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Investigating the effect of an ionisable lipid on layer structure and dynamics in a simplified system

Content

Cationic ionizable lipids (CILs) have become relevant in the formulation of delivery systems for mRNA therapeutics. In this work, we have focussed on the CIL DLin-MC3-DMA (MC3), currently the most potent CIL used in research. [1] Although many reports have investigated the in vitro efficacy of these LNPs, MC3 itself has not been widely studied.

In this work, we have characterised the properties of MC3 in simplified lipid systems (MC3/DOPC) over a cell relevant pH range and varying MC3 content (0 – 15mol%). We have employed quartz crystal microbalance with dissipation monitoring (QCM-D), ellipsometry and total internal reflection fluorescence (TIRF) microscopy to investigate the characteristics of the deposited lipid layers and the adsorption of mRNA and polyadenylic acid (polyA), an mRNA model, to these layers. Although the adsorption of the nucleic acids was strongly pH dependent, indicating structural variation of the layer with pH, these methods showed that the dynamics within the lipid layer alone were not significantly affected.

Additionally, neutron reflectometry measurements were used to investigate the structure of the different MC3/DOPC compositions, where small but notable differences were observed between the 5mol% and 15mol% MC3 samples. The collective information from the surface characterisation point to the likelihood that MC3/DOPC mixtures do not form simple bilayer structures. This hypothesis is further supported by comparison to molecular dynamics simulations, which also showed pH dependent behaviour for all compositions.

As the delivery process for mRNA lipid nanoparticles is still unclear, understanding the contributions of the individual lipids can help to elucidate the dynamics and structures of complex lipid systems.

[1] M. Yanez Arteta, T. Kjellmana, S. Bartesaghi, S. Wallin, X. Wu, A. J. Kvist,
A. Dabkowska, N. Székely, A. Radulescu, J. Bergenholtz, and L. Lindfors, Proceedings of the National Academy of Science, 2018, 115 (15), 3351.

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