Mini-Review

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Up-frameshift protein 1 (UPF1): Multitalented entertainer in RNA decay

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ABSTRACT: Up-frameshift protein 1 (UPF1) is an evolutionarily conserved protein with RNA/DNA-dependent ATPase and RNA helicase activity. The protein is well known for its central role in nonsense-mediated mRNA decay (NMD), which eliminates aberrant mRNAs harboring premature termination codon (PTC), preventing the accumulation of nonfunctional or potentially harmful truncated proteins. NMD is also involved in the regulation of the state-levels of many normal physiological mRNAs. Moreover UPF1 is not only a key player in NMD but is also involved in non-NMD RNA degradation, such as staufen1 (STAU1)-mediated mRNA decay (SMD) and replication-dependent histone mRNA decay. Thus, UPF1 is an important factor for the RNA quality control system and the regulation of physiological gene expression. Further, recent studies have clarified that UPF1 contributes to DNA replication, DNA repair, telomere metabolism, and stabilization of HIV-1 genomic RNA. In the review, we summarize numerous functions of UPF1.

Keywords: UPF1, RNA surveillance, post-transcriptional gene regulation, RNA replication, S phase progression, telomere, HIV-1

1. Introduction

Up-frameshift protein 1 (UPF1) is evolutionarily conserved and ubiquitously expressed phosphoprotein with RNA/DNA-dependent ATPase and RNA helicase activity (*1*). UPF1 has been characterized as an essential factor for nonsense-mediated mRNA decay (NMD), which eliminates aberrant mRNAs harboring premature termination codon (PTC) generated by a nonsense mutation or frameshift (*2*). NMD is one of the important RNA surveillance mechanisms, which prevent the accumulation of nonfunctional or potentially harmful truncated proteins (*3,4*). The pathway is also involved in regulating the expression of 1-10% normal physiological mRNAs (*5*). UPF1 interacts with several NMD factors, such as UPF2, NCBP1 (also known as CBP80), SMG1, SMG5-SMG7, SMG6, and eRF1-eRF3 (*6-16*). In addition to its role in quality control mechanism by NMD, UPF1 also functions two non-NMD decay pathways: staufen1 (STAU1)-mediated mRNA decay (SMD) and replication-dependent histone mRNA decay. SMD, unlike NMD, involves in the regulation of functional mRNAs harboring double-stranded RNA region called STAU1-binding site (SBS) in their 3'-untranslated region (3' UTR) (*17,18*). Replication-dependent histone mRNA decay degrades cell cycle-regulated histone mRNAs harboring stem-loop structure in the 3' UTR (*19*). Thus, UPF1 is an important factor in RNA surveillance mechanism for the degradation of abnormal mRNAs and the post-transcriptional regulation of gene expression for the degradation of normal mRNAs.

Interestingly, recent studies have revealed that UPF1 is not only a key player in several RNA degradation pathways but is also involved in several unique roles such as DNA replication, DNA repair, telomere metabolism, and stabilization of HIV-1 genomic RNA. UPF1 physically interacts with the DNA polymerase δ during S-phase of the cell cycle, controls telomere length and telomeric silencing, and regulates the HIV-1 RNA metabolism and translation (*20-23*). In the review, we describe that the roles of UPF1 in RNA surveillance mechanism, the post-transcriptional regulation of physiological mRNAs, and several unique functions in the cells.

2. Evolutional conservation of UPF1

UPF1 (Figure 1) was originally isolated in yeast (*24*). UPF1 is known as regulator of nonsense transcript 1 (Rent1) in mice, and suppressor with morphogenetic defects in genitalia 2 (Smg2) in fruitfly (*1,25*). For UPF1, the sequence identities among human, plant, fruitfly, nematode, and yeast are between 40-62% compared to 59-67% for ribosomal proteins. Especially,

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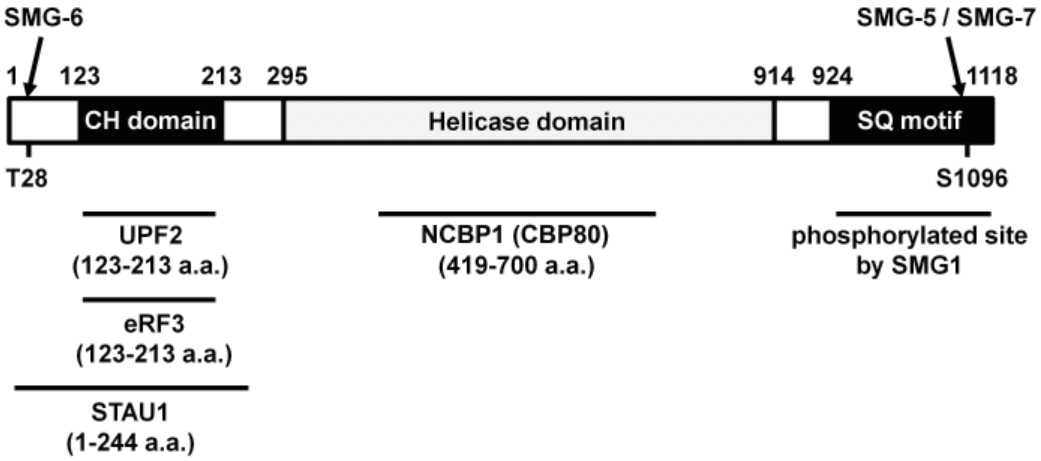

Figure 1. The structure of UPF1 protein. Schematic diagram explaining domains of human UPF1 protein. Cysteine/histidine-rich domain (CH domain) is present at N-terminus. Helicase domain is important for NMD. Serine/glutamine motif (SQ motif) is present at C-terminus. The numbers above the schematic diagram represent the animo acid positions of the domain or the motif boundary. The alphameric characters below the schematic diagram represent the phosphorylated positions. Phosphorylation of UPF1 at T28 is important for SMG6 binding to UPF1. Phosphorylation of UPF1 at S1096 is important for SMG5/SMG7 binding to UPF1. UPF1 is phosphorylated by SMG1 at SQ motif. The binding site of each NMD factor is represented below the schematic diagram. a.a., amino acids.

the sequence identities among zebrafish, mouse, and human are over 90% (*26*). Thus, UPF1 is highly conserved throughout eukaryotes. High evolutional conservation suggests its importance in biological systems. Actually, UPF1 is essential for embryonic viability in plant, fruitfly, zebrafish, and mice (*27-31*). For instance, loss of UPF1 function inhibits cell growth and induces apoptosis in Drosophila melanogaster (*27*). Thus, UPF1 plays important roles in various organisms.

3. Nonsense-mediated mRNA decay (NMD)

RNA degradation, as well as RNA transcription, plays a crucial role in the regulation of gene expression. RNA degradation can be divided into two classes; the mechanisms for regulating of gene expression and the mechanisms for rapidly degrading aberrant mRNAs (*32*). Generally, mRNA decay rates of house-keeping genes are slow, while those of regulatory genes such as transcription factor and replication-dependent histones are comparatively fast (*33*). The expression level of regulatory genes is frequently modulated by RNA decay pathway (*34*). Rapid degradation is also occurred by the generation of aberrant mRNAs, such as mRNAs harboring PTC (*35*). NMD is best known as mRNA surveillance mechanism for the elimination of such aberrant PTC-containing mRNAs generated as a result of a nonsense mutation or frameshift (*3,4*). Previous bioinformatic analyses predicted that one-third alternatively spliced transcripts have the potential to contain PTCs, which trigger NMD (*36*). Thus, the NMD pathway is essential to ensure the fidelity of transcripts, preventing the production of harmful truncated proteins with dominant-negative or deleterious gain-of-function activities and, as a consequence, human diseases (*37,38*). Interestingly, NMD contributes to not only the degradation of aberrant mRNAs harboring PTC, but also the regulation of normal physiological mRNAs. The previous studies suggested that NMD is involved in the degradation of 1-10% physiological transcripts from a wide variety of species, including yeast, nematode, fruitfly, plants, and mammals (*5,39-47*).

The NMD pathway in human cells comprises the factors UPF1, UPF2, UPF3A, UPF3B, SMG1, SMG5, SMG6, SMG7, SMG8, SMG9, NAG, and DHX34 (*4,48*). Among these factors, the UPF proteins constitute the core NMD machinery. Of all the UPF genes, UPF1 is functionally the most important factor for NMD (*26,49*). Newly synthesized mRNAs harbor cap-binding protein heterodimer NCBP1-NCBP2 (also known as CBP80-CBP20) at the 5' cap structure and exon-exon junction complex (EJC) as result of precursor mRNA (pre-mRNA) splicing (*32,50*). An important step in NMD is the translation-dependent recognition of transcripts with aberrant termination events and then targeting those mRNAs for degradation. EJC, deposited 20-24 nucleotides upstream of exon-exon junctions, plays a central role to distinguish aberrant PTC-containing mRNA from normal mRNA in mammalian cells (*51*). Although EJCs locating within an open reading frame (ORF) are removed by elongating ribosomes, EJCs locating downstream of the termination codon remain associated with the ribonucleoprotein (RNP) (*52*). This remaining EJC during a pioneer round of translation recruits NMD factors, including UPF1, to PTC-containing mRNAs and stimulates mRNA degradation (*51*). NCBP1-NCBP2 complex is also retained in PTC-containing mRNAs during the pioneer-round of translation (*3,4*). UPF1 interacts with NCBP1, and this interaction

contributes to the process of NMD at the initial step (*16*). The NCBP1-UPF1 interaction promotes the binding of SMG1-UPF1 to eRF1-eRF3 so as to form the SURF (SMG1-UPF1-eRF1-eRF3) complex and then promotes the interaction of SMG1-UPF1 with EJC (*6-9,15,16,51*). Thus, UPF1 plays a central role in NMD pathway, especially initial step.

UPF1 regulates the degradation of NMD-sensitive mRNAs and the remodeling of the mRNA surveillance complex through phosphorylation/dephosphorylation cycle (*10-14*). Namely, UPF1 is phosphorylated by SMG1, a phosphatidylinositol 3-kinase-related protein kinase (PIKK), at specific serine residues in its C-terminus serine/glutamine motifs (SQ motifs: 924-1,118 amino acids) (*10,11*). UPF1 phosphorylation facilitates the assembly of degradation factor, consequently, triggers the degradation of NMD-sensitive mRNAs (*53*). RNA degradation requires for the assembly of degradation factors and translational repression during NMD. UPF1 phosphorylation triggers eIF3-dependent translational repression during the process of NMD. Phosphorylated UPF1 but not hypophosphorylated UPF1 directly interacts with eIF3, a component of the 43S pre-initiation complex and then prevents the joining of 60S ribosomal subunit (*54*). Thus, UPF1 phosphorylation induces translational repression. Moreover, phosphorylated UPF1 also interacts with SMG5, SMG6, SMG7, and human proline-rich nuclear receptor coregulatory protein 2 (PNRC2) and then triggers the degradation of NMD-sensitive mRNAs (*53,55-59*). The association of SMG6 with phosphorylated UPF1 triggers RNA degradation by SMG6 endonuclease (SMG6-mediated endonucleolytic decay) (*55,56,58,59*). In contrast, the association of heterodimer SMG5/SMG7 with phosphorylated UPF1 triggers RNA degradation by deadenylase and decapping enzyme (SMG5/SMG7-mediated exonucleolytic decay) (*57,59*). PNRC2 interacts with UPF1 and DCP1a, a component of decapping complex. The mediation of PNRC2 triggers 5'-to-3' exonucleolytic decay (*53*). However, the biological importance of multiple decay pathways is still unclear.

Disassembly of mRNP complex is critical in the final step of RNA degradation. The recent study revealed that ATP hydrolysis by UPF1 leads to disassemble mRNP complex targeted to NMD (*60*). Thus, disassembly of mRNP complex by UPF1 is involved in recycling of NMD factors and other RNA-binding proteins derived from NMD substrates and UPF1 ATPase activity plays an important role in ATPase-dependent mRNP disassembly in NMD.

4. Staufen1-mediated mRNA decay (SMD)

Staufen, a double-stranded RNA-binding protein, was originally identified as maternal factor required for the localization of *bicoid* mRNAs at the anterior pole and *oskar* mRNAs at the posterior pole during oogenesis (*61*). Mammalian genomes encode two homologous Staufen genes, STAU1 and STAU2, although the functional discrimination between STAU1 and STAU2 is largely unknown (*62*). STAU1 is involved in the degradation of certain mRNAs containing SBS in their 3' UTR. SBS is divided into two groups: intramolecular base-pairing within a 3' UTR or intermolecular base-pairing between an mRNA 3' UTR and a long noncoding RNA named half-STAU1-binding site RNAs (1/2-sbsRNAs) (*17,63*). STAU1-dependent RNA degradation is named as SMD (*64*). SMD targets not only NCBP1-NCBP2-bound mRNAs but also eIF4E-bound mRNAs. SMD does not require EJC for the target selection (*15*). To date, the best-characterized SMD target is ADP-ribosylation factor 1 (ARF1) mRNA, containing a 19-bp stem loop structure recognized by STAU1 (*17*). Plasminogen activator inhibitor 1 (SERPINE1) and paired box 2 (PAX2) mRNAs are also targeted by SMD (*14*). In contrast to NMD, SMD regulates the stability of mRNAs encoding functional protein, namely, regulates physiological transcripts (*18*). NMD and SMD share several features; both systems require translation process (*7*). UPF1 is also involved in SMD through the direct binding with STAU1 (*17*). Hence, UPF1 regulates physiological transcripts as well as NMD-targeted mRNAs.

Intriguingly, recent studies revealed that SMD and NMD pathways fight over UPF1. STAU1-binding domain within UPF1 is overlapped with UPF2, a core factor of NMD. siRNA-mediated knockdown of STAU1, which inhibits SMD, increases the NMD activity while siRNA-mediated knockdown of UPF2, which consequently inhibits NMD, increases SMD (*64*). Moreover, the differentiation of myoblasts to myotubes in the mouse skeletal C2C12 cells is associated with the decreased contribution of SMD and the increased contribution of NMD. For example, the mRNA expression level of SMD targets such as JUN or SERPINE1 are decreased upon differentiation while those of NMD targets such as BAG1 or TGM2 are increased (*64*). The competition of SMD and NMD also contributes to the differentiation process. PAX3 mRNA, which inhibits myogenic differentiation, is an SMD target while myogenin mRNA, which encodes a protein required for myogenesis, is a UPF2-dependent NMD target (*64*). Thus, the interaction between SMD and NMD pathways forms an important gene expression network, where UPF1 plays a central role.

5. Replication-dependent histone mRNA decay

Histone proteins are essential components of chromosomes. In mammalian cells, the regulation of histone proteins is coupled to the rate of DNA replication. Replication-dependent histone genes encode the core histones (H2A, H2B, H3, and H4) and the

linker histones (H1). The expression of histone mRNAs increases when cells progress G1 to S phase of the cell cycle, and these mRNAs rapidly decrease at the end of S phase. Regulation of histone mRNA levels contributes for the coordination between DNA replication and chromatin assembly during S phase to ensure the proper replication of chromatin structure (*65,66*). The rapid destabilization of mRNA mainly contributes to rapidly reduce the mRNA level. Therefore, rapid degradation of histone mRNAs plays a crucial role in a main regulatory step to ensure proper histone mRNA levels at the end of S phase. Transcripts encoding histone proteins lack polyadenylated tails, although they are transcribed by RNA polymerase II (*19*). This conjures up an image of presence of special mechanism for the regulation of histone mRNA stabilities. Actually, 3' UTRs of replication-dependent histone mRNAs harbor the special stem-loop structure that is required for rapid regulatory degradation of histone mRNAs (*19,66*). The structure at the 3' end of histone mRNA interacts with the stem-loop binding proteins (SLBP) (*65,66*). UPF1 plays a crucial role in histone mRNA degradation through an interaction with SLBP at the end of S phase or after the inhibition of DNA synthesis (*19*). Moreover, the function of UPF1 in histone mRNA degradation is regulated by phosphorylation (*19,67*). The serine/glutamine motifs (SQ motifs) and threonine/glutamine motifs (TQ motifs) of UPF1 are phosphorylated by phosphatidylinositol 3-kinase-related protein kinase (PIKK) family (*11*). The phosphorylation of UPF1 triggers histone mRNA degradation (*19,67*).

Ataxia telangiectasia mutated (ATM) and DNA-dependent protein kinase (DNA-PK) are mainly activated by double-strand breaks (DSBs) generated by ionizing radiation. Ataxia telangiectasia and Rad3 related (ATR) is by single stranded DNA and stalled replication forks generated by UV light, replication block, and hypoxia. ATR, DNA-PK, and ATM are other members of the PIKK family (*68*). Recent studies revealed that the phosphorylation activity of ATR and DNA-PK but not ATM is required for histone mRNA degradation after the inhibition of DNA synthesis (*67*).

6. S phase progression & DNA replication

Recent studies revealed that UPF1 physically interacts with DNA polymerase δ and is crucial to S phase progression and DNA replication in NMD-independent manner (*20,69*). It was found that 4% of UPF1 proteins were bound chromatin-associated protein fraction while UPF1 mostly exists in the soluble fraction. The amount of chromatin-associated UPF1 is low in M phase and early G1 phase, starts to increase in mid-G1, and is highest level in S phase. Depletion of UPF1 but not UPF2 results in an early S phase arrest and stalls replication fork progression (*20,69*). This inhibition of replication fork progression triggers ATR-dependent DNA damage response and replication block (*64,70*). UPF1 may be involved in DNA damage response in S phase of the cell cycle. In support of the physiological importance of UPF1 in S phase, UPF1 depletion also induces the accumulation of nuclear foci containing a sensitive marker for DNA damage such as phosphorylated histone H2AX (γ-H2AX) (*20,69*). Moreover, chromatin-associated and phosphorylated UPF1 are reduced in cells depleted for ATR, while UPF1 accumulates on the chromatin in cells irradiated gamma-ray for induction of DNA damage (*20,69*). Those results suggest that gamma-ray irradiation triggers ATR-mediated phosphorylation and then chromatin-associated UPF1 is phosphorylated by active ATR. Futhermore, UPF1 interacts with the p66 subunit and p125 catalytic subunit of DNA polymerase δ. In contrast, UPF2 does not detectably interact with DNA polymerase δ. UPF1 may assist DNA polymerase δ to trigger replication fork progression or DNA repair in NMD-independent manner (*20,69*). Thus, UPF1 plays an important role in DNA replication and S phase progression through non-NMD pathway.

7. Telomere homeostasis

Telomeres are the heterochromatic structures located at the end of eukaryotic chromosomes. In mammal, telomeres consist of tandem arrays of duplex 5'-TTAGGG-3' repeats. The structure plays a crucial role in genome stability at the cellular level and contributes to tumor suppressors at the organismal level (*71*). There are a lot of proteins associated with telomeric DNA and these proteins are involved in telomere length regulation and telomere protection. The association of NMD factor with telomere function was previously reported. Mutations of UPF1, UPF2, and UPF3 shorten telomere length and reduced telomeric silencing in *Saccharomyces cerevisiae* (*72,73*). UPF mutant strains lead to increased mRNA levels of telomere-related proteins such as telomerase catalytic subunit (EST2), regulators of telomerase (EST1, EST3, STN1, and TEN1), and telomeric chromatin structure-related genes (SAS2 and ORC5) (*73*).

Telomeres originally are believed to be transcriptionally silent. However, recent studies revealed that telomeric repeats are transcribed by DNA-dependent RNA polymerase II into telomeric repeat-containing RNA (TERRA: also known as TelRNA) (*72-74*). TERRA is a long-noncoding RNA in animals and fungi, co-localizes with telomeres not only in interphase cells but also in transcriptionally inactive metaphase cells and blocks the activity of telomerase, a reverse transcriptase-like enzyme required for the maintenance of telomere length. Knockdown of *UPF1, SMG1* or *SMG6* leads to increase the number of telomere-associated TERRA foci on RNA fluorescence in situ hybridization (RNA-FISH). However, neither

the mRNA expression level nor the half-life of TERRA are not increased in cells depleted for UPF1 or SMG6 on northern blot (*73,74*). Thus, NMD factors including UPF1 may be not likely to be involved in the degradation of TERRA and be only required for the disassembly of TERRA and telomeres. Otherwise, there is the possibility that those NMD factors are involved in TERRA degradation locally at the telomere because the local change of TERRA mRNA level may be undetectable on northern blot.

8. HIV-1 genomic RNA stability

The stability of viral genomic RNA is crucial to a successful viral infection and proper replication within the cells. Therefore, viral RNAs have an ability to avoid RNA degradation by the host machinery. Interestingly, viruses have evolved mechanisms not only to escape the elimination by these decay pathways, but also to manipulate them for enhanced viral replication and gene expression (*75*).

The HIV-1 RNP consists of HIV-1 genomic RNA, $pr55^{Gag}$ (the major structural protein), STAU1 (the host protein) (*76,77*). Recent study revealed that UPF1 is one of HIV-1 RNP components and is involved in HIV-1 genomic RNA stability (*23*). Knockdown of *UPF1* decreases the level of HIV-1 genomic RNA and $pr55^{Gag}$ synthesis. Conversely, overexpression of UPF1 increases the level of HIV-1 genomic RNA and $pr55^{Gag}$ synthesis (*23*). The effects of UPF1 on HIV-1 genomic RNA stability are dependent on ATPase domain of UPF1 but not the association of UPF1 with UPF2 (*23*). Thus, the association of UPF1 with HIV-1 genomic RNA is important for the stability of the virus RNA, and the effect may be on NMD-independent manner.

9. Conclusion

UPF1 was originally known as a central factor in NMD. As we have seen in this review, UPF1 is a multitalented entertainer to be involved in RNA surveillance, the regulation of physiological transcripts, DNA replication, S phase progression, telomere homeostasis, and HIV-1 metabolism (Figure 1). However, the overview of UPF1 is still unclear. It is hoped that future studies will uncover new insights into the complicated roles of UPF1.

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