RNA surveillance by the nuclear RNA exosome: mechanisms and significance

Koichi Ogami¹,*, Yaqiong Chen², and James L. Manley²
Koichi Ogami: koichi_ogami@phar.nagoya-cu.ac.jp; Yaqiong Chen: yc2906@columbia.edu; James L. Manley: jlm2@columbia.edu
¹Department of Biological Chemistry, Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya 467-8603 Japan
²Department of Biological Sciences, Columbia University, New York, New York 10027, USA

Abstract

The nuclear RNA exosome is an essential and versatile machinery that regulates maturation and degradation of a huge plethora of RNA species. The past two decades have witnessed remarkable progress in understanding the whole picture of its RNA substrates and the structural basis of its functions. In addition to the exosome itself, recent studies focusing on associated co-factors have been elucidating how the exosome is directed towards specific substrates. Moreover, it has been gradually realized that loss-of-function of exosome subunits affect multiple biological processes such as the DNA damage response, R-loop resolution, maintenance of genome integrity, RNA export, translation and cell differentiation. In this review, we summarize the current knowledge of the mechanisms of nuclear exosome-mediated RNA metabolism and discuss their physiological significance.

Keywords

exosome; RNA surveillance; RNA processing; RNA degradation

1. Introduction

Regulation of RNA maturation and degradation is a crucial step in gene expression. The nuclear RNA exosome has a central role in monitoring nearly every type of transcript produced by RNA polymerase I, II and III (Pol I, II and III). The exosome guarantees fidelity of the mature 3′ ends of certain stable RNA species such as rRNAs, tRNAs, telomeric RNAs, small nuclear and nucleolar RNAs (snRNAs and snoRNAs) not only by catalyzing 3′ end trimming but also by degrading transcripts containing an incomplete 3′ end [1–3]. Besides, processing of messenger RNA precursors (pre-mRNAs), such as by...
splicing and 3′ end formation, is also under the surveillance of the exosome (Figure 1) [4–13].

Intriguingly, recent advances in RNA-sequencing techniques have enabled detection of novel PolII transcripts (Figure 1), which are expressed at extremely low levels because of rapid RNA turnover by the exosome. A large fraction of these RNAs can be categorized as long non-coding RNA (lncRNA). The most well-known lncRNA substrates for the exosome are cryptic unstable transcripts (CUTs) in yeast [14–16], and its human counterpart, promoter upstream transcripts (PROMPTs) or upstream antisense RNAs (uaRNAs) [17,18], which arise due to antisense transcription from divergent gene promoters. The exosome removes sense non-coding transcripts, such as prematurely terminated RNAs (ptRNAs) [19], which are prematurely terminated and polyadenylated at a poly(A) signal (PAS) typically located in an intron of a protein-coding gene [20], and transcription start site (TSS)-associated RNAs (tssRNAs), which are infrequent short ncRNAs (20~65nt) generated as a result of promoter-proximal termination of sense transcription [21]. Transcriptional enhancers are also transcribed bi-directionally and produce a class of lncRNA called enhancer RNAs (eRNAs). It was reported that exosome-sensitive eRNAs emerge from virtually all active enhancer regions, determined by comprehensive cap analysis of gene expression (CAGE) analyses [22]. Furthermore, long intergenic RNAs (lincRNAs) are also exosome targets [23], although they are generally more stable than uaRNA and eRNA [24].

Strikingly, recent studies have been gradually revealing that the exosome is involved in multiple important biological processes. Those include the DNA damage response (DDR), R-loop resolution, maintenance of genome integrity, RNA export, translation and cell differentiation. In this work, we review and update our current understanding regarding structural insights into RNA degradation by the exosome and its associated co-factors. We also summarize how abrogation of the functions of the exosome impacts cellular processes in mammals.

2. The nuclear RNA exosome: structure and RNA degradation mechanisms

The eukaryotic nuclear RNA exosome is a 3′-5′ exonuclease complex, consisting of a 9-protein catalytically inactive core complex (EXO-9) and two catalytic subunits, Rrp6 (also known as PM/Scl-100 or EXOSC10) and Dis3 (also known as Rrp44 or EXOSC11). EXO-9 forms a double-layered barrel-like structure that comprises six RNase PH-like proteins (Rrp41, Rrp42, Rrp43, Rrp45, Rrp46 and Mtr3) and three S1/K homology (KH) “cap” proteins (Rrp4, Rrp40 and Csl4) [3]. The two catalytic subunits occupy opposite ends of EXO-9 to constitute EXO-11. Rrp6 is placed at the top of the S1/KH cap ring near the RNA entry pore, and Dis3 is tethered to the bottom of EXO-9 near the RNA exit pore [25–27]. Both Rrp6 and Dis3 are 3′-5′ exonucleases, but the later also has an endonucleolytic activity [28–30]. Rrp6 widens the central channel of core EXO-9 and allosterically stimulates Dis3 activity [26]. Recently, a study focused on the last 100 amino acids of Rrp6, referred to as a “lasso,” revealed that the lasso binds RNA proximal to the EXO-9 channel and enhances RNA decay [31]. In humans, both Rrp6 and Dis3 are mostly nuclear, but Rrp6 shows significant nucleolar enrichment [32,33], whereas Dis3 is excluded from the nucleoli.
In contrast to humans, yeast Rrp6 is restricted to the nucleus, but Rrp6 and Dis3 are both present in the nucleoplasm and nucleolus [32,35]. Three additional co-factors, Mtr4 (in humans, also known as SKIV2L2 or MTREX (nomenclature recently suggested by HUGO)), Rrp47 (also known as C1D) and Mpp6, are required for maximal activity of the nuclear exosome. Rrp47 interacts with Rrp6 to provide a binding platform for Mtr4, an essential DExH-box RNA helicase [36]. Mpp6 binds to the cap subunit Rrp40 and enhances Mtr4 helicase activity [37,38]. This activity is required to unwind secondary structures formed at the 3′ end of RNA substrates so that the resultant single-stranded RNA substrates can be threaded into the central channel of the core complex in a 3′ to 5′ orientation [39]. Dis3 degrades RNAs threaded through the entire central channel (Figure 2a), whereas Rrp6 degrades or trims the RNA that enters into the S1/KH cap ring and then traverses the cap to reach the Rrp6 active site (Figure 2b) [26,40,41]. In addition, there is an alternative path by which the RNA can directly access the Dis3 active site (Figure 2c) [42]. The RNA channeling but not the direct route induces a conformational change in Dis3 [42]. The estimated path lengths of the threading and direct access in vitro are ~30nt and ~10nt, respectively [42–45]. Recent studies in *S. cerevisiae* have revealed that RNA substrates show preferences for a specific path to Dis3 [46,47]. Notably, identification of transcriptome-wide interactions of RNAs with individual exosome subunits using the UV crosslinking and analysis of cDNA (CRAC) technique in growing budding yeast cells showed that RNA substrates produced by all three RNA polymerases (Pol I, II and III) exhibit preferences [47]. Interestingly, whichever the route is, Mtr4 is required for RNA degradation [47]. In addition to these two paths, a potential new route to Dis3 was recently suggested [48]: by assessing the average length of RNAs protected by the exosome in living budding yeast using CRAC analysis, it was found that there are not only ~10nt (reflecting direct access) and 39 and 44nt (likely reflecting RNAs threaded through the channel and also protected by co-factors) peaks, but also a ~20nt broad peak that was not described in in vitro studies.

3. Molecular apparatus for RNA targeting of the exosome in yeasts and humans

The fact that the exosome targets a wide variety of transcripts raises an important question: How is the exosome specifically recruited to particular RNA substrates? Recent studies have identified a number of nuclear exosome-adaptor complexes, which help the exosome load onto selective RNAs [2,3,49]. The components of the adaptors are largely conserved, especially between fission yeast and humans (Table 1). Importantly, Mtr4 is contained in all of the adaptor complexes, indicating that Mtr4 is a central and essential factor for formation of the complexes and for their functions (Figure 3).

3.1. *S. cerevisiae*

The Trf4/5-Air1/2-Mtr4 polyadenylation complex (TRAMP) was first described in *S. cerevisiae* and now is the most well-characterized co-factor that assists exosome-mediated RNA degradation and processing in budding yeast nuclei. Soon after recognizing the importance of polyadenylation of hypomodified tRNA\textsubscript{Met} by the non-canonical poly(A)
polymerase Trf4 for exosome-dependent tRNA quality control [50], the full composition of the responsible protein complex, TRAMP (Mtr4, Trf4 and the Zn-knuckle RNA-binding protein Air1 or Air2), was determined [14,51,52]. Later, another TRAMP complex containing Trf5, a close homolog of Trf4, was identified [53]. Air1/2 provides RNA-binding capability and is also critical for TRAMP assembly [54–56]. TRAMP recognizes a variety of transcripts [12], such as tRNAs [50,52,57–59], rRNAs [59–61], sn/snoRNAs [59,62,63], telomeric RNAs [64], CUTs [14,59,64] and pre-mRNAs [59,65–67], and these substrates are commonly polyadenylated by Trf4/5. In TRAMP, Mtr4 plays roles in RNA unwinding and modulation of poly(A)-tail length of RNA substrates [57,68–73]. Although TRAMP itself has an RNA-binding capacity, its efficient recruitment to RNA substrates is further assisted by the Nrd1-Nab3-Sen1 (NNS) complex [74]. Nrd1 and Nab3 are RNA-binding proteins that recognize specific sequence elements [59,75,76], whereas Sen1 has DNA/RNA helicase activity, which promotes dissociation of PolII from the template DNA [77–79]. Importantly, NNS travels with a transcribing PolII by interacting with the C-terminal domain of the PolII largest subunit (CTD) and terminates transcription when the sequence elements emerge on the nascent RNAs [78,80–85]. NNS-dependent transcription termination is further promoted by the cleavage/polyadenylation factor Pcf11 [86]. Nrd1 interacts with the CTD containing heptapeptide repeats (YSPTPSP) phosphorylated on Ser5 (Ser5P) through its CTD interaction domain (CID) [83,87,88]. The Nrd1 CID also binds to a CTD mimic motif in Trf4 [89]. The Nrd1 CID interacts with Trf4 and PolII in a mutually exclusive manner, and therefore NNS-mediated transcription termination and TRAMP/exosome-mediated RNA degradation are coordinated [89]. Notably, proteins homologous to the NNS components were found in S. pombe and humans (Table 1). Both S. pombe and humans have Sen1 homologs, Sen1 and Senataxin (SETX), respectively. S. pombe has the Nrd1 homolog Seb1 [90], which has Ser5P-CTD- and RNA-binding abilities [91,92]. However, although Seb1 is involved in transcription termination and alternative polyadenylation, no NNS-like function was observed [91,93,94]. Functions of the human CID-containing homolog of Nrd1, SCAF8 [95], remains unexplored, except that SCAF8 can bind to the elongating phosphorylated CTD [96,97]. Also, human RALY protein is somewhat similar to Nab3; the RNA recognition motif (RRM) in RALY shares 31% amino acid identity with the Nab3 RRM [98]. However, there is currently no evidence that these putative homologs of NNS subunits form an NNS-like complex and regulate human TRAMP functions.

Several other exosome partners exist in budding yeast. Utp18 and Nop53, an early and late associating small subunit processome factor, respectively, were shown to interact with the exosome to regulate pre-rRNA processing [99]. Both proteins contain a conserved motif termed an arch-interacting motif (AIM), which directly dock to the arch domain of Mtr4. Recent X-ray crystallography and NMR analyses revealed the structural basis of Mtr4-Nop53 interaction and showed that the Mtr4 arch can bind Nop53 and RNA simultaneously [100]. The G-patch protein Sqs1/Pfa1 also contains a perfect AIM consensus sequence and thus binds to the Mtr4 arch domain; however, the roles of the interaction remain elusive [99]. In addition, Babour et al. reported that the chromatin remodeling complex ISW1 physically interacts with the exosome in an RNase-insensitive manner [101]. Interestingly, this interaction is enhanced in the export-incompetent thermo-sensitive np13-I mutant strain. ISW1 is required to retain export-defective poly(A)-tailed RNAs on chromatin and remove
them by recruiting the exosome. This finding implies that ISW1/exosome participates in an mRNP nuclear export surveillance system.

3.2. S. pombe

The fission yeast S. pombe has a complex similar to S. cerevisiae TRAMP, consisting of Mtr4, Air1 and the Trf4/5 family of poly(A) polymerase Cid14 [102]. It functions in heterochromatin gene silencing at centromeric repeats [102–104] and polyadenylation-dependent decay of centromeric RNAs [105,106], snoRNA precursors [107] and Argonaute-bound small RNAs [108]. The precise mechanism of TRAMP recruitment to target transcripts remains unclear; however, Mlo3, the S. pombe homolog of mRNA export factor Yra1 or ALYREF, was shown to interact with TRAMP to silence centromeric transcripts [103,104]. Besides, the THO complex, which coordinates the steps from transcription to RNA export, is required to maintain TRAMP at snoRNA genes, and these complexes cooperate in the control of snoRNA expression, thus linking transcription and nuclear surveillance machineries [107]. Notably, Yra1 physically associates with the THO complex in S. cerevisiae [109,110], and therefore, it is possible that both Mlo3 and the THO complex work in the same pathway for TRAMP-mediated RNA metabolism.

S. pombe has a second Mtr4 homologue protein named Mt1 (Mtr4-like protein 1), which is independent of TRAMP. Mt1 interacts with the zinc-finger protein Red1 and various other proteins to form a complex called Mt1-Red1 core (MTREC) or nuclear RNA silencing (NURS) [111,112]. MTREC interacts with the exosome presumably through Red1 but not Mt1 [113]. In agreement with this, Mt1 lacks the N-terminal motif that mediates the interaction of Mtr4 with Rrp6 and Rrp41 [36]. MTREC further associates with several sub-modules such as Iss10-Mmi1, Red5-Pab2-Rmn1, Ars2-Cbc1-Cbc2, and the canonical poly(A) polymerase Pla1 [111–113]. All of these sub-modules can bind to MTREC simultaneously, forming a large 11 subunit complex [113]. However, since the sub-modules show different stoichiometry for MTREC-binding, there might be various forms of the MTREC complex. The sub-modules enable MTREC to direct specific RNA targets for exosome-mediated decay. The YTH protein Mmi1 is a well-characterized regulator of meiotic gene expression [114–116]. Mmi1 programs meiotic transcripts for co-transcriptional decay by recognizing repeats of a short nucleotide motif termed determinant of selective removal (DSR), which are found within introns in some target genes [116–119]. Iss10 is required for stable interaction between Mmi1 and Red1, and thus, involved in meiotic gene regulation [120]. Red5 and Pab2 contribute to degradation of meiotic mRNAs [121,122] and CUTs [113], whereas depletion of the associating factor Rmn1 does not affect the amount of either meiotic mRNA or CUTs [112,113]. The cap-associated complex Ars2-Cbc1-Cbc2 is responsible for efficient CUT degradation [113], which is reminiscent to the function of the human cap-binding complex (CBC)-ARS2 (CBCA) complex. The human CBCA complex is required for degradation of PROMPTs/uaRNAs [123], which are comparable to yeast CUTs [17] (discussed below).

Mt1 also forms a Red1-independent protein complex with the C. elegans NRDE-2 homologue Nr11 and the coiled-coil- and DUF4078 domain-containing protein Ctr1
[111,113]. The Mt1-Ctr1-Nrl1 complex further associates with splicing factors and is suggested to degrade unspliced pre-mRNA [111,113].

3.3. H. sapiens

In addition to Mtr4, factors homologous to the yeast TRAMP subunits are present in humans; the closest orthologues of Air1/Air2 and Trf4/Trf5 are the Zinc-knuckle protein ZCCHC7 and the non-canonical poly(A) polymerase PAPD5 (also known as Trf4-2), respectively. These three proteins form the TRAMP-like complex [124]. Functions of TRAMP-like are thought to be restricted to nucleoli under normal cellular conditions due to the strict nucleolar localization of ZCCHC7 [124]. The other subunits Mtr4 and PAPD5 are restricted to the nucleus with nucleolar enrichment [124–126]. Interestingly, it was recently shown that viral infection induces cytoplasmic translocalization of ZCCHC7 and Mtr4 to facilitate exosome-mediated viral RNA decay in the cytoplasm [127]. It has been shown that PAPD5 is responsible for poly- or oligo-adenylation of nucleolar RNAs such as snoRNAs [128] and aberrant pre-rRNA species [124,129], suggesting that polyadenylation assists RNA 3′ processing and/or degradation by TRAMP-like. Of note, PAPD5 has a close paralog, PAPD7 (also known as Trf4-1), that has been suggested to interact with ZCCHC7 [56]. However, roles of PAPD7 in TRAMP-like remain unclear; PAPD7 is excluded from nucleoli [126] and in agreement with this, PAPD7 is dispensable for polyadenylation of aberrant pre-rRNA species [129]. In addition, there is no evidence of an interaction between PAPD7 and Mtr4 in several independent proteomics analyses [20,124,130].

Human TRAMP-like interacts with several additional proteins. It has been shown that TRAMP-like-mediated pre-rRNA processing is modulated by the AAA-ATPase NVL2 [131,132] and its regulatory factor WD repeat-containing protein WDR74 [133–135]. Moreover, splicing factors such as U4/U6·U5 tri-snRNP subunits and hnRNPs are found to associate with TRAMP-like complex [20,124,130]. The function of the interaction with splicing factors awaits further investigation. The nucleolar exosome can interact with the double-stranded RNA-binding protein DGCR8, which is well known as a Microprocessor subunit, to degrade mature snoRNAs and telomerase RNA (hTR) [136]. It is noteworthy that although the physical interaction between DGCR8 and TRAMP-like has not been reported, both snoRNAs and hTR are targeted by the TRAMP-like complex [136–139].

In the nucleoplasm, at least two distinct exosome adaptors are present. One is Mtr4-ZFC3H1 or poly(A) tail exosome targeting complex (PAXT), which brings the exosome to various kinds of lncRNAs including snoRNA host gene (SNHG) transcripts, eRNAs [49], uaRNAs [20,49] and ptRNAs [20]. Another is nuclear exosome targeting complex (NEXT) [124], comprising Mtr4, the RNA binding protein RBM7 and the Zn-knuckle protein ZCCHC8, which degrades PROMPTs/uaRNAs [124], replication-dependent histone mRNAs [123], eRNAs [140], snRNAs [123,141] and snoRNAs [140]. Of note, ZFC3H1 is a close homolog of S. pombe Red1, and therefore, Mtr4-ZFC3H1 is the human MTREC. Although RNA substrates of Mtr4-ZFC3H1 and NEXT partly overlap, there are clear differences in their features; Mtr4-ZFC3H1 substrates are longer in RNA body size and have a long poly(A)-tail [20,49]. The precise molecular fundamentals of substrate recognition by Mtr4-ZFC3H1 await further characterization. However, Meola et al. suggested the transient and partially
RNA-dependent interaction between Mtr4-ZFC3H1 and the nuclear poly(A)-binding protein PABPN1 [49]. It has been shown that PABPN1 promotes exosome-dependent decay of nuclear poly(A)-tailed transcripts [142–144]. PABPN1-mediated RNA decay is dependent on RNA polyadenylation, which requires the canonical poly(A) polymerases PAPα/γ but not the TRAMP subunit PAPD5 [142–144], and is thus termed PABPN1- and PAPα/γ-mediated RNA decay pathway (PPD) [143]. Notably, subsets of the PABPN1 substrates overlap with those of Mtr4-ZFC3H1 [20,49]. Yet, the fact that co-depletion of Mtr4 and PABPN1 resulted in synergistic accumulation of target transcripts suggests that Mtr4-ZFC3H1 and PABPN1 may work in both the same and redundant pathways [144]. It will be interesting to investigate if and how Mtr4-ZFC3H1 participates in the PPD pathway. RNA recognition by NEXT involves the connection with the ARS2-associated cap-binding complex CBCA [123], U-rich RNA binding capacity of RBM7 [140,141] and possibly the pre-mRNA 3′ processing complex [145]. CBCA and NEXT further associate with the zinc-finger CCCH domain-containing protein ZC3H18 (also known as NHN1) [123,146], and this interaction is important for cap-proximal PolII stalling, transcription termination, 3′ end formation and RNA decay [123,146,147]. The significance of the interaction between NEXT and the pre-mRNA 3′ processing complex remains undetermined.

A nucleoplasmic protein NRDE2, which is the homolog of S.pombe Nrl1, also interacts with Mtr4. However, in contrast to the S. pombe counterpart, it is unlikely that Mtr4/NRDE2 associates with the whole exosome since analysis using size-exclusion chromatography-coupled mass spectrometry (MS) revealed that Mtr4/NRDE2 elutes around 440kDa, which is smaller than the exosome/Mtr4 complex (>600kDa) [20]. In agreement with this, our recent MS analysis of NRDE2-interacting proteins did not detect any exosome subunits (Richard P, Ogami K, Chen Y, Feng S, Moresco JJ, Yates JR and Manley JL, unpibl.).

4. Significance of the nuclear RNA exosome in mammalian biological processes

Loss-of-function of the exosome due to mutation or depletion of its subunits and co-factors can cause alterations in various biological processes [2], and ultimately contribute to human disease such as multiple myeloma [148–150]. Despite various interesting phenotypes in yeast, such as altered chromatin modifications in exosome-deficient cells, we restrict discussion here to evidence provided using mammalian cells.

4.1. DNA damage response

The activity of the nuclear exosome is altered during the cellular DDR. The change is triggered by phosphorylation of the NEXT subunit RBM7 by the stress-related kinase p38 MAPK/MK2 [151,152]. Phosphorylated RBM7 is bound by the phosphoserine-binding protein 14-3-3 and loses its RNA-binding ability, which consequently leads to stabilization and accumulation of NEXT substrates such as PROMPTs [151]. Interestingly, cells become hypersensitive to a DNA damaging reagent when RBM7 is depleted, and cells lacking RBM7 exhibit poor survival after drug treatment [151]. Although it is still largely unclear how these changes in the DDR affect cell physiology, there are interesting suggestions that a fraction of promoter-associated lncRNAs can modulate transcription of neighboring genes.
For example, *cyclin D1* (CCND1) PROMPTs upregulated in response to DNA damage by ionizing irradiation provide a binding platform for the RNA-binding protein FUS/TLS. FUS/TLS recruited to the CCND1 promoter through PROMPTs represses the histone acetyltransferase activity of CBP/p300, which results in decreased CCND1 transcription [153]. However, it seems that PROMPT-mediated gene regulation is not widespread, since no correlation was observed between altered expression of the downstream gene and increased PROMPT levels in DNA damage or Rrp40 depletion [154]. This might possibly indicate that most PROMPTs lack sequence elements necessary for recruiting specific RNA-binding proteins, and the action of only a small fraction of PROMPTs may be required for the DDR.

### 4.2. R-loop resolution and genomic integrity

R loops are three-stranded structures composed of the nascent RNA hybridized with DNA template and the resultant displaced single-stranded DNA (ssDNA). R-loop resolution is a critical step to maintain genome integrity since the displaced ssDNA is vulnerable to DNA damage [155–158]. Moreover, R loops are associated with human disease (reviewed in ref. [159–162]). Intriguingly, multiple studies have reported the involvement of the exosome in R-loop resolution and genome integrity. In yeast, depletion of Rrp6 or Trf4 leads to R loop-mediated genomic instability and hyperrecombination [163,164] as well as accumulation of aberrant truncated RNA products released from an R loop [165]. These factors also promote the loading of ssDNA binding protein RPA to double-strand breaks (DSBs) and activate the checkpoint kinase Mec1/ATR, which facilitates the formation of continuous Rad51 filaments to initiate homologous recombination [166]. Strikingly, overexpression of RNase H, which removes R loops by digesting the RNA strand of RNA:DNA hybrids, dramatically rescued the rate of genome instability in TRAMP-depleted cells [167]. In human cells, the DNA/RNA helicase SETX (Senataxin), which plays a key role in R-loop resolution [168], directly interacts with the exosome subunit Rrp45 [169]. The interaction requires sumoylation of SETX, which interestingly is blocked by certain SETX mutations in ataxia oculomotor apraxia 2 (AOA2) patients. It is speculated that SETX recruits the exosome to R loops to promote degradation of the RNA unwound and released by SETX, and thus prevents possible rehybridization and the resultant DNA damage.

Over the last decade, the concept has emerged that exosome-mediated R-loop prevention is a critical step in immunoglobulin class switch recombination (CSR) and somatic hypermutation (SHM) in B lymphocytes [170]. To initiate CSR and SHM, activation-induced cytidine deaminase (AID) deaminates cytidines on both template and non-template DNA strands of transcribing switch regions. However, the template DNA strand hybridized with a nascent transcript cannot be modified by AID because of limited access to the template strand. Basu et al. identified the core RNA exosome EXO-9 as a key factor that promotes AID access to the template strand in the context of RNA:DNA hybrids, and thus, CSR and SHM [171]. The interaction between AID and the RNA exosome is promoted by the E3 ubiquitin ligase NEDD4, which regulates clearance of PolII from the immunoglobulin switch region [172]. In mouse B cells and embryonic stem cells (ESCs) containing a conditional inversion allele of *Exosc3* (Rrp40) or *Exosc10* (Rrp6), which allows conditional ablation of the exosome by drug treatment, loss of the exosome results in enhanced R-loop formation and genomic
instability due to an increase of ncRNAs associated with TSS and superenhancers [173–175]. More recently, it was shown that Mtr4 has an RNA:DNA hybrid unwinding activity, and Mt4-deficient B cells exhibited greater R-loop formation at the immunoglobulin heavy chain locus [176].

4.3. RNA export and translation

In addition to its role in NEXT loading to nascent transcript 5′ ends, the CBC is required to initiate nuclear RNA export by recruiting various proteins. The TREX mRNA export complex is recruited to the 5′ end of mRNAs through the export adaptor proteins ALYREF and THO associating with CBC [177–179]. While splicing enhances TREX recruitment [180], the interaction of ALYREF with the cap-binding protein CBP20 was shown to stimulate nuclear export of capped intronless mRNAs [179]. CBC-associating factor ZC3H18 can also enhance export of intronless mRNAs [181]. Recently, Fan et al. showed that Mtr4 competes with the export adaptor protein ALYREF for binding to ARS2, and thus inhibits nuclear export, providing an important checkpoint to prevent undesired transport of aberrant RNAs into the cytoplasm [182]. Intriguingly, CBCA (CBC-ARS2) and ZC3H18 are also found in the ZFC3H1 interactomes [49], suggesting that Mtr4-ZFC3H1 can also be recruited to CBCA assembled on the 5′ cap structure. Therefore, it is possible that both NEXT and Mtr4-ZFC3H1 can antagonize ALYREF binding to CBCA. This competition, as well as the rapid RNA degradation of poly(A)-tailed IncRNAs by Mtr4-ZFC3H1, is particularly important since normally unstable IncRNAs are exported to the cytoplasm in cells lacking Mtr4-ZFC3H1 [20,183]. Of note, there is a link between RNA 3′ end cleavage/polyadenylation and export. Several 3′ cleavage and polyadenylation factors interact with RNA export factors. For example, Pcf11 directly interacts with the yeast homolog of ALYREF, Yra1 [184]; CFIm68 directly binds to the mRNA export receptor NXF1 [185]; CPSF100 and CFIm proteins associate with the THO subunit THOC5 [186,187]; and CstF64 and PABPN1 help ALYREF-binding to mRNA 3′ ends [188]. Therefore, effective recruitment of RNA export complex including ALYREF is mediated not only by CBC but also the 3′ processing machinery and a poly(A)-tail. Recent remarkable progress in ribosome profiling technologies [189] has led to the realization that ribosome binding or even translation of IncRNAs is pervasive in mammals [190–196]. Concordantly, exported IncRNAs in Mtr4-ZFC3H1 deficient cells become ribosome-associated and likely translated. Because of the translatability of IncRNAs as well as the more mRNA-like structures of Mtr4-ZFC3H1 substrates (presence of the cap and a poly(A)-tail) than those of NEXT substrates [49], the aberrantly exported Mtr4-ZFC3H1 substrates appear to overwhelm translation machinery and disrupt the quantitative balance between ribosomes and translatable RNAs, which leads to global reduction in heavy polysomes and translation [20,183].

Recently, Sinturel et al. reported intriguing findings that diurnal oscillations in liver mass and hepatocyte size are regulated by rhythmic changes in ribosome biogenesis, in which the nuclear exosome plays a role [197]. In this study, using mice, they demonstrated that these changes are controlled by feeding time: diurnal changes were observed only in mice fed during night and ad libitum timing but not in day-fed mice. Importantly, they found that the number of ribosomes also exhibited diurnal fluctuations. In the active/dark phase, translation

Noncoding RNA. Author manuscript; available in PMC 2018 April 05.
of ribosomal protein mRNAs was found to be significantly enhanced, and thus protein synthesis rates increased; while in the resting/light phase, ribosomal protein synthesis was decreased, leading to an imbalance between ribosomal proteins and rRNAs. TRAMP functions to rebalance the amount of these factors by polyadenylating and degrading excess rRNAs in incomplete ribosomal subunits. These events contribute to a daily rhythm of mouse liver protein content.

4.4. Stem cell self-renewal and differentiation

Precise regulation of the activity and maintenance of the fidelity of gene expression is vital for stem cell self-renewal, differentiation and development. Studies have suggested that the nuclear RNA exosome is essential for maintaining progenitor cell function and preventing premature differentiation. A defective exosome pathway can lead to aberrant accumulation of RNAs, among which are mRNAs encoding differentiation-specific transcription factors, and ultimately breaks the balance between proliferation and differentiation. For example, the nuclear exosome directly degrades GRHL3 transcripts, which encode a transcription factor critical for epidermal differentiation [198]. Depletion of the exosome subunit Rrp45 (EXOSC9) leads to loss of progenitor cells from the basal epidermal layer and premature differentiation. More recently, Skamagki et al. suggested that the exosome plays an important role in maintaining pluripotent stem cell redox status in mice [199]. They found that the transcription factor ZSCAN10, which activates transcription of EXOSCI/2/5 genes, is expressed at a low level in induced pluripotent stem cell clones generated from aged tissue donors, and the decreased expression of RNA exosome subunits causes the accumulation of AU-rich element-containing RNAs, including glutathione peroxidase 2 (Gpx2). Overexpression of GPX2 increases the reduced form of glutathione, thus scavenging glutathione-mediated reactive oxygen species, which consequently blunts the DDR and reduces apoptosis. Similar defects were observed following knockdown (KD) of exosome subunits EXOSC2 and/or EXOSC8 in ESCs. Mtr4 is also important in cell proliferation and differentiation. On the one hand, Mtr4 expression is highly upregulated when the self-renewal state of ESCs is induced by inhibitors of kinases, known as 2 inhibitors (2i) [200]. On the other hand, KD of Mtr4 resulted in moderate to severe mouse ESC death [201]. Additionally, depletion of Mtr4 impairs mitosis and induces cell differentiation in the murine cancer cell lines Neuro2A and P19 cells [202]. All the above indicates that levels of the exosome subunits correlates with cell differentiation. Indeed, Rrp4/Rrp40/Rrp42/Rrp45 (EXOSC2/3/7/9) expression is enriched in progenitor cells but decreased upon epidermal differentiation in humans [198]. These observations strongly suggest that an abundance of the exosome is a critical prerequisite to maintain stem and progenitor cells undifferentiated.

4.5. Influenza A virus (IAV) ribogenesis and infectivity

A recent study revealed the significance of the exosome in influenza A virus (IAV) ribogenesis and growth [203]. In this study, Rialdi et al. analyzed the proteome of viral polymerase complex-interacting proteins and identified the core exosome subunits. Intriguingly, they found that viral polymerase activity is attenuated in cells transfected with siRNAs against exosome subunits and in patient-derived cells harboring an EXOSC3 (Rrp40) mutation. Importantly, viral growth was suppressed in these cells, indicating the essential role of the exosome in viral biogenesis. NEXT-assisted exosome seems to be co-
opted by the viral RNA polymerase since similar results were obtained following RBM7 KD. Moreover, synthesis of host:viral chimeric transcripts generated as a result of “cap snatching”, in which initiation of viral transcription is primed using 5′ ends of host transcripts (cap with 10–20 downstream nucleotides), is decreased upon exosome-depletion. Collectively, these results suggest that the nuclear exosome coordinates with viral polymerase during the initial steps of viral transcription with PolIII at host promoters to enhance influenza A virus ribogenesis and infectivity. From the evolutionary point of view, viruses need to integrate their biological activities into hosts by recycling regulatory RNAs generated by hosts. The exosome, as the hub of RNA surveillance system, can be co-opted by viruses to facilitate the efficient formation of cellular:viral hybrid RNAs and cap-snatching.

5. Conclusions and perspectives

The RNA exosome and its co-factors monitor the versatility and specificity of a huge variety of RNA substrates, and thus plays a crucial role in regulating the activity and maintaining the fidelity of gene expression. Numerous studies have revealed that an impaired RNA surveillance system can break RNA homeostasis, and thus cause detrimental consequences in multiple biological processes leading to human diseases (reviewed by Morton et al. [148]). However, there are still many unanswered questions about both the fundamental and the pathological mechanisms of the nuclear exosome: How are both specificity and versatility of RNA substrates guaranteed at the same time in the RNA surveillance system? What is the comprehensive mechanism of the nuclear exosome in multiple biological processes, including maintenance of genome integrity and cell differentiation? Deeper understanding of the complexities of the RNA surveillance system has the potential to lead to novel therapeutic remedies to fight human disease.

Acknowledgments

This work was supported by a National Institute of Health grant R35 GM118136 to J.L.M.

References

1. Mitchell P. Exosome substrate targeting: The long and short of it. Biochem Soc Trans. 2014; 42:1129–1134. [PubMed: 25110014]
2. Kilchert C, Wittmann S, Vasiljeva L. The regulation and functions of the nuclear RNA exosome complex. Nat Rev Mol Cell Biol. 2016; 17:227–239. [PubMed: 26726035]
3. Zinder JC, Lima CD. Targeting RNA for processing or destruction by the eukaryotic RNA exosome and its cofactors. Genes Dev. 2017; 31:88–100. [PubMed: 28202538]
4. Hilleren P, McCarthy T, Rosbash M, Parker R, Jensen TH. Quality control of mRNA 3′-end processing is linked to the nuclear exosome. Nature. 2001; 413:538–542. [PubMed: 11586364]
5. Milligan L, Torchet C, Allmang C, Shipman T, Tollervey D. A nuclear surveillance pathway for mRNAs with defective polyadenylation. Mol Cell Biol. 2005; 25:9996–10004. [PubMed: 16260613]
6. Torchet C, Bousquet-Antonelli C, Milligan L, Thompson E, Kufel J, Tollervey D. Processing of 3′-extended read-through transcripts by the exosome can generate functional mRNAs. Mol Cell. 2002; 9:1285–1296. [PubMed: 12086625]
7. Kazerouninia A, Ngo B, Martinson HG. Poly(A) signal-dependent degradation of unprocessed nascent transcripts accompanies poly(A) signal-dependent transcriptional pausing in vitro. RNA. 2010; 16:197–210. [PubMed: 19926725]

8. Di Giammartino DC, Li W, Ogami K, Yashinskiie JJ, Hoque M, Tian B, Manley JL. RBBP6 isoforms regulate the human polyadenylation machinery and modulate expression of mRNAs with AU-rich 3’ utrs. Genes Dev. 2014; 28:2248–2260. [PubMed: 25319826]

9. Lemieux C, Marguerat S, Lafontaine J, Barbezier N, Bahler J, Bachand F. A pre-mRNA degradation pathway that selectively targets intron-containing genes requires the nuclear poly(A)-binding protein. Mol Cell. 2011; 44:108–119. [PubMed: 21981922]

10. Bousquet-Antonelli C, Presutti C, Tollervey D. Identification of a regulated pathway for nuclear pre-mRNA turnover. Cell. 2000; 102:765–775. [PubMed: 11030620]

11. Gudipati RK, Xu Z, Lebreton A, Seraphin B, Steinmetz LM, Jacquier A, Libri D. Extensive degradation of RNA precursors by the exosome in wild-type cells. Mol Cell. 2012; 48:409–421. [PubMed: 23000176]

12. Schneider C, Kudla G, Wlótzka W, Tuck A, Tollervey D. Transcripome-wide analysis of exosome targets. Mol Cell. 2012; 48:422–433. [PubMed: 23000172]

13. West S, Gromak N, Norbury CJ, Proudfoot NJ. Adenylation and exosome-mediated degradation of cotranscriptionally cleaved pre-messenger RNA in human cells. Mol Cell. 2006; 21:437–443. [PubMed: 16554989]

14. Wyers F, Rougemaille M, Badis G, Rousselle JC, Dufour ME, Boulay J, Regnault B, Devaux F, Namane A, Seraphin B, et al. Cryptic Pol II transcripts are degraded by a nuclear quality control pathway involving a new poly(A) polymerase. Cell. 2005; 121:725–737. [PubMed: 15935759]

15. Neil H, Malabat C, d’Aubenton-Carafa Y, Xu Z, Steinmetz LM, Jacquier A. Widespread bidirectional promoters are the major source of cryptic transcripts in yeast. Nature. 2009; 457:1038–1042. [PubMed: 19169244]

16. Xu Z, Wei W, Gagneur J, Perocchi F, Claude-Munster S, Camblong J, Guffanti E, Stutz F, Huber W, Steinmetz LM. Bidirectional promoters generate pervasive transcription in yeast. Nature. 2009; 457:1033–1037. [PubMed: 19169243]

17. Preker P, Nielsen J, Kammler S, Lykke-Andersen S, Christensen MS, Mapendano CK, Schierup MH, Jensen TH. RNA exosome depletion reveals transcription upstream of active human promoters. Science. 2008; 322:1851–1854. [PubMed: 19056938]

18. Flynn RA, Almada AE, Zamudio JR, Sharp PA. Antisense RNA polymerase II divergent transcripts are P-TEFb dependent and substrates for the RNA exosome. Proc Natl Acad Sci U S A. 2011; 108:10460–10465. [PubMed: 21670248]

19. Szczepinska T, Kalisiak K, Tomecki R, Labno A, Borowski LS, Kulinski TM, Adamska D, Kosinska J, Dziembowski A. DIS3 shapes the RNA polymerase II transciptome in humans by degrading a variety of unwanted transcripts. Genome Res. 2015; 25:1622–1633. [PubMed: 26294688]

20. Ogami K, Richard P, Chen Y, Hoque M, Li W, Moresco JJ, Yates JR 3rd, Tian B, Manley JL. An Mtr4/ZFC3H1 complex facilitates turnover of unstable nuclear RNAs to prevent their cytoplasmic transport and global translational repression. Genes Dev. 2017

21. Henriques T, Gilchrist DA, Nechaev S, Bern M, Muse GW, Burkholder A, Fargo DC, Adelman K. Stable pausing by RNA polymerase II provides an opportunity to target and integrate regulatory signals. Mol Cell. 2013; 52:517–528. [PubMed: 24184211]

22. Andersson R, Gebhard C, Miguel-Escalada I, Hoof I, Bornholdt J, Boyd M, Chen Y, Zhao X, Schmidt C, Suzuki T, et al. An atlas of active enhancers across human cell types and tissues. Nature. 2014; 507:455–461. [PubMed: 24670763]

23. Schlackow M, Nojima T, Gomes T, Dhir A, Carmo-Fonseca M, Proudfoot NJ. Distinctive patterns of transcription and RNA processing for human lincRNAs. Mol Cell. 2017; 65:25–38. [PubMed: 28017589]

24. Schwalb B, Michel M, Zacher B, Fruhauf K, Demel C, Tresch A, Gagneur J, Cramer P. TT-seq maps the human transient transcriptome. Science. 2016; 352:1225–1228. [PubMed: 27257258]
25. Makino DL, Conti E. Structure determination of an 11-subunit exosome in complex with RNA by molecular replacement. Acta Crystallogr D Biol Crystallogr. 2013; 69:2226–2235. [PubMed: 24189234]

26. Wasmuth EV, Januszky K, Lima CD. Structure of an Rrp6-RNA exosome complex bound to poly(A) RNA. Nature. 2014; 511:435–439. [PubMed: 25043052]

27. Makino DL, Schuch B, Stegmann E, Baumgartner M, Basquin C, Conti E. RNA degradation paths in a 12-subunit nuclear exosome complex. Nature. 2015; 524:54–58. [PubMed: 26222026]

28. Lebreton A, Tomecki R, Dziembowski A, Seraphin B. Endonucleolytic RNA cleavage by a eukaryotic exosome. Nature. 2008; 456:993–996. [PubMed: 19060886]

29. Schaeffer D, Tsonava B, Barbas A, Reis FP, Dastidar EG, Sanchez-Rotunno M, Arriaino CM, van Hoof A. The exosome contains domains with specific endoribonuclease, exoribonuclease and cytoplasmic mRNA decay activities. Nat Struct Mol Biol. 2009; 16:56–62. [PubMed: 19060898]

30. Schneider C, Leung E, Brown J, Tollervey D. The N-terminal pin domain of the exosome subunit Rrp44 harbors endonuclease activity and tethers Rrp44 to the yeast core exosome. Nucleic Acids Res. 2009; 37:1127–1140. [PubMed: 19129231]

31. Wasmuth EV, Lima CD. The Rrp6 C-terminal domain binds RNA and activates the nuclear RNA exosome. Nucleic Acids Res. 2017; 45:846–860. [PubMed: 27899565]

32. Allmang C, Petfalski E, Podtelejnikov A, Mann M, Tollervey D, Mitchell P. The yeast exosome and human PM-Scl are related complexes of 3′ → 5′ exonucleases. Genes Dev. 1999; 13:2148–2158. [PubMed: 10465791]

33. Tomecki R, Kristiansen MS, Lykke-Andersen S, Chlebowski A, Larsen KM, Szczesny RJ, Drazkowska K, Pastula A, Andersen JS, Stepien PP, et al. The human core exosome interacts with differentially localized processive RNases: hDis3 and hDis3L. EMBO J. 2010; 29:2342–2357. [PubMed: 20531386]

34. Staals RH, Bronkhorst AW, Schilders G, Slomovic S, Schuster G, Heck AJ, Rajmakers R, Pruijn GJ. Dis3-like 1: A novel exoribonuclease associated with the human exosome. EMBO J. 2010; 29:2358–2367. [PubMed: 20531389]

35. Shion T, Fukushima K, Suzuki N, Nakashima N, Noguchi E, Nishimoto T. Human Dis3p, which binds to either GTP- or GDP-Ran, complements Saccharomyces cerevisiae Dis3. J Biochem. 1998; 123:883–890. [PubMed: 9562621]

36. Schuch B, Feigenbutz M, Makino DL, Falk S, Basquin C, Mitchell P, Conti E. The exosome-binding factors Rrp6 and Rrp47 form a composite surface for recruiting the Mtr4 helicase. EMBO J. 2014; 33:2829–2846. [PubMed: 25319414]

37. Falk S, Bonneau F, Ebert J, Kogel A, Conti E. Mpp6 incorporation in the nuclear exosome contributes to RNA channeling through the Mtr4 helicase. Cell Rep. 2017; 20:2279–2286. [PubMed: 28877463]

38. Wasmuth EV, Zinder JC, Zattas D, Das M, Lima CD. Structure and reconstitution of yeast MPP6-nuclear exosome complexes reveals that MPP6 stimulates RNA decay and recruits the Mtr4 helicase. Elife. 2017; 6

39. Schneider C, Tollervey D. Threading the barrel of the RNA exosome. Trends Biochem Sci. 2013; 38:485–493. [PubMed: 23910895]

40. Wasmuth EV, Lima CD. Structure and activities of the eukaryotic RNA exosome. Enzymes. 2012; 31:53–75. [PubMed: 27166440]

41. Zinder JC, Wasmuth EV, Lima CD. Nuclear RNA exosome at 3.1 A reveals substrate specificities, RNA paths, and allosteric inhibition of Rrp44/Dis3. Mol Cell. 2016; 64:734–745. [PubMed: 27818140]

42. Liu JJ, Bratkowski MA, Liu X, Niu CY, Ke A, Wang HW. Visualization of distinct substrate-recruitment pathways in the yeast exosome by em. Nat Struct Mol Biol. 2014; 21:95–102. [PubMed: 24336220]

43. Bonneau F, Basquin J, Ebert J, Lorentzen E, Conti E. The yeast exosome functions as a macromolecular cage to channel RNA substrates for degradation. Cell. 2009; 139:547–559. [PubMed: 19879841]
44. Malet H, Topf M, Clare DK, Ebert J, Bonneau F, Basquin J, Drazkowska K, Tomecki R, Dziembowski A, Conti E, et al. RNA channelling by the eukaryotic exosome. EMBO Rep. 2010; 11:936–942. [PubMed: 21072061]

45. Wang HW, Wang J, Ding F, Callahan K, Bratkowski MA, Butler JS, Nogales E, Ke A. Architecture of the yeast Rrp44 exosome complex suggests routes of RNA recruitment for 3′ end processing. Proc Natl Acad Sci U S A. 2007; 104:16844–16849. [PubMed: 17942686]

46. Han J, van Hoof A. The RNA exosome channeling and direct access conformations have distinct in vivo functions. Cell Rep. 2016; 16:3348–3358. [PubMed: 27653695]

47. Delan-Forino C, Schneider C, Tollervey D. Transcriptome-wide analysis of alternative routes for RNA substrates into the exosome complex. PLoS Genet. 2017; 13:e1006699. [PubMed: 28355211]

48. Delan-Forino C, Schneider C, Tollervey D. RNA substrate length as an indicator of exosome interactions in vivo. Wellcome Open Res. 2017; 2:34. [PubMed: 28748221]

49. Meola N, Domanski M, Karadoulama E, Chen Y, Gentil C, Pultz D, Vitting-Seerup K, Lykke-Andersen S, Andersen Jens S, Sandelin A, et al. Identification of a nuclear exosome decay pathway for processed transcripts. Molecular Cell. 2016; 64:520–533. [PubMed: 27871484]

50. Kadaba S, Krueger A, Trice T, Krecic AM, Hinnebusch AG, Anderson J. Nuclear surveillance and degradation of hypomodified initiator tRNAmet in S. cerevisiae. Genes Dev. 2004; 18:1227–1240. [PubMed: 15145828]

51. LaCava J, Houseley J, Saveanu C, Petfalski E, Thompson E, Jacquier A, Tollervey D. RNA degradation by the exosome is promoted by a nuclear polyadenylation complex. Cell. 2005; 121:713–724. [PubMed: 15935758]

52. Vanacova S, Wolf J, Martin G, Blank D, Dettwiler S, Friedlein A, Langen H, Keith G, Keller W. A new yeast poly(A) polymerase complex involved in RNA quality control. PLoS Biol. 2005; 3:e189. [PubMed: 15828860]

53. Houseley J, Tollervey D. Yeast Trf5p is a nuclear poly(A) polymerase. EMBO Rep. 2006; 7:205–211. [PubMed: 16374505]

54. Hamill S, Wolin SL, Reinish KM. Structure and function of the polymerase core of TRAMP, a RNA surveillance complex. Proc Natl Acad Sci U S A. 2010; 107:15045–15050. [PubMed: 20696927]

55. Holub P, Lalakova J, Cerna H, Pasulka J, Sarazova M, Hrazdilova K, Arce MS, Hobor F, Stefl R, Vanacova S. Air2p is critical for the assembly and RNA-binding of the TRAMP complex and the KOW domain of Mtr4p is crucial for exosome activation. Nucleic Acids Res. 2012; 40:5679–5693. [PubMed: 22402490]

56. Fasken MB, Leung SW, Banerjee A, Kodani MO, Chavez R, Bowman EA, Purohit MK, Rubinson ME, Rubinson EH, Corbett AH. Air1 zinc knuckles 4 and 5 and a conserved iwrxy motif are critical for the function and integrity of the Trf4/5-Air1/2-Mtr4 polyadenylation (TRAMP) RNA quality control complex. J Biol Chem. 2011; 286:37429–37445. [PubMed: 21878619]

57. Wang X, Jia H, Jankowsky E, Anderson JT. Degradation of hypomethylated tRNA(imet) in vivo involves RNA-dependent ATPase activity of the DExH helicase Mtr4p. RNA. 2008; 14:107–116. [PubMed: 18000032]

58. Schneider C, Anderson JT, Tollervey D. The exosome subunit Rrp44 plays a direct role in RNA substrate recognition. Mol Cell. 2007; 27:324–331. [PubMed: 17643380]

59. Wiotzka W, Kudla G, Grammner S, Tollervey D. The nuclear RNA polymerase II surveillance system targets polymerase III transcripts. EMBO J. 2011; 30:1790–1803. [PubMed: 21460797]

60. Kadaba S, Wang X, Anderson JT. Nuclear RNA surveillance in Saccharomyces cerevisiae: Trf4p-dependent polyadenylation of nascent hypomethylated tRNA and an aberrant form of 5s rRNA. RNA. 2006; 12:508–521. [PubMed: 16431988]

61. Dez C, Houseley J, Tollervey D. Surveillance of nuclear-restricted pre-ribosomes within a subnucleolar region of Saccharomyces cerevisiae. EMBO J. 2006; 25:1534–1546. [PubMed: 16541108]

62. Grzechnik P, Kufel J. Polyadenylation linked to transcription termination directs the processing of snoRNA precursors in yeast. Mol Cell. 2008; 32:247–258. [PubMed: 18951092]
63. Losh JS, King AK, Bakelar J, Taylor L, Loomis J, Rosenzweig JA, Johnson SJ, van Hoof A. Interaction between the RNA-dependent atpase and poly(A) polymerase subunits of the TRAMP complex is mediated by short peptides and important for snoRNA processing. Nucleic Acids Res. 2015; 43:1848–1858. [PubMed: 25589546]

64. Houseley J, Kotovic K, El Hage A, Tollervey D. Trf4 targets ncRNAs from telomeric and rDNA spacer regions and functions in rDNA copy number control. EMBO J. 2007; 26:4996–5006. [PubMed: 18007593]

65. Ciais D, Bohnsack MT, Tollervey D. The mRNA encoding the yeast are-binding protein cth2 is generated by a novel 3′ processing pathway. Nucleic Acids Res. 2008; 36:3075–3084. [PubMed: 18400782]

66. Roth KM, Byam J, Fang F, Butler JS. Regulation of Nab2 mRNA 3′-end formation requires the core exosome and the Trf4p component of the TRAMP complex. RNA. 2009; 15:1045–1058. [PubMed: 19369424]

67. Bresson S, Tuck A, Staneva D, Tollervey D. Nuclear RNA decay pathways aid rapid remodeling of gene expression in yeast. Mol Cell. 2017; 65:787–800 e785. [PubMed: 28190770]

68. Bernstein J, Patterson DN, Wilson GM, Toth EA. Characterization of the essential activities of Saccharomyces cerevisiae Mtr4p, a 3′→5′ helicase partner of the nuclear exosome. J Biol Chem. 2008; 283:4930–4942. [PubMed: 18096702]

69. Jia H, Wang X, Liu F, Guenther UP, Srinivasan S, Anderson JT, Jankowsky E. The RNA helicase Mtr4p modulates polyadenylation in the TRAMP complex. Cell. 2011; 145:890–901. [PubMed: 21663793]

70. Weir JR, Bonneau F, Hentschel J, Conti E. Structural analysis reveals the characteristic features of Mtr4, a dExh helicase involved in nuclear RNA processing and surveillance. Proc Natl Acad Sci U S A. 2010; 107:12139–12144. [PubMed: 20566885]

71. Jia H, Wang X, Anderson JT, Jankowsky E. RNA unwinding by the Trf4/Air2/Mtr4 polyadenylation (TRAMP) complex. Proc Natl Acad Sci U S A. 2012; 109:7292–7297. [PubMed: 22532666]

72. Falk S, Weir JR, Hentschel J, Reichelt P, Bonneau F, Conti E. The molecular architecture of the TRAMP complex reveals the organization and interplay of its two catalytic activities. Mol Cell. 2014; 55:856–867. [PubMed: 25175027]

73. Patrick EM, Srinivasan S, Jankowsky E, Comstock MJ. The RNA helicase Mtr4p is a duplex-sensing translocase. Nat Chem Biol. 2017; 13:99–104. [PubMed: 27870836]

74. Vasiljeva L, Buratowski S. Nrd1 interacts with the nuclear exosome for 3′ processing of RNA polymerase II transcripts. Mol Cell. 2006; 21:239–248. [PubMed: 16427013]

75. Porrúa O, Hobor F, Boulay J, Kubicek K, D’Aubenton-Carafa Y, Gudipati RK, Stefl R, Libri D. In vivo selex reveals novel sequence and structural determinants of Nrd1-Nab3-Sen1-dependent transcription termination. EMBO J. 2012; 31:3935–3948. [PubMed: 23032188]

76. Creamer TJ, Darby MM, Jamonnak N, Schaughency P, Hao H, Wheelan SJ, Corden JL. Transcriptome-wide binding sites for components of the Saccharomyces cerevisiae non-poly(A) termination pathway: Nrd1, Nab3, and Sen1. PLoS Genet. 2011; 7:e1002329. [PubMed: 22028667]

77. Porrua O, Libri D. A bacterial-like mechanism for transcription termination by the Sen1p helicase in budding yeast. Nat Struct Mol Biol. 2013; 20:884–891. [PubMed: 23748379]

78. Hazeltaker DZ, Marquardt S, Wlotzka W, Buratowski S. Kinetic competition between RNA polymerase II and Sen1-dependent transcription termination. Mol Cell. 2013; 49:55–66. [PubMed: 23177741]

79. Han Z, Libri D, Porrúa O. Biochemical characterization of the helicase Sen1 provides new insights into the mechanisms of non-coding transcription termination. Nucleic Acids Res. 2017; 45:1355–1370. [PubMed: 28180347]

80. Arigo JT, Carroll KL, Ames JM, Corden JL. Regulation of yeast Nrd1 expression by premature transcription termination. Mol Cell. 2006; 21:641–651. [PubMed: 16507362]

81. Arigo JT, Eyler DE, Carroll KL, Corden JL. Termination of cryptic unstable transcripts is directed by yeast RNA-binding proteins Nrd1 and Nab3. Mol Cell. 2006; 23:841–851. [PubMed: 16973436]
82. Conrad NK, Wilson SM, Steinmetz EJ, Patturajan M, Brow DA, Swanson MS, Corden JL. A yeast heterogeneous nuclear ribonucleoprotein complex associated with RNA polymerase II. Genetics. 2000; 154:557–571. [PubMed: 10655211]

83. Mayer A, Heidemann M, Lidschreiber M, Schreieck A, Sun M, Hintermair C, Kremmer E, Eick D, Cramer P. Ctd tyrosine phosphorylation impairs termination factor recruitment to RNA polymerase II. Science. 2012; 336:1723–1725. [PubMed: 22745433]

84. Schulz D, Schwab B, Kiesel A, Baejen C, Torkler P, Gagneur J, Soeding J, Cramer P. Transcriptome surveillance by selective termination of noncoding RNA synthesis. Cell. 2013; 155:1075–1087. [PubMed: 24210918]

85. Steinmetz EJ, Conrad NK, Brow DA, Corden JL. RNA-binding protein Nrd1 directs poly(A)-independent 3′-end formation of RNA polymerase II transcripts. Nature. 2001; 413:327–331. [PubMed: 11565036]

86. Grzechnik P, Gdula MR, Proudfoot NJ. Pcf11 orchestrates transcription termination pathways in yeast. Genes Dev. 2015; 29:849–861. [PubMed: 25877920]

87. Kubicek K, Cerna H, Holub P, Pasulka J, Hrossova D, Loehr F, Hofer C, Vanacova S, Stefl R. Serine phosphorylation and proline isomerization in RNAP II CTD control recruitment of Nrd1. Genes Dev. 2012; 26:1891–1896. [PubMed: 22892239]

88. Vasiljeva L, Kim M, Mutschler H, Buratowski S, Meinhart A. The Nrd1-Nab3-Sen1 termination complex interacts with the ser5-phosphorylated RNA polymerase II C-terminal domain. Nat Struct Mol Biol. 2008; 15:795–804. [PubMed: 18660819]

89. Tudek A, Porrua O, Kabzinski T, Lidschreiber M, Kubicek K, Fortova A, Lacroute F, Vanacova S, Cramer P, Stefl R, et al. Molecular basis for coordinating transcription termination with noncoding RNA degradation. Mol Cell. 2013; 55:467–481. [PubMed: 25066235]

90. Mitsuzawa H, Kanda E, Ishihama A. Rpb7 subunit of RNA polymerase II interacts with an RNA-binding protein involved in processing of transcripts. Nucleic Acids Res. 2003; 31:4696–4701. [PubMed: 12907709]

91. Lemay JF, Marguerat S, Larochelle M, Liu X, van Nues R, Hunyad Kurti J, Hoque M, Tian B, Granneman S, Bahl J, et al. The Nrd1-like protein seb1 coordinates cotranscriptional 3′ end processing and polyadenylation site selection. Genes Dev. 2016; 30:1558–1572. [PubMed: 27401558]

92. Marina DB, Shankar S, Natarajan P, Finn KJ, Madhani HD. A conserved ncRNA-binding protein recruits silencing factors to heterochromatin through an RNAi-independent mechanism. Genes Dev. 2013; 27:1851–1856. [PubMed: 24013500]

93. Wittmann S, Renner M, Watts BR, Adams O, Huseyn M, Baejen C, El Omari K, Kilchert C, Heo DH, Kecman T, et al. The conserved protein seb1 drives transcription termination by binding RNA polymerase II and nascent RNA. Nat Commun. 2017; 8:14861. [PubMed: 28367989]

94. Liu X, Hoque M, Larochelle M, Lemay JF, Yurko N, Manley JL, Bachand F, Tian B. Comparative analysis of alternative polyadenylation in S. cerevisiae and S. pombe. Genome Res. 2017; 27:1685–1695. [PubMed: 28916539]

95. Larochelle M, Hunyad Kurti J, Bachand F. Polyadenylation site selection: Linking transcription and RNA processing via a conserved carboxy-terminal domain (CTD)-interacting protein. Curr Genet. 2017; 63:195–199. [PubMed: 27582274]

96. Patturajan M, Wei X, Berezney R, Corden JL. A nuclear matrix protein interacts with the phosphorylated C-terminal domain of RNA polymerase II. Mol Cell Biol. 1998; 18:2406–2415. [PubMed: 9528809]

97. Becker R, Loll B, Meinhart A. Snapshots of the RNA processing factor scaf8 bound to different phosphorylated forms of the carboxy-terminal domain of RNA polymerase II. J Biol Chem. 2008; 283:22659–22669. [PubMed: 18550522]

98. Fasken MB, Laribee RN, Corbett AH. Nab3 facilitates the function of the TRAMP complex in RNA processing via recruitment of Rrp6 independent of Nrd1. PLoS Genet. 2015; 11:e1005044. [PubMed: 25775092]

99. Thoms M, Thomson E, Bassler J, Gnadig M, Griesel S, Hurt E. The exosome is recruited to RNA substrates through specific adaptor proteins. Cell. 2015; 162:1029–1038. [PubMed: 26317469]
100. Falk S, Tants JN, Basquin J, Thoms M, Hurt E, Sattler M, Conti E. Structural insights into the interaction of the nuclear exosome helicase Mtr4 with the pre-ribosomal protein nop53. RNA. 2017

101. Babour A, Shen Q, Dos-Santos J, Murray S, Gay A, Challal D, Fasken M, Palancade B, Corbett A, Libri D, et al. The chromatin remodeler isw1 is a quality control factor that surveys nuclear mrnp biogenesis. Cell. 2016; 167:1201–1214 e1215. [PubMed: 27863241]

102. Buhler M, Haas W, Gygi SP, Moazed D. RNAi-dependent and -independent RNA turnover mechanisms contribute to heterochromatin gene silencing. Cell. 2007; 129:707–721. [PubMed: 17512405]

103. Reyes-Turcu FE, Zhang K, Zofall M, Chen E, Grewal SI. Defects in RNA quality control factors reveal RNAi-independent nucleation of heterochromatin. Nat Struct Mol Biol. 2011; 18:1132–1138. [PubMed: 21892171]

104. Zhang K, Fischer T, Porter RL, Dhakshnamoorthy J, Zofall M, Zhou M, Veenstra T, Grewal SI. Clr4/suv39 and RNA quality control factors cooperate to trigger RNAi and suppress antisense RNA. Science. 2011; 331:1624–1627. [PubMed: 21436456]

105. Wang SW, Stevenson AL, Kearsey SE, Watt S, Buhler J. Global role for polyadenylation-assisted nuclear RNA degradation in posttranscriptional gene silencing. Mol Cell Biol. 2008; 28:656–665. [PubMed: 18025105]

106. Buhler M, Spies N, Bartel DP, Moazed D. Tramp-mediated RNA surveillance prevents spurious entry of RNAs into the Schizosaccharomyces pombe siRNA pathway. Nat Struct Mol Biol. 2008; 15:1015–1023. [PubMed: 18776903]

107. Larochelle M, Lemay JF, Bachand F. The tho complex cooperates with the nuclear RNA surveillance machinery to control small nucleolar RNA expression. Nucleic Acids Res. 2012; 40:10240–10253. [PubMed: 22965128]

108. Pisacane P, Halic M. Tailing and degradation of argonaute-bound small RNAs protect the genome from uncontrolled RNAi. Nat Commun. 2017; 8:15332. [PubMed: 28541282]

109. Strasser K, Masuda S, Mason P, Pfannstiel J, Oppizzi M, Rodriguez-Navarro S, Rondon AG, Aguilara A, Struhl K, Reed R, et al. TREX is a conserved complex coupling transcription with messenger RNA export. Nature. 2002; 417:304–308. [PubMed: 11979277]

110. Zenklusen D, Vinciguerra P, Wyss JC, Stutz F. Stable mrnp formation and export require cotranscriptional recruitment of the mRNA export factors Yra1p and Sub2p by hpr1p. Mol Cell Biol. 2002; 22:8241–8253. [PubMed: 12417727]

111. Lee NN, Chalamcharla VR, Reyes-Turcu F, Mehta S, Zofall M, Balachandran V, Dhakshnamoorthy J, Taneya N, Yanamaka S, Zhou M, et al. Mtr4-like protein coordinates nuclear RNA processing for heterochromatin assembly and for telomere maintenance. Cell. 2013; 155:1061–1074. [PubMed: 24210919]

112. Egan ED, Braun CR, Gygi SP, Moazed D. Post-transcriptional regulation of meiotic genes by a nuclear RNA silencing complex. RNA. 2014; 20:867–881. [PubMed: 24713849]

113. Zhou Y, Zhu J, Schermann G, Ohle C, Bendrin K, Sugioaka-Sugiyama R, Sugiyama T, Fischer T. The fission yeast MTREC complex targets cuts and unspliced pre-mRNAs to the nuclear exosome. Nat Commun. 2015; 6:7050. [PubMed: 25989903]

114. Harigaya Y, Tanaka H, Yanamaka S, Tanaka K, Watanabe Y, Tsutsumi C, Chikashige Y, Hiraoka Y, Yamashita A, Yamamoto M.Selective elimination of messenger RNA prevents an incidence of untimely meiosis. Nature. 2006; 442:45–50. [PubMed: 16823445]

115. Shichino Y, Yamashita A, Yamamoto M. Meiotic long non-coding meiRNA accumulates as a dot at its genetic locus facilitated by Mmi1 and plays as a decoy to lure Mmi1. Open Biol. 2014; 4:140022. [PubMed: 24920274]

116. Kilchert C, Wittmann S, Passoni M, Shah S, Granneman S, Vasiljeva L. Regulation of mRNA levels by decay-promoting introns that recruit the exosome specificity factor Mmi1. Cell Rep. 2015; 13:2504–2515. [PubMed: 26670050]

117. Yamashita A, Shichino Y, Tanaka H, Hiriart E, Touat-Todeschini L, Vavasseur A, Ding DQ, Hiraoka Y, Verdel A, Yamamoto M. Hexanucleotide motifs mediate recruitment of the RNA elimination machinery to silent meiotic genes. Open Biol. 2012; 2:120014. [PubMed: 22645662]
118. Chen HM, Futcher B, Leatherwood J. The fission yeast RNA binding protein Mmi1 regulates meiotic genes by controlling intron specific splicing and polyadenylation coupled RNA turnover. PLoS One. 2011; 6:e26804. [PubMed: 22046364]

119. Hiriart E, Vavasseur A, Touat-Todeschini L, Yamashita A, Gilquin B, Lambert E, Perot J, Shichino Y, Nazaret N, Boyault C, et al. Mmi1 RNA surveillance machinery directs RNAi complex rts to specific meiotic genes in fission yeast. EMBO J. 2012; 31:2296–2308. [PubMed: 22522705]

120. Yamashita A, Takayama T, Iwata R, Yamamoto M. A novel factor Iss10 regulates Mmi1-mediated selective elimination of meiotic transcripts. Nucleic Acids Res. 2013; 41:9680–9687. [PubMed: 23980030]

121. St-Andre O, Lemieux C, Perreault A, Lackner DH, Bahler J, Bachand F. Negative regulation of meiotic gene expression by the nuclear poly(A)-binding protein in fission yeast. J Biol Chem. 2010; 285:27859–27868. [PubMed: 20622014]

122. Sugiyama T, Wanatabe N, Kitahata E, Tani T, Sugiooka-Sugiyama R. Red5 and three nuclear pore components are essential for efficient suppression of specific mRNAs during vegetative growth of fission yeast. Nucleic Acids Res. 2013; 41:6674–6686. [PubMed: 23658229]

123. Andersen PR, Domanski M, Kristiansen MS, Storvall H, Ntinis E, Verheggen C, Schein A, Bunkenborg J, Poser I, Hallais M, et al. The human cap-binding complex is functionally connected to the nuclear RNA exosome. Nat Struct Mol Biol. 2013; 20:1367–1376. [PubMed: 24270879]

124. Sugiyama T, Wanatabe N, Kitahata E, Tani T, Sugiooka-Sugiyama R. Red5 and three nuclear pore components are essential for efficient suppression of specific mRNAs during vegetative growth of fission yeast. Nucleic Acids Res. 2013; 41:6674–6686. [PubMed: 23658229]

125. Andersen PR, Domanski M, Kristiansen MS, Storvall H, Ntinis E, Verheggen C, Schein A, Bunkenborg J, Poser I, Hallais M, et al. The human cap-binding complex is functionally connected to the nuclear RNA exosome. Nat Struct Mol Biol. 2013; 20:1367–1376. [PubMed: 24270879]

126. Ogami et al. Page 18

127. Molleston JM, Sabin LR, Moy RH, Menghani SV, Rausch K, Gordesky-Gold B, Hopkins KC, Zhou R, Jensen TH, Wilusz JE, et al. A conserved virus-induced cytoplasmic TRAMP-like complex recuits the exosome to target viral RNA for degradation. Genes Dev. 2016; 30:1658–1670. [PubMed: 27474443]

128. Berndt H, Harnisch C, Rammelt C, Stohr N, Zirkel A, Dohm JC, Himmelbauer H, Tavanaz JP, Huttelmaier S, Wahle E. Maturation of mammalian h/aca box snoRNAs: PAPD5-dependent adenylation and parr-dependent trimming. RNA. 2012; 18:958–972. [PubMed: 22442037]

129. Shcherbik N, Wang M, Lapik YR, Srivastava L, Pestov DG. Polyadenylation and degradation of incompletely spliced RNA poly(A) polymerase I transcripts in mammalian cells. EMBO Rep. 2010; 11:106–111. [PubMed: 20062005]

130. Nag A, Steitz JA. Tri-snurp-associated proteins interact with subunits of the TRAMP and nuclear exosome complexes, linking RNA decay and pre-mRNA splicing. RNA Biol. 2012; 9:334–342. [PubMed: 22336707]

131. Nagahama M, Yamazoe T, Haru Y, Tani K, Tsuji A, Tagaya M. The aatpase nvl2 is a component of pre-ribosomal particles that interacts with the DEXD/H-box RNA helicase dobl. Biochem Biophys Res Commun. 2006; 346:1075–1082. [PubMed: 16782053]

132. Sudo H, Nozaki A, Uno H, Ishida Y, Nagahama M. Interaction properties of human TRAMP-like proteins and their role in pre-rRNA 5'ets turnover. FEBS Lett. 2016; 590:2963–2972. [PubMed: 27434818]

133. Hiraishi N, Ishida Y, Nagahama M. Aaa-aptase NVL2 acts on Mtr4-exosome complex to dissociate the nucleolar protein WDR74. Biochem Biophys Res Commun. 2015; 467:534–540. [PubMed: 26456651]

134. Hiraishi N, Ishida YI, Sudo H, Nagahama M. WDR74 participates in an early cleavage of the pre-rRNA processing pathway in cooperation with the nucleolar aatpase NVL2. Biochem Biophys Res Commun. 2017

*Noncoding RNA. Author manuscript; available in PMC 2018 April 05.*
135. Yoshikatsu Y, Ishida Y, Sudo H, Yuasa K, Tsuji A, Nagahama M. NVL2, a nucleolar AAA-Atpase, is associated with the nuclear exosome and is involved in pre-rRNA processing. Biochem Biophys Res Commun. 2015; 464:780–786. [PubMed: 26166824]

136. Macias S, Cordiner RA, Gautier P, Plass M, Caceres JF. DGCR8 acts as an adaptor for the exosome complex to degrade double-stranded structured RNAs. Mol Cell. 2015; 60:873–885. [PubMed: 26687677]

137. Tseng CK, Wang HF, Burns AM, Schroeder MR, Gaspari M, Baumann P. Human telomerase RNA processing and quality control. Cell Rep. 2015; 13:2232–2243. [PubMed: 26628367]

138. Nguyen D, Grenier St-Sauveur V, Bergeron D, Dupuis-Sandoval F, Scott MS, Bachand F. A polyadenylation-dependent 3’ end maturation pathway is required for the synthesis of the human telomerase RNA. Cell Rep. 2015; 13:2244–2257. [PubMed: 26628368]

139. Shukla S, Schmidt JC, Goldfarb KC, Cech TR, Parker R. Inhibition of telomerase RNA decay rescues telomerase deficiency caused by Dyskerin or PARN defects. Nat Struct Mol Biol. 2016; 23:286–292. [PubMed: 26950371]

140. Lubas M, Andersen PR, Schein A, Dziembowski A, Kudla G, Jensen TH. The human nuclear exosome targeting complex is loaded onto newly synthesized RNA to direct early ribonucleolysis. Cell Rep. 2015; 10:178–192. [PubMed: 25578728]

141. Hrossova D, Sikorsky T, Potesil D, Bartosovic M, Pasulka J, Zdrahal Z, Stef1 R, Vanacova S. RBM7 subunit of the NEXT complex binds U-rich sequences and targets 3’-end extended forms of snRNAs. Nucleic Acids Res. 2015; 43:4236–4248. [PubMed: 25852104]

142. Bresson SM, Conrad NK. The human nuclear poly(A)-binding protein promotes RNA hyperadenylation and decay. PLoS Genet. 2013; 9:e1003893. [PubMed: 24146636]

143. Bresson SM, Hunter OV, Hunter AC, Conrad NK. Canonical poly(A) polymerase activity promotes the decay of a wide variety of mammalian nuclear RNAs. PLoS Genet. 2015; 11:e1005610. [PubMed: 26484760]

144. Beaulieu YB, Kleinman CL, Landry-Voyer AM, Majewski J, Bachand F. Polyadenylation-dependent control of long noncoding RNA expression by the poly(A)-binding protein nuclear 1. PLoS Genet. 2012; 8:e1003078. [PubMed: 23166521]

145. Shi Y, Di Giammartino DC, Taylor D, Sarkeshik A, Rice WJ, Yates JR 3rd, Frank I, Manley JL. Molecular architecture of the human pre-mRNA 3’ processing complex. Mol Cell. 2009; 33:365–376. [PubMed: 19217410]

146. Giacometti S, Bembahouche NEH, Domanski M, Robert MC, Meola N, Lubas M, Bukenborg J, Andersen JS, Schulze WM, Verheggen C, et al. Mutually exclusive CBC-containing complexes contribute to RNA fate. Cell Rep. 2017; 18:2635–2650. [PubMed: 28297668]

147. Iasillo C, Schmid M, Yahia Y, Maqbool MA, Descostes N, Karadoulama E, Bertrand E, Andrau JC, Jensen TH. ARS2 is a general suppressor of pervasive transcription. Nucleic Acids Res. 2017; 45:10229–10241. [PubMed: 28973446]

148. Morton DJ, Kuiper EG, Jones SK, Leung SW, Corbett AH, Fasken MB. The RNA exosome and RNA exosome-linked disease. RNA. 2017

149. Chapman MA, Lawrence MS, Keats JJ, Cibulskis K, Sougnez C, Schinzel AC, Harview CL, Brunet JP, Ahmann GJ, Adli M, et al. Initial genome sequencing and analysis of multiple myeloma. Nature. 2011; 471:467–472. [PubMed: 21430775]

150. Tomecki R, Drzakowska K, Kucinski I, Stodus K, Szczenysy RJ, Gruchota J, Owczarek EP, Kalisiak K, Dziembowski A. Multiple myeloma-associated hDis3 mutations cause perturbations in cellular RNA metabolism and suggest hDis3 PIN domain as a potential drug target. Nucleic Acids Res. 2014; 42:1270–1290. [PubMed: 24150935]

151. Blasius M, Wagner SA, Choudhary C, Bartek J, Jackson SP. A quantitative 14-3-3 interaction screen connects the nuclear exosome targeting complex to the DNA damage response. Genes Dev. 2014; 28:1977–1982. [PubMed: 25189701]

152. Tiedje C, Lubas M, Tehrani M, Menon MB, Ronkina N,ousseau S, Cohen P, Kotlyarov A, Gaestel M. p38MAPK/MK2-mediated phosphorylation of RBM7 regulates the human nuclear exosome targeting complex. RNA. 2015; 21:262–278. [PubMed: 25525152]
153. Wang X, Arai S, Song X, Reichart D, Du K, Pascual G, Tempst P, Rosenfeld MG, Glass CK, Kurokawa R. Induced ncRNAs allosterically modify RNA-binding proteins in cis to inhibit transcription. Nature. 2008; 454:126–130. [PubMed: 18509338]

154. Lloret-Llinares M, Mapendano CK, Martlev LH, Lykke-Andersen S, Jensen TH. Relationships between PROMPT and gene expression. RNA Biol. 2016; 13:6–14. [PubMed: 26574648]

155. Li X, Manley JL. Cotranscriptional processes and their influence on genome stability. Genes Dev. 2006; 20:1838–1847. [PubMed: 16847344]

156. Li X, Manley JL. Inactivation of the SR protein splicing factor ASF/SF2 results in genomic instability. Cell. 2005; 122:365–378. [PubMed: 16096057]

157. Huertas P, Aguilera A. Cotranscriptionally formed DNA:RNA hybrids mediate transcription elongation impairment and transcription-associated recombination. Mol Cell. 2003; 12:711–721. [PubMed: 14527416]

158. Gaillard H, Aguilera A. Transcription as a threat to genome integrity. Annu Rev Biochem. 2016; 85:291–317. [PubMed: 27023844]

159. Richard P, Manley JL. R loops and links to human disease. J Mol Biol. 2017; 429:3168–3180. [PubMed: 27600412]

160. Santos-Pereira JM, Aguilera A. R loops: New modulators of genome dynamics and function. Nat Rev Genet. 2015; 16:583–597. [PubMed: 26370899]

161. Skourti-Stathaki K, Proudfoot NJ. A double-edged sword: R loops as threats to genome integrity and powerful regulators of gene expression. Genes Dev. 2014; 28:1384–1396. [PubMed: 24990962]

162. Richard P, Feng S, Manley JL. A SUMO-dependent interaction between Senataxin and the exosome, disrupted in the neurodegenerative disease AOA2, targets the exosome to sites of transcription-induced DNA damage. Genes Dev. 2013; 27:2227–2232. [PubMed: 24105744]

163. El Hage A, French SL, Beyer AL, Tollervey D. Loss of topoisomerase I leads to R-loop-mediated transcriptional blocks during ribosomal RNA synthesis. Genes Dev. 2010; 24:1546–1558. [PubMed: 20634320]

164. Manfrini N, Trovesi C, Wery M, Martina M, Cesena D, Descrimes M, Morillon A, d’Adda di Fagagna F, Longhese MP. RNA-processing proteins regulate Mec1/ATR activation by promoting generation of RPA-coated ssDNA. EMBO Rep. 2015; 16:221–231. [PubMed: 25527408]

165. Wahba L, Amor JD, Koshland D, Vuica-Ross M. RNase H and multiple RNA biogenesis factors cooperate to prevent RNA:DNA hybrids from generating genome instability. Mol Cell. 2011; 44:978–988. [PubMed: 22195970]

166. Skourtı-Stathaki K, Proudfoot NJ, Gromak N. Human senataxin resolves RNA/DNA hybrids formed at transcriptional pause sites to promote Xrn2-dependent termination. Mol Cell. 2011; 42:794–805. [PubMed: 21700224]

167. Basu U, Meng FL, Keim C, Grinstein V, Pefanis E, Eccleston J, Zhang T, Myers D, Wasserman CR, Wesemann DR, et al. The RNA exosome targets the AID cytidine deaminase to both strands of transcribed duplex DNA substrates. Cell. 2011; 144:353–363. [PubMed: 21255825]

168. Sun J, Keim CD, Wang J, Kazadi D, Oliver PM, Rabadan R, Basu U. E3-ubiquitin ligase NEDD4 determines the fate of AID-associated RNA polymerase II in B cells. Genes Dev. 2013; 27:1821–1833. [PubMed: 23964096]

169. Pefanis E, Basu U. RNA exosome regulates AID DNA mutator activity in the B cell genome. Adv Immunol. 2015; 127:257–308. [PubMed: 26073986]
174. Pefanis E, Wang J, Rothschild G, Lim J, Chao J, Rabadan R, Economides AN, Basu U. Noncoding RNA transcription targets AID to divergently transcribed loci in B cells. Nature. 2014; 514:389–393. [PubMed: 2519026]

175. Pefanis E, Wang J, Rothschild G, Lim J, Kazadi D, Sun J, Federation A, Chao J, Elliott O, Liu ZP, et al. RNA exosome-regulated long non-coding RNA transcription controls super-enhancer activity. Cell. 2015; 161:774–789. [PubMed: 2597685]

176. Lim J, Giri PK, Kazadi D, Laffleur B, Zhang W, Grinstein V, Pefanis E, Brown LM, Ladewig E, Martin O, et al. Nuclear proximity of Mtr4 to RNA exosome restricts DNA mutational asymmetry. Cell. 2017; 169:523–537 e515. [PubMed: 28431250]

177. Chi B, Wang Q, Wu G, Tan M, Wang L, Shi M, Chang X, Cheng H. Aly and tho are required for assembly of the human TREX complex and association of TREX components with the spliced mRNA. Nucleic Acids Res. 2013; 41:1294–1306. [PubMed: 23222130]

178. Cheng H, Dufu K, Lee CS, Hsu JL, Dias A, Reed R. Human mRNA export machinery recruited to the 5′ end of mRNA. Cell. 2006; 127:1389–1400. [PubMed: 17190602]

179. Nojima T, Hirose T, Kimura H, Hagiwara M. The interaction between cap-binding complex and RNA export factor is required for intronless mRNA export. J Biol Chem. 2007; 282:15645–15651. [PubMed: 17363367]

180. Masuda S, Das R, Cheng H, Hurt E, Dorman N, Reed R. Recruitment of the human TREX complex to mRNA during splicing. Genes Dev. 2005; 19:1512–1517. [PubMed: 15998806]

181. Chi B, Wang K, Du Y, Gui B, Chang X, Wang L, Fan J, Chen S, Wu X, Li G, et al. A sub-element in pre-enhances nuclear export of intronless mRNAs by recruiting the TREX complex via ZC3H18. Nucleic Acids Res. 2014; 42:7305–7318. [PubMed: 24782531]

182. Fan J, Kuai B, Wu G, Wu X, Chi B, Wang L, Wang K, Shi Z, Zhang H, Chen S, et al. Exosome cofactor hMtr4 competes with export adaptor ALYREF to ensure balanced nuclear RNA pools for degradation and export. EMBO J. 2017; 36:2870–2886. [PubMed: 28801509]

183. Ogami K, Manley JL. Mtr4/zfc3h1 protects polysomes through nuclear RNA surveillance. Cell Cycle. 2017:1–2.

184. Johnson SA, Cubberley G, Bentley DL. Cotranscriptional recruitment of the mRNA export factor Yral by direct interaction with the 3′ end processing factor Pcf11. Mol Cell. 2009; 33:215–226. [PubMed: 19110458]

185. Raepp MD, Aringhieri C, Vivarelli S, Cardinale S, Paro S, Schumperli D, Barabino SM. Mammalian pre-mRNA 3′ end processing factor CFIm 68 functions in mRNA export. Mol Biol Cell. 2009; 20:5211–5223. [PubMed: 19864460]

186. Tran DD, Saran S, Williamson AJ, Pierce A, Dittrich-Breiholz O, Wiehlmann L, Koch A, Whetten AD, Tamura T. THOC5 controls 3′ end-processing of immediate early genes via interaction with polyadenylation specific factor 100 (CPSF100). Nucleic Acids Res. 2014; 42:12249–12260. [PubMed: 25274738]

187. Katahira J, Okuzaki D, Inoue H, Yoneda Y, Maehara K, Ohkawa Y. Human TREX component THOC5 affects alternative polyadenylation site choice by recruiting mammalian cleavage factor i. Nucleic Acids Res. 2013; 41:7060–7072. [PubMed: 23685434]

188. Shi M, Zhang H, Wu X, He Z, Wang L, Yin S, Tian B, Li G, Cheng H. ALYREF mainly binds to the 5′ and the 3′ regions of the mRNA in vivo. Nucleic Acids Res. 2017; 45:9640–9653. [PubMed: 28934468]

189. Ingolia NT. Ribosome footprint profiling of translation throughout the genome. Cell. 2016; 165:22–33. [PubMed: 27015305]

190. Chew GL, Pauli A, Rinn JL, Regev A, Schier AF, Valen E. Ribosome profiling reveals resemblance between long non-coding RNAs and 5′ leaders of coding RNAs. Development. 2013; 140:2828–2834. [PubMed: 23698349]

191. Zhou P, Zhang Y, Ma Q, Gu F, Day DS, He A, Zhou B, Li J, Stevens SM, Romo D, et al. Interrogating translational efficiency and lineage-specific transcriptomes using ribosome affinity purification. Proc Natl Acad Sci U S A. 2013; 110:15395–15400. [PubMed: 24003143]

192. Ingolia NT, Brar GA, Sarn-Ginossar N, Harris MS, Talhouarne GJ, Jackson SE, Wills MR, Weissman JS. Ribosome profiling reveals pervasive translation outside of annotated protein-coding genes. Cell Rep. 2014; 8:1365–1379. [PubMed: 25159147]
193. van Heesch S, van Iterson M, Jacobi J, Boymans S, Essers PB, de Bruijn E, Hao W, Maclnnes AW, Cuppen E, Simonis M. Extensive localization of long noncoding RNAs to the cytosol and mono- and polyribosomal complexes. Genome Biol. 2014; 15:R6. [PubMed: 24393600]

194. Fields AP, Rodriguez EH, Jovanovic M, Stern-Ginossar N, Haas BJ, Mertins P, Raychowdhury R, Hacohen N, Carr SA, Ingolia NT, et al. A regression-based analysis of ribosome-profiling data reveals a conserved complexity to mammalian translation. Mol Cell. 2015; 60:816–827. [PubMed: 26638175]

195. Ji Z, Song R, Regev A, Struhl K. Many IncRNAs, 5′ UTRs, and pseudogenes are translated and some are likely to express functional proteins. Elife. 2015; 4:e08890. [PubMed: 26687005]

196. Calviello L, Mukherjee N, Wyler E, Zauber H, Hirsekorn A, Selbach M, Landthaler M, Obermayer B, Ohler U. Detecting actively translated open reading frames in ribosome profiling data. Nat Methods. 2016; 13:165–170. [PubMed: 26657557]

197. Sinturel F, Gerber A, Mauvoisin D, Wang J, Gatfield D, Stubblefield JJ, Green CB, Gachon F, Schibler U. Diurnal oscillations in liver mass and cell size accompany ribosome assembly cycles. Cell. 2017; 169:651–663 e614. [PubMed: 28475894]

198. Mistry DS, Chen Y, Sen GL. Progenitor function in self-renewing human epidermis is maintained by the exosome. Cell Stem Cell. 2012; 11:127–135. [PubMed: 22770246]

199. Skamagki M, Zhang C, Ross CA, Ananthanarayanan A, Liu Z, Mu Q, Basu U, Wang J, Zhao R, Li H, et al. RNA exosome complex-mediated control of redox status in pluripotent stem cells. Stem Cell Reports. 2017; 9:1053–1061. [PubMed: 29020613]

200. Taleahmad S, Mirzaei M, Parker LM, Hassani SN, Mollamohammadi S, Sharifi-Zarchi A, Haynes PA, Baharvand H, Salekdeh GH. Proteome analysis of ground state pluripotency. Sci Rep. 2015; 5:17985. [PubMed: 26671762]

201. Fazzio TG, Huff JT, Panning B. An RNAi screen of chromatin proteins identifies Tip60-p400 as a regulator of embryonic stem cell identity. Cell. 2008; 134:162–174. [PubMed: 18614019]

202. Onderak AM, Anderson JT. Loss of the RNA helicase SKIV2L2 impairs mitotic progression and replication-dependent histone mRNA turnover in murine cell lines. RNA. 2017; 23:910–926. [PubMed: 28351885]

203. Rialdi A, Hultquist J, Jimenez-Morales D, Peralta Z, Campisi L, Fenouil R, Moshkina N, Wang ZZ, Laffleur B, Kaake RM, et al. The RNA exosome syncs IAV-RNAPII transcription to promote viral ribogenesis and infectivity. Cell. 2017; 169:679–692 e614. [PubMed: 28475896]
Figure 1. Schematic depiction of PolII transcripts generated from enhancers and gene promoters
Both enhancers and promoters are transcribed bi-directionally and produce various types of transcripts including pre-mRNA, transcription start site-associated RNA (tssRNA), prematurely terminated RNA (ptRNA), upstream antisense RNA (uaRNA) or promoter upstream transcript (PROMPT), and enhancer RNA (eRNA). The exosome functions in nuclear RNA surveillance to degrade these RNAs as well as misprocessed mRNA precursors such as intron-retained and poly(A) signal-mediated cleavage and polyadenylation-defective pre-mRNAs.
Figure 2. Structure of the RNA exosome and paths for RNA substrates to the catalytic subunits

a) Threading route: RNA enters the central channel of the core exosome and reaches the active site of Dis3. b) Route to Rrp6: RNA traverses the cap structure and reaches the active site of Rrp6. c) Direct access to Dis3. RNA bypasses the central channel and directly accesses Dis3.
The RNA helicase Mtr4 participates in multiple distinct exosome adaptor complexes to complete degradation and/or processing of specific RNA substrates. Mtr4-containing complexes identified in *S. cerevisiae* (upper left), *S. pombe* (lower left) and *H. sapiens* (right) are shown.

Figure 3. Overview of Mtr4-containing exosome adaptor complexes in yeasts and humans
| Complex | S. cerevisiae | S. pombe | H. sapiens |
|---------|---------------|-----------|------------|
| **TRAMP** | Mr4 | Mr4 | Mr4/SKIV2L2/MTREX |
| | Air1, Air2 | Air1 | ZCCHC7 |
| | Trf4, Trf5 | Cid14 | PAPD5, PAPD7 |
| **NNS** | Nrd1 | Seb1 | SCAF4, SCAF8 |
| | Nab3 | Nab3 | RALY, RALYL, hnRNPC, hnRNPL1, hnRNPL2, hnRNPL3, hnRNPL4 |
| | Sen1 | Sen1 | SETX |
| **MTREC** | Mtr4 | Mtl1 | Mtr4/SKIV2L2/MTREX |
| | – | Red1 | ZFC3H1 |
| | – | Iss10 | – |
| | Pho92 | Mmi1 | YTHDF1, YTHDF2, YTHDF3 |
| | Sto1 | Cbc1 | CBP80/NCBP1 |
| | Cbc2 | Cbc2 | CBP20/NCBP2, NCBP2L |
| | – | Ars2/Pr2 | ARS2/SRRT |
| | – | Red5 | ZC3H3 |
| | Sgn1/Rbp1/Rbp29 | Pab2 | PABPN1, PABPN1L |
| | – | Rnn1 | RBM26, RBM27 |
| | Pap1 | Pla1 | PAPOLA, PAPOLB, PAPOLG |
| **Mtr1-Ctr1-Nrl1** | Mtr4 | Mtl1 | Mtr4/SKIV2L2/MTREX |
| | – | Ctr1 | CCDC174 |
| | – | Nrl1 | NRDE2 |
| **NEXT** | Mr4 | Mtr4 | Mr4 |
| | – | – | RBM7 |
| | – | – | ZCCHC8 |
| **Other** | Utp18 | Utp18 | UTP18 |
| | Nop53 | Rnp16 | NOP53 |
| | ISW1 | – | SMARCA5 |
| | Rix7 | Rix7 | NVL/NVL2 |
| | Nsa1 | Wdr74 | WDR74 |
| | – | – | DGCR8 |