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## Fusion mechanisms of small extracellular vesicles with model membranes

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Extracellular vesicles (EVs) are a potent intercellular communication system. Such small vesicles transport biomolecules between cells and throughout the body, strongly influencing the fate of recipient cells. Due to their specific biological functions they have been proposed as biomarkers for various diseases and as optimal candidates for therapeutic applications. Despite of their extreme biological relevance, their mechanisms of interaction with the membrane of recipient cells are still hotly debated. We performed a multiscale investigation based on AFM, SAXS, SANS and Neutron Reflectometry to reveal structure-function correlations of purified EVs in interaction with model membrane systems of variably complex composition, to spot the role of different membrane phases on the vesicles internalization routes. Our analysis reveals a strong interaction of EVs with the model membranes and preferentially with the borders of protruding phase domains. Moreover, we found that upon vesicle breaking on the model membrane surface, the biomolecules carried by/on EVs diffuse in a way that departs from the expected simple fusion. Our approach has clear implications on the modulation of EVs internalization routes by targeting specific domains at the plasma cell membrane and, as a consequence, on EVs-based therapies.

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