Nonsense Mediated mRNA Decay (NMD) Mechanism in *Drosophila*: A Short Review

Mubbara Minhas¹, Muhammad Usman Mirza²

¹Institute of Molecular Biology and Biotechnology, The University of Lahore, Pakistan
²Center for Research in Molecular Medicine (CRiMM), The University of Lahore, Pakistan

Abstract: Nonsense-mediated mRNA decay (NMD) is a mechanism that prevents the accumulation of malfunctioning protein and also regulates the clinical manifestation of many genetic disorders. This pathway not only degrades mRNA containing frame shift and nonsense mutation but also regulate the expression of naturally occurring transcript having features recognized by the NMD machinery. NMD contributes to the post translational regulation of about 10% of the transcriptome in Drosophila, yeast, and human cell. In Drosophila, the degradation of non-sense transcript is initiated by endonucleolytic cleavage near the PTC and RNA fragments are degraded from the newly generated ends. The 5’ fragmentis degraded by exosome and 3’ fragment is degraded by Xrn1. In Drosophila, many proteins involved in the mechanism of NMD mainly are SMG1, SMG5, SMG6, UPF1, UPF2, UPF3. For the activation of NMD, recognition of pre-mature termination codon (PTC) is necessary. In this review we have discussed the current knowledge of NMD mechanism in Drosophila that will help us in future studies.

Keywords: NMD, Nucleus, UPF1, Drosophila, Ribosome

1. Introduction

Nonsense mediate mRNA decay (NMD) is a mechanism that detects and degrades the mRNA which contains premature translation termination codon (PTC). This PTC makes abnormal and harmful protein. At this point NMD safeguards the cell, accumulate and delete the abnormal protein to improve the expression of gene [1, 2]. It is a mechanism that also differentiates PTC and natural stop codons [3]. This mechanism is involved in the rapid degradation of mRNA whose translation is not terminated properly by a ribosome. In this way, NMD contributes to the degradation of abnormal mRNA to improve the fidelity of gene expression and also to regulate the gene expression at the post transcriptional level [4]. PTC occurs in mRNA at both DNA and RNA level. At DNA level it occurs due to mutation in genes, and at RNA level due to alternative splicing or transcriptional error [5]. NMD regulates the expression of gene in yeast, fruit fly (*Drosophila*) and human and also plays a role in biological processes such as cell cycle, cell proliferation, cellular transport, telomere maintenance and metabolism [6]. Initially, NMD recognizes the PTC and then triggers the degradation. If the ribosomes are unable to terminate translation properly or the open reading frame gets truncated, an error occurs in gene expression that leads to introduction of PTC. NMD can also be initiated by deadenylation, decapping or endonucleolytic cleavage near the PTC [4]. In *Drosophila*, PABC1 is a basic determinant for PTC [3]. Recognition of PTC in yeast and *Drosophila* is independent of an intron and RNA splicing [7]. Downstream sequence elements within the coding region are required to trigger NMD in yeast and *Drosophila* [8]. NMD mechanism requires some factors including UPF1, UPF2, UPF3, SMG1, SMG5, SMG6 and SMG7 called SMGs [9,10,11]. UPF proteins develop the core of NMD machinery whereas UPF1 is an important factor for NMD [12,13]. The SMG1 protein catalyzes the phosphorylation of UPF1 at serine residues [14]. SMG5, SMG6 and SMG7 are involved in the dephosphorylation of UPF1 [12] and SMG7 is absent in *Drosophila* [15].

2. Activation of NMD Mechanism

In *Drosophila*, activation of NMD mechanism depends on PTC recognition. Factors that recognize the PTC and activate the NMD mechanism includes:
- Proper interaction of 3’UTR associated proteins with ribosome.
- Length of 3’UTR.
- Binding of PABC1.

2.1 Proper interaction of 3’UTR associated proteins with ribosome

For efficient termination, ribosome must interact with 3’UTR associated protein. In case of natural stop codon, the ribosome interacts with 3’UTR associated proteins and terminates the translation efficiently without any need of degradation. However, if PTC is present, the ribosome cannot interact with the 3’UTR associated proteins as a result the termination is impaired or slow and is responsible for the activation of NMD mechanism that start the process of degradation [16].

2.2 Length of 3’UTR

The activation of NMD also depends on the length of 3’UTR. The length of 3’UTR is also responsible for activation of NMD and initiation of degradation process [3]. Where transcripts have an exceptionally natural long 3’UTR the NMD does not get activated [2].

2.3 Binding of PABC1

Binding of poly A binding protein cytoplasmic 1 (PABC1) to the downstream sequence of promoter region is necessary for the NMD activation because its depletion inactivates the
NMD and translation efficiency is not affected [17]. The binding of PABPC1 and cleavage and polyadenylation reaction also provide positional information for PTC recognition [19]. To explain this point scientists designed an ADH reporter (alcohol dehydrogenate) whose polyadenylation and cleavage signals are replaced by histone H3 stem loop structure [18] or by the ribozyme elements [20]. Later on, they observed that the reporter bearing a PTC at codon 64 is not regulated by NMD. For the regulation of PTC at 64th codon, scientist artificially inserted adenosine at codon 64 is not regulated by NMD. For the regulation of PTC at 64th codon, scientist artificially inserted adenosine seed. Interaction and degradation in Drosophila and functional relationship between UPF1, SMG5, SMG6 and SMG7. These topics can be subject of active research in the future.

References

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