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Unleashing Immune Power: How mRNA-Encoded Modulators Suppress Tumor Growth

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Introduction

Subsequent to the emergence of the COVID-19 pandemic, an increased number of nucleic acid-based therapeutics have secured clinical endorsement. Unlike conventional protein-targeted therapies, nucleic acid therapeutics provide the potential for long-lasting effects and can be further categorized into oligonucleotides, single-guide RNA (sgRNA), and messenger RNA (mRNA). In this study, we aim to explore the anti-tumor properties of mRNA-encoded CD3-EpCAM Bispecific Antibody (BsAb) and mRNA-encoded IL-12 protein.

Method

We conducted qPCR, flow cytometry, and ELISA analysis to assess the dynamic concentration of mRNA-encoded CD3-EpCAM BsAb and mRNA-encoded IL-12 protein within tumor cells post-transfection. Subsequently, we evaluated their effects on anti-tumor and immune activation *in vitro* via flow cytometry and ELISA. Efficacy was further evaluated in subcutaneous tumor xenograft models in humanized mice. Moreover, we analyzed the activation of tumor-infiltrating immune cells following mRNA-encoded IL-12 treatment. Finally, to ascertain the preliminary safety of mRNA-encoded BsAb and mRNA-encoded IL-12 protein, we conducted serum biochemistry analysis and histopathological examination of various organs.

Results

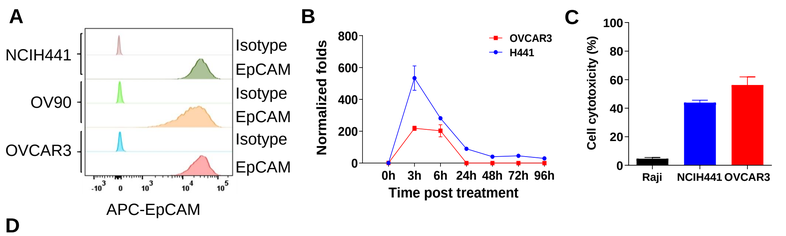

Figure 1. mRNA encoded EpCAM-CD3 BsAb produced *in vitro* is biologically active (A) Flow cytometry analysis illustrating EpCAM expression levels on tumor cell lines. (B) qPCR analysis of CD3 expression on different time points following mRNA transfection. (C) Flow cytometry analysis of cytotoxicity. (D) Flow cytometry analysis of T cell activation.

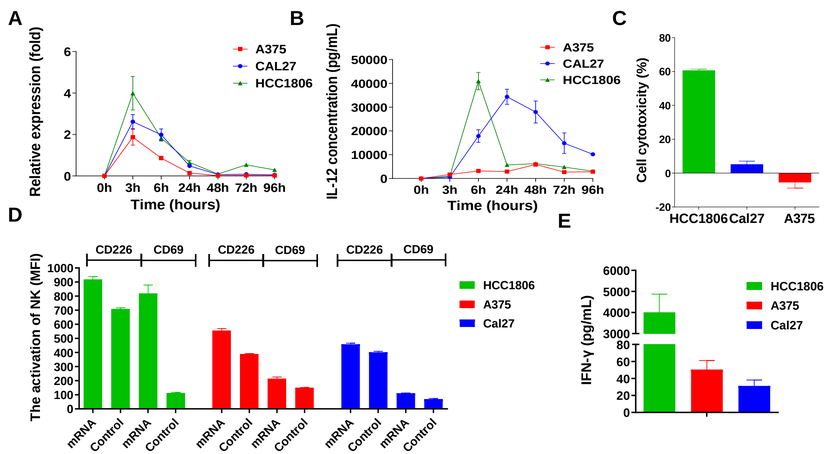

Figure 2. Bioactivity of mRNA encoded IL-12 *in vitro* (A) qPCR analysis of IL-12 expression on different time points following mRNA transfection. (B) ELISA analysis of IL-12 protein in supernatant on different time points following mRNA transfection. (C) Flow cytometry analysis of cytotoxicity. (D) Flow cytometry analysis of NK cell activation. (E) ELISA analysis of IFNg protein in supernatant.

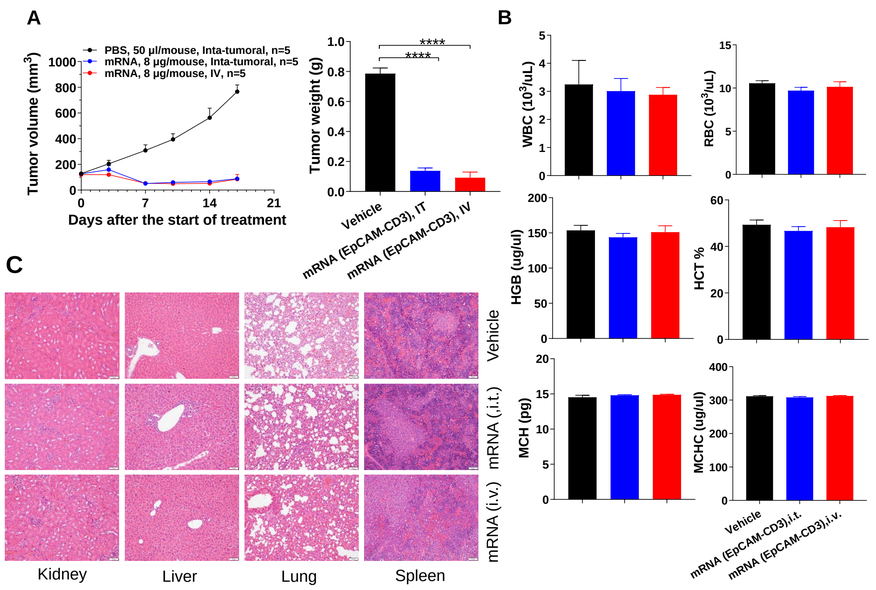

Figure 3. EpCAM-CD3 mRNA-LNP inhibited tumor growth and showed no obvious toxicity *in vivo* (A) Tumor growth and tumor weight of H441 xenograft model in PBMC humanized mice treated with mRNA LNP. (B) Complete blood count (CBC) analysis of H441 model. (C) HE staining of various organs collected from H441 tumor-bearing mice.

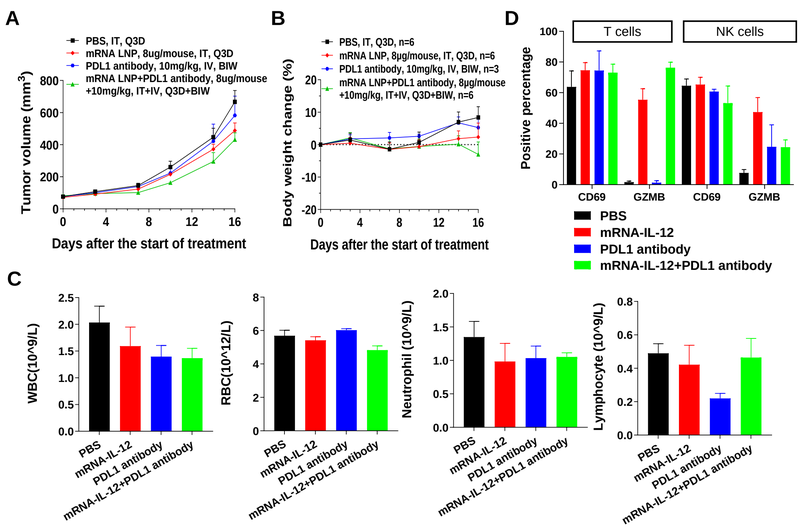

Figure 4. IL-12 mRNA-LNP restrained tumor growth and activated immune cells *in vivo* (A) Tumor growth of HCC1806 xenograft model in HSC humanized mice treated with mRNA LNP. (B) Body weight of mice in each treatment group. (C) Complete blood count (CBC) analysis of HCC1806 model. (D) Flow cytometry analysis of NK and T cell activation in tumor.

Conclusions

In this study, we evaluated the bioactivity of both EpCAM-CD3 encoded mRNA and IL-12 encoded mRNA. Our results indicated these two mRNAs showed anti-tumor activity and activated immune cells both *in vitro* and *in vivo*. Our findings highlight the significant research value of mRNA therapeutics and underscore their promising potential for clinical applications.

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