

# The protein carriers of hundreds of lipids have been identified

Different types of lipid molecule are transported around the cell by lipid-transfer proteins. Biochemical approaches have been adapted to measure which lipids are captured by the more than 130 known human lipid-transfer proteins, providing a valuable resource that reveals some principles of how these transporters work.

**This is a summary of:**

Titeca, K. *et al.* Systematic analyses of lipid mobilization by human lipid transfer proteins. *Nature* <https://doi.org/10.1038/s41586-025-10040-y> (2026).

**Cite this as:**

*Nature* <https://doi.org/10.1038/d41586-026-00570-4> (2026).

## The mission

Human cells generate thousands of types of lipid molecule that, owing to their water-repelling nature, cannot move freely through the cell's aqueous environment to where they are needed<sup>1</sup>. Lipids therefore require lipid-transfer proteins (LTPs) to carry them<sup>2</sup>. LTPs are soluble lipid-handling machines whose dysfunction in humans can lead to disease, including neurodegenerative conditions<sup>3</sup>. LTPs bind to lipid cargoes, and sometimes to cofactors – other membrane lipids that can facilitate the uptake and release of cargoes where and when they are needed. LTPs thus ensure the directionality of lipid transfer, as well as the coupling of this process to metabolism. The cargoes and cofactors of most of the more than 130 human LTPs remain unknown, limiting our understanding of the logistics of LTP-mediated lipid flows and how they adapt to metabolic needs.

## The discovery

We systematically characterized LTP-bound lipids, measuring LTP specificity for lipid species across the complete set of lipids in the cell – the lipidome. We added small tags to human LTPs that allowed us to purify them. Using mass spectrometry, we characterized the lipids that bound stably to LTPs, either in human cells or in an assay in which lipids reside in simplified artificial membranes (Fig. 1). Each approach has limitations, but they are complementary and enable the detection of different yet overlapping sets of LTP–lipid complexes. We identified nearly 500 previously unknown LTP–ligand pairs, including both well-studied LTPs and ones whose cargoes had not been identified. We also discovered pairs that include lipids not previously known to be part of these transport systems.

Using 3D structures and molecular simulations, we determined how the lipids in newly identified pairings fit into the LTP binding pocket, and explained the specificity of three LTPs for the lipids they carry. We also measured how manipulations that increase LTP function affect cellular lipidomes. Lipid transport is often coupled to lipid metabolism, so perturbations of the former should affect the abundance of lipids and/or metabolic products. Integrating the various data provides an initial map of LTP-handled lipids.

The chemical structure of lipid species' 'head' groups and fatty acid 'tails' differ. We found that LTPs were selective not only for specific head groups, but also for certain fatty acids; this specificity seems to define functional pools of lipid species with

differing levels of accessibility to transport machineries. Another widespread feature of LTPs is their ability to bind to structurally diverse classes of lipids, including cargoes and the regulatory lipids that act as LTP cofactors. Our initial map of LTP–lipid and cargo lipid–regulatory lipid pairings reveals previously unknown functional links between lipids and possible regulatory mechanisms that link lipid transport to lipid metabolism.

## Future directions

This work provides valuable information about LTP cargoes and possible cofactors that could explain the directionality of lipid transport and its coupling to metabolism. It should motivate further research on LTP-mediated lipid transport, for example through the development of data sets describing levels of LTP–lipid complexes in different cell types, metabolic states and disease conditions.

Lipids are essential cellular components but remain understudied. In the longer term, the development of larger protein–lipid data sets would inform computational models for predicting protein–lipid interactions, similarly to models that predict protein–protein or protein–ligand interactions.

We have only begun to study the cellular roles of LTPs, analysing the impact of increases in LTP function on cellular lipidomes. However, the identity of the organelles that LTPs connect, and the role of LTPs in organelle function, remain largely unexplored. How LTPs function at the molecular level also remains mysterious: how can they selectively mobilize lipids with such diverse chemical structures? How do they differentiate between membranes donating and accepting lipid molecules? And what membrane-induced mechanisms facilitate the extraction and release of cargo at the appropriate location or organelle?

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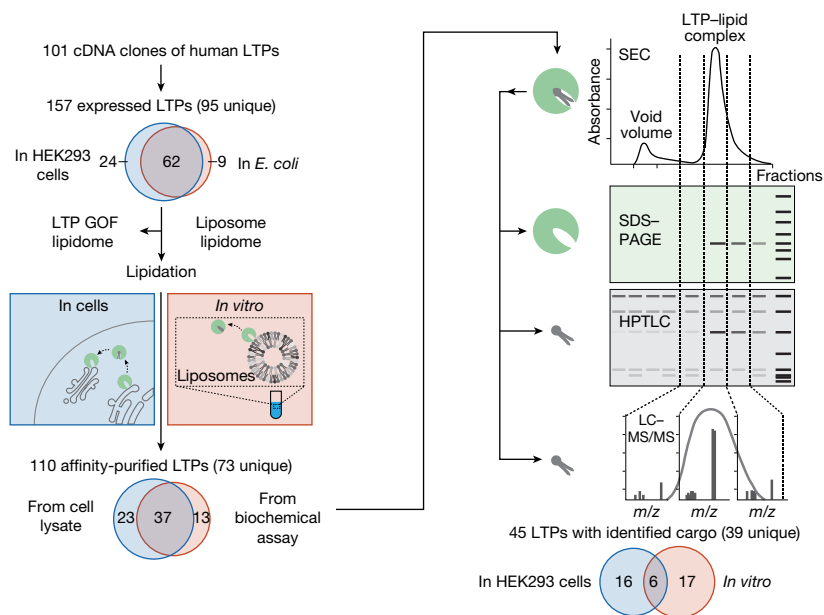
## EXPERT OPINION

**||** This study provides a systematic analysis of the lipid-binding properties of human lipid-transfer proteins (LTPs). The authors identified lipid cargoes for 39 human LTPs using two complementary approaches. The study is a tour de force, yielding many previously unknown lipid-binding partners and

establishing a methodological pipeline for exploring protein–lipid interactions. The LTP–lipid interaction map provides a useful resource for future work to unravel the architecture of the metabolic lipid network.” (CC BY 4.0)

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## FIGURE



**Figure 1 | Creating a resource on lipid-transfer proteins.** Lipid-transfer proteins (LTPs; green) extract lipid molecules (grey) from membranes and carry them to the membrane of target organelles, into which they are released. We expressed 101 complementary DNA (cDNA) templates encoding human LTPs in the HEK293 cell line and/or bacteria (*Escherichia coli*). LTPs were labelled with a tag and purified from cell contents (lysates) or preparations containing small lipid vesicles called liposomes. Size-exclusion chromatography (SEC) was used to separate sample fractions containing LTP–lipid complexes from those without LTPs. LTPs were analysed using sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS–PAGE). High-performance thin layer chromatography (HPTLC) and a mass-spectrometry technique (LC–MS/MS) were used to analyse bound lipids.  $m/z$  is the ion mass-to-charge ratio. The effects of gain of LTP function (LTP GOF) on the full set of lipids in the cell (lipidome) were examined. Created in BioRender; Gavin, A. C. <https://biorender.com/0mht878> (2025). Titeca, K. *et al./Nature* (CC BY 4.0).

## BEHIND THE PAPER

Investigating lipids is methodologically challenging. We initially developed our protocols in the single-celled organism *Saccharomyces cerevisiae* (yeast), which has a simple LTP system for which most ligands were known, with the idea of subsequently applying the protocols to human cells. However, the unexpected discovery that a lipid called phosphatidylserine, which was not previously thought to be carried by LTPs, is bound by an LTP that was thought to transport sterols<sup>4</sup>, kept us busy with yeast for much longer than expected. When we finally

finished mapping LTP–lipid complexes in humans, the amount and complexity of the data were staggering. That is when we met N. R. and won the Lipotype Excellence Award. Our collaborations enabled us to develop strategies for investigating LTP structures and functions, enabling us to validate as many previously unknown LTP–ligand pairs as possible, and to illustrate their relevance in cellular context.

**A.-C.G.**

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## FROM THE EDITOR

One reason why lipid-transfer proteins are of interest to cell biologists is their role in mediating inter-organelle communication through membrane contact sites. The resource that Titeca *et al.* provide through their study should aid this area of research, which is relevant for understanding not only basic biology, but also health and disease.

**Sadaf Shadan**, Senior Editor, *Nature*