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Messenger RNA Surveillance Systems Monitoring Proper Translation Termination

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Organisms have evolved an elaborate set of quality control systems to ensure the fidelity of the genetic information flow. The mRNA surveillance systems work in this context by monitoring the quality of mRNAs to ensure that they are suitable for translation. In this review, recent achievements in the investigation of mRNA surveillance pathways, including nonsense-mediated mRNA decay and nonstop-mediated mRNA surveillance pathway, will be discussed.

Key words: mRNA quality control, mRNA surveillance, ribosome, stop codon, translation.

Abbreviations: NMD, nonsense-mediated mRNA decay; PTC, premature termination codon; EJC, exon-exon junction complex.

All cellular biochemical processes rely on the accuracy of the expression of genetic information. To ensure the fidelity of the genetic information flow, organisms have evolved surveillance systems to assess the quality of genetic entities. Although mRNA is an important genetic material, its cellular quality control was discounted for a long time because it was thought that abnormal mRNA would not seriously affect the gross expression of genetic information due to the short half-life of independent mRNA transcripts in the cells. Recent researches, however, have revealed that mRNA surveillance systems are important for the maintenance of cellular functions. In addition to having a damage-control function, mRNA surveillance systems play critical regulatory roles in normal gene expression. Thus, mRNA surveillance mechanisms play important roles both in depleting aberrant transcripts from cells and in maintaining the proper level of normal transcripts. This review will focus on recent researches investigating mRNA surveillance pathways, with particular reference to metazoans.

NONSENSE-MEDIATED mRNA DECAY (NMD)

One of the best-studied mRNA surveillance pathways is nonsense-mediated mRNA decay (NMD), which selectively degrades aberrant transcripts harbouring in-frame premature termination (nonsense) codons (PTCs) (*1–5*). This kind of abnormal mRNA has the potential to produce truncated proteins with dominant-negative or deleterious gain-of-function activities. PTCs can arise in a variety of ways, such as random nonsense and frameshift mutations in the genomic DNA sequence, programmed genomic DNA arrangements or errors in mRNA splicing. Although the NMD pathway is conserved in all eukaryotes examined to date, recent studies in several organisms have revealed that different mechanisms have evolved to discriminate PTCs from natural stop codons and to degrade the targeted mRNAs (*6*). The recent excellent review by Chang *et al*. summarizes conserved factors that are involved in NMD in all eukaryotes (*7*). Namely, (i) PTCs are recognized by the translating ribosome, (ii) three core trans-acting factors, the up-frameshift (UPF) proteins 1, 2 and 3, form the NMD machinery on the PTC-containing mRNA and (iii) mRNAs containing the NMD complex of UPF proteins are subsequently degraded. It was reported that the SMG-1-mediated phosphorylation of UPF1 remodels the mRNA surveillance complex (*8–11*). In *S. cerevisiae*, a *cis*-acting element destabilizes mRNAs when located downstream of a nonsense codon (Fig. 1A) (*12*). This downstream sequence element (DSE) appears to be required for the recognition of premature stop codons in yeast (*13*). The hnRNP-like protein Hrp1p/Nab4 interacts with the DSE to mark the PTC for recognition by the NMD pathway (*14*). Newly transported mRNAs associate with exon–exon junction complexes (EJCs), which are formed by a splicing reaction and persist during export and until the mRNA is translated (*15–17*). The EJC, including eIF4AIII, MLN51 and Y14/MAGOH, makes an mRNP that recruits UPF complexes for NMD substrate in mammalian cells (Fig. 1B) (*18–23*). The quality of mRNA is surveyed by a pioneer round of translation, during which premature translation termination occurring upstream of the EJC results in the formation of a protein complex on mRNA that initiates the degradation of the aberrant mRNA during its export from the nucleus to the cytoplasm (*24–27*). The role of the EJC in NMD has been identified only in mammalian cells. Recently, EJC-independent NMD in mammalian cells was reported (*28*). This EJC-independent NMD depends on the distance between the PTC and the poly(A) tail, as in the yeast NMD pathway. Moreover, a UPF3-independent NMD pathway is also present in mammalian cells (*29*). Thus, mammalian NMD appears to be more variable than previously suspected.

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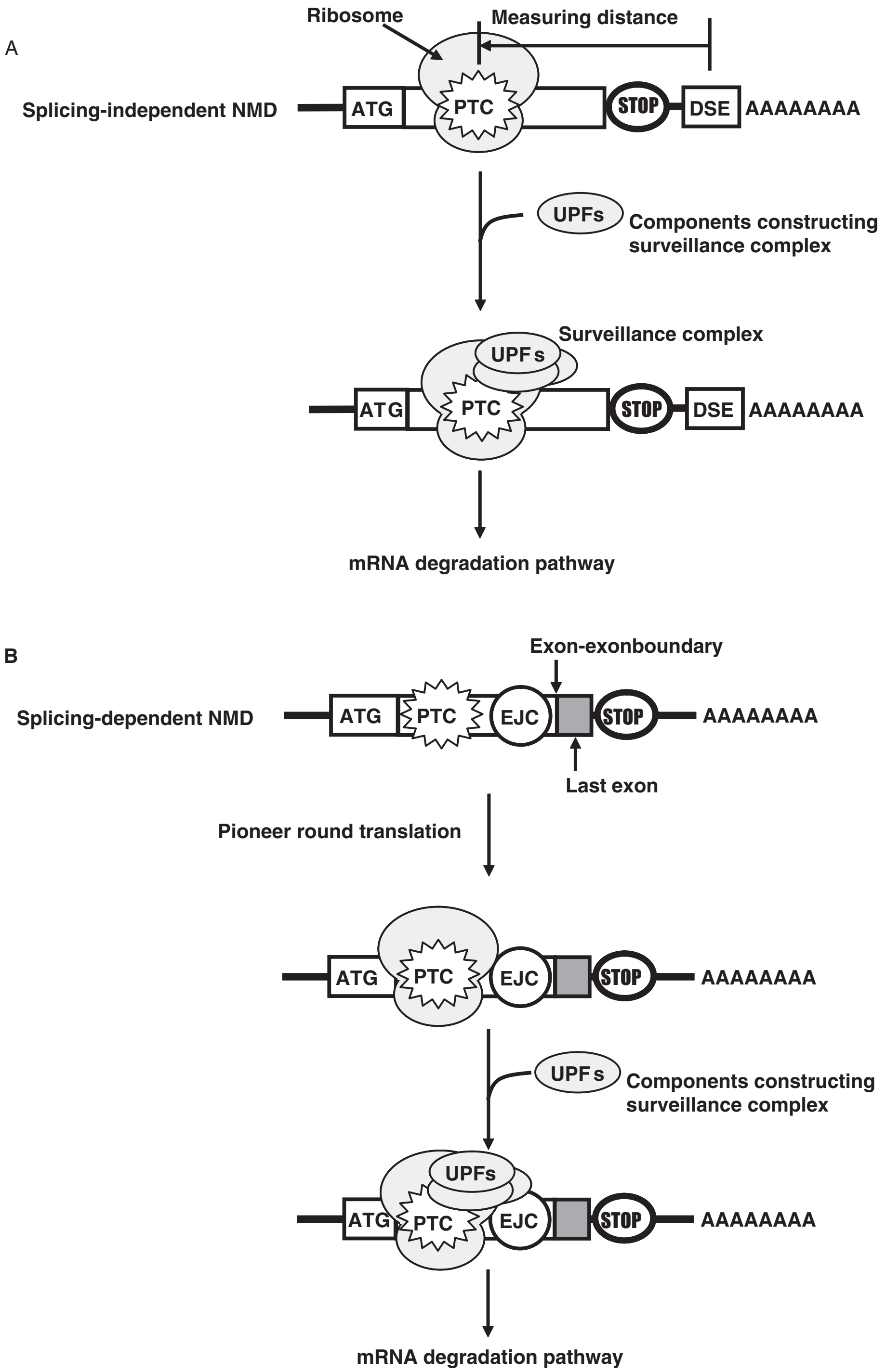

Fig. 1. **Schematic drawing of aberrant mRNAs and surveillance complexes.** (A) The open box indicates the ORF. ATG, PTC, STOP and DSE indicate initiation codon, premature termination codon, termination codon and downstream sequence element, respectively. After the ribosome stalls at the PTC, a certain element, such as DSE in yeast, measures the distance between the stalled position of the ribosome and the natural termination codon. Aberrant termination of the ribosome triggers the formation of a surveillance complex on PTC-containing mRNA, resulting in the facilitated degradation of PTC-containing mRNA. (B) EJC indicates exon–exon junction complex. Aberrant termination of the ribosome at the PTC, which is upstream of the EJC, triggers the formation of a surveillance complex on PTC-containing mRNA, resulting in facilitated degradation of PTC-containing mRNA. (C) The ribosome translating nonSTOP mRNA reaches and stalls at the 3′-end of the nonSTOP mRNA. TmRNA and protein factors associate with the stalling ribosome, resulting in the release of the ribosome for recycling and the mRNA for enhanced degradation. A tag sequence encoded by tmRNA is added to the C-terminal of the polypeptide, and degradation of the tagged polypeptide is accelerated. (D) A stalled ribosome at the poly(A) tail of a nonSTOP transcript in yeast is recognized by Ski7p, then the nonSTOP mRNA is degraded by the decapping-dependent 5′-to-3′-decay pathway and the Ski7p-dependent 3′-to-5′-decay pathway. Translation of nonSTOP mRNA in eukaryotes is repressed at the post-initiation step.

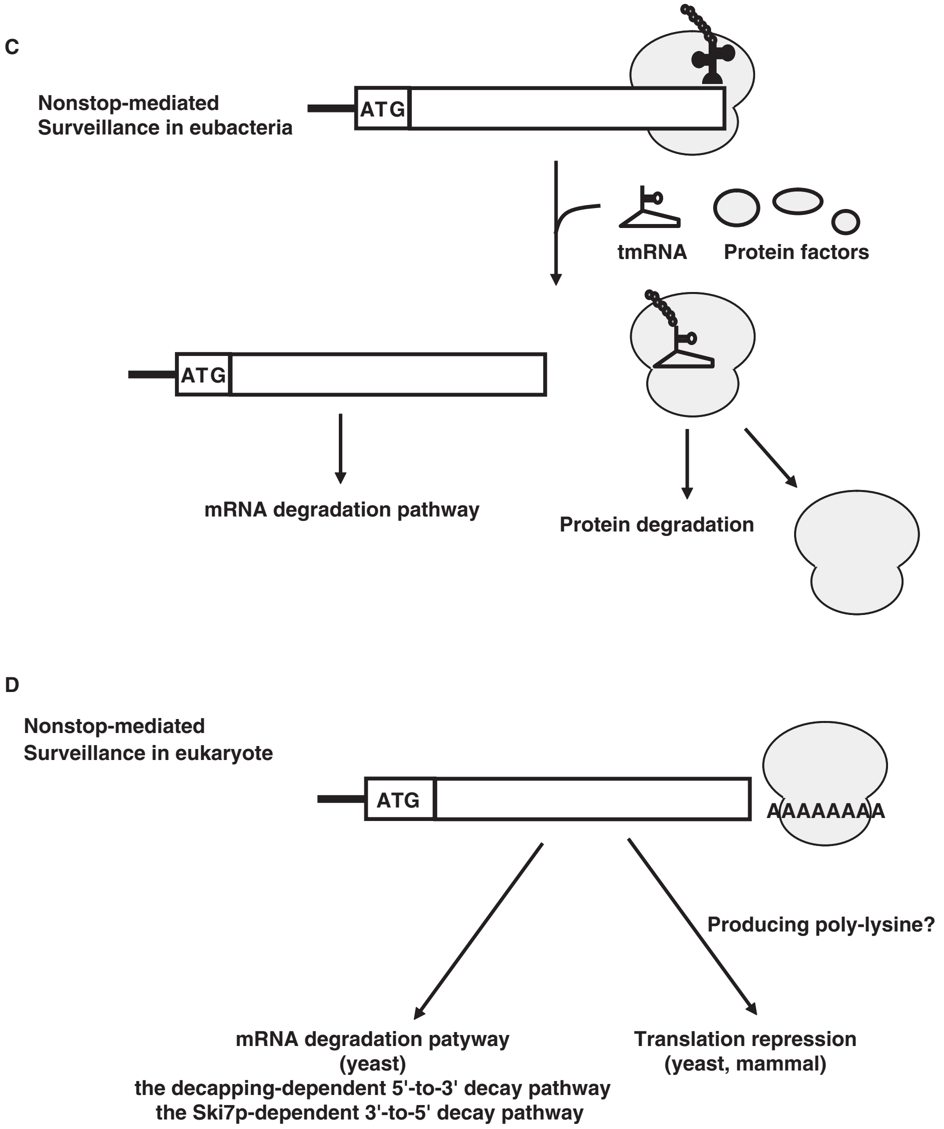

Fig. 1. **Continued.**

NON-TERMINATION (nonSTOP)-MEDIATED mRNA SURVEILLANCE SYSTEM IN BACTERIA

Another example of aberrant mRNA in cells is nonSTOP mRNA, which lacks in-frame termination codons. In eubacteria, translation of nonSTOP mRNAs results in stalled ribosomes at the 3′ end of the mRNA. Accumulation of unproductively stalled ribosomes leads to undesirable consequences for the cell; for example, ribosomes are sequestrated from translation of other normal mRNAs. To resolve this problem, eubacteria species have evolved a unique quality-control system comprised of tmRNA (also called as SsrA RNA or 10Sa RNA), a unique molecule having properties of both tRNA and mRNA (Fig. 1C) (*30–32*). The tRNA-like region of tmRNA acts first as an alanyl-tRNA and donates alanine to the stalled peptide chain using the empty A-site of the ribosome, and the mRNA-like region of tmRNA displaces the nonSTOP mRNA and directs the addition of a short peptide tail to the C-terminus of the polypeptide. The resulting carboxyl-terminal tagged proteins are processed for proteolysis by several ATP-dependent proteases. Three protein factors, alanyl-tRNA synthetase (Ala-RS), small protein B (SmpB) and elongation factor Tu (EF-Tu), play essential roles in this system by decoding the tag sequence of tmRNA (*33–35*). Thus, the trans-translation pathway plays central roles to orchestrate the rescue of ribosomes stalling on nonstop transcripts and the addition of a degradation tag to ribosome-associated protein fragments for proteolysis. At the same time, this system works to dispose of aberrant mRNAs. Recently, it was reported that the trans-translation pathway facilitates the degradation of nonSTOP mRNAs (*36*).

NonSTOP-MEDIATED mRNA SURVEILLANCE SYSTEM IN EUKARYOTES

The mechanism that has evolved in yeast to ensure that aberrant proteins from nonSTOP mRNAs are not produced is distinct from the tmRNA system (Fig. 1D).

It was proposed that nonSTOP mRNAs can be generated when 3′ end formation occurs within the coding region of cistrons as a consequence of genetic mutations (*37*, *38*), transcriptional pausing (*39*) or usage of cryptic polyadenylation sites (*40*, *41*). Indeed, it has been estimated that 40 of 3622 yeast ESTs have 3′ ends located upstream of the bona fide termination codon, suggesting that nonSTOP mRNAs are truly produced in eukaryotic cells (*42*). Genetic studies in *S. cerevisiae* have shown that degradation of nonSTOP mRNA was facilitated by a 3′-to-5′-degradation pathway mediated by the ski complex and exosomes (*43*, *44*). Although both the NMD pathway and the nonSTOP-mediated mRNA decay pathway in yeast require a translation event, Upf1 function is required for only the NMD pathway but not the nonSTOP-mediated mRNA decay pathway. Therefore, the nonSTOP-mediated mRNA decay pathway is mechanistically distinguished from NMD. Inada and Aiba proposed that the 5′-to-3′-degradation pathway is also involved in the facilitated degradation of nonSTOP mRNA in addition to exosome-mediated 3′-to-5′-degradation, because double mutation of the decapping-dependent 5′-to-3′ decay pathway and the Ski7p-dependent 3′-to-5′ decay pathway had a significantly greater effect than sole s*ki* mutations (*45*). Ski7p resembles the GTPase domains of the translation factors EF1A and eRF3, and its function is required for facilitated degradation of nonSTOP mRNA in yeast. Because EF1A and eRF3 interact with the ribosomal A-site occupied by the sense codon and nonsense codon, respectively, a model was proposed that the ribosome stalls at the 3′-end of the poly(A) tail of nonSTOP mRNA and Ski7p recognizes and enters the A-site of the stalling ribosome. Ski7p recruits the exosome complex of the 3′-to-5′ exonucleases as well as the Ski complex, which stimulates the degradation of nonSTOP mRNA by a 3′-to-5′ decay pathway.

In addition to the facilitated degradation of nonSTOP mRNA in yeast, Inada and Aiba reported that protein expression from a nonSTOP reporter gene is greatly reduced (*45*). Most nonSTOP transcripts were distributed in the EDTA-sensitive polysome fraction, and the nonSTOP mRNA: ribosome complexes were stable after inhibition of initiation even after sufficient time for ribosomes translating wild-type mRNA to be released. Inada and Aiba proposed that the translation of yeast nonSTOP mRNA is repressed at the post-initiation step(s), probably because of road-blocking ribosomes translating nonSTOP mRNA immediately following the leading translating ribosomes. However, Meaux and van Hoof detected significant protein production from nonSTOP mRNAs in yeast (*46*). Ito-Harashima *et al*. (*47*) pointed out that the absence of a poly(A) tract at the 3′-end of nonSTOP mRNA in the study by Meaux and van Hoof affects the translation repression of nonstop mRNA. It was assumed that the translation of nonSTOP mRNA containing a poly(A) tail results in the addition of poly-lysine residues to the C-terminal of proteins produced from nonSTOP mRNA caused by the translation of the poly(A) tract. In fact, Ito-Harashima *et al*. reported that the insertion of a long poly(A) tract immediately upstream of a termination codon of a reporter gene strongly reduced the protein expression (*47*). They suggested that the amino acid sequence, but not the nucleotide sequence, determines the repression of protein production from reporter genes harbouring a poly(A) tract. Namely, greater than 10 consecutive lysine residues translated from poly(A) are involved in translational repression. Although it is unclear why consecutive lysine residues reduce protein production, the interaction between poly-lysine and a component of ribosome tunnel might be involved in translational repression.

Doma and Parker described a significantly different type of RNA quality control system ‘no-go decay’ pathway in yeast (*48*). In this pathway, the presence of mRNAs with stalled ribosomes results in cleavage in the middle of the mRNA close to the ribosome-stalling position, followed by degradation. This pathway provides a mechanism for clearing the cell of stalled translation elongation complexes and a mechanism of post-transcriptional control. The main targets for no-go decay in the cell might be chemically damaged mRNAs, which can cause a complete translation block (*49*). It is not clear whether the no-go decay pathway is conserved in other animals.

TRANSLATIONAL REPRESSION OF nonSTOP mRNA IN MAMMALIAN CELLS

Several examples of nonstop transcripts produced in mammalian cells have been reported (*38*, *50*, *51*), although in some cases it is unclear if they really lacked in-frame termination codons. A loss of two nucleotides removes the termination codon from the mitochondrial *RNA14* transcript and results in the production of nonSTOP mRNA in human mitochondria (*37*). The steady-state level of nonSTOP *RNA14* is markedly decreased, and the polyadenylation profile of the processed nonSTOP *RNA14* is substantially abnormal. The majority of nonSTOP *RNA14* is terminated with short poly(A) extensions. Temperley *et al*. proposed that the loss of a termination codon causes enhanced mitochondrial mRNA decay by translation-dependent deadenylation. The protein production from nonSTOP *RNA14* is still at issue. Jesina *et al*. (*52*) reported that translation of nonSTOP mRNA is repressed in human mitochondria. In contrast, Chrzanowska-Lightowlers *et al*. (*53*) reported that functional polypeptides are produced from nonSTOP *RNA14* mRNA. Thus, there is an apparent contradiction in the protein production from mitochondrial nonSTOP mRNA.

The fate of nonSTOP mRNA expressed from the nucleus in mammalian cells was examined by using a reporter gene, such as luciferase or green fluorescence protein (*54*). Although degradation of nonSTOP mRNA in human mitochondria, yeast and bacteria is facilitated as mentioned earlier, enhanced degradation of nuclear-transcribed nonSTOP mRNA was not observed in mammalian cells. However, translation of nonSTOP mRNA was significantly repressed at a post-initiation step in the cytoplasm because: (i) repressed nonSTOP mRNAs were associated with polysomes, and (ii) translation of internal ribosome entry site (IRES)-initiated and uncapped nonSTOP mRNA was still repressed. Full-length protein production from nonSTOP mRNA:polysomes complexes formed *in vivo* was significantly reduced when used to program an *in vitro* run-off translation assay, indicating that the translation elongation step of nonSTOP mRNA is inhibited. Interestingly, most nonSTOP mRNAs were distributed in lighter polysome fractions than control mRNAs that contained a stop codon, and a significant amount of heterogeneous polypeptides were produced during *in vitro* translation of nonSTOP mRNAs, suggesting premature termination of ribosomes translating nonSTOP mRNA. Moreover, ribosome-protected poly(A) fragments were produced from nonSTOP mRNA in a cell-free translation system, indicating the presence of a ribosome stalled at the 3′-end of nonSTOP mRNAs. Taken together, a model was proposed that a ribosome stalling at the 3′-end of nonSTOP mRNAs prevents upstream translation by enhancing premature termination of translation (Fig. 2). This is an interesting observation, because it implies that the lack of a termination codon in nonSTOP transcripts causes the accumulation of stalled ribosomes at the 3′-end of mRNA as the result of the nonSTOP-mediated RNA surveillance system in yeast and eubacteria.

REGULATION OF NATURALLY OCCURRING TRANSCRIPTS IN nonSTOP-MEDIATED mRNA METABOLISM

It was proposed that NMD is crucial for not only muting genetic noise, but also for the expression of normal transcripts, including the upstream open reading frame. For example, NMD regulates the expression of naturally occurring transcripts that represent ~10% of the transcriptome in yeast (*55*, *56*), worm (*57*, *58*), fly (*59*) and mammalian cells (*60*). By the same token, one might speculate that the cellular mechanism recognizing nonSTOP mRNAs regulates the expression of naturally occurring transcripts. In fact, a subset of normal genes produces natural nonSTOP transcripts, such as CBP1, AEP/ATP13, RNA14 and SIR1 in yeast (*61–64*), nad6 and ccmC in plants (*65*) and GHR in chicken (*66*), although there is no experimental proof that expression of these genes is regulated by the cellular system that recognizes nonSTOP transcripts. Recently, it was proposed that degradation of pseudogenes by the NMD pathway is implicated in protein/gene evolution (*58*). Interestingly, there is genetic interaction between the [*PSI*$^+$] phenotype and the mechanism recognizing nonSTOP mRNAs in yeast (*67*). It was proposed that the [*PSI*$^+$] phenotype can be a capacitor for evolutionary change, because the presence of [*PSI*$^+$], which has several unique and beneficial abilities such as the epigenetic feature to adapt to environmental conditions without permanent genetic change and plasticity to respond to fluctuating environments, may provide enhanced fitness for *S. cerevisiae* to survive in different severe growth conditions (*68–70*). One might speculate that the nonSTOP-mediated RNA surveillance pathway is involved not only in muting aberrant transcripts and regulating naturally occurring transcripts, but also in environmental adaptations via genetic and epigenetic mechanisms.

CONCLUDING REMARKS

Translating ribosomes play a central role in the mRNA surveillance systems described earlier. Recently, the production of vast amounts of non-coding RNAs in eukaryotes was discovered. Because of their ‘non-coding’ properties, ribosomes are not involved in quality control of non-coding RNA. A cellular surveillance pathway also monitors the quality of nuclear-retained mRNAs. The DRN (degradation of mRNA in nucleus) pathway is one candidate for the translation-independent nuclear RNA surveillance system (*71–73*). Moreover, the existence of a quality control system to limit inappropriate transcripts in the nucleus has been proposed (*74*). Degradation of aberrant tRNA and ribosomal RNA is facilitated in nucleus (*75*, *76*). The clarification of not only the ribosome-mediated mRNA surveillance system but also translation-independent RNA, especially in the nucleus, will be the next major issue in this field.

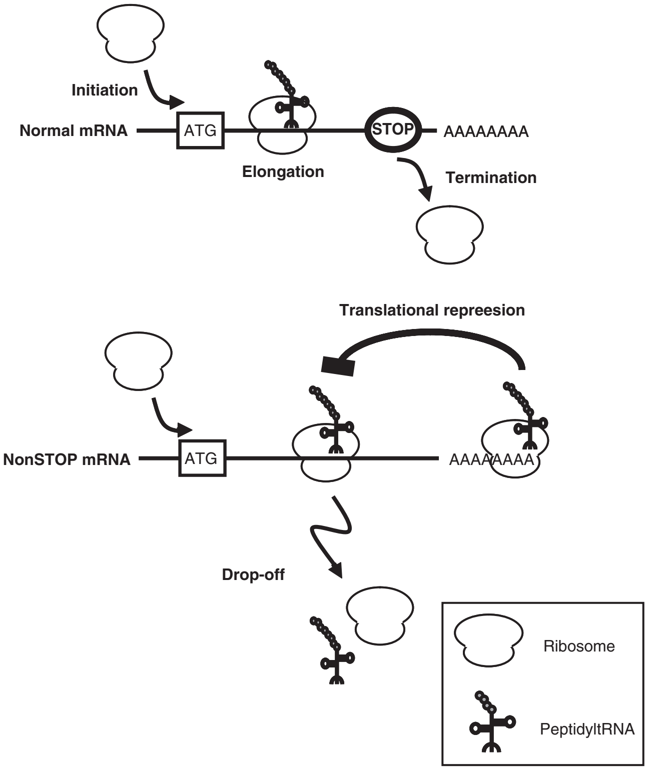

Fig. 2. **A model of nonSTOP-mediated translational repression in mammalian cells.** A model for translational repression of nonSTOP mRNA in mammalian cells. The translation initiation of nonSTOP mRNA occurs normally. The first ribosome translating the nonSTOP mRNA reaches and stalls at the 3′-end of the mRNA. An aberrant ribosome-nonSTOP mRNA complex at the 3′-end of the mRNA signals upstream and represses the completion of translation by elongating ribosomes. Ribosomes are released from the nonSTOP mRNA before completion of translation with premature peptidyl tRNAs released from the translation complexes.

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