

Assembly of multicomponent machines in RNA metabolism: A common theme in mRNA decay pathways

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Abstract

Multicomponent protein–RNA complexes comprising a ribonuclease and partner RNA helicase facilitate the turnover of mRNA in all domains of life. While these higher-order complexes provide an effective means of physically and functionally coupling the processes of RNA remodeling and decay, most ribonucleases and RNA helicases do not exhibit sequence specificity in RNA binding. This raises the question as to how these assemblies select substrates for processing and how the activities are orchestrated at the precise moment to ensure efficient decay. The answers to these apparent puzzles lie in the auxiliary components of the assemblies that might relay decay-triggering signals. Given their function within the assemblies, these components may be viewed as “sensors.” The functions and mechanisms of action of the sensor components in various degradation complexes in bacteria and eukaryotes are highlighted here to discuss their roles in RNA decay processes.

This article is categorized under:

RNA Turnover and Surveillance > Regulation of RNA Stability

RNA Turnover and Surveillance > Turnover/Surveillance Mechanisms

RNA Interactions with Proteins and Other Molecules > Protein-RNA Recognition

KEYWORDS

RNA degradation, RNA helicases, sensors

1 | INTRODUCTION

Biochemical processes in a cell seem to never be at rest. A striking illustration of this in all forms of life is the regulation of gene expression, which involves an ever-changing balance between the processes of transcription and RNA degradation. These changes, in turn, allow adaptation to environmental cues and lead to cellular development. Degradation of mRNA serves as a rapid method of responding to intrinsic and extrinsic signals and contributes towards controlling the fidelity and the level of gene expression. In the bacterial model organism, *Escherichia coli*, mRNA degradation is primarily mediated by the endoribonuclease RNase E (Arraiano et al., 1988; Babitzke & Kushner, 1991; Mudd et al., 1990). Bacterial species that lack RNase E contain other endoribonucleases or 5′→3′ exoribonucleases. In eukaryotes, bulk

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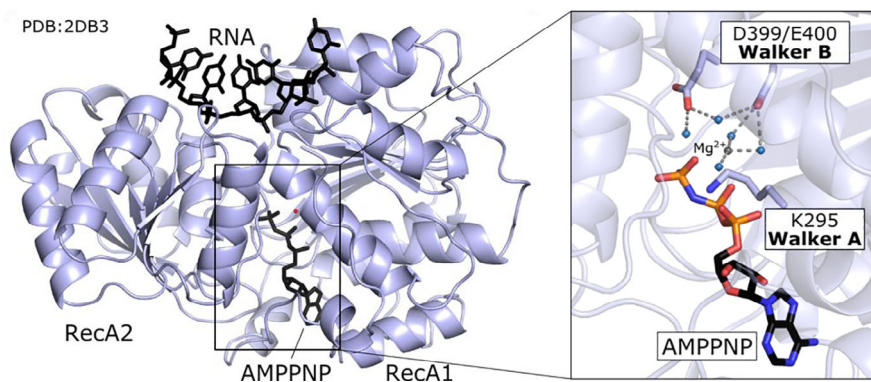
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mRNA decay relies on exoribonucleases which degrade the mRNA from the 5'→3' end or the 3'→5' end after removal of the terminal m⁷G-cap and poly(A)-tail structures (Parker & Song, 2004). Endoribonucleases play a relatively small role in eukaryotic mRNA decay. Most exo- and endoribonucleases can only act upon single-stranded RNA, a constraint that is usually imposed by the architecture of the degrading enzyme. However, mRNA transcripts adopt complex secondary structures and are usually associated with mRNA-binding proteins in cells to form RNA-protein complexes (mRNPs) (Gehring et al., 2017). Therefore, the mRNAs are seldom in a form that is amenable to degradation and need to undergo remodeling prior to degradation. While this might seem like a cumbersome process, particularly when rapid mRNA decay is necessary, secondary structure and association with protein factors impart stability to mRNA transcripts, which is essential for their efficient translation.

Remodeling of RNA is brought about by a class of enzymes known as RNA helicases, which are molecular motors that harness the energy of ATP binding and hydrolysis to this effect (Jankowsky, 2011, also refer to Box 1). Several RNA helicases are known to play an important role in bacterial and eukaryotic mRNA decay where they work in conjunction with exo- and endoribonucleases to unwind/remodel the mRNA in preparation for degradation (Hardwick &

BOX 1 RNA helicases

All eukaryotic and non-oligomeric (non-toroidal) bacterial RNA helicases belong to the superfamily (SF) 1 and 2 of helicases. Helicases within these two superfamilies contain at least two RecA-like domains (named for their similarity to the bacterial DNA-recombination promoting protein, RecA). The RecA-like domains consist of a central β -sheet flanked by α -helices on either side, and together comprise a cleft for ATP-binding and a shallow surface for RNA binding. These enzymes do not display a strong sequence specificity in binding RNA. The universally conserved Walker A and Walker B sequence motifs within the RecA-like domains play important roles in ATP binding and hydrolysis. Based on sequence conservation, the SF1 and SF2 helicases are further categorized into separate families. Each helicase family has characteristic sequence and structural features, which also correlate to distinct mechanisms of RNA unwinding and RNP remodeling. The DEAD-box proteins of the SF2 superfamily can only bind RNA in the presence of ATP and unwind RNA by local strand separation. These helicases are not processive and do not exhibit a preferred direction of RNA unwinding. In contrast, all other SF2 helicases as well as SF1 helicases bind single-stranded RNA independent of ATP. Unwinding of an RNA duplex is brought about by binding of the helicase on a single-stranded RNA overhang, and translocating on the RNA in a particular direction in an ATP-dependent manner. Therefore, translocating helicases are highly processive as they remain bound to the RNA substrate even after ATP hydrolysis, and unwind RNA in the 3'→5' or the 5'→3' direction.



Structure of the *Drosophila* DEAD-box RNA helicase Vasa, bound to RNA and a non-hydrolysable ATP analogue, AMPPNP (shown in stick representation) (Sengoku et al., 2006). The RecA domains are indicated. The inset shows the conserved Walker A and Walker B motifs. The magnesium ion and water molecules that are essential for ATP hydrolysis are shown as gray and cyan spheres, respectively.

Luisi, 2013; Khemici & Linder, 2018). Additionally, RNA helicases are also involved in the maturation of structured RNA precursors (during ribosome biogenesis) and in cellular surveillance pathways, all of which have an overall impact on the regulation of gene expression (Lingaraju, Johnsen, et al., 2019). In many such RNA decay and maturation events, the helicase and ribonuclease assemble into a complex to function as one unit that streamlines the degradation process. The first assembly of such a kind, comprising the endoribonuclease RNase E and the DEAD-box protein RhlB, was discovered in *E. coli* and was referred to as the “degradosome” (Carpousis, 2007; Carpousis et al., 1994). In addition to the endoribonuclease and the helicase, the *E. coli* degradosome also contains the exoribonuclease polynucleotide phosphorylase (PNPase) and the metabolic enzyme enolase (Py et al., 1996; Vanzo et al., 1998). Subsequently, helicase-ribonuclease assemblies of varying degrees of complexity were also found in eukaryotes. The architecture of these assemblies and how they modulate helicase and nuclease activities have been extensively discussed already (Lingaraju, Johnsen, et al., 2019; Weick & Lima, 2020). This review instead focuses on the diverse protein factors that associate with the helicase-ribonuclease complexes to build up a degradosome or degradosome-like assembly that mediates efficient timely decay of RNA. These additional factors lack RNA unwinding and ribonucleolytic activities, but nevertheless play an important role in degradation due to their ability to relay decay-inducing signals to the assemblies and to recruit them to the RNA substrate at the correct time. As such, these proteins act as physical or functional adaptors between the RNA substrate and the degradosome or degradosome-like complex. Given their role in “sensing” the impending degradation activity, these components are referred to as “sensors” here. The interplay of the helicase, ribonuclease, and sensor components of various bacterial degradosomes and eukaryotic degradosome-like assemblies, and their effect on the fate of RNA will be discussed.

2 | DEGRADOSOMES IN BACTERIA

2.1 | The *E. coli* RNase E degradosome

The endoribonuclease RNase E is the scaffold of the *E. coli* RNA degradosome (Figure 1). The structured N-terminal catalytic domain of RNase E shows high sequence conservation across species and is organized into a homotetramer, which is essential for formation of the active site of the enzyme (Figure 1, inset) (Callaghan et al., 2005). The divergent C-terminus is largely unstructured and interspersed with short motifs of higher structural propensity that bind PNPase,

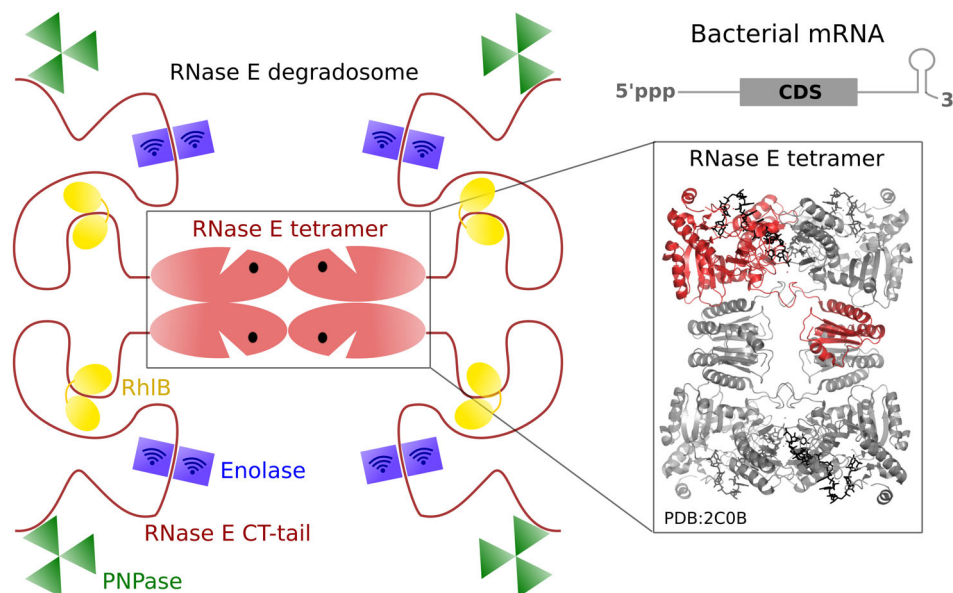


FIGURE 1 The *Escherichia coli* degradosome. A tetramer of the endoribonuclease RNase E (inset, one monomer shown in red) forms the scaffold of this degradosome. The C-terminal unstructured tail of RNase E (red) acts as a binding platform for the helicase RhlB, the exoribonuclease/polymerase PNPase and the metabolic enzyme enolase, which acts as a sensor. The stem-loop structure at the 3'-end of the bacterial transcript is unwound and degraded by RhlB/PNPase. This figure is adapted from Carpousis (2007)

RhlB, and enolase to assemble the degradosome (Callaghan et al., 2004). While RNase E and PNPase are functional on their own, RhlB is only active in the context of the degradosome or upon binding its cognate recognition motif in the RNase E C-terminus in vitro (Chandran et al., 2007; Vanzo et al., 1998). The roles of RhlB and PNPase are evident from the structural organization of bacterial mRNA. All bacterial mRNA transcripts end in a 3'-stem loop structure that is resistant to decay by RNase E (Figure 1). Partial unwinding of the stem loop by RhlB, followed by rapid exoribonucleolytic decay by PNPase, ensure complete turnover of the transcript (Coburn et al., 1999).

In contrast to these three components, the role of enolase in the degradosome is much less clear. Enolase (also known as phosphopyruvate hydratase) is a metabolic enzyme that converts 2-phosphoglycerate to 2-phosphoenolpyruvate in the penultimate step of glycolysis. A short, conserved motif of RNase E binds an enolase dimer, positioning an arginine-rich segment (AR2) of the endoribonuclease that has been implicated in RNA binding in close proximity to the enolase surface (Chandran & Luisi, 2006; Nurmohamed et al., 2010). It is possible that binding of enolase to RNase E appropriately positions the AR2 segment for RNA binding, and therefore indirectly facilitates RNA binding. While there are no reports of bacterial enolase interacting with RNA, mammalian enolase was found to bind mRNA in a high-throughput study using HeLa cells (Castello et al., 2012). Interestingly, enolase within the degradosome was shown to regulate the levels of the glucose transporter (ptsG) mRNA upon accumulation of glucose 6-phosphate (phosphosugar stress) and to stabilize the small regulatory RNA (sRNA) DicF under anaerobic conditions, suggesting that this enzyme is capable of sensing the metabolic state of the cell and relaying the need for degradation to the degradosome (Morita et al., 2004; Murashko & Lin-Chao, 2017).

Apart from the protein factors described above, RNase E can associate with a number of other proteins, either independently or in context of the degradosome. The cold shock helicase CsdA can associate with the degradosome at low temperatures and is functionally capable of replacing RhlB, although the binding sites of the two helicases on RNase E are distinct (Prud'homme-Genereux et al., 2004). CsdA is expressed, albeit at low levels, at normal temperatures and yet, is not part of the regular degradosome. Therefore, it appears that the cold shock must be sensed and relayed to the degradosome to induce its remodeling, although the mechanism of recruitment of CsdA to RNase E remains elusive. Additional factors interacting with RNase E to redirect or regulate its catalytic activity are the sRNA chaperone Hfq in complex with its sRNA, and the inhibitory proteins RraA and RraB (Masse et al., 2003; Morita et al., 2005). The Hfq-RyhB sRNA complex, for example, targets the degradosome to transcripts encoding for iron storage and iron transport proteins when iron is available in limiting amounts. Such factors therefore have the capacity to expand the substrate diversity of RNase E and to influence the composition of the assembly it builds. This raises the question what are the signals that trigger these changes and how are they relayed?

2.2 | Degradosomes in other bacteria

The sequence diversity of the C-terminal unstructured tail of RNase E across different species of proteobacteria gives rise to a diversity in the protein factors that can be recruited by this enzyme. While most RNase E degradosomes comprise at least one DEAD-box protein, additional factors such as the ribonucleases RNase R, RNase D, and the Rho transcription termination factor have been found to be part of the degradosome in other proteobacteria (Purusharth et al., 2005; Voss et al., 2014). Studies on degradosome assembly in the α -proteobacterium *Caulobacter crescentus* revealed that the C-terminal tail of RNase E recruits the metabolic enzyme aconitase, instead of enolase as in *E. coli* (Hardwick et al., 2011). Furthermore, *C. crescentus* RNase E recruits an additional DEAD-box protein, RhlE upon cold-shock, reminiscent of binding of CsdA to the *E. coli* RNase E under similar conditions (Aguirre et al., 2017).

As mentioned earlier, bacteria that lack RNase E (such as *Bacillus subtilis* and *Staphylococcus aureus*), invariably contain the RNase J1/J2 enzymes, which have both 5'→3' exoribonucleolytic activity and endoribonucleolytic activity, and/or the endoribonuclease RNase Y (Bechhofer & Deutscher, 2019; Commichau et al., 2009; Even et al., 2005; Mathy et al., 2007). Although RNase E, RNase J1/J2, and RNase Y are not homologs and do not share an evolutionary ancestry, *B. subtilis* and *S. aureus* nevertheless assemble degradosomes comprising these ribonucleases, an RNA helicase CshA and the glycolytic enzyme phosphofructokinase, in addition to enolase (Lehnik-Habrink et al., 2010; Roux et al., 2011). A minimal degradosome, comprising only a ribonuclease and a DExD-helicase, was observed in the bacterial pathogen *Helicobacter pylori* (Redko et al., 2013). The ribonuclease in this degradosome is RNase J; RNase Y and PNPase do not associate with the *H. pylori* degradosome. At first glance it appears that this degradosome lacks a sensor component to relay decay-inducing signals and trigger mRNA degradation. However, the *H. pylori* degradosome was found to associate with translating ribosomes, but not with the 30S and 50S subunits, implying that

Organism	Ribonuclease	RNA helicase	Sensor
<i>Escherichia coli</i>	RNase E PNPase	RhIB CsdA	Enolase/ Hfq-sRNA
<i>Caulobacter crescentus</i>	RNase E	RhIB RhIE	Aconitase
<i>Bacillus subtilis</i>	RNase Y RNase J1/J2 PNPase	CshA	Enolase/ Phospho- fructokinase
<i>Staphylococcus aureus</i>	RNase Y RNase J1/J2 PNPase	CshA	Enolase/ Phospho- fructokinase
<i>Helicobacter pylori</i>	RNase J	RhpA	Translating ribosome

FIGURE 2 An overview of the ribonucleases, helicases, and sensor components that make up prototype degradosomes in different species of bacteria. While metabolic enzymes are the typical sensors of the bacterial degradosome, the RNA chaperone Hfq and its associated sRNA as well as the translating ribosome have also been shown to be associated with degradosomes in certain cases

the degradosome is involved in regulation of gene expression at the post-transcriptional level but not in rRNA maturation and ribosome biogenesis (Redko et al., 2013). Interestingly, the *E. coli* degradosome was also shown to associate with the 70S ribosome and polysomes wherein, assisted by an Hfq-bound sRNA that recognizes the target mRNA, it mediates decay of a transcript undergoing active translation (Bandyra et al., 2013; Tsai et al., 2012). Here the polysomes are thought to serve as “antennae” that actively recruit the comparatively few degradosomes present in *E. coli* when a need for degradation of a translating transcript arises. The Hfq-sRNA complex also promotes mRNA decay via an RNase E degradosome in the Gram-negative bacteria *Salmonella typhimurium* (Bandyra et al., 2012), as well as in the Gram-positive bacteria *Listeria monocytogenes*, although the RNase involved in this species remains to be identified (Nielsen et al., 2010; Ross et al., 2019). These observations suggest that the overarching principles of degradosome assembly are conserved across different species of bacteria, although the mode of protein–protein interactions within the assemblies and the mechanisms of signal relay to the ribonucleolytic components might differ. An overview of the various ribonuclease, helicase, and sensor components that give rise to degradosomes across different bacterial species is shown in Figure 2.

3 | DEGRADOSOME-LIKE MACHINES IN EUKARYOTES

3.1 | The minimal mitochondrial degradosome

Evidence of a minimal eukaryotic degradosome, similar to that of the bacteria *H. pylori* described above, was first obtained from investigating yeast mitochondria (Margossian & Butow, 1996). A complex comprising Dss1, a 3′→5′ exoribonuclease of the RNase R family, and Suv3, an SF2 helicase, was shown to be responsible for mitochondrial RNA surveillance and mitochondrial biogenesis in yeast (Dziembowski et al., 2003). The two enzymes display remarkable functional interdependence: Dss1 has low intrinsic RNase activity that is augmented by the helicase activity of Suv3, while Suv3 unwinds RNA in the 3′→5′ direction more efficiently in the presence of Dss1 (Dziembowski et al., 2003; Malecki et al., 2007). The X-ray crystal structure of the *Candida glabrata* mitochondrial exoribonuclease complex (mtEXO) suggests that the functional coupling of catalytic activities is directed by the structural organization of the

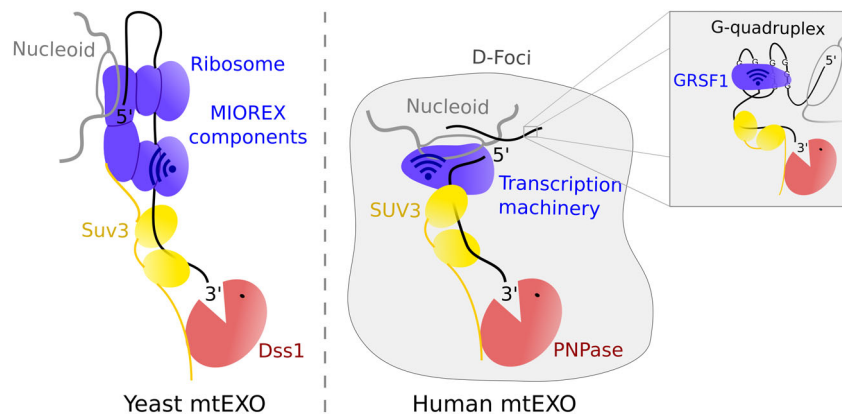


FIGURE 3 Mitochondrial exoribonuclease complexes (mtEXO) in yeast and humans. The conserved Suv3 helicase associates with the exoribonuclease Dss1 in most species, other than in humans where it engages PNPase. The sensors of the yeast and human mtEXO differ, suggesting different functional roles for these assemblies in the two species. Sensors of human mtEXO also vary depending on the nature of the RNA species targeted for degradation (the transcription machinery for most RNA species including mRNA, and GRSF1 for non-coding RNAs rich in G-quadruplexes)

assembly (Figure 3). Although Dss1 has a number of auxiliary RNA binding domains, these are involved in contacts with Suv3 and into channeling of RNA towards the active site (Razew et al., 2018). Therefore, it is unclear how mtEXO achieves substrate selectivity and what the sensor component of this minimal degradosome is.

Early studies on identification of the components of yeast mtEXO showed that the mitochondrial ribosome co-purifies with Dss1 and Suv3 (Dziembowski et al., 2003). Quantitative mass spectrometric analyses revealed that the mitochondrial ribosome associates with a number of components of the gene expression machinery, resulting in the assembly of large transcription-translation complexes reminiscent of bacterial expressomes. These assemblies are collectively referred to as MIOREX (mitochondrial organization of gene expression complexes) and include, among other factors, the Dss1 and Suv3 proteins (Figure 3, left panel) (Kehrein et al., 2015). As with bacterial degradosomes, association of mtEXO with the ribosome appears to facilitate mRNA turnover as well as decay of aberrant and unprocessed RNA in mitochondria, although the factors that bridge this interaction remain unknown. The mitochondrial degradosome appears to be conserved from some of the earliest mitochondria-containing eukaryotes, such as *Trypanosoma brucei*, to humans. The *T. brucei* Dss1 enzyme associates with the *T. brucei* Suv3 helicase and plays an important role in degradation and surveillance of 12S rRNA maturation byproducts and intermediates (Mattiaccio & Read, 2008, 2009). However, unlike the yeast mtEXO, it does not stably associate with mitochondrial ribosomes, implying that this system probably uses another form of a sensor for degradation (Penschow et al., 2004). Interestingly, the mitochondrial degradosome in humans is more similar to the *E. coli* degradosome than yeast mtEXO in that the helicase SUV3 associates with PNPase instead of Dss1 (Figure 3, right panel) (Wang et al., 2009). The human mtEXO complex has an important role in clearance of double-stranded RNA, accumulation of which would lead to innate immune responses (Dhir et al., 2018) and in preventing R-loop formation, and therefore in maintaining mtDNA integrity and stability (Silva et al., 2018). This suggests that the sensor of the human mtEXO might be the transcription machinery, instead of the translation machinery as in the yeast system. Consistent with this idea are the findings that SUV3 is a core protein of the mitochondrial nucleoid (a DNA-protein assembly that efficiently packages mtDNA) and that PNPase is peripherally associated with the nucleoid through its association with SUV3 (Bogenhagen et al., 2008). Interestingly, the human mtEXO also plays an important role in clearance of non-coding RNAs rich in G-quadruplex structures through functional coupling with the G-rich sequence binding factor 1 (GRSF1) protein, which promotes melting of G-quadruplexes and thereby facilitates decay by mtEXO (Figure 3) (Pietras et al., 2018). It appears that, similar to bacteria, a variety of sensors can be recruited by the mitochondrial degradosome to expand the repertoire of its substrates and functional impact in cells.

3.2 | Degradosome-like assemblies of the cytoplasmic and the nuclear exosomes

Messenger RNA turnover and translation-dependent RNA surveillance are the major RNA degradation processes occurring in the cytoplasm. Nuclear RNA degradation involves processing of precursor RNAs, surveillance of the processing

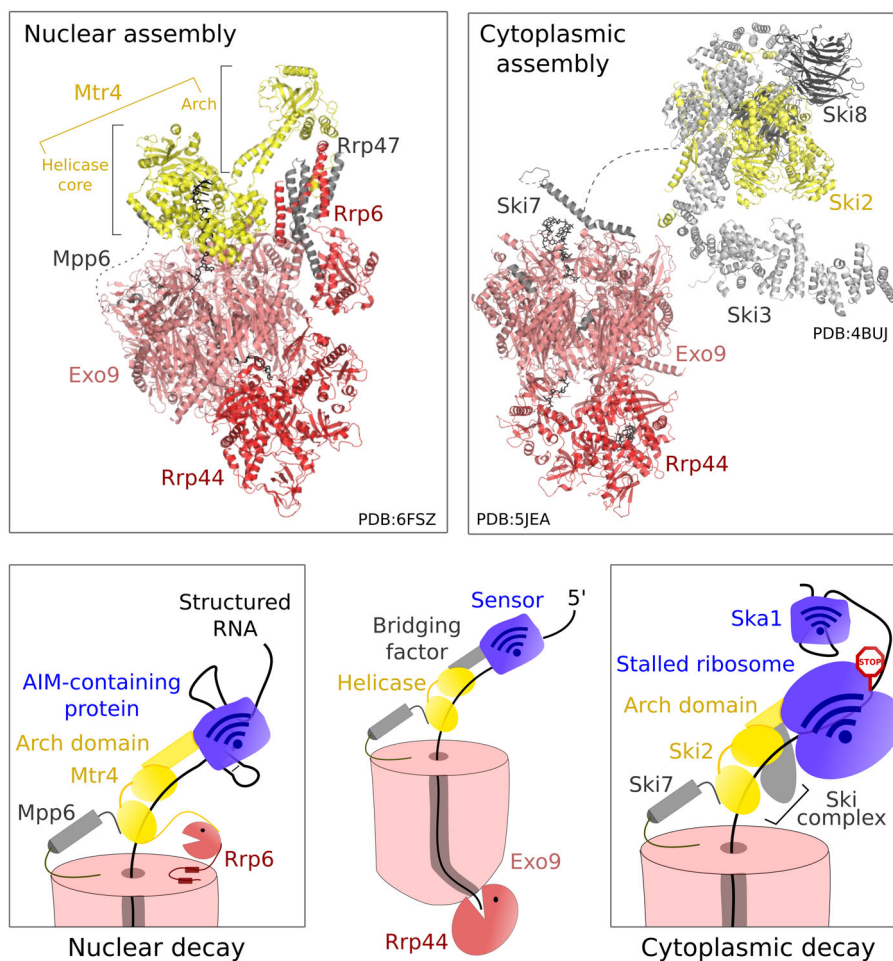


FIGURE 4 Assembly of nuclear and cytoplasmic degradosome-like complexes in eukaryotes. These assemblies are involved in RNA processing and surveillance in the nucleus and mRNA turnover in the cytoplasm. The nine structural components of the exosome, Exo9, assemble into a barrel in all eukaryotes other than plants. The helicases Mtr4 and Ski2 associate with the nuclear and cytoplasmic exosomes respectively, via different scaffolding factors (Mpp6, Rrp47/Rrp6 in the nucleus and Ski7 and Ski3-Ski8 in the cytoplasm). The helicase-exosome assemblies contact the sensor components (the AIM-containing proteins in the nucleus, and the ribosome stalled on an mRNA or the Ska1 protein bound to an untranslated RNA in the cytoplasm) via their respective arch domains to build up a degradosome and mediate decay. This figure is adapted from Makino, Halbach, and Conti (2013) and Lingaraju, Johnsen, et al. (2019)

products, and removal of stalled intermediates, byproducts and products of pervasive transcription. Among the plethora of RNA degradation enzymes present in eukaryotes, the exosome is the primary nuclease that degrades RNA in the 3'→5' direction in the nucleus and the cytoplasm (Allmann et al., 1999; Labno et al., 2016; Mitchell et al., 1997; Zinder & Lima, 2017). The cytoplasmic and nuclear exosomes associate with RNA helicases and a diverse array of other factors that facilitate substrate recognition and degradation, leading to the assembly of complexes that are often similar to the *E. coli* degradosome in organization principles and function.

Most studies on the eukaryotic exosome were carried out in yeast, and more recently in the human system. In both systems, the core exosome consists of 10 subunits, 9 of which (Rrp41, Rrp42, Rrp43, Rrp45, Rrp46, Mtr3, Rrp40, Rrp4, and Csl4) are devoid of catalytic activity but assemble into a barrel (Exo9 in Figure 4) through which RNA is threaded to reach the active subunit, Rrp44 (also known as Dis3) (Bonneau et al., 2009; Dziembowski et al., 2007; Liu et al., 2006). The processive enzyme Rrp44 has endoribonucleolytic activity in addition to its primary 3'→5' exoribonucleolytic activity, and is associated with both nuclear and cytoplasmic exosomes in yeast (Lebreton et al., 2008; Lorentzen et al., 2008; Schneider & Tollervy, 2013; Wasmuth & Lima, 2012). Additionally, the nuclear exosome can engage another exoribonuclease Rrp6, which is distributive in nature (Briggs et al., 1998; Burkard & Butler, 2000). In humans, the cytoplasmic exosome associates with DIS3L (a homolog of Rrp44), while the nuclear exosome can associate with RRP44 and RRP6 (localized in the nucleoli) (Tomecki et al., 2010). The barrel architecture of the exosome

dictates that only single-stranded RNA, free of any proteins, can be accommodated in the central channel and delivered to Rrp44 for decay (Drazkowska et al., 2013; Makino, Baumgartner, & Conti, 2013). This entails that the exosome be functionally coupled to an RNA helicase that unwinds RNA and remodels RNA–protein complexes (RNPs) to generate a substrate that is amenable for degradation (Figure 4) (Weick & Lima, 2020). To date, two RNA helicases are known to be associated with the exosome in yeast and humans: Ski2 (SKI2W in humans) in the cytoplasm and Mtr4 (MTR4/SKIV2L2 in humans) in the nucleus (Figure 4, right and left panels, respectively) (Anderson & Parker, 1998; de la Cruz et al., 1998; Kilchert et al., 2016). Both helicases contain a DExH core (consisting of two RecA domains, a winged helix domain and a helical bundle) and an insertion domain, also known as “arch,” that plays a significant regulatory role in both helicases (Halbach et al., 2012, 2013; Jackson et al., 2010; Weir et al., 2010). Consistent with their role in 3′→5′ RNA decay, both helicases unwind RNA in the 3′→5′ direction.

Despite their structural similarities, the protein factors that Ski2 and Mtr4 associate with are considerably different. Ski2 associates with two non-enzymatic components, Ski3 and two copies of Ski8 (TTC37 and WDR61 in human, respectively), to form the hetero-tetrameric Ski complex (Brown et al., 2000; Synowsky & Heck, 2008). The yeast Ski complex is physically linked to the exosome via the GTP-binding protein Ski7 (Figure 4, right panel) (Araki et al., 2001; Kowalinski et al., 2015). In humans, the protein HBS1LV3, encoded by a short splicing variant of the *HBS1L* gene, functions as a Ski7 homolog, linking the human SKI complex with the exosome (Kalisiak et al., 2017). Together, Ski3 and Ski8 regulate the catalytic activity of Ski2 and form an extended RNA channel through which the emerging RNA 3′-end can be fed into the exosome (Halbach et al., 2013). They also act as adaptors bridging the Ski complex to the exosome via interactions with Ski7 (Kowalinski et al., 2016).

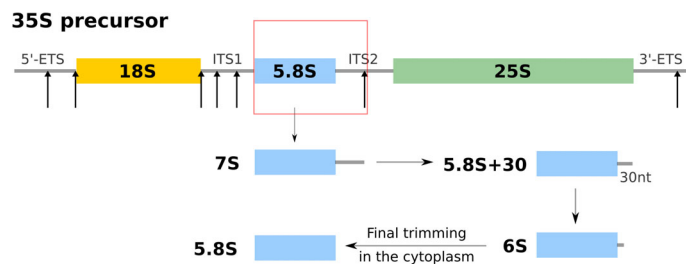
Unlike Ski2 which is present as an obligate Ski complex in the cytoplasm, Mtr4 can associate with the nuclear exosome either independently or in context of various protein complexes where it is a central factor. A heterodimer of Rrp6 and its interacting partner Rrp47 engage the N-terminus of Mtr4 (Schuch et al., 2014; Stead et al., 2007), while the conserved factor Mpp6 tethers Mtr4 to the exosome core and extends the path of the RNA into the barrel of the exosome, facilitating substrate channeling as observed in the Ski complex (Figure 4, left panel) (Butler & Mitchell, 2011; Falk, Bonneau, et al., 2017; Wasmuth et al., 2017; Weick et al., 2018).

Across eukaryotes, Mtr4 exists in several complexes, such as in the NEXT complex in humans (nuclear exosome targeting complex, comprising the zinc-finger protein ZCCHC8 and the RNA-binding protein RBM7, in addition to MTR4), in TRAMP in yeast (a complex of the poly(A)polymerase Trf4/Trf5, the zinc-knuckle protein Air2/Air1 and Mtr4), and in complex with the preribosomal Nop53 protein in yeast (Falk, Tants, et al., 2017; LaCava et al., 2005; Lubas et al., 2011; Thoms et al., 2015). Association with the bridging factors of these complexes dictates whether the Mtr4-exosome assembly triggers complete decay of its RNA substrate or carries out a very specific processing event as in the case of generation of the 5.8S rRNA from its 7S rRNA precursor (Gudipati et al., 2012; Kadaba et al., 2004; Kilchert et al., 2016; Lingaraju, Johnsen, et al., 2019; Thoms et al., 2015, also refer to Box 2). The TRAMP complex oligoadenylates the 3′-end of specific substrates and facilitates their degradation (Kadaba et al., 2006; Vanacova et al., 2005). Substrates such as aberrant tRNA_i^{Met} and cryptic unstable transcripts are detected and degraded by the TRAMP-exosome complex, while those such as precursors of snoRNAs and rRNAs are processed to generate mature products (Allmang et al., 2000; van Hoof et al., 2000; Wyers et al., 2005). In addition to processing, TRAMP also participates in surveillance of incorrectly processed snoRNAs and rRNAs (Milligan et al., 2005). The arch domain of Mtr4 plays an important role in expanding the range of substrates that the helicase can target. It comprises of two pairs of long “stalk” helices that connect to a β-barrel KOW domain (usually found in ribosomal proteins). The KOW domain enables binding to structured RNA such as tRNA_i^{Met} and 25S rRNA, and facilitates unwinding by the helicase core from the 3′-end (Jackson et al., 2010; Weir et al., 2010). The Trf4/Trf5 poly(A)polymerases add a short oligo(A) tail to the 3′-end of the RNA, which further facilitates its degradation by the exosome (Falk et al., 2014; Houseley & Tollervey, 2006). In this sense, the TRAMP-exosome complex is very similar to the *E. coli* degradosome, where the factors necessary to unwind, oligo-adenylate, and degrade a specific RNA substrate are assembled into a single complex.

In addition to binding structured RNA, the KOW domain is also capable of interacting with a number of protein factors. These include the ribosome biogenesis factors Utp18, Nop53 (in yeast) and NVL (in humans), as well as ZCCHC8, a component of the human NEXT complex (Falk, Tants, et al., 2017; Lingaraju, Schuller, et al., 2019; Thoms et al., 2015). These proteins engage the Mtr4 arch domain using short peptide sequences, collectively referred to as the arch-interaction motif (AIM). The AIMs of different interacting factors can vary considerably, resulting in a wide range of binding affinities of these adaptors for Mtr4. An unusual interaction partner of MTR4, which also contains an AIM is the nuclear speckle protein NRDE2. It was reported that NRDE2 acts as a negative regulator of the nuclear exosome by preventing MTR4 from interacting with other AIM-bearing proteins, thereby inhibiting MTR4 recruitment to the target

BOX 2 Processing of ribosomal RNA in eukaryotes

The eukaryotic 80S ribosome consists of a small 40S subunit and a large 60S subunit. The 40S subunit consists of an 18S ribosomal RNA (rRNA) and 33 ribosomal proteins, while the 60S subunit contains 3 rRNA components, 5S, 5.8S and 25S rRNA, in addition to 47 ribosomal proteins. All rRNA fragments, except for the 5S rRNA are generated from a single precursor 35S rRNA. In order to generate these rRNA fragments, four regions of the 35S rRNA must be removed or processed: the 5'-external transcribed spacer (5'-ETS), the 3'-ETS and two internal transcribed spacers (ITS1 and ITS2). Liberation of the 18S, 5.8S, and 25S rRNA from the 35S precursor requires processing/degradation by both ribonucleases (Rrp44 and Rrp6) associated with the nuclear exosome. The exosome is engaged fairly early on in the ribosome biogenesis pathway, through interactions of the helicase Mtr4 with the 90 pre-ribosome (Bassler & Hurt, 2019).



Schematic of the 35S precursor rRNA. The 18S, 5.8S, and 25S rRNA fragments are shown as colored rectangles, while the ETS and ITS segments are represented as gray lines. The cleavage sites are indicated by rounded arrows. Processing of the 7S precursor into the 6S rRNA involves the action of the Mtr4 degradosome. For further insights into processing of the 35S rRNA, please refer to the review article (Bassler & Hurt, 2019).

RNPs (Wang et al., 2019). All other known interaction partners of Mtr4 facilitate its role in RNA degradation by bridging the interaction between the Mtr4-bound exosome and the target RNA. Studies on the Nop53-Mtr4 interaction revealed that the Mtr4 arch is capable of simultaneously engaging Nop53 and structured RNA using adjacent surfaces on the KOW domain (Falk, Tants, et al., 2017). This indicates that Mtr4 can bind a pre-ribosomal protein as well as rRNA precursors during ribosome biogenesis. A cryo-electron microscopy (cryo-EM) structure of the nuclear-exosome in complex with the pre-60S (precursor large ribosomal subunit) illustrates how the exosome latches on to the pre-60S particle, via interactions mediated by Mtr4 to the exosome on one hand (through Mpp6 and the Rrp6/Rrp47 complex) and to the precursor ribosome (via the 25S rRNA and Nop53) on the other (Schuller et al., 2018). Binding of Mtr4 threads the 3'-end of the precursor 7S rRNA through the helicase channel to the exosome channel where it is processively degraded by Rrp44 to a 5.8S rRNA precursor with an additional 30 nucleotides at the 3'-end (5.8S + 30 RNA, Box 2). Further trimming by the distributive exonuclease Rrp6 generates an intermediate 6S rRNA that is finally processed in the cytoplasm to generate the mature 5.8S rRNA (Bassler & Hurt, 2019).

A recent study on the association of the nuclear exosome with the 90S pre-ribosome highlighted the ability of Mtr4 to engage with precursor ribosomes fairly early on in the biogenesis program. The AIM-containing protein Utp18 plays an important role in initial targeting of Mtr4-exosome to the 90S and in transition from a 90S to a pre-40S subunit (Lau et al., 2021). The AIM-proteins can be thought of as sensors for assemblies containing the helicase Mtr4 as they recruit the helicase-exonuclease complex to the sites of RNA processing and degradation, thereby physically and functionally coupling substrate recognition and RNA degradation (Figure 4).

The ability of the arch domain to interact with structured RNA is also conserved in the cytoplasmic Ski2 helicase and is utilized by the Ski complex to directly associate with ribosomes (Schmidt et al., 2016). The function of the cytoplasmic exosome is intricately coupled with translation. The cryo-EM structure of the ribosome-Ski complex demonstrated that the Ski complex can bind the ribosome without any additional adaptor proteins. Although certain adaptors such as the GTP-binding protein Ski7 and its paralogue Hbs1 were found to be essential for surveillance pathways such as non-stop decay and no-go decay (degradation of aberrant transcripts that lack a stop codon or where translation

elongation is stalled), they are dispensable for the Ski-ribosome interaction (Kowalinski et al., 2016; Shoemaker et al., 2010; Tsuboi et al., 2012; van Hoof et al., 2002). The arch of Ski2 interacts with the ribosomal proteins uS3 and uS10 and the rRNA. Additionally, the RecA2 domain of the Ski2-DExH core, the N-terminal arm of the scaffolding protein Ski3, and one out of the two copies of Ski8 make a multi-pronged interaction with the 40S subunit of the ribosome. The interaction of the Ski complex with the ribosome also appears to be important to activate the Ski2 helicase in this context (Schmidt et al., 2016). Although it is unclear how the Ski complex “senses” a need to associate with the ribosome, it can be envisioned that an initial endonucleolytic cleavage event, as is common in mRNA surveillance pathways, or prior deadenylation in bulk mRNA turnover generates a short free 3'-end in the mRNA that is used by the Ski complex to fasten on to the ribosome. Subsequent unwinding and remodeling by the Ski complex would lead to extraction of the mRNA from the ribosome and its channeling into the exosome. In addition to its role in co-translational decay, the Ski-exosome complex is also involved in turnover of poorly translated mRNAs, mRNAs with long 3'-untranslated regions (UTRs) and cytoplasmic long non-coding RNAs. Targeting of the Ski complex to ribosome-free RNA stretches is mediated by the Ska1 protein (Ski-associated component 1) in yeast (Zhang et al., 2019). Overexpression of the Ska1 protein was shown to ameliorate the Ski-ribosome interaction. Our current understanding of Ski-exosome mediated decay suggests that, depending on the extent of translation of the target RNA, the Ski complex associates with Ska1 or the ribosome to gain access to its RNA substrate.

At first glance, complexes of the exosome with the Ski2/Mtr4 helicases do not appear to have a defined “sensor” component that relays decay-inducing signals to this assembly. However, a closer look reveals how the exosome-helicase complexes mediate interactions with different factors or machineries in the cell to target a wide repertoire of RNA substrates and regulate gene expression in multiple ways. While the core degradosome composition consisting of the Ski2/Mtr4 helicase and the cytoplasmic/nuclear exosome remains unchanged, the sensor components diverge considerably to extend the functional capacity of these complexes. As yet, there is only one known adaptor for binding of Ski2 to the cytoplasmic exosome, whereas several adaptors bridging Mtr4 to the nuclear exosome have already been discovered. The association of both the nuclear and cytoplasmic assemblies with the ribosome is reminiscent of the bacterial and mitochondrial degradosomes which also interact with ribosomes at certain stages to regulate gene expression at a post-transcriptional level.

3.3 | Degradosome assembly in targeted mRNA decay

Apart from bulk mRNA turnover, many transcripts are degraded in a signal-dependent manner, in response to intrinsic or extrinsic cues, through specific decay pathways. Typically, mRNAs contain distinct sequence or structural elements, usually located in their 3'-UTR, that dictate the specific pathway of their degradation (Schoenberg & Maquat, 2012). These *cis*-acting signals are recognized by specific *trans*-acting protein factors which further recruit a host of proteins, including the degradation machinery, to assemble a decay-competent mRNP. A protein factor that is involved in many pathways of targeted mRNA decay, but not directly recruited by mRNA *cis*-acting elements, is the RNA helicase Upf1 (Kim & Maquat, 2019; Lavysch & Neu-Yilik, 2020). Upf1 was first identified in yeast as a protein essential for the nonsense-mediated mRNA decay (NMD) pathway, where a transcript bearing a premature termination codon (PTC) is detected and degraded by the cellular machinery (Leeds et al., 1991). With the emerging body of work on NMD, it is now clear that this pathway acts not only as a cellular surveillance mechanism but also as a sophisticated mode of fine-tuning regulation of gene expression in conjunction with other mRNA processing events, such as alternative splicing (Hamid & Makeyev, 2014; Kishor et al., 2019; Lareau et al., 2007). Although the number and complexity of NMD factors increase from yeast to humans, Upf1 remains the central player and is indispensable for NMD (Gowravaram et al., 2018; Gregersen et al., 2014; Hug et al., 2016; Hug & Caceres, 2014; Karousis & Muhlemann, 2019). A unifying model of NMD posits that increased occupancy of Upf1 on an mRNA transcript renders it susceptible to decay (Fritz et al., 2020; Hogg & Goff, 2010). It is, therefore, not surprising that the recruitment and catalytic activity of Upf1 are stringently regulated in cells. The ATP-dependent unwinding activity of human UPF1 (also known as RENT1) is regulated by interaction with the conserved core NMD factors, UPF2 and UPF3 (Chakrabarti et al., 2011; Chamieh et al., 2008; Clerici et al., 2009).

Many mechanistic models for PTC recognition and triggering of NMD have been proposed thus far (Kishor et al., 2019; Morris et al., 2021). A prevailing model in higher eukaryotes depends on the presence of the exon-junction complex (EJC) downstream of a PTC. The EJC, deposited at exon-exon junctions upon splicing, remains bound to the mRNA when it is exported to the cytoplasm (Le Hir et al., 2001). The X-ray crystal structures of the EJC illustrate how

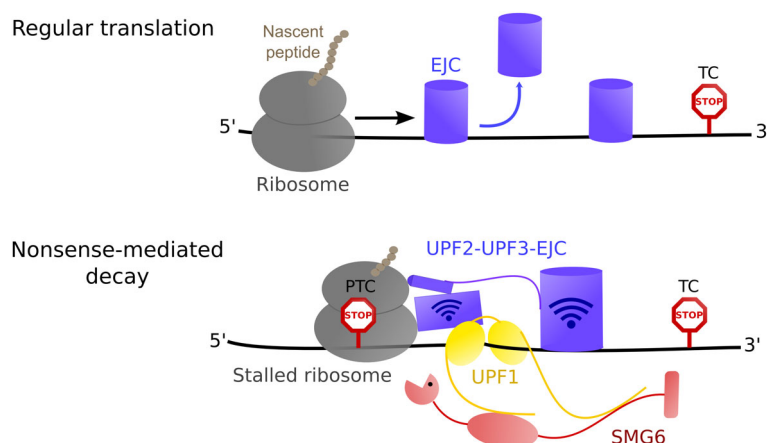


FIGURE 5 The exon junction complex (EJC) deposited at exon–exon junctions is displaced by the translating ribosome (top panel). However, presence of an EJC downstream of a stop codon identifies it as a premature termination codon (PTC). The EJC and associated factors act as the sensor component to signal nonsense-mediated transcript decay (NMD) and trigger cooperative degradation (bottom panel). Assembly of the core NMD factors UPF3 and UPF2 on the EJC leads to recruitment of the RNA helicase UPF1, which in turn recruits the endoribonuclease SMG6

this complex is stably bound to RNA, despite containing the active DEAD-box protein eIF4AIII (Andersen et al., 2006; Bono et al., 2006). In the cytoplasm, the EJC is displaced from a “normal” mRNA by the translating ribosome and its associated factors (Figure 5, top panel) (Gehring et al., 2009). However, presence of a stop codon approximately 50 nucleotides upstream of an EJC leads to stalling of the ribosome, and eventually an interaction of UPF1 with the UPF2-UPF3-EJC complex (Figure 5, bottom panel) (Buchwald et al., 2010; Clerici et al., 2009; Gehring et al., 2003; Kadlec et al., 2004; Lykke-Andersen et al., 2001; Melero et al., 2012). Activation of UPF1 in context of this complex, its phosphorylation and dephosphorylation, and recruitment of the endoribonuclease SMG6 via interactions with the EJC or UPF1 are thought to commit the mRNA transcript unequivocally to NMD (Chakrabarti et al., 2014; Kashima et al., 2006; Kashima et al., 2010; Nicholson et al., 2014). The UPF1-2-3-EJC-SMG6 complex is remarkably similar to the *E. coli* degradosome consisting of ribonucleases, an RNA helicase and a sensor. The EJC-UPF3-UPF2 complex can be regarded as the sensor component of the NMD degradosome since its presence downstream of a stop codon triggers assembly of a decay-competent complex consisting of the helicase UPF1 and the endoribonuclease SMG6. In NMD events that occur independent of the EJC, UPF3, or UPF2, UPF1 must associate with other factors to delineate the bound mRNA as a bona fide target for decay (Chan et al., 2007; Gehring et al., 2005; Hug et al., 2016). Indeed, specific subsets of mRNA transcripts appear to use different mechanisms of triggering NMD and mediating mRNA decay to fulfill specific physiological functions, adding another level of complexity to the regulation of this pathway (Yi et al., 2021).

In recent years, a large number of UPF1-dependent decay pathways have been identified in metazoans. The earliest examples of involvement of UPF1 in functional mRNA decay (as opposed to decay of “aberrant” PTC-containing mRNA) are the pathways of Staufen-mediated mRNA decay (SMD) and decay of replication-dependent histone mRNAs at the end of the S-phase (DNA synthesis phase) of the cell cycle. In both pathways, UPF1 was shown to interact with a *trans*-acting protein factor that is specific to the particular decay pathway: the double-stranded RNA-binding protein Staufen (STAU1 in mammals) and the histone stem-loop binding protein, SLBP (Kaygun & Marzluff, 2005; Kim et al., 2005). The binding of UPF1 to these RNA-bound protein factors leads to the assembly of an mRNP that must be directly capable of mediating mRNA decay or in recruiting the mRNA degradation machinery. The assembly of an SMD-competent mRNP involves the UPF1-activator, UPF2 which plays an important role in bridging the STAU1-UPF1 interaction in addition to stimulating UPF1 catalytic activity in this context (Chakrabarti et al., 2011; Gowravaram et al., 2019). While STAU1-UPF2 can be considered as the “sensor” that recruits UPF1 to the Staufen-binding sites located in the 3′-UTR of the target mRNA, referring to the STAU1-UPF2-UPF1 complex as a degradosome-like assembly is premature as its nuclease component remains unknown. It is possible that, as in the case of NMD, a specific endonuclease is recruited for decay. Alternatively, the complex might bind to an adaptor protein that links it to the general mRNA degradation machinery.

	Functional outcome	Ribonuclease	RNA helicase	Sensor
Mitochondrial mRNA decay	Yeast	Dss1	Suv3	Translational machinery
	Human	PNPase		Transcriptional machinery GRSF1
Bulk mRNA decay/ RNA processing	Nucleus	Rrp6	Mtr4	TRAMP complex AIM-containing proteins
	Cytoplasm	Exosome (active subunit: Rrp44)		Ski2
Targeted mRNA decay	Nonsense-mediated decay	SMG6	UPF1	UPF2-UPF3-EJC complex
	Staufen-mediated decay	Unknown		STAU1-UPF2
	Histone mRNA decay	3'hExo		Unknown
	Regnase-1-mediated decay	Regnase-1		Unknown
	Structure-mediated mRNA decay	Unknown		G3BP1/GRBP2
	Tudor-mediated miRNA decay	TSN		Unknown

FIGURE 6 An overview of the components of the eukaryotic degradosome-like assemblies discussed above. The sensors in eukaryotes are more diverse and complex, which is reflected in the variety of the functions and the effects on RNA processing that these assemblies can mediate. The ribonuclease or the sensor component of the degradosome-like assemblies in many UPF1-mediated targeted mRNA decay pathways still remain unknown

In contrast to the SMD pathway, the ribonuclease involved in histone mRNA decay is known. The 3'→5' exonuclease 3'hExo (ERI1) mediates initial degradation of the histone stem-loop, which is a trigger for rapid decay (Dominski et al., 2003; Hoefig et al., 2013). The degradosome-like complex of histone mRNA decay is assembled on the stem-loop RNA scaffold, as all three components (UPF1, SLBP, and 3'hExo) are capable of binding RNA independent of each other (Brooks et al., 2015; Tan et al., 2013). Although cell-cycle dependent rapid histone mRNA decay relies on recruitment of UPF1 by SLBP, it must be considered that SLBP binds to the stem-loop as soon as it is transcribed in the nucleus and is involved in every aspect of the histone mRNA's life, including pre-mRNA processing, export, translation, and decay (Marzluff & Koreski, 2017). Therefore, SLBP alone cannot act as a sensor for the complex assembled on the stem-loop RNA. A tantalizing possibility is that the sensor in this degradosome-like complex is not an additional protein factor, but rather post-translational modification of an existing component of the complex, such as SLBP or UPF1 (Ohnishi et al., 2003; Zhang et al., 2014).

Other UPF1-mediated pathways also depend on the interaction of UPF1 with one or more pathway specific protein factors: UPF1 interacts with the endonuclease Regnase-1 in the Reg1-mediated mRNA decay pathway, with the proteins G3BP1 and G3BP2 in structure-mediated mRNA decay, and even plays a role in Tudor-mediated miRNA decay by

interacting with the Tudor-staphylococcal/micrococcal-like nuclease (Elbarbary et al., 2017; Fischer et al., 2020; Mino et al., 2015). In all these pathways, the helicase activity of UPF1 was found to be essential for target RNA decay. However, the role of UPF1 is different from the other helicases in eukaryotic degradosome-like assemblies discussed above, in that UPF1 does not “feed” the RNA substrate into the ribonuclease but rather facilitates RNA decay by remodeling the RNP and by acting as an interaction platform to assemble the decay-competent mRNP in each pathway. Given the diverse modes by which substrate recognition and degradation can be mediated by UPF1 and its associated factors, it appears that process of targeted mRNA decay is driven by the nature and unique composition of the mRNP assembled in each case. Overall, the sensors for eukaryotic degradosome-like assemblies are more complex than those of their bacterial and mitochondrial counterparts as they are recruited and tuned in response to the desired functional outcome. An overview of the ribonucleases, helicases, and sensors that assemble into diverse degradosome-like complexes in eukaryotes is shown in Figure 6.

4 | CONCLUSION

Bacterial degradosomes and analogous degradosome-like assemblies in the eukaryotes have typically been considered to be complexes comprising an RNA helicase and a ribonuclease that together mediate efficient RNA degradation. In this review, we highlight the importance of the sensor component of these assemblies. We expand the definition of the term “sensor” to include factors that directly bind the target RNA and sense the need for degradation or relay decay-inducing signals to a pre-assembled degradation complex, thereby acting as a physical or functional adaptor between the RNA substrate and the degradosome assembly. The sensor is also the most versatile component of the degradosome. In eukaryotes, the ribosome (and its interacting factors) acts as a sensor for both nuclear and cytoplasmic degradosome-like complexes, mediating processes as diverse as ribosome biogenesis in the nucleus and mRNA surveillance in the cytoplasm. Other macromolecular machines that act as sensors include the mitochondrial nucleoid and the mitochondrial expressome (assembly of the ribosome and gene expression machinery). The sensor also plays an important role in expanding the functionality of the helicase and ribonuclease components of the eukaryotic degradosome-like assemblies. This is evident in the case of the RNA helicase UPF1 and its role in multiple pathways of targeted RNA decay. The helicase can associate with a variety of different factors, which serve to recruit it to different target mRNA transcripts. As such, the degradosome can be viewed as a dynamic complex that is assembled upon a scaffolding protein or target RNA depending on the biological context and function. Until fairly recently, insights into the architecture of degradosome-like complexes at an atomic level were limited due to constraints in structure determination of dynamic complexes by X-ray crystallography. However, the current revolution in cryo-EM has allowed us glimpses into the composition and architecture of certain degradation complexes. A combination of proteomics and structural biology methods will enable us to identify new sensor components of degradosomes and analogous complexes, and determine molecular mechanisms of target recognition, activation, and degradation by these assemblies.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

AUTHOR CONTRIBUTIONS

Alexandrina Machado de Amorim: Formal analysis; investigation; writing-review & editing. **Sutapa Chakrabarti:** Conceptualization; formal analysis; funding acquisition; investigation; project administration; writing - original draft; writing-review & editing.

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