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Structural characterization of lipid droplets using molecular dynamics simulations

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Lipid droplets (LDs) are organelles with a central role in lipid and energy homeostasis. Defects in their biogenesis and growth are associated with multiple diseases, therefore it is crucial to understand the molecular mechanisms of fat storage. Neutral lipids (NLs), mainly triglycerides (TG) and cholesteryl esters (CE), are produced in the endoplasmic reticulum (ER). Then, NLs are stored between the two ER monolayers where they aggregate in lenses that subsequently grow into mature LDs.

Molecular dynamics simulations were used to investigate how lipids and proteins modulate LD formation and growth.

First, parameters for NLs, in particular for TG and their precursor diacylglycerol (DG), were developed. Then, these parameters where used to show that pre-existing bilayer stresses modulate the propensity of TG to aggregate in nascent LDs or to remain diluted in the bilayer.

Subsequently, seipin, a protein present at sites of LD formation, was shown to trap and accumulate TG and DG already at low concentrations. The key amino acids involved in the interactions between the protein and TG were identified and mutated, resulting in defects in TG accumulation.

Next, curvature was shown to promote LD formation by slowing TG diffusion and, as a consequence, by increasing the local concentration of TG in curved regions compared to flat ones.

Finally, the properties of mature LDs with a core consisting of TG and CE were studied. CE were shown to be enriched at the periphery of the LD core and to modulate the surface properties of LDs.

Overall, a significant contribution towards a better understanding of the mechanisms of LD formation was provided.

Jury:

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