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Disrupting RNA Modification Machinery in Head and Neck Squamous Cell Carcinoma

More than 150 proteins contribute to the formation and regulation of various RNA modifications in humans. These modifications play a crucial role in cell function by influencing RNA splicing, stability, translocation, translation, and ultimately gene expression. To explore the impact of RNA-modifying proteins on cancer cell function, we conducted comprehensive CRISPR-Cas9 dropout screens targeting all known RNA-modifying proteins, both in vitro and in vivo. Our analysis identified a set of RNA-modifying factors essential for the survival of Head and Neck Squamous Cell Carcinoma (HNSCC). Among them, VIRMA, a key subunit of the m6A RNA-modifying enzyme complex, was specifically required for cancer cell survival but not for healthy primary cells. VIRMA depletion significantly reduced HNSCC survival and growth both in vitro and in human tumors xenografted into host mice. Acute depletion of VIRMA using the dTAG system globally inhibited m6A RNA modifications, leading to widespread effects such as reduced proliferation, elevated MHC-I expression, and disrupted DNA damage response. Notably, VIRMA depletion impairs the transcription of bi-directional promoters, which play a crucial role in the DNA damage response. These findings highlight VIRMA as a potential therapeutic target for HNSCC treatment.

Research type

Basic research

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