Partition of anionic nanoparticles in cholesterol-containing membranes occurs via a local lipid phase transition

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Abstract

Engineered nanomaterials, such as diagnostic and therapeutic nanoparticles (NPs) with applications in medicine, are required to translocate across human cells without damaging essential tissues. Intracellular uptake of NPs may induce phase transitions, restructuring, stretching, or even complete disruption of the cellular membrane. Therefore, NP cytotoxicity assessment requires a thorough understanding of the mechanisms with which these nanostructures interact with the cell membrane. Molecular simulations can help rationalize the experimental behavior by providing a detailed atomic-level picture of the NP-membrane interactions and translocation processes. Simulation studies of NP-membrane interactions may be performed with Coarse-Grained (CG) force fields[1] in order to achieve longer time and length scales compared to all-atom MD simulations.[2,3,4] In this study, extensive Coarse-Grained Molecular Dynamics (MD) studies were performed to investigate the partition of an anionic ligand-decorated NP in model membranes containing dipalmitoylphosphatidylcholine (DPPC) phospholipids and different concentrations of cholesterol. In unbiased MD simulations spanning 10 μs, spontaneous fusion and translocation of the anionic NP is not observed, which is confirmed by free energy calculations that indicate a barrier for translocation beyond this timescale. The free energy calculations also point to dramatically different anionic NP bilayer permeabilities, depending on cholesterol concentration. Inside cholesterol-containing bilayers, the NP triggers a local phase transition from the liquid-ordered to the liquid phase spanning a distance twice its radius (8-10 nm), suggesting a possibly cooperative mechanism for cellular uptake. Moreover, we observe that the hydrophobic and hydrophilic moieties of the NP surface ligands rearrange to form optimal contacts with the lipid bilayer. Based on the physical insights obtained in this study, we propose a mechanism of cellular anionic NP partition, which requires structural rearrangements of both the NP and the bilayer and postulate that the translocation of anionic NPs through cholesterol-rich membranes is accompanied by a local lipid phase transition to create cholesterol-free regions.

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