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Surface Composition of mRNA-Lipid Nanoparticles Determines Extent and Effect of Protein Binding

Content

Therapeutic treatments based on the production of proteins by delivering messenger RNA (mRNA) represent a promising approach to treat many diseases that currently lack other alternatives. One of the major challenges for designing such treatments is the adequate protection of these macromolecules from enzymatic degradation and their safe deliver into the target cells.

Lipid nanoparticles (LNPs) are promising vehicles for mRNA delivery and are formed by a cationic ionizable lipid (CIL), DSPC, cholesterol (Chol) and a pegylated (PEG) lipid. A good understanding of the physical and chemical characteristics of the LNPs under study is necessary to progress from pre-clinical testing. For example, the surface composition of LNPs seems to play a role on their bio-distribution and cellular uptake. The affinity of extracellular protein to the LNP surface varies with LNP composition.

A common component found in the "protein corona" of LNPs is Apolipoprotein E (ApoE), which is responsible for the transport of fats in the systemic circulation and it triggers the fat uptake by cell-rich in low-density lipoprotein (LDL) receptors. This recognition step is critical to control the LNP's circulation time and thus its pharmacological efficiency.

We employed small angle neutron scattering (SANS) to investigate the distribution of components in the LNP and the effect that ApoE has on the LNP structure. We found that the surface of LNPs have a different lipid composition than the core of the particle (ACS Nano 2021 (15) 6709-6722). In addition, we have developed a sensor platform based on Quartz Crystal Microbalance with Dissipation (QCM-D) to assess the binding affinity of serum protein to LNPs with different size and surface composition (JCIS 2022 (610) 766-774).

Combining these approaches, we could determine: (i) how changes in the LNP formulation affect the component distribution across the particle and (ii) how the LNP surface structure influences the protein binding to LNPs.

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