Lipid lateral heterogeneity in plasma membranes: role in cell deformation?

Donatienne Tyteca

CELL Unit, de Duve Institute, Université catholique de Louvain, Brussels, Belgium

Cell deformation is a critical feature for numerous physiological processes, including squeezing of red blood cell (RBC) to allow optimal gas transfer between blood and tissues, cytodieresis or cell migration. Cell deformation is generally attributed to a dynamic cytoskeleton. However, whether and how membrane lateral heterogeneity in lipid domains can regulate cell deformation in coordination with the cytoskeleton remain poorly understood. To explore this question, we focus on RBCs since these exhibit (i) a unique deformability, allowing them to pass through narrow capillaries and splenic pores; (ii) a lower deformability together with vesiculation upon aging and in membrane fragility diseases; (iii) a cytoskeleton strongly anchored to the membrane; and (iv) a featureless surface and no vesicular trafficking. By confocal imaging of living RBCs and complementary labeling approaches (trace insertion of fluorescent lipid analogs, direct decoration of endogenous lipids using specific proteins derived from bacterial toxins, laurdan labeling), we discovered that sphingomyelin and cholesterol cluster into stable submicrometric domains in the outer plasma membrane leaflet. Although sphingomyelin- and cholesterol-enriched domains show similar temperature behavior and reciprocal dependence, they only partially colocalize and differ in abundance and dependence to membrane tension and anchorage to the underlying cytoskeleton. Altogether, these data suggest the coexistence of two types of domains, respectively enriched in cholesterol mainly and sphingomyelin/cholesterol. Cholesterol- and sphingomyelin/cholesterol-enriched domains specifically associate with distinct curvature areas of the RBC biconcave membrane and exhibit a differential fluidity, higher than the surrounding bulk membrane. Upon RBC deformation, cholesterol-enriched domains gather to modulate/stabilize high curvature areas. In contrast, sphingomyelin/cholesterol-enriched domains increase in abundance, allowing for subsequent shape restoration through calcium efflux. Upon RBC aging, both lipid domains appear as specific vesiculation sites. In genetic RBC membrane fragility diseases that impair resistance to shear stress and cause hemolytic anemia, such as spherocytosis and elliptocytosis, lipid domain abundance and the differential fluidity of domains *vs* bulk membrane are impaired. Our data suggest that lipid domains contribute to RBC deformation and vesiculation in a process driven by the differential fluidity (line tension) of domains *vs* bulk membrane.