Biochimica et Biophysica Acta 1819 (2012) 507–513

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagrm

Review

mRNA export and the TREX complex ☆

Jun Katahira *

Biomolecular Networks Laboratories, Graduate School of Frontier Biosciences, Osaka University, 1-3 Yamadaoka, Suita, Osaka 565-0871, Japan
Department of Biochemistry, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

ARTICLE INFO

Article history:
Received 4 October 2011
Received in revised form 29 November 2011
Accepted 1 December 2011
Available online 8 December 2011

Keywords:
Nucleo-cytoplasmic transport
TREX complex
Transcription
mRNA 3′-end formation
Gene expression

ABSTRACT

Over the past few decades, we have learned that eukaryotes have evolved sophisticated means to coordinate the nuclear export of mRNAs with different steps of gene expression. This functional orchestration is important for the maintenance of the efficiency and fidelity of gene expression processes. The TREX (TRanscription-EXport) complex is an evolutionarily conserved multiprotein complex that plays a major role in the functional coupling of different steps during mRNA biogenesis, including mRNA transcription, processing, decay, and nuclear export. Furthermore, recent gene knockout studies in mice have revealed that the metazoan TREX complex is required for cell differentiation and development, likely because this complex regulates the expression of key genes. These newly identified roles for the TREX complex suggest the existence of a relationship between mRNA nuclear biogenesis and more complex cellular processes. This review describes the functional roles of the TREX complex in gene expression and the nuclear export of mRNAs. This article is part of a Special Issue entitled: Nuclear Transport and RNA Processing.

1. Introduction

One of the most prominent features of eukaryotic organisms is the physical and functional compartmentalization of the cells into organelles that serve as the sites of different cellular activities. The efficient and accurate targeting of various functional macromolecules to the correct cellular compartments is crucial for sustaining cellular activities, including growth, development, and differentiation. The cell nucleus, where genetic information is stored in the form of chromosomal DNA, is the cellular compartment in which DNA repli-

tein translation occurs exclusively in the cytoplasm. The nuclear envelope, a double membrane that surrounds the nucleus, separates these different activities. Thus, the mRNAs harboring the genetic information must be transported into the cytoplasm for decoding by the translational machinery (Fig. 1). In addition, some proteins that have been translated in the cytoplasm must be imported into the nucleus by active and selective mechanisms.

2. The mechanism of mRNA nuclear export: an overview

Nuclear pore complexes (NPCs) are the passages through which molecules are trafficked between the nucleus and the cytoplasm. NPCs also function as molecular sieves that limit the free and unnecessary exchange of soluble macromolecules, including RNAs and proteins, between the two compartments. Most of the RNAs and proteins that have been investigated to date pass through the NPCs by selective and active mechanisms and require transport receptors to overcome this barrier [1,2]. The majority of cellular RNAs, such as tRNAs, miRNAs, and UsnRNAs, require importin/karyopherin-β-type transport receptors for nuclear export. In contrast, the nuclear export of mRNAs does not directly rely on importin/karyopherin-β type transport receptors; instead, these molecules are exported by a distinct

…15 (also called …*charomyces cerevisiae* [3–7]. The nuclear accumulation of bulk poly(A)$^+$ RNAs was observed when these transport receptors were downregulated [8–10]. Therefore, it is likely that the vast majority of cellular mRNAs require Tap–p15/Mex67–Mtr2 for nuclear export, although some minor exceptions have been reported in metazoans [11]. In addition, human Tap–p15 was able to functionally complement the lack of Mex67–Mtr2, rescuing the lethality of the *mex67–mtr2* double-knockout strain [12]. Thus, the mechanism of mRNA export at this stage is evolutionarily conserved between yeast and metazoan species.

In receptor-mediated active transport processes, transport receptors recognize specific cargo molecules through interactions with signals encoded in each transported cargo molecule. For example, the T-loop of tRNAs is directly recognized by the importin/karyopherin-β type transport receptor Exportin-t. Similarly, the short double-stranded stem and the 2- to 3-nucleotide single-stranded 3′-overhang of pre-microRNAs are recognized by Exportin-5 [13–17]. In contrast to these small RNAs, mRNAs are highly divergent in size, sequence, and

☆ This article is part of a Special Issue entitled: Nuclear Transport and RNA Processing.

* Tel.: +81 6 6879 4606; fax: +81 6 6879 4609.
E-mail address: katahira@anat3.med.osaka-u.ac.jp.

1874-9399
doi:10.1016/j.bbagrm.2011.12.001

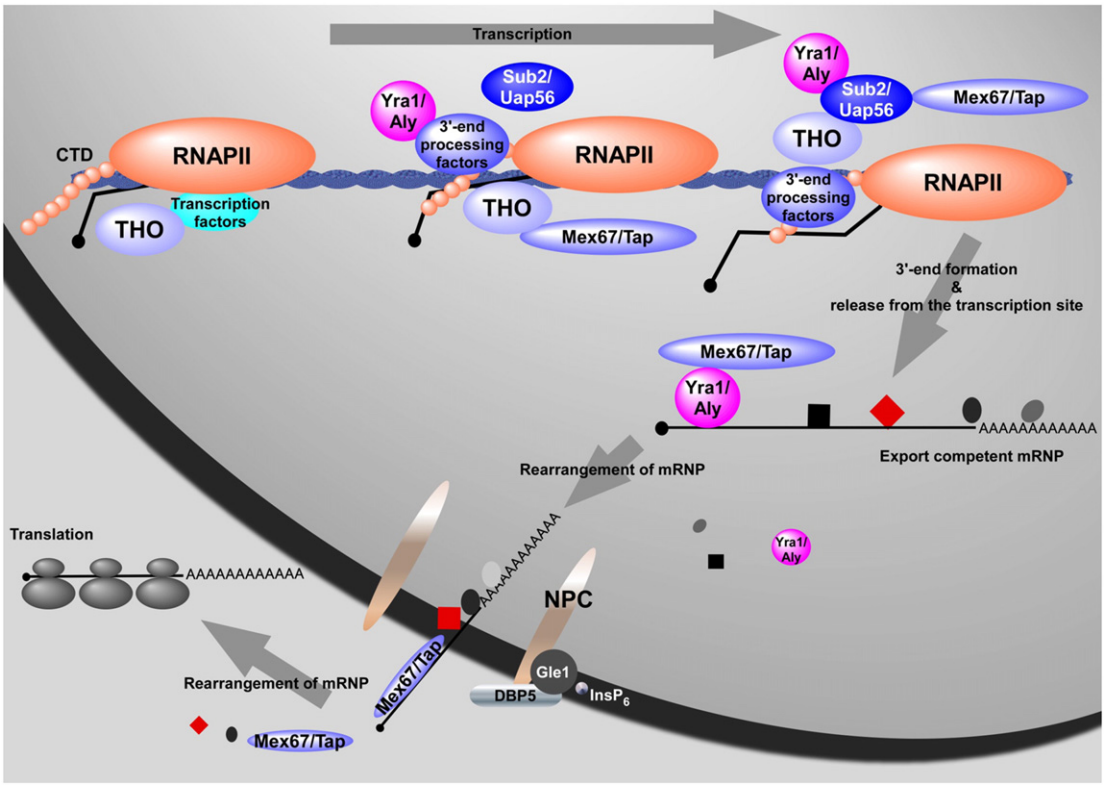

Fig. 1. The nuclear export of mRNAs. During transcription, various factors that are required for pre-mRNA processing and nuclear export are loaded onto the nascent transcript. The THO complex associates with the transcribing RNA polymerase II (RNAPII) through various interactions with transcription factors, such as the yeast Syf1 protein, and travels along the entire transcribed region. The carboxyl-terminal domain (CTD) of RNAPII also plays a major role in the recruitment and deposition of various molecules, including the 3′-end processing/transcription termination factors. It is proposed that the DEAD-box-type RNA helicase Sub2 (Uap56 in metazoan) and the adaptor mRNA binding protein Yra1 (Aly in metazoans) associate at the 3′-end of the gene, forming the active TREX complex. Interactions with the 3′-end processing factor Pcf11, which exhibits CTD binding activity, plays a pivotal role in the recruitment of the latter two factors (see also Fig. 2). In yeast, the heterodimeric mRNA export receptor Mex67–Mtr2 is also recruited to the proximity of the transcribed locus through an interaction with ubiquitylated Hpr1, an evolutionarily conserved component of the THO complex. The adaptor mRNA binding proteins are transferred to mRNAs by the activity of the DEAD-box type RNA helicases Sub2 and Uap56. The Mex67–Mtr2 (Tap–p15 in metazoans) heterodimer indirectly recognizes cargo mRNAs through its interaction with the adaptor Yra1 (Aly in metazoans), resulting in the formation of export competent mRNA-protein complexes (mRNPs). During or after release from the gene locus, the mRNPs undergo further rearrangements that include the "hand-over" of the mRNAs from the adaptors to the mRNA export receptors. In yeast, these steps take place in close proximity to both the gene locus and the NPCs due to the gene-NPC interactions [3,6,7]. Finally, the bound mRNAs translocate through the NPCs and are translated in the cytoplasm. Yeast Gle1, Dbp5, Nup159 (not shown), and the small molecule inositol hexakisphosphate ($InsP_6$) function at the last step of the nuclear export of mRNAs. Gray and black ovals, a black square, and a red diamond indicate the various mRNA binding proteins that associate with or dissociate from mRNPs during mRNA processing.

structure. Thus, mRNA export receptors must adopt different strategies to recognize mRNAs as their proper cargoes. Although both Tap–p15 and Mex67–Mtr2 are able to interact directly with RNA *in vitro*, they exploit other mRNA binding proteins as "adaptors" *in vivo*; these adaptors become associated with mRNAs in various ways during mRNA biogenesis (see below).

The transport receptor facilitates the passage of bound mRNAs through their direct interactions with nucleoporins, which contain phenylalanine–glycine (FG-) repeat sequences and occupy the inside of NPCs [18–21]. During or soon after translocation into the cytoplasm, mRNAs change their structures drastically, releasing the transport receptors (see Bjork and Wieslander [22] for a recent review). Eventually, these RNAs serve as templates for protein translation. Recent reports indicate that the mRNA export protein Gle1, the cytoplasmically localized nucleoporin Nup159, the RNA helicase Dbp5, and the small molecule inositol hexakisphosphate ($InsP_6$) play pivotal roles in this final step of mRNA export in yeast [23,24] (Fig. 1). Whether this mechanism is also conserved in higher eukaryotes has not yet been determined.

3. The TREX complex is required for various nuclear activities

Although the individual steps of mRNA biogenesis, such as transcription, capping, splicing, and cleavage/3′-end formation, can be reconstituted as separate reactions *in vitro*, they proceed interdependently *in vivo*. The failure of any one of these steps during mRNA biogenesis impedes the progression of the other steps. This interdependence is important for rapid responses to different stimuli and for maintaining the fidelity of gene expression by blocking the expression of faulty mRNAs [6,25–30]. The nuclear export step is no exception and is fully integrated with other steps in the process of mRNA biogenesis (Fig. 1). The "TREX" (TRanscription-EXport) complex, an evolutionarily conserved multiprotein complex, lies at the center of such functional couplings [3,31–35]. As the name implies, the TREX complex consists of factors involved in both the transcription and the nuclear export of mRNAs (see Table 1). During transcription elongation, the TREX complex travels with the RNA polymerase II (RNAP II) transcriptional machinery along the transcribed gene and interacts with various factors. Then, the TREX complex facilitates the loading of the associated factors onto the mRNA and the packaging of the functional mRNA–protein complexes (mRNPs) for nuclear export [36–38] (Fig. 1). A defect in mRNA export is the most prominent phenotype of yeast *tho/trex* mutants [36]. However, these mutants also exhibit a variety of other phenotypes, including defects in mRNA 3′-end formation and genome instability, due to the multiple interactions of TREX components with different factors (see below).

The dynamics of the TREX components on active genes have been examined in yeast using chromatin immunoprecipitation (ChIP) assays [36,39–41]. Consistent with the observation that bulk poly(A)$^+$ RNA accumulation occurs in yeast *tho/trex* mutants, a recent genome-wide ChIP-chip analysis revealed that the yeast TREX components were bound to virtually all actively transcribed genes [42]. The yeast TREX complex shows an apparent localization bias toward

the 3′-ends of genes [36,39–41], yet it does not associate with chromatin downstream of the polyadenylation site [40–42]. These observations imply that the loading of the TREX complex is coupled to transcriptional elongation and/or 3′-end processing (see the next section) and that the TREX complex is released from the template DNA along with the mature mRNA. Consistent with this model, the components of the yeast TREX complex exhibit both physical and genetic interactions with mRNA cleavage/polyadenylation factors [43–46]. Defects in correct 3′-end formation and in the release of mature mRNA from the transcription site [45,47,48], both of which resemble the phenotypes of cleavage/polyadenylation factor mutants [49–52], are observed in *tho*/*trex* mutants. Moreover, the release of the polyadenylation factors from the mRNA is impeded in *tho*/*trex* mutants [53]. It has also been reported that the depletion of THO components in *Drosophila* cells resulted in the impairment of 3′-end formation in *hsp70* mRNA [54].

Incorrectly packaged mRNPs in the nuclei of the *tho*/*trex* mutants form "heavy chromatin" in which the defective mRNPs are confined together with the DNA, 3′-end processing factors, and nucleoporins [55]. The aberrant mRNPs are eventually subjected to quality control by a nuclear surveillance mechanism [45]. The yeast THO complex is known to be required for the efficient transcriptional elongation of genes; notably, the expression of long and GC-rich or repeat-containing genes is particularly affected in the *tho*/*trex* mutants [56,57]. It has been suggested that the heavy chromatin formed at the 3′-ends of genes in *tho*/*trex* mutants may physically collide with the elongating RNAP II. Thus, the heavy chromatin might act as a molecular roadblock, impairing efficient transcriptional elongation beyond the polyadenylation site [55,58]. In addition, an unusual hybridization between nascent transcripts and the non-template strand of DNA, resulting in structures called R-loops, occurs in yeast *tho*/*trex* mutants [59,60]. By inhibiting the formation of R-loops, the THO complex prevents hyper-recombination [61], thus linking transcription to genome stability. A recent study indicated that R-loops can be obstacles for transcriptional elongation and other nuclear activities, including DNA replication [42].

4. The loading of the TREX complex onto active genes: coupling to different steps in gene expression

The recruitment of the TREX complex to cargo mRNAs is linked to different steps in gene expression, and the molecular mechanisms of this recruitment are now being uncovered. The loading of the TREX complex seems to be divided into at least two consecutive steps. Initially, the THO complex recruits other components to assemble the "active" TREX complex at the activated gene loci. This initial assembly could be facilitated by the concentration of the necessary components through various interactions with the RNAP II transcriptional machinery (. 1). In fact, earlier studies indicated that the loading of the yeast THO/TREX complex is coupled with transcriptional elongation [36,43]. Subsequently, Yra1–Sub2 or Aly–Uap56 is transferred to the cargo mRNA [39,62] for recognition by the mRNA export receptor. Because the majority of protein-coding genes in yeast do not harbor introns, it is thought that the yeast TREX components are recruited to active genes by splicing-independent mechanisms [37,39,63]. In contrast, splicing-dependent mechanisms are thought to dominate in metazoan species, whose protein-coding genes often contain multiple introns [63,64]. However, several studies have indicated that splicing-independent mechanisms also seem to operate in higher eukaryotes [65,66].

Yeast Pcf11, an RNAP II CTD-binding subunit of the CF1A cleavage factor (Table 2), participates in the recruitment of Yra1 to the THO complex through a physical interaction [46]. Interestingly, the same interaction domain mediates the binding of Yra1 to either Sub2 or Pcf11. Therefore, the Pcf11–Yra1 and Sub2–Yra1 complexes are formed in a mutually exclusive manner. These observations led Johnson et al. [46] to propose a model in which the formation of the active cleavage/polyadenylation complex (*i.e.*, the release of Yra1 and the formation of CF1A) and the nuclear export complex (*i.e.*, the formation of the Sub2–Yra1 complex) are synchronized. Thus, the efficient assembly of the active TREX complex is linked to the formation of the 3′-end of the mRNA (Fig. 2).

The Syf1 component of the Prp19 complex, which plays an essential role in splicing [67], was recently found to be a THO-interacting factor (Table 2). Mutant yeast strains harboring a specific allele of the *SYF1* gene show defects in RNAP II processivity that do not affect splicing efficiency [68]. The tetratrico peptide repeat (TPR) motifs in the C-terminal region, which are deleted in the *syf1* mutant, are required for the recruitment of the entire Prp19 complex to the elongating RNAP II. Notably, the occupancy of the TREX complex on active genes is also reduced in the *syf1* mutant. Thus, because it mediates the interaction with the elongating RNAP II, Syf1 is required for the recruitment of the TREX complex to active genes in a transcription-coupled manner [68]. It is noteworthy, however, that the crosslinking of the TREX complex to the 5′-regions of several genes occurred even in the strain harboring the *syf1* mutation. Therefore, other mechanisms that bypass the requirement for the Prp19 complex may participate in the recruitment of the TREX complex to the 5′-regions of active genes.

Drosophila melanogaster ENY2, the yeast Sus1 orthologue, has been shown to co-purify with the TREX complex. Like yeast Sus1, ENY2 is a component of the TREX-2 complex (called AMEX in *D. melanogaster*) and the SAGA/TFTC histone acetylation complex [69] (Table 2). Gene knockdown experiments, however, indicated that the THO–ENY2 complex functions independently of SAGA and AMEX [54]. *Drosophila* THO and ENY2 are recruited to activated genes, including *hsp70*, which is a well-characterized metazoan target of the TREX complex [66,70]. Interestingly, the knockdown of ENY2 reduced the recruitment of the THO complex to the activated *hsp70* locus. Because the *Drosophila hsp70* gene is intron-less, THO recruitment through ENY2 may be coupled with transcription. However, neither ENY2 nor the THO stably associate with the RNAP II transcription machinery [54]. Therefore, the mechanisms by which ENY2 recruits the TREX complex to activated genes remain elusive.

Mammalian Aly has been shown to be transferred to mature mRNAs through an interaction with Iws1 (Table 2), which is tethered to elongating RNAPII via the histone chaperone Spt6 [71]. A yeast *spt6* mutant also has a poly(A)$^+$ RNA export defect and the *SPT6* gene exhibits a genetic interaction with *MEX67* [72], suggesting that the Iws1–Spt6-

Table 1
Components of the TREX complex.

	Yeast	*Drosophila*	Mammals
THO components			
	Hpr1	Thoc1	Thoc1 (hHpr1)
	Tho2	Thoc2	Thoc2
	Thp2		
	Mft1[a]	Thoc7[a]	Thoc7[a]
		Thoc5	Thoc5 (FMIP)
		Thoc6	Thoc6
	Tex1[b]	Thoc3[b]	Thoc3 (hTEX1)[b]
DEAD-box type helicase			
	Sub2	Uap56	Uap56
			DDX39[c]
Adaptor mRNA binding protein			
	Yra1	Aly	Aly (REF, Thoc4)

[a] These proteins share a sequence motif of unknown function (pfam05615).
[b] Tex1/Thoc3 is not a stable component of the THO complex in different species [31,55,61], and thus, it could be categorized as a THO-interacting factor.
[c] DDX39 is structurally very similar to Uap56 (human DDX39 and Uap56 show 90% amino acid sequence identity to each other), but its inclusion in the TREX complex has not yet been formally confirmed.

Table 2
THO/TREX-interacting factors described in this review.

Yeast	Metazoan	Remarks
Mex67–Mtr2	Tap–p15	The hetero-dimeric mRNA export receptor
Pcf11	Pcf11	Yeast Pcf11 forms the cleavage factor 1A (CF 1A) complex together with Rna14, Rna15, and Clp1. In human cells, Pcf11 and Clp1 comprise the mammalian cleavage factor II (CFIIm) complex.
Syf1	XAB2	Yeast Syf1 comprises the Prp19 complex together with Prp19, Ntc20 Snt309, Isy1, Syf2, Cwc2, Prp46, C1f1, and Cef1.
Sus1	ENY2	*Drosophila* ENY2 is a component of two different complexes called the TREX-2/AMEX together with Xmas-2 and the SAGA/TFTC histone-acetyltransferase complex together with dSgf11 and dNonstop.
Iws1	Iws1	Human Iws1 is a putative transcription elongation factor. It binds to Ser2-phosphorylated RNAPII CTD through an interaction with Spt6.
STO1	CBP80	The large subunit of the nuclear cap binding complex (CBC).
	UIF1	**U**ap56-**I**nteracting **F**actor 1. The official name is Forty-two-three domain containing 1 (FYTTD1).
Tho1	CIP29	The yeast gene was named after its ability to suppress the **T**ranscriptional defect of **H**pr1 by **O**verexpression. The official name of the human ortholog is SAP domain containing ribonucleoprotein (SARNP).

mediated mechanism could be evolutionarily conserved. It has not yet been examined how the THO complex functions together with Iws1–Spt6; therefore, the step at which the Iws1–Spt6-mediated loading mechanism functions is not known. It is possible that the Iws1–Spt6-mediated mechanism could operate in parallel with other loading mechanisms. Alternatively, this mechanism might be necessary for the efficient targeting of Aly to form the active TREX complex on activated genes.

The components of the human TREX complex localize to a splicing factor-rich nuclear compartment, and the TREX complex is recruited to spliced mRNAs, but not unspliced pre-mRNA *in vitro* [64]. CBP80, the large subunit of the nuclear cap-binding complex (CBC, see Table 2), co-purifies with the TREX complex and plays an important role in splicing-dependent recruitment. Furthermore, the TREX components have been shown to bind to the 5′-most region of spliced mRNAs [73]. CBC is also required for the recruitment of the TREX complex to an exogenously injected intron-less mRNA [65]. Thus, CBC may act as a landing pad that ensures the correct positioning of the TREX complex on mature mRNAs. The association of the mRNA export machinery with the 5′-end may allow the translocation of the mRNAs through the NPCs in a 5′ to 3′ direction [22]. A recent report indicated that the formation of the mammalian TREX complex is strictly regulated by ATP [74]. These authors found that the addition of ATP to a nuclear extract facilitated the assembly of the TREX complex. In dilute samples, the interaction between Aly and Uap56 occurred efficiently only in the presence of ATP. The splicing-coupled assembly of the active TREX complex may proceed synchronously with the late steps of spliceosome formation, which also require ATP.

5. Cargo mRNA recognition via the TREX complex

ChIP assays indicated that the yeast mRNA export receptor Mex67 is recruited to actively transcribed genes via an interaction with the RNAP II transcriptional machinery [75]. This interaction is mediated by Hpr1, a component of the THO complex [76] (Table 1). In yeast, active genes are spatially positioned in proximity to the NPCs. Therefore, the initial recognition of cargo mRNAs by the transport receptor and the preparation for and commitment to their nuclear export could be an early event in gene expression. In contrast, due to the

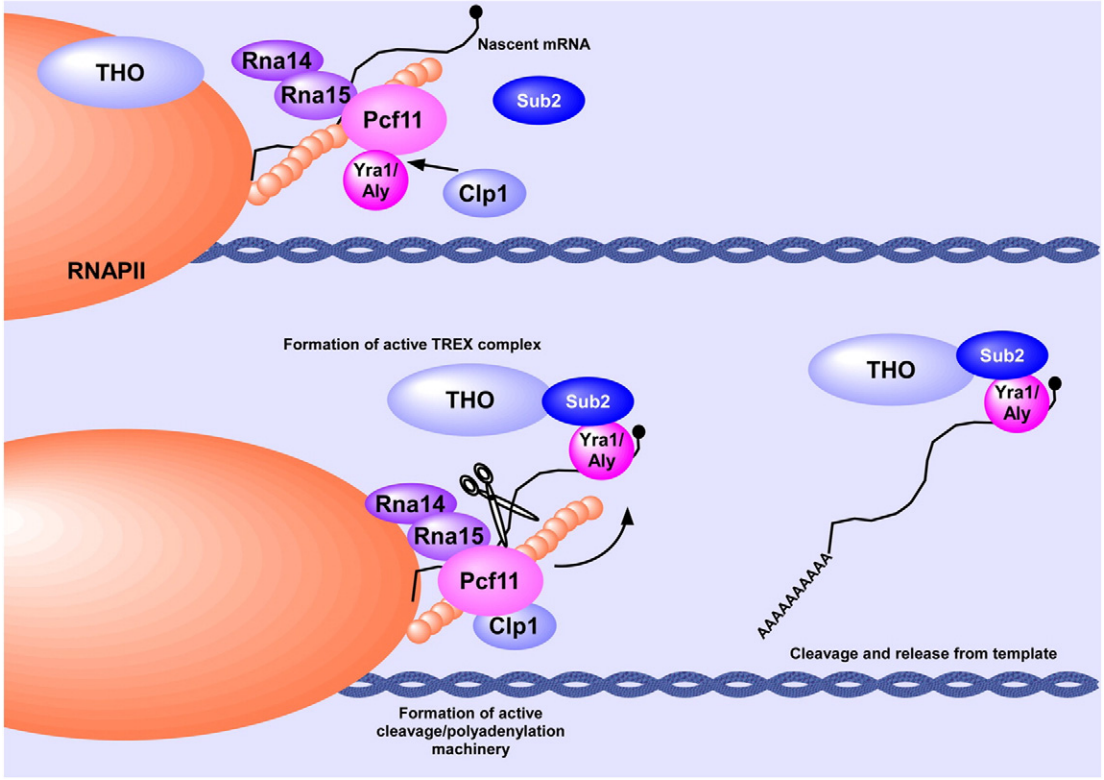

Fig. 2. The coupling of 3′-end formation and the loading of the adaptor mRNA binding protein Yra1. Yeast Pcf11, an RNAPII CTD-binding component of cleavage factor 1A (CF 1A), interacts with the adaptor mRNA binding protein Yra1. The Pcf11-binding domain of Yra1 is also involved in its interaction with Sub2. Therefore, the Yra1–Pcf11 and Yra1–Sub2 complexes are formed in a mutually exclusive manner. It has been proposed that Clp1, another component of CF 1A, displaces Yra1 at the 3′-ends of the transcribed genes to form the functional CF 1A complex. Concomitant with its release from Pcf11, Yra1 interacts with Sub2, and Yra1 and Sub2 are transferred to the THO complex to form the "active" TREX complex. Concomitant with the cleavage and polyadenylation of the pre-mRNA, the TREX complex is loaded onto the mature mRNA and acts as an adaptor. An interaction between human Pcf11 and Aly was also observed, suggesting that this coupling mechanism may also be conserved in metazoan species.

increased size of metazoan nuclei, the formation of export competent mRNPs is thought to occur much deeper inside the nucleus. Thus, a distinct mechanism for the delivery of mRNPs to the NPCs has been proposed to operate in metazoan cells [77].

Both Yra1 and Aly have been shown to interact directly with the mRNA export receptor Mex67–Mtr2/Tap–p15 [78–80]. Recent data, however, indicate that cargo mRNA recognition mediated by the interaction between Aly and Tap–p15 is transient and that the mRNA is transferred to Tap–p15 for direct binding. Moreover, the transfer of mRNA to Tap–p15 from the metazoan non-TREX type adaptor mRNA binding proteins 9G8 and SRp20 was also observed [81]. In contrast to these metazoan adaptor mRNA binding proteins [66,82–85], yeast Yra1 is confined to the nucleus [78], suggesting that the nucleo-cytoplasmic shuttling activity of the adaptors is not necessarily required for mRNA export. Moreover, the ubiquitination of Yra1 promotes its dissociation from mRNPs before nuclear export [80]. These data suggest that the transfer of mRNAs from the adaptors to the export receptor may also take place in yeast. Thus, adaptor mRNA binding proteins probably act as intranuclear chaperones to allow specific and efficient binding of the transport receptors to the cargo mRNPs. Given that various adaptor mRNA binding proteins seem to function *in vivo* (see Ref. [86] for review), the "hand-over" model may also explain why the down regulation of the transport receptor Tap–p15, but not of individual adaptors, induces a bulk poly(A)$^+$ RNA export defect in higher eukaryotes [9,70,87,88].

6. The diversity of the TREX complex in metazoan species

The THO complexes in yeast and metazoans have different compositions (Table 1) [33,36,70]. The recent identification of additional TREX-interacting factors (Table 2) may be indicative of further compositional (and perhaps functional) diversity and complexity in the mammalian TREX complex [7].

UIF1 is a recently identified protein that harbors a peptide motif similar to that in the amino-terminal region of Aly, to which Uap56 binds [89]. Indeed, UIF1 binds both Uap56 and Tap *in vitro*. Moreover, the components of the THO complex co-purified with UIF1. Although the knockdown of either Aly or UIF1 alone did not have a major impact on mRNA export, the simultaneous knockdown of both Aly and UIF1 induced the nuclear retention of bulk poly(A)$^+$ RNAs. This finding suggests that UIF1 functions along with Aly as an additional adaptor mRNA binding protein. Interestingly, the histone chaperone FACT is specifically required for the recruitment of UIF1, but not Aly, to mRNAs. This difference may indicate that UIF1 and Aly are recruited to the TREX complex through different mechanisms.

Tho1 was originally identified as a multi-copy suppressor of an *hpr1* deletion mutant in yeast [90]. Human CIP29, an orthologue of yeast Tho1, has been shown to bind Uap56 and its close paralog DDX39 in two-hybrid assays [91]. A recent report revealed that human CIP29 is indeed a TREX-interacting protein, and it can be co-immunoprecipitated with the TREX complex (Table 2) [74]. Although the step at which CIP29 functions has not yet been determined, CIP29 is reportedly able to regulate the helicase activity of DDX39 [92]. Thus, it is possible that CIP29 facilitates the loading of the TREX complex onto mRNAs by regulating the activity of Uap56.

Intriguingly, a subsequent study indicated that the knockdown of either Uap56 or DDX39 downregulated different sets of mRNAs and caused defects at different stages of mitosis. A microarray analysis revealed that the knockdown of either Uap56 or DDX39 affected the expression of different sets of genes [93]. These observations suggest that these two closely related RNA helicases are involved in the expression of different sets of genes. However, there was a discrepancy in these two studies regarding the involvement of the THO components in the compositions of the Uap56- (*i.e.*, TREX) and DDX39-containing complexes [74,93]. Thus, the mechanisms by which these different sets of genes are distinguished await further analysis.

7. The metazoan TREX complex affects intricate cellular activities

Studies in knockout mice have shown that the metazoan THO/TREX complex is required for development and cellular differentiation because of its ability to specifically regulate the expression of a subset of genes [94–96]. In addition, several studies have implicated THO/TREX components in cancer development [97,98], which could be related to the functions of the THO/TREX complex in genome stability. These data highlight the relevance of the TREX complex in intricate cellular activities in metazoans.

Thoc1, an ortholog of the yeast THO component Hpr1, has been shown to be required for early development in mouse embryos [94]. More recently, the analysis of a mouse strain harboring a hypomorphic *Thoc1* allele showed that Thoc1 is required for spermatogenesis and male fertility. In contrast to the lethality of the *Thoc1* knockout, the mice harboring the hypomorphic *Thoc1* allele were viable. Furthermore, a subset of genes was downregulated in the *Thoc1* hypomorph [95], including *Gata1* and *Rhox5*, which play roles in Sertoli cells in the testes [99]. The association of Thoc1 with these genes was observed by ChIP analysis. These findings indicate that there may be tissue- and gene-specific regulatory roles for metazoan TREX components.

Thoc5 (also called Fms-interacting protein FMIP), a metazoan specific component of the THO complex (Table 1), is involved in the nuclear export of *HSP70* mRNA as a co-adaptor of Aly [66]. However, the extent to which Thoc5 activity is required for non-heat shock gene expression is not yet fully understood. A recent analysis of a *Thoc5* gene knockout mouse strain showed that Thoc5 depletion causes embryonic lethality as is observed in the Thoc1 knockout, confirming the requirement of the THO complex during the early development. Further analysis using conditional and inducible *Thoc5* knockout mice revealed that Thoc5 depletion causes neonatal death due to the insufficient growth and differentiation of hematopoietic cells, including leukocytes and erythrocytes [96]. These data are consistent with previous results from the same group showing that Thoc5 controls adipocyte lineage differentiation [100]. In accordance with the previously reported data that bulk poly(A)$^+$ RNA export is not strongly affected by the downregulation of the TREX components in metazoans [66,70], a recent transcriptomic analysis of *Thoc5* gene-deleted mouse embryonic fibroblasts (MEFs) indicated that only several hundred genes are regulated by Thoc5. Intriguingly, the genes regulated by Thoc5 in MEFs include those that are required for hematopoietic development [101]. Although these authors concluded that the observed developmental phenotypes are caused by a defect in the nuclear export of the target mRNAs, it is also possible that Thoc5 plays unknown regulatory roles that do not require all of the TREX components. Moreover, the genes controlled by Thoc1 and Thoc5 did not show any readily identifiable structural or sequence similarities. Therefore, further analysis is required to elucidate the mechanisms, by which these genes are specifically selected and targeted by the mammalian TREX complex.

8. Conclusions

Extensive studies using yeast as a model system have greatly clarified the molecular mechanisms of nuclear mRNA export. Nuclear mRNA export and other steps in gene expression are streamlined, and they proceed interdependently through the activities of multifunctional proteins that act at different steps of gene expression. The yeast TREX complex is one such factor, connecting transcription elongation and correct 3′-end formation to nuclear export. Intriguingly, it has also been suggested that the yeast TREX complex may affect events further downstream, such as the fidelity of translation in the cytoplasm [63,102]. In metazoan species, the TREX complex affects the expression of only a subset of genes, including several key factors required for cellular differentiation and development. These emerging data may provide clues to the mechanisms by which the TREX complex is recruited to its target genes in metazoans. Furthermore,

these observations suggest a new connection between the nuclear biogenesis and/or export of mRNAs and complex cellular activities. The efficient 3′-end formation of target genes, which affects the efficiency of gene expression in human cells [103], may be regulated by the TREX complex, as has been shown in yeast. Another unanswered question is whether the observed effects on the expression of key genes in different tissues are due to the function of the entire THO/TREX complex or of specific components. The compositional diversity of the THO/TREX complex in metazoans could provide another layer of regulation of the expression of different target genes in different tissues. The solution of the THO/TREX complex structure would also certainly be helpful in finding answers to these questions. In the next several years, we may obtain a more comprehensive and clear view of the functional roles played by the TREX complex in higher eukaryotes.

Abbreviations

mRNP	mRNA–protein complex
NPC	nuclear pore complex
TREX	transcription-export
RNAPII	RNA polymerase II;
ChIP	chromatin immunoprecipitation
CTD	C-terminal domain
CF1A	cleavage factor 1A
TPR	tetratrico peptide repeat
SAGA	Spt5-Ada-Gcn5 acetyltransferase
TFTC	TATA-binding protein-free TAF_{II}-containing complex
CBC	nuclear cap binding complex
MEF	mouse embryonic fibroblast

Acknowledgements

I thank Drs. Yoshihiro Yoneda and Miki Hieda for their critical reading and constructive comments on the manuscript. I also thank the anonymous reviewers for their help in improving the manuscript. This work was supported in part by a Grant-in-Aid for Scientific Research on Innovative Areas “RNA regulation” (no. 23112713) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and a Grant-in Aid for Scientific Research (no. 21570195) from the Japan Society for the Promotion of Science.

References

[1] M.W. Hetzer, S.R. Wente, Border control at the nucleus: biogenesis and organization of the nuclear membrane and pore complexes, Dev. Cell 17 (5) (2009) 606–616.
[2] C. Strambio-de-Castillia, M. Niepel, M.P. Rout, The nuclear pore complex: bridging nuclear transport and gene regulation, Nat. Rev. Mol. Cell Biol. 11 (7) (2010) 490–501.
[3] A. Kohler, E. Hurt, Exporting RNA from the nucleus to the cytoplasm, Nat. Rev. Mol. Cell Biol. 8 (10) (2007) 761–773.
[4] L.J. Terry, E.B. Shows, S.R. Wente, Crossing the nuclear envelope: hierarchical regulation of nucleocytoplasmic transport, Science 318 (5855) (2007) 1412–1416.
[5] M. Stewart, Nuclear export of mRNA, Trends Biochem. Sci. 35 (11) (2010) 609–617.
[6] E. Tutucci, F. Stutz, Keeping mRNPs in check during assembly and nuclear export, Nat. Rev. Mol. Cell Biol. 12 (6) (2011) 377–384.
[7] S. Rodriguez-Navarro, E. Hurt, Linking gene regulation to mRNA production and export, Curr. Opin. Cell Biol. 23 (3) (2011) 302–309.
[8] A. Segref, K. Sharma, V. Doye, A. Hellwig, J. Huber, R. Luhrmann, E. Hurt, Mex67p, a novel factor for nuclear mRNA export, binds to both poly(A)$^+$ RNA and nuclear pores, EMBO J. 16 (11) (1997) 3256–3271.
[9] A. Herold, T. Klymenko, E. Izaurralde, NXF1/p15 heterodimers are essential for mRNA nuclear export in *Drosophila*, RNA 7 (12) (2001) 1768–1780.
[10] W. Tan, A.S. Zolotukhin, J. Bear, D.J. Patenaude, B.K. Felber, The mRNA export in *Caenorhabditis elegans* is mediated by Ce-NXF-1, an ortholog of human TAP/NXF and *Saccharomyces cerevisiae* Mex67p, RNA 6 (12) (2000) 1762–1772.
[11] C.M. Brennan, I.E. Gallouzi, J.A. Steitz, Protein ligands to HuR modulate its interaction with target mRNAs in vivo, J. Cell Biol. 151 (1) (2000) 1–14.
[12] J. Katahira, K. Strasser, A. Podtelejnikov, M. Mann, J.U. Jung, E. Hurt, The Mex67p-mediated nuclear mRNA export pathway is conserved from yeast to human, EMBO J. 18 (9) (1999) 2593–2609.
[13] A.G. Cook, N. Fukuhara, M. Jinek, E. Conti, Structures of the tRNA export factor in the nuclear and cytosolic states, Nature 461 (7260) (2009) 60–65.
[14] C. Okada, E. Yamashita, S.J. Lee, S. Shibata, J. Katahira, A. Nakagawa, Y. Yoneda, T. Tsukihara, A high-resolution structure of the pre-microRNA nuclear export machinery, Science 326 (5957) (2009) 1275–1279.
[15] A.G. Cook, E. Conti, Nuclear export complexes in the frame, Curr. Opin. Struct. Biol. 20 (2) (2010) 247–252.
[16] S.J. Lee, C. Jiko, E. Yamashita, T. Tsukihara, Selective nuclear export mechanism of small RNAs, Curr. Opin. Struct. Biol. 21 (1) (2011) 101–108.
[17] J. Katahira, Y. Yoneda, Nucleocytoplasmic transport of microRNAs and related small RNAs, Traffic 12 (2011) 1468–1474.
[18] K. Strasser, J. Basler, E. Hurt, Binding of the Mex67p/Mtr2p heterodimer to FXFG, GLFG, and FG repeat nucleoporins is essential for nuclear mRNA export, J Cell Biol 150 (4) (2000) 695–706.
[19] S. Fribourg, I.C. Braun, E. Izaurralde, E. Conti, Structural basis for the recognition of a nucleoporin FG repeat by the NTF2-like domain of the TAP/p15 mRNA nuclear exprot factor, Mol. Cell 8 (2001) 645–656.
[20] H.L. Wiegand, G.A. Coburn, Y. Zeng, Y. Kang, H.P. Bogerd, B.R. Cullen, Formation of Tap/NXT1 heterodimers activates Tap-dependent nuclear mRNA export by enhancing recruitment to nuclear pore complexes, Mol. Cell. Biol. 22 (1) (2002) 245–256.
[21] J. Katahira, K. Straesser, T. Saiwaki, Y. Yoneda, E. Hurt, Complex formation between Tap and p15 affects binding to FG-repeat nucleoporins and nucleocytoplasmic shuttling, J. Biol. Chem. 277 (11) (2002) 9242–9246.
[22] P. Bjork, L. Wieslander, Nucleocytoplasmic mRNP export is an integral part of mRNP biogenesis, Chromosoma 120 (1) (2011) 23–38.
[23] T.A. Bolger, A.W. Folkmann, E.J. Tran, S.R. Wente, The mRNA export factor Gle1 and inositol hexakisphosphate regulate distinct stages of translation, Cell 134 (4) (2008) 624–633.
[24] S.R. Wente, M.P. Rout, The nuclear pore complex and nuclear transport, Cold Spring Harb. Perspect. Biol. 2 (10) (2010) a000562.
[25] L. Minvielle-Sebastia, W. Keller, mRNA polyadenylation and its coupling to other RNA processing reactions and to transcription, Curr. Opin. Cell Biol. 11 (3) (1999) 352–357.
[26] K.M. Neugebauer, On the importance of being co-transcriptional, J. Cell Sci. 115 (Pt 20) (2002) 3865–3871.
[27] M.K. Doma, R. Parker, RNA quality control in eukaryotes, Cell 131 (4) (2007) 660–668.
[28] M. Schmid, T.H. Jensen, Quality control of mRNP in the nucleus, Chromosoma 117 (5) (2008) 419–429.
[29] M.J. Moore, N.J. Proudfoot, Pre-mRNA processing reaches back to transcription and ahead to translation, Cell 136 (4) (2009) 688–700.
[30] R. Perales, D. Bentley, “Cotranscriptionality”: the transcription elongation complex as a nexus for nuclear transactions, Mol Cell 36 (2) (2009) 178–191.
[31] T.H. Jensen, K. Dower, D. Libri, M. Rosbash, Early formation of mRNP: license for export or quality control? Mol Cell 11 (5) (2003) 1129–1138.
[32] A. Aguilera, Cotranscriptional mRNP assembly: from the DNA to the nuclear pore, Curr. Opin. Cell Biol. 17 (3) (2005) 242–250.
[33] R. Reed, H. Cheng, TREX, SR proteins and export of mRNA, Curr. Opin. Cell Biol. 17 (3) (2005) 269–273.
[34] J. Katahira, Y. Yoneda, Roles of the TREX complex in nuclear export of mRNA, RNA Biol. 6 (2) (2009) 149–152.
[35] A.G. Rondon, S. Jimeno, A. Aguilera, The interface between transcription and mRNP export: from THO to THSC/TREX-2, Biochim. Biophys. Acta 1799 (8) (2010) 533–538.
[36] K. Strasser, S. Masuda, P. Mason, J. Pfannstiel, M. Oppizzi, S. Rodriguez-Navarro, A.G. Rondon, A. Aguilera, K. Struhl, R. Reed, E. Hurt, TREX is a conserved complex coupling transcription with messenger RNA export, Nature 417 (6886) (2002) 304–308.
[37] D. Zenklusen, P. Vinciguerra, J.C. Wyss, F. Stutz, Stable mRNP formation and export require cotranscriptional recruitment of the mRNA export factors Yra1p and Sub2p by Hpr1p, Mol. Cell. Biol. 22 (23) (2002) 8241–8253.
[38] T.H. Jensen, J. Boulay, J.R. Olesen, J. Colin, M. Weyler, D. Libri, Modulation of transcription affects mRNP quality, Mol Cell 16 (2) (2004) 235–244.
[39] K.C. Abruzzi, S. Lacadie, M. Rosbash, Biochemical analysis of TREX complex recruitment to intronless and intron-containing yeast genes, EMBO J. 23 (13) (2004) 2620–2631.
[40] S.H. Ahn, M. Kim, S. Buratowski, Phosphorylation of serine 2 within the RNA polymerase II C-terminal domain couples transcription and 3′ end processing, Mol Cell 13 (1) (2004) 67–76.
[41] M. Kim, S.H. Ahn, N.J. Krogan, J.F. Greenblatt, S. Buratowski, Transitions in RNA polymerase II elongation complexes at the 3′ ends of genes, EMBO J. 23 (2) (2004) 354–364.
[42] B. Gomez-Gonzalez, M. Garcia-Rubio, R. Bermejo, H. Gaillard, K. Shirahige, A. Marin, M. Foiani, A. Aguilera, Genome-wide function of THO/TREX in active genes prevents R-loop-dependent replication obstacles, EMBO J. 30 (15) (2011) 3106–3119.
[43] R. Luna, S. Jimeno, M. Marin, P. Huertas, M. Garcia-Rubio, A. Aguilera, Interdependence between transcription and mRNP processing and export, and its impact on genetic stability, Mol Cell 18 (6) (2005) 711–722.
[44] M. Oeffinger, K.E. Wei, R. Rogers, J.A. DeGrasse, B.T. Chait, J.D. Aitchison, M.P. Rout, Comprehensive analysis of diverse ribonucleoprotein complexes, Nat. Methods 4 (11) (2007) 951–956.
[45] C. Saguez, M. Schmid, J.R. Olesen, M.A. Ghazy, X. Qu, M.B. Poulsen, T. Nasser, C. Moore, T.H. Jensen, Nuclear mRNA surveillance in THO/sub2 mutants is triggered by inefficient polyadenylation, Mol Cell 31 (1) (2008) 91–103.

[46] S.A. Johnson, G. Cubberley, D.L. Bentley, Cotranscriptional recruitment of the mRNA export factor Yra1 by direct interaction with the 3′ end processing factor Pcf11, Mol Cell 33 (2) (2009) 215–226.
[47] D. Libri, K. Dower, J. Boulay, R. Thomsen, M. Rosbash, T.H. Jensen, Interactions between mRNA export commitment, 3′-end quality control, and nuclear degradation, Mol. Cell. Biol. 22 (23) (2002) 8254–8266.
[48] M. Rougemaille, R.K. Gudipati, J.R. Olesen, R. Thomsen, B. Seraphin, D. Libri, T.H. Jensen, Dissecting mechanisms of nuclear mRNA surveillance in THO/sub2 complex mutants, EMBO J. 26 (9) (2007) 2317–2326.
[49] A.S. Brodsky, P.A. Silver, Pre-mRNA processing factors are required for nuclear export, RNA 6 (12) (2000) 1737–1749.
[50] P. Hilleren, T. McCarthy, M. Rosbash, R. Parker, T.H. Jensen, Quality control of mRNA 3′-end processing is linked to the nuclear exosome, Nature 413 (6855) (2001) 538–542.
[51] K. Dower, M. Rosbash, T7 RNA polymerase-directed transcripts are processed in yeast and link 3′ end formation to mRNA nuclear export, RNA 8 (5) (2002) 686–697.
[52] T.H. Jensen, K. Patricio, T. McCarthy, M. Rosbash, A block to mRNA nuclear export in *S. cerevisiae* leads to hyperadenylation of transcripts that accumulate at the site of transcription, Mol. Cell 7 (4) (2001) 887–898.
[53] X. Qu, S. Lykke-Andersen, T. Nasser, C. Saguez, E. Bertrand, T.H. Jensen, C. Moore, Assembly of an export-competent mRNP is needed for efficient release of the 3′-end processing complex after polyadenylation, Mol. Cell. Biol. 29 (19) (2009) 5327–5338.
[54] D.V. Kopytova, A.V. Orlova, A.N. Krasnov, D.Y. Gurskiy, J.V. Nikolenko, E.N. Nabirochkina, Y.V. Shidlovskii, S.G. Georgieva, Multifunctional factor ENY2 is associated with the THO complex and promotes its recruitment onto nascent mRNA, Genes Dev. 24 (1) (2010) 86–96.
[55] M. Rougemaille, G. Dieppois, E. Kisseleva-Romanova, R.K. Gudipati, S. Lemoine, C. Blugeon, J. Boulay, T.H. Jensen, F. Stutz, F. Devaux, D. Libri, THO/Sub2p functions to coordinate 3′-end processing with gene-nuclear pore association, Cell 135 (2) (2008) 308–321.
[56] S. Chavez, M. Garcia-Rubio, F. Prado, A. Aguilera, Hpr1 is preferentially required for transcription of either long or G+C-rich DNA sequences in *Saccharomyces cerevisiae*, Mol. Cell. Biol. 21 (20) (2001) 7054–7064.
[57] V. Voynov, K.J. Verstrepen, A. Jansen, V.M. Runner, S. Buratowski, G.R. Fink, Genes with internal repeats require the THO complex for transcription, Proc. Natl. Acad. Sci. U. S. A. 103 (39) (2006) 14423–14428.
[58] A.G. Rondon, N.J. Proudfoot, Nuclear roadblocks for mRNA export, Cell 135 (2) (2008) 207–208.
[59] P. Huertas, A. Aguilera, Cotranscriptionally formed DNA:RNA hybrids mediate transcription elongation impairment and transcription-associated recombination, Mol Cell 12 (3) (2003) 711–721.
[60] A. Aguilera, B. Gomez-Gonzalez, Genome instability: a mechanistic view of its causes and consequences, Nat. Rev. Genet. 9 (3) (2008) 204–217.
[61] S. Jimeno, A.G. Rondon, R. Luna, A. Aguilera, The yeast THO complex and mRNA export factors link RNA metabolism with transcription and genome instability, EMBO J. 21 (13) (2002) 3526–3535.
[62] I. Taniguchi, M. Ohno, ATP-dependent recruitment of export factor Aly/REF onto intronless mRNAs by RNA helicase UAP56, Mol. Cell. Biol. 28 (2) (2008) 601–608.
[63] S. Rother, K. Straesser, mRNA export—an integrative component of gene expression, in: Ralph Kehlenbach (Ed.), Nuclear Transport, Landes Bioscience, Austin, 2009, pp. 101–117.
[64] S. Masuda, R. Das, H. Cheng, E. Hurt, N. Dorman, R. Reed, Recruitment of the human TREX complex to mRNA during splicing, Genes Dev. 19 (13) (2005) 1512–1517.
[65] T. Nojima, T. Hirose, H. Kimura, M. Hagiwara, The interaction between cap-binding complex and RNA export factor is required for intronless mRNA export, J. Biol. Chem. 282 (21) (2007) 15645–15651.
[66] J. Katahira, H. Inoue, E. Hurt, Y. Yoneda, Adaptor Aly and co-adaptor Thoc5 function in the Tap–p15-mediated nuclear export of HSP70 mRNA, EMBO J. 28 (5) (2009) 556–567.
[67] W.Y. Tarn, C.H. Hsu, K.T. Huang, H.R. Chen, H.Y. Kao, K.R. Lee, S.C. Cheng, Functional association of essential splicing factor(s) with PRP19 in a protein complex, EMBO J. 13 (10) (1994) 2421–2431.
[68] S. Chanarat, M. Seizl, K. Strasser, The Prp19 complex is a novel transcription elongation factor required for TREX occupancy at transcribed genes, Genes Dev. 25 (11) (2011) 1147–1158.
[69] M.M. Kurshakova, A.N. Krasnov, D.V. Kopytova, Y.V. Shidlovskii, J.V. Nikolenko, E.N. Nabirochkina, D. Spehner, P. Schultz, L. Tora, S.G. Georgieva, SAGA and a novel *Drosophila* export complex anchor efficient transcription and mRNA export to NPC, EMBO J. 26 (24) (2007) 4956–4965.
[70] J. Rehwinkel, A. Herold, K. Gari, T. Kocher, M. Rode, F.L. Ciccarelli, M. Wilm, E. Izaurralde, Genome-wide analysis of mRNAs regulated by the THO complex in *Drosophila melanogaster*, Nat. Struct. Mol. Biol. 11 (6) (2004) 558–566.
[71] S.M. Yoh, H. Cho, L. Pickle, R.M. Evans, K.A. Jones, The Spt6 SH2 domain binds Ser2-P RNAPII to direct Iws1-dependent mRNA splicing and export, Genes Dev. 21 (2) (2007) 160–174.
[72] F. Estruch, L. Peiro-Chova, N. Gomez-Navarro, J. Durban, C. Hodge, M. Del Olmo, C.N. Cole, A genetic screen in *Saccharomyces cerevisiae* identifies new genes that interact with mex67-5, a temperature-sensitive allele of the gene encoding the mRNA export receptor, Mol. Genet. Genomics 281 (1) (2009) 125–134.
[73] H. Cheng, K. Dufu, C.S. Lee, J.L. Hsu, A. Dias, R. Reed, Human mRNA export machinery recruited to the 5′ end of mRNA, Cell 127 (7) (2006) 1389–1400.
[74] K. Dufu, M.J. Livingstone, J. Seebacher, S.P. Gygi, S.A. Wilson, R. Reed, ATP is required for interactions between UAP56 and two conserved mRNA export proteins, Aly and CIP29, to assemble the TREX complex, Genes Dev. 24 (18) (2010) 2043–2053.
[75] G. Dieppois, N. Iglesias, F. Stutz, Cotranscriptional recruitment to the mRNA export receptor Mex67p contributes to nuclear pore anchoring of activated genes, Mol. Cell. Biol. 26 (21) (2006) 7858–7870.
[76] C. Gwizdek, N. Iglesias, M.S. Rodriguez, B. Ossareh-Nazari, M. Hobeika, G. Divita, F. Stutz, C. Dargemont, Ubiquitin-associated domain of Mex67 synchronizes recruitment of the mRNA export machinery with transcription, Proc. Natl. Acad. Sci. U. S. A. 103 (44) (2006) 16376–16381.
[77] V.O. Wickramasinghe, P.I. McMurtrie, A.D. Mills, Y. Takei, S. Penrhyn-Lowe, Y. Amagase, S. Main, J. Marr, M. Stewart, R.A. Laskey, mRNA export from mammalian cell nuclei is dependent on GANP, Curr. Biol. 20 (1) (2010) 25–31.
[78] F. Stutz, A. Bachi, T. Doerks, I.C. Braun, B. Seraphin, M. Wilm, P. Bork, E. Izaurralde, REF, an evolutionary conserved family of hnRNP-like proteins, interacts with TAP/-Mex67p and participates in mRNA nuclear export, RNA 6 (4) (2000) 638–650.
[79] K. Strasser, E. Hurt, Yra1p, a conserved nuclear RNA-binding protein, interacts directly with Mex67p and is required for mRNA export, EMBO J. 19 (3) (2000) 410–420.
[80] N. Iglesias, E. Tutucci, C. Gwizdek, P. Vinciguerra, E. Von Dach, A.H. Corbett, C. Dargemont, F. Stutz, Ubiquitin-mediated mRNP dynamics and surveillance prior to budding yeast mRNA export, Genes Dev. 24 (17) (2010) 1927–1938.
[81] G.M. Hautbergue, M.L. Hung, A.P. Golovanov, L.Y. Lian, S.A. Wilson, Mutually exclusive interactions drive handover of mRNA from export adaptors to TAP, Proc. Natl. Acad. Sci. U. S. A. 105 (13) (2008) 5154–5159.
[82] J.F. Caceres, G.R. Screaton, A.R. Krainer, A specific subset of SR proteins shuttles continuously between the nucleus and the cytoplasm, Genes Dev. 12 (1) (1998) 55–66.
[83] Z. Zhou, M.J. Luo, K. Straesser, J. Katahira, E. Hurt, R. Reed, The protein Aly links pre-messenger-RNA splicing to nuclear export in metazoans, Nature 407 (6802) (2000) 401–405.
[84] J.P. Rodrigues, M. Rode, D. Gatfield, B. Blencowe, M. Carmo-Fonseca, E. Izaurralde, REF proteins mediate the export of spliced and unspliced mRNAs from the nucleus, Proc. Natl. Acad. Sci. U. S. A. 98 (3) (2001) 1030–1035.
[85] O. El Bounkari, A. Guria, S. Klebba-Faerber, M. Claussen, T. Pieler, J.R. Griffiths, A.D. Whetton, A. Koch, T. Tamura, Nuclear localization of the pre-mRNA associating protein THOC7 depends upon its direct interaction with Fms tyrosine kinase interacting protein (FMIP), FEBS Lett. 583 (1) (2009) 13–18.
[86] M.J. Walsh, G.M. Hautbergue, S.A. Wilson, Structure and function of mRNA export adaptors, Biochem. Soc. Trans. 38 (Pt 1) (2010) 232–236.
[87] D. Gatfield, E. Izaurralde, REF1/Aly and the additional exon junction complex proteins are dispensable for nuclear mRNA export, J Cell Biol 159 (4) (2002) 579–588.
[88] D. Longman, I.L. Johnstone, J.F. Caceres, The Ref/Aly proteins are dispensable for mRNA export and development in *Caenorhabditis elegans*, RNA 9 (7) (2003) 881–891.
[89] G.M. Hautbergue, M.L. Hung, M.J. Walsh, A.P. Snijders, C.T. Chang, R. Jones, C.P. Ponting, M.J. Dickman, S.A. Wilson, UIF, a New mRNA export adaptor that works together with REF/ALY, requires FACT for recruitment to mRNA, Curr. Biol. 19 (22) (2009) 1918–1924.
[90] S. Jimeno, R. Luna, M. Garcia-Rubio, A. Aguilera, Tho1, a novel hnRNP, and Sub2 provide alternative pathways for mRNP biogenesis in yeast THO mutants, Mol. Cell. Biol. 26 (12) (2006) 4387–4398.
[91] C.L. Leaw, E.C. Ren, M.L. Choong, Hcc-1 is a novel component of the nuclear matrix with growth inhibitory function, Cell. Mol. Life Sci. 61 (17) (2004) 2264–2273.
[92] T. Sugiura, K. Sakurai, Y. Nagano, Intracellular characterization of DDX39, a novel growth-associated RNA helicase, Exp. Cell Res. 313 (4) (2007) 782–790.
[93] T. Yamazaki, N. Fujiwara, H. Yukinaga, M. Ebisuya, T. Shiki, T. Kurihara, N. Kioka, T. Kambe, M. Nagao, E. Nishida, S. Masuda, The closely related RNA helicases, UAP56 and URH49, preferentially form distinct mRNA export machineries and coordinately regulate mitotic progression, Mol. Biol. Cell 21 (16) (2010) 2953–2965.
[94] X. Wang, Y. Chang, Y. Li, X. Zhang, D.W. Goodrich, Thoc1/Hpr1/p84 is essential for early embryonic development in the mouse, Mol. Cell. Biol. 26 (11) (2006) 4362–4367.
[95] X. Wang, M. Chinnam, J. Wang, Y. Wang, X. Zhang, E. Marcon, P. Moens, D.W. Goodrich, Thoc1 deficiency compromises gene expression necessary for normal testis development in the mouse, Mol. Cell. Biol. 29 (10) (2009) 2794–2803.
[96] A. Mancini, S.C. Niemann-Seyde, R. Pankow, O. El Bounkari, S. Klebba-Farber, A. Koch, E. Jaworska, E. Spooncer, A.D. Gruber, A.D. Whetton, T. Tamura, THOC5/FMIP, an mRNA export TREX complex protein, is essential for hematopoietic primitive cell survival in vivo, BMC Biol. 8 (2010) 1.
[97] Y. Li, A.W. Lin, X. Zhang, Y. Wang, X. Wang, D.W. Goodrich, Cancer cells and normal cells differ in their requirements for Thoc1, Cancer Res. 67 (14) (2007) 6657–6664.
[98] M.S. Dominguez-Sanchez, C. Saez, M.A. Japon, A. Aguilera, R. Luna, Differential expression of THOC1 and ALY mRNP biogenesis/export factors in human cancers, BMC Cancer 11 (2011) 77.
[99] J.A. MacLean II, M.A. Chen, C.M. Wayne, S.R. Bruce, M. Rao, M.L. Meistrich, C. Macleod, M.F. Wilkinson, Rhox: a new homeobox gene cluster, Cell 120 (3) (2005) 369–382.
[100] A. Mancini, O. El Bounkari, A.F. Norrenbrock, M. Scherr, D. Schaefer, M. Eder, A.H. Banham, K. Pulford, L. Lyne, A.D. Whetton, T. Tamura, FMIP controls the adipocyte lineage commitment of C2C12 cells by downmodulation of C/EBP alpha, Oncogene 26 (7) (2007) 1020–1027.
[101] A. Guria, D.D. Tran, S. Ramachandran, A. Koch, O. El Bounkari, P. Dutta, H. Hauser, T. Tamura, Identification of mRNAs that are spliced but not exported to the cytoplasm in the absence of THOC5 in mouse embryo fibroblasts, RNA 17 (6) (2011) 1048–1056.
[102] S. Rother, K. Strasser, The RNA polymerase II CTD kinase Ctk1 functions in translation elongation, Genes Dev. 21 (11) (2007) 1409–1421.
[103] S. West, N.J. Proudfoot, Transcriptional termination enhances protein expression in human cells, Mol Cell 33 (3) (2009) 354–364.