Distribution of proteins in nascent lipid droplets

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Lipid droplets (LDs) are organelles regulating lipid and energy metabolism in cells, generated in the endoplasmic reticulum (ER). From a chemical point of view, they are an emulsion of oil in water, bounded by a monolayer of phospholipids. Despite their fundamental role in metabolism; their mechanism of formation remains unknown.

One project of my PhD thesis focuses on the distribution of proteins in nascent lipid droplets. Mature LDs have on their surface proteins from two origins: hydrophobic proteins from the ER (Class I), and amphipathic proteins from the cytosol (Class II). These proteins are linked to the lipid droplet functions. Class I proteins enter LDs probably during the early stages of LD formation, by diffusing from the ER membrane to the lens monolayer. However, mature LDs do not have the same protein composition as the ER, implying that during the formation of LDs, some proteins go to the lipid droplet monolayer, and others stay in the ER bilayer. The reason why protein partitions differently between ER and LDs remains unknown.

Experiments realized on synthetic LDs by our collaborators show that all hydrophobic proteins partition to the LD monolayer. I used molecular dynamics simulations to interpret the experiments at the molecular level. I simulated peptides of the KWALP family in nascent LDs, and characterized their distribution between lipid bilayers and LD monolayers in conditions mimicking the experiments. KWALP is a peptide that can be modified to model different types of proteins. I found that the distribution of KWALP depends on the exact nature of the protein. The protein distribution observed in the experiments is reproduced by simulations, and transmembrane peptides distribute to the rim of the LD, which has never been observed in experiments nor simulations.