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Opinion Article

Function of Regulatory Lipids in Intracellular Membrane Fusion

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DESCRIPTION

Different cellular membranes exhibit a highly diverse distribution of lipids. Only a small percentage of lipids are transported by vesicles to their final intracellular distribution. Instead, a vast number of Lipid Transfer Proteins (LTPs) move modest amounts of lipids at a time using hydrophobic cavities that stabilize lipid molecules outside of membranes to carry out the majority of lipid traffic. Despite the fact that the first LTPs were found about 50 years ago, the majority of the advancements in our understanding of these proteins have been made in the last few years, which has greatly improved our understanding of the temporal and spatial dynamics of these lipid transporters. With new discoveries of their multimeric assembly, there are now more known as LTPs.

Dynamic structural techniques have replaced static crystal structures in structural investigations of LTPs, which demonstrate how conformational changes affect lipid processing at a sub-millisecond timeframe. The discovery that several intracellular LTPs localize to two organelles simultaneously, forming a shuttle, bridge or tube that connects the donor and acceptor compartments, is a significant development. The possibility of designing medicines that particularly target lipid transfer is made possible by a greater understanding of the molecular mechanisms by which various lipids arrive at their destination in disorders linked to lipid transport and distribution.

There are non-vesicular routes for intracellular traffic in addition to vesicular traffic, which is a key topic in membrane cell biology. Lipids that are exchanged between organelles that are membrane-bound are among the molecules that move non-vesicularly with the greatest frequency. While lipids are carried through membrane vesicles, organelles like the mitochondria obtain all of their lipids through non-vesicular pathways. The Endoplasmic Reticulum (ER)-mitochondria pathway, which has a high capacity in both directions, was the focus of early research on non-vesicular lipid flow. Other non-vesicular pathways were later discovered, including inside the secretory pathway. For instance, lipid traffic (half-life, 1–5 min) between the ER and the plasma membrane occurs more quickly than can be explained by vesicular traffic.

Lipid transfer proteins were proposed as functions that mediate lipid transfer across the cytoplasm in order to explain the mystery of all of this non-vesicular traffic. By definition, LTPs promote one or more of the following processes: removing lipid from a membrane, reintroducing lipid into a different membrane, and mobilizing lipid into the aqueous cytoplasm. By replicating lipid transfer in cell-free studies with radiolabelled donor membranes and cold acceptor liposomes, the first LTPs were found. Different levels of lipid selectivity are displayed by LTPs. Numerous LTPs protect the hydrophobic regions of the lipid, according to structural analyses, frequently in interior cavities that enclose the lipid with a movable protein segment, like a box with a lid. This allows the energetic transport of lipids into the cytoplasm feasible.

A hydrophilic binding site, which may be inside or outside the cavity, is what underlies any specificity an LTP may have for a lipid head group. Large LTP families have developed as a result of gene duplication, some with radically different lipid specialisations. In prokaryotes, several families have analogues since these organisms similarly use LTPs to transport lipids between membranes. In this study, the function of regulatory lipids in GTPase-mediated intracellular membrane fusion is discussed, with particular attention paid to how these lipids influence the proteins involved in membrane fusion. While some regulatory lipids may bind directly to fusion proteins and act as an anchoring site for partner proteins, concentrating them at the site of membrane fusion, others may act in a more indirect manner.

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