Mechanism of lipid bilayer insertion by amphiphilic, monolayer-protected nanoparticles

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Abstract

Monolayer-protected nanoparticles (NPs) are a versatile materials platform useful for biological applications because features of the protecting monolayer can be engineered to tailor interactions with the biological milieu. Recently, amphiphilic NPs with surface properties that mimic typical globular proteins were shown to enter cells via a non-endocytic, non-disruptive process that could be of broad interest for applications in drug or gene delivery. The same NPs were shown to insert into single-component model lipid bilayers and access the interior of multilamellar vesicles despite no mechanism for endocytic uptake. This behavior is surprising because insertion requires the NPs to translocate charged groups across the hydrophobic bilayer core. Here, we use atomistic molecular dynamics simulations to gain molecular insight into these experimental observations. We find that the amphiphilic NPs insert into the bilayer to obtain a configuration resembling a membrane-embedded protein due to favorable interactions between hydrophobic molecules on the NP surface and the hydrophobic bilayer core. We identify a kinetic pathway for insertion that mimics the early onset of vesicle-vesicle fusion. Our calculations also suggest that charged ligand end groups cross the bilayer on experimentally relevant timescales that are significantly more rapid than expected. Finally, we leverage this mechanistic understanding to provide design guidelines for monolayer compositions optimized for bilayer insertion and cellular uptake, enabling the development of new nanomaterials for delivery applications.