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mRNA-Based Strategies for Targeted Tumor Microenvironment Modulation to Enhance Antitumor Immunity

The tumor microenvironment (TME) is a complex and dynamic ecosystem composed of cancer cells, stromal cells, immune cells, various signaling molecules, and extracellular matrix components. Dynamic processes within the solid TME drive response or resistance to treatment, highlighting the importance of developing tools capable of precisely targeting these intricate mechanisms. Beyond vaccination, mRNA technology provides a versatile tool for fine-tuning specific targets within the TME, enabling modulation of complex processes such as immune cell migration, activation, and engagement. In this study, we used *in vitro* transcription to synthesize reporter protein and cytokine mRNAs, which were then encapsulated in various lipid nanoparticle (LNP) formulations to evaluate and optimize their efficiency in delivering mRNA to target cells. The mRNA-LNPs efficiently transfected human PBMCs and multiple cell lines *in vitro*, and outperformed commercial Lipofectamine. Interleukin 12 single-chain (IL-12sc) mRNA-LNPs induced robust production of bioactive IL-12p70, as demonstrated by the activation of PBMC-derived human T cells. Subsequently, we applied IL-12sc-LNPs *ex vivo* to primary colorectal cancer and liver metastasis specimens. Expression of IL-12sc in these tissues was associated with elevated levels of CD3+ cells and inflammatory cytokines. Thus, LNP-encapsulated mRNA holds strong potential as a tool for immune modulation within the TME and may offer a promising avenue for innovative cancer therapies.

Research type

Translational research

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