**The Impact of DHA on Physical Properties of Model Cell Membrane**

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**ABSTRACT**

As an important omega-3 polyunsaturated fatty acid, the uptake of docosahexaenoic acid (DHA) into cells may change a series of biological processes such as increasing the ratio of polyunsaturated lipids in the plasma membrane. However, the detailed physical impact of DHA molecules on the plasma membrane is still far from clear. On the other hand, the plasma membrane can segregate into raft-like and non-raft-like membrane domains due to differential interactions between lipids and proteins. Hence, in this work, we performed µs-scale coarse-grained molecular dynamics (MD) simulations to reveal the detailed interactions between DHA molecules and the phase-separated model cell membrane. Our results indicated that both neutral and anionic DHA molecules could spontaneously self-assemble into the nanoclusters, fuse with the lipid membrane and preferably locate in the liquid-disordered membrane domains. The incorporation of DHA molecules increased the membrane thickness. Besides, DHA can also flip-flop between the two membrane leaflets, and its effect on the flip-flop rate of cholesterol molecules is concentration-dependent. Moreover, both neutral and anionic DHA molecules can change the intrinsic transmembrane potential of the lipid membrane during the fusion process. Effects of the latter are much more significant. Our results reveal the physical impact of DHA molecules on the plasma membrane, which may provide useful insights into the elucidation of DHA’s physiological functions.

**Keywords:** DHA; Lipid domains; Transmembrane potential; Coarse-grained model; Molecular dynamics simulation.