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REVIEW

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Proteins involved in the degradation of cytoplasmic mRNA in the major eukaryotic model systems

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The process of mRNA decay and surveillance is considered to be one of the main posttranscriptional gene expression regulation platforms in eukaryotes. The degradation of stable, protein-coding transcripts is normally initiated by removal of the poly(A) tail followed by 5′-cap hydrolysis and degradation of the remaining mRNA body by Xrn1. Alternatively, the exosome complex degrades mRNA in the 3′>5′direction. The newly discovered uridinylation-dependent pathway, which is present in many different organisms, also seems to play a role in bulk mRNA degradation. Simultaneously, to avoid the synthesis of incorrect proteins, special cellular machinery is responsible for the removal of faulty transcripts via nonsense-mediated, no-go, non-stop or non-functional 18S rRNA decay. This review is focused on the major eukaryotic cytoplasmic mRNA degradation pathways showing many similarities and pointing out main differences between the main model-species: yeast, *Drosophila*, plants and mammals.

Introduction

mRNA molecules synthesized in the nucleus by RNA polymerase II are relatively unstable. In the cytoplasm, they are protected from the attack of exonucleases by the 5′-cap structure and the 3′-poly(A) tail. The stability of mRNAs depends on its innate features, but is predetermined by the nucleotide sequence and relates to the functions of the protein it encodes. Therefore, mRNA decay is considered the main posttranscriptional gene expression regulation platform. The cytoplasmic bulk mRNA degradation pathway in eukaryotic cells starts with shortening of the poly(A) tail. This process is performed by 3′>5′ exonucleases. To date, 8 different deadenylases have been characterized in metazoan, primarily including the CCR4-NOT complex, PAN2-PAN3 and PARN.[1] Deadenylation is the first and therefore often rate-limiting step of mRNA decay; however, it is reversible to some extent, as transcripts can be readenylated and translated into functional proteins.[2] Furthermore, the 5′-cap may be removed in the process known as decapping by the Dcp1-Dcp2 complex and mRNA may subsequently be subjected to degradation by Xrn1 exonuclease. Alternatively, the exosome complex degrades mRNA in the 3′>5′ direction. Deletions of the main enzymes of the 3′>5′ or 5′>3′ degradation pathways do not result in the total accumulation of aberrant mRNA, which suggests that those enzymes work in cooperation.[2] In this article, we review and compare our knowledge regarding dominant cytoplasmic RNA decay pathways, excluding RNAi, in the major model systems: yeast, human, *Drosophila* and plants.

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General mRNA degradation pathways

Deadenylation

The length of the poly(A) tail in a newly synthesized mRNA molecule depends on the organism. After entering the cytoplasm, it is either stabilized by poly(A) binding proteins (PABP), which facilitates translation, or shortened by cytoplasmic nucleases.[3] Poly(A) tail removal triggers mRNA degradation in almost all eukaryotic decay pathways (**Fig. 1**). This includes the degradation of stable, protein-coding mRNAs, ARE-mediated decay (for transcripts containing AU-rich destabilizing elements (AREs) in their 3′ UTRs[4]), nonsense-mediated decay (for mRNAs with premature stop codons),[5] miRNA-mediated decay[6,7] and the degradation mediated by destabilizing elements in protein coding regions, as in the case of the proto-oncogene *c*-fos.[8] Therefore, eukaryotic genomes encode a wide variety of deadenylases.

Based on biochemical and bioinformatic approaches, deadenylases can be divided into 2 main groups: DEDD or EEP nucleases.[1,9] Enzymes from both groups are Mg^{2+}-dependent exoribonucleases, which degrade RNA in a 3′>5′ direction, releasing 5′-AMP. The DEDD group is characterized by the presence of Asp and Glu residues in 3 active motifs that coordinate divalent metal ions.[10] This group includes Caf1 (Pop2), Caf1Z, PARN and PAN2. Deadenylases from the EEP (exonuclease-endonuclease-phosphatase) superfamily contain conserved catalytic Asp and His residues in their active site and catalyze

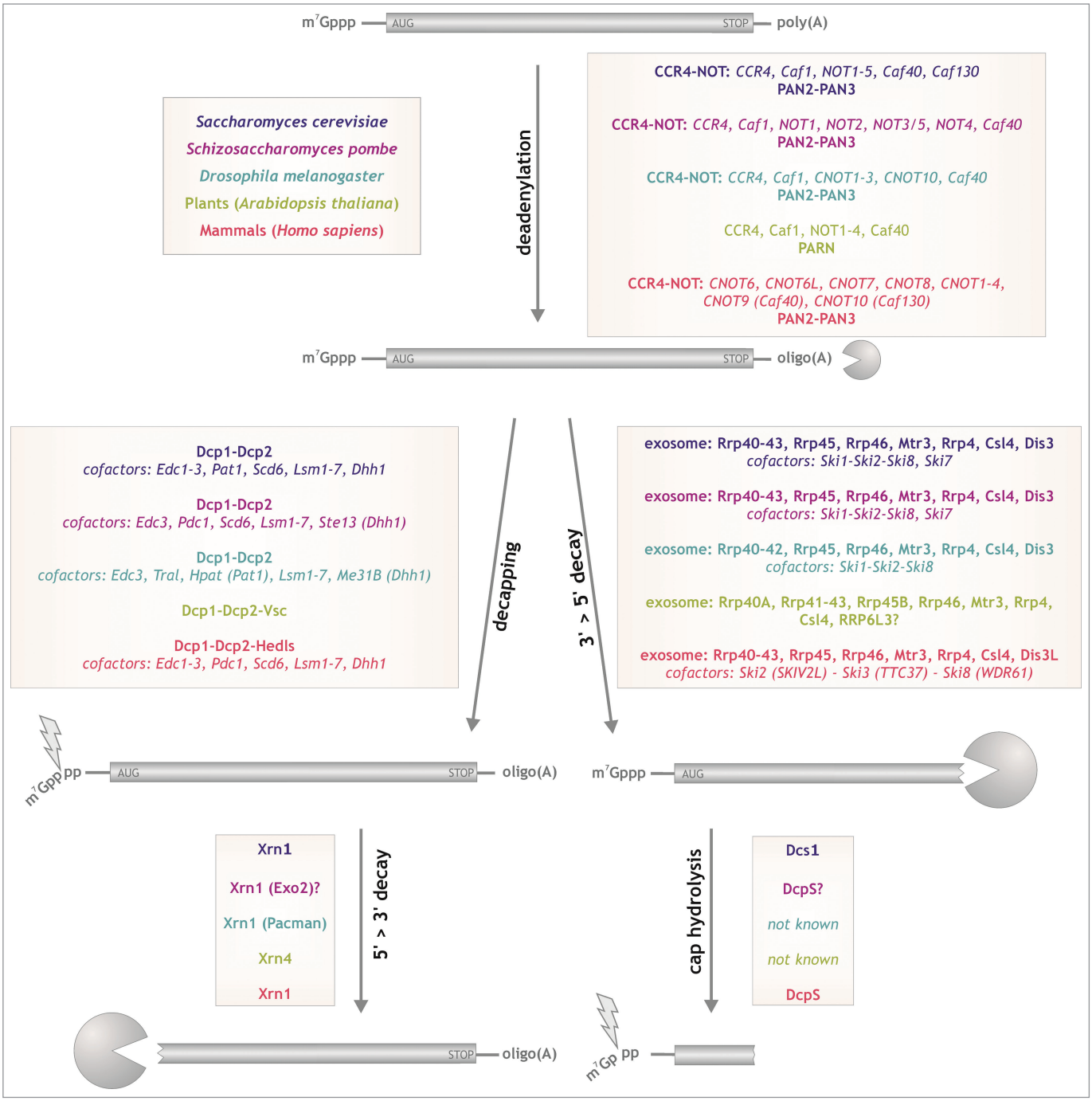

Figure 1. |Deadenylation-dependent degradation: pathways and enzymes. Degradation of properly synthesized mRNAs starts with shortening of the poly(A) tail (deadenylation), which is followed by decapping and subsequent 5′>3′ degradation by Xrn1 or exosome-mediated 3′>5′ degradation and cap hydrolysis. Color coding represents homologs from different organisms. Question mark indicates that relevant homolog is present in a database of a given species but its involvement in the process was not confirmed experimentally.

phosphate ester hydrolysis with the help of 2 magnesium ions.[11] CCR4, NOCTURNIN, ANGEL and 2′PDE are the enzymes that have been assigned to this group.

Saccharomyces cerevisiae

In *S. cerevisiae,* all cytoplasmic mRNA degradation pathways are initiated by removal of the poly(A) tail. This process is performed by 2 main complexes, CCR4-NOT and PAN2-PAN3. The CCR4-NOT complex is a multifunctional protein assembly that has been extensively studied in yeast.[12] It consists of 9 main subunits, 2 of which, CCR4 and Caf1 (Pop2), belong to the exonuclease families.[13] CCR4, an EEP nuclease, is the main deadenylase in the *S. cerevisiae* CCR4-NOT complex: deleting *ccr4* along with *pan2* blocks deadenylation

entirely.[14] CCR4 is incorporated into the whole complex through Caf1 via a leucine-rich repeat motif (LRR)[15] and this interaction is conserved across the entire eukaryotic domain. Caf1 (Pop2), the second exonuclease of the complex, is not required for the deadenylation of mRNA *in vitro* as it lacks the canonical catalytic residues in its active site.[10] It might be active under certain conditions or able to enhance the activity of CCR4; however, biochemical evidence shows that CCR4 is mainly responsible for deadenylation in yeast cells.[16,17] The eukaryotic CCR4-NOT complex, apart from 2 deadenylases, consists of 7 more subunits with distinct yet not fully characterized functions. NOT1 is the scaffold protein of the complex, without any enzymatic activity, NOT2, NOT3 and NOT5 form a NOT module interacting with the C-terminus of NOT1[18] and NOT4 (Mot2) is an active E3 ubiquitin ligase.[19] Caf130 and Caf40, which are also incorporated into the yeast complex, possess no clear function.[13] Their role in the deadenylation process is probably regulatory, as the deletion of either of them impairs poly(A) tail removal.[16]

The second deadenylation complex present in yeast, but also well conserved in higher eukaryotes, is a heterotrimer formed by the PAN2 protein interacting with the homodimer of PAN3. PAN2 is a distributive, hydrolytic 3′-exonuclease, belonging to the DEDD superfamily.[11] Its activity depends on Pab1,[20] and it is involved in the initial shortening of the poly(A) tail to a length of around 60–80 nt.[21] As Pab1 promotes activity of the PAN2-PAN3 complex and inhibits CCR4-NOT,[16,20] the model of cooperative cytoplasmic deadenylation was proposed. According to this model, PAN2-PAN3 nuclease is responsible for the rapid removal of the first exposed adenine residues,[22] leaving the poly (A) tail of around 65 nucleotides. After this, the poly(A) tail is slowly and distributively degraded by the CCR4 nuclease.[23] However, it seems that the activity of both deadenylating complexes is partially redundant. Deletion of *ccr4* gene gives slower deadenylation rates, but only the *ccr4*Δ, *pan2*Δ double mutant accumulates poly(A) tailed mRNAs and has severe growth defects.[16]

Schizosaccharomyces pombe

In fission yeast, *Schizosaccharomyces pombe,* mRNA turnover has been less extensively studied; however, the main pathways and enzymes are well conserved. Orthologs of the components of CCR4-NOT and PAN2-PAN3 deadenylases are present,[24,25] indicating a similar role in the initiation or mRNA degradation by poly(A) tail removal. The CCR4-NOT complex in *S. pombe* consists of 7 main subunits (CCR4, Caf1 (Pop2), NOT1, NOT2, NOT3/5, NOT4 (Mot2), Caf40 (Rcd1)). Unlike in *S. cerevisiae,* Caf1 has a fully conserved DEDD active site and has been shown to be a functional 3′>5′ exonuclease.[26] Activity of PAN2-PAN3 complex has not been proven.

In the genome of *S. pombe,* an ortholog of PARN, a mainly nuclear deadenylase which is absent in *S. cerevisiae,* has been identified.[25] Its physiological role in fission yeast is unclear, but it was suggested to be involved in the Dicer-independent RNAi pathway in the nucleus.[27]

Drosophila melanogaster

The deadenylation-dependent mRNA decay pathway has also been quite extensively studied in *Drosophila melanogaster* cells. The genome of the fruit fly encodes homologs of all yeast deadenylases: Caf1, CCR4, and PAN2-PAN3. However, no homolog of mammalian PARN has been identified.[28] It was shown that Caf1, CCR4, NOT1, NOT2, NOT3, Caf40 and the fly ortholog of human CNOT10 form a stable complex, with the main deadenylation activity assigned to Caf1 subunit, rather than to CCR4, as was observed in *S. cerevisiae.*[29] Interestingly, NOT4, a stable component of the complex in yeast, does not seem to be incorporated into the fly CCR4-NOT.[29]

Homologs of different exonucleases from EEP nuclease family can be found in the *D. melanogaster* genome: ANGEL, 2′PDE and Nocturnin, with the latter interacting with NOT1 protein and also probably affecting the deadenylation rates.[29] The mechanism of deadenylation by PAN2-PAN3 complex in fly cells was not well studied. It was shown, however, that it interacts with the GW182 protein and is responsible for the deadenylation of miRNA targets.[30]

Plants

The main mRNA degradation pathways are also proposed to exist in plants, as most of the enzymes can be found in genomes of various plant species.[31] Genes encoding deadenylating enzymes are often present in many copies. The *Arabidopsis thaliana* genome encodes 11 paralogs of Caf1; 16 can be found in rice *Oryza sativa* and 4 in grapes (*Vitis vinifera*). It was not shown whether all of those proteins are active deadenylases; however, all, as in *S. pombe*, contain the fully conserved DEDD motif of an active site.[32] Two of the 11 *A. thaliana* Caf1 homologs were examined. Studies have shown their deadenylation activity *in vitro* and involvement in stress response.[32,33] Other homologs of CCR4-NOT subunits were identified in the *A. thaliana* genome: CCR4, NOT1, NOT2, NOT3, NOT4, Caf40. However, their function and whether they form a stable complex, as in other organisms, remains unknown.[34] Poly(A) ribonuclease (PARN), absent in budding yeast and fruit fly, plays an important role in *A. thaliana* embryogenesis as an active cytoplasmic deadenylase.[35] Plant genomes encode also PAN homologs; nevertheless, their potential activity and function has not yet been examined.

Mammals

The majority of mammalian cytoplasmic mRNAs are degraded through a deadenylation-dependent pathway. The human genome encodes 12 deadenylases from both superfamilies.[9] Nevertheless, removal of the poly(A) tail is performed by the cooperative work of 2 deadenylases: CCR4-NOT and PAN2-PAN3.[36] The human CCR4-NOT complex consist of 10 subunits: CNOT1, CNOT2, CNOT3, CNOT4 (probably not a stable component), CNOT9/Caf40/Rcd1, CNOT10/Caf130, 2 copies of CCR4 homologs: CNOT6, CNOT6L, and 2 of Caf1: CNOT7, CNOT8.[37] All 4 nucleases are enzymatically active; however, they demonstrate different substrate specificity.[36-38]

Human PAN2 is a distributive exonuclease that interacts with PAN3, which binds through its PAM2 motif with

poly(A)-binding protein (PABP).[39] Initially, poly(A) tails of a stable mammalian mRNAs are deadenylated by the PAN2-PAN3 complex to the length of ~110 nt and subsequently degraded by CCR4-NOT complex until the length is ~10 adenine residues.[40,41] PARN, PARNL, ANGEL, ANGEL2, Nocturnin and 2′PDE deadenylases are encoded in the human genome. Among them, PARN has been shown to be involved in the deadenylation of specific mRNAs.[9,42]

Decapping and Xrn1-mediated 5′ to 3′ mRNA degradation

One of the 2 possible scenarios for mRNA degradation after initial deadenylation is removal of the 5′-cap structure *(***Fig. 1**). This process is performed by the Dcp2 enzyme, which belongs to the Nudix hydrolase family and is conserved among eukaryotes.[43] The reaction products are m^7GDP and 5′ monophosphate RNA. Activity of the decapping enzyme depends on divalent cations and specific cap methylation on N7.[44] The RNA body is also involved in catalysis and the enzyme has a preference for RNA substrates no shorter than 25 nucleotides.[45] Dcp2 forms a complex with Dcp1,[46,47] which is a small protein containing an EVH1 domain which is a common platform, bridging protein-protein interactions.[48] Moreover, Dcp1 is the main activator of Dcp2.[49] The decapping process is regulated by a plethora of activators and inhibitors, but their composition varies between the organisms.[43,50,51] The best defined decapping activator is a conserved in all eukaryotes. The Lsm1-7-Pat1 complex, which preferentially binds the 3′-end of oligoadenylated mRNA,[52,53] enhances decapping and inhibits exosome attachment.[54] Decapped (5′ monophosphorylated) RNA is exposed to attack and complete degradation by Xrn1, a processive 5′>3′ exonuclease.[44] Decapping and the 5′>3′ degradation are coupled, as Xrn1 nuclease interacts directly with one of the components of the decapping machinery, Dcp1, Pat1 or Edc4, depending on the organism.[55,56] This Xrn1-dependent decapping mechanism supports a model in which Xrn1 is a global transcript level buffering protein.[57]

Saccharomyces cerevisiae

In yeast, the main mRNA degradation pathway starts with removal of the poly(A) tail followed by decapping and rapid degradation of the RNA body from the 5′ end by Xrn1 nuclease.[46,58] Decapping is performed by the Dcp2 protein in a complex with Dcp1.[45,46] The conserved region of Dcp2 (residues 248-300) interacts with the decapping activator Edc3 and possibly also mediates interactions with some other factors.[58] The *Saccharomyces cerevisiae* genome encodes a range of decapping regulators: Edc1-3 (enhancers of decapping 1, 2, 3), Pat1, Scd6, Lsm1-7 and Dhh1. All of these have been demonstrated to bind RNA and activate decapping *in vivo.*[55] Except for Edc1 and Edc2, which seem to be specific to *S. cerevisiae*, all of the activators are conserved in evolution. Among them, the Lsm1-7-Pat1 complex seems to be crucial for the activation of decapping. The crystal structure of the yeast Lsm1-7-Pat1 complex shows that Lsm2-Lsm3 conserved helices bind the C-terminus of Pat1[53,59] and the latter interacts with Xrn1 nuclease.[55]

Schizosaccharomyces pombe

Fission yeast Dcp2 also forms a complex with its activator, Dcp1, and is responsible for the decapping of mRNA molecules.[48,60,61] Its activity is also stimulated by the set of activators: Edc3, Pdc1 (functional homolog of Helds), Lsm1-7, Ste13 (Dhh1) and Scd6.[62,63] Moreover, in *Schizosaccharomyces pombe,* decapping can be stimulated by 3′ uridylation, which is a novel pathway of mRNA degradation.[64] The *S. pombe* genome encodes a homolog of Xrn1 exonuclease, Exo2. However, direct evidence for its role in 5′>3′ mRNA degradation has not yet been shown.[65]

Drosophila melanogaster

In *Drosophila melanogaster,* the decapping machinery includes the decapping enzyme Dcp2, which directly interacts with its activators: Dcp1, Tral, Edc3, Lsm1-7, helicase Me31B (homolog of Dhh1)[66] and HPat homologs to the yeast Pat1.[67] For the efficient decapping of mRNA, the interaction between Dcp1 and Xrn1/Pacman is also required.[56]

Plants

Removal of the 5′-cap structure in plants is performed by the complex consisting of Dcp1, Dcp2 and Varicose (Vsc), a homolog of mammalian Hedls/Ge-1. The Dcp2 Hudix domain displays enzymatic activity, which is stimulated by Dcp1 and Vsc.[68] While decapping in yeast is regulated by a variety of decapping activators, in plants, the Dcp5 protein has been found to associate with Dcp1, Dcp2 and influence translation repression, P-body formation and postembryonic development.[69] *Arabidopsis thaliana* has 3 orthologs of yeast Xrn1: Xrn2, Xrn3, Xrn4.[34] Xrn2 and Xrn3 are involved in the processing of rRNA and snoRNA in the nucleus, while Xrn4 is located in the cytoplasm[70] and is responsible for the 5′>3′ degradation of specific transcripts.[71]

Mammals

The 5′>3′ degradation machinery has been best studied in yeast and mammals. Dcp2 is the main decapping enzyme, with RNA binding properties.[72] Unique to mammalian cells, the Hedls protein (also called Edc4, Ge-1), bridges the interaction between Dcp2 and its activator Dcp1 and also influences its activity.[73] A range of other decapping enhancers stimulate the activity of Dcp2, like Edc1-3, Dhh1, Lsm1-7.[50] In the mammalian genome, 20 2 genes of the Nudix family of hydrolases can be found.[74] Similarly to Dcp2, they contain a conserved consensus motif GX5EX7REUXEEXGU, where X represents any residue and U a hydrophobic one. Among them, cytoplasmic Nudt16 (X29), first identified in *Xenopus laevis*, also possesses decapping activity and RNA binding properties.[75,76] Decapped mRNA is a substrate for subsequent 5′>3′ degradation by Xrn1 exonuclease and this process is also associated and regulated by the decapping efficiency, since Xrn1 directly interacts with Hedls (Edc4) (part of the decapping complex).[56]

Exosome-mediated 3′ to 5′ mRNA degradation

In the cytoplasmic deadenylation-dependent pathway, alternatively to 5′>3′ decay, mRNA can be degraded in the 3′>5′ direction by the cytoplasmic exosome; the remaining cap is hydrolyzed by a scavenger decapping enzyme, DcpS, which shows a specificity toward short RNA fragments *(***Fig. 1**). The exosome is a multi-subunit complex involved in the degradation, processing and quality control of many groups of RNA in eukaryotic cells. The cytoplasmic enzyme consists of 9 core subunits and the enzymatically active ribonuclease.[77] Exosome composition is extremely well conserved among different organisms. Six subunits, Rrp41, Rrp42, Rrp43, Rrp45, Rrp46 and Mtr3, share 20-30% sequence similarity with *E. coli* polynucleotide phosphorylase (PNPase) and RNase PH domains. Moreover, they form a hexameric core ring.[78] Rrp4, Rrp40 and Csl4 possess RNA binding properties through their, also well conserved, S1 and KH motifs and are present across the eukaryotic domain. The tenth essential subunit of the cytoplasmic eukaryotic exosome, Rrp44 (Dis3), a homolog of bacterial RNase II,[79,80,81] is an active 3′- 5′ nuclease which contains N-terminal PIN domain responsible for endonucleolytic activity and the exosome ring attachment.[82,83,84] In higher eukaryotes, this subunit is present in more than one form. Three or 4 cofactors called superkillers or Ski proteins associate and regulate the activity of the exosome: Ski2, Ski3 and Ski8 which form a heterotetramer in the stoichiometry of 1:1:2[85] and yeast Ski7 protein, which can associate both with the Ski complex and the exosome.[86] After the degradation of the mRNA body by the exosome complex, the remaining m^7GpppN cap is hydrolyzed by the m^7G-specific pyrophosphatase, DcpS. This enzyme, unlike Dcp2, carries a histidine triad motif (HXHXH) and forms an asymmetric homodimer.[87,88]

Saccharomyces cerevisiae

In yeast, mRNA degradation from the 3′ end is a minor pathway. However, most of the proteins involved in this process are well conserved and have been extensively studied in this organism. The *S. cerevisiae* cytoplasmic exosome consists of a 9-subunit, enzymatically inactive, ring, formed by Rrp41, Rrp42, Rrp43, Rrp45, Rrp46 and Mtr3 and cap made of Rrp4, Rrp40 and Csl4. Endo- and exoribonucleolytic activity is provided by the Rrp44 (Dis3) protein, which possesses S1, PIN, RNB and 2 cold-shock (CSD1 and CSD2) domains.[79,82-84] Broad biochemical and structural studies of yeast exosome and exosome-associated Ski complex allowed for the in-depth understanding of the mechanism of RNA substrates′ degradation.[85,89-91] The exosome is functionally and physically associated with the Ski complex. In yeast, the Ski complex is formed by Ski2, the active helicase, Ski3 and 2 Ski8 proteins that modulate the RNA-binding and ATPase properties of Ski2.[85] Moreover, the Ski7 protein bridges the interaction between the Ski complex and the exosome.[86] This protein has an interesting evolutionary history since most fungi, excluding yeasts, have a single Ski7/Hbs1 gene which is alternatively spliced into Ski7 and Hbs1-like proteins.

The yeast genome encodes 2 homologs of mammalian DcpS scavenger decapping enzyme, Dcs1 and Dcs2.[92] They are both members of the HIT family of pyrophosphatases; however, only the Dcs1 protein has been shown to hydrolyze the cap structure.[92]

Schizosaccharomyces pombe

Very recently, the 10-subunit cytoplasmic exosome was purified from *Schizosaccharomyces pombe*, confirming its existence in this organism and probable role in cytoplasmic mRNA degradation.[93] The Ski complex as well as Ski7 was also identified,[94] pointing to the connection of the exosome with its partner. Interestingly, an independent duplication of Ski7/Hsb1 gene occurred in *S. pombe.*[94]

Drosophila melanogaster

To date, the entire exosome complex in flies, as the main enzyme responsible for the 3′>5′ mRNA degradation, has not been studied, even though the *Drosophila melanogaster* genome encodes 9 main cytoplasmic exosome subunits: Mtr3, Ski6/Rrp41, Rrp42, Rrp45, Rrp46, Rrp40, Rrp4, Csl4, Dis3. The Rrp43 protein could not be purified as a part of the core exosome.[95,96] This fact does not exclude, however, the possibility that it is incorporated into the complex *in vivo*. *In vitro* studies of fly Dis3 showed its endonucleolytic activity and main localization in the nucleus.[97] Moreover, immunolocalization experiments pointed out that in *D. melanogaster,* different sub-complexes might be formed, apart from the core exosome, with distinct functionalities.[95,98] Yeast homologs of the Ski complex were also identified in fruit fly. While in yeast they are the regulators of 3′>5′mRNA degradation by the exosome, in *Drosophila,* they play an important role in degradation of the 5′ends in miRNA-mediated mRNA degradation.[99] The ortholog of Ski7 has not been identified.

Plants

In the *Arabidopsis thaliana* genome, the first exosome subunits identified were Rrp4 and Rrp41. Interestingly, unlike in yeast and humans, Rrp4 was shown to be catalytically active 3′>5′ phosphorolytic ribonuclease from the RNase PH family.[100] Further experiments allowed for the recognition of the whole 9-subunit core: KH or S1 containing domain Rrp4, Rrp40 and Csl4, and with the RNase PH domain, Rrp41, Rrp42, Rrp43, Rrp45B, Rrp46 and Mtr3.[101] Genes encoding Rrp40 and Rrp45 are duplicated. However, only one of each gene isoform was purified with the complex.[101] Two Dis3 (Rrp44) paralogs were identified as Rrp44A and Rrp44B/SOV. Nonetheless, the cytoplasmic catalytic subunit remains to be determined, as Rrp44A was proposed to be nuclear and Rrp44B/SOV does not interact with the core exosome due to the absence of a PIN domain.[102] The *A. thaliana* genome encodes 3 genes of the Rrp6 family, 2 of which are nuclear (RRP6L1 and RRP6L2) and one which is strictly cytoplasmic (RRP6L3); thus, the latter is a plausible candidate for a cytoplasmic catalytic subunit with hydrolytic activity associated with the core exosome.[103] The Ski complex but not Ski7 has been characterized in plants.

Mammals

The human exosome, as the main enzyme responsible for 3′>5′ transcripts degradation, has been widely studied. The crystal structure reveals the conserved composition: Rrp41, Rrp45, Rrp46, Rrp43, Mtr3 and Rrp42 form a PH domain ring, Csl4, Rrp4 and Rrp40 form a cap.[78] Enzymatic activity is performed, like in yeast, by the Dis3 protein. Nevertheless, there is an additional exosome-associated Dis3 homolog in humans, called Dis3L. While Dis3 is mainly localized in the nucleus, Dis3L is cytoplasmic.[77,104] Dis3 and Dis3L possess conserved S1, CSD1, CSD2, PIN and RNB domains and associate with the exosome core.[104] The residual cap structure, a product of mRNA degradation by the exosome, is hydrolyzed by a scavenger decapping enzyme, DcpS.[88] DcpS forms a functional homodimer and decaps substrates with no more than 10 nucleotides.[87] Human homologs of the superkiller family – Ski2 (SKIV2L, Ski2W), Ski3 (TTC37) and Ski8 (WDR61), form a complex.[105] The Ski8 homolog is also a part of the PAF complex.[105]

Uridylation-dependent mRNA degradation

CytoplasmiC-terminal uridyl transferases, although absent in budding yeast, are present in a variety of organisms.[106] Nowadays, new roles for 3′ end uridylation in the cytoplasmic mRNA degradation pathways are becoming more evident, yet still remain abstruse.

In *S. pombe* cells, the Cid1 protein is responsible for terminal mono-, di- and oligouridylation of polyadenylated transcripts which promotes Lsm-dependent decapping and deadenylation-independent mRNA decay.[64] Interestingly, a new ribonuclease from the RNase II family, a homolog of human Dis3L2, was identified in fission yeast.[93] As in humans, Dis3L2 does not have a conserved PIN domain and does not associate with the exosome. Both human and fission yeast Dis3L2 proteins function independently of the exosome complex and show a preference for 3′ uridylated RNAs.[93,107,108] What is more, human Dis3L2 is responsible for the degradation of mammalian pre-let-7 precursor miRNA oligouridylated by Lin28.[109] On the other hand, monouridylation of pre-let-7 favors maturation of this miRNA.[110,111] The addition of uridyl residues was also shown to promote the degradation of miRNA and siRNA in Caenorhabditis elegans, zebrafish, Chlamydomonas reinhardtii and *Arabidopsis*.[112-115] Human Dis3L2 is the closest homolog of *A. thaliana*'s cytoplasmic protein AtRRP44B/SOV (Suppressor of Varicose), which indicates that AtRRP44B/SOV might also be involved in this degradation process[102] (**Fig. 2**).

Moreover, metazoan replication-dependent histone mRNA degradation again involves 3′ end uridylation. As levels of those transcripts undergo significant changes during the cell cycle, and they have to be rapidly degraded after S-phase when DNA replication is completed, new effective decay mechanisms have emerged during evolution.[116] Histone transcripts form a conserved stem-loop at their 3′ end rather than a poly(A) tail, as in lower eukaryotes, and this structure is indispensable for their replication-dependent degradation. The RNA hairpin forms a complex with SLBP protein (hairpin-binding factor, HBF in *S. cerevisiae*) and a conserved exoribonuclease Eri1 (human 3′hExo).[117,118] Histone mRNA decay is triggered when SLBP recruits NMD-related UPF1 protein[119] and TUTase(s) (most likely ZCCHC11[120]) which adds an oligo(U) tail on the 3′ end of the transcript.[121] The oligo(U) tract serves as a binding site for the Lsm1-7 heptamer, which enhances 3′hExo activity and exposes a single-stranded transcript to subsequent degradation by the exosome.[117] Decapping factors Lsm1 and Dcp2 were also shown to play a role in histone mRNA decay.[117,122]

Thus far, conservation of known TUTases and emerging evidence of their impact on RNA stability suggest that uridylation might be another common posttranscriptional gene expression regulating mechanism which remains to be determined.

Aberrant mRNA Degradation

There are several cytoplasmic RNA quality-control mechanisms that prevent the formation of aberrantly synthesized and potentially toxic proteins. According to the error present in the mRNA, nonsense-mediated decay (NMD), no-go decay (NGD) or non-stop decay (NSG) can be triggered.[123,124] Moreover, mutated 18S rRNA transcripts are degraded by the non-functional 18S rRNA decay pathway.

Nonsense-mediated decay (NMD)

NMD eliminates transcripts containing premature termination codon (a PTC can be inserted into the molecule as a result of a transcription error, genetic mutation or during splicing[125]), normal mRNA molecules with long 3′ UTRs, transcripts with an upstream ORF (uORF) in the 5′ UTR and mRNAs with introns present in their 3′ UTRs.[126-128] A model of how the PTC-containing mRNAs are recognized and targeted to degradation is based on the synergy between the kinetic difference of ribosome release from normal and premature stop codon and the interaction between the terminating ribosome and downstream *cis*-acting signals that vary across species (e.g. Hrp1 helicase in yeast and exon-junction complex EJC in mammals)[129,130] (**Fig. 3**).

Despite the fact that there are huge differences between species in the conservation of NMD factors (i.e. SMG1 and SMG5-9), 3 core proteins are present in each examined case. They were initially identified in *S. cerevisiae* as UPF1-3 (up frameshift) and in *C. elegans* as SMG2-4 (suppressor with morphological effect on genitalia).[131-135]

The key player, UPF1, is an ATP-dependent RNA helicase[136] with N-terminal Cys- and His-rich zinc-finger domain, 2 recombinase A (RecA)-like domains common to superfamily I (SFI) helicases and 2 regulatory domains (1B and 1C).[137] UPF1 binds to UPF2, an acidic protein with 3 conserved domains that are homologous to eIF4G.[138] UPF2 in turn interacts with UPF3, a protein with an unspecific RNP-type RNA-binding domain.[139] UPF1, along with UPF2 and UPF3, promote accelerated mRNA degradation by endonucleolytic cleavage, 5′>3′ decay or 3′>5′ decay. Furthermore, UPF1 and presumably other UPF proteins play an important role in post-termination ribosome release from PTC and in its recycling.[140,141]

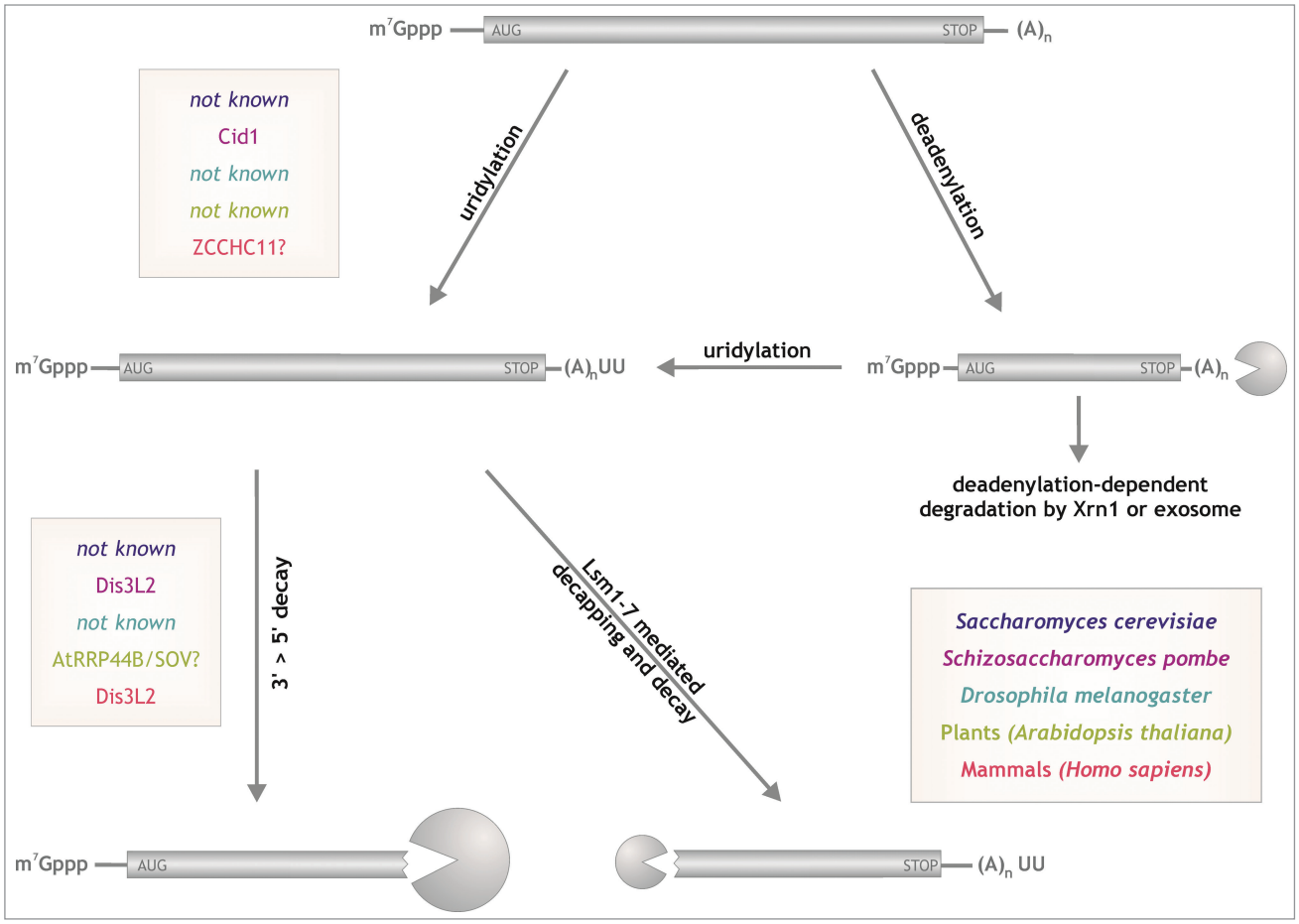

Figure 2. | Uridylation-dependent degradation. Properly synthesized mRNAs may be subjected to uridylation even after initial shortening of the poly(A) tail64. Uridylation can lead to Dis3L2-mediated 3′>5′ degradation or Lsm1-7-mediated decapping and decay. Color coding and question marks as in **Figure 1**.

Saccharomyces cerevisiae

UPF1 helicase plays a central, nonetheless not completely understood, role in yeast NMD. This protein is most likely recruited to the prematurely terminating ribosome in an inactive form, as UPF1 interaction with release factors eRF1 and eRF3 inhibits UPF1 ATPase activity.[142,143] Direct interaction between UPF1 and UPF2[144] takes place after recognition of the PTC by the UPF2-UPF3 complex and causes activation of the NMD pathway. The N-terminal domain of UPF1 interacts with decapping factors: Edc3, Pat1 and Dcp2 (indirectly, through Edc3) which stimulates rapid, deadenylation-independent decapping followed by Xrn1 degradation.[145] Alternatively, UPF1 stimulates accelerated deadenylation and 3′>5′ decay orchestrated by the Ski complex and performed by the exosome.[146] The exact mechanism of deadenylation stimulation has not been described, but it may relate to UPF1 helicase activity and potential mRNP structure destabilization.

NMD in *S. cerevisiae* is triggered by at least 2 *cis*-acting elements. Firstly, the surveillance complex interacts with downstream sequence elements (DSE) associated with Hrp1 helicase, which subsequently interacts with phosphorylated UPF2.[147] An absence of this interaction in Hrp1 mutants stabilizes nonsense-containing mRNAs.[147] Secondly, deletion of the coding region between PTC and 3′ UTR causes stabilization of the NMD substrates.[148] What is more, transcripts with extended 3′ UTRs are NMD substrates in *S. cerevisiae*, *D. melanogaster*, human and plant cells (*faux* 3′ UTR model),[127,149,150] which suggests the role of poly(A) binding protein (or other 3′ UTR-associated proteins) and proper mRNP structure in the recognition of a PTC.

Schizosaccharomyces pombe

Fission yeast genome contains introns in about 43% of genes.[151] UPF1 and UPF2 homologs were identified in *S. pombe*[138,152] and the UPF3 sequence was predicted in the genome.[153] Despite this, *S. pombe* was not widely studied in the context of NMD. Recent discoveries indicate, however, that fission yeast NMD could possibly lay somewhere in between mammalian (dependent on exon-junction complex) and budding yeast pathways: introns enhance NMD in *S. pombe* but most probably in an EJC-independent manner and it is not relevant whether PTC is inserted downstream or upstream of an intron.[154]

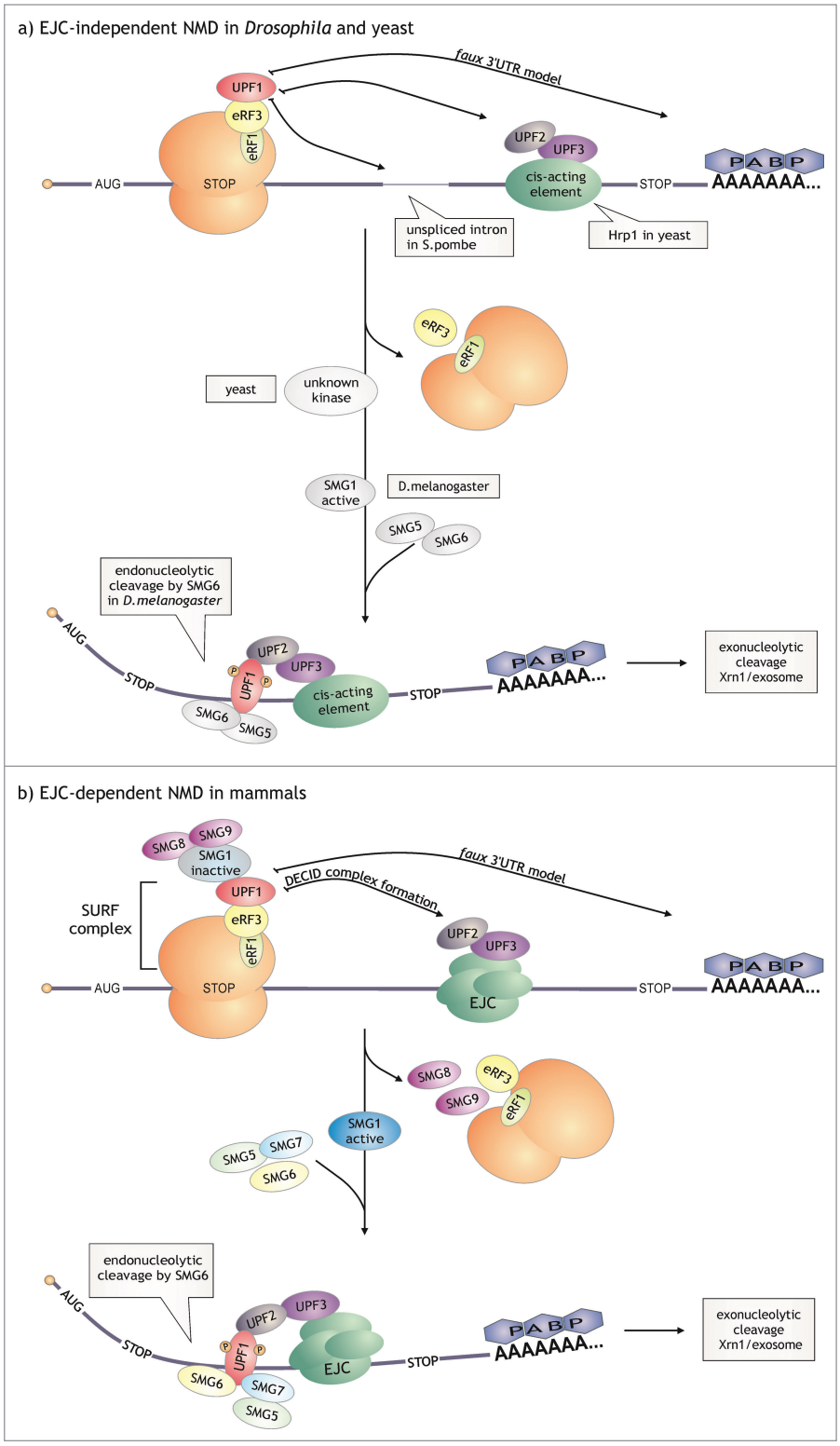

Figure 3. | Nonsense-mediated decay. NMD in mammals often depends on the insertion of the exon-junction complex downstream of the PTC, which is not true in the case of lower eukaryotes. So far, the only model that appears to be conserved among species is the faux 3′ UTR model. a) EJC-independent NMD. In S. cerevisiae, S. pombe and D. melanogaster NMD is independent of EJC. Hrp1 downstream of a PTC (S. cerevisiae, S. pombe?), unspliced introns (S. pombe, D. melanogaster?) and extended 3′ UTRs (S. cerevisiae, S. pombe?, D. melanogaster) are the elements that can trigger NMD in these organisms. In D. melanogaster SMG1 activates UPF1 by phosphorylation. In S. cerevisiae UPF1 undergoes phosphorylation-dephosphorylation cycles193,194, which may indicate that, similar to higher eukaryotes, this protein is activated by an as yet unknown kinase. Activation of NMD in S. cerevisiae (and probably in S. pombe) results in rapid decapping and accelerated deadenylation followed by an exonucleolytic degradation. In fruit fly cells, SMG6 endonuclease cleaves the aberrant transcripts before exonucleolytic decay. b) EJC-dependent NMD. The mammalian NMD model assumes the formation of SURF and subsequent DECID complex (ribosome:SURF:EJC). Active SMG1 phopshorylates UPF1, which causes interaction between the helicase and SMG5, SMG6 and SMG7. After the endonucleolytic cleavage by SMG6, the resulting fragments are degraded by the exosome and Xrn1.

Drosophila melanogaster

Similar to fission yeast, the fly exon-junction complex (EJC) components are dispensable for NMD.[155] *Drosophila* genome encodes all 3 UPF proteins and homologs of mammalian SMG1 (UPF1 phosphorylating kinase), SMG5 and SMG6 (endonuclease with PIN domain[156]), but not SMG7.[155] It is believed that fruit fly cells initiate NMD only by SMG6-directed endonucleolytic cleavage and subsequent exonucleolytic decay.[157]

Plants

In plant cells, NMD substrates are recognized either by their long 3′ UTRs or by the presence of EJC-like complex downstream of the PTC127,158. UPF1, UPF2, UPF3 and SMG7 are conserved and essential for both types of NMD[159] and UPF1 undergoes phosphorylation.[160] SMG7 mediates PTC-containing transcript to degradation by Xrn4-independent pathway.[161] No SMG1, SMG5 and SMG6 orthologs were found in *A. thaliana*.

Mammals

Mammalian genomes encode all UPF proteins – UPF1, UPF2 and 2 UPF3 paralogs, UPF3A and UPF3B (or UPF3 and UPF3X, respectively). UPF3B is believed to be slightly more effective in NMD.[162] Additional factors include SMG1 and SMG5-9.

Even though NMD can act independently of the splicing event,[163] the best studied mammalian model describes the role of the exon-junction complex (EJC) in the recognition of PTC. After the event of splicing, the EJC is deposited on the mRNA molecule ~20-24 nucleotides upstream of the exon-exon junction.[164] Introduction of the PTC upstream of the EJC triggers the NMD degradation pathway through UPF3, which is deposited on the EJC during splicing.

It is believed that stalling of the ribosome on the PTC causes the formation of the SURF complex between NMD and release factors (SMG1-UPF1-eRF1-eRF3).[165] SMG1 kinase activity is inhibited by SMG8/SMG9 until the ribosome-SURF locates an EJC bound to the UPF2-UPF3 complex.[166] Phosphorylation of UPF1 by SMG1 causes the interaction between the helicase and SMG5, SMG6 and SMG7. SMG6 has an endonucleolytic activity, cleaves a PTC-containing transcript and creates 5′ and 3′ mRNA fragments which are subsequently degraded by the exosome and Xrn1, respectively.[156,167] SMG5 and SMG7 form a heterodimer that associates with UPF1 and provokes mRNA degradation.[168]

Dom34-Hbs1: at the intersection of NGD, NSD and NRD

There are several different RNA defects causing translational stalling of the ribosome.[169] According to the error present in the RNA molecule, no-go (NGD), non-stop (NSG) or non-functional 18S rRNA decay (NRD) is triggered. Recently, it has been proposed that the evolutionarily conserved Dom34-Hbs1 complex plays a role in all 3 of those pathways by allowing the dissociation of ribosomal subunits[170,171] (**Fig. 4**). However, all of the correlations between NGD, NSD and 18S NRD are not yet clear.

No-go decay (NGD) takes place when the elongation complex ($_{EC}$) is blocked during translation by e.g., mRNA secondary structures or more than 6 consecutive positively charged amino acid residues present in a newly synthesized polypeptide. In those cases, subsequent to transcript degradation, Asc1 (RACK1 in mammals) mediates translation arrest and thereby leads to degradation of the aberrant protein by the E3 ubiquitin ligases Ltn1 and NOT4 (which is outside the scope of this review).[172-174] Transcripts lacking an in-frame stop codon, triggering non-stop decay (NSD), can be generated by cryptic polyadenylation signals within the ORF or premature 3′ polyadenylation.[175] The ribosome therefore proceeds along the poly(A) tail and is finally stalled/slowed down, probably by electrostatic interaction between positively charged poly-lysine residues and the negatively charged ribosomal tunnel.[176,177] Finally, defects in ribosomal 18S rRNA may be caused by mutations, chemical damage or faulty biogenesis and lead to translational stalls and subsequent non-functional 18S rRNA decay (NRD).[171]

Saccharomyces cerevisiae

During NDG and NSD, the Dom34-Hbs1 complex recognizes a stalled ribosome, induces subunit dissociation[178-180] and stimulates mRNA endonucleolytic cleavage by unknown endonuclease(s).[181,182] It is dispensable but facilitates no-go and non-stop mRNA degradation by the exosome and is required for the complete degradation of NGD and NSD intermediates.[170,183]

Neither PAN2-PAN3, nor the CCR4-NOT deadenylase activity is involved in those aberrant transcripts′ degradation – the exosome is stimulated by Ski7 and is dependent on Ski2-Ski3-Ski8 heterotrimer.[170,184] No-go and non-stop reporter transcripts and their intermediates are also more abundant in *xrn1*Δ mutant.[183-185]

The yeast ATPase Rli1 along with Dom34-Hbs1 complex significantly accelerates dissociation of stalled ribosome subunits,[186] whereas Dom34 andRli1 are involved in the final round of ribosomal cytoplasmic maturation.[187]

The same factors, i.e., Dom34-Hbs1, Ski7, exosome and Xrn1, are involved in 18S NRD. However, the mechanistic differences became evident when a Dom34 interaction disrupting mutation was introduced to Hbs1 – it strongly impaired NGD but had almost no effect on 18S NRD.[179] On the other hand, Dom34 mutants were defective in both NGD and 18S-NRD.[183]

Schizosaccharomyces pombe

In 2010, the crystal structure of fission yeast Dom34-Hbs1 complex was solved.[188] Dom34 is a paralog of eRF1[189] with 2 similar (M and C) and one significantly different N-terminal domain.[188] Hbs1 is a conserved member of GTPase family and a paralog of eRF3.[189,190] It contains a GTPase domain, and 2 domains (II and III) by which it interacts with Dom34.[188] The crystal structure of fission yeast Dom34-Hbs1 and overall shape of eRF1-eRF3-GTP are alike.[188]

As all of the Ski complex subunits and Ski7 are present in *S. pombe* cells, it is reasonable to assume that NGD and NSD pathways are similar to the one in *S. cerevisiae*.

Drosophila melanogaster

Homologs of both Dom34 (Pelota) and Hbs1 are encoded in the fruit fly genome. Nevertheless, there are no studies concerning their involvement in RNA decay pathways in *D. melanogaster*. It was shown that Pelota is required for male meiosis and controls the self-renewal of germline stem cells in *Drosophila.*[191]

Plants

The *A. thaliana* genome encodes Pelota, homolog of Dom34. Nothing is known, however, about its involvement in RNA decay.

Mammals

Pelota is a mammalian homolog of Dom34, which forms a complex with Hbs1. Unlike yeast Dom34-Hbs1 complex, Pelota-Hbs1 has the ability to dissociate stalled ribosomes only in the presence of ABCE1 (homolog of yeast Rli1), a member of an ATP-binding cassette (ABC) transporters′ superfamily. This dissociation depends on Pelota and ABCE1 and Hbs1 has only stimulatory effect. Ribosomes which are stalled on transcripts containing more than 9 nt downstream of the P-site are not disassembled. This suggests that – contrary to that seen in the *S. cerevisiae* complex – Pelota-Hbs1-ABCE1 may be involved only in

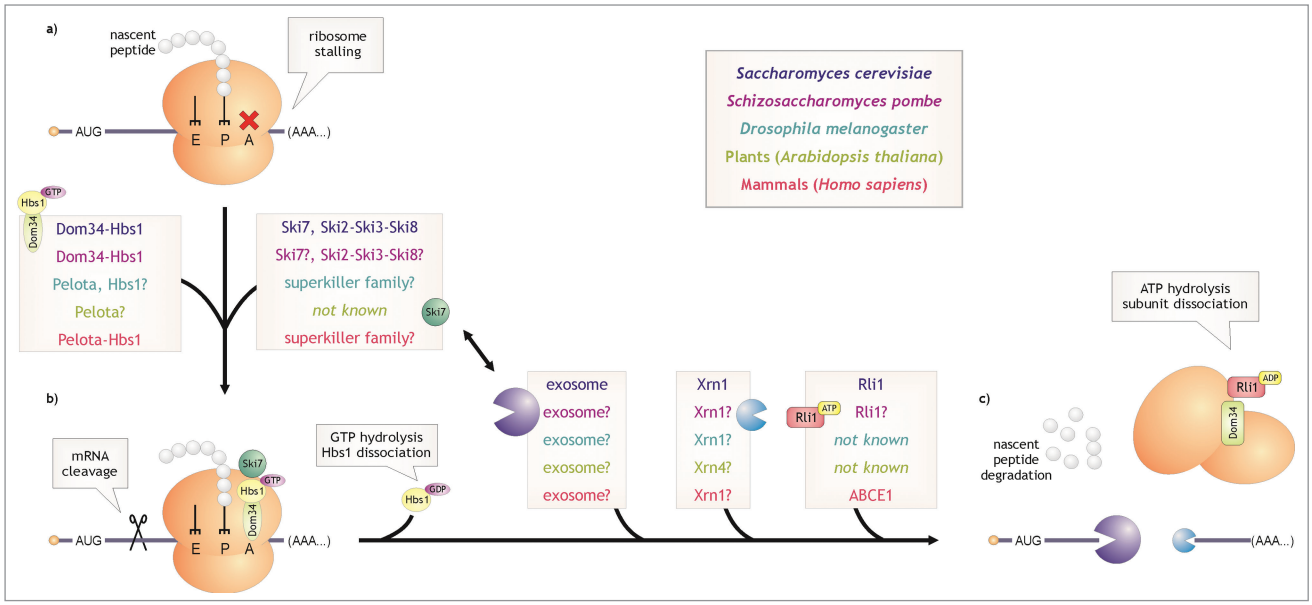

Figure 4. |A unified model of mRNA degradation pathways triggered by ribosome stalling. a) Ribosome stalling leads to recruitment of Dom34-Hbs1 complex and yeast Ski7 protein during NGD, NSD and 18S NRD pathways. b) In the case of NGD and NSD, the recruitment of Dom34-Hbs1 induces mRNA endonucleolytic cleavage by an unknown endonuclease (mainly upstream of the stalled ribosome)183. GTP hydrolysis results in Hbs1 dissociation and causes conformational changes in Dom34178. Rli1 binds to Dom34. c) ATP hydrolysis enables subunit dissociation186. In the case of NGD and NSD, fragments of endonucleotically cleaved mRNA are degraded by the exosome and Xrn1; nascent peptide is eliminated from the cytoplasm by the proteasome. Color coding and question marks as in **Figure 1**.

mammalian non-stop decay.[192] Degradation by exosome pathways is plausible, as Hbs1L co-purifies with human Dis3L.[104]

The ability of dissociating vacant 80S ribosomes[192] and the fact that Dom34-Rli1 (ABCE1 yeast homolog) is involved in the final round of ribosomal cytoplasmic maturation[187] imply that this complex may be also involved in other cellular processes.

Concluding remarks

Pathways and enzymes of cytoplasmic mRNA degradation have been extensively studied in many different organisms. However, many questions still remain unanswered. Most information has been provided by studies in *S. cerevisiae* and humans, but there are still many gaps concerning other species. For instance, no-go, non-stop and 18S NRD decay in *S. pombe*, *D. melanogaster* and plants have not been studied and only limited information is available. Uridylation-dependent mRNA degradation is a newly discovered and thus poorly understood pathway involved in posttranscriptional gene expression regulation. Another interesting aspect is the tissue specific expression of various components of mRNA degradation pathway in metazoa, as still limited information is available on this matter.

What is more, genomes of various organisms encode many different enzymes assigned to perform the same processes, as in the case of deadenylases. Identification of their specific mRNA substrates, the exact composition of complexes or establishing possible cooperative action between them would be crucial to understand the process of, for example, the removal of the poly (A) tail, as a trigger for mRNA degradation.

Moreover, structural information is often indispensable in revealing the exact function and the mechanism of action of a single protein or a whole protein complex. Structural changes across the various species provide insight into the evolution or conservation of the protein architecture. For instance, the structure of ring-shaped exonucleases from bacteria, archaea and eukaryotes has broadened our understanding of mRNA substrate degradation mechanisms. Thus, structural studies should be performed regarding other single proteins or macromolecular complexes.

All named authors hereby declare that they have no conflicts of interest to disclose.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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