UNIVERSITÀ DEGLI STUDI
DI TRENTO
Dipartimento di Fisica

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Room A110 – Polo Ferrari 1

Birth of an organelle: molecular mechanism of lipid droplet biogenesis

Abstract:

Lipid droplets (LDs) are cellular organelles regulating energy and lipid metabolism. They are generated mostly in the tubular regions of the endoplasmic reticulum (ER) by the accumulation of neutral lipids, such as triglycerides, into lens-shaped blisters. When the lens- shaped nascent lipid droplet grows beyond a certain threshold, it emerges from the ER bilayer membrane, generally towards the cytosol – a process known as budding. Images of mature, micrometer-sized LDs are available, as well as a few images of lens-shaped nascent LDs trapped in the ER bilayer, but the mechanism of biogenesis has never been observed experimentally.
Here we developed a novel, robust computational methodology to simulate the initial steps in lipid droplet biogenesis, from the nucleation of the nascent LD to the budding towards the cytosol. Our simulations show that LDs do not bud in the absence of sufficient asymmetry between the two leaflets of a membrane, independently of membrane morphology; leaflet asymmetry is necessary and sufficient to promote the budding transition. Seipin, a membrane anchored protein essential for the correct functioning of LDs, promotes an asymmetric shape of nascent LDs but it is not sufficient per se to promote the budding transition. However, we predict that seipin increases the mechanical stability to the LD-tubule connection. The simulations also allow to understand the role of the complex ER composition in allowing for a stable, defect-less, high curvature LD-tubule connection, and suggest that regulation of the oil/phospholipid synthesis ratio is crucial to preserve the mechanical stability of the ER network. Our new methodology paves the way to simulations of complex transformations of membrane systems, including the biogenesis of other organelles, the formation of viral envelopes, and bacterial division.

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