

Exploiting the Protein Corona for Functional LNP Design and Hepatic Gene Silencing

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Lipid nanoparticles (LNPs) are clinically advanced vehicles for nucleic acid delivery and exhibit intrinsic accumulation in the liver following systemic administration. However, hepatic tropism does not necessarily translate into functional intracellular delivery. The protein corona (PC), a layer of biomolecules -particularly proteins- that forms on the LNP surface upon exposure to biological fluids, is a key determinant of LNP biological identity, influencing biodistribution, cellular uptake, and intracellular trafficking [1,2].

Here, we investigated whether modulation of the LNP-biomolecule interface could improve functional hepatic RNA delivery. Four LNP formulations with systematically varied cholesterol content were generated to modulate PC composition and biological performance. Physicochemical characterization and proteomic analysis revealed formulation-dependent differences in the adsorption of apolipoproteins, complement proteins, immunoglobulins, and coagulation factors. Comparative screening identified a lead formulation with a favorable PC profile, enhanced colloidal stability, and efficient interaction with hepatic cells, particularly Kupffer cells (KCs). Following systemic administration, the selected formulation showed enhanced liver accumulation and efficient KC uptake in vivo. siTIMP1-loaded LNPs mediated robust TIMP-1 silencing in KCs in a mouse model of primary biliary cholangitis, resulting in reactivation of extracellular matrix degradation pathways, modulation of inflammatory chemokines, reduced macrophage infiltration, and attenuation of cholestasis and liver fibrosis [3].

This concept was further extended by engineering the LNP surface after formulation to modulate its interaction with the biological environment. PEGylated LNPs bearing surface-bound DNA and proteins promoted the formation of a multicomponent stealth bionanoarchitecture upon plasma exposure. This engineered interface reduced uptake by circulating immune cells and sequestration by monocytes and macrophages in the liver and spleen, while retaining predominant hepatic accumulation [4]. Together, these findings demonstrate that the LNP-biomolecule interface can be rationally engineered to direct nanoparticle-cell interactions toward different functional objectives, including enhancing delivery to selected hepatic cell populations or limiting immune sequestration, according to the desired biological outcome.

References:

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