005; Greber and Fornerod, 2005). This includes DNA tumor viruses, RNA viruses, DNA retroviruses, and RNA retrotransposons, retroviruses and some negative-sense viruses. In regard to viral mRNA export, there are several distinct mechanisms that target the endogenous mRNA export machinery (Cullen, 2003; Fontoura et al., 2005). For example, HIV-encoded mRNA is exported via the karyopherin Crm1 (Cullen, 2003; Fischer et al., 1995; Greber and Fornerod, 2005), but also potentially utilizes the endogenous DEAD-box protein DDX3 for efficient mRNA export (Yedavalli et al., 2004). By contrast, to efficiently export its mRNA, influenza virus expresses the NS1 protein that forms inhibitory complexes with essential export factors, including Nxf1-Nxt1, and blocks the export of endogenous mRNA (Satterly et al., 2007). In this manner, the influenza virus ensures that its transcripts are preferentially exported. More defined and continued analyses of how viruses utilize and target the endogenous mRNA export machinery could potentially yield targets for future drug development.

## Conclusion

Many outstanding questions remain in the field of mRNA nuclear export. It is currently unclear whether the transport of every mRNA occurs via the paradigm outlined above. The precise biochemical determinants of an export-competent mRNP, and whether they are the same for every mRNA, have not been fully defined. Genetic and biochemical studies in *S. cerevisiae* have hinted that there are distinct, differential requirements for export competency that are defined by the presence of different mRNA-associated hnRNPs (Duncan et al., 2000; Guisbert et al., 2005). Another outstanding issue in the field is whether mRNA export depends on the same core set of export factors and occurs in precisely the same manner in every organism, or in every cell type. Although the export factors discussed here are highly conserved, studies of different model organisms have provided potentially conflicting reports of their absolute necessity. For example, Mex67 is essential for mRNA export in the budding yeast *S. cerevisiae* (Segref et al., 1997), but not in the fission yeast *Schizosaccharomyces pombe* (Yoon et al., 2000); Yra1 is essential for export in *S. cerevisiae* (Strasser and Hurt, 2000), but not in *Drosophila* or *Caenorhabditis elegans* (Gatfield and Izaurralde, 2002; Longman et al., 2003). A thorough understanding of mRNA export will require analysis of these species-specific differences. Future studies offer the promise of insights into the mRNA export mechanism that will impact studies of overall gene expression regulation in both normal human development and pathophysiology.

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