Nonsense-mediated mRNA decay and metal ion homeostasis and detoxification in *Saccharomyces cerevisiae*

Xinyi Zhang · Bessie W. Kebaara

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Abstract The highly conserved Nonsense-mediated mRNA decay (NMD) pathway is a translation dependent mRNA degradation pathway. Although NMD is best known for its role in degrading mRNAs with premature termination codons (PTCs) generated during transcription, splicing, or damage to the mRNAs, NMD is now also recognized as a pathway with additional important functions. Notably, NMD precisely regulates protein coding natural mRNAs, hence controlling gene expression within several physiologically significant pathways. Such pathways affected by NMD include nutritional bio-metal homeostasis and metal ion detoxification, as well as cross-talk between these pathways. Here, we focus on the relationships between NMD and various metal homeostasis and detoxification pathways. We review the described role that the NMD pathway plays in magnesium, zinc, iron, and copper homeostasis, as well as cadmium detoxification.

Keywords Nonsense-mediated mRNA decay (NMD) · Metal ions · Magnesium · Zinc · Copper · Iron

The NMD pathway

The highly conserved Nonsense-mediated mRNA degradation (NMD) pathway is a translation dependent mRNA degradation pathway. Although it is best known as a surveillance pathway that degrades mRNAs with premature termination codons (PTCs) due to errors during transcription, splicing, or damage to the mRNA, NMD is now also recognized to possess additional functions. Previous studies have elucidated NMD as a regulatory pathway for gene expression through controlling the expression of fully functional protein-coding natural mRNAs. The targeting of natural mRNAs by NMD has been observed in multiple organisms including *Saccharomyces cerevisiae*, *Drosophila melanogaster*, *Arabidopsis*, *Caenorhabditis elegans*, and humans (Cheng and Maquat 1993; Drechsel et al. 2013; Fribourg et al. 2003; Karousis and Mühlemann 2022; Kim and Maquat 2019; Kurosaki et al. 2019; Peccarelli and Kebaara 2014; Peltz et al. 1993).

The proteins that are required for NMD to function are three highly conserved up-frameshift (UPF) factors: Upf1, Upf2 and Upf3 proteins. (Cui et al. 1995; He and Jacobson 1995; Sun et al. 1998). Involvement of these three proteins in NMD was originally identified in *S. cerevisiae* (He et al. 1993; He et al. 1997; Leeds et al. 1991) and later found in multicellular eukaryotes (Hodgkin et al. 1989; Pulak and Anderson 1993; Serin et al. 2001; Sun et al. 1998). In *C. elegans* and other multicellular organisms, NMD is regulated

X. Zhang · B. W. Kebaara (*)
Department of Biology, Baylor University, One Bear Place #97388, Waco, TX 76798, USA
e-mail: Bessie_Kebaara@baylor.edu
by Suppressors with Morphological effects on Genitalia (SMG) factors (Pulak and Anderson 1993). SMG1, SMG5, SMG6, SMG7, SMG8, and SMG9 perform a variety of functions including regulating the phosphorylation status of Upf1p (Cali et al. 1999; Grimson et al. 2004; Ohnishi et al. 2003; Yamashita et al. 2009).

In S. cerevisiae, hundreds of endogenous RNA Polymerase II transcripts achieve steady-state levels that are dependent on NMD. Changes in the accumulation of NMD-sensitive transcripts are sometimes associated with a change in the rate of mRNA decay. Transcripts that behave in this manner are referred to as direct targets of NMD. For others, NMD-sensitive changes in steady-state accumulation are not always accompanied by altered decay rates. These transcripts are referred to as indirect targets of NMD (Guan et al. 2006). A model accounting for indirect targets was proposed on the basis that mRNAs encoding several transcription factors are sensitive to NMD. Changes in the abundance of these transcription factors might cause changes in the rates of transcription of downstream-regulated genes in NMD-deficient cells, which could indirectly affect their abundance (Dahlseid et al. 2003).

S. cerevisiae has been extensively used as a model to study the regulation of natural mRNAs by NMD and several NMD targeting features have been described in previous studies. Characterized NMD-inducing features in S. cerevisiae include inefficiently or nonproductive alternatively spliced pre-mRNAs (He et al. 1993; Kawashima et al. 2014), mRNAs containing atypically long 3′ untranslated regions (UTRs) (Kebaara and Atkin 2009; Muhlrad and Parker 1999), mRNAs containing upstream open reading frames (uORFs) (Gaba et al. 2005; Guan et al. 2006), mRNAs subject to programmed ribosomal frameshifting, and mRNAs subject to out-of-frame translation initiation caused by leaky ribosomal scanning (Guan et al. 2006; Parker 2012; Welch and Jacobson 1999).

The abovementioned NMD targeting features have been found to target mRNAs to NMD in multiple organisms (Peccarelli and Kebaara 2014). A highly conserved NMD targeting mechanism is the presence of atypically long 3′-UTRs (Kebaara and Atkin 2009; Peccarelli and Kebaara 2014). In S. cerevisiae, mRNA 3′-UTRs are fairly short and typically range in size from 50 to 200 nucleotides (nts) with a median size of ~121 nts (Graber et al. 2002). In general, mRNAs with 3′-UTRs that are 350 nts or longer are considered atypically long and are likely to be regulated by NMD (Deliz-Aguirre et al. 2011; Kebaara and Atkin 2009). Furthermore, some mRNAs produce different isoforms of the same mRNA that vary in their 5′ and 3′-UTR lengths. These mRNA isoforms may have different sensitivity to NMD. Genes produce multiple transcripts that vary in the 3′-UTR lengths because of alternative 3′-end processing. Moreover, mRNA 3′-end processing can be sensitive to growth conditions, and varying environmental conditions may produce mRNA isoforms of varying lengths (Kim Guisbert et al. 2007). Thus, genes that produce mRNA isoforms of different 3′-UTR length may generate one form of the transcript that is degraded by NMD while the other may not be regulated by the pathway (Peccarelli et al. 2016).

In addition to 3′-end processing, transcript heterogeneity at the 5′-end is particularly relevant for NMD targeting. The use of different transcription start sites (TSSs) may generate mRNAs with distinct 5′-UTRs that could include uORFs. uORFs are potent regulatory elements located in 5′-UTRs of transcripts that can inhibit the translation of the downstream main ORF, but some uORFs enhance expression. If the uORF of an mRNA is translated, the stop codon can be recognized as a PTC, resulting in degradation of the mRNA by NMD. However, several naturally occurring uORF-containing transcripts are resistant to NMD. For example, yeast GCN4 and YAP1 contain uORFs and are resistant to NMD because they contain stabilizer elements (STEs) in the 5′-UTR that inactivate NMD (Ruiz-Echevarría et al. 1998; Vilela et al. 1998). Pub1p was identified as the factor that interacts with the leader region of the YAP1 transcript (Ruiz-Echevarría and Peltz 2000). STE-containing transcripts are destabilized in the pub1 Δ strain (Ruiz-Echevarría and Peltz 2000). On the other hand, CPA1 mRNA containing uORF is sensitive to NMD pathway (Gaba et al. 2005; Guan et al. 2006; F. He et al. 2003). Thus, transcripts containing uORFs may be substrates for NMD mediated degradation while the ones containing STEs may not be regulated by the pathway.

In addition to containing NMD-targeting features that activate their degradation, regulation of natural mRNAs occurs in specific cellular contexts and environmental conditions. Multiple conditions affect
NMD-mediated degradation of mRNAs. Here we focus on NMD-mediated control of genes involved in bio-metal homeostasis and metal ion detoxification. We review the described role NMD plays in magnesium, zinc, iron, and copper homeostasis and cadmium detoxication.

**Magnesium, zinc, copper, and iron homeostasis in yeast**

Bio-metals are essential for normal cellular functions but can be highly toxic. Organisms have evolved subtle mechanisms to utilize essential metals and to detoxify excess toxic levels. Magnesium (Mg^{2+}) is an essential metal that serves as a cofactor for many cellular enzymes and is required for normal cellular growth. Yeast cells regulate cytoplasmic magnesium levels and store magnesium in the vacuole and mitochondria. In yeast, magnesium homeostasis is regulated by the controlled activity of magnesium uptake transporters in the plasma membrane and transporters responsible for intracellular magnesium storage. **ALR1** and **ALR2** were the first magnesium transporters identified on the plasma membrane (MacDiarmid and Gardner 1998). Yeast strains lacking **ALR** gene activity require additional magnesium for growth, and expression of either **ALR1** or **ALR2** corrects the magnesium requiring phenotype (MacDiarmid and Gardner 1998). Yeast strains lacking **ALR** gene activity require additional magnesium for growth, and expression of either **ALR1** or **ALR2** corrects the magnesium requiring phenotype (MacDiarmid and Gardner 1998). An additional protein, **Mnr2p** is also required for magnesium homeostasis (Pisat et al. 2009). **Mnr2p** is localized to the vacuolar membrane, implicating this organelle in magnesium storage. In magnesium replete conditions, yeast cells accumulate intracellular stores of magnesium that supports growth under magnesium deplete conditions. Expression of **MNR2** suppresses the growth defect of an **alr1Δ alr2Δ** mutant, indicating that **MNR2** could function independently of the **ALR** genes (Pisat et al. 2009). Lastly, **Mme1p** has been characterized as a mitochondrial magnesium exporter in yeast (Cui et al. 2015). When yeast cells are grown in magnesium deplete conditions, mitochondrial transporters reallocate mitochondrial magnesium to the cytoplasm for immediate use.

It is believed that nearly 10% of the eukaryotic proteome requires zinc to function (Bird and Wilson 2020). Zinc can function catalytically at active sites of enzymes or structurally as zinc fingers (Eide 2009). Cells have evolved homeostatic mechanisms to cope with zinc deplete or replete conditions. Transcriptional response to zinc deplete conditions is facilitated by **Zap1p**. **Zap1p** regulates target genes by binding to the Zap1 responsive elements (ZREs) in the promoters of target genes (Eide 2009). For a majority of the genes **Zap1p** activates transcription, but for a few genes **Zap1p** represses transcription (Eide 2009). A primary function of **Zap1p** activated genes is zinc uptake. Zinc specific transporters are encoded by **ZRT1** and **ZRT2** (Zhao and Eide 1996a, b), while **FET4** transports zinc, copper, and iron (Eide 2009). **Zrt1p** provides high affinity zinc uptake while **Zrt2p** functions in low affinity zinc uptake (Zhao and Eide 1996a, b). The expression of **ZRT1** is regulated at post-translational level as well. The post-translational inactivation of **Zrt1p** is important for zinc homeostasis and may be an important mechanism for preventing cadmium uptake and toxicity in zinc-limited cells (Gitan et al. 2003). Under zinc replete conditions, yeast cells store zinc in the vacuole. This prevents excessive zinc mediated toxicity and further provides a zinc source in zinc deplete conditions. **Cot1p** and **Zrc1p** mediate zinc storage (Eide 2009). Additionally, **ZRT3** encodes a Zap1p regulated protein that transports zinc out of the vacuole in zinc deplete conditions.

Copper is essential for multiple cellular functions in eukaryotes. In yeast, it serves as an important cofactor for enzymes, including cytochrome c oxidase for respiration and Cu, Zn-superoxide dismutase (Sod1) for oxidative stress protection (Karlin 1993; Linder and Hazegh-Azam 1996). As copper is a redox-active metal with two forms, Cu^{2+} and Cu^{+}, oxidative damage of macromolecules can occur when copper accumulates to excessive amounts within the cell (Halliwell and Gutteridge 1984). Copper-responsive transcriptional regulation is of importance in fungi, where a variety of factors control genes required for copper uptake and detoxification (Bird 2008). Intracellular [Cu]_{free} is limited to less than one free copper ion per cell, and a pool of free copper ions is not used in the physiological activation of metalloenzymes (Rae et al. 1999).

Iron (Fe^{2+}) is an essential element for all eukaryotes and functions as a cofactor for many enzymes involved in cellular functions including DNA replication and repair, cellular respiration, photosynthesis, oxygen transport, lipid metabolism and...
Studies have shown that iron acquisition systems in yeast are regulated at the transcriptional and post-transcriptional levels (Martins et al. 2018). Under iron deplete conditions, yeast cells initiate iron uptake, activate intracellular iron stores, and undergo metabolic adaptations to iron deficiency. Under these conditions, yeast cells activate a group of genes known as the iron regulon which includes genes involved in high-affinity iron uptake. The yeast AFT1 and AFT2 paralogs are the major transcription factors that regulate the activation of genes in iron deplete conditions (Martinez-Pastor et al. 2017). Aft1p is constitutively expressed even under iron replete conditions but does not activate transcription. However, under low iron conditions, Aft1p is imported from the cytoplasm to the nucleus and activates transcription of genes required for iron uptake from the environment, mobilization of stored iron, and metabolic changes that occur under iron deplete conditions (Bird 2008). Post-transcriptional control under iron deplete conditions involves Cth1 and Cth2 proteins, two tristetraprolin family members that interact directly with target mRNAs through adenosine and uridine rich elements (AREs) in the 3′-UTRs of the mRNAs. Cth1 and Cth2 proteins downregulate mRNAs that encode proteins involved in many iron-dependent processes, thus resulting in conservation and metabolic adjustment to iron availability (Bird 2008; Puig et al. 2005, 2008).

Copper and iron homeostasis are linked and NMD plays a role in both bio-metal homeostatic mechanisms as discussed below (Deliz-Aguirre et al. 2011; Guan et al. 2006; Peccarelli et al. 2016; Peccarelli et al. 2019; Wang et al. 2013). Copper is required for iron acquisition and both metals are essential elements that function in multiple metabolic pathways. Although copper and iron are required for normal cellular function, excessive amounts of either metal can lead to oxidative damage of macromolecules. Thus, cells have evolved subtle ways for homeostatic metabolism of copper and iron. Furthermore, defects in copper and iron homeostasis are implicated in several human diseases. These include defects in growth and development, organ damage, degenerative diseases, anemia, and cancer.

NMD and magnesium homeostasis

Inactivation of the NMD pathway can cause ribosome readthrough of some nonsense and frameshift mutations resulting in nonsense suppression (Wu et al. 2020). Ribosome readthrough of the three stop codons (UGA, UAA and UAG) depends on various factors, including the specific stop codon (Wu et al. 2020). To understand how NMD factors affect the efficiency of translation, Johansson and Jacobsson (2010) screened for mutations that counteract nonsense suppression of NMD mutants. One complementation group identified strains with mutations in ALR1, which as described above, encodes a plasma membrane transporter required for efficient magnesium uptake (Graschopf et al. 2001; MacDiarmid and Gardner 1998). A mutation in the ALR1 gene eliminates the translation termination defect of NMD deficient cells. Notably, ALR1 and the closely related gene ALR2 encode mRNAs that are directly regulated by NMD (Table 1) (Johansson and Jacobson 2010). The reduced translational fidelity in NMD mutants is due to increased Alr1p and Alr2p and consequently elevated intracellular level of magnesium. Magnesium influences translational fidelity because increasing magnesium concentrations increases readthrough at nonsense codons and misreading at sense codons. The reduced translational fidelity seen in NMD mutants is an indirect consequence of elevated Alr1p levels. Additionally, the NMD targeting feature of the ALR1 mRNA was identified as a uORF (Johansson and Jacobson 2010). Thus, NMD and magnesium homeostasis are interlinked, and precise regulation of both processes is essential for normal cellular function.

NMD and zinc homeostasis

Transcription of non-coding RNA (ncRNA) close to protein coding genes has been shown to function as a mode of transcriptional control (Neil et al. 2009). Most ncRNAs found to regulate gene expression in S. cerevisiae are antisense transcripts (e.g., PHO84, Ty1 and GAL10 locus) which control chromatin modification marks at these genes (Berretta et al. 2008; Camblong et al. 2007, 2009; Houseley et al. 2008). Toesca et al. (2011) showed that S. cerevisiae NMD mutants accumulate 5′-extended RNAs (CD-CUTs) produced
from cryptic upstream transcription. Transcription of these CD-CUTs mediates repression at promoters by preventing premature binding of RNA polymerase II in conditions of metal repletion. CD-CUTs are targeted by cytoplasmic turnover pathways that include the exoribonuclease Xrn1p and the core NMD factor Upf1p. Importantly, CD-CUT transcription or accumulation also interferes with binding of the transcriptional activators AFT1 and ZAP1, which modulate transcriptional accumulation of metal homeostasis.

Table 1 Genes encoding mRNAs involved in metal homeostasis and regulated by NMD

| Metal ion | mRNA regulated by NMD and the function of the encoded protein | References |
|-----------|---------------------------------------------------------------|-------------|
| Magnesium | ALR1- Plasma membrane protein required for efficient magnesium uptake, essential gene | (Guan et al. 2006; Johansson et al. 2007; Johansson and Jacobson 2010) |
| Zinc      | ZRT1—High-affinity zinc transporter of the plasma membrane | (Johansson et al. 2007; Toesca et al. 2011) |
| Copper    | CTR2- Copper transporter of the vacuolar membrane CTR3- High-affinity copper transporter of the plasma membrane MAC1- Copper-sensing transcription factor involved in regulation of genes required for high affinity copper transport COX19- Protein requires for cytochrome c oxidase assembly COX23- Mitochondrial intermembrane space protein that functions in mitochondrial copper homeostasis, important for functional cytochrome oxidase expression COX17- Copper metallochaperone that delivers copper to cytochrome c oxidase (CcO) through two copper-binding intermembrane space-associated proteins Sco1 and Cox11 CRS5- Copper-binding metallothionein PCA1- Cadmium transporting P-type ATPase; may also have a role in copper and iron homeostasis |
| Cadmium   | PCA1- Cadmium transporting P-type ATPase; may also have a role in copper and iron homeostasis | (Guan et al. 2006; Wong et al. 2021) |
| Iron      | FRE2- Ferric and cupric reductase reduces siderophore-bound Fe^{2+} and oxidized copper prior to uptake by transporters. Expression induced by low Fe^{2+} levels FRE3- Ferric reductase; reduces siderophore-bound Fe^{2+} prior to uptake by transporters; expression induced by low Fe^{2+} levels FRE6- Putative ferric reductase with similarity to Fre2p; expression induced by low Fe^{2+} levels. Reduces vacuolar Fe^{2+} and copper prior to export to the cytosol AFT2- AFT2 is a paralog of AFT1. AFT2 is a transcription factor that activates genes required for Fe^{2+} homeostasis and resistance to oxidative stress ARN1- A ferrichrome-type siderophore transporter ARN2- A member of the ARN family of transporters that recognizes siderophore-iron chelates ENB1 (ARN4)- Ferric enterobactin transmembrane transporter FET3- Ferrous iron transporter FIT1- Cell wall mannoprotein facilitating iron uptake FIT3- Cell wall mannoprotein facilitating iron uptake | (Guan et al. 2006; Johansson et al. 2007; Peccarelli et al. 2019; Toesca et al. 2011) |
mRNAs such as \textit{FIT3} and \textit{ZRT1} (Table 1). \textit{FIT3} and \textit{ZRT1} are involved in iron homeostasis and zinc homeostasis, respectively. Thus, NMD controls the accumulation of transcripts that negatively interfere with the transcription of genes involved in zinc and iron homeostasis (Toesca et al. 2011).

**The role NMD plays in copper homeostasis**

Global expression profiling studies identified genes involved in copper homeostasis as potential NMD targets in \textit{S. cerevisiae}. These genes include \textit{CTR2, CTR3, MAC1, COX23, CRS5, PCA1, FRE2} and \textit{COX19} (Table 1) (Guan et al. 2006; Johansson et al. 2007). The proteins encoded by these eight mRNAs are involved in various aspects of copper homeostasis. \textit{MAC1} is a transcription factor which plays a vital role in regulating high-affinity copper uptake system (Yamaguchi-Iwai et al. 1997). Mac1 protein comprises an N-terminal DNA-binding copper-fist domain and a C-terminal half responsible for transactivation, including two cysteine-rich sequences that bind to a total of eight Cu(I) ions (Graden and Winge 1997). Copper inactivates Mac1p due to an intramolecular interaction between the N- and C-terminal cysteine-rich motifs by the formation of a poly-copper cluster (Jensen and Winge 1998). In response to copper deplete conditions, Mac1p binds to Cu-responsive \textit{cis}-acting (CuRE) promoter elements of target genes and activates the high-affinity copper uptake systems encoded by \textit{CTR1} and \textit{CTR3} (Fig. 1). (Peña et al. 1998).

The \textit{MAC1} transcript was first identified as a potential NMD substrate because it preferentially associates with Upf1p (Johansson et al. 2007). Subsequently, it was confirmed that \textit{MAC1} mRNA is a direct NMD target in rich media with altered decay rates in wild-type and NMD mutant strains (Peccarelli et al. 2016). \textit{MAC1} encodes two transcripts that differ in their 3’-UTR length. Interestingly, under low copper conditions, two predominant \textit{MAC1} transcripts are transcribed. The decay rates of both \textit{MAC1} mRNA isoforms encoded under low copper vary as compared to the decay of \textit{MAC1} mRNA in rich media (Peccarelli et al. 2016). Under low copper conditions, both \textit{MAC1} mRNA isoforms evade NMD despite having atypical long 3’-UTRs (Peccarelli et al. 2016) (Fig. 1). Thus, regulation of \textit{MAC1} mRNA isoforms

![Fig. 1 Schematic representation of condition specific NMD regulation of genes involved in copper homeostasis in \textit{S. cerevisiae}. An arrow pointing to an mRNA from Upf1p indicates NMD regulates the mRNA, an X through the arrow indicates that NMD does not regulate the mRNA. a Genes involved in copper homeostasis regulated by NMD under normal growth conditions. \textit{MAC1, COX17, COX19, COX23} are NMD targets. Copper (Cu) is delivered to Mac1p by Ccs1p and Sod1p, thus Mac1p can no longer bind to the promoter regions of \textit{CTR1/CTR3} and \textit{FRE1/FRE7}. The detailed mechanism of Cu delivered to Cox17p is not well elucidated. Cox17p transfers Cu to Sco1p and Cox11p and eventually delivers to cytochrome c oxidase. b Condition specific NMD regulation of \textit{MAC1} and \textit{COX17} mRNAs under low copper conditions. In low copper conditions, \textit{MAC1} and \textit{COX17} mRNAs escape NMD-mediated degradation. Therefore, more Mac1p is translated, and it is not bound to Cu\textsuperscript{+}. Consequently, Mac1p binds to the transcription activation region of \textit{CTR1/CTR3} and \textit{FRE1/FRE7} genes. Mac1p also regulates the expression of two cell-surface ferric and cupric reductases encoded by \textit{FRE1} and \textit{FRE7} (L. J. Martins et al. 1998; Peña et al. 1998).](image-url)
by NMD is conditional, based on copper levels. Under low copper conditions NMD is functional as CYH2 pre-mRNA which is usually used as an NMD control is regulated by NMD in low copper (Murtha et al. 2019).

An additional mRNA involved in copper homeostasis and regulated by NMD is the CTR2 mRNA. CTR2 encodes a copper transporter of the vacuolar membrane that controls the flux of copper into the vacuole (Rees et al. 2004). S. cerevisiae CTR2 mRNAs have long 3′-UTRs that contribute to the degradation of the mRNAs by NMD (Peccarelli et al. 2014). Overexpression of CTR2 generates yeast strains with an increased copper tolerance phenotype (Peccarelli et al. 2014). This phenotype was observed in NMD mutant strains with a functional Ctr2p as well (Deliz-Aguirre et al. 2011).

In S. cerevisiae, cytochrome c oxidase requires copper to be fully functional in mitochondrial aerobic respiration. COX19 and COX23 encode proteins required for cytochrome c oxidase assembly and were identified as potential NMD targets in S. cerevisiae (Guan et al. 2006; Johansson et al. 2007). The COX19 transcript has an atypical long 3′-UTR that contributes to the degradation of the mRNA by NMD (Peccarelli et al. 2016). In rich media, COX19 was found to be a direct NMD target, while COX23 was an indirect NMD target (Peccarelli et al. 2016). COX17 is a homologous copper metallochaperone required for the assembly of cytochrome c oxidase. Cox17p transfers copper to two proteins associated with the mitochondrial intermembrane space, Sco1p and Cox11p, which eventually deliver copper to cytochrome c oxidase (Horng et al. 2004). Cox17p, Cox19p and Cox23p are required for mitochondrial copper utilization. When yeast cells were grown in varying amounts of copper, the regulation of COX17, COX19 and COX23 mRNAs by NMD was variable (Murtha et al. 2019). Specifically, COX19 mRNA was a direct NMD target under all conditions tested with varying copper levels. COX17 mRNA was directly regulated by NMD only in rich media but not under low or high copper conditions (Fig. 1). COX23 mRNA was immune to NMD under low copper conditions and was found to be an indirect target in rich media (Murtha et al. 2019).

NMD also regulates mRNAs encoding proteins involved in protection from metal toxicity. Two mRNAs found to be regulated by NMD and are involved in protection from metal toxicity are PCA1 and CRS5 (Peccarelli et al. 2016). Interestingly, both CRS5 and CUP1 genes encode metallothioneins, which bind to excessive amounts of copper in yeast cells and are differentially regulated by NMD. The major metallothionein CUP1 is induced by the ACE1 transcription factor when yeast cells are exposed to elevated copper levels (Evans et al. 1990). CRS5 is an indirect NMD target under normal growth conditions, while CUP1 is not regulated by NMD (Murtha et al. 2019; Peccarelli et al. 2016).

PCA1 mRNA is also regulated by NMD and involved in the protection of the cell from metal toxicity (Guan et al. 2006; Wong et al. 2021) PCA1 is an evolutionarily conserved P1B-type cation-transporting ATPase that is widely distributed from bacteria to humans (Rad et al. 1994). PCA1 has been proposed to be involved in copper and iron homeostasis (De Freitas et al. 2004; Rad et al. 1994). Copper resistance mediated by PCA1 is not dependent on catalytic activity but is understood that a cysteine-rich region located in the N-terminal sequesters excess copper. In addition to the PCA1 allele found in most common lab yeast strains, CAD2, an alias of PCA1 has been identified (Shirai et al. 2000). The protein encoded by CAD2 functions in the cadmium efflux system of yeast cells (hereafter referred as PCA1 970R). The PCA1 allele found in most common lab yeast strains possess a missense mutation in the ATP-binding residue conserved in P1B-type ATPases [hereafter referred as PCA1 970R; (Adle et al. 2007; Wong et al. 2021)]. In humans, a substitution in the ATP7B similar to the one found in PCA1 leads to Wilson’s disease. Wilson’s disease is characterized by excessive accumulation of copper in hepatic and neuronal tissues (Vulpe and Packman 1995).

Overall, the condition-specific regulation of mRNAs by the NMD pathway allow yeast cells to control the expression of select mRNAs in response to environmental copper conditions. The control of copper homeostasis genes occurs at multiple levels including mRNA levels via the NMD pathway. As reviewed here, the NMD pathway regulates mRNA involved with copper transport, adaptation to low copper conditions, mitochondrial copper utilization, and excess copper detoxification.
Toxic metal detoxification

Cadmium (Cd) is a non-essential and toxic environmental contaminant (Wysocki and Tamás 2010). In *S. cerevisiae*, cadmium is detoxified by ATP-binding cassette transporters after conjugation to glutathione (Prévéral et al. 2009). Pca1p is the major cadmium detoxification mechanism in yeast. In addition to PCA1, yeast cadmium factor gene (*YCF1*), a vacuolar transporter, sequesters cadmium and other heavy metals as well as glutathione into the vacuole to counter cell stress (Li et al. 1996; Li et al. 1997).

In the lab strain W303a, *PCA1 970R* mRNA was identified as an indirect NMD target in rich media (Wong et al. 2021b). The decay rate of the *PCA1 970R* mRNAs was similar in wild-type and NMD mutant strains (Guan et al. 2006; Peccarelli et al. 2016). The *PCA1* gene encodes two major transcripts. The longer *PCA1* transcript has an atypical long 3'-UTR of 650 nts and may be subject to programmed ribosomal frameshifting. These are two known NMD targeting features (Belew et al. 2011; Kebaara and Atkin 2009), suggesting that *PCA1* may be differently regulated by NMD depending on different environmental conditions.

Notably, *PCA1* transcripts produced by the natural yeast strains RM11-1a and lab strain W303a were differentially regulated by NMD in the presence of Cadmium. *PCA1 970R* mRNAs encoded by W303a were regulated by NMD under all the conditions tested, including cadmium. On the other hand, *PCA1 970G* mRNAs from RM11-1a were regulated by NMD under all conditions tested except when the cells were grown in media containing cadmium, suggesting that *PCA1 970G* transcripts may evade NMD under inducing conditions (Fig. 2). In the presence of copper, the *PCA1 970R* mRNA from W303a was an indirect NMD target. (Wong et al. 2021b).

**The role NMD plays in iron homeostasis**

As previously mentioned, Aft1p and Aft2p induce transcription of genes in the iron regulon during iron scarcity. These Aft1p and Aft2p target genes include proteins that have ferric and cupric reductase activity. Select mRNAs in this group are regulated by NMD in a manner specific to growth conditions (Peccarelli et al. 2019). *FRE1* and *FRE2* encode for the major ferric and cupric reductases in *S. cerevisiae*, and they transcribe mRNAs that are differentially regulated by NMD (Table 1). *FRE1* mRNA is induced under low copper and low iron levels, but this mRNA is not regulated by NMD under all the conditions examined. On the other hand, *FRE2* mRNAs are regulated by NMD under normal growth conditions and low copper levels, but not under low iron levels (Peccarelli et al. 2019). These results suggest that condition-specific NMD-mediated degradation of mRNAs can be selective and differential.
As previously stated, Toesca et al. 2011, reported that NMD degrades 5'-extended transcripts produced from cryptic upstream transcription from authentic promoters, and that the upstream transcription is responsible for the repression of metal homeostasis genes in conditions of metal repletion. Importantly, the CD-CUTs facilitate transcriptional repression of metal homeostasis genes such as FIT3 and ZRT1. The FIT3 and ZRT1 CD-CUTs prevent the premature binding of the RNA polymerase, or of transcriptional activators such as Zap1p and Aft1p when these genes are transcriptionally repressed. The FIT3 gene is involved in siderophore-iron transport facilitating.

NMD targets are distinguished from non-targets by an aberrant translation termination event that results in rapid degradation of NMD targets. It has been demonstrated that the essential Fe–S protein Rli1 (ABCE1 in humans), which is involved in ribosome biogenesis and recycling, is required for maintaining regulatory pathways including NMD (Zhu et al. 2020). In the absence of Rli1, unrecycled yeast ribosomes move into the 3′-UTR of the mRNA where they initiate translation abnormally and indiscriminately displace trans factors bound to the mRNAs 3′-UTR. These displaced factors include proteins bound to adenosine and uridine-rich elements (AREs) in the 3′-UTR of mRNAs, such as Cth1p and Cth2p resulting in mis-regulation of iron homeostasis (Puig et al. 2005, 2008). Conversely, mis-regulation of iron homeostasis disrupts Rli1 function, which in turn could disrupt NMD function because the translation termination event determines whether the NMD pathway will take place. Thus, NMD and iron homeostasis are also interlinked, and accurate regulation of both processes is essential for normal cellular function.

**Evolutionary aspect of NMD-mediated regulation of Bio-metal homeostasis and toxic metal detoxification**

A study on the evolution of metal resistance in natural yeast populations found that cadmium tolerance was controlled primarily by the PCA1 locus, which classifies cadmium resistance as the ancestral phenotype (Chang and Leu 2011). It is postulated that during yeast evolution, PCA1 experienced several rounds of selective adaptation on the promoter sequence (Chang and Leu 2011). Notably, yeast cells overexpressing PCA1 in a medium without cadmium suffered reduced fitness (Rad et al. 1994). As a result of a tradeoff between metal resistance and fitness, most S. cerevisiae populations contain an altered PCA1 allele (Chang and Leu 2011). This study found that the enhancement of cadmium resistance can be largely attributed to mutations in the promoter sequence.

A further study proposed that the cadmium-resistant strain was a gain-of-function mutation within PCA1 Arg970gly, generating cadmium efflux and tolerance (Shiraishi et al. 2000). Furthermore, a phylogenetic analysis based on PCA1 screened the two alleles of PCA1 970G and PCA1 970R among yeast populations and revealed that 970R was the ancestral allele while 970G evolved from that ancestral lineage (Wong et al. 2021). A single nucleotide difference at codon 970 is associated with response to cadmium (Wong et al. 2021). The 970G allele that facilitates tolerance to cadmium was the most common allele. These two studies demonstrate that the evolution of PCA1 with regards to cadmium tolerance can be in different regions of the gene. Further, the studies suggest that the evolution of metal tolerance by different yeast strains can affect the regulation of mRNAs generated from different alleles by NMD.

**Conclusions**

The importance of NMD in metal ion homeostasis and toxic metal detoxification is highlighted here. The NMD pathway regulates select mRNAs involved in magnesium, zinc, iron, and copper homeostasis, as well as cadmium detoxication. NMD is a translation dependent process that ensues once translation is terminated aberrantly, and metal ions can affect the reliability of translation. Bio-metal homeostasis is related to NMD mediated regulation of gene expression in the case of magnesium homeostasis (Johansson and Jacobson 2010), which facilitates NMD fidelity. Furthermore, translation and iron homeostasis are closely interconnected. Fe–S proteins such as Rli1 (ABCE1 in humans), are involved in ribosome biogenesis and recycling and are required for maintaining regulatory pathways including NMD. Further studies investigating the extent to which NMD regulates mRNAs involved in the adaptation of yeast cells to changes in levels of metal ions and the role these metals ions play in translation and its reliability will elucidate metal ion homeostasis and NMD. Additionally, there are likely other metal ion homeostatic mechanisms impacted by NMD that need to be explored.
In terms of specific mRNA targets regulated by NMD and involved in metal ion homeostasis, one of the questions that have arisen leads inquiries as to why there is variability in NMD-mediated regulation of the mRNAs that encode proteins with similar functions. For example, of the two copper binding metallothionein in yeast CRS5 and CUP1, CRS5 is regulated by NMD while CUP1 is not. Moreover, mRNAs encoded by different alleles are differentially regulated by NMD based on environmental conditions. For example, PCA1 970G and PCA1 970R mRNAs are differentially regulated by NMD in the presence of cadmium. It would be significant to understand how prevalent this environmentally specific differential regulation of mRNAs by NMD is.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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References

Adle DJ et al (2007) A cadmium-transporting P1B-type ATPase in yeast Saccharomyces cerevisiae. J Biol Chem 282(2):947–955

Belew AT, Advani VM, Dinman JD (2011) Endogenous ribosomal frameshift signals operate as mRNA destabilizing elements through at least two molecular pathways in yeast. Nucleic Acids Res 39(7):2799–2808

Berretta J, Pinskaya M, Morillon A (2008) A cryptic unstable transcript mediates transcriptional trans-silencing of the Ty1 retrotransposon in S. cerevisiae. Genes Dev 22(5):615–626

Bird AJ (2008) Metallosensors, the ups and downs of gene regulation. Adv Microb Physiol 53:231–267

Bird AJ, Wilson S (2020) Zinc homeostasis in the secretary pathway in yeast. Curr Opin Chem Biol 55:145–150

Cali BM et al (1999) smg-7 is required for mRNA surveillance in Caenorhabditis elegans. Genetics 151(2):605–616

Camblong J et al (2007) Antisense RNA stabilization induces transcriptional gene silencing via histone deacetylation in S. cerevisiae. Cell 131(4):706–717

Camblong J et al (2009) Trans-acting antisense RNAs mediate transcriptional gene cosuppression in S. cerevisiae. Genes Dev 23(13):1534–1545

Chang SL, Leu JY (2011) A tradeoff drives the evolution of reduced metal resistance in natural populations of yeast. PLoS Genet 7(3):e1002034

Cheng J, Maquat LE (1993) Nonsense codons can reduce the abundance of nuclear mRNA without affecting the abundance of pre-mRNA or the half-life of cytoplasmic mRNA. Mol Cell Biol 13(3):1892–1902

Cui Y et al (1995) Identification and characterization of genes that are required for the accelerated degradation of mRNAs containing a premature translational termination codon. Genes Dev 9(4):423–436

Cui Y et al (2015) A novel mitochondrial carrier protein Mme1 acts as a yeast mitochondrial magnesium exporter. Biochim Biophys Acta 3:724–732

Dahlseid JN et al (2003) mRNAs encoding telomerase components and regulators are controlled by UPF genes in Saccharomyces cerevisiae. Eukaryot Cell 2(1):134–142

De Freitas JM et al (2004) Exploratory and confirmatory gene expression profiling of mac1ΔDelta. J Biol Chem 279(6):4450–4458

Deliz-Aguirre R, Atkin AL, Kebaara BW (2011) Copper tolerance of Saccharomyces cerevisiae nonsense-mediated mRNA decay mutants. Curr Genet 57(6):421–430

Drechsel G et al (2013) Nonsense-mediated decay of alternative precursor mRNA splicing variants is a major determinant of the Arabidopsis steady state transcriptome. Plant Cell 25(10):3726–3742

Eide DJ (2009) Homeostatic and adaptive responses to zinc deficiency in Saccharomyces cerevisiae. J Biol Chem 284(28):18565–18569

Evans CF, Engelke DR, Thiele DJ (1990) ACE1 transcription factor produced in Escherichia coli binds multiple regions within yeast metallothionein upstream activation sequences. Mol Cell Biol 10(1):426–429

Fribourg S et al (2003) A novel mode of RBD-protein recognition in the Y14-Mago complex. Nat Struct Biol 10(6):433–439

Gaba A, Jacobson A, Sachs MS (2005) Ribosome occupancy of the yeast CPA1 upstream open reading frame termination codon modulates nonsense-mediated mRNA decay. Mol Cell 20(3):449–460

Gitan RS et al (2003) A cytosolic domain of the yeast Zrt1 zinc transporter is required for its post-translational
inactivation in response to zinc and cadmium. J Biol Chem 278(41):39558–39564

Graber BH, McAllister GD, Smith TF (2002) Probabilistic prediction of Saccharomyces cerevisiae mRNA 3'-processing sites. Nucleic Acids Res 30(8):1851–1858

Graden JA, Winge DR (1997) Copper-mediated repression of the activation domain in the yeast Mac1p transcription factor. Proc Natl Acad Sci U S A 94(11):5550–5555

Graschopf A et al (2001) The yeast plasma membrane protein Afl1 controls Mg2+ homeostasis and is subject to Mg2+-dependent control of its synthesis and degradation. J Biol Chem 276(19):16216–16222

Grimson A et al (2004) SMG-1 is a phosphatidylinositol kinase-related protein kinase required for nonsense-mediated mRNA decay in Caenorhabditis elegans. Mol Cell Biol 24(17):7483–7490

Guan Q et al (2006) Impact of nonsense-mediated mRNA decay on the global expression profile of budding yeast. PLoS Genet 2(11):e203

Halliwell B, Gutteridge JM (1984) Oxygen toxicity, oxygen radicals, transition metals and disease. Biochem J 219(1):1–14

He F, Jacobson A (1995) Identification of a novel component of the nonsense-mediated mRNA decay pathway by use of an interacting protein screen. Genes Dev 9(4):437–454

He F et al (1993) Stabilization and ribosome association of unspliced pre-mRNAs in a yeast upf1- mutant. Proc Natl Acad Sci U S A 90(15):7034–7038

He F, Brown AH, Jacobson A (1997) Upf1p, Nmd2p, and Upf3p are interacting components of the yeast nonsense-mediated mRNA decay pathway. Mol Cell Biol 17(3):1580–1594

He F et al (2003) Genome-wide analysis of mRNAs regulated by the nonsense-mediated and 5’ to 3’ mRNA decay pathways in yeast. Mol Cell 12(6):1439–1452

Hodgkin J et al (1989) A new kind of informational suppression in the nematode Caenorhabditis elegans. Genetics 123(2):301–313

HorngYC et al (2004) Specific copper transfer from the Cox17 metallochaperone to both Sco1 and Cox11 in the assembly of yeast cytochrome C oxidase. J Biol Chem 279(34):35334–35340

Houseley J et al (2008) AcRNA modulates histone modification and mRNA induction in the yeast GAL gene cluster. Mol Cell 32(5):685–695

Jensen LT, Winge DR (1998) Identification of a copper-induced intramolecular interaction in the transcription factor Mac1 from Saccharomyces cerevisiae. EMBO J 17(18):5400–5408

Johansson MJ, Jacobson A (2010) Nonsense-mediated mRNA decay maintains translational fidelity by limiting magnesium uptake. Genes Dev 24(14):1491–1495

Johansson MJ et al (2007) Association of yeast Upf1p with direct substrates of the NMD pathway. Proc Natl Acad Sci U S A 104(52):20872–20877

Karlin KD (1993) Metalloenzymes, structural motifs, and inorganic models. Science 261(5122):701–708

Karousis ED, Mühlemann O (2022) The broader sense of nonsense. Trends Biochem Sci. https://doi.org/10.1016/j.tibs.2022.06.003

Kawashima T et al (2014) Widespread use of non-productive alternative splice sites in Saccharomyces cerevisiae. PLoS Genet 10(4):e1004249

Kebaara BW, Atkin AL (2009) Long 3’-UTRs target wild-type mRNAs for nonsense-mediated mRNA decay in Saccharomyces cerevisiae. Nucleic Acids Res 37(9):2771–2778

Kim Guisbert KS, Li H, Guthrie C (2007) Alternative 3’ pre-mRNA processing in Saccharomyces cerevisiae is modulated by Nab4/Hrp1 in vivo. PLoS Biol 5(1):e6

Kim YK, Maquat LE (2019) UPFront and center in RNA decay: UPF1 in nonsense-mediated mRNA decay and beyond. RNA 25(4):407–422

Kurotsuki T, Popp MW, Maquat LE (2019) Quality and quantity control of gene expression by nonsense-mediated mRNA decay. Nat Rev Mol Cell Biol 20(7):406–420

Leeds P et al (1991) The product of the yeast UPF1 gene is required for rapid turnover of mRNAs containing a premature translational termination codon. Genes Dev 5(12a):2303–2314

Li ZS et al (1996) The yeast cadmium factor protein (YCF1) is a vacuolar glutathione S-conjugate pump. J Biol Chem 271(11):6509–6517

Li ZS et al (1997) A new pathway for vacuolar cadmium sequestration in Saccharomyces cerevisiae: YCF1-catalyzed transport of bis(glutathionato)cadmium. Proc Natl Acad Sci U S A 94(1):42–47

Linder MC, Hazegh-Azam M (1996) Copper biochemistry and molecular biology. Am J Clin Nutr 63(5):797S–811S

MacDiamid CW, Gardner RC (1998) Overexpression of the Saccharomyces cerevisiae magnesium transport system confers resistance to aluminum ion. J Biol Chem 273(3):1727–1732

Martinez-Pastor MT, Perea-Garcia A, Puig S (2017) Mechanisms of iron sensing and regulation in the yeast Saccharomyces cerevisiae. World J Microbiol Biotechnol 33(4):75

Martins LJ et al (1998) Metalloregulation of FRE1 and FRE2 homologs in Saccharomyces cerevisiae. J Biol Chem 273(37):23716–23721

Martins TS, Costa V, Pereira C (2018) Signaling pathways governing iron homeostasis in budding yeast. Mol Microbiol 109(4):422–432

Muhlrad D, Parker R (1999) Aberrant mRNAs with extended 3’ UTRs are substrates for rapid degradation by mRNA surveillance. RNA 5(10):1299–1307

Murftha K et al (2019) The nonsense-mediated mRNA decay (NMD) pathway differentially regulates COX17, COX19 and COX23 mRNAs. Curr Genet 65(2):507–521

Neil H et al (2009) Widespread bidirectional promoters are the major source of cryptic transcripts in yeast. Nature 457(7232):1038–1042

Ohnishi T et al (2003) Phosphorylation of hUPF1 induces formation of mRNA surveillance complexes containing hSMG-5 and hSMG-7. Mol Cell 12(5):1187–1200

Parker R (2012) RNA degradation in Saccharomyces cerevisiae. Genetics 191(3):671–702

Peccarelli M, Kebara BW (2014) Regulation of natural mRNAs by the nonsense-mediated mRNA decay pathway. Eukaryot Cell 13(9):1126–1135
Peccarelli M et al (2014) Regulation of CTR2 mRNA by the nonsense-mediated mRNA decay pathway. Biochim Biophys Acta 1839(11):1283–1294

Peccarelli M et al (2016) mRNAs involved in copper homeostasis are regulated by the nonsense-mediated mRNA decay pathway depending on environmental conditions. Fungal Genet Biol 86:81–90

Peccarelli M, Scott TD, Kebaara BW (2019) Nonsense-mediated mRNA decay of the ferric and cupric reductase mRNAs FRE1 and FRE2 in Saccharomyces cerevisiae. FEBS Lett. https://doi.org/10.1002/1873-3468.13545

Peltz SW, Brown AH, Jacobson A (1993) mRNA destabilization triggered by premature translational termination depends on at least three cis-acting sequence elements and one trans-acting factor. Genes Dev 7(9):1737–1754

Peña MM, Koch KA, Thiele DJ (1998) Dynamic regulation of copper uptake and detoxification genes in Saccharomyces cerevisiae. Mol Cell Biol 18(5):2514–2523

Pisat NP, Pandey A, Macdiarmid CW (2009) MNR2 regulates intracellular magnesium storage in Saccharomyces cerevisiae. Genetics 183(3):873–884

Prévéral S et al (2009) A common highly conserved cadmium detoxification mechanism from bacteria to humans: heavy metal tolerance conferred by the ATP-binding cassette (ABC) transporter SpHMT1 requires glutathione but not metal-chelating phytochelatin peptides. J Biol Chem 284(8):4936–4943

Puig S, Askeland E, Thiele DJ (2005) Coordinated remodeling of cellular metabolism during iron deficiency through targeted mRNA degradation. Cell 120(1):99–110

Puig S, Vergara SV, Thiele DJ (2008) Cooperation of two mRNA-binding proteins drives metabolic adaptation to iron deficiency. Cell Metab 7(6):555–564

Pulak R, Anderson P (1993) mRNA surveillance by the Caenorhabditis elegans smg genes. Genes Dev 7(10):1885–1897

Rad MR, Kirchrath L, Hollenberg CP (1994) A putative P-type Ca2+-transporting ATPase gene on chromosome II of Saccharomyces cerevisiae. Yeast 10(9):1217–1225

Rae TD et al (1999) Undetectable intracellular free copper: the requirement of a copper chaperone for superoxide dismutase. Science 284(5415):805–808

Rees EM, Lee J, Thiele DJ (2004) Mobilization of intracellular copper stores by the ctr2 vacuolar copper transporter. J Biol Chem 279(52):54221–54229

Romero AM, Martinez-Pastor MT, Puig S (2021) Iron in translation: from the beginning to the end. Microorganisms 9(5):1058

Ruiz-Echevarría MJ, Peltz SW (2000) The RNA binding protein Pub1 modulates the stability of transcripts containing upstream open reading frames. Cell 101(7):741–751

Ruiz-Echevarría MJ, González CI, Peltz SW (1998) Identifying the right stop: determining how the surveillance complex recognizes and degrades an aberrant mRNA. Embo j 17(2):575–589

Serin G et al (2001) Identification and characterization of human orthologues to Saccharomyces cerevisiae Upf2 protein and Upf3 protein (Caenorhabditis elegans SMG-4). Mol Cell Biol 21(1):209–223

Shiraishi E et al (2000) The cadmium-resistant gene, CAD2, which is a mutated putative copper-transporter gene (PCA1), controls the intracellular cadmium-level in the yeast S. cerevisiae. Curr Genet 37(2):79–86

Sun X et al (1998) A mutated human homologue to yeast Upf1 protein has a dominant-negative effect on the decay of nonsense-containing mRNAs in mammalian cells. Proc Natl Acad Sci U S A 95(17):10009–10014

Toesca I et al (2011) Cryptic transcription mediates repression of subtelomeric metal homeostasis genes. PLoS Genet 7(6):e1002163

Vilela C et al (1998) The yeast transcription factor genes YAP1 and YAP2 are subject to differential control at the levels of both translation and mRNA stability. Nucleic Acids Res 26(5):1150–1159

Vulpe CD, Packman S (1995) Cellular copper transport. Annu Rev Nutr 15:293–322

Wang X, Okonkwo O, Kebaara BW (2013) Physiological basis of copper tolerance of Saccharomyces cerevisiae nonsense-mediated mRNA decay mutants. Yeast 30(5):179–190

Welch EM, Jacobson A (1999) An internal open reading frame triggers nonsense-mediated decay of the yeast SPT10 mRNA. Embo J 18(21):6134–6145

Wong A et al (2021) Variation of the response to metal ions and nonsense-mediated mRNA decay across different Saccharomyces cerevisiae genetic backgrounds. Yeast 38(9):507–20

Wu C et al (2020) Poly(A)-binding protein regulates the efficiency of translation termination. Cell Rep 33(7):108399

Wysoki R, Tamás MJ (2010) How Saccharomyces cerevisiae copes with toxic metals and metalloids. FEMS Microbiol Rev 34(6):925–951

Yamaguchi-Iwai Y et al (1997) Homeostatic regulation of copper uptake in yeast via direct binding of MAC1 protein to upstream regulatory sequences of FRE1 and CTR1. J Biol Chem 272(28):17711–17718

Yamaschita A et al (2009) SMG-8 and SMG-9, two novel subunits of the SMG-1 complex, regulate remodeling of the mRNA surveillance complex during nonsense-mediated mRNA decay. Genes Dev 23(9):1091–1105

Zhang H, Mendell JT (2020) Ribosome recycling by the RNA-binding protein and Upf3 protein (Caenorhabditis elegans SMG-4). Mol Cell Biol 21(1):209–223

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