Regulation of Non-Canonical Proteins Encoded by Small Open Reading Frames via the Nonsense-Mediated Decay Pathway

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Abstract

Immunotherapy harnesses neoantigens encoded within the human genome, but their therapeutic potential is hampered by low expression, which may be controlled by the Nonsense-Mediated Decay (NMD) pathway. This study investigates the impact of UPF1-knockdown on the expression of non-canonical/mutant proteins, employing proteogenomic to explore UPF1 role within the NMD pathway. Additionally, we conducted a comprehensive pan-cancer analysis of UPF1 expression and evaluated UPF1 expression in Triple-Negative Breast Cancer (TNBC) tissue in-vivo. Our findings reveal that UPF1-knockdown leads to increased transcription of non-canonical/mutant proteins, particularly those originating from retained-introns, pseudogenes, long non-coding RNAs, and unannotated transcript biotypes. Moreover, our analysis demonstrates elevated UPF1 expression in various cancer types, with notably heightened protein levels in patient-derived TNBC tumours compared to adjacent tissues. This study elucidates UPF1 role in mitigating transcriptional noise by degrading transcripts encoding non-canonical/mutant proteins. Intriguingly, we observe an upregulation of the NMD pathway in cancer, potentially acting as a "neoantigen-masking" mechanism that suppresses non-canonical/mutant protein expression. Targeting this mechanism may reveal a new spectrum of neoantigens accessible to the antigen presentation pathway. Our novel findings provide a strong foundation for the development of therapeutic strategies aimed at targeting UPF1 or modulating the NMD pathway.

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