O-05.6 Short talk

The Multi-faceted Role of Cholesterol in Cellular Membranes and Lipid Nanoparticles

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Cellular membranes serve as dynamic interfaces regulating numerous biological processes, with cholesterol playing a central role in shaping their structure, dynamics, and function. Likewise, cholesterol is crucial for stabilizing lipid nanoparticles (LNPs) in pharmaceutical applications and for enhancing their therapeutic efficacy. Here, we elucidate the multifaceted functions of cholesterol in both biological membranes and LNPs using atomistic molecular dynamics simulations, including constant-pH approaches.

Our findings challenge conventional views of membrane organization by revealing that thermal membrane bending and local cholesterol distribution can collaborate to soften membranes [1], even though cholesterol is widely associated with membrane thickening and reduced permeability. Turning to LNPs, we demonstrate that cholesterol is enriched in the LNP shell [2], resulting in shifts of the pKa of aminolipids by 2–4 units, contingent on the specific lipid composition [3]. This insight underscores the importance of cholesterol-lipid interactions in modulating the physicochemical properties of LNPs, with direct implications for the design and optimization of cholesterol-containing nanocarriers in drug delivery.

[1] Pöhnl et al. Nat. Commun. 14, 8038 (2023)

[2] Trollmann et al. Biophys. J. 121, 3927 (2022)

[3] Trollmann et al. bioRxiv 2024,10.1101/2024.11.27.625717