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Opinion Article

Nucleic Acid Therapeutics for Targeted Cancer Immunotherapy

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DESCRIPTION

Cancer immunotherapy has demonstrated great ability in recent years, marked by a surge in the approval of immuno-oncology drugs. Alongside this progress, the field of nucleic acid therapeutics has also made significant advancements. These therapies, including plasmids, Anti Sense Oligonucleotides (ASO), small interfering Ribo Nucleic Acid (siRNA), microRNA, messenger Ribo Nucleic Acid (mRNA), immunomodulatory Deoxy Ribo Nucleic Acid (DNA)/ Ribo Nucleic Acid (RNA) and gene-editing guide Ribo Nucleic Acid (gRNA), have become appealing due to their ability to modify the expression of endogenous or synthetic genes and regulate immune responses. This versatility plays a important role in developing novel strategies for cancer immunotherapy. However, despite their potential, the delivery of nucleic acid therapeutics remains a significant challenge. The inherent physicochemical properties of these molecules, such as their negative charges, hydrophilicity and vulnerability to enzymatic degradation, complicate their efficient delivery to target tissues and cells. Therefore, developing robust drug delivery systems that can protect, carry and release these therapeutics at the right place and time is essential.

Nucleic acid therapeutics have shown potential in various forms. Gene-regulating therapeutics like siRNA and ASO target specific genes, altering their expression to modulate intracellular signaling pathways involved in cancer progression. Immunomodulatory nucleic acids, such as unmethylated cytosine-guanosine deoxynucleotides, poly and cyclic dinucleotides, activate immune pathways that enhance antitumor responses. mRNA and plasmid DNA can be engineered to express proteins or peptides, such as tumor-specific antigens, that trigger immune responses. Additionally, aptamers, short single-stranded nucleic acids, have been discovered as alternatives to antibodies in cancer immunotherapy, while gene-editing nucleic acids like gRNA can be used to precisely modify genes, contributing to more effective treatments.

The success of nucleic acid therapeutics in cancer immunotherapy depends heavily on overcoming the complex Tumor Microenvironment (TME). Tumors often present physical barriers, including hypoxia, acidosis and high interstitial fluid pressure, which hinder the penetration and delivery of therapeutics. Furthermore, stromal cells like Cancer-Associated Fibroblasts (CAFs) contribute to the immune suppression within the TME, further complicating drug delivery. Additionally, targeting lymphoid tissues, where immune cells orchestrate immune responses, is critical for therapies aimed at modulating the immune system. To overcome these challenges, it is important to design delivery systems tailored to the specific needs of nucleic acid therapeutics, ensuring they reach the appropriate tissues and cells.

Traditional small-molecule drugs or large biologics differ from nucleic acid therapeutics in their delivery challenges. Nucleic acids, due to their unique properties, face several obstacles, including rapid clearance, enzymatic degradation and potential off-target effects. Over the years, researchers have developed various strategies to improve the stability and delivery of nucleic acids, such as chemical modifications to enhance their resistance to degradation or to reduce immunogenicity. For instance, modifying the sugar backbone with 2'-F or 2'-O-methyl groups or adding phosphorothioates can improve biostability. Additionally, nanocarriers, including Lipid Nano Particles (LNPs) and polymer nanoparticles, have been employed to protect nucleic acids from degradation by sterically hindering access to nucleases.

Nanodrug delivery systems have emerged as powerful tools for enhancing the efficacy of nucleic acid therapeutics. These systems can facilitate passive targeting to tumor sites or lymph nodes, with further modifications to the nanocarriers enabling active targeting and improving cellular uptake. LNPs and polymer nanoparticles are among the most widely used nanocarriers for nucleic acid delivery. Molecular bioconjugates, such as N-acetylgalactosamine, are also favorable for delivering nucleic acids specifically to the liver.

Immunostimulatory nucleic acids, which activate immune responses, play a pivotal role in cancer immunotherapy. These include agents that activate various pattern recognition receptors, such as Toll-Like Receptors (TLRs), retinoic acid-inducible gene I and stimulator of interferon genes.

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CONCLUSION

The field of nucleic acid therapeutics in cancer immunotherapy has made remarkable strides, with numerous approaches now in preclinical and clinical testing. These include gene-regulating therapies, immunostimulatory nucleic acids, mRNA-based treatments and gene-editing tools. The continued development of novel delivery systems, such as lipid nanoparticles, polymer nanoparticles, and molecular bioconjugates, is essential to improving the clinical translation of these therapies. As our understanding of cancer immunology expands, the potential for nucleic acid therapeutics to overcome current limitations in immunotherapy is vast, offering new hope for more effective and personalized cancer treatments.