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Review

Nonsense-mediated decay in genetic disease: Friend or foe?

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ABSTRACT

Eukaryotic cells utilize various RNA quality control mechanisms to ensure high fidelity of gene expression, thus protecting against the accumulation of nonfunctional RNA and the subsequent production of abnormal peptides. Messenger RNAs (mRNAs) are largely responsible for protein production, and mRNA quality control is particularly important for protecting the cell against the downstream effects of genetic mutations. Nonsense-mediated decay (NMD) is an evolutionarily conserved mRNA quality control system in all eukaryotes that degrades transcripts containing premature termination codons (PTCs). By degrading these aberrant transcripts, NMD acts to prevent the production of truncated proteins that could otherwise harm the cell through various insults, such as dominant negative effects or the ER stress response. Although NMD functions to protect the cell against the deleterious effects of aberrant mRNA, there is a growing body of evidence that mutation-, codon-, gene-, cell-, and tissue-specific differences in NMD efficiency can alter the underlying pathology of genetic disease. In addition, the protective role that NMD plays in genetic disease can undermine current therapeutic strategies aimed at increasing the production of full-length functional protein from genes harboring nonsense mutations. Here, we review the normal function of this RNA surveillance pathway and how it is regulated, provide current evidence for the role that it plays in modulating genetic disease phenotypes, and how NMD can be used as a therapeutic target.

Contents

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1. Introduction

According to the National Organization for Rare Disorders (NORD), there are nearly 7000 known rare genetic disorders. In the US, there are approximately 30 million people who have a genetic disorder, of which approximately 30% arise as a consequence of a nonsense or frameshift mutation that introduces a premature termination codon (PTC, also called a nonsense codon or premature stop codon) [1,2]. Nonsense mutations in particular account for 20.3% of all disease-associated single-base pair mutations, and are three times more likely to come to clinical attention than missense mutations [3,4]. These mutations commonly inactivate gene function due to the production of truncated protein products, as well as leading to a significant decrease in cytoplasmic mRNA abundance due to targeted degradation by nonsense-mediated mRNA decay (NMD).

NMD is an evolutionarily conserved translation-dependent mechanism in all eukaryotes that is responsible for recognizing and eliminating aberrant messenger RNA (mRNA) transcripts to prevent the production of truncated peptides that could have toxic and detrimental effects on the cell [5–9]. NMD plays a critical role in preventing the potential dominant-negative effect of non-functional protein within the cell, as well as the prevention of misfolded protein accumulation and subsequent initiation of the ER stress response. NMD primarily protects the cell against the deleterious effects of PTCs, but there is a growing body of evidence that mutation-, codon-, gene-, cell-, and tissue-specific differences in NMD efficiency can alter the underlying disease pathology [2,10–12]. In fact, there is evidence that in certain genetic disorders, NMD can act to aggravate disease pathology and worsen the clinical phenotype, because degradation of the mutated mRNA prevents translation and accumulation of truncated peptides that retain residual activity [9–11]. In addition, there is evidence that inter-individual variability in NMD efficiency leads to differences in disease presentation and therapeutic outcome [13]. Therefore, NMD has emerged as a potent modulator of disease severity and clinical phenotype in light of its important role in recognizing and degrading mutated transcripts. The variable involvement of NMD in genetic disease has important implications for therapy, including decreased efficacy of read-through compounds intended to suppress the effects of nonsense mutations. In this review, we summarize current evidence that shows how NMD can modulate genetic disease pathology, why variability in NMD efficiency is important, and how NMD can be used as a therapeutic target.

2. Mechanism of substrate recognition and degradation

Eukaryotic cells contain a number of RNA quality control mechanisms to ensure the high fidelity of genetic expression, which protects the cell against the accumulation of nonfunctional RNA and the production of abnormal peptides [14]. mRNAs are largely responsible for protein production, and mRNA quality control is particularly important for protecting the cell against the harmful effects of genetic mutations. The synthesis and processing of mRNA involves transcription, capping, splicing, polyadenylation, nuclear membrane transport, translation, and degradation [14]. An aberrant mRNA containing a PTC can arise as a consequence of a variety of events, and must be recognized before it is fully processed into a mature mRNA capable of producing truncated protein products. NMD is a critical RNA quality control mechanism that involves multiple cellular components that recognize the presence of a PTC within a mRNA transcript. During synthesis by RNA polymerase II, mRNA is cotranscriptionally processed into a messenger ribonucleoprotein complex (mRNP) that contains a 5′-m^{7}GpppN cap structure at the 5′ end and a poly(A)-tail at the 3′ end, which protect the newly synthesized RNA transcript from premature degradation. In addition, the cap-binding protein (CBP) heterodimer CBP80-CBP20 complex (CBC) binds to and protects the 5′-cap, and the nuclear poly(A)-binding protein N1 (PABPN1) and the primarily cytoplasmic poly(A)-binding protein C1 (PABPC1) bind to the poly(A) tail. Another important factor, eIF4G, also binds to and stabilizes the poly(A)-tail. More than 90% of human mRNA transcripts undergo alternative splicing to remove introns and ligate the coding regions of the transcript (exons) together [15]. During this process, a complex of proteins (eIF4AIII, MAGOH, MLN51, and Y14) called the exon junction complex (EJC) is deposited 20–24 nucleotides upstream of every exon–exon splice site within the mRNP [16]. The CBC-bound mRNA then undergoes the pioneer round of translation, in which one or more ribosomes load onto the mRNP. During this process, the CBC is replaced by eukaryotic translation initiation factor 4E (eIF4E), the EJCs are displaced, PABPN1 is entirely replaced by PABPC1, and the mature mRNA is directed into steady-state rounds of bulk translation [17]. Within mammalian cells, mature transcripts are bound by eIF4E at their caps and PABPC1 at their poly(A) tails, lack EJCs, and are immune to NMD.

The processing of pre-mRNA into mature mRNA relies heavily on the correct placement of splicing factors during early biogenesis. These factors are functionally coupled to every step of mRNA synthesis, including 5′ capping, 3′ polyadenylation, splicing, regulation of transcript stability, nuclear export, cytoplasmic transport, and translation [18,19]. The EJC is essential for the initiation of NMD for transcripts harboring PTCs and is crucial for the decay of most aberrant mRNA transcripts. This is exemplified by the fact that all transcripts from intronless genes studied to date are invulnerable to NMD [15,20,21].

There are several parallel mRNA decay pathways, including the UPF2-independent NMD branch, the EJC-independent NMD branch, the UPF3-independent NMD branch, and the classical NMD branch [22–24]. In addition, there are alternative mRNA decay pathways that involve NMD factors, such as the Stau1-mediated decay pathway, which recruits up-frameshift 1 (UPF1) [25]. For the purposes of this review, we will focus only to the classical branch of the NMD pathway.

The classical NMD pathway (Fig. 1) is thought to be triggered during the pioneer round of translation when the first ribosome translates the processed CBC-bound mRNA and stalls at a PTC that is located more than 50–55 nucleotides upstream of the last EJC-bearing exon–exon junction [5–9,26]. During ribosomal stalling, the PTC moves into the A-site of the ribosome and is subsequently bound by eukaryotic release factor 1 (eRF1) and eRF3. CBP80 loosely associates with the key NMD factor, UPF1, prior to the pioneer round of translation. During NMD, CBP80 promotes recruitment of UPF1 by eRF1-bound eRF3 to the stalled ribosome. Next, the suppressor of morphogenetic effect on genitalia 1 (SMG1), a serine/threonine protein kinase, binds together with UPF1 to eRF1/3 to form the SMG1-UPF1-eRF1-eRF3 (SURF) complex. SMG8 and SMG9 also bind to the SURF complex, temporarily blocking phosphorylation of UPF1 by SMG1. This entire complex is then translocated from the ribosome to UPF2 and UPF3, which are bound to a downstream EJC. This releases SMG8 and SMG9 from SURF, allowing SMG1 to phosphorylate and subsequently activate UPF1. Phosphorylated UPF1 triggers the dissociation of the ribosome from the mRNP, blocks further translation initiation by targeting eIF3, and recruits SMG5, SMG6, and SMG7. This is followed by SMG5-SMG7-mediated decay of the transcript, which occurs by decapping and/or deadenylation, followed by degradation in the 5′–3′ direction from the decapped 5′ end by XRN1, and degradation in the 3′–5′ direction from the deadenylated 3′ end by the exosome complex [27]. UPF1 ATPase activity is required for stimulating the complete removal of NMD