

# The lipidomic, biophysical, and functional asymmetry of the mammalian plasma membrane

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A fundamental feature of cellular plasma membranes (PMs) is an asymmetric lipid distribution between the bilayer leaflets. However, neither the detailed, comprehensive compositions of individual PM leaflets nor how these contribute to structural membrane asymmetries have been defined. We report the distinct lipidomes and biophysical properties of both monolayers in living mammalian PMs. Phospholipid unsaturation is dramatically asymmetric, with the cytoplasmic leaflet being approximately twofold more unsaturated than the exoplasmic leaflet. Atomistic simulations and spectroscopy of leaflet-selective fluorescent probes reveal that the outer PM leaflet is more packed and less diffusive than the inner leaflet, with this biophysical asymmetry maintained in the endocytic system. The structural asymmetry of the PM is reflected in the asymmetric structures of protein transmembrane domains. These structural asymmetries are conserved throughout Eukaryota, suggesting fundamental cellular design principles.