OPEN ACCESS

IJABR

International Journal of Advanced Biotechnology and Research (IJABR)
ISSN 0976-2612, Online ISSN 2278–599X,
Vol-16, Issue3, 2025, p-105-138

DOI: 10.5281/zenodo.16736779

**Review Article**

# The Messenger RNA Surveillance in the Nucleus: Principle, Function and Links to Human Diseases

**Bhaswar Nandi, Satarupa Das and Biswadip Das***

**Article Info**

RNA Biology Laboratory, Department of Life Science and Biotechnology, Jadavpur University, Kolkata-700032, West Bengal, India

---

**Running title:** Role of mRNA Surveillance in Human Diseases.

---

***Correspondence**:
Dr. Biswadip Das
Department of Life Science and Biotechnology, Jadavpur University, 188 Raja S.C. Mullick Road, Kolkata – 700 032
West Bengal, India
Phone: 91-9748324755 (Cell)

---

Received: 11/07/2025
Accepted: 03/08/2025
Published: 04/08/2025

---

DOI: 10.5281/zenodo.16736779

---

**Publisher's Note:** IJABR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



---

**Abbreviations:**
CTEXT, **C**BC-**T**if4631p-dependent **EX**osomal **t**argeting,
TRAMP, **TR**f4p/5p-**A**ir1p/2p-**M**tr4p-**P**olyadenylation,
NEXT: **N**uclear-**EX**osome **T**argeting,

---

## Abstract

Productive expression of a gene involves the nuclear events of mRNP biogenesis consisting of transcription and multiple processing/modification events of the nascent mRNAs. Complexities involved in mRNP biogenesis leads to various errors in the resulting mRNPs, which potentially increases the possibility of production of abnormal, aggregation-prone and otherwise non-functional polypeptide chains. To prevent formation of such aberrant proteins, all eukaryotic cells evolve a wide array of mechanisms which constantly monitors the transcription and nuclear mRNP biogenesis events. Dubbed as the mRNA surveillance, these mechanisms principally require the activity of the eukaryotic RNA processing exosome and its cofactors, which promptly detect these faulty messages and selectively degrade them to prevent their undesired translation. Ranging from yeasts to humans, mRNA surveillance thus limits the accumulation of aberrant messages and safeguards the cells from their detrimental effects. Remarkably, recent research underscored that the mRNA surveillance machinery, the RNA exosome and its cofactor CTEXT together target and degrade a small of group of normal and functional messages and thereby control the cellular abundance of these mRNAs and thereby regulate a few crucial cellular processes including unfolded protein response and cellular response to nutrient stress. Remarkably, mutations in the components of the exosome and its cofactors lead to the dysfunction of the surveillance machinery, which are linked to a variety of human diseases and disorders. In this article, we examine the composition of the mRNA surveillance components, narrate their functions and finally illustrate the defects of surveillance machinery involved in various diseases with predicted mechanism of mutation induced disorders and finally project the frontline and forthcoming avenues of the future research.

**Keywords:** mRNA degradation; Nuclear Exosome, CTEXT, TRAMP, Tif4631p, Rrp6p, Cbc1p, Dbp2p.

## 1. Introduction

Messenger RNA surveillance mechanisms are of paramount importance since they protect the cells from the damaging effects of the faulty messages, which are spontaneously generated from the error-prone mRNA biogenesis events in all eukaryotic cells (Reviewed in 1-3). These surveillance mechanisms constantly monitor various steps involved in the mRNA biogenesis and promptly detect diverse kinds of aberrant messages and eventually degrade them in a selective fashion to prevent their undesired accumulation in the cells (Reviewed in 1-5). Ranging from simple model eukaryote, *Saccharomyces cerevisiae* to humans, all eukaryotes have evolved a wide array of mRNA surveillance mechanisms that consist of a multi-protein complex, dubbed eukaryotic RNA exosome and its various co-factors, which play key roles in limiting the concentration of these faulty messages in the cell (1–8). Consistently, dysfunctions of mRNA surveillance machinery owing to the mutations in specific functional components are associated with diverse diseases in humans (2). This article is aimed to examine the composition, structure and functions of various mRNA surveillance machinery in budding yeasts and humans and further assess the connections between the mutations/defects in the surveillance machinery and various diseases.

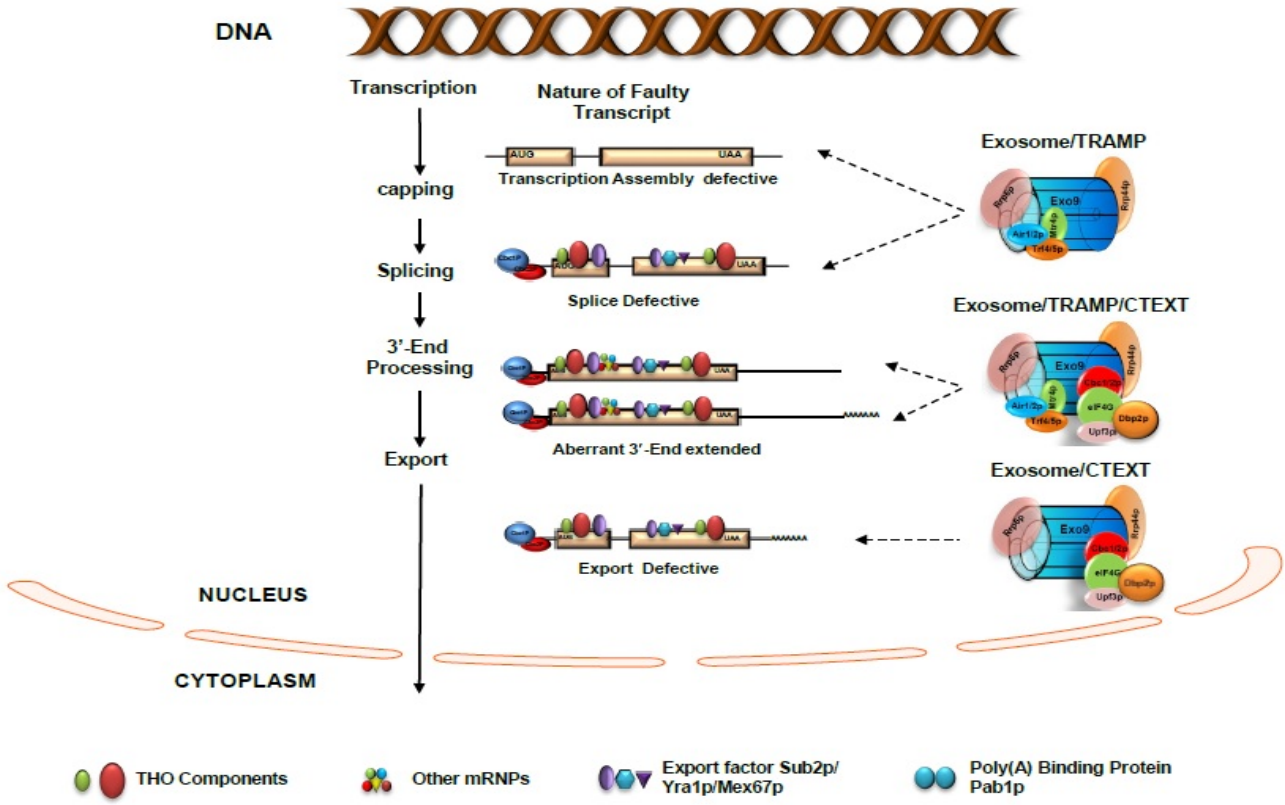
## 2. Nuclear mRNA biogenesis: Birth of the mRNA and its early life in the Nucleus

In all eukaryotes, mRNA biogenesis is a nuclear event which starts with the transcription of the protein-coding genes by RNA polymerase II (RNAPII) and subsequently progresses through the major covalent modification events. These events include the capping of the nascent transcript at the 5′-end, splicing to remove the intron(s) and a maturation event at the 3′-termini that comprises a site-specific cleavage and a template-independent addition of adenylate residues (7, 9–13) (Fig. 1). In parallel to these covalent modification events, each maturing message undergoes physical association with a wide spectrum of mRNA-binding factors and heterogeneous ribonucleoproteins (hnRNPs) (14–19). For example, mRNP assembly initiates with the binding of heterodimeric nuclear cap complex called CBC to the $m^7G$ cap right after the capping event (18). This is followed by the recruitment of the transcription/export (TREX) complex onto the maturing transcript. TREX complex consists of THO proteins (Hpr1p, Mft1p, Tho2p, and Thp2p), the mRNA export factor/RNA helicase Sub2p and the RNA binding protein Yra1p (11, 20–22). Binding of these proteins with the nascent peptides facilitates splicing followed by the binding with export receptor Mex67p:Mtr2p, various ribonucleoproteins and poly (A) tail binding protein Pab1p (17, 19). Concerted actions of the three covalent modification events and association with the multitude of protein factors eventually generates an export-competent mRNP, which is 5′-capped, devoid of introns carrying a polyadenylated tail at the 3′-terminus harboring myriads of appropriate complements of mRNA-binding proteins, maturing and export factors (20, 23–25) (Fig. 1). Formation of export-competent mRNP is tightly accompanied with their nuclear export from the nucleus to the cytoplasm (12, 26) (Fig. 1), which ensues the second phase of the life of the mRNA comprising of their translation to produce appropriate abundance of its protein product under a given condition.

## 3. Adult Life of the mRNAs in the Cytoplasm: mRNA Localization, Translation and Degradation.

Traditional view about the life of the eukaryotic mRNAs propose that once the messenger RNA arrives at the cytoplasm, it typically becomes engaged in the cytoplasmic translation leading to the production of the corresponding protein. However, many recent research from various laboratories emphasize that once mRNAs arrive in the cytoplasm, newly exported mRNAs are first transported to a specific subcellular territory before being translated (Reviewed in 27-28). During the time of their transit, the translation of the given mRNAs remain suppressed in highly regulated fashions to avoid unwanted protein production at an inappropriate site where the function of the given protein is not warranted (29, 30). Regulated mRNA localization/transport is therefore, a highly regulated event of eukaryotic gene expression pipeline, which addresses how a specific mRNA is transported from the nuclear periphery to a specific sub-cellular destiny such as the vicinity of endoplasmic reticulum, mitochondria, peroxisome and cellular boundary near the cell

membrane (27, 28, 31, 32).




**Source:** Self designed by corresponding author (Fig 1-Nandi et al . (2025))

**Fig. 1.** mRNP biogenesis and surveillance in baker's yeast *S. cerevisiae*. Schematic representation depicting the stages of mRNA biogenesis in the nucleus each of which is subject to quality control by the nuclear surveillance systems (nuclear exosome/TRAMP/ CTEXT).
The normal and functional mRNAs are exported quickly out of the nucleus (indicated in the left half of the figure). Aberrant messages, on the other hand, are subjected to the degradation by the exosome/TRAMP, the exosome/TRAMP/CTEXT or the exosome/CTEXT. Faulty messages generated in the early, middle and later phases of biogenesis are targeted by the exosome/TRAMP, the exosome/TRAMP/CTEXT and the exosome/CTEXT complex, respectively (see text for details). Proteins binding to maturing transcripts during different stages, are schematically indicated by different solid coloured symbols. Adapted from Maity et al (2016).

This intracellular transport of mRNAs at the destined location follows a local translation causing the production of the corresponding protein with a very high local abundance. The local concentration of that protein, consequently impact diverse important cellular processes including establishment of cell polarity, cell asymmetry, and determination of embryonic axis during development and plasticity in the neuron (31). Targeting of a specific message to a destined sub-cellular region is thus extremely controlled physiological processes aimed to accomplish a specific spatial and temporal distribution of the corresponding protein in response to a set of environmental cues. Regulated intracellular distribution of specific messages thus governs the optimum functionality and capacity of a cell to respond to such cues. Interestingly, recent findings indicate that specific *cis*-acting RNA localization elements (LEs) or RNA zip codes present in various mRNA cargoes play an instrumental role in the localization and trafficking of these targeted mRNAs by providing critical binding sites for the specific RNA-binding proteins (RBPs) that affect their trafficking (Reviewed in 28).
Once a specific message land at its destined sub-cytoplasmic destiny, the mRNAs after shedding off the RBPs inhibiting the translation, undergo another round of remodeling event to enter a unique event called pioneer round of translation while they still carry the nuclear CBC (33, 34). This exceptional round of translation is aimed to detect any mutation causing potential in frame premature termination codon (PTC) in the translating message. If such a PTC is found, it is promptly targeted for degradation by a translation-dependent cytoplasmic surveillance event called non-sense mediated decay (NMD) pathway to

avoid production of truncated proteins (35). Messages devoid of any PTC, on the other hand, endure the NMD action and subsequently experience another round of mRNP remodeling involving the exchange of the nuclear cap-binding-protein (CBC) at the 5′-cap of mRNA with the translation initiation factor eIF4F (consisting of eIF4E and eIF4G) (35). The remodeled message is then engaged for the steady-state and productive translation to produce the required cellular pool of proteins (33, 34).

After predestined rounds of protein-synthesis cycle, a translating mRNA is converted into a degradation-committed message by a poorly understood mechanism and eventually separates from polysomes (actively translating ribosomes) to subsequently associate with the cytoplasmic P-bodies, which were believed to be the cellular sites of mRNA degradation in *S. cerevisiae*. Many earlier studies, consequently showed that degradation-committed messages are subsequently destroyed by the default degradation pathway within the P-bodies (36–38). Default degradation of mRNAs consists of a tightly controlled process that is governed by a distinct set of genes/proteins and contributes to the basal steady state level of all mRNAs, which, in turn, determines the total cellular pool of proteins (36, 39–41). However, many recent studies are inconsistent with the idea that P-bodies constitute the cellular sites for mRNA degradation as many mRNAs that enter P-bodies, were demonstrated to exit the same and re-initiate translation (42, 43).

## 4. The need for mRNP surveillance and quality control in the nucleus

Remarkably in all eukaryotes, the transcription and nuclear pre-mRNA processing events are physically and functionally coupled via the C-terminal domain (CTD) of the Rpb1p (largest subunit of RNAPII) (11, 25, 44–46). The CTD acts as a recruiting platform for transcription and other mRNA processing factors, which are loaded initially onto the CTD and then transferred onto the transcribing/maturing message (9, 21, 46–51). This efficient functional coupling between CTD and the transcription/maturation factors was shown (i) to enhance the likelihood of the formation of export-competent and productive mRNPs and (ii) to decrease the probability of generating defective/aberrant transcripts (Maniatis and Reed 2002; Reed 2003; Rodriguez et al. 2004; Aguilera 2005; Bentley 2005; Bird et al. 2005; Reed and Cheng 2005; Miller and Reese 2012). Interestingly, despite the existence of the functional coupling, defective/faulty messages are still produced. To prevent the concentration of such aberrant/faulty messages, all eukaryotic cells evolve an elaborate array of surveillance mechanisms, which constantly monitors the presence of such aberrant messages and if detected, are rapidly eliminated (1, 2, 5, 36, 52–60). Recent studies uncovered that diverse kinds of aberrant messages are generated in the nucleus at various stages of transcription or mRNA processing events including capping, splicing and polyadenylation. These aberrancies includes transcription elongation and packaging-defective, splice-defective mRNAs, aberrantly long of 3′-extended transcripts and export defective messages (Fig. 1) (2, 8). In the nucleus of all eukaryotes the selective degradation of these faulty messages are carried out by the nuclear exosome and its associated co-factors (Fig.1) (2, 8, 61–69). A detailed account of the structure of the core exosome and its various co-factors in yeasts and humans are presented below.

### 4.1 Structure of the core nuclear exosome in yeasts and humans

In *Saccharomyces cerevisiae*, the nuclear exosome is a multi-protein complex, consisting of eleven subunits, which is subdivided into the two parts: core exosome and the catalytic components. The core of the exosome is denoted as Exo9, which comprises of nine protein subunits (each one dubbed as Rrp proteins for **R**ibosomal **R**NA **P**rocessing), which are arranged in a two-layered stacked ring structure along with a central channel (Fig. 2) (70–75). The top layer is called the trimeric ‘Cap’ that is composed of Rrp4p, Rrp40p and Csl4p (Fig. 2) (Table 1). This ‘Cap’ structure is placed on the top of the hexameric ‘Ring’ consisting of Rrp41p, Rrp42p, Rrp43p, Rrp45p, Rrp46p and Mtr3p (Fig. 2) (Table 1) (70–75). All the ‘Ring’ proteins harbor an RNase PH domain and thus shares a structural resemblance with bacterial phosphorolytic nuclease (Table 1) (70–75). In contrast, both the Rrp40p and Rrp4p carries one S1 and one KH RNA domains and Csl4p contains one KH domain and a zinc ribbon motif, which binds RNA (Table 1) (70–75). The central channel that spans the top of trimeric ‘Cap’ and the bottommost part of the hexameric ‘Ring’ is able to accommodate the single stranded RNA (Fig. 2) (70). The entire EXO9 core subunits together shape the core and basic structure of the exosome and plays an important role in the interaction with the RNA substrates and in guiding the single stranded RNA molecule in the central channel for its degradation. Interestingly, despite having potential exonuclease domains in all nine core subunits, the central EXO9 is catalytically inactive. The catalytic activity of EXO9 complex is achieved by the union with the tenth subunit,

Rrp44p/Dis3p, which is a 110 KDa protein and is strongly associated with both nuclear and cytoplasmic forms of the exosome (Fig. 2) (Table 1) (76–78). Rrp44p possess both the endo- and exonucleolytic activities resulting in the formation of $Exo10^{Dis3p}$ complex (70, 71). $Exo10^{Dis3p}$ complex additionally interacts with the eleventh subunit, Rrp6 (79), which is a 3′→5′ exoribonuclease to form the complete $Exo11^{Dis3p+Rrp6}$ (72, 80) and interact with the Exo9 complex from the top of the cap structure (opposite face of Exo9, through which the Dis3p subunit contacts this complex (Fig. 2) (75, 81–83). The single stranded RNA substrates either thread through the central canal of EXO9 to reach the active catalytic site of Dis3p/Rrp44p or can bypass the central channel to directly bind to the active catalytic site of Dis3p/ Rrp44p in a channel-independent fashion (Fig. 2) (84, 85). It should be noted here that $Exo10^{Dis3}$ is distributed in both the nucleus and cytoplasm, whereas $Exo11^{Dis3p+Rrp6p}$ is localized exclusively in the nucleus owing to the characteristic nuclear distribution of Rrp6p (79). Additionally, the $Exo11^{Dis3p+Rrp6p}$ engages in the interaction with its obligate interacting partner Lrp1p/Rrp47p (C1D in humans) to form a 12-subunit multiprotein complex in the nucleus ($Exo12^{Dis3/Rrp6/Rrp47}$ in yeast and $Exo12^{Dis3/Rrp6/C1D}$ in humans) (Table 1) (80, 86). Markedly, Rrp6p also interacts with M-phase phosphoprotein-6 (Mpp6p) protein (Table 2), which is necessary for its function (87–89). Rrp47p and Mpp6p participate in RNA binding and interaction with structured/pyrimidine rich sequences (90).

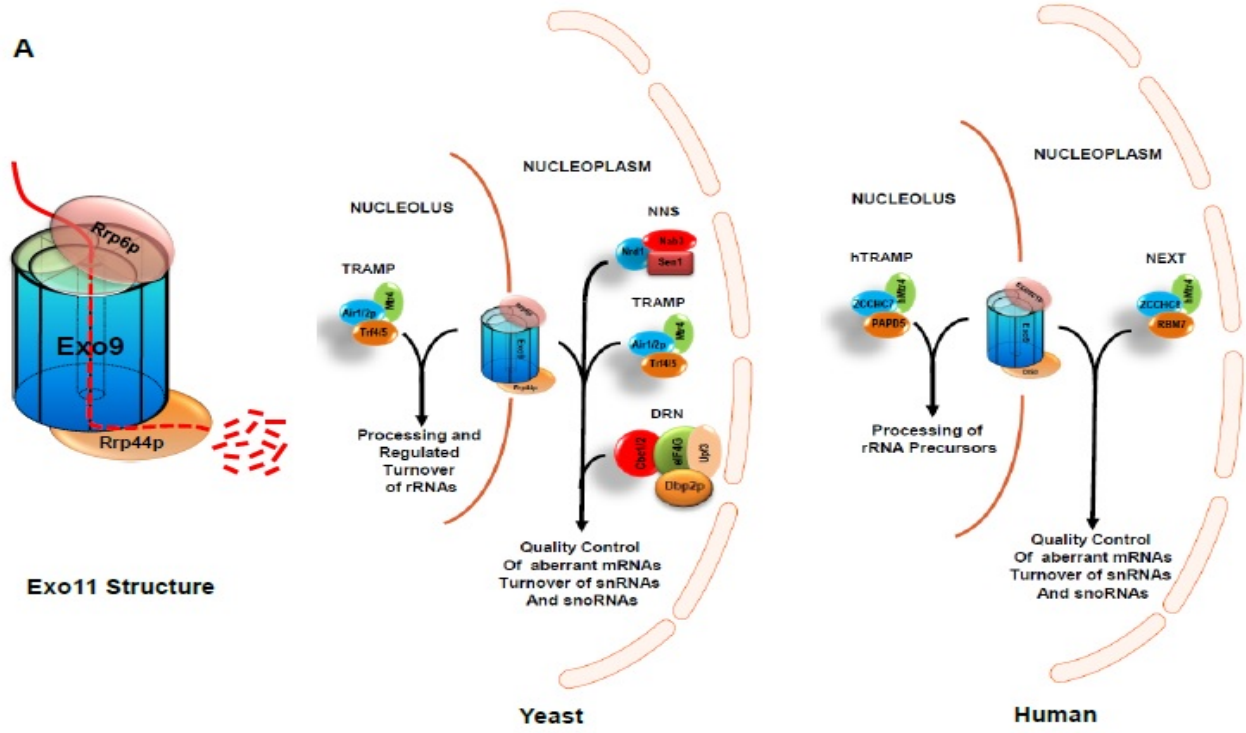
Remarkably, structural composition of the exosome subunits from yeasts reveals a high degree of conservation with the composition and structure of the exosome from humans with a few notable differences. The subunits of human exosome are named either as **h**uman **R**ibosomal **R**NA **P**rocessing (hRRP; after the yeast Rrp proteins) or as **EXOS**ome **C**omponent (EXOSC) proteins (Table 1). One key difference between the two involves the existence of three different isoforms of the yeast Rrp44p in humans, DIS3, DIS3L1 and DIS3L2 (91, 92) with a distinctive intracellular distribution of each one. While, DIS3 primarily localizes to the nucleoplasm (but is excluded from nucleolus), DIS3L1 are exclusively distributed in the cytoplasm (Tomecki et al. 2010). Furthermore, although DIS3L2 is cytoplasmic, it often distributes in the cytoplasmic foci associated with the P-bodies (93). Accordingly, only DIS3 and DIS3L1 contact with the nuclear and cytoplasmic forms of the exosome respectively via the "hexameric" ring subunits opposite to their surfaces that interact with the "cap" structure, whereas DIS3L2 does not interact with the core exosome (84). The second key difference between the yeast and human exosome lies in the intracellular distribution of the Rrp6p in yeasts and that of its human orthologue PM-Scl100/hRRP6/EXOSC10. While the yeast Rrp6p is strictly localized in the nucleus, hRRP6/EXOSC10 is localized to both the nucleus and the cytoplasm (91, 92, 94, 95). Thus, the nuclear RNA exosome in humans includes Exo9, DIS3 and EXOSC10/C1D (Exo12DIS3/EXOSC10/C1D) (Table 1) (73).

**Table 1.** Composition and functions of the yeast and human nuclear exosome and its cofactors.

| Subunit | Yeast Ortholog | Human Name | Cellular Function | Functional Features | Key Refrences |
|---|---|---|---|---|---|
| **EXOSOME** | Rrp4p | hRrp4p/ EXOSC2 | Exosome non-catalytic core component; involved in assembly and determination of trimeric cap structure | S1,KH RNA binding domain | (80, 249, 266) |
| | Rrp40p | hRrp40p/ EXOSC3 | Exosome non-catalytic core component; involved in assembly and determination of trimeric cap structure | S1,KH RNA binding domain | (80, 249, 266)) |
| | Rrp41p/ Ski6p | hRrp41p/ EXOSC4 | Exosome non-catalytic core component; involved in assembly and determination of hexameric ring structure | RNase PH domain | (80, 249, 266) |
| | Rrp42p | hRrp42p/ EXOSC7 | Exosome non-catalytic core component; involved in assembly and determination of hexameric ring structure | RNase PH domain | (80, 249, 266) |
| | Rrp43p | EXOSC8 | Exosome non-catalytic core component; involved in assembly and determination of hexameric ring structure | RNase PH domain | (80, 249, 266) |
| | Rrp44p/ Dis3p | hRrp44p/ hDis3p/ | Exosome core complex catalytic component with both endonuclease & processive 3'→5' | RNase R ,CSD1/2 and PIN domains | (76, 82, 267). |

| | | | | | |
|---|---|---|---|---|---|
| | | EXOSC11 | exonuclease involved in RNA processing and degradation | | |
| | Rrp45p | PM/Scl-75/ EXOSC9 | Exosome non-catalytic core component; involved in assembly and determination of hexameric ring structure | RNase PH domain | (80, 249, 266) |
| | Rrp46p | hRrp46p/ EXOSC5 | Exosome non-catalytic core component; involved in assembly and determination of hexameric ring structure | RNase PH domain | (80, 249, 266) |
| | Rrp6p | PM/Scl-100/ EXOSC10 | Nuclear Exosome exonuclease component; a distributive 3′→5′ exonuclease involved in RNA processing, maturation, degradation | RNase D PMC2NT,HRDC and Lasso domains | (62, 79, 80, 268) |
| | Mtr3p | EXOSC6 | Exosome non-catalytic core component; involved in assembly and determination of hexameric ring structure | RNase PH domain | (80, 266, 268, 269) |
| | Csl4p/Ski4p | hCsl4p/ EXOSC1 | Exosome non-catalytic core component; involved in assembly and determination of trimeric cap structure | S1 and Zn-ribbon RNA binding domain | (80, 266, 268, 269) |
| **TRAMP** | Mtr4p | hMTR4p/ DOB1 | ATP dependent 3'-5'RNA helicase of the DExD/H family; involved in RNA processing, degradation both as dependent or independent of TRAMP complex; unwinds RNA duplexes; required for 5.8s rRNA processing | Arch domain, with two coiled-coil arms/stalks and a globular fist/KOW domain with RNA binding activity | (112, 114, 115) |
| | Trf4p | hTRF4p | Non-canonical poly(A)polymerase; involved in nuclear RNA degradation as a component of the TRAMP complex; catalyzes polyadenylation of hypomodified tRNAs, snoRNA and rRNA precursor | CAT and Central domains | (96, 107, 109, 216) |
| | Trf5p | PAPD5 | Non-canonical poly(A)polymerase; involved in nuclear RNA degradation as a component of the TRAMP complex; catalyzes polyadenylation of hypomodified tRNAs, snoRNA and rRNA precursor; required for mRNA surveillance and maintenance of genome integrity | CAT and Central domains | (96, 107, 109, 216) |
| | Air1p | ZCCHC7 | Zinc Knuckle Protein; involved in nuclear RNA degradation as a component of the TRAMP complex; stimulates the poly (A)polymerase activity of Pap2p in vitro | Zinc Knuckle domain | (96, 119, 270) |
| | Air2p | ZCCHC7 | RNA binding subunit of the TRAMP nuclear RNA surveillance Complex; catalyzes polyadenylation of hypomodified tRNAs and snoRNA and rRNA precursor; required for mRNA surveillance and maintenance of genome integrity; serving as a link between RNA and DNA metabolism | | (110, 270) |
| | RBM7 | | Putative RNA binding protein, component of NEXT complex and involved in degradation of PROMPTs and aberrant forms of non-coding snRNAs | RRM domain | (148, 214) |
| **CTEXT** | CBC1 | CBP80, NCBP1, | Large subunit of cap-binding protein complex; interacts with Npl3p to carry nuclear poly(A)+mRNA to cytoplasm ;involved in nuclear mRNA degradation and telomere maintenance. | Three MIF4G domains | (64, 168) |
| | CBC2 | CBP20, NUD13, SAE1, NCBP2 | Small subunit of the heterodimeric cap binding complex with STO1p; interacts with NPl3p,possibly to package mRNA for export from the nucleus; telomere maintenance | RMP fold | (64) |

| | | | | | |
|---|---|---|---|---|---|
| | TIF4631/4632 | eIF4G1/ eIF4GII | Involved in translational initiation, Stress granules assembly, ribosomal large subunit biogenesis; localizes to the cytoplasm, cytoplasmic stress granules and cytoplasmic mRNA processing body Translation initiation factor eIF4G; subunit of mRNA cap-binding protein complex(eIF4F) that also contains eIF4E(Cdc33p) | Three RRM domains, one PAB, MIF and CBC binding domain RRM,NES and NLS domains | (251, 271–273) |
| | Dbp2p | DDX5 | Plays a crucial role in various aspects of mRNA metabolism, ATP dependent DEAD Box helicase, binds mRNA and implicated in the nuclear retention of special mRNAs, regulates the glucose/nitrogen stress response by controlling reversible nuclear retention and decay of *SKS1* mRNA. | Two RecA like domains, Q-motifs and one N-terminal and one C-terminal extensions. | (125, 170) |
| **NNS Complex** | Nrd1p | No clear homologue | Involved in 3'end formation of some mRNAs, snRNAs, snoRNAs and CUTs; interacts with CTD of RNA pol II large subunit Rpo21 at phosphorylated Ser5 to direct transcription termination of non polyadenylated transcript; nuclear mRNA surveillance, Binds and degrades aberrant mRNAs | CTD,RE/RS,RRM,P/Q domains | (105, 106, 131, 134) |
| | Nab3p | No clear homologue | Involved in 3'end formation of some mRNAs, snRNAs, snoRNAs and CUTs and termination of non-poly(A) transcripts and efficient splicing, Binds and degrades aberrant mRNAs | D/E,RRM,P/Q domains | (106, 131, 135, 274) |
| | Sen1p | SETX | ATP dependent 5'to 3' RNA-DNA hybrid and DNA helicase; Component of NNS complex involved in 3'end formation of some mRNAs, snRNAs, snoRNAs and CUTs, Binds and degrades aberrant mRNAs | Protein interacting domain, ATPase helicase domain,NLS,Rbp1p and Rnt1p domain | (106, 274–276) |




**Source:** Self designed by corresponding author (Fig 2-Nandi et al . (2025))

**Fig. 2. Structure and distribution of the nuclear exosome complex. (A) Schematic representation of core exosome (Exo11$^{Dis3p + Rrp6p}$) from *S. cerevisiae*.**

The hexameric bottom PH ring complex is shown in blue; the trimeric cap complex, pale green; Rrp6, pink; and Dis3p/Rrp44p, orange. The threading single stranded RNA (indicated with red line) is moving 3′→5′

through the central channel of the complex to the Dis3p/Rrp44 exonucleolytic centre, where it is degraded. (B) The composition of the exosome complex is shown along with various cofactors in different compartments in yeasts and humans.

### 4.2 Co-factors of the nuclear exosome and their RNA targets in yeasts

Fascinatingly, the nuclear exosome, $Exo11^{Dis3p+Rrp6p}$ lacks any catalytic specificity and in principle can target and degrade a wide range of RNAs in the cell, which offers a challenge for this mRNA decay machine to ensure that only the aberrant and specific exosomal RNA targets are degraded in a selective fashion without degrading the normal functional messages. This is accomplished by evolving a set of exosomal co-factors consisting a group of ancillary protein complexes, which impart RNA substrate specificity to the $Exo11^{Dis3p+Rrp6p}$ by associating with it under a given set of conditions. These cofactors collectively (i) modulate/stimulate the exonuclease activity of the $Exo11^{Dis3p+Rrp6p}$ *in vivo* and (ii) assists the nuclear exosome to properly recognize aberrant RNA targets by distinguishing them from the normal functional messages. To date three cofactors are reported in the literature, which include the TRAMP complex (96–99), the CTEXT complex (8, 100–102) and the NNS complex (103–106). Each of these complexes primarily recognize a specific class of RNA targets to be degraded and recruit these specific target RNAs to $Exo11^{Dis3p+Rrp6p}$ complex to enable their degradation.

#### 4.2.1. TRAMP Complex and its various RNA targets

One of the best-understood and well-studied ancillary co-factor of the exosome is the TRAMP (**TR**f4/5-**A**ir1/2-**M**tr4-**P**olyadenylation) complex in baker's yeast, *Saccharomyces cerevisiae*, which contains a non-canonical poly(A) polymerase, Trf4p(Pap2p)/Trf5p, Zn- knuckle RNA binding proteins-Air1p/2p, Mtr4p and DExH box RNA helicase (Table 1) (96–99, 107–109). They facilitate the exosomal degradation various sets of target RNAs. Trf4/5p constitutes two distributive poly(A) polymerases and are localized in the nucleolus and nucleoplasm, which typically add short poly(A) tails to the substrates RNAs (110, 111). The helicase activity of Mtr4p is thought to (i) relax the secondary structures of target RNA, (ii) dislocate any RNA-bound proteins to promote nucleolytic cleavage, (iii) modulate adenylation reaction of Trf4/5p and (iv) catalyze dissociation of the TRAMP complex from target RNA to restrict the number of adenylate residues to 4-5 (Table 1) (112–115). Five Zinc-knuckle motifs of Air1p/2p is believed to increase the fidelity of the binding of TRAMP complex to the target RNAs (Table 1). Thus, the TRAMP complex simulates the degradation via adding short poly (A) tails to the RNA substrates and facilitates the exonucleolytic degradation by exosome.

Remarkably, TRAMP complex is known to assist the nuclear exosome to target both non-coding and coding RNA targets *in vivo*. Previous reports implicated TRAMP in the nuclear surveillance and degradation of hypomodified initiator pre-tRNAs (116, 117), polyadenylation of improperly processed ribosomal RNAs, snRNAs and snoRNAs (96, 98, 99, 117–120) and their subsequent degradation by the nuclear RNA processing exosome. In addition to the non-coding transcripts, the TRAMP complex along with the nuclear exosome complex plays a pivotal role in the targeting and selective degradation of faulty mRNAs resulting from earlier phase of mRNP biogenesis as exemplified by transcription-assembly-defective mRNAs and intron containing un-spliced pre mRNA (Fig. 1) (Table 2) (Das et al. 2014; Maity et al. 2016; Saha et al. 2024). Thus TRAMP complex constitute a key co-factor of the nuclear RNA processing exosome, which helps the healthy cell in ridding various aberrant non-coding and messenger RNAs and defends the cell from their catastrophic impacts.

#### 4.2.2. CTEXT Complex and its various RNA targets

The CTEXT complex constitutes the second important co-factor of the nuclear exosome, which was discovered as a nuclear decay system in *Saccharomyces cerevisiae* and was initially named DRN (Decay of RNA in the Nucleus). DRN was initially identified from the genetic suppressor analysis of a mutation in *CYC1* gene encoding iso-1-cytochrome C protein in baker's yeast. This mutation, called *cyc1-512* consisted of a 38 base pair deletion in the 3′-untranslated region of the *CYC1* gene, which eliminated the key signal sequences required for the transcription termination of this gene and appropriate cleavage and polyadenylation reaction and proper 3′-end maturation of *CYC1* mRNA (121, 122). Consequently, the resulting mutant *cyc1-512* mRNAs have abnormally long 3′-untranslated region, all of which were polyadenylated at much further downstream sites (123). These aberrant messages with abnormally long 3′-UTR and polyadenylated at further downstream sites were

found to be retained in the nucleus and were rapidly degraded by two proteins, the nuclear mRNA cap binding protein, Cbc1p and the nuclear exosome component, Rrp6p (123, 124). Further research demonstrated that apart from the *cyc1-512* mRNAs, the DRN system also targets and degrades export defective *lys2-187* mutant mRNAs (65). Extension of this interesting finding further revealed that in addition to Cbc1p and Rrp6p, two other shuttling proteins, Tif4631p (previously known as the translation initiation factor gamma, eIF4GI) and Upf3p (UP Frameshift 3 protein, a key component of cytoplasmic non-sense mediated RNA decay) (100), and a DEAD box double-stranded RNA helicase Dbp2p (Table 1) (61, 125) also participate in the degradation of these abnormally long 3′-end maturation defective *cyc1-512* mRNAs. Mutation or deletion of any of these genes showed stabilization and diminished decay of both of the 3′-end maturation defective *cyc1-512* and export defective *lys2-187* mRNA targets (123, 126). Further investigation revealed that at least four different kinds of aberrant messages are generated in the nucleus of baker's yeast at various stages of mRNA biogenesis events (Fig. 1) (Table 2). They include the transcription-elongation defective, splice-defective, aberrantly long 3′-end formation defective and export-defective messages (Table 2) (8). An effort to determine the functional relationships of the DRN system with the nuclear exosome and TRAMP complex with respect to the elimination of aberrant mRNAs unveiled that (i) DRN system consisting of Cbc1p, Tif4631p, Upf3p and Dbp2p together constitute a second co-factor of the nuclear exosome, which was redesignated as CTEXT (**C**bc1p-**T**if4631p-dependent **EX**osomal **T**argeting) complex, (ii) there is a clear division of duties between the TRAMP and CTEXT complexes in terms of their specificity towards the aberrant nuclear messages. While TRAMP assists the nuclear exosome to recognize the transcription-elongation defective and splice defective messages (those which arise in the earlier phases of mRNP biogenesis namely during transcription and splicing), CTEXT is responsible for recognition and degradation of export-defective messages (faulty messages that are produced during the late phase of mRNP biogenesis namely during the export) (Fig. 1) (Table 2) (8). The defective messages generated in the middle phase of mRNP biogenesis such as the 3′-maturation defective transcripts during the 3′-end processing events are recognized and degraded both by the TRAMP and CTEXT (Fig. 1) (Table 2). Recent investigation has established that all the CTEXT components physically interact among one another (Saha et al. 2024a, Gaine and Das, unpublished) and they exist together as a separate, independent four-protein distinct complex (Gaine and Das, unpublished). Collectively, all these findings thus established that CTEXT constitutes the second co-factor of the nuclear exosome that plays a pivotal role in degradation of aberrant mRNAs produced during the late phase of nuclear mRNP biogenesis (8, 61, 100).

**Table 2:** Various Kinds of Aberrant mRNPs generated in the nucleus of *Saccharomyces cerevisiae*

| mRNP Biogenesis Stage | Events during mRNP Biogenesis | Type of aberrant mRNAs | References |
|---|---|---|---|
| **Early** | Transcription | Transcription assembly-defective transcripts generated in *THO* mutants | (120, 277–279) |
| | Splicing | Intron containing splice-defective messages generated in *prp2-1* mutant | (63, 280, 281) |
| **Intermediate** | 3′-end processing, cleavage & polyadenylation | Transcription-read through messages produced in *rna14-1*, *rna15-2* and *pap1-1* mutants<br>*cis*-acting 3′-end extended *cyc1-512* mRNAs | (62, 64, 66) |
| **Late** | Nuclear export | Export Defective messages generated in *rat7-1* and *nup116*- mutants<br>Export inefficient non-aberrant special messages<br>*cis*-acting export defective *lys2-187* mRNA | (65, 168, 282) |

Another independent study uncovered that CTEXT also targets and degrades almost 243 normal functional messages in a selective fashion, which were termed as 'special' mRNAs (127). Although this finding initially came as a big surprise, soon it became very clear that the preferential decay of these mRNAs represents a post-transcriptional mechanism of regulation of the expression of genes that eventually determines cellular abundance/repertoire of these 'special' messages

under various environmental cues. Recent research showed that by preferentially degrading specific functional messages, CTEXT and the nuclear exosome controls various cellular processes like activation of Unfolded Protein Response (101, 128), Cell's ability to respond to the glucose/nitrogen starving conditions (129), regulation of telomere length and silencing (Banerjea et al., unpublished) (See below in **Section 5**).

#### 4.2.2. NNS Complex and its various RNA targets

In baker's yeast, the trimeric protein complex called NNS (**N**rd1p-**N**ab3p-**S**en1p) complex was previously implicated in the non-canonical pathway involving transcription termination and 3′-end maturation of several non-coding RNAs (Table 1) (130–135). Notably, the transcription termination and 3′-end maturation of these non-coding RNAs including pre-snRNAs, pre-snoRNAs, and **C**ryptic **U**nstable **T**ranscripts (CUTs) follows an alternative mechanism of formation of 3′-end, which is completely different from 3′-end formation of the messenger RNAs as described above in **Section 2** (136, 137). NNS complex was reported to play an essential role in the 3′-end maturation of these non-coding RNAs, thereby leading either to their maturation (if their 3′-ends are formed correctly) or degradation by the exosome and TRAMP (if they are formed aberrantly) (104, 138). Remarkably, the NNS complex was also demonstrated to bind numerous mRNAs (133, 139–143). However, the major NNS component, Nrd1p was shown to promote degradation of only handful of functional mRNAs and only one kinds of aberrant mRNAs (130, 132, 144–146). Therefore, the functional significance of binding of NNS complex to multitude of mRNAs remained inexplicable and enigmatic. In an effort to evaluate if NNS complex directs the degradation of all kinds of aberrant mRNAs, as a general mRNA surveillance factor, Singh et al. (2021) showed that indeed NNS complex plays a seminal role in the degradation of all kinds of aberrant messages as described above (Table 1) (106). The study further showed that NNS complex is selectively recruited onto all kinds of faulty transcripts in co-transcriptional manner in RNAPII-dependent manner and this co-transcriptional loading of NNS complex serve as a molecular "mark" to categorize these loaded aberrant messages as "faulty" (106). Furthermore, recruitment of NNS complex is followed by the recruitment of either TRAMP (if the NNS recruitment is carried out directly by RNAPII onto the aberrant messages, which happens in earlier phase of mRNP biogenesis) or CTEXT (if the NNS recruitment is indirect and is taking place via another protein called Pcf11p, which happens during terminal phase of mRNP biogenesis) (106). Remarkably, the study also established that NNS complex as the general "exosomal specificity factor" (ESF) and is essential for marking every exosomal target messages (including the special messages) as the target for the nuclear RNA processing exosome (106).

In summary, the nuclear RNA processing exosome is assisted by three different kinds of cofactors in baker's yeast in recognizing and efficiently targeting specific classes of aberrant mRNAs. These aberrant mRNAs are marked by the selective loading of the NNS complex onto these faulty messages, which is accompanied by the sequential recruitment of either the TRAMP or the CTEXT complex proteins and finally of the nuclear exosome complex for their preferential decay. In contrast, the NNS complex are recruited seldom onto the normal functional mRNAs which thereby escape the degradative action of the nuclear mRNA surveillance system.

### 4.3 Co-factors of the nuclear exosome and their RNA targets in humans

Humans possess three distinct exosomal cofactors as exemplified by the nucleolus-localized hTRAMP complex (147, 148) and the nucleoplasm-specific nuclear exosome targeting (NEXT) (**N**uclear **EX**osome **T**argeting) (148) and PAXT (**P**oly**A** taile**X**osome **T**argeting) (148, 149) complex. The hTRAMP complex consists of human orthologues of Mtr4p (dubbed hMTR4), Air1p (ZCCHC7) and Trf4p (PAPD5/hTRF4-2) (148, 150). The NEXT complex, in contrast, is composed of the three components, hMTR4, RBM7 (having an RNA recognition motif, RRM) and the ZCCHC8 protein (148). PAXT, includes hMTR4, a zinc finger protein ZFC3H1 and an RNA binding PABPN1 protein (148, 149). Notably, both NEXT and PAXT complexes were known to physically associate with the cap-binding complex containing ARS2 (CBCA complex) via an adaptor protein, ZC3H18. This adapter protein physically tethers the exosome to nascent capped transcripts to promote their degradation following termination (149, 151). Surprisingly, humans do not have any known ortholog of Nrd1p and Nab3p, thereby indicating that the function of these proteins are dispensable in higher eukaryotes. Interestingly, in fission yeast, *Schizosaccharomyces pombe*, a Mtr4-like nuclear helicase, dubbed Mtl1p, interacts with a zinc finger protein, Red1p and form the MTREC complex,

which is involved in the silencing of heterochromatic and meiotic RNAs, CUTs and unspliced transcripts (152–154). Remarkably, all the CTEXT in *S. cerevisiae*, MTREC in *S. pombe* and NEXT/PAXT in humans are reported to interact with the cap-binding complex (CBC in yeasts and CBCA/ARS2 in humans) and the exosome (152, 154, 155) and all of them lack 3′-polyadenylation activity. This attribute of these protein complexes suggests that (i) the CTEXT/MTREC in the baker's/fission yeasts and the NEXT/PAXT complex in humans display a conservation in their modes of function, and (ii) their RNA binding and helicase activities are capable of generating a single-stranded 3′-termini that are sufficient to recruit the exosome.

In accordance with their intra-nuclear localization, the hTRAMP and NEXT complexes act on different classes of RNA substrates. While hTRAMP principally participates in the oligoadenylation of the aberrant improperly processed nucleolar rRNAs to facilitate their decay, the depletion of the NEXT components causes the accumulation/stabilization of the nuclear exosome substrates e.g. PROMoter uPstream Transcripts (PROMPTs) and 3′-extended products from U1/U2 snRNAs and replication-dependent histone (RDH) mRNAs (148, 151, 156, 157). Recent findings are suggestive of the fact that the collaboration between NEXT and the RNA cap-binding complex (CBC) is vital for the identification of the RNA targets by NEXT (151, 158). Utilizing the individual nucleotide-resolution UV crosslinking and immunoprecipitation (iCLIP) procedure, a recent transcriptome-wide study of target RNAs of the human exosome (using RBM7 as bait) revealed that the nuclear exosome majorly targets RNAPII-derived RNAs such as PROMPTs, pre-mRNA introns, long noncoding RNA (lncRNA), repetitive elements, pre-mRNA exon, short ncRNAs (miRNA, snoRNA, tRNA, snRNA), unannotated rRNA, 3′-extended snoRNAs and newly synthesized RNAs (159). Further research will identify the entire ranges of the target RNA classes in humans, which would unveil if the division of duty between various exosomal co-factors exists in humans like yeasts, which specifically target distinct RNA classes.

## 5. Role of Nuclear mRNA Surveillance in Regulating Various Cellular Processes

As stated above in **Section 4.2.1.**, the CTEXT complex in yeast assists the nuclear exosome to target and degrade the export defective messages in baker's yeast (155). A quest to determine if the Nuclear RNA processing exosome also degrades normal functional messages, a transcriptome-wide analysis of steady-state levels and stability of the global messages in WT and yeast strains defective in the RNA exosome and CTEXT complex was carried out, which showed that almost 243 messenger RNAs displayed dramatic upregulation in these mutant yeast strains (127). This finding indicated that these normal messages are degraded by the nuclear exosome/CTEXT, which in turn determines their cellular repertoire and this phenomenon reflects a novel paradigm of gene expression in post-transcriptional level. These normal pool messages exhibiting susceptibility to the nuclear exosome/CTEXT, were subsequently dubbed as "Special" mRNAs (127). Emerging evidence in last ten years clearly established that the selective nuclear degradation of the some of these normal mRNAs dependent on the nuclear exosome/CTEXT is directed to control diverse physiological process especially under various stress conditions. Each of these processes controlled by the nuclear mRNA surveillance machinery are briefly described below.

### 5.1. The RNA processing exosome and CTEXT controls the activation and attenuation of Unfolded Protein Response (UPR) in baker's Yeast

Massive accumulation of unfolded proteins within the endoplasmic lumen (ER) that undergo in response to various stressors such as exposure of the yeast cells to drug like tunicamycin, reducing agents such as DTT and high temperature leads to a major threat to the survival of the cells. Yeast cells respond to this stressors (Called ER stressors) by activating an intracellular signalling pathway called Unfolded Protein Response (UPR) Pathway (160–162). This UPR response is accompanied by the massive and dramatic activation of a group of genes encoding ER-chaperones and heat-shock proteins, which are promptly brought into the ER lumen followed by the quick refolding of the unfolded proteins thereby mitigating the stress and restoring ER homeostasis (160–162). Hac1p, a b*ZIP* class of transcription factor, plays a seminal role in the activation of UPR response by trans-activating the genes encoding ER chaperone and heat-shock proteins. Remarkably, the transcriptomic data published by Kuai et al. (2205) revealed that *HAC1* mRNA is one special mRNAs which may potentially undergo degradation by the CTEXT component, Cbc1p and the nuclear exosome component, Rrp6p (127). This observation prompted a naïve quest if the UPR is regulated by the activity of the nuclear exosome/CTEXT. Studies by Sarkar et al. (2018) and Paira et al. (2023) uncovered that indeed the pre-*HAC1* mRNA (but not the mature *HAC1*

mRNA) undergoes degradation actively by the NNS complex, CTEXT and exosome components in the absence of ER stress and mutation in any of these components led to the dramatic stabilization of this pre-mRNA (101, 128). Additional research established an attractive model of regulation of expression of pre-*HAC1* mRNA that suggests an active functional involvement of the CTEXT/Exosome in the activation of UPR in baker's yeast. In the absence of ER stress, *HAC1* pre-mRNA harboring an intron and a secondary stem-loop structure (called bipartite element or BE) at the 3′-UTR of the mRNA undergoes rapid degradation from 3′→5′ direction, which produces a nested population of pre-*HAC1* mRNA, most of which does not carry this BE (101, 128). Notably, the BE was reported to play a pivotal role in the transport of these nested messages from the site of transcription in the nucleus to the site of non-canonical splicing (163) by the Ire1p and Rlg1p present on the ER surface (164–167). Consequently, this nested population of *HAC1* pre-mRNA lacking the BE fails to be transported from nucleus to ER surface at a site called Ire1p foci and does not undergo splicing. However, a small residual amount of pre-*HAC1* mRNA is exported to the cytoplasm and undergo ribosome loading. But the translation of the pre-*HAC1* mRNA stops immediately owing to the presence of a RNA secondary structure formed between the 5′-UTR of the RNA and the intron resulting in very little Hac1p production (164). In the presence of the ER stress, the nuclear degradation of pre-*HAC1* mRNA is sharply diminished to produce a population of pre-*HAC1* mRNA, most of which harbor BE and are efficiently transported to ER surface and undergoes extensive splicing and translation to produce copious amount of Hac1p protein, which are quickly imported to the nucleus to engage in the transcriptional activation of the ER-Chaperone and heat-shock protein gene (101, 128). A Rab-GTPase protein, Ypt1p was recently demonstrated to play a seminal role in the initial recognition of the *HAC1* pre-mRNA by binding to this message in the vast background of other mRNAs and promotes further recruitment of the NNS, CTEXT and the nuclear exosome in a sequential manner in the absence of ER stress (128). This study also established that Ypt1p is also acting as a sensor of ER stress and in presence of the ER stressors, it rapidly relocates from the nucleus to cytoplasm leading to the diminished degradation and subsequent downstream events as described above (128). This finding thus suggests that activation of UPR in baker's yeast is under the control of the nuclear mRNA surveillance mechanism that is accomplished by the preferential and reversible degradation of pre-*HAC1* mRNA.

**5.2. The RNA processing exosome and CTEXT regulates the ability of the yeast cells to respond and survive under glucose and nitrogen limiting conditions.**

The transcriptomic dataset by Kuai et al. (2005) also unveiled that *SKS1* mRNA encoding a serine-threonine kinase essential for glucose uptake under glucose and nitrogen limiting environment undergo a massive stabilization/upregulation in the yeast strains lacking functional exosome and CTEXT complex (127). Further investigation revealed that *SKS1* indeed undergo a rapid decay in the nucleus by the CTEXT and the nuclear exosome partly because, this mRNA undergoes a slow and sluggish export like the aberrant mRNAs. Via imposing an artificial export block at the restrictive temperature of 37°C in a temperature sensitive mRNA export-defective yeast strain, a previous study revealed that a "Kinetic Competition" exists in the nucleus between the nuclear export of mRNA and nuclear mRNA degradation (168) such that messenger RNAs that are exported rapidly from the nucleus will escape from the nuclear degradation by the CTEXT and the exosome. This class of mRNAs are exemplified by the bulk-normal functional mRNAs. In contrast, those mRNAs displaying slow and inefficient export as exemplified by the aberrant mRNAs are rapidly degraded by the nuclear mRNA surveillance mechanism. Towards finding the explanation of susceptibility of *SKS1* mRNA to the nuclear exosome/CTEXT, an investigation aimed to characterize its attribute revealed that the *SKS1* is export incompetent and spends a prolonged time in the nucleus and is thereby actively targeted and degraded by the nuclear degradation machinery (127, 129). Remarkably, studies to explain the mechanism of nuclear retention of *SKS1* mRNA uncovered that it is accomplished by the concerted interaction of Dbp2p, an ATP-dependent RNA helicase (a major component of CTEXT) with a *cis*-acting export-retarding nuclear zip-code element, called *NZ* element present in the *SKS1* transcript body (169, 170). Elimination of either *NZ* element from the *SKS1* transcript body or the deletion of Dbp2p leads to the rapid export of *SKS1* messages from the nucleus to the cytoplasm resulting in the stabilization and enhancement of the steady-state level of *SKS1* mRNA (169). A recent study finally showed that under nutrient rich condition, when Sks1p-serine-threonine kinase activity is not required for the cell, the nuclear pool of Dbp2p binds tightly to the *SKS1* mRNA, which prevents its association with the export factors

Mex67 and Yra1p (129). Inability of the export factors to associate with *SKS1* leads to its strong nuclear retention that in turn promotes its intra-nuclear degradation by the nuclear exosome/CTEXT leading to very low abundance of the *SKS1* (129).

Upon starvation of the cells from glucose/nitrogen in the growth medium leads to the rapid relocalization of the Dbp2p to the cytoplasm causing prompt binding of the export factors Mex67p/Yra1p to the *SKS1* that in turn further stimulate rapid export of the *SKS1* mRNA from the nucleus to the cytoplasm (129). Once in the cytoplasm, *SKS1* is actively translated to produce a huge burst of Sks1p protein pool in the cytoplasm, which assists the cell to dramatically increase the glucose/nitrogen uptake from the medium under nutrient limiting state (129). This phenomenon thus represents another paradigm of regulation of a key physiological process by the nuclear mRNA surveillance machinery that is achieved by the reversible nuclear retention and preferential degradation of *SKS1* mRNA in baker's yeast.

**5.3. The RNA processing exosome and CTEXT regulates the telomere length during ethanol stress and survival of the yeast cell during arsenic stress.**

Telomeres are nucleoprotein structures located at the ends of every chromosome, which play a critical role in protecting the ends to prevent loss of genetic information owing to the inability of the DNA polymerase to synthesize the lagging strand at the very end of the chromosome. Second, telomeres also possesses specific features that prevents the fusion of two chromosome ends (171). By carrying out these two duties, the eukaryotic telomeres play a pivotal role in maintaining the genome integrity in all organisms. Consistent with their importance, defects in telomeric functions are associated with many kinds of diseases including several types of cancers (172). A rigorous analysis of the transcriptomic dataset of Kuai et al. (2005) also uncovered that a group of transcripts associated with telomere functions were upregulated in yeast mutant strains carrying mutations in the CTEXT component, Cbc1p and exosome component, Rrp6p, which indicates that these transcripts may undergo degradation by the nuclear exosome. Subsequent examination of steady-state levels of some of these messages in WT and CTEXT and exosome mutant yeast strains indicated that a few transcripts, *EST2*, *TEL1* and *MTC7*, which play a role in elongating the telomere length have increased dramatically in the mutant yeast strains indicating that the nuclear exosome and CTEXT target and degrade these messages (Banerjea and Das, unpublished). This finding raised an important question if telomere length in baker's yeast is controlled by the nuclear mRNA surveillance. Further studies showed that, telomere length becomes increased in the yeast mutant strain lacking either functional CTEXT or exosome (Banerjea and Das, unpublished). Finally, imposition of 6% ethanol stress to the WT yeast cells which was previously known to increase telomere length (173) is also accompanied by the upregulation of the *EST2*, *TEL1* and *MTC7* transcripts (which elongate the telomere length) and downregulation of the CTEXT and exosome components (Banerjea and Das, unpublished). These preliminary findings argue in favor of the idea that the nuclear mRNA surveillance indeed govern the telomere length maintenance during ethanol stress. However, further research is necessary to completely uncover the mechanistic insights into this novel phenomenon.

More recently, the preliminary data from Das laboratory also hint at the possibility that the nuclear mRNA surveillance also plays a vital role in governing the rapid response of the yeast cells during stress impinged by the presence of sodium arsenate in the medium. A scrutiny into the transcriptomic datasets by Kuai et al. (2005) revealed that the *ACR2* mRNA encoding an arsenic reductase – a key protein implicated in the detoxification of arsenic (174) may undergo degradation in CTEXT and the nuclear exosome dependent manner. Initial evaluation revealed that indeed the levels of *ACR2* is dramatically enhanced in the yeast mutant strains carrying mutant alleles of the CTEXT and the nuclear exosome (Nandi, Kundu and Das, unpublished).

It also appears that the enhancement of steady-state levels of *ACR2* that typically occurs in the elevated levels of arsenic is partially contributed by its diminished degradation that is accomplished by reduced decay of the *ACR2* message by the nuclear exosome and CTEXT. Further research is necessary to gain an insight into the mechanism of this interesting phenomenon.

In summary, the findings appended above are indicative of the fact that the apart from the selective elimination of the aberrant messages, the second function of the nuclear mRNA surveillance machinery is to selectively degrade specific 'special' mRNAs and thereby control various physiological/cellular processes associated chiefly with various stress responses (see the concluding **Section 7** below).

## 6. Connections between mRNA surveillance machinery and human diseases

A large body of information emerged over the last two decades of active research established a strong link between mRNA surveillance machinery and human diseases. A comprehensive account of the putative roles played by various components of the nuclear mRNA surveillance machinery including the nuclear exosome and its various co-factors in diverse human diseases/disorders are appended below.

### 6.1. Cancer

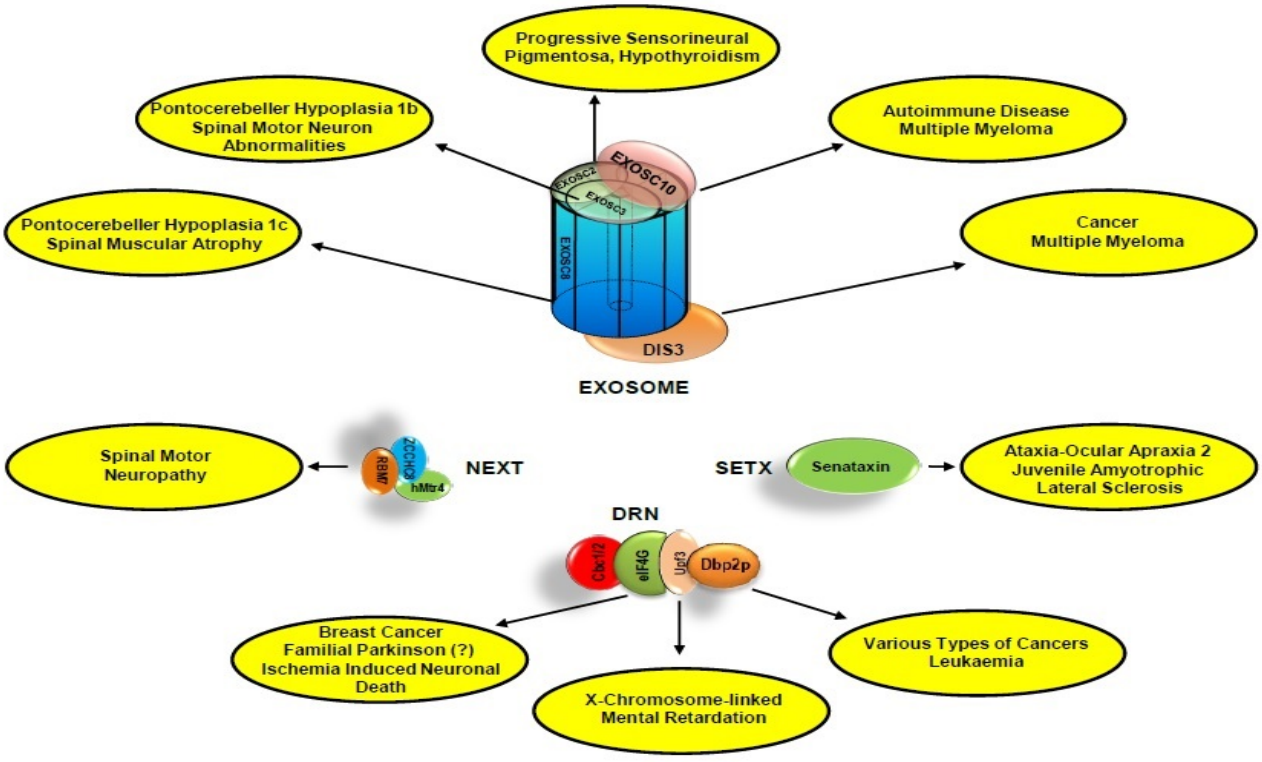
#### 6.1.1. h*DIS3*-the major catalytic subunit of the exosome is linked to cancer

Numerous studies implicated the human h*DIS3* gene (involved in the cellular and proliferation process) in multiple myeloma (MM), in which h*DIS3* was found to be mutated (Fig. 3) (Table 3) (92, 175–178). Remarkably, these mutations are clustered around the exonuclease domain of *DIS3* in approximately 10%–15% of all the MM cases, affecting its 3′→5′ exonuclease activity (175). In model organisms, it was demonstrated that DIS3 gene depletion led to the activation of RAS oncogene, which presumably is a secondary consequence of the accumulation of LET28B because of its diminished decay. Enhanced amount LET28B protein inhibits the maturation of let-7 family of micro-RNAs (179), which in turn silences the *MYC*, *RAS* and other mRNAs. In conclusion, *RAS* is activated upon DIS3 inactivation leading to MM and pancreatic cancer (180, 181).

**Table 3:** Nuclear Exosome/Co-factor variants connected to human diseases

| Subunit | Associated disease | Amino acid Substitution | Type of mutation | Reference |
|---|---|---|---|---|
| ***EXOSC2*/hRrp4p** | Novel syndrome characterized by progressive sensorineural pigmentosa and hearing loss, hypothyroidism, premature aging, mild intellectual disability | p.Gly30Val, p.Gly198Asp | Missense variant c.89G>T in exon 1 & c.593G>A in exon 7 altering the N-terminal and KH domain respectively | (212) |
| ***EXOSC3*/hRrp40p** | Pontocerebellar Hypoplasia Type 1b (PCH1b) and Spinal motor neuron abnormalities | p.Gly31Ala, p.Asp132Ala, p.Trp238Arg, p.Ala139Pro, 99fsX11 | Missense mutations c.395A>C,c.92G>C, 712T>C&415G>C; frameshift c.294_303del & splice site mutation c.475-12A>G altering NT,KH & S1domains | (209) |
| ***EXOSC8*/hRrp43p** | Pontocerebellar Hypoplasia Type 1C (PCH1c), hypo myelination, spinal muscular atrophy (SMA) and cerebellar hypoplasia | p.Ala2Val, p.Ser272Thr | Missense mutations c.815G>C & c.5C>T alter opening of the RNA channel & interfere with kozak sequence and/or cause mRNA instability | (210) |
| ***EXOSC11*/hRrp44p /h*DIS3*** | Multiple myeloma (MM) | p.Asp488Asn, p.Asp784His, p.Glu665Lys, p.Arg780Lys | Translocation and deletion mutations alter the PIN & RNB domain | (176–178) |
| ***EXOSC10*/PMScl-100/h*RRP6* & *EXOSC9*/PMScl-75/hRRP45** | Raynaud's phenomenon, arthritis, pulmonary disease, and calcinosis | Not known | Anti-PM/Scl autoantibody is targeted against (PM/Scl-100) and (PM/Scl-75) | (283) |
| ***RBM7*** | Spinal Motor Neuropathy | p.Pro79Arg | Missense mutations, mutation c.236C > G in RRM domain affects RNA binding. | (211, 214) |
| ***TIF4631*/ eIF4GI** | Autosomal dominant | p.Arg1205His, p.Ala502Val, p.Gly686Cys, p.Ser1164Arg, p.Arg1197Trp | Missense mutation c.3614G>A, c.1505C>T c.2056G>T, c.3490A>C c.3589C>T disrupt | (236) |
| | Parkinsonism | | eIF4E binding | (202) |
| | Breast Cancer | | Overexpression of eIF4GI | (203) |
| | Ischemia induced neuronal death | | depleting eIF4GI | (241, |

| | | | | |
|---|---|---|---|---|
| | Regulates life span | | reduction of eIF4GI | 242) (196, 251–255, 284, 285) |
| ***UPF3B/UPF3*** | X-Chromosome linked syndromic and non-syndromic mental retardation | Tyr160Asp | Frameshift mutations 674_677delGAAA, 867_868delAG & Nonsense mutations 1288C4>T cause premature protein truncation Missense mutation 478T> G | (230) |
| ***DDX5*/p68** | Breast cancer, colon cancer, prostrate cancer, lung cancer, gastric cancer, liver cancer, squamous cell carcinoma, neuroblastoma and thyroid cancer and leukaemia | | Overexpression of DDX5 regulation of various tumorigenic factors, including c-Myc, VEGF, c-jun, AKT, fra-1, MMP2, and MMP9 | (186–192, 194, 286) |
| | Obesity, Down syndrome, myotonic dystrophies type I and II, neurological disorders, RNA virus infections Polycystic kidney disease,Amyotrophic lateral sclerosis | | Abnormal expression of DDX5 | (259–265) |
| ***SETX*** | Ataxia-Ocular Apraxia 2 (AOA2) | Stop codon introductions<br><br>Polymorphisms | Homozygous mutations causing protein truncation 2602C→T, 915G→T 5070insT, 2622–2625delAGTT etc. 3147C→T, 3455G→T 3576T→G, 3754G→A 4156G→A | (219) |




**Source:** Self designed by corresponding author (Fig 3-Nandi et al . (2025))

**Fig. 3.** Schematic diagram showing the links between the various nuclear exosome and its cofactors in different human diseases.

Connections are presented with an arrow to the relevant nuclear mRNA surveillance components. Note of integration indicates the uncertainty associated with the link of eIF4G with PD (see text for details).

#### 6.1.2. DEAD-box RNA helicase DDX5/P68 is implicated in various kinds of Cancers

Yeast Dbp2, human DDX5/P68 and fly Rm62 belong to a subfamily of DEAD-box proteins and are the largest class of enzymes active in eukaryotic RNA metabolism. It is therefore not surprizing that mutation and dysregulation of such important enzymes will be associated to a multitude of diseases, including cancer (Fig. 3) (182–185). It has been reported that DDX5 undergo dramatic overexpression in breast cancer (186), colon cancer (187), prostrate cancer (188), lung cancer (189) gastric cancer (190), liver cancer (191) squamous cell carcinoma (192), neuroblastoma, thyroid cancer (193) and leukaemia (194) (Fig. 3) (Table 3). Consequently, it is quite evident now that DDX5/p68 is involved in the regulation of various tumorigenic factors, including c-Myc, VEGF, c-jun, AKT, fra-1, MMP2, and MMP9 (187, 195), implying its critical functional role in tumour development. It is currently believed that the modulation of these tumorigenic factors by DDX5/p68 through direct physical interaction may lead to the cancer progression and drug resistance associated with these cancers. Consequently, current evidence project the DDX5 an attractive and potential target for therapeutic interventions for them.

#### 6.1.3. The crucial component of the nuclear exosome cofactor CTEXT, Tif4631p/eIF4G1 is involved in various Cancers

Overexpression of Tif4631p (also known as eIF4GI) was reported to associate with malignant transformation of cells (Fig. 3) (Table 3) (196). In mouse fibroblast cell lines, overexpressed Tif4631p/eIF4GI results in continuous cell-growth and injection into mice promotes tumour formation (197). Overexpression of Tif4631p/eIF4GI is associated with increased incidence of hypo-pharyngeal and nasopharyngeal carcinoma (198, 199), squamous cell carcinomas, large and small cell carcinomas, adenocarcinomas (200) (Fig. 3) (Table 3). The observation of a dramatic loss of tumour size in the xenografted mice when Tif4631p/eIF4GI was inactivated actually led to the concept of using Tif4631p/eIF4GI level as a biomarker for these cancers (201). A drastic increase in Tif4631p/eIF4GI expression was reported from biopsies of breast cancer patients (202). Inflammatory breast cancer tumour formation is promoted when IRES-mediated translation of mRNAs is increased due to overexpression of Tif4631p/eIF4GI (203).

### 6.2. Neurological disorders and neurodegenerative diseases

#### 6.2.1. Mutations in the core exosomal components EXOSC2/3/8/9 are associated to diverse neurological disorders and neurodegenerative diseases

Mutations in various components of the core exosome are the cause of some rare neurological disorders like pontocerebellar hypoplasia (PCH), spinal motor atrophy, a novel neurological syndrome, and a unique form of cerebellar hypoplasia (Fig. 3). Mutations in the gene encoding one of the three exosomal cap subunits, EXOSC3 (a homolog of yeast Rrp40p) is the cause of PCH subtypes 1b (204) (Table 3). The altered amino residues G31 (located in N-terminus) D132 (located in S1 domain) and W238 (located in KH domain) all alter the point of contact of EXOSC3 with EXOSC5 (yeast Rrp46) and EXOSC9 (yeast Rrp45) (72) (Table 3) suggesting that these residues play a critical role in interaction. Impaired interactions between EXOSC3 and EXOSC5/EXOSC9 leads to the generation of a functionally compromised exosome under disease state. Recent studies were conducted in the model organism *S. cerevisiae* as well as in mouse neuronal cell line carrying these mutations in the equivalent locations (205, 206). No dramatic defect in cell growth and abundance/stability of the corresponding variant exosome containing rrp40G8A, rrp40G148C, rrp40S87A and rrp40W195R (corresponding to the human EXOSC3-G31A, EXOSC3-G191C, EXOSC3-D132A variants, respectively) (Table 3) was observed suggesting that these substitutions have hardly any noticeable effect despite being present in the conserved residues (205, 206). On the contrary, significant reduction in the abundance and stability was observed in the rrp40W195R variant in yeast and EXOSC3-W237R variant in mouse N2a neuronal cell line (both equivalent to human EXOSC3-W238R) (Table 3). This observation suggested that this variant rrp40W195R subunit associated much less efficiently with the other exosome subunits to form a functional exosome complex (205), thereby dramatically impairing the ribosomal RNA processing function of the exosome, while having a modest impact on snRNA processing, degradation of cryptic unstable transcripts and selective subsets of mRNA (205, 206) indicating the crucial role played by this residue in the assembly and quality control of the exosome, further impacting the

function of this critical molecular machine in the neuronal cells (205).

The degree of suffering of the PCH patients differ depending on the various kinds of mutations they carry. Some of them live less than 2 years displaying severe phenotype. These patients are further subdivided into four groups. A homozygous G31A (located at the N-terminal domain of EXOSC3) is harboured by the first group, second group harbours compound heterozygous mutations (D132A/Y109N, and D132A/A139P, Y109 are located at the N-terminal and D132 and A139 in S1 domain both conferring null allele) (Table 3). Severe disease phenotypes are noted in the third and fourth groups carrying either a homozygous G135E mutation (located at the N terminus domain) or compound heterozygous G31A/W238R mutations (located at the N-terminal and KH domains, respectively) (Table 3). Those individuals carrying homozygous D132A substitutions in the S1 domain of the protein exhibit a little higher life expectancy (usually greater than 3 years). Whereas a homozygous G191C or a compound heterozygous V80F/D132A mutations located in the conserved N-terminus and S1 domain show a mild form of the disease. These data indicate that various disease phenotypes affecting different regions of the brain (207) are contributed by different amino acid substitutions in the distinct domains of this protein.

Most or half of the PCH1b patients who did not live past childhood (208), displayed certain features like major atrophy of the pons and the cerebellum, abnormalities in the Purkinje cell (209) degeneration of the spinal motor neurons (208), microcephaly, muscle growth/ developmental retardation (204). A similar symptoms were noticed when EXOSC3 knockdown in Zebrafish embryos led to the reduced body length, a shrunken or collapsed hindbrain with undifferentiated cerebellar Purkinje neurons, curved spine with poor motility and death around 3 days post fertilization (209) suggesting EXOSC3 is essential in survival and development of cerebellar and spinal motor neurons.

In order to further understand the functionality of the variant exosome in the tissue, knowledge regarding the target RNAs of the exosome needs to be identified in the specific neuronal tissue from the normal and affected individuals. This information will enlighten about the processing and degradation abilities of the variant exosome carrying different mutations and how that contributes to the onset and progression of this disorder.

Spinal muscular atrophy (SMA) and PCH type 1c (PCH1c), which affect children is caused by a mutation in EXOSC8 gene, the human homolog of yeast RRP43 (210). Two different kinds of homozygous mutations in EXOSC8 gene, a S272T mutation conferring a severe phenotype (life span less than 2 years) and an A2V substitution conferring a less severe phenotype (life span more than 2 years 6 months) were identified from exome sequencing of individuals suffering from PCH1c (Table 3). The residue S272 is located towards the C-terminus of the protein within the PH domain, which plays a vital role in the interaction between EXOSC8 (yeast Rrp43p) and EXOSC9 (yeast Rrp45p) and forms the bottom opening of the central channel through which single stranded RNA is fed (72). The interaction between EXOSC8 with EXOSC1 (yeast Csl4p) is contributed by the A2 residue. These two missense mutations act as hypomorphic allele (210) that in turn leads to a reduction in the EXOSC8 protein resulting in an overall depletion of the entire exosome complex as detected from patient myoblasts and fibroblasts (Table 3). Increased levels of developmental *HOX* mRNAs and the *HOTAIR* long ncRNA (critical epigenetic regulator of gene expression) and some myelin-related, AU-rich element (ARE)-containing mRNAs (e.g., *MBP*, *MOBP*) were exhibited from EXOSC8-A2V-expressing fibroblasts and EXOSC8-S272T-expressing myoblasts of affected individuals respectively(211). Decreased level of the variant EXOSC8 in PCH1c affected individuals leads to the accumulation of *HOX* and myelin-related mRNAs, since ARE mRNAs are the known targets of the RNA exosome (210), which is in support with the above view. This causes disruption of the neuro-development and myelin synthesis. ARE containing mRNAs encoding myelin proteins on the other hand is increased due to the depletion of EXOSC8 in human oligodendroglia disrupting myelin formation. Patients suffering from PCH1c features cerebellar and corpus callosum hypoplasia, psychomotor deficit, SMA at birth and hypomyelination, muscle weakness, impaired hearing/vision and respiratory trouble and developmental defects in spinal motor neuron as well as in Purkinje cells. (210).

A novel syndrome arose from bi-allelic mutations in the EXOSC2 gene, the human ortholog of yeast RRP4. Studies from sequence analysis from two individuals from two families revealed a homozygous (G30V) mutation in the conserved N terminal domain and a heterozygous mutation (G30V and G198D substitutions) in N-terminal and conserved KH domains were observed from another individual (207, 212) (Table 3). G30 is

highly conserved and is a critical residue required for the interaction between EXOSC2 and EXOSC4, supporting the idea that G30V mutation may affect the interaction of these two exosomal subunits as determined from structural modelling studies. The other mutation (G198D) is predicted to destabilize the hairpin structure that forms at the end of the β-strand in the KH domain and interferes with the structural stability of the EXOSC2 (Table 3). Some of the features of the patients suffering from this syndrome exhibit childhood myopia with an early onset of retinitis pigmentosa, progressive sensorineural hearing loss, hypothyroidism and short stature, premature aging, mild intellectual disability and distinctive gestalt (212).

EXOSC9- the human ortholog of yeast Rrp45p is implicated in a novel form of cerebellar hypoplasia/atrophy with early motor neuronopathy (213). A homozygous recessive mutation in EXOSC9 (L14P) were detected in two suffering patients. Among them the first patient (a 23-month-old female) displayed normal tone at birth, but slowly developed developmental arrest, hypotonia, esotropia, severe progressive weakness, feeding/respiratory difficulties and distal joint contractures. They also exhibited cerebellar hypoplasia/atrophy with lack of reflexes and widespread neuronopathy. While the other one showed some inborn defects including fractures, arthrogryposis, severe hypotonia and respiratory insufficiency, cerebellar hypoplasia, neurogenic changes and delayed myelination. The presence of these mutations L14P and R161X lead to a general destabilization of the entire exosome complex with a reduction in the abundance-associated core exosome subunits, EXOSC3 and EXOSC8 as observed from the cultured patient fibroblast of the first patient. Further studies would enlighten the downstream connections of the process conferring the disease. But in a nutshell, a defect in the exosome subunit EXOSC9 destabilizes the entire exosome function resulting in a severe clinical presentation related to PCH1 (Fig. 3).

### 6.2.2. Mutation in Exosomal component RBM7 is linked to spinal motor neuropathy

RBM7 gene encodes a subunit of the NEXT complex. The RRM domain present in RBM7 is implicated in the binding of the U-rich pyrimidine sequence (214) and splicing (215). The proline-rich sequence present in the RRM interacts with the NEXT component ZCCHC8 and spliceosome component SAP145 (216). A homozygous missense mutation P79R in this gene leads to spinal motor neuropathy, which is similar to SMA (211) (Fig. 3) (Table 3). This mutation is located close to the junction of two β-stranded regions (β4 and β4add) within the highly conserved RRM domain that presumably makes contact with ZCCHC8 (214) and is predicted to affect the interaction of RBM7 with ZCCHC8 and subsequent binding of the target RNA. The patient carrying this mutation developed hypotonia and failure to thrive at the age of 1 month, followed by a delayed motor development, muscle weakness, and respiratory problems with normal cognition, and died of respiratory failure at 28 months of age. It has been demonstrated that the level of the RBM7 is reduced (37% of the levels in control cells) in the fibroblasts of patients suffering from PCH1c, who carry EXOSC8-A2V variant (210) indicating that the lower stability of the defective EXOSC8-containing exosome lead to the reduced stability of the exosome cofactor RBM7/NEXT. A higher accumulation of HOX mRNAs and the HOTAIR ncRNA (211), was exhibited in fibroblasts that expressed mutant RBM7-P79R mimicking the EXOSC8-A2V-expressing fibroblasts (Table 3), indicating that both mutations impair the degradation of the same target RNAs by the NEXT/RNA-exosome complex. Another finding that led to the alteration of the hindbrain structure (specifically affected the vagal brachimotor neurons) and the Purkinje cell layer/cerebellum (211) occurred when RBM7 in Zebrafish embryos was knocked down suggesting its role in the brain development. Detailed studies are required to understand all the molecular events of this disease.

### 6.2.3. Mutations in the exosomal component SETX are linked to the clinically distinct neurological diseases

Two clinically distinct neurological diseases, ataxia-ocular apraxia 2 (AOA2) and juvenile amyotrophic lateral sclerosis results from the mutations in human SETX gene encoding senataxin, SETX which is the human ortholog of yeast Sen1p (a component of the primary exosome cofactor NNS) (Fig 3) (Table 3) (217–222). SETX is known to be involved to resolve the R-loops that are formed as the bi-products of transcription elongation in the exosome in eukaryotes. Basically they are a DNA-RNA hybrid region, that leads to polymerase stalling, the formation of double-strand breaks and genomic instabilities. Notably, R-loops are involved in a number of cancers and other diseases (223, 224). Interestingly, R-loop formation is prevented by coating the nascent RNAs with THO/TREX proteins. But if formed, then exosome is recruited to selectively degrade the RNA moieties in the hybrid (223–226). In some of the cases either there are alterations in the

ATP-helicase domain of the protein or affect the N-terminal protein-binding region. It is predicted that the ability of SUMO-dependent binding of SETX to its partner EXOSC9/hRRP45 gets impaired which is in turn necessary for the exosome recruitment to R-loops in humans (225) causing AOA2 and amyotrophic lateral sclerosis (225, 227–229) (Fig. 3) (Table 3).

#### 6.2.4. Mutations in *UPF3B* are connected to X-chromosome-linked mental retardation

X-chromosome-linked syndromic and non-syndromic mental retardation has been found to be associated with the UPF3B gene which is the human orthologs of yeast UPF3 gene (Fig. 3) (Table 3) (230, 231). Three families with this phenotype were the subject of study. For all of them resequencing studies revealed that alteration in *UPF3B* gene caused protein truncations and two families exhibited the Lujan–Fryns phenotype (232, 233) and one exhibited the FG phenotype (234). A premature termination codon (PTC) was introduced by the mutation in *UPF3B* gene guiding this PTC containing *UPF3B* mRNA for nonsense-mediated decay. This resulted in a complete loss of the protein in two families. However, it was difficult to comprehend how mental retardation could have any connection with the UPF3B mRNA decay. Although this phenomenon is not clear at this point, it is conceivable that partial or near-complete loss of NMD can occur when *UPF3B* is absent (particularly in those tissue types where *UPF3A* expression is very low), which in turn causes the increased accumulation of some normal transcripts targeted by this pathway (230)(231). In yeast *S. cerevisiae*, *UPF3* is an essential component of CTEXT, which is a co-factor of the nuclear exosome, involved in degrading both abnormal and some special messages (155, 235). No such function has been assigned to UPF3B in the nuclear mRNA degradation in humans. Further studies are needed to see if it participates in to the nuclear decay in humans and that its participation could explain the link of X-linked mental retardation.

#### 6.2.5. Mutations in Tif4631p/eIF4G1 are implicated in Parkinson's disease

It is predicted that Parkinson's disease (PD) are caused by mutations in the human TIF4631 (eIF4G1) that affects the interactions between eIF4G1 and eIF3/eIF4A (Fig. 3) (Table 3) (236). R1205H variant of eIF4G1 is a confirmed risk factor for PD (237). However, this mutation was not detected among 425 PD patients in the Chinese Han population (238). Also in another study of European population, this mutation was not assigned as a genetic determinant of PD (239). Interestingly, a French family suffering from familial Parkinson's disease has been attributed to a mutation in the eIF4GI gene (236). But, insufficient knowledge could not establish any direct or convincing link between eIF4G1 mutations and pathogenesis with PD (239). A very important observation on the studies of nuclear mRNA decay focussed on the establishment of this process with neurodegenerative diseases. The nuclear exosome and its novel cofactor CTEXT tune the output of unfolded protein response in *S. cerevisiae* (101). The nuclear exosome/CTEXT selectively degrades the *HAC1* pre-mRNA dictating the retention/loss of bipartite element, a *cis*-element in the 3′-UTR of the pre-mRNA, which in turn the targets and recruits this pre-mRNA to ER surface rich in splicing modulator Ire1p/Rlg1p (163) where it undergoes Ire1p-dependent splicing and subsequent translation to produce mature Hac1p, which activates UPR. The absence of stress causes rapid decay of *HAC1* pre-mRNA leading to the low level of targeting to Ire1p foci, and little or no production of Hac1p. ER stress induces diminished decay, increased targeting to Ire1 sites and massive production of protein in the subsequent level. In this connection, elevation of ER stress and UPR response was noted in a study in MM cell line when human eIF4G1 was knocked down (240). It was previously known that UPR has a connection to aging-related neurodegenerative diseases like AD and PD, apoptosis and autophagy. Now UPR being controlled at the nuclear mRNA decay level in yeast might help in understanding the underlying mechanisms involved in neurodegenerative disorders (101).

Ischemia induced neuronal death has been correlated with degrading eIF4G *in vivo* (241)(242) where protein synthesis in neurons decreases after ischemic brain injury. But overexpression of eIF4G-I in cultured neurons results in increased protein synthesis, providing protection from this neuronal death (242)

### 6.3. Autoimmune diseases

#### 6.3.1. Exosome-linked autoimmune diseases

Myositis, scleroderma, and PM/Scl overlap Syndrome represent some of the severe autoimmune diseases. In these diseases, the patient's sera was reported to detect anti-PM/Scl autoantibody (243–245) that targets the nuclear exosome components EXOSC10/PM/Scl-100 and EXOSC9/PM/Scl-75 (human orthologs of yeast Rrp6p and Rrp45p) (Fig. 3) (Table 3) (80, 246, 247). Subsequently, research suggested spreading of the intermolecular epitope in the subsequent stage may be responsible for the autoantibody

response directed against the other associated antigens/exosomal components. However, how the initial autoantibody response is initiated is not clear but it could be predicted to involve defective apoptosis (Reviewed in 249). Notably the patients who fall in this group are featured by an elevated incidence of Raynaud's phenomenon, arthritis, pulmonary disease and calcinosis (248, 249).

**6.3.2. The crucial component of CTEXT Tif4631p/eIF4G1 regulates lifespan**

Studies of the lifespan of yeast and nematodes demonstrate a link in the expression of eIF4GI with the stage of development of these organisms (196). For example, in yeast and nematodes, developmental arrest and lethality *in vivo* happens when eIF4GI expression is absent (250, 251) in their early developmental stage (Fig. 3) (Table 3). However, during adulthood, when the organism is fully developed, lifespan of these organisms can increase when expression of eIF4GI is reduced (252–256). Studies reported that a deletion in gene, *TIF4631* encoding eIF4GI results in the production of a long lived mutant yeast. In adult nematodes, reducing overall eIF4G expression definitely increases lifespan. It has been interpreted as a modest shift in translation efficiency from transcripts associated with growth to those associated with homeostasis and increased longevity apart from globally reducing translation (257).

**6.4. DDX5/p68 the RNA Helicase is involved in non-cancerous diseases**

Being ubiquitously expressed in human tissues, this helicase plays a multifunctional role in a number of the cellular processes (182–185). It has been demonstrated experimentally that DDX5/p68 plays a role in variety of non-cancerous diseases. Some of the examples of diseases concerned with DDX5/p68, includes obesity (258, 259), Down syndrome (260), myotonic dystrophies (261) and neurological disorders (262). Dbp2 is also implicated in RNA virus infections (263). Polycystic kidney disease (264), Myotonic dystrophy type 1 (262) and myotonic dystrophy type 2 (265) are the non-cancerous diseases caused due to DDX5 dysfunction (Fig. 3) (Table 3).

**7. Conclusion and Future Directions**

After an extensive research by many laboratories for nearly three decades, a considerable advancement in the understanding on the fundamental nature of mRNA surveillance has now become clear. A substantial amount of knowledge concerning the structure of the nuclear exosome complexes from yeasts and humans and their co-factors TRAMP and NEXT (human counterpart of CTEXT) are now available and their mode of function have become much clearer in the past decade. As described above we now have more or less clear picture available about how the single stranded mRNA targets are bound to the Exo11 and is threaded through the central channel to reach to Rrp44/Dis3 or to the Rrp6p for their final degradation. Furthermore, our understanding on how the aberrant/faulty and 'special' mRNA targets are distinguished from the bulk functional mRNAs in yeasts via the selective loading of the NNS complex onto the exosomal target messages. However, many crucial aspects of modes of distinction between the aberrant vs. normal mRNA targets still remained enigma and our understandings of the exosomal function in humans are still far from complete.

In the context of the various disease phenotype/pathology, an in-depth knowledge of the structural organization and assembly of the altered/mutant exosome is key to comprehend how a given alteration in amino acid residue at a given position in DIS3/EXOSC2/3/8/9 proteins brings about the abnormal physiological consequences observed in these disorders. It is extremely baffling to conceptualize how the amino acid replacements in similar locations in the same N-terminal domain in EXOSC2 (G30) and EXOSC3 (G31) proteins may lead to such diverse phenotypes found in the novel syndrome and PCH1b, respectively. Similarly, how the different amino acid substitutions at various locations in EXOSC3 and EXOSC8 proteins yield PCH type 1b and 1c, respectively, with resembling and overlapping clinical symptoms is inexplicable under our current knowledge. Furthermore, it still remains a paradox about how amino acid substitutions in different exosomal subunits can cause such varied tissue-specific symptoms. It should be noted here that recent structural studies start to shed some hints on the probable mechanisms regarding how the variant exosomes may cause dysfunction. It is speculated that amino acid substitutions may primarily result in both the changes in the levels and the stabilities of the variant exosomal subunits, which may drastically affect the assembly of the variant exosome complex in a cell-specific or tissue-specific manner. Alternatively, it is also possible that either the altered polypeptides are impaired in the interaction with the tissue-specific substrate RNAs and thereby affect their decay kinetics or the interactions between the altered/mutant exosome with various co-factors may get abrogated leading to the accumulation of tissue-specific RNA targets. Additional research addressing these issues will

soon clarify the current and existing enigma concerning these issues.

A significant amount of future research efforts are predicted to be invested on the roles of the well-conserved amino acids concerning the exosomal functions, many of which were found to be altered in these diseases. In particular, how these mutations impact the structural and functional outcomes of the mutant/altered nuclear exosome, and its various co-factors would be addressed with a long-term goal of understanding of the mechanisms of these diseases. It would be interesting to uncover if any of these altered amino acids results in the dysfunction of the variant exosome in a tissue-specific manner (such as in brain or in cerebellum).

A challenging question demanding urgent attention is to address how each of the various yeast and human exosome co-factor complexes compete with one another to associate with the exosome either to promote the exosome localization in diverse cellular compartments or to facilitate exosomal recruitment to the specific RNA targets. Unfolding the comprehensive physiological repertoire of RNA targets of the nuclear exosome in both yeasts and humans will be crucial in this respect to identify the cellular pathways and gene expression programs regulated by this systems. In particular, understanding the nature of the RNA targets and the critical elements used in their recognition would be vital to have an insight into this issue. Furthermore, the extensive knowledge regarding the cell-type and tissue specificity of the RNA targets would be very crucial to unveil the mechanistic insight of the tissue-specific impact of the mutant and variant human exosome and its co-factors.

As stated above, the current evidence support the active involvement of the yeast nuclear exosome/CTEXT in various cellular processes associated with the activation of several stress responses such as Unfolded Protein Response, cell's response to nutrient starvation stress, arsenic stress, and telomere elongation in response to ethanol stress. Consequently, it is speculated that future research in the next few years will witness an insight into the functional role of the nuclear exosome and CTEXT complex in the regulation of additional pathways associated with diverse stress response in yeast. More importantly, extension of the knowledge gained from the baker's yeast concerning the role of mRNA surveillance to control stress response pathways in humans will be of particular relevance in the context of gaining the mechanistic insight into the involvement of the exosome in neurodegenerative diseases, apoptosis and cancer. A better understanding of the physiological role of the human exosome and its connections to the components of other cellular processes would pave the way to gain further insight into the mechanism of onset and progression of these diseases, which would catalyze the development of their novel therapeutic strategies.

**Acknowledgement**

The authors gratefully acknowledge the critical comments and useful suggestions on the manuscript from the members of Das laboratory for critically reading and commenting on the manuscript. We are extremely grateful to the anonymous reviewers for their constructive criticisms, suggestions and comments, which certainly enriched this review article.

**Funding**

Research in the laboratory of the authors is supported by the research grants from CSIR (Ref. No. 38/1427/16/EMR-II and 38/1280/11/EMR-II), ANRF (File No. SR/SO/BB/0066/2012 and CRG/2021/005449) and DBT (BT/PR27917/BRB/10/1673/2018, and BT/PR6078/ BRB/10/1114/2012 and BT/PR52607/BSA/33/151/2024) to B.D.

**Author Contributions**

**Bhaswar Nandi:** Data curation; investigation; writing and editing. **Satarupa Das:** Conceptualization, Data curation; investigation; methodology, writing-review and editing. **Biswadip Das:** Conceptualization; data curation; funding acquisition; investigation; methodology; supervision; writing-original draft; writing-review and editing.

**Conflict of Interest**

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

**References**

1. Das,S. and Das,B. (2013) MRNA quality control pathways in Saccharomyces cerevisiae. *J. Biosci.*, **38**.
2. Singh,P., Saha,U., Paira,S. and Das,B. (2018) Nuclear mRNA Surveillance Mechanisms: Function and Links to Human Disease. *J. Mol. Biol.*, 10.1016/j.jmb.2018.05.009.
3. Kilchert,C., Wittmann,S. and Vasiljeva,L. (2016) The regulation and functions of the nuclear RNA exosome complex. *Nat Rev Mol Cell Biol*, **17**, 227–239.
4. Schmid,M. and Jensen,T.H. (2018) Controlling

nuclear RNA levels. *Nat. Rev. Genet.*, **19**, 518–529.
5. Schmid,M. and Jensen,T.H. (2008) Quality control of mRNP in the nucleus. *Chromosoma*, **117**, 419–429.
6. Chlebowski,A., Lubas,M., Jensen,T.H. and Dziembowski,A. (2013) RNA decay machines: the exosome. *Biochim Biophys Acta*, **1829**, 552–560.
7. Fasken,M.B. and Corbett,A.H. (2016) Links between mRNA splicing, mRNA quality control, and intellectual disability. *RNA Dis*, **3**.
8. Maity,A., Chaudhuri,A. and Das,B. (2016) DRN and TRAMP degrade specific and overlapping aberrant mRNAs formed at various stages of mRNP biogenesis in *Saccharomyces cerevisiae*. *FEMS Yeast Res.*, **16**, fow088.
9. Bird,G., Fong,N., Gatlin,J.C., Farabaugh,S. and Bentley,D.L. (2005) Ribozyme cleavage reveals connections between mRNA release from the site of transcription and pre-mRNA processing. *Mol Cell*, **20**, 747–758.
10. Luna,R., Gaillard,H., Gonzalez-Aguilera,C. and Aguilera,A. (2008) Biogenesis of mRNPs: integrating different processes in the eukaryotic nucleus. *Chromosoma*, **117**, 319–331.
11. Perales,R. and Bentley,D. (2009) 'Cotranscriptionality': the transcription elongation complex as a nexus for nuclear transactions. *Mol Cell*, **36**, 178–191.
12. Bjork,P. and Wieslander,L. (2014) Mechanisms of mRNA export. *Semin Cell Dev Biol*, **32**, 47–54.
13. Bentley,D.L. (2015) The union of transcription and mRNA processing: 20 years of coupling. *Rna*, **21**, 569–570.
14. Wahle,E. (1991) A novel poly(A)-binding protein acts as a specificity factor in the second phase of messenger RNA polyadenylation. *Cell*, **66**, 759–68.
15. Le Hir,H., Gatfield,D., Izaurralde,E. and Moore,M.J. (2001) The exon-exon junction complex provides a binding platform for factors involved in mRNA export and nonsense-mediated mRNA decay. *EMBO J*, **20**, 4987–4997.
16. Dreyfuss,G., Kim,V.N. and Kataoka,N. (2002) Messenger-RNA-binding proteins and the messages they carry. *Nat. Rev. Mol. Cell Biol.*, **3**, 195–205.
17. Muller-McNicoll,M. and Neugebauer,K.M. (2013) How cells get the message: dynamic assembly and function of mRNA-protein complexes. *Nat Rev Genet*, **14**, 275–287.
18. Gonatopoulos-Pournatzis,T. and Cowling,V.H. (2014) Cap-binding complex (CBC). *Biochem. J.*, **457**, 231–42.
19. Singh,G., Pratt,G., Yeo,G.W. and Moore,M.J. (2015) The Clothes Make the mRNA: Past and Present Trends in mRNP Fashion. *Annu. Rev. Biochem.*, **84**, 325–354.
20. Vinciguerra,P. and Stutz,F. (2004) mRNA export: an assembly line from genes to nuclear pores. *Curr Opin Cell Biol*, **16**, 285–292.
21. Rodriguez,M.S., Dargemont,C. and Stutz,F. (2004) Nuclear export of RNA. *Biol Cell*, **96**, 639–655.
22. Köhler,A. and Hurt,E. (2007) Exporting RNA from the nucleus to the cytoplasm. *Nat. Rev. Mol. Cell Biol.*, **8**, 761–773.
23. Proudfoot,N.J., Furger,A. and Dye,M.J. (2002) Integrating mRNA processing with transcription. *Cell*, **108**, 501–512.
24. Stutz,F. and Izaurralde,E. (2003) The interplay of nuclear mRNP assembly, mRNA surveillance and export. *Trends Cell Biol*, **13**, 319–327.
25. Moore,M.J. and Proudfoot,N.J. (2009) Pre-mRNA processing reaches back to transcription and ahead to translation. *Cell*, **136**, 688–700.
26. Schnell,S.J., Ma,J. and Yang,W. (2014) Three-Dimensional Mapping of mRNA Export through the Nuclear Pore Complex. *Genes (Basel).*, **5**, 1032–49.
27. Chin,A. and Lécuyer,E. (2017) RNA localization: Making its way to the center stage. *Biochim. Biophys. Acta - Gen. Subj.*, **1861**, 2956–2970.
28. Chaudhuri,A., Das,S. and Das,B. (2020) Localization elements and zip codes in the intracellular transport and localization of messenger RNAs in *Saccharomyces cerevisiae*. *WIREs RNA*, **11**.
29. Gu,W., Deng,Y., Zenklusen,D. and Singer,R.H. (2004) A new yeast PUF family protein, Puf6p, represses ASH1 mRNA translation and is required for its localization. *Genes Dev.*, **18**, 1452–1465.
30. Irie,K., Tadauchi,T., Takizawa,P.A., Vale,R.D., Matsumoto,K. and Herskowitz,I. (2002) The Khd1 protein, which has three KH RNA-binding motifs, is required for proper localization of ASH1 mRNA in yeast. *EMBO J.*, **21**, 1158–67.
31. Bergalet,J. and Lécuyer,E. (2014) The functions and regulatory principles of mRNA intracellular trafficking. *Adv. Exp. Med. Biol.*, **825**, 57–96.
32. Lécuyer,E., Yoshida,H. and Krause,H.M. (2009) Global implications of mRNA localization pathways in cellular organization. *Curr. Opin. Cell Biol.*, **21**, 409–415.

33. Ishigaki,Y., Li,X., Serin,G. and Maquat,L.E. (2001) Evidence for a pioneer round of mRNA translation: mRNAs subject to nonsense-mediated decay in mammalian cells are bound by CBP80 and CBP20. *Cell*, **106**, 607–617.
34. Gao,Q., Das,B., Sherman,F. and Maquat,L.E. (2005) Cap-binding protein 1-mediated and eukaryotic translation initiation factor 4E-mediated pioneer rounds of translation in yeast. *Proc. Natl. Acad. Sci. U. S. A.*, **102**.
35. Maquat,L.E., Hwang,J., Sato,H. and Tang,Y. (2010) CBP80-promoted mRNP rearrangements during the pioneer round of translation, nonsense-mediated mRNA decay, and thereafter. *Cold Spring Harb Symp Quant Biol*, **75**, 127–134.
36. Parker,R. (2012) RNA degradation in Saccharomyces cerevisae. *Genetics*, **191**, 671–702.
37. Sheth,U. and Parker,R. (2006) Targeting of aberrant mRNAs to cytoplasmic processing bodies. *Cell*, **125**, 1095–1109.
38. Balagopal,V. and Parker,R. (2009) Polysomes, P bodies and stress granules: states and fates of eukaryotic mRNAs. *Curr Opin Cell Biol*, **21**, 403–408.
39. Beelman,C.A. and Parker,R. (1994) Differential effects of translational inhibition in cis and in trans on the decay of the unstable yeast MFA2 mRNA. *J Biol Chem*, **269**, 9687–9692.
40. Caponigro,G. and Parker,R. (1996) Mechanisms and Control of mRNA Turnover in Saccharomyces cerevisiae.
41. Caponigro,G. and Parker,R. (1996) mRNA turnover in yeast promoted by the MATalpha1 instability element. *Nucleic Acids Res*, **24**, 4304–4312.
42. Brengues,M., Teixeira,D. and Parker,R. (2005) Movement of eukaryotic mRNAs between polysomes and cytoplasmic processing bodies. *Science*, **310**, 486–9.
43. Bhattacharyya,S.N., Habermacher,R., Martine,U., Closs,E.I. and Filipowicz,W. (2006) Relief of microRNA-mediated translational repression in human cells subjected to stress. *Cell*, **125**, 1111–24.
44. Neugebauer,K.M. (2002) On the importance of being co-transcriptional. *J Cell Sci*, **115**, 3865–3871.
45. Buratowski,S. (2009) Progression through the RNA polymerase II CTD cycle. *Mol Cell*, **36**, 541–546.
46. Bentley,D.L. (2005) Rules of engagement: co-transcriptional recruitment of pre-mRNA processing factors. *Curr Opin Cell Biol*, **17**, 251–256.
47. Reed,R. and Cheng,H. (2005) TREX, SR proteins and export of mRNA. *Curr. Opin. Cell Biol.*, **17**, 269–273.
48. Reed,R. (2003) Coupling transcription, splicing and mRNA export. *Curr Opin Cell Biol*, **15**, 326–331.
49. Maniatis,T. and Reed,R. (2002) An extensive network of coupling among gene expression machines. *Nature*, **416**, 499–506.
50. Miller,J.E. and Reese,J.C. (2012) Ccr4-Not complex: the control freak of eukaryotic cells. *Crit Rev Biochem Mol Biol*, **47**, 315–333.
51. Aguilera,A. (2005) Cotranscriptional mRNP assembly: from the DNA to the nuclear pore. *Curr Opin Cell Biol*, **17**, 242–250.
52. Lykke-Andersen,S. and Jensen,T.H. (2015) Nonsense-mediated mRNA decay: an intricate machinery that shapes transcriptomes. *Nat Rev Mol Cell Biol*, **16**, 665–677.
53. Tuck,A.C. and Tollervey,D. (2011) RNA in pieces. *Trends Genet*, **27**, 422–432.
54. Schneider,C. and Tollervey,D. (2013) Threading the barrel of the RNA exosome. *Trends Biochem Sci*, **38**, 485–493.
55. Klauer,A.A. and van Hoof,A. (2012) Degradation of mRNAs that lack a stop codon: a decade of nonstop progress. *Wiley Interdiscip Rev RNA*, **3**, 649–660.
56. Ghosh,S. and Jacobson,A. (2010) RNA decay modulates gene expression and controls its fidelity. *Wiley Interdiscip Rev RNA*, **1**, 351–361.
57. Neu-Yilik,G. and Kulozik,A.E. (2008) NMD: multitasking between mRNA surveillance and modulation of gene expression. *Adv Genet*, **62**, 185–243.
58. Schmid,M. and Jensen,T.H. (2013) Transcription-associated quality control of mRNP. *Biochim Biophys Acta*, **1829**, 158–168.
59. Olesen,J.R., Libri,D. and Jensen,T.H. (2005) A link between transcription and mRNP quality in Saccharomyces cerevisiae. *RNA Biol*, **2**, 45–48.
60. Saguez,C., Olesen,J.R. and Jensen,T.H. (2005) Formation of export-competent mRNP: escaping nuclear destruction. *Curr Opin Cell Biol*, **17**, 287–293.
61. Saha,U., Gaine,R., Paira,S., Das,S. and Das,B. (2024) <scp>RRM1</scp> and <scp>PAB</scp> domains of translation initiation factor <scp>eIF4G</scp> (Tif4631p) play a crucial role in the nuclear degradation of export-defective <scp>mRNAs</scp> in *Saccharomyces cerevisiae*. *FEBS J.*, **291**, 897–926.
62. Burkard,K.T. and Butler,J.S. (2000) A nuclear 3’-5’ exonuclease involved in mRNA

degradation interacts with Poly(A) polymerase and the hnRNA protein Npl3p. *Mol Cell Biol*, **20**, 604–616.
63. Bousquet-Antonelli,C., Presutti,C. and Tollervey,D. (2000) Identification of a regulated pathway for nuclear pre-mRNA turnover. *Cell*, **102**, 765–775.
64. Das,B., Guo,Z., Russo,P., Chartrand,P. and Sherman,F. (2000) The Role of Nuclear Cap Binding Protein Cbc1p of Yeast in mRNA Termination and Degradation. *Mol. Cell. Biol.*, 10.1128/mcb.20.8.2827-2838.2000.
65. Das,B., Das,S. and Sherman,F. (2006) Mutant LYS2 mRNAs retained and degraded in the nucleus of Saccharomyces cerevisiae. *Proc. Natl. Acad. Sci.*, **103**, 10871–10876.
66. Torchet,C., Bousquet-Antonelli,C., Milligan,L., Thompson,E., Kufel,J. and Tollervey,D. (2002) Processing of 3'-extended read-through transcripts by the exosome can generate functional mRNAs. *Mol Cell*, **9**, 1285–1296.
67. Fasken,M.B. and Corbett,A.H. (2005) Process or perish: quality control in mRNA biogenesis. *Nat Struct Mol Biol*, **12**, 482–488.
68. Doma,M.K. and Parker,R. (2007) RNA Quality Control in Eukaryotes. *Cell*, **131**, 660–668.
69. Isken,O. and Maquat,L.E. (2007) Quality control of eukaryotic mRNA: safeguarding cells from abnormal mRNA function. *Genes Dev*, **21**, 1833–1856.
70. Chlebowski,A., Lubas,M., Jensen,T.H. and Dziembowski,A. (2013) RNA decay machines: The exosome. *Biochim. Biophys. Acta - Gene Regul. Mech.*, **1829**, 552–560.
71. Lykke-Andersen,S., Tomecki,R., Jensen,T.H. and Dziembowski,A. (2011) The eukaryotic RNA exosome: same scaffold but variable catalytic subunits. *RNA Biol*, **8**, 61–66.
72. Liu,Q., Greimann,J.C. and Lima,C.D. (2006) Reconstitution, activities, and structure of the eukaryotic RNA exosome. *Cell*, **127**, 1223–1237.
73. Zinder,J.C. and Lima,C.D. (2017) Targeting RNA for processing or destruction by the eukaryotic RNA exosome and its cofactors. *Genes Dev*, **31**, 88–100.
74. Januszyk,K. and Lima,C.D. (2014) The eukaryotic RNA exosome. *Curr Opin Struct Biol*, **24**, 132–140.
75. Wasmuth,E. V, Januszyk,K. and Lima,C.D. (2014) Structure of an Rrp6-RNA exosome complex bound to poly(A) RNA. *Nature*, **511**, 435–439.
76. Schneider,C., Leung,E., Brown,J. and Tollervey,D. (2009) The N-terminal PIN domain of the exosome subunit Rrp44 harbors endonuclease activity and tethers Rrp44 to the yeast core exosome. *Nucleic Acids Res*, **37**, 1127–1140.
77. Schaeffer,D., Tsanova,B., Barbas,A., Reis,F.P., Dastidar,E.G., Sanchez-Rotunno,M., Arraiano,C.M. and van Hoof,A. (2009) The exosome contains domains with specific endoribonuclease, exoribonuclease and cytoplasmic mRNA decay activities. *Nat Struct Mol Biol*, **16**, 56–62.
78. Lorentzen,E. and Conti,E. (2008) Expression, reconstitution, and structure of an archaeal RNA degrading exosome. *Methods Enzym.*, **447**, 417–435.
79. Briggs,M.W., Burkard,K.T.D. and Butler,J.S. (1998) Rrp6p, the yeast homologue of the human PM-Scl 100-kDa autoantigen, is essential for efficient 5.8 S rRNA 3' end formation. *J. Biol. Chem.*, **273**, 13255–13263.
80. Allmang,C., Petfalski,E., Podtelejnikov,A., Mann,M., Tollervey,D. and Mitchell,P. (1999) The yeast exosome and human PM-Scl are related complexes of 3' → 5' exonucleases. *Genes Dev.*, **13**, 2148–2158.
81. Cristodero,M., Bottcher,B., Diepholz,M., Scheffzek,K. and Clayton,C. (2008) The Leishmania tarentolae exosome: purification and structural analysis by electron microscopy. *Mol Biochem Parasitol*, **159**, 24–29.
82. Dziembowski,A., Lorentzen,E., Conti,E. and Seraphin,B. (2007) A single subunit, Dis3, is essentially responsible for yeast exosome core activity. *Nat Struct Mol Biol*, **14**, 15–22.
83. Makino,D.L., Baumgartner,M. and Conti,E. (2013) Crystal structure of an RNA-bound 11-subunit eukaryotic exosome complex. *Nature*, **495**, 70–75.
84. Bonneau,F., Basquin,J., Ebert,J., Lorentzen,E. and Conti,E. (2009) The yeast exosome functions as a macromolecular cage to channel RNA substrates for degradation. *Cell*, **139**, 547–559.
85. Wang,H.W., Wang,J., Ding,F., Callahan,K., Bratkowski,M.A., Butler,J.S., Nogales,E. and Ke,A. (2007) Architecture of the yeast Rrp44 exosome complex suggests routes of RNA recruitment for 3' end processing. *Proc Natl Acad Sci U S A*, **104**, 16844–16849.
86. Feigenbutz,M., Garland,W., Turner,M. and Mitchell,P. (2013) The exosome cofactor Rrp47 is critical for the stability and normal expression of its associated exoribonuclease Rrp6 in Saccharomyces cerevisiae. *PLoS One*, **8**, e80752.
87. Mitchell,P., Petfalski,E., Houalla,R., Podtelejnikov,A., Mann,M. and Tollervey,D.

(2003) Rrp47p is an exosome-associated protein required for the 3' processing of stable RNAs. *Mol Cell Biol*, **23**, 6982–6992.
88. Butler,J.S. and Mitchell,P. (2011) Rrp6, rrp47 and cofactors of the nuclear exosome. *Adv Exp Med Biol*, **702**, 91–104.
89. Milligan,L., Decourty,L., Saveanu,C., Rappsilber,J., Ceulemans,H., Jacquier,A. and Tollervey,D. (2008) A yeast exosome cofactor, Mpp6, functions in RNA surveillance and in the degradation of noncoding RNA transcripts. *Mol Cell Biol*, **28**, 5446–5457.
90. Stead,J.A., Costello,J.L., Livingstone,M.J. and Mitchell,P. (2007) The PMC2NT domain of the catalytic exosome subunit Rrp6p provides the interface for binding with its cofactor Rrp47p, a nucleic acid-binding protein. *Nucleic Acids Res*, **35**, 5556–5567.
91. Staals,R.H., Bronkhorst,A.W., Schilders,G., Slomovic,S., Schuster,G., Heck,A.J., Raijmakers,R. and Pruijn,G.J. (2010) Dis3-like 1: a novel exoribonuclease associated with the human exosome. *EMBO J*, **29**, 2358–2367.
92. Tomecki,R., Kristiansen,M.S., Lykke-Andersen,S., Chlebowski,A., Larsen,K.M., Szczesny,R.J., Drazkowska,K., Pastula,A., Andersen,J.S., Stepien,P.P., *et al.* (2010) The human core exosome interacts with differentially localized processive RNases: hDIS3 and hDIS3L. *EMBO J*, **29**, 2342–2357.
93. Malecki,M., Viegas,S.C., Carneiro,T., Golik,P., Dressaire,C., Ferreira,M.G. and Arraiano,C.M. (2013) The exoribonuclease Dis3L2 defines a novel eukaryotic RNA degradation pathway. *EMBO J.*, **32**, 1842–1854.
94. Targoff,I.N. and Reichlin,M. (1985) Nucleolar localization of the PM-Scl antigen. *Arthritis Rheum*, **28**, 226–230.
95. van Dijk,E.L., Schilders,G. and Pruijn,G.J. (2007) Human cell growth requires a functional cytoplasmic exosome, which is involved in various mRNA decay pathways. *RNA*, **13**, 1027–1035.
96. LaCava,J., Houseley,J., Saveanu,C., Petfalski,E., Thompson,E., Jacquier,A. and Tollervey,D. (2005) RNA degradation by the exosome is promoted by a nuclear polyadenylation complex. *Cell*, **121**, 713–724.
97. Vanacova,S., Wolf,J., Martin,G., Blank,D., Dettwiler,S., Friedlein,A., Langen,H., Keith,G. and Keller,W. (2005) A new yeast poly(A) polymerase complex involved in RNA quality control. *PLoS Biol*, **3**, e189.
98. Wyers,F., Rougemaille,M., Badis,G., Rousselle,J.C., Dufour,M.E., Boulay,J., Régnault,B., Devaux,F., Namane,A., Séraphin,B., *et al.* (2005) Cryptic Pol II transcripts are degraded by a nuclear quality control pathway involving a new poly(A) polymerase. *Cell*, **121**, 725–737.
99. Houseley,J. and Tollervey,D. (2006) Yeast Trf5p is a nuclear poly(A) polymerase. *EMBO Rep*, **7**, 205–211.
100. Das,S., Saha,U. and Das,B. (2014) Cbc2p, Upf3p and eIF4G are components of the DRN (Degradation of mRNA in the Nucleus) in Saccharomyces cerevisiae. *FEMS Yeast Res.*, **14**.
101. Sarkar,D., Paira,S. and Das,B. (2018) Nuclear mRNA degradation tunes the gain of the unfolded protein response in Saccharo myces cerevisiae. *Nucleic Acids Res.*, **46**.
102. Saha,U., Gaine,R., Paira,S., Das,S. and Das,B. (2024) RRM1 and PAB domains of translation initiation factor eIF4G (Tif4631p) play a crucial role in the nuclear degradation of export-defective mRNAs in Saccharomyces cerevisiae. *FEBS J.*, **291**, 897–926.
103. Kilchert,C., Wittmann,S. and Vasiljeva,L. (2016) The regulation and functions of the nuclear RNA exosome complex. *Nat. Rev. Mol. Cell Biol.*, **17**, 227–239.
104. Vasiljeva,L. and Buratowski,S. (2006) Nrd1 interacts with the nuclear exosome for 3' processing of RNA polymerase II transcripts. *Mol Cell*, **21**, 239–248.
105. Vasiljeva,L., Kim,M., Mutschler,H., Buratowski,S. and Meinhart,A. (2008) The Nrd1-Nab3-Sen1 termination complex interacts with the Ser5-phosphorylated RNA polymerase II C-terminal domain. *Nat. Struct. Mol. Biol.*, **15**, 795–804.
106. Singh,P., Chaudhuri,A., Banerjea,M., Marathe,N. and Das,B. (2021) Nrd1p identifies aberrant and natural exosomal target messages during the nuclear mRNA surveillance in Saccharomyces cerevisiae. *Nucleic Acids Res.*, **49**, 11512.
107. Hamill,S., Wolin,S.L. and Reinisch,K.M. (2010) Structure and function of the polymerase core of TRAMP, a RNA surveillance complex. *Proc Natl Acad Sci U S A*, **107**, 15045–15050.
108. Schuch,B., Feigenbutz,M., Makino,D.L., Falk,S., Basquin,C., Mitchell,P. and Conti,E. (2014) The exosome-binding factors Rrp6 and Rrp47 form a composite surface for recruiting the Mtr4 helicase. *EMBO J*, **33**, 2829–2846.
109. Losh,J.S., King,A.K., Bakelar,J., Taylor,L., Loomis,J., Rosenzweig,J.A., Johnson,S.J. and van Hoof,A. (2015) Interaction between the RNA-dependent ATPase and poly(A) polymerase subunits of the TRAMP complex is

mediated by short peptides and important for snoRNA processing. *Nucleic Acids Res*, **43**, 1848–1858.
110. Vanacova,S. and Stefl,R. (2007) The exosome and RNA quality control in the nucleus. *EMBO Rep*, **8**, 651–657.
111. Wery,M., Ruidant,S., Schillewaert,S., Lepore,N. and Lafontaine,D.L. (2009) The nuclear poly(A) polymerase and Exosome cofactor Trf5 is recruited cotranscriptionally to nucleolar surveillance. *RNA*, **15**, 406–419.
112. Jia,H., Wang,X., Liu,F., Guenther,U.P., Srinivasan,S., Anderson,J.T. and Jankowsky,E. (2011) The RNA helicase Mtr4p modulates polyadenylation in the TRAMP complex. *Cell*, **145**, 890–901.
113. Wlotzka,W., Kudla,G., Granneman,S. and Tollervey,D. (2011) The nuclear RNA polymerase II surveillance system targets polymerase III transcripts. *EMBO J*, **30**, 1790–1803.
114. Jackson,R.N., Klauer,A.A., Hintze,B.J., Robinson,H., van Hoof,A. and Johnson,S.J. (2010) The crystal structure of Mtr4 reveals a novel arch domain required for rRNA processing. *EMBO J*, **29**, 2205–2216.
115. Weir,J.R., Bonneau,F., Hentschel,J. and Conti,E. (2010) Structural analysis reveals the characteristic features of Mtr4, a DExH helicase involved in nuclear RNA processing and surveillance. *Proc Natl Acad Sci U S A*, **107**, 12139–12144.
116. Kadaba,S., Krueger,A., Trice,T., Krecic,A.M., Hinnebusch,A.G. and Anderson,J. (2004) Nuclear surveillance and degradation of hypomodified initiator tRNA Met in S. cerevisiae. *Genes Dev.*, **18**, 1227–1240.
117. Wang,X., Jia,H., Jankowsky,E. and Anderson,J.T. (2008) Degradation of hypomodified tRNA(iMet) in vivo involves RNA-dependent ATPase activity of the DExH helicase Mtr4p. *RNA*, **14**, 107–116.
118. Kadaba,S., Wang,X. and Anderson,J.T. (2006) Nuclear RNA surveillance in Saccharomyces cerevisiae: Trf4p-dependent polyadenylation of nascent hypomethylated tRNA and an aberrant form of 5S rRNA. *RNA*, **12**, 508.
119. Houseley,J. and Tollervey,D. (2008) The nuclear RNA surveillance machinery: The link between ncRNAs and genome structure in budding yeast? *Biochim. Biophys. Acta - Gene Regul. Mech.*, 10.1016/j.bbagrm.2007.12.008.
120. Rougemaille,M., Gudipati,R.K., Olesen,J.R., Thomsen,R., Seraphin,B., Libri,D. and Jensen,T.H. (2007) Dissecting mechanisms of nuclear mRNA surveillance in THO/sub2 complex mutants. *EMBO J*, **26**, 2317–2326.
121. Zaret,K.S. and Sherman,F. (1982) DNA sequence required for efficient transcription termination in yeast. *Cell*, **28**, 563–573.
122.Zaret,K.S. and Sherman,F. (1984) Mutationally altered 3′ ends of yeast CYC1 mRNA affect transcript stability and translational efficiency. *J. Mol. Biol.*, **177**, 107–135.
123. Das,B., Guo,Z., Russo,P., Chartrand,P. and Sherman,F. (2000) The role of nuclear cap binding protein Cbc1p of yeast in mRNA termination and degradation. *Mol. Cell. Biol.*, **20**.
124. Das,B., Butler,J.S. and Sherman,F. (2003) Degradation of normal mRNA in the nucleus of Saccharomyces cerevisiae. *Mol. Cell. Biol.*, **23**.
125. Banroques,J., Cordin,O., Doère,M., Linder,P. and Tanner,N.K. (2011) Analyses of the Functional Regions of DEAD-Box RNA "Helicases" with Deletion and Chimera Constructs Tested In Vivo and In Vitro. *J. Mol. Biol.*, **413**, 451–472.
126. Das,B., Das,S. and Sherman,F. (2006) Mutant LYS2 mRNAs retained and degraded in the nucleus of Saccharomyces cerevisiae. *Proc. Natl. Acad. Sci. U. S. A.*, **103**.
127. Kuai,L., Das,B. and Sherman,F. (2005) A nuclear degradation pathway controls the abundance of normal mRNAs in Saccharomyces cerevisiae. *Proc. Natl. Acad. Sci. U. S. A.*, **102**.
128. Paira,S.C.A. and D.B. (2023) The sequential recruitments of Rab-GTPase Ypt1p and the NNS complex onto pre-HAC1 mRNA promote its nuclear degradation in baker's yeast . *Mol. Cell. Biol.*, **43**, 371–400.
129. Paul,S., Das,S., Banerjea,M., Chaudhuri,S. and Das,B. (2025) The ATP-dependent DEAD-box RNA helicase Dbp2 regulates the glucose/nitrogen stress response in baker's yeast by modulating reversible nuclear retention and decay of *SKS1* mRNA. *Genetics*, **229**.
130.Arigo,J.T., Carroll,K.L., Ames,J.M. and Corden,J.L. (2006) Regulation of yeast NRD1 expression by premature transcription termination. *Mol Cell*, **21**, 641–651.
131. Conrad,N.K., Wilson,S.M., Steinmetz,E.J., Patturajan,M., Brow,D.A., Swanson,M.S. and Corden,J.L. (2000) A yeast heterogeneous nuclear ribonucleoprotein complex associated with RNA polymerase II. *Genetics*, **154**, 557–571.
132. Steinmetz,E.J., Conrad,N.K., Brow,D.A. and Corden,J.L. (2001) RNA-binding protein Nrd1

directs poly(A)-independent 3′-end formation of RNA polymerase II transcripts. *Nature*, **413**, 327–331.

133. Schulz,D., Schwalb,B., Kiesel,A., Baejen,C., Torkler,P., Gagneur,J., Soeding,J. and Cramer,P. (2013) XTranscriptome surveillance by selective termination of noncoding RNA synthesis. *Cell*, **155**, 1075.
134. Steinmetz,E.J. and Brow,D.A. (1996) Repression of gene expression by an exogenous sequence element acting in concert with a heterogeneous nuclear ribonucleoprotein-like protein, Nrd1, and the putative helicase Sen1. *Mol. Cell. Biol.*, **16**, 6993–7003.
135. Arigo,J.T., Eyler,D.E., Carroll,K.L. and Corden,J.L. (2006) Termination of cryptic unstable transcripts is directed by yeast RNA-binding proteins Nrd1 and Nab3. *Mol Cell*, **23**, 841–851.
136. Mayer,A., Heidemann,M., Lidschreiber,M., Schreieck,A., Sun,M., Hintermair,C., Kremmer,E., Eick,D. and Cramer,P. (2012) CTD Tyrosine phosphorylation impairs termination factor recruitment to RNA polymerase II. *Science (80-. ).*, **336**, 1723–1725.
137. Tuck,A.C. and Tollervey,D. (2013) A transcriptome-wide atlas of RNP composition reveals diverse classes of mRNAs and lncRNAs. *Cell*, **154**, 996–1009.
138. Steinmetz,E.J. and Brow,D.A. (1998) Control of pre-mRNA accumulation by the essential yeast protein Nrd1 requires high-affinity transcript binding and a domain implicated in RNA polymerase II association. *Proc. Natl. Acad. Sci. U. S. A.*, **95**, 6699–6704.
139. Bresson,S., Tuck,A., Staneva,D. and Tollervey,D. (2017) Nuclear RNA Decay Pathways Aid Rapid Remodeling of Gene Expression in Yeast. *Mol Cell*, **65**, 787-800 e5.
140. Creamer,T.J., Darby,M.M., Jamonnak,N., Schaughency,P., Hao,H., Wheelan,S.J. and Corden,J.L. (2011) Transcriptome-wide binding sites for components of the Saccharomyces cerevisiae non-poly(A) termination pathway: Nrd1, Nab3, and Sen1. *PLoS Genet.*, **7**.
141. Jamonnak,N., Creamer,T.J., Darby,M.M., Schaughency,P., Wheelan,S.J. and Corden,J.L. (2011) Yeast Nrd1, Nab3, and Sen1 transcriptome-wide binding maps suggest multiple roles in post-transcriptional RNA processing. *RNA*, **17**, 2011–2025.
142. Van Nues,R., Schweikert,G., De Leau,E., Selega,A., Langford,A., Franklin,R., Iosub,I., Wadsworth,P., Sanguinetti,G. and Granneman,S. (2017) Kinetic CRAC uncovers a role for Nab3 in determining gene expression profiles during stress. *Nat. Commun.*, **8**.
143.Webb,S., Hector,R.D., Kudla,G. and Granneman,S. (2014) PAR-CLIP data indicate that Nrd1-Nab3-dependent transcription termination regulates expression of hundreds of protein coding genes in yeast. *Genome Biol.*, **15**.
144. Kuehner,J.N. and Brow,D.A. (2008) Regulation of a Eukaryotic Gene by GTP-Dependent Start Site Selection and Transcription Attenuation. *Mol. Cell*, **31**, 201–211.
145. Thiebaut,M., Colin,J., Neil,H., Jacquier,A., Séraphin,B., Lacroute,F. and Libri,D. (2008) Futile cycle of transcription initiation and termination modulates the response to nucleotide shortage in S. cerevisiae. *Mol. Cell*, **31**, 671–682.
146. Kim,K.Y. and Levin,D.E. (2011) Mpk1 MAPK association with the paf1 complex blocks sen1-mediated premature transcription termination. *Cell*, **144**, 745–756.
147. Fasken,M.B., Leung,S.W., Banerjee,A., Kodani,M.O., Chavez,R., Bowman,E.A., Purohit,M.K., Rubinson,M.E., Rubinson,E.H. and Corbett,A.H. (2011) Air1 zinc knuckles 4 and 5 and a conserved IWRXY motif are critical for the function and integrity of the Trf4/5-Air1/2-Mtr4 polyadenylation (TRAMP) RNA quality control complex. *J Biol Chem*, **286**, 37429–37445.
148.Lubas,M., Christensen,M.S., Kristiansen,M.S., Domanski,M., Falkenby,L.G., Lykke-Andersen,S., Andersen,J.S., Dziembowski,A. and Jensen,T.H. (2011) Interaction profiling identifies the human nuclear exosome targeting complex. *Mol Cell*, **43**, 624–637.
149. Meola,N., Domanski,M., Karadoulama,E., Chen,Y., Gentil,C., Pultz,D., Vitting-Seerup,K., Lykke-Andersen,S., Andersen,J.S., Sandelin,A., *et al.* (2016) Identification of a Nuclear Exosome Decay Pathway for Processed Transcripts. *Mol Cell*, **64**, 520–533.
150. Schilders,G., van Dijk,E. and Pruijn,G.J. (2007) C1D and hMtr4p associate with the human exosome subunit PM/Scl-100 and are involved in pre-rRNA processing. *Nucleic Acids Res*, **35**, 2564–2572.
151.Andersen,P.R., Domanski,M., Kristiansen,M.S., Storvall,H., Ntini,E., Verheggen,C., Schein,A., Bunkenborg,J., Poser,I., Hallais,M., *et al.* (2013) The human cap-binding complex is functionally connected to the nuclear RNA exosome. *Nat Struct Mol Biol*, **20**, 1367–1376.
152.Lee,N.N., Chalamcharla,V.R., Reyes-Turcu,F.,

Mehta,S., Zofall,M., Balachandran,V., Dhakshnamoorthy,J., Taneja,N., Yamanaka,S., Zhou,M., *et al.* (2013) Mtr4-like protein coordinates nuclear RNA processing for heterochromatin assembly and for telomere maintenance. *Cell*, **155**, 1061–1074.

153.Egan,E.D., Braun,C.R., Gygi,S.P. and Moazed,D. (2014) Post-transcriptional regulation of meiotic genes by a nuclear RNA silencing complex. *RNA*, **20**, 867–881.

154. Zhou,Y., Zhu,J., Schermann,G., Ohle,C., Bendrin,K., Sugioka-Sugiyama,R., Sugiyama,T. and Fischer,T. (2015) The fission yeast MTREC complex targets CUTs and unspliced pre-mRNAs to the nuclear exosome. *Nat Commun*, **6**, 7050.

155. Maity,A., Chaudhuri,A. and Das,B. (2016) DRN and TRAMP degrade specific and overlapping aberrant mRNAs formed at various stages of mRNP biogenesis in Saccharomyces cerevisiae. *FEMS Yeast Res.*, **16**.

156. Ntini,E., Jarvelin,A.I., Bornholdt,J., Chen,Y., Boyd,M., Jorgensen,M., Andersson,R., Hoof,I., Schein,A., Andersen,P.R., *et al.* (2013) Polyadenylation site-induced decay of upstream transcripts enforces promoter directionality. *Nat Struct Mol Biol*, **20**, 923–928.

157.Shcherbik,N., Wang,M., Lapik,Y.R., Srivastava,L. and Pestov,D.G. (2010) Polyadenylation and degradation of incomplete RNA polymerase I transcripts in mammalian cells. *EMBO Rep*, **11**, 106–111.

158. Hallais,M., Pontvianne,F., Andersen,P.R., Clerici,M., Lener,D., Benbahouche Nel,H., Gostan,T., Vandermoere,F., Robert,M.C., Cusack,S., *et al.* (2013) CBC-ARS2 stimulates 3'-end maturation of multiple RNA families and favors cap-proximal processing. *Nat Struct Mol Biol*, **20**, 1358–1366.

159.Lubas,M., Andersen,P.R., Schein,A., Dziembowski,A., Kudla,G. and Jensen,T.H. (2015) The human nuclear exosome targeting complex is loaded onto newly synthesized RNA to direct early ribonucleolysis. *Cell Rep*, **10**, 178–192.

160. Walter,P. and Ron,D. (2011) The unfolded protein response: From stress pathway to homeostatic regulation. *Science (80-. ).*, **334**, 1081–1086.

161. Bernales,S., Papa,F.R. and Walter,P. (2006) Intracellular Signaling by the Unfolded Protein Response. *Annu. Rev. Cell Dev. Biol.*, **22**, 487–508.

162. Kawahara,T., Yanagi,H., Yura,T. and Mori,K. (1997) Endoplasmic reticulum stress-induced mRNA splicing permits synthesis of transcription factor Hac1p/Ern4p that activates the unfolded protein response. *Mol. Biol. Cell*, **8**, 1845–1862.

163.Aragon,T., van Anken,E., Pincus,D., Serafimova,I.M., Korennykh,A. V, Rubio,C.A. and Walter,P. (2009) Messenger RNA targeting to endoplasmic reticulum stress signalling sites. *Nature*, **457**, 736–740.

164. Rüegsegger,U., Leber,J.H. and Walter,P. (2001) Block of HAC1 mRNA translation by long-range base pairing is released by cytoplasmic splicing upon induction of the unfolded protein response. *Cell*, **107**, 103–114.

165. Lee,K.P.K., Dey,M., Neculai,D., Cao,C., Dever,T.E. and Sicheri,F. (2008) Structure of the dual enzyme Ire1 reveals the basis for catalysis and regulation in nonconventional RNA splicing. *Cell*, **132**, 89–100.

166. Sidrauski,C. and Walter,P. (1997) The transmembrane kinase Ire1p is a site-specific endonuclease that initiates mRNA splicing in the unfolded protein response. *Cell*, **90**, 1031–9.

167. Kohno,K., Normington,K., Sambrook,J., Gething,M.J. and Mori,K. (1993) The promoter region of the yeast KAR2 (BiP) gene contains a regulatory domain that responds to the presence of unfolded proteins in the endoplasmic reticulum. *Mol. Cell. Biol.*, **13**, 877–890.

168. Das,B., Butler,J.S. and Sherman,F. (2003) Degradation of Normal mRNA in the Nucleus of *Saccharomyces cerevisiae*. *Mol. Cell. Biol.*, **23**, 5502–5515.

169.Das,S.,Biswas,S.,Chaudhuri,S., Bhattacharyya,A. and Das,B. (2019) A Nuclear Zip Code in SKS1 mRNA Promotes Its Slow Export, Nuclear Retention, and Degradation by the Nuclear Exosome/DRN in Saccharomyces cerevisiae. *J. Mol. Biol.*, **431**, 3626–3646.

170. Paul,S., Das,S., Banerjea,M., Chaudhuri,S. and Das,B. (2024) The ATP-dependent DEAD-box RNA helicase Dbp2 regulates the glucose/nitrogen stress response in baker's yeast by modulating reversible nuclear retention and decay of *SKS1* mRNA. *Genetics*, 10.1093/genetics/iyae221.

171. Wellinger,R.J. and Zakian,V.A. (2012) Everything You Ever Wanted to Know About *Saccharomyces cerevisiae* Telomeres: Beginning to End. *Genetics*, **191**, 1073–1105.

172. Young,N.S. (2010) Telomere Biology and Telomere Diseases: Implications for Practice and Research. *Hematology*, **2010**, 30–35.

173.Romano,G.H., Harari,Y., Yehuda,T., Podhorzer,A., Rubinstein,L., Shamir,R., Gottlieb,A., Silberberg,Y., Pe'er,D., Ruppin,E., *et al.* (2013) Environmental Stresses Disrupt

Telomere Length Homeostasis. *PLoS Genet.*, **9**, e1003721.
174. Kumar,N.V., Yang,J., Pillai,J.K., Rawat,S., Solano,C., Kumar,A., Grøtli,M., Stemmler,T.L., Rosen,B.P. and Tamás,M.J. (2016) Arsenic Directly Binds to and Activates the Yeast AP-1-Like Transcription Factor Yap8. *Mol. Cell. Biol.*, **36**, 913–922.
175. Tomecki,R., Drazkowska,K., Kucinski,I., Stodus,K., Szczesny,R.J., Gruchota,J., Owczarek,E.P., Kalisiak,K. and Dziembowski,A. (2014) Multiple myeloma-associated hDIS3 mutations cause perturbations in cellular RNA metabolism and suggest hDIS3 PIN domain as a potential drug target. *Nucleic Acids Res*, **42**, 1270–1290.
176. Chapman,M.A., Lawrence,M.S., Keats,J.J., Cibulskis,K., Sougnez,C., Schinzel,A.C., Harview,C.L., Brunet,J.P., Ahmann,G.J., Adli,M., *et al.* (2011) Initial genome sequencing and analysis of multiple myeloma. *Nature*, **471**, 467–472.
177. Walker,B.A., Wardell,C.P., Melchor,L., Hulkki,S., Potter,N.E., Johnson,D.C., Fenwick,K., Kozarewa,I., Gonzalez,D., Lord,C.J., *et al.* (2012) Intraclonal heterogeneity and distinct molecular mechanisms characterize the development of t(4;14) and t(11;14) myeloma. *Blood*, **120**, 1077–1086.
178. Lohr,J.G., Stojanov,P., Carter,S.L., Cruz-Gordillo,P., Lawrence,M.S., Auclair,D., Sougnez,C., Knoechel,B., Gould,J., Saksena,G., *et al.* (2014) Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. *Cancer Cell*, **25**, 91–101.
179. Segalla,S., Pivetti,S., Todoerti,K., Chudzik,M.A., Giuliani,E.C., Lazzaro,F., Volta,V., Lazarevic,D., Musco,G., Muzi-Falconi,M., *et al.* (2015) The ribonuclease DIS3 promotes let-7 miRNA maturation by degrading the pluripotency factor LIN28B mRNA. *Nucleic Acids Res*, **43**, 5182–5193.
180. Hoskins,J.W., Ibrahim,A., Emmanuel,M.A., Manmiller,S.M., Wu,Y., O'Neill,M., Jia,J., Collins,I., Zhang,M., Thomas,J. V, *et al.* (2016) Functional characterization of a chr13q22.1 pancreatic cancer risk locus reveals long-range interaction and allele-specific effects on DIS3 expression. *Hum Mol Genet*, **25**, 4726–4738.
181. Eser,S., Schnieke,A., Schneider,G. and Saur,D. (2014) Oncogenic KRAS signalling in pancreatic cancer. *Br J Cancer*, **111**, 817–822.
182. Xing,Z., Ma,W.K. and Tran,E.J. (2019) The DDX5/Dbp2 subfamily of DEAD-box RNA helicases. *WIREs RNA*, **10**.
183. Song,Q.-X., Liu,N.-N., Liu,Z.-X., Zhang,Y.-Z., Rety,S., Hou,X.-M. and Xi,X.-G. (2023) Nonstructural N- and C-tails of Dbp2 confer the protein full helicase activities. *J. Biol. Chem.*, **299**, 104592.
184. Cloutier,S.C., Ma,W.K., Nguyen,L.T. and Tran,E.J. (2012) The DEAD-box RNA helicase Dbp2 connects RNA quality control with repression of aberrant transcription. *J. Biol. Chem.*, **287**, 26155–26166.
185. Bohnsack,K.E., Yi,S., Venus,S., Jankowsky,E. and Bohnsack,M.T. (2023) Cellular functions of eukaryotic RNA helicases and their links to human diseases. *Nat. Rev. Mol. Cell Biol.*, **24**, 749–769.
186. Hashemi,V., Masjedi,A., Hazhir-karzar,B., Tanomand,A., Shotorbani,S.S., Hojjat-Farsangi,M., Ghalamfarsa,G., Azizi,G., Anvari,E., Baradaran,B., *et al.* (2019) The role of DEAD-box RNA helicase p68 (DDX5) in the development and treatment of breast cancer. *J. Cell. Physiol.*, **234**, 5478–5487.
187. Shin,S., Rossow,K.L., Grande,J.P. and Janknecht,R. (2007) Involvement of RNA Helicases p68 and p72 in Colon Cancer. *Cancer Res.*, **67**, 7572–7578.
188. Clark,E.L., Coulson,A., Dalgliesh,C., Rajan,P., Nicol,S.M., Fleming,S., Heer,R., Gaughan,L., Leung,H.Y., Elliott,D.J., *et al.* (2008) The RNA Helicase p68 Is a Novel Androgen Receptor Coactivator Involved in Splicing and Is Overexpressed in Prostate Cancer. *Cancer Res.*, **68**, 7938–7946.
189. Wang,Z., Luo,Z., Zhou,L., Li,X., Jiang,T. and Fu,E. (2015) <scp>DDX</scp> 5 promotes proliferation and tumorigenesis of non-small-cell lung cancer cells by activating β-catenin signaling pathway. *Cancer Sci.*, **106**, 1303–1312.
190. Du,C., Li,D., Li,N., Chen,L., Li,S., Yang,Y., Hou,M., Xie,M. and Zheng,Z. (2017) DDX5 promotes gastric cancer cell proliferation in vitro and in vivo through mTOR signaling pathway. *Sci. Rep.*, **7**, 42876.
191. Kitagawa,N., Ojima,H., Shirakihara,T., Shimizu,H., Kokubu,A., Urushidate,T., Totoki,Y., Kosuge,T., Miyagawa,S. and Shibata,T. (2013) Downregulation of the micro <scp>RNA</scp> biogenesis components and its association with poor prognosis in hepatocellular carcinoma. *Cancer Sci.*, **104**, 543–551.
192. Wang,S.J., Zhang,C., You,Y. and Shi,C.M. (2012) Overexpression of RNA helicase p68 protein in cutaneous squamous cell carcinoma. *Clin. Exp. Dermatol.*, **37**, 882–888.

193. Zhao,X., Li,D., Yang,F., Lian,H., Wang,J., Wang,X., Fang,E., Song,H., Hu,A., Guo,Y., *et al.* (2020) Long Noncoding RNA NHEG1 Drives β-Catenin Transactivation and Neuroblastoma Progression through Interacting with DDX5. *Mol. Ther.*, **28**, 946–962.
194. Lin,S., Tian,L., Shen,H., Gu,Y., Li,J.-L., Chen,Z., Sun,X., James You,M. and Wu,L. (2013) DDX5 is a positive regulator of oncogenic NOTCH1 signaling in T cell acute lymphoblastic leukemia. *Oncogene*, **32**, 4845–4853.
195. Sarkar,M., Khare,V. and Ghosh,M.K. (2017) The DEAD box protein p68: a novel coactivator of Stat3 in mediating oncogenesis. *Oncogene*, **36**, 3080–3093.
196. Howard,A. and Rogers,A.N. (2014) Role of translation initiation factor 4G in lifespan regulation and age-related health. *Ageing Res Rev*, **13**, 115–124.
197. Fukuchi-Shimogori,T., Ishii,I., Kashiwagi,K., Mashiba,H., Ekimoto,H. and Igarashi,K. (1997) Malignant transformation by overproduction of translation initiation factor eIF4G. *Cancer Res*, **57**, 5041–5044.
198. Cromer,A., Carles,A., Millon,R., Ganguli,G., Chalmel,F., Lemaire,F., Young,J., Dembele,D., Thibault,C., Muller,D., *et al.* (2004) Identification of genes associated with tumorigenesis and metastatic potential of hypopharyngeal cancer by microarray analysis. *Oncogene*, **23**, 2484–2498.
199. Fang,W., Li,X., Jiang,Q., Liu,Z., Yang,H., Wang,S., Xie,S., Liu,Q., Liu,T., Huang,J., *et al.* (2008) Transcriptional patterns, biomarkers and pathways characterizing nasopharyngeal carcinoma of Southern China. *J Transl Med*, **6**, 32.
200.Comtesse,N., Keller,A., Diesinger,I., Bauer,C., Kayser,K., Huwer,H., Lenhof,H.P. and Meese,E. (2007) Frequent overexpression of the genes FXR1, CLAPM1 and EIF4G located on amplicon 3q26-27 in squamous cell carcinoma of the lung. *Int J Cancer*, **120**, 2538–2544.
201. Tu,L., Liu,Z., He,X., He,Y., Yang,H., Jiang,Q., Xie,S., Xiao,G., Li,X., Yao,K., *et al.* (2010) Over-expression of eukaryotic translation initiation factor 4 gamma 1 correlates with tumor progression and poor prognosis in nasopharyngeal carcinoma. *Mol Cancer*, **9**, 78.
202.Braunstein,S., Karpisheva,K., Pola,C., Goldberg,J., Hochman,T., Yee,H., Cangiarella,J., Arju,R., Formenti,S.C. and Schneider,R.J. (2007) A Hypoxia-Controlled Cap-Dependent to Cap-Independent Translation Switch in Breast Cancer. *Mol. Cell*, **28**, 501–512.
203.Silvera,D., Arju,R., Darvishian,F., Levine,P.H., Zolfaghari,L., Goldberg,J., Hochman,T., Formenti,S.C. and Schneider,R.J. (2009) Essential role for eIF4GI overexpression in the pathogenesis of inflammatory breast cancer. *Nat. Cell Biol.*, **11**, 903–908.
204. Rudnik-Schoneborn,S., Senderek,J., Jen,J.C., Houge,G., Seeman,P., Puchmajerova,A., Graul-Neumann,L., Seidel,U., Korinthenberg,R., Kirschner,J., *et al.* (2013) Pontocerebellar hypoplasia type 1: clinical spectrum and relevance of EXOSC3 mutations. *Neurology*, **80**, 438–446.
205.Fasken,M.B., Losh,J.S., Leung,S.W., Brutus,S., Avin,B., Vaught,J.C., Potter-Birriel,J., Craig,T., Conn,G.L., Mills-Lujan,K., *et al.* (2017) Insight into the RNA Exosome Complex Through Modeling Pontocerebellar Hypoplasia Type 1b Disease Mutations in Yeast. *Genetics*, **205**, 221–237.
206. Gillespie,A., Gabunilas,J., Jen,J.C. and Chanfreau,G.F. (2017) Mutations of EXOSC3/Rrp40p associated with neurological diseases impact ribosomal RNA processing functions of the exosome in *S. cerevisiae*. *RNA*, **23**, 466–472.
207.Morton,D.J., Kuiper,E.G., Jones,S.K., Leung,S.W., Corbett,A.H. and Fasken,M.B. (2017) The RNA Exosome and RNA Exosome-linked Disease. *RNA*, rna.064626.117 [pii]10.1261/rna.064626.117.
208.Eggens,V.R., Barth,P.G., Niermeijer,J.M., Berg,J.N., Darin,N., Dixit,A., Fluss,J., Foulds,N., Fowler,D., Hortobagyi,T., *et al.* (2014) EXOSC3 mutations in pontocerebellar hypoplasia type 1: novel mutations and genotype-phenotype correlations. *Orphanet J Rare Dis*, **9**, 23.
209. Wan,J., Yourshaw,M., Mamsa,H., Rudnik-Schoneborn,S., Menezes,M.P., Hong,J.E., Leong,D.W., Senderek,J., Salman,M.S., Chitayat,D., *et al.* (2012) Mutations in the RNA exosome component gene EXOSC3 cause pontocerebellar hypoplasia and spinal motor neuron degeneration. *Nat Genet*, **44**, 704–708.
210.Boczonadi,V., Muller,J.S., Pyle,A., Munkley,J., Dor,T., Quartararo,J., Ferrero,I., Karcagi,V., Giunta,M., Polvikoski,T., *et al.* (2014) EXOSC8 mutations alter mRNA metabolism and cause hypomyelination with spinal muscular atrophy and cerebellar hypoplasia. *Nat Commun*, **5**, 4287.
211. Giunta,M., Edvardson,S., Xu,Y., Schuelke,M., Gomez-Duran,A., Boczonadi,V.,

Elpeleg,O., Muller,J.S. and Horvath,R. (2016) Altered RNA metabolism due to a homozygous RBM7 mutation in a patient with spinal motor neuropathy. *Hum Mol Genet*, **25**, 2985–2996.

212. Di Donato,N., Neuhann,T., Kahlert,A.K., Klink,B., Hackmann,K., Neuhann,I., Novotna,B., Schallner,J., Krause,C., Glass,I.A., *et al.* (2016) Mutations in EXOSC2 are associated with a novel syndrome characterised by retinitis pigmentosa, progressive hearing loss, premature ageing, short stature, mild intellectual disability and distinctive gestalt. *J Med Genet*, **53**, 419–425.
213. Burns,D.T., Donkervoort,S., Müller,J.S., Knierim,E., Bharucha-Goebel,D., Faqeih,E.A., Bell,S.K., AlFaifi,A.Y., Monies,D., Millan,F., *et al.* (2018) Variants in EXOSC9 Disrupt the RNA Exosome and Result in Cerebellar Atrophy with Spinal Motor Neuronopathy. *Am. J. Hum. Genet.*, **102**, 858–873.
214.Hrossova,D., Sikorsky,T., Potesil,D., Bartosovic,M., Pasulka,J., Zdrahal,Z., Stefl,R. and Vanacova,S. (2015) RBM7 subunit of the NEXT complex binds U-rich sequences and targets 3'-end extended forms of snRNAs. *Nucleic Acids Res*, **43**, 4236–4248.
215.Guo,T.B., Boros,L.G., Chan,K.C., Hikim,A.P., Hudson,A.P., Swerdloff,R.S., Mitchell,A.P. and Salameh,W.A. (2003) Spermatogenetic expression of RNA-binding motif protein 7, a protein that interacts with splicing factors. *J Androl*, **24**, 204–214.
216. Falk,S., Weir,J.R., Hentschel,J., Reichelt,P., Bonneau,F. and Conti,E. (2014) The molecular architecture of the TRAMP complex reveals the organization and interplay of its two catalytic activities. *Mol Cell*, **55**, 856–867.
217. Chen,Y.Z., Bennett,C.L., Huynh,H.M., Blair,I.P., Puls,I., Irobi,J., Dierick,I., Abel,A., Kennerson,M.L., Rabin,B.A., *et al.* (2004) DNA/RNA helicase gene mutations in a form of juvenile amyotrophic lateral sclerosis (ALS4). *Am J Hum Genet*, **74**, 1128–1135.
218. Chen,Y.Z., Hashemi,S.H., Anderson,S.K., Huang,Y., Moreira,M.C., Lynch,D.R., Glass,I.A., Chance,P.F. and Bennett,C.L. (2006) Senataxin, the yeast Sen1p orthologue: characterization of a unique protein in which recessive mutations cause ataxia and dominant mutations cause motor neuron disease. *Neurobiol Dis*, **23**, 97–108.
219.Moreira,M.C., Klur,S., Watanabe,M., Nemeth,A.H., Le Ber,I., Moniz,J.C., Tranchant,C., Aubourg,P., Tazir,M., Schols,L., *et al.* (2004) Senataxin, the ortholog of a yeast RNA helicase, is mutant in ataxia-ocular apraxia 2. *Nat Genet*, **36**, 225–227.
220. Duquette,A., Roddier,K., McNabb-Baltar,J., Gosselin,I., St-Denis,A., Dicaire,M.J., Loisel,L., Labuda,D., Marchand,L., Mathieu,J., *et al.* (2005) Mutations in senataxin responsible for Quebec cluster of ataxia with neuropathy. *Ann Neurol*, **57**, 408–414.
221.Suraweera,A., Lim,Y., Woods,R., Birrell,G.W., Nasim,T., Becherel,O.J. and Lavin,M.F. (2009) Functional role for senataxin, defective in ataxia oculomotor apraxia type 2, in transcriptional regulation. *Hum Mol Genet*, **18**, 3384–3396.
222.Suraweera,A., Becherel,O.J., Chen,P., Rundle,N., Woods,R., Nakamura,J., Gatei,M., Criscuolo,C., Filla,A., Chessa,L., *et al.* (2007) Senataxin, defective in ataxia oculomotor apraxia type 2, is involved in the defense against oxidative DNA damage. *J Cell Biol*, **177**, 969–979.
223.Aguilera,A. and Garcia-Muse,T. (2012) R loops: from transcription byproducts to threats to genome stability. *Mol Cell*, **46**, 115–124.
224. Sollier,J. and Cimprich,K.A. (2015) Breaking bad: R-loops and genome integrity. *Trends Cell Biol*, **25**, 514–522.
225. Richard,P., Feng,S. and Manley,J.L. (2013) A SUMO-dependent interaction between Senataxin and the exosome, disrupted in the neurodegenerative disease AOA2, targets the exosome to sites of transcription-induced DNA damage. *Genes Dev*, **27**, 2227–2232.
226. Basu,U., Meng,F.L., Keim,C., Grinstein,V., Pefanis,E., Eccleston,J., Zhang,T., Myers,D., Wasserman,C.R., Wesemann,D.R., *et al.* (2011) The RNA exosome targets the AID cytidine deaminase to both strands of transcribed duplex DNA substrates. *Cell*, **144**, 353–363.
227. Wahba,L., Amon,J.D., Koshland,D. and Vuica-Ross,M. (2011) RNase H and multiple RNA biogenesis factors cooperate to prevent RNA:DNA hybrids from generating genome instability. *Mol Cell*, **44**, 978–988.
228.Mischo,H.E., Gomez-Gonzalez,B., Grzechnik,P., Rondon,A.G., Wei,W., Steinmetz,L., Aguilera,A. and Proudfoot,N.J. (2011) Yeast Sen1 helicase protects the genome from transcription-associated instability. *Mol Cell*, **41**, 21–32.
229.Skourti-Stathaki,K., Proudfoot,N.J. and Gromak,N. (2011) Human senataxin resolves RNA/DNA hybrids formed at transcriptional pause sites to promote Xrn2-dependent termination. *Mol Cell*, **42**, 794–805.
230.Tarpey,P.S., Raymond,F.L., Nguyen,L.S., Rodriguez,J., Hackett,A., Vandeleur,L.,

Smith,R., Shoubridge,C., Edkins,S., Stevens,C., *et al.* (2007) Mutations in UPF3B, a member of the nonsense-mediated mRNA decay complex, cause syndromic and nonsyndromic mental retardation. *Nat Genet*, **39**, 1127–1133.

231.Tarpey,P.S., Smith,R., Pleasance,E., Whibley,A., Edkins,S., Hardy,C., O'Meara,S., Latimer,C., Dicks,E., Menzies,A., *et al.* (2009) A systematic, large-scale resequencing screen of X-chromosome coding exons in mental retardation. *Nat Genet*, **41**, 535–543.

232. Lujan,J.E., Carlin,M.E. and Lubs,H.A. (1984) A form of X-linked mental retardation with marfanoid habitus. *Am J Med Genet*, **17**, 311–322.

233. Fryns,J.P. and Buttiens,M. (1987) X-linked mental retardation with marfanoid habitus. *Am J Med Genet*, **28**, 267–274.

234. Opitz,J.M. and Kaveggia,E.G. (1974) Studies of malformation syndromes of man 33: the FG syndrome. An X-linked recessive syndrome of multiple congenital anomalies and mental retardation. *Z Kinderheilkd*, **117**, 1–18.

235. Das,S., Saha,U. and Das,B. (2014) Cbc2p, Upf3p and eIF4G are components of the DRN (Degradation of mRNA in the Nucleus) in *Saccharomyces cerevisiae*. *FEMS Yeast Res.*, **14**, 922–932.

236. Chartier-Harlin,M.C., Dachsel,J.C., Vilarino-Guell,C., Lincoln,S.J., Lepretre,F., Hulihan,M.M., Kachergus,J., Milnerwood,A.J., Tapia,L., Song,M.S., *et al.* (2011) Translation initiator EIF4G1 mutations in familial Parkinson disease. *Am J Hum Genet*, **89**, 398–406.

237.Nuytemans,K., Bademci,G., Inchausti,V., Dressen,A., Kinnamon,D.D., Mehta,A., Wang,L., Zuchner,S., Beecham,G.W., Martin,E.R., *et al.* (2013) Whole exome sequencing of rare variants in EIF4G1 and VPS35 in Parkinson disease. *Neurology*, **80**, 982–989.

238.Yuan,L., Song,Z., Xu,H., Gu,S., Zhu,A., Gong,L., Zhao,Y. and Deng,H. (2013) EIF4G1 Ala502Val and Arg1205His variants in Chinese patients with Parkinson disease. *Neurosci Lett*, **543**, 69–71.

239.Lesage,S., Condroyer,C., Klebe,S., Lohmann,E., Durif,F., Damier,P., Tison,F., Anheim,M., Honore,A., Viallet,F., *et al.* (2012) EIF4G1 in familial Parkinson's disease: pathogenic mutations or rare benign variants? *Neurobiol Aging*, **33**, 2233 e1-2233 e5.

240.Attar-Schneider,O., Pasmanik-Chor,M., Tartakover-Matalon,S., Drucker,L. and Lishner,M. (2015) eIF4E and eIF4GI have distinct and differential imprints on multiple myeloma's proteome and signaling. *Oncotarget*, **6**, 4315–4329.

241. Neumar,R.W., DeGracia,D.J., Konkoly,L.L., Khoury,J.I., White,B.C. and Krause,G.S. (1998) Calpain Mediates Eukaryotic Initiation Factor 4G Degradation during Global Brain Ischemia. *J. Cereb. Blood Flow Metab.*, **18**, 876–881.

242.Vosler,P.S., Gao,Y., Brennan,C.S., Yanagiya,A., Gan,Y., Cao,G., Zhang,F., Morley,S.J., Sonenberg,N., Bennett,M.V.L., *et al.* (2011) Ischemia-induced calpain activation causes eukaryotic (translation) initiation factor 4G1 (eIF4GI) degradation, protein synthesis inhibition, and neuronal death. *Proc. Natl. Acad. Sci.*, **108**, 18102–18107.

243.Wolfe,J.F., Adelstein,E. and Sharp,G.C. (1977) Antinuclear antibody with distinct specificity for polymyositis. *J Clin Invest*, **59**, 176–178.

244. Oddis,C. V, Okano,Y., Rudert,W.A., Trucco,M., Duquesnoy,R.J. and Medsger Jr.,T.A. (1992) Serum autoantibody to the nucleolar antigen PM-Scl. Clinical and immunogenetic associations. *Arthritis Rheum*, **35**, 1211–1217.

245. Schnitz,W., Taylor-Albert,E., Targoff,I.N., Reichlin,M. and Scofield,R.H. (1996) Anti-PM/Scl autoantibodies in patients without clinical polymyositis or scleroderma. *J Rheumatol*, **23**, 1729–1733.

246. Gelpi,C., Alguero,A., Angeles Martinez,M., Vidal,S., Juarez,C. and Rodriguez-Sanchez,J.L. (1990) Identification of protein components reactive with anti-PM/Scl autoantibodies. *Clin Exp Immunol*, **81**, 59–64.

247.Reimer,G., Scheer,U., Peters,J.M. and Tan,E.M. (1986) Immunolocalization and partial characterization of a nucleolar autoantigen (PM-Scl) associated with polymyositis/scleroderma overlap syndromes. *J Immunol*, **137**, 3802–3808.

248.Marguerie,C., Bunn,C.C., Copier,J., Bernstein,R.M., Gilroy,J.M., Black,C.M., So,A.K. and Walport,M.J. (1992) The clinical and immunogenetic features of patients with autoantibodies to the nucleolar antigen PM-Scl. *Med.*, **71**, 327–336.

249.Mitchell,P., Petfalski,E. and Tollervey,D. (1996) The 3' end of yeast 5.8S rRNA is generated by an exonuclease processing mechanism. *Genes Dev.*, **10**, 502–513.

250.Contreras,V., Richardson,M.A., Hao,E. and Keiper,B.D. (2008) Depletion of the cap-associated isoform of translation factor eIF4G induces germline apoptosis in C. elegans. *Cell*

*Death Differ*, **15**, 1232–1242.
251. Goyer,C., Altmann,M., Lee,H.S., Blanc,A., Deshmukh,M., Woolford Jr.,J.L., Trachsel,H. and Sonenberg,N. (1993) TIF4631 and TIF4632: two yeast genes encoding the high-molecular-weight subunits of the cap-binding protein complex (eukaryotic initiation factor 4F) contain an RNA recognition motif-like sequence and carry out an essential function. *Mol Cell Biol*, **13**, 4860–4874.
252.Curran,S.P. and Ruvkun,G. (2007) Lifespan Regulation by Evolutionarily Conserved Genes Essential for Viability. *PLoS Genet.*, **3**, e56.
253.Hansen,M., Taubert,S., Crawford,D., Libina,N., Lee,S. and Kenyon,C. (2007) Lifespan extension by conditions that inhibit translation in *Caenorhabditis elegans*. *Aging Cell*, **6**, 95–110.
254. Henderson,S.T., Bonafe,M. and Johnson,T.E. (2006) daf-16 Protects the Nematode Caenorhabditis elegans During Food Deprivation. *Journals Gerontol. Ser. A Biol. Sci. Med. Sci.*, **61**, 444–460.
255. Pan,K.Z., Palter,J.E., Rogers,A.N., Olsen,A., Chen,D., Lithgow,G.J. and Kapahi,P. (2007) Inhibition of mRNA translation extends lifespan in *Caenorhabditis elegans*. *Aging Cell*, **6**, 111–119.
256. Smith,E.D., Tsuchiya,M., Fox,L.A., Dang,N., Hu,D., Kerr,E.O., Johnston,E.D., Tchao,B.N., Pak,D.N., Welton,K.L., *et al.* (2008) Quantitative evidence for conserved longevity pathways between divergent eukaryotic species. *Genome Res*, **18**, 564–570.
257.Rogers,A.N., Chen,D., McColl,G., Czerwieniec,G., Felkey,K., Gibson,B.W., Hubbard,A., Melov,S., Lithgow,G.J. and Kapahi,P. (2011) Life span extension via eIF4G inhibition is mediated by posttranscriptional remodeling of stress response gene expression in C. elegans. *Cell Metab*, **14**, 55–66.
258.Hokimoto,S., Funakoshi-Tago,M. and Tago,K. (2023) Identification of <scp>DDX5</scp> as an indispensable activator of the glucocorticoid receptor in adipocyte differentiation. *FEBS J.*, **290**, 988–1007.
259. Kitamura,A., Nishizuka,M., Tominaga,K., Tsuchiya,T., Nishihara,T. and Imagawa,M. (2001) Expression of p68 RNA Helicase Is Closely Related to the Early Stage of Adipocyte Differentiation of Mouse 3T3-L1 Cells. *Biochem. Biophys. Res. Commun.*, **287**, 435–439.
260. Kircher,S.G., Kim,S.H., Fountoulakis,M. and Lubec,G. (2002) Reduced Levels of DEAD-Box Proteins DBP-RB and p72 in Fetal Down Syndrome Brains. *Neurochem. Res.*, **27**, 1141–1146.
261. Giovanni Meola, Karlie Jones, Christina Wei and Lubov T Timchenko (2013) Dysfunction of protein homeostasis in myotonic dystrophies. *Histol Histopathol .*, **28**, 1089–1098.
262.Jones,K., Wei,C., Schoser,B., Meola,G., Timchenko,N. and Timchenko,L. (2015) Reduction of toxic RNAs in myotonic dystrophies type 1 and type 2 by the RNA helicase p68/DDX5. *Proc. Natl. Acad. Sci.*, **112**, 8041–8045.
263. Kovalev,N., Barajas,D. and Nagy,P.D. (2012) Similar roles for yeast Dbp2 and Arabidopsis RH20 DEAD-box RNA helicases to Ded1 helicase in tombusvirus plus-strand synthesis. *Virology*, **432**, 470–484.
264. Zhang,L., Li,L.X., Zhou,J.X., Harris,P.C., Calvet,J.P. and Li,X. (2020) RNA helicase p68 inhibits the transcription and post-transcription of *Pkd1* in ADPKD. *Theranostics*, **10**, 8281–8297.
265.Laurent,F.-X., Sureau,A., Klein,A.F., Trouslard,F., Gasnier,E., Furling,D. and Marie,J. (2012) New function for the RNA helicase p68/DDX5 as a modifier of MBNL1 activity on expanded CUG repeats. *Nucleic Acids Res.*, **40**, 3159–3171.
266.Allmang,C., Mitchell,P., Petfalski,E. and Tollervey,D. (2000) Degradation of ribosomal RNA precursors by the exosome. *Nucleic Acids Res*, **28**, 1684–1691.
267. Lebreton,A. and Seraphin,B. (2008) Exosome-mediated quality control: substrate recruitment and molecular activity. *Biochim Biophys Acta*, **1779**, 558–565.
268.Mitchell,P., Petfalski,E., Shevchenko,A., Mann,M. and Tollervey,D. (1997) The exosome: A conserved eukaryotic RNA processing complex containing multiple 3'→5' exoribonucleases. *Cell*, **91**, 457–466.
269. Anderson,J.S. and Parker,R.P. (1998) The 3' to 5' degradation of yeast mRNAs is a general mechanism for mRNA turnover that requires the SKI2 DEVH box protein and 3' to 5' exonucleases of the exosome complex. *EMBO J*, **17**, 1497–1506.
270.Vaňáčová,Š., Wolf,J., Martin,G., Blank,D., Dettwiler,S., Friedlein,A., Langen,H., Keith,G. and Keller,W. (2005) A new yeast poly(A) polymerase complex involved in RNA quality control. *PLoS Biol.*, **3**, 0986–0997.
271.Dominguez,D., Altmann,M., Benz,J., Baumann,U. and Trachsel,H. (1999) Interaction of translation initiation factor eIF4G with eIF4A in the yeast Saccharomyces cerevisiae. *J Biol*

*Chem*, **274**, 26720–26726.
272.Tarun,J., Wells,S.E., Deardorff,J.A. and Sachs,A.B. (1997) Translation initiation factor eIF4G mediates in vitro poly(A) tail- dependent translation. *Proc. Natl. Acad. Sci. U. S. A.*, **94**, 9046–9051.
273.Clarkson,B.K., Gilbert,W. V. and Doudna,J.A. (2010) Functional Overlap between eIF4G Isoforms in Saccharomyces cerevisiae. *PLoS One*, **5**, e9114.
274. Steinmetz,E.J., Conrad,N.K., Brow,D.A. and Corden,J.L. (2001) RNA-binding protein Nrd1 directs poly(A)-independent 3'-end formation of RNA polymerase II transcripts. *Nature*, **413**, 327–331.
275. Ursic,D., Himmel,K.L., Gurley,K.A., Webb,F. and Culbertson,M.R. (1997) The yeast SEN1 gene is required for the processing of diverse RNA classes. *Nucleic Acids Res*, **25**, 4778–4785.
276.Ursic,D., Chinchilla,K., Finkel,J.S. and Culbertson,M.R. (2004) Multiple protein/protein and protein/RNA interactions suggest roles for yeast DNA/RNA helicase Sen1p in transcription, transcription-coupled DNA repair and RNA processing. *Nucleic Acids Res*, **32**, 2441–2452.
277. Libri,D., Dower,K., Boulay,J., Thomsen,R., Rosbash,M. and Jensen,T.H. (2002) Interactions between mRNA export commitment, 3'-end quality control, and nuclear degradation. *Mol Cell Biol*, **22**, 8254–8266.
278. Zenklusen,D., Vinciguerra,P., Wyss,J.C. and Stutz,F. (2002) Stable mRNP formation and export require cotranscriptional recruitment of the mRNA export factors Yra1p and Sub2p by Hpr1p. *Mol Cell Biol*, **22**, 8241–8253.
279. Assenholt,J., Mouaikel,J., Andersen,K.R., Brodersen,D.E., Libri,D. and Jensen,T.H. (2008) Exonucleolysis is required for nuclear mRNA quality control in yeast THO mutants. *RNA*, **14**, 2305–2313.
280.Gudipati,R.K., Xu,Z., Lebreton,A., Seraphin,B., Steinmetz,L.M., Jacquier,A. and Libri,D. (2012) Extensive degradation of RNA precursors by the exosome in wild-type cells. *Mol Cell*, **48**, 409–421.
281. Schneider,C., Kudla,G., Wlotzka,W., Tuck,A. and Tollervey,D. (2012) Transcriptome-wide analysis of exosome targets. *Mol Cell*, **48**, 422–433.
282.Kuai,L., Das,B. and Sherman,F. (2005) A nuclear degradation pathway controls the abundance of normal mRNAs in *Saccharomyces cerevisiae*. *Proc. Natl. Acad. Sci.*, **102**, 13962–13967.
283.Brouwer,R., Pruijn,G.J.M. and van Venrooij,W.J. (2001) The human exosome: An autoantigenic complex of exoribonucleases in myositis and scleroderma. *Arthritis Res.*, **3**, 102–106.
284. Smith,E.D., Tsuchiya,M., Fox,L.A., Dang,N., Hu,D., Kerr,E.O., Johnston,E.D., Tchao,B.N., Pak,D.N., Welton,K.L., *et al.* (2008) Quantitative evidence for conserved longevity pathways between divergent eukaryotic species. *Genome Res.*, **18**, 564–570.
285. Contreras,V., Richardson,M.A., Hao,E. and Keiper,B.D. (2008) Depletion of the cap-associated isoform of translation factor eIF4G induces germline apoptosis in C. elegans. *Cell Death Differ.*, **15**, 1232–1242.
286. Sarkar,D., Paira,S. and Das,B. (2017) Nuclear mRNA degradation tunes the gain of the unfolded protein response in Saccharomyces cerevisiae. *Nucleic Acids Res*, 10.1093/nar/gkx11604641908 [pii].