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Abstract

The advent of the nucleus during the evolutionary development of the eukaryotic cell necessitated the development of a transport system to convey messenger RNA (mRNA) from the site of transcription in the nucleus to ribosomes in the cytoplasm. In this review, we highlight components of each step in mRNA biogenesis, from transcription to processing, that are coupled with mRNA export from the nucleus. We also review the mechanism by which proteins from one step in the mRNA assembly line are replaced by those required for the next. These ‘molecular wardrobe changes’ appear to be key steps in facilitating the rapid and efficient nuclear export of mRNA transcripts.

Keywords

3′-end processing; export factor adaptor proteins; Mex67/TAP; mRNA; mRNA-binding proteins; mRNA export; mRNA processing

Before messenger RNA (mRNA) transcripts are exported from the nucleus, they must first be extensively processed. Each of these processing events, including addition of a 5′-cap, the splicing out of introns, and 3′-end cleavage and polyadenylation, as well as mRNA export itself, is tightly regulated allowing for plasticity in modulating gene expression (1). Particular aspects of transcription, as well as each of these processing events, are coupled with mRNA export, making the entire process one dynamic assembly line from start to finish. This assembly line can produce thousands of copies of a single transcript constitutively or only several copies of a transcript once during the development of an organism. The complex regulatory system that dictates when and where a gene is expressed is controlled not only by a complicated series of transcriptional regulators but also by an equally elaborate network of RNA-binding proteins that associate with the mRNA transcript during post-transcriptional events (See Table 1 for a summary of factors). These mRNA-binding proteins function in diverse processes ranging from splicing to cytoplasmic RNA localization, but collectively they dictate the fate of each transcript. Like any assembly line, each sequential step constitutes a function that is a necessary prerequisite for the next.

In order for a transcript to leave the transcription ‘assembly line’ in the nucleus and be delivered to ribosomes in the cytoplasm, it must first recruit mRNA export factors. Conventionally, export factors have been defined based on their capacity to bind both the RNA transcript and components of the nuclear pore complex (NPC), and they are, therefore, thought to actively escort mRNA transcripts through the NPC and out of the nucleus. One of the overarching themes in mRNA export is the use of adaptor proteins to recruit these export
factors. Although export receptors can bind directly to mRNA transcripts (2–4), their recruitment to mature export-competent mRNA transcripts is thought to be greatly enhanced when they are recruited via adaptor proteins (5,6). These adaptor proteins are hypothesized to specifically recognize RNA sequences to signal that a particular processing step is complete, and consequently that the transcript is competent for export to the cytoplasm. Many of these proteins function not only as adaptors but also as important components of other processes, such as splicing or 3′-end processing; hence these processes are ‘coupled’ with mRNA export via these adaptor proteins. Although many of the individual proteins involved in mRNA biogenesis are highly conserved from yeast to higher eukaryotes, the particular processes that are coupled with nuclear export are more divergent. In Saccharomyces cerevisiae, the primary mRNA export factor, Mex67 and its heterodimeric partner Mtr2, appears to be recruited through a transcription- and 3′-end processing-dependent mechanism. In higher eukaryotes, however, the recruitment of the Mex67:Mtr2 orthologues, called TAP:p15 (or NXF1:NXT1), to mature mRNA transcripts appears to be dependent upon 5′-cap addition and splicing.

Studies using the budding yeast S. cerevisiae as a model system have provided a valuable initial framework for understanding the process of mRNA export; elegant studies performed in higher eukaryotes have offered further insight. Throughout this review, we will highlight the mechanisms by which eukaryotic cells couple transcription and processing to mRNA export from the nucleus. We also focus on the complex molecular displacements that occur throughout the life cycle of an mRNA transcript and the mechanisms by which these ‘molecular wardrobe changes’ facilitate coupling of transcription and processing to mRNA export.

### Coupling Transcription to mRNA Export from the Nucleus

#### References

During transcription and before mRNA export, adaptor proteins are deposited along nascent transcripts. Recent studies have shown that a multi-protein complex, termed the transcription and export (TREX) complex, is assembled upon the nascent transcript during transcription and is a critical component in determining the efficiency of mRNA export from the nucleus (7–9). Once deposited, components of this complex recruit adaptor proteins to the newly synthesized transcript. The S. cerevisiae TREX complex consists of the mRNA export adaptor proteins, Sub2 and Yra1, and components of the THO complex (Hpr1, Mft1, Thp2 and Tho2) (7–10). Sub2, and its mammalian counterpart UAP56, are putative ATP-dependent helicases that function in splicing and export (11–13). Yra1 (Aly/REF in higher eukaryotes) has also been implicated in pre-mRNA metabolism (14) and mRNA export (5,15). The THO complex components, several of which are conserved in higher eukaryotes, are required for a wide variety of processes including transcriptional elongation (16,17) and genome stability (16).

The S. cerevisiae THO component, Hpr1, is co-transcriptionally recruited to actively transcribed loci (10,18) and directly contacts the mRNA export adaptor protein, Sub2 (18). Furthermore, components of the THO complex can be co-purified with both Yra1 and Sub2 (10), although THO subunits do not directly interact with Yra1, suggesting that the interaction between THO and Yra1 is bridged by Sub2 (18). These data suggest a model (Figure 1A) whereby THO components, specifically Hpr1, are recruited to actively transcribed loci and subsequently recruit Sub2 and Yra1. Yra1 can then serve as an adaptor protein for the primary S. cerevisiae mRNA export factor, Mex67 (5,15). In order for this complicated recruitment scheme to function correctly, the transcript must undergo several ‘molecular wardrobe changes’ to properly recruit and subsequently displace these adaptor proteins. For example, Sub2 and Mex67 both interact with the same domain of Yra1 (10),
suggesting that these interactions with Yra1 are mutually exclusive. This exclusivity is necessary to displace Sub2 from the transcripts when Yra1 recruits Mex67 (Figure 1A). Yra1 directly interacts with Mex67 but does not exit the nucleus (5), suggesting that before Mex67 can escort transcripts through the NPC, Yra1 must first be removed.

Although Sub2 directly interacts with both Hpr1 and Yra1 and likely bridges this interaction (18), additional evidence suggests that both Yra1 and Mex67 can be recruited to mRNA transcripts via alternative mechanisms (Figure 1B) (19). Notably, several studies have shown that the Ubiquitin-associated (UBA) domain of Mex67 interacts with the THO component, Hpr1 (20), suggesting that the THO complex can directly recruit Mex67 to mRNA transcripts independent of Yra1 and Sub2. In addition to THO complex-mediated recruitment, other RNA-binding proteins can also recruit Mex67 to mRNA transcripts. In particular, the RNA-binding protein Npl3 has been implicated in Mex67 recruitment to mRNA transcripts (21). Npl3 is an essential serine–arginine rich (SR) protein that is co-transcriptionally loaded onto nascent transcripts (22,23) and is required for proper nuclear export of poly(A) RNA (24). Interestingly, Npl3 plays roles in both polyadenylation site choice (22,25) and early recruitment of spliceosomal proteins to intron-containing transcripts (23), suggesting that these processes could be coupled with Mex67 recruitment.

In addition to the alternative routes for Mex67 recruitment to mRNA transcripts, Yra1, one of the principle Mex67 adaptors, may itself have additional adaptors beyond the commonly accepted Sub2 helicase. Specifically, inactivation of a component of the 3′-end cleavage machinery, Pcf11, causes an approximately twofold reduction in recruitment of Yra1 to the actively transcribed PMA1 locus without affecting Sub2 recruitment. Yra1 interacts with components of the 3′-end cleavage machinery, including Pcf11 and Rna15 (19).

Furthermore, Pcf11 and other components of the 3′-end processing machinery can be recruited to actively transcribed loci via interaction with the C-terminal domain of RNA polymerase II (26–28). Together, these data suggest a revised model (Figure 1C) in which Yra1 can be recruited to actively transcribed loci in a Sub2-independent manner via an interaction with the 3′-end processing machinery component, Pcf11. Yra1 is then transferred from Pcf11 to the TREX complex via an interaction with Sub2. Yra1, now bound to the mRNA transcript, recruits the mRNA export heterodimer, Mex67:Mtr2, and the mature mRNA can exit the nucleus.

Even though millions of distinct transcripts are constantly transcribed, most current models for mRNA export suggest that one heterodimeric receptor, Mex67:Mtr2 (TAP:p15 or NXF1:NXT1 in higher eukaryotes), transports all transcripts through the NPC into the cytoplasm. These models rely on the initial observation that Mex67:Mtr2 could bind to both RNA and nuclear pore components (2,29). However, recent genome-wide studies raise the possibility that Mex67-dependent export is not the only route for mRNAs to exit the nucleus. One such study showed that Mex67 and Yra1 were bound to 1142 and 1002 transcripts, respectively. Notably, only 349 transcripts were found in common among the pools of transcripts bound to each protein (30). This finding raises several interesting points. First, Mex67 and Yra1 each associated with distinct classes of RNAs (30), suggesting that expression of functionally related RNAs, such as those that encode proteins required for cell wall biosynthesis, can be post-transcriptionally co-ordinated by regulation of these RNA export factors (30). Interestingly, a separate genome-wide study investigating the transcripts associated with the S. cerevisiae RNA-binding proteins, Npl3, Nab2 and Hrp1, showed that these proteins preferentially associate with functionally distinct classes of RNAs (31), providing further evidence that particular RNA-binding proteins associate with specific transcripts. Second, these genome-wide studies indicate that the Yra1 and Mex67-centric mRNA export model may not be applicable for all mRNA transcripts and suggest that other
RNA-binding proteins and protein complexes may actively facilitate mRNA export from the nucleus by interacting with both mRNA transcripts and nucleoporins (Nups).

**Coupling 3′-End Formation and mRNA Export**

Although there are some discrepancies between yeast and higher eukaryotes in 3′-end formation, the overall processes of cleavage and polyadenylation are remarkably conserved [reviewed by (32)]. The initial step in 3′-end formation involves the recognition of specific sequences within the pre-mRNA 3′-untranslated region (3′-UTR) and cleavage of the transcript. Once the transcript has been cleaved, poly(A) polymerase (PAP) adds the 200–250 adenosines (70–90 adenosines in S. cerevisiae) that comprise the poly(A) tail. In both budding yeast and mammalian cells, the poly(A) tail is bound by a complement of poly(A)-binding proteins (Pabs) (33). Although coupling of mRNA export and 3′-end processing is somewhat controversial in metazoans, in S. cerevisiae 3′-end processing has been more directly implicated in mRNA export from the nucleus. Notably, mutations within several yeast 3′-end processing factors, including Rna14, Rna15, Pcf11 and Pap1 cause accumulation of bulk poly(A) RNA in the nucleus (34–36). In addition, mutations in numerous S. cerevisiae mRNA export factors, including Mex67, Yra1, and the cytoplasmic NPC-associated helicase Dbp5 (see below), cause hyperpolyadenylation of transcripts (34,37). Components of the 3′-end processing machinery also genetically interact with mRNA export factors (38,39).

Several studies in S. cerevisiae have investigated the link between 3′-end processing and mRNA export using reporter transcripts truncated by a hammerhead ribozyme rather than processed by the normal 3′-cleavage and polyadenylation machinery (40,41). Hammerhead ribozymes are self-cleaving RNA sequences, which were originally isolated from plant viruses (42). RNA transcripts synthesized by RNA polymerase II that contain a ribozyme sequence in lieu of a standard 3′-UTR are not polyadenylated efficiently and are also not efficiently exported from the nucleus (40). Export of these ribozyme truncated reporter RNAs is not entirely blocked, however, as deletion of the gene encoding the cytoplasmic riboexonuclease, XRN1, results in an increase in cytoplasmic reporter RNA, suggesting that a fraction of these reporter transcripts exits the nucleus but is rapidly degraded because of the absence of a poly(A) tail (40). Interestingly, export of these reporters is rescued by an encoded stretch of adenosines immediately upstream of the self-cleaving ribozyme sequence that mimics a poly(A) tail. This result suggests that although the presence of a poly(A) tail helps facilitate mRNA export from the nucleus, the poly(A) tail is not an absolute requirement. Indeed, TRP4 transcripts terminated at their 3′-ends by a hammerhead ribozyme can partially complement a trp4 deletion mutant, indicating that a fraction of these non-polyadenylated transcripts can exit the nucleus and be translated (43). Whether these ribozyme-terminated transcripts are exported by Mex67 and the canonical mRNA export machinery or by components of another RNA export pathway remains unclear.

Although 3′-end formation appears to be coupled with mRNA export from the nucleus in S. cerevisiae(34,37,39,40), little information exists as to the actual physical link between components of the 3′-end processing machinery and mRNA export factors. One candidate class of proteins consists of the Pabs. Pabs are conserved from yeast to higher eukaryotes and are important in the regulation of transcript polyadenylation, stability, translation and nuclear export (44). The most well-characterized S. cerevisiae Pab, Pab1, localizes to the cytoplasm at steady state and regulates both translation and mRNA stability (44). In addition, Pab1 shuttles into the nucleus (45,46) and regulates poly(A) tail length (47,48). This collection of observations, along with the fact that mutations within Pab1 only show limited effects on poly(A) RNA export (46), suggests that although Pab1 may enter the nucleus, its principle role is likely in the cytoplasm and not in coupling mRNA 3′-end
formation to nuclear export. More likely candidate proteins that couple 3′-end processing and mRNA export are nuclear Pabs, such as S. pombe Pab2 [PABN1 in higher eukaryotes (44)] or S. cerevisiae Nab2 [ZC3H14 in higher eukaryotes (49)]. Although Pab2 and its orthologue PABN1 bind specifically to polyadenosine RNA and modulate polyadenylation (50,51), neither protein has been linked to mRNA export from the nucleus. A more likely candidate Pab that couples mRNA 3′-end processing to nuclear export may be Nab2, which binds specifically to polyadenosine RNA in vitro (49,52,53) and also regulates poly(A) tail length (53,54). Nab2 mutants also show nuclear accumulation of bulk poly(A) RNA (53,55) and genetically interact with both Mex67 (39,56) and Yra1 (57). Therefore, Nab2 could function as a factor involved in 3′-end formation that serves as an adaptor for Mex67 recruitment to export-competent transcripts.

**Coupling Splicing and mRNA Export from the Nucleus**

**References**

Although both yeast and higher eukaryotes use a conserved set of factors to facilitate the nuclear export of mRNA transcripts, the mechanisms that recruit these factors are somewhat divergent. In higher eukaryotes, where most transcripts are subject to splicing, mRNA export receptors seem to be recruited to the 5′-end of transcripts in a splicing-dependent manner.

The human TREX (hTREX) complex contains the adaptor proteins UAP56 and Aly/REF, orthologues of budding yeast Sub2 and Yra1, respectively, as well as the human THO complex members, hHpr1, hTho2, Thoc5/fSAP79, Thoc6/fSAP35 and Thoc7/fSAP24 (58). Unlike their S. cerevisiae counterparts, hTREX constituents (including UAP56, Aly/REF and THO members) have not been directly linked to transcription but instead have more directly been linked to the addition of the 5′-7-methyl guanosine cap and the splicing out of introns (58–61). Early studies suggested that hTREX recruitment may be coupled with splicing because UAP56 co-purified with spliceosomal proteins, specifically U2AF65 (62,63), and Aly/REF associates with the exon junction complex (EJC), a multi-protein complex deposited 20–24 nucleotides upstream of exon–exon junctions (64). hTREX components also preferentially associate with mRNA transcripts that have undergone splicing rather than artificial transcripts manufactured from complementary DNA (cDNA) constructs (60). Furthermore, Aly and Thoc5 colocalize with nuclear speckles, which are subnuclear domains thought to store processing factors and components of the spliceosome (58,61,65). Together, these results suggested that hTREX is associated with spliceosomes and potentially is recruited as a part of the EJC.

Interestingly, more recent studies have shed some doubt on the idea that TREX is recruited to nascent transcripts as part of the spliceosome or the EJC in higher eukaryotes. In particular, both hTREX and Aly are recruited to the 5′-end of mRNA transcripts (58,60). Several hTREX components, including Aly, UAP56 and hTho2, interact with the cap-binding complex, which specifically recognizes the 7-methyl guanosine cap on the 5′-end of mRNA transcripts (60,66). In addition, recruitment of Aly and a component of the hTHO complex, hTho2, to decapped reporter transcripts is dramatically decreased compared with properly capped transcripts (60). Moreover, eIF4A3, a component of the EJC, is recruited to capped and decapped transcripts equally well (60), suggesting that TREX recruitment is dependent upon the 5′-cap, whereas recruitment of the EJC is not. As the addition of a 5′-cap dramatically increases the efficiency of nuclear export of spliced transcripts (60), recruitment of hTREX, and thus mRNA export receptors, is highly likely to be dependent upon both capping and splicing.
Translocation Through the NPC

Once an mRNA transcript has been properly processed, packaged and has recruited the correct export receptors, the resulting mRNA ribonucleoprotein (mRNP) complex is translocated through NPCs to the cytoplasm. The NPC consists of several classes of Nups, including structural Nups and Nups-containing domains rich with phenylalanine–glycine (FG) repeats. FG-Nups line the interior cavity of the NPC and allow for regulated macromolecular transport in and out of the nucleus (67). Multiple hypotheses exist (68) as to the exact mechanism by which nuclear pores maintain cargo selectivity while still retaining the capacity to transport cargoes efficiently and rapidly. Generally, these FG repeats are thought to extend into the central cavity of the NPC and form multiple low affinity interactions with soluble transport factors, such as Mex67/TAP (2,29,67), as they transit the NPC. Interestingly, recent work has shown that different transport receptors (i.e. mRNA export versus different pathways for protein import) may require different subsets of FG-Nups (3,67,69), suggesting that different transport receptors may take different routes through NPCs.

A Molecular Wardrobe Change Completes Nuclear Export

Throughout the assembly line of mRNA processing that culminates in export from the nucleus, a multitude of different proteins associate with the mRNA transcript (Figure 2). Initially, mRNA processing proteins are recruited to the nascent transcript during transcription via interactions with the C-terminal domain of RNA polymerase II. Many of these processing factors are displaced following completion of processing or before export from the nucleus. Export factors then recognize the mature transcripts and convey them through the NPC to the cytoplasm. The export factors are subsequently displaced and factors that regulate the cytoplasmic destiny of the transcript bind. These cycles of protein displacement occur continually throughout the life cycle of an mRNA transcript and help functionally co-ordinate mRNA biogenesis. One of the best-characterized examples of this cycle of molecular displacement occurs immediately following translocation of the mRNP through the NPC. Upon reaching the cytoplasmic side of the NPC, the mRNP must undergo a significant remodeling event to replace nuclear export factors with a new complement of proteins that regulate the cytoplasmic fate of the transcript. For example, in S. cerevisiae the nuclear Pab, Nab2, is not detected in polyribosomes (70) in the cytoplasm, suggesting that it most likely is removed and replaced by Pab1, the principle cytoplasmic Pabs important for mRNA stability and translation efficacy (44).

One component of the machinery in S. cerevisiae responsible for mRNP reorganization upon entry into the cytoplasm is the RNA helicase, Dbp5 (71). Dbp5 (also known as Rat8) is conserved from yeast to higher eukaryotes (71,72) and belongs to the family of DEAD-box RNA helicases, which unwind short stretches of double-stranded RNA or remodel RNA–protein interactions (73). Early work showed that Dbp5 is localized to the cytoplasmic fibrils of the NPC at steady state (72) and is required for proper nuclear export of poly(A) RNA (71), hinting at a role for Dbp5 in the terminal stages of poly(A) RNA export as mRNPs exit the NPC. More recent studies have corroborated that idea and provided new insight into the role of Dbp5 in poly(A) RNA export. During the final stage of nuclear export, Dbp5 contacts its activator, the NPC-associated Gle1, as well as the small coactivator molecule, inositol hexakisphosphate (InsP6) (72,74), leading to activation of Dbp5 at the cytoplasmic face of the NPC. Once activated, Dbp5 facilitates the removal of mRNA export factors, including Nab2 and Mex67 (74,75). Whether it is Dbp5 removing proteins from transcripts as they exit the NPC or other RNA helicases remodeling complexes during the splicing out of introns or other processing events (73), a collection of RNA helicases play critical roles in remodeling mRNP complexes throughout mRNA biogenesis. Future studies investigating the specificity and activity of each of these helicases will provide necessary insight into the
mechanisms by which ‘molecular wardrobe changes’ couple various steps of mRNA biogenesis.

Concluding Remarks

Along the mRNA assembly line from transcription in the nucleus to translation in the cytoplasm, several important unanswered questions remain. Key among these questions is the principle molecular function of many of the proteins involved in mRNA export. Although numerous proteins have been implicated in mRNA export, these implications are primarily because of the fact that disruption of gene product function results in the nuclear accumulation of poly(A) RNA and not because their role in mRNA export is defined. Many of these proteins may play specific roles during mRNA biogenesis beyond acting as mere adaptors for mRNA export receptors. For example, Yra1, a principle adaptor for Mex67, has RNA-annealing activity (14), and its higher eukaryotic orthologue, Aly/REF, has been found associated with the EJC (64), but beyond acting as an adaptor for Mex67, no precise molecular function of Yra1 in mRNA processing has yet been described. Future studies investigating the cellular function of Yra1 and other similar RNA-binding proteins may give critical insight into the mechanisms by which processing events in the mRNA assembly line are coupled with mRNA export.

Another question that has yet to be addressed is the mechanism by which the cell distinguishes those transcripts that are competent for export from those that are not. Several quality control mechanisms exist within the cell to degrade faulty transcripts (76). Instead of examining the sequence of the mRNA transcript itself, these quality control systems presumably detect marker proteins deposited upon the transcript following processing. Like shipping labels on newly manufactured products, these markers would be scanned by the quality control machinery as the transcripts roll off the RNA assembly line. Future studies investigating the identity of these markers will provide insight into yet another level of post-transcriptional regulation of gene expression.

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Figure 1.
Schematics illustrating possible mechanisms for recruitment of the S. cerevisiae mRNA export receptor, Mex67, to mRNA transcripts are shown. A) ‘Classical’ model of Mex67 recruitment. The principle mRNA export heterodimer, Mex67:Mtr2, is recruited via direct interactions with Yra1 in a Sub2- and THO complex-dependent manner. THO complex members are initially deposited upon nascent transcripts via interactions with the C-terminal domain (CTD) of RNA polymerase II (RNA Pol II). Following THO deposition, Sub2 and Yra1 are recruited to the transcript. Finally, the heterodimeric complex of Mex67:Mtr2 is recruited via interactions between Yra1 and Mex67. Binding of Mex67 to Yra1 displaces Sub2. B) Sub2/Yra1-independent recruitment of Mex67. The heterodimeric export receptor,
Mex67:Mtr2, can also be recruited to mRNA transcripts via direct interactions with both components of the THO complex, Hpr1, and the RNA-binding protein, Npl3. C) Revised ‘classical’ model of Mex67 recruitment. Mex67:Mtr2 is recruited to mRNA transcripts via interactions with 3′-end processing components. Although initial studies (5,15) showed that Yra1 was recruited to transcripts directly via THO components and Sub2, more recent data suggest a revised model where Yra1 is initially recruited to the mRNA transcript via interactions with the 3′-end processing factor, Pcf11 (19) and subsequently transferred to the TREX complex via an interaction with Sub2. Yra1 then recruits Mex67 and transcripts are exported.
Figure 2.
A timeline for the molecular displacements that occur in the course of mRNA export. In S. cerevisiae, adaptor proteins responsible for the recruitment of mRNA export receptors are deposited upon transcripts (denoted by black curved lines above the large directional arrow) during transcription and processing, coupling these processes to mRNA export. During transcription, components of the THO complex are initially deposited on the nascent transcript. Other processing factors and RNA-binding proteins, such as Hrp1, Npl3, Sub2, Yra1 and Nab2 are subsequently recruited to the maturing transcript through a combination of interactions with THO components, the C-terminal domain of RNA polymerase II, and other mechanisms. The principle yeast mRNA export receptor heterodimer, Mex67:Mtr2, is subsequently recruited via interactions with adaptor proteins. Recruitment of Mex67:Mtr2 displaces Sub2 (denoted by black curved lines below the large directional arrow), eventually Yra1 is also displaced from the mRNA transcript, and the mRNA exits the nucleus through the nuclear pore complex. Once in the cytoplasm, the Dbp5 helicase remodels the mRNA, displacing export factors, such as Mex67 and Nab2, and subsequently allowing translation factors to bind to the transcript. As both Npl3 and Hrp1 associate with polyribosomes, the mechanism by which these proteins dissociate from the transcript is unclear (represented by white dashed lines below the large directional arrow). The mechanism and compartment of THO displacement also remains unclear, as the hTHO components shuttle between the nucleus and the cytoplasm, but shuttling of S. cerevisiae THO components has not been reported.
### Table 1

Protein factors implicated in mRNA export from the nucleus.

<table>
<thead>
<tr>
<th><strong>S. cerevisiae</strong> protein</th>
<th><strong>Higher eukaryotic orthologue</strong></th>
<th><strong>RNA accumulation in nucleus?</strong>&lt;sup&gt;a&lt;/sup&gt;</th>
<th><strong>Function in mRNA export functions</strong></th>
<th><strong>Other described</strong></th>
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<td><strong>hHpr1</strong></td>
<td>Poly(A) and heat shock RNA</td>
<td>Component of yeast/human TREX and direct recruiter of Mex67 (yHpr1)</td>
<td>Transcriptional Elongation (yTREX), Genome Stability (yHpr1)</td>
<td>(7,8,18,10)</td>
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<td><strong>hTho2</strong></td>
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<td><strong>TAP:p15/Nxf1: Nxt1</strong></td>
<td>Poly(A) and heat shock RNA</td>
<td>Primary mRNA export factor; contacts mRNA (directly and via adaptors) and nucleoporins</td>
<td>Nuclear export of 60s ribosomes</td>
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<td>mRNA 3′-end formation</td>
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<tr>
<td><strong>Npl3</strong></td>
<td></td>
<td>Poly(A) RNA only&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Mex67 adaptor protein</td>
<td>mRNA 3′-end cleavage and polyadenylation site selection, promotes pre-mRNA splicing</td>
<td>(21±25)</td>
</tr>
<tr>
<td><strong>Dbp5/Rat8</strong></td>
<td><strong>hDbp5/DDX19</strong></td>
<td>Poly(A) and heat shock RNA</td>
<td>mRNA remodeling in the cytoplasm following nuclear export</td>
<td>Interacts with transcription and translation-termination factors</td>
<td>(72,74,75,87)</td>
</tr>
</tbody>
</table>

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<sup>a</sup>In either yeast cells expressing mutant proteins or higher eukaryotic cells depleted for the specified factor, does poly(A) or heat shock RNA accumulate in the nucleus as detected by fluorescence in situ hybridization (FISH)?

<sup>b</sup>N/A: information on RNA accumulation is, to the best of our knowledge, not available.

<sup>c</sup>As specified, either poly(A) RNA or heat shock RNA accumulates in the nucleus, but not both.

<sup>d</sup>Mutants accumulate poly(A) RNA but, to the best of our knowledge, nuclear accumulation of heat shock RNA has not been tested.
<table>
<thead>
<tr>
<th>S. cerevisiae protein</th>
<th>Higher eukaryotic orthologue</th>
<th>RNA accumulation in nucleus?a</th>
<th>Function in mRNA export functions</th>
<th>Other described</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gle1</td>
<td>hGle1</td>
<td>Poly(A) and heat shock RNA</td>
<td>Activator of Dbp5 (in combination with hNup214/ yNup159)</td>
<td>Regulation of translation</td>
<td>(88–93)</td>
</tr>
<tr>
<td>Thp1</td>
<td>—</td>
<td>Poly(A) and heat shock RNA</td>
<td>Component of yTREX2 complex involved in nuclear export of mRNA</td>
<td>Regulation of genomic integrity</td>
<td>(78,94–97)</td>
</tr>
<tr>
<td>Sac3</td>
<td>GANP/Shd1</td>
<td>Poly(A) and heat shock RNA</td>
<td>Component of yTREX2 complex involved in nuclear export of mRNA</td>
<td>Regulation of genomic integrity</td>
<td>(78,95–98)</td>
</tr>
<tr>
<td>Sus1</td>
<td>DC6/Eny2</td>
<td>Poly(A) RNA/d</td>
<td>Component of yTREX2 complex involved in nuclear export of mRNA, possible ‘bridge’ protein between transcription and mRNA export</td>
<td>Component of SAGA histone modification complex, regulation of genomic integrity</td>
<td>(95,98–100)</td>
</tr>
<tr>
<td>Cdc31</td>
<td>CETN3</td>
<td>Poly(A) RNA/d</td>
<td>Component of yTREX2 complex involved in nuclear export of mRNA</td>
<td>Duplication of microtubule-organizing centers</td>
<td>(95,96,98, 101,102)</td>
</tr>
</tbody>
</table>