

## **Establishing a fine-resolution topology map of the monolayer-integrated hairpin protein UBXD8**

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Lipid droplets (LDs) are hubs of cellular metabolic energy stored in the form of neutral lipids, particularly triacylglycerols (TGs). These ubiquitous cytoplasmic organelles are derived from the endoplasmic reticulum (ER) and consist of a hydrophobic core encircled by a phospholipid monolayer. Hence, LDs are unique as they do not separate the two aqueous compartments like other organelles. The lipid monolayer is decorated with either peripheral proteins or with integral membrane proteins that adopt an unorthodox monotopic hairpin topology [1]. The functions of the LDs are mainly executed and regulated by these surface proteins. Current bioinformatics tools are suitable for the topology prediction of transmembrane-spanning proteins; however, are limited in determining the topology of monotopic hairpin proteins [2]. Recent work from our group has unraveled the targeting pathway of UBXD8- a putative hairpin protein, which localizes to both ER and LDs [3]. It is initially inserted into the cytoplasmic face of the ER bilayer before translocation to the LD monolayer. So far, the intricate details of the UBXD8 topology have not been determined. The goal of this project is to determine the key elements regulating the topology of hairpin proteins using state-of-the-art biophysics, computational, and classical biochemical approaches.

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