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PERSPECTIVE

Current issues with antibody-conjugated lipid nanoparticles

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Lipid Nanoparticles (LNPs) have been utilised for many years to transfer nucleic acid cargos, such as therapeutic mRNAs and siRNAs [1]. The US FDA approved LNPs for use in humans after extensive development and optimisation. This includes the delivery of therapeutic siRNAs to hepatocytes via intravenous administration [2] and the delivery of mRNA vaccines via intramuscular administration. However, in the liver, the majority of intravenously injected nanoparticles are concentrated [1]. In particular, many LNPs obtain blood-borne ApoE lipoprotein coatings, encouraging hepatocytes to take up LNPs through interactions with the ApoE: LDL receptor [1].

It isn't easy to achieve nonliver gene editing mediated by LNPs since the majority of intravenously delivered LNPs naturally accumulate in the liver. [3] One way to counteract the inherent liver-targeting properties of LNPs is to inject them locally as opposed to intravenously. Several labs have shown successful nuclease and base editing in the mouse inner ear following local administration of lipid-encapsulated ribonucleoproteins (RNPs) [3]. However, the therapeutic utility of LNP administration would be expanded if it were possible to employ systemically given LNPs to transport gene-editing medicines to nonliver organs. LNPs can also be directed to nonliver tissues by conjugating targeting components, such as antibody fragments, to their surface [1] [2] [4]. One notable example of this approach is Epstein and colleagues' intravenously delivered anti-CD5 antibody-conjugated LNPs to attack T cells and temporarily develop chimeric antigen receptor T lymphocytes that may heal heart damage in rats [4].

The problem starts when we use antibody fragments to direct the LNPs to nonliver sites. Patients may become immunogenic due to antibody fragments. The absence of an Fc domain and in vivo mechanisms that prevent B cells from producing unstable antibody species are the causes of this. It can increase the risk of self-epitope formation through mechanisms such as structural exposure, high binding affinity, and lack of effector function modulation. These elements may increase the possibility of aggregation while producing or purifying antibody fragments [4]. Antibody fragments can also generate new epitopes that are potentially immunogenic. Multiple studies have shown antibodies to the top hinge region of Fab fragments and to the hinge portion of the F(ab')2 of IgG [4]. Without appreciable cell growth, allogeneic membrane fragments can activate cytotoxic T lymphocytes (CTLs) and elicit a secondary immunological response, indicating that specific antigens are sufficient to activate alloimmune T cells. [5].

Key messages

Lipid nanoparticles have only been used for liver-targeted gene editing due to their hepatocytic uptake. To target non-liver delivery systems, antibody-conjugated lipid nanoparticles are not the solution due to their ability to cause self-epitopes.

Integrating antibody fragments into LNPs presents several challenges that need to be addressed to optimise therapeutic efficacy. Compared with nontargeted LNPs, antibody fragment-conjugated lipid NPs may not always result in increased tumour localisation, as both can achieve similar tumour tissue accumulation [6]. acLNPs may not significantly improve tumour localisation compared to non-targeted LNPs due to systemic distribution challenges, such as rapid clearance by the immune system and the heterogeneous nature of tumour microenvironments. Additionally, off-target effects and variability in receptor expression can further limit the effectiveness of active targeting strategies, leading to unintended accumulation in healthy tissues. The physicochemical properties of antibody fragment-LNPs, such as size and charge, require careful optimisation to enhance tumour uptake, with smaller sizes resulting in improved uptake. For instance, the incorporation of PEGylation has been shown to produce smaller, more homogeneous LNPs with improved transfection efficiency and reduced cytotoxicity, while optimising formulations using design-of-experiment approaches has led to significant increases in encapsulation efficiency and targeted delivery capabilities, as demonstrated with biodegradable block copolymer-stabilized LNPs that achieved up to a 40-fold increase in transfection efficiency in certain cell lines6. While antibody fragments can improve the internalisation of lipid NPs into cancer cells, this does not necessarily translate to increased tumour localisation, indicating a need for further research into the mechanisms of NP distribution and uptake [7]. Developmental challenges such as low thermostability and weak binding to affinity purification resins can hinder the progress of antibody fragment-based LNPs from preclinical stages to clinical application.

In conclusion, while antibody fragments conjugated to lipid nanoparticles offer a targeted approach to cancer therapy, their use is not without disadvantages. The lack of increased tumour localisation, the necessity for optimisation of physicochemical properties, and developmental challenges such as stability and purification issues are key considerations that must be addressed to improve the efficacy of these therapeutic constructs. Despite these challenges, the potential for enhanced internalisation into cancer cells remains a promising aspect of antibody fragment-conjugated lipid NPs, suggesting that these systems could become more effective in clinical settings with further research and development. To enhance the targeting of LNPs to non-liver tissues, strategies such as using alternative targeting ligands, developing dual delivery systems, and employing novel conjugation techniques can be effective. These approaches aim to improve specificity, reduce immunogenicity, and enhance the overall therapeutic efficacy of LNPs in clinical applications.

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