Bilayers at the ILL

Contribution ID: **40** Type: **Oral presentation**

Asymmetric membranes and the study of lipid movement across single lipid bilayers

Thursday, 12 December 2019 15:20 (20 minutes)

Over the past few years, our lab has put forth an effort to measure the rate and energetics of the diffusion of cholesterol and lipids. Using small angle neutron scattering (SANS), we found that the diffusion rate of cholesterol was much slower (hundreds of minutes) rather than the accepted value of under a second. Our group's work showed that the discrepancy was likely due to artifacts produced by differences between cholesterol and the analogues used by other experiments or by the use of extraneous compounds such as cyclodextrin, which our group argued, disrupts the membrane itself. However, the dispute has remained unresolved since our group's measurement of cholesterol's diffusion within membranes was occurring while cholesterol was also diffusion between different membranes (a process we called exchange). So, our team has been taking steps to eliminate exchange from the measurement and therefore measure the intra-membrane diffusion rate directly. We are using a new non-disruptive method to craft an asymmetric distribution of cholesterol and lipids in the lipid bilayers of unilamellar vesicles to then measure the rate at which they diffuses through the bilayer. To track the diffusion rates we are using nuclear magnetic resonance spectroscopy (NMR), and small angle neutron scattering (SANS).

The great variety of lipid molecules in the cell membrane suggests their complex and unique role in cell function. The cell has further established unique lipid composition indifferent membranes within the cell for directed functionality. In addition, in membranes like the plasma membrane(PM), there is an asymmetric distribution of lipids between the outer or exoplasmic and the inner or cytoplasmic leaflets and the physiological fate of cells depends on the strict maintenance of this asymmetry. However, the
exact mechanisms and energetic toll by which these lipids arrive and particularly remain at their locations, such as in the PM, are not fully
understood. Reliable values of passive lipid translocation rates are a necessary starting point for a detailed mechanistic understanding of
the lipid distribution landscape in cellular membranes. However,
obtaining these values has been hampered by artifacts emerging from different
methodologies. As a result, the reported rates for similar
lipids can vary by several orders of magnitude, from less than a second to
hours. Work in the last few years by several groups including ours, have shown that only those techniques free of artifacts can free of artifacts can potentially be used in the study of the transport of lipids across membranes.
Here we present our recent results on the production of asymmetric membranes
without the requirement of molecules such as cyclodextrin to study the
intra-membrane flip-flop of lipids and cholesterol across a single lipid bilayer using Small Angle Neutron Scattering, NMR, and fluorescence techniques.

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Session Classification: Session E