BIOMOLECULAR CORONA AND THERAPEUTIC LIPID NANOPARTICLES: A WORKFLOW FOR HIGH-THROUGHPUT CORONA ISOLATION AND ANALYSIS

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Background: Lipid nanoparticles (LNPs) as an excellent delivery platform for gene therapy, are increasingly utilized into routine clinical practice. To optimize the delivery efficacy in various diseases, it is necessary to acquire a mechanistic understanding of how LNPs adapt to the biological systems in both normal physiological and pathological states. A key aspect of how the biological systems affect LNPs performance, and vice versa, is the formation of a corona around the nanoparticles when they contact biological fluids. Most nanoparticles acquire a corona of biomolecules derived from the biological context they are exposed to. The formation of the biomolecular corona is believed to create a new biological identity for nanoparticles, and this is what biological systems actually perceive, rather than the pristine, uncomplexed nanoparticles. However, a solid method for rapid and high-throughput corona isolation for clinically relevant LNPs from plasma proteins, extracellular vesicles, and lipoprotein particles is still absent.

Methods: A clinically relevant lipid nanoparticle formulation was employed to understand their corona composition within the lean and obese animal plasma. To address the separation of LNPs from lipoproteins, extracellular vesicles and plasma proteins, a novel affinity-based magnetic isolation protocol was developed, without modifying the LNPs formulation. Following corona isolation, physiochemical characterization and proteomics procedures were used to evaluate the efficacy of the corona isolation.

Results: The corona harvest of up to 96 samples were achieved within 50 minutes, requiring a minimal amount of LNP formulation. A clear separation between the LNPs/corona complex from plasma components was successfully achieved. To date, this workflow identified significant differences in coronal apolipoproteins, glycoproteins, and lipids between lean and obese conditions.

Conclusions: The workflow became our handle to tailor LNPs for specific therapeutic contexts. It allows us to quantify the interactions between nanoparticle features (e.g. formulation methods, novel lipids selection, helper lipids selection, components ratio matrix), and hundreds of coronal components and, how this affects the delivery system function. It holds great promise to improve LNPs' efficacy, reduces side effects, and lower costs.