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Adaptive Responses and the Physiological Effects of Nonsense-mediated Decay

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Introduction

Nonsense-Mediated Decay (NMD) is a crucial cellular mechanism that degrades mRNA transcripts containing premature stop codons (nonsense mutations). These aberrant transcripts, if translated, could produce truncated and potentially harmful, proteins. NMD serves not only as a quality control system but also plays roles in regulating normal gene expression. Understanding the physiological effects of NMD and how cells adapt to changes in NMD activity is vital for insights into genetic diseases and therapeutic approaches. NMD is initiated when ribosomes encounter Premature Termination Codons (PTCs) during translation. A typical PTC arises from mutations that introduce a stop codon before the normal end of the coding sequence. The ribosome stalls at this site, triggering a cascade of events that recruit NMD factors. Key players include Upf1, Upf2, and Upf3, with Upf1 acting as a central ATP-dependent RNA helicase. The Exon-Junction Complex (EJC), deposited upstream of exon-exon junctions during splicing, also plays a significant role in marking transcripts for NMD. Upon recognition of a PTC, Upf1 undergoes phosphorylation, leading to the recruitment of additional NMD factors and ultimately promoting the degradation of the defective mRNA. This degradation process typically occurs via the SMG (suppressor with morphogenetic effect on genitalia) proteins, which are crucial in both the recognition and decay steps of NMD [1].

Description

NMD's primary function is the surveillance and elimination of faulty mRNAs, preventing the synthesis of truncated proteins that could interfere with normal cellular functions. However, NMD also modulates the expression of numerous normal genes. This regulation affects various physiological processes, including NMD is essential during development, influencing processes such as differentiation and organogenesis. Mutations that impair NMD can lead to developmental disorders. Proper NMD activity is crucial for neural function and homeostasis. Defects in NMD are associated with neurological diseases, including intellectual disability and neurodegeneration. NMD regulates components of the immune system, including cytokine signaling and the expression of immune receptors. Dysregulation can impact immune surveillance and response. By controlling the stability of mRNAs encoding cell cycle regulators and pro-apoptotic factors, NMD influences cell proliferation and programmed cell death. When NMD is impaired, cells exhibit a range of adaptive responses to mitigate the potential damage from accumulated faulty mRNAs [2]. Compensatory gene expression cells may alter the expression of genes to compensate for the increased load of defective proteins. This includes upregulating proteasome components and molecular chaperones to enhance protein quality control. Alternative splicing can be modulated in response to NMD deficiency, potentially bypassing PTCs or reducing the production of aberrant mRNAs. Impaired NMD can trigger cellular stress responses, such as the Unfolded Protein Response (UPR) and oxidative stress pathways, aiming to restore homeostasis. Chronic NMD impairment may lead to sustained inflammatory signaling, as misfolded or aberrant proteins accumulate, potentially contributing to inflammation-related diseases [3].

Many genetic diseases are caused by mutations that introduce PTCs, leading to NMD-mediated degradation of crucial mRNAs. For example, Duchenne Muscular Dystrophy (DMD) and cystic fibrosis often involve such mutations. NMD can influence tumorigenesis by regulating the expression of oncogenes and tumor suppressor genes. Both hyperactivation and suppression of NMD have been observed in different cancers, affecting tumor growth and response to therapy. Impaired NMD is linked to neurodegenerative conditions, such as Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD), where the accumulation of faulty proteins contributes to neuronal damage. NMD influences immune regulation, and its dysregulation may contribute to autoimmune diseases by affecting the stability of mRNAs encoding immune-related proteins [4].

Understanding the physiological effects of NMD and the adaptive responses to its deficiency has led to therapeutic strategies aimed at modulating NMD activity for diseases caused by haploinsufficiency or dominant-negative effects of PTC-containing mRNAs, inhibiting NMD can be beneficial. This allows the production of truncated proteins that retain partial function. Small molecules like NMDI14 and NMDI14 have been explored for this purpose. Compounds that promote translational readthrough of PTCs, such as aminoglycosides and ataluren, can restore the production of full-length, functional proteins in cases where NMD targets mRNAs with nonsense mutations. Gene therapy approaches like exon skipping and CRISPR-Cas9 mediated genome editing aim to correct the underlying mutations that trigger NMD, thereby restoring normal gene expression and protein function. Targeting specific NMD factors (e.g., Upf1) to fine-tune NMD activity holds promise for diseases where either excessive or insufficient NMD contributes to pathology [5].

Conclusion

Nonsense-mediated decay is a vital cellular mechanism with significant implications for health and disease. It ensures the quality control of mRNAs, thereby preventing the synthesis of potentially deleterious proteins. However, NMD also modulates the expression of normal genes, influencing various physiological processes. Understanding how cells adapt to changes in NMD activity and the physiological effects of such adaptations is crucial for developing targeted therapies for genetic, neurodegenerative, and autoimmune diseases. As research continues to unravel the complexities of NMD, new therapeutic avenues may emerge, offering hope for patients with NMD-related conditions.

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Conflict of Interest

There are no conflicts of interest by author.

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