Effects of membrane shape and lipid composition in extracellular vesicle and platelet biology

by

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In this work, I examine the importance of fundamental properties of lipid membranes, such as membrane curvature or lipid composition, in the context of extracellular vesicle and platelet biology. Although differing in biologic function, both extracellular vesicles and platelets are comparatively small in size, anucleate, and expose phosphatidylserine on their outer membrane leaflet. Phosphatidylserine is an anionic lipid that is generally sequestered to the inner leaflet of bilayer membranes. The exposure of phosphatidylserine on the outer membrane leaflet of extracellular vesicles appears necessary for their signaling, and the exposure of phosphatidylserine on platelets facilitates the assembly of enzymatically active coagulation protein complexes. I first highlight the basic biology of extracellular vesicles and address biochemical and biophysical detection methods that depend on the lipid composition and particle size of the extracellular vesicles. Next, I use all-atom molecular dynamics simulations to show that increasing the lateral density of lipids can induce a bilayer membrane to form a curved shape. These membranes provide a model system for studying interactions in curved membranes, as well as demonstrate that curved membranes display an increased number of lipid packing defects. Next, I adapt theoretical models of membrane-membrane interactions to examine the interaction energies between extracellular vesicles and cells. These estimates show that smaller vesicles such as

exosomes are more likely to signal via endocytosis, while larger vesicles like microvesicles are more likely to signal via receptor-ligand interactions. Finally, I examine the effects of phosphatidylserine-targeting peptides on the platelet procoagulant response. I show that these peptides can compete with coagulation factors for phosphatidylserine binding sites and target phosphatidylserine exposed on activated platelets *in vitro* and *in vivo*. Together, this work supports a broader understanding of how membrane shape and lipid composition influences, and is a potential target for modulation of, the biology of extracellular vesicles and platelets.