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Birth of an organelle, in silico: molecular mechanism of lipid droplet budding

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Lipid droplets (LDs) are organelles regulating lipid storage and metabolism in cells. LD biogenesis takes place mostly in the endoplasmic reticulum (ER), and starts with the synthesis of neutral lipids, such as triglycerides. When the concentration of neutral lipids reaches a certain threshold, oil droplets form by phase-separation, yielding a lens-shaped nascent lipid droplet – a process known as nucleation. As more neutral lipids are synthesized, the lens grows and eventually buds out of the ER membrane, generally towards the cytosol, at sites marked by a specific protein named seipin. Several open questions remain regarding the mechanism of LD budding, because the initial steps of LD biogenesis are extremely difficult to observe experimentally. Notably, the roles of ER topology, leaflet asymmetry, and membrane composition in the budding mechanism are substantially unknown.

Here we develop a new, simple methodology allowing to simulate the generation of lipid droplets in membranes mimicking the topology and composition of the ER, and we explore possible mechanisms of LD budding. Molecular dynamics simulations at the coarse-grained level are performed out of equilibrium, as in real life experiments. First, we build ER tubular membranes with realistic size and different compositions, including a realistic ER composition, then we progressively increase the number of triglyceride molecules in the system to mimic the effect of triglyceride synthesis and induce budding. We explore different possibilities for the driving forces of the budding process, including LD volume and ER leaflet asymmetry, and observe LD budding with different mechanisms depending on the specific conditions imposed on the system. The simulations allow us to make prediction on the role of seipin, the localization of phospholipid synthesis, and the stability of the ER-LD connection. Our methodology pushes the limit of biological simulations allowing, for the first time, simulations of organelle biogenesis.

Session

Computational methods

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