Passive membrane penetration by ZnO nanoparticles is driven by the interplay of electrostatic and phase boundary conditions

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The internalization of nanoparticles through the biological membrane is of immense importance for biomedical applications. A fundamental understanding of the lipid specificity and the role of the membrane biochemical and physical forces at play in modulating penetration are lacking. The current understanding of nanoparticle–membrane interaction is drawn mostly from computational studies and lacks sufficient experimental evidence. In the current study, we use confocal fluorescence imaging and potentiometric dye based fluorimetry to investigate the changes in dipole potential, fluidity and hydrophobicity, triggered by ZnONP, in both multi-component as well as single lipid membranes using biomimetic cell model membrane systems. We find that ZnONP preferentially interacts with phosphatidylinositol and phosphatidylcholine head-group containing lipids. Further, to mimic the cellular phase separation, relevant membrane conditions of three varying compositions of lipids were used. Partial-to-complete phase separation was triggered by ZnONP on these three membrane composition, in a cholesterol dependent manner. Interestingly, the dipole potential remained unchanged for partially phase separated membrane on ZnONP crowding, whereas an increase in dipole potential was observed in the fully-phase separated membrane on ZnONP crowding. The ZnONP crowding also made the two membrane conditions elicit a contrasting change in fluorescence anisotropy which was in accordance with the diffusion coefficient measured for the two membrane conditions. ZnONP prefers the liquid disordered region along with the edge of the phase separated boundaries of the membrane for its penetration. This penetration is driven by the the interfacial energy and phase boundary conditions which are dependent on the composition and ZnONP induced lipid reorganization. More in ***RSC Nanoscale*** **2018.** (DOI: 10.1039/C7NR08351C)