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Physical Determinants of Nanoparticle-mediated Lipid Membrane Fusion

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Synthetic fusion approaches offer a novel strategy to investigate membrane fusion mechanisms and develop advanced drug delivery systems. Recently, membrane-embedded amphiphilic gold nanoparticles (AuNPs) have been used as artificial fusogens in vitro, but the physical factors driving AuNP-mediated fusion remain largely unclear. Here, we explore how lipid membrane curvature and AuNP size influence fusion. We used AuNPs with the same surface chemistry but different core diameters (~2 nm and ~4 nm) interacting with phosphatidylcholine unilamellar vesicles of different membrane curvatures and containing a biologically relevant percentage of cholesterol. Based on a combination of fluorescence spectroscopy assays, dissipative quartz microbalance, and molecular dynamics simulations, our findings reveal that small AuNPs promote vesicle fusion regardless of the membrane curvature. In contrast, large AuNPs do not exhibit fusogenic properties with low curvature membranes and can induce fusion events only with significantly curved membranes. Steric hindrance of large NPs prevents the progression from the stalk state to the hemifused state, an effect that is only partially compensated by membrane curvature. These findings provide key insights into the interplay of AuNP size and membrane curvature in fusion processes, expanding the potential of synthetic fusion systems.