Phosphatidylserine lipids affect the location of chondroitin sulfate at the membrane surface

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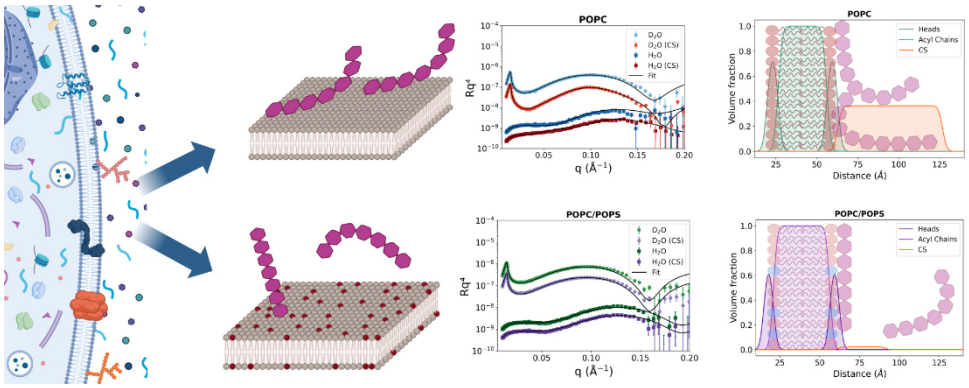
Chondroitin Sulfate (CS) is a negatively charged polysaccharide constituting one of the key components of the extracellular matrix [1]. CS can be found anchored directly to the plasma membrane, in close proximity to membrane phospholipids. Despite its potential role in pathological conditions such as cancer, i.e. CS is overexpressed at the surface of cancer cells[2], and its potential application as a biomarker [3], only a limited number of studies have investigated CS–lipid interactions [4,5]. Most of these studies used lipid monolayers at the air–water interface, with a prevailing focus on phosphatidylcholine (PC) systems. In this work, quartz crystal microbalance with dissipation monitoring (QCM-D), neutron reflectometry (NR), fourier-transform infrared spectroscopy (FTIR), and molecular dynamics (MD) simulations were combined to investigate CS interaction with PC bilayers, as well asbilayers containing a negatively charged phospholipid, phosphatidylserine (PS) in mixture with PC.: While healthy cells predominantly expose PC at the outer leaflet, PS exposure occurs during inflammation and is also observed within cancer cells [6]. QCM-D and NR confirmed stable CS adsorption on POPC bilayers, consistent with prior studies on DPPC monolayers [5]. MD simulations identified electrostatic interactions between CS sulfate groups and the choline moiety of POPC as the primary stabilising contacts, a finding further supported by FTIR spectroscopy. In contrast, CS adsorption on PC/PS bilayers was undetectable by both QCM-D and NR; MD simulations attributed this to a reduction in sulfate–lipid contacts, likely due to electrostatic repulsion from the anionic serine headgroups of POPS.
To the best of our knowledge, this is the first study probing CS–bilayer interactions in a physiologically relevant PC/PS mixture.Comparison with previous data on DPPG monolayers [5] suggests that negatively charged PS and PG lipids affect CS association differently, indicating that the specific headgroup composition, rather than net charge alone, governs CS–membrane interactions. These findings provide mechanistic insight into how plasma membrane lipid composition modulates the structural organisation of extracellular matrix components at the cell surface.

Keywords:
Chondroitin sulfate, supported lipid bilayers, neutron reflectometry, molecular dynamics simulations, infrared spectroscopy



Neutron reflectometry reveals how chondroitin sulfate interacts differently with POPC and POPC/POPS lipid bilayers.

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