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Highly tail-asymmetric lipids improve interdigitation minimizing their changes to fluid membrane properties

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Membranes of a highly pathogenic bacterium, *Francisella tularensis*, contain tail-asymmetric phosphatidylethanolamine (XJPE) lipids which were previously shown to inhibit inflammatory responses in host cells. These tails (24:0/10:0) have unusually high length asymmetry, and their impact on membrane properties is unknown. In this study, we use small angle X-ray scattering and molecular dynamics simulations to examine the structures and properties of simple membranes with varying XJPE ratios. With increasing proportions of XJPE lipids, DOPC or POPC membranes get only get slightly thicker, similar to DOPE addition, but do pack tighter and more prone to ordering/forming gel-phase. XJPE achieves this modest effect on bilayer properties by frequently extending the longer 24 carbon tail into the opposing leaflet, with the tail interdigitation distributing the lipid effect between the leaflets. However, when XJPE is incorporated asymmetrically (i.e. only to one leaflet of a membrane), the longer 24 carbon trail is more prone to bending up, occupying their own leaflet, and perturbing membrane properties. XJPE lipids can dynamically adopt two conformations where their long tails are either extended or in a bent-back orientation. The former means increased interdigitation and tail ordering while the latter impacted lipid packing, interleaflet contacts and membrane elasticity. The presented data clearly shows this XJPE biphasic tail configuration in simple membranes but the effect of tail-asymmetric lipids on more complex membrane-associated events should be further investigated to reveal how *Francisella tularensis* uses tail asymmetry to facilitate vesicle fusion and destabilize host cells. This work was funded by Laboratory Directed Research and Development at the Lawrence Livermore National Laboratory (24-ERD-027) and performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344. LLNL-CONF-2001889