

Editorial on Special Collection in *Contact*: VPS13 and Bridge-Like Lipid Transfer Proteins: A New Mode of Intracellular Continuity

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There has been an explosion of interest in vacuolar protein sorting 13 (VPS13) and related proteins, with a 10-fold increase in the rate of publication of papers from 10 per year before 2015 to 100 now. The path that led to this started with developments that strongly implicated the yeast Vps13 protein in lipid transfer (Lang et al., 2015). The landmark discovery came in 2018, when it was shown that these large proteins transfer lipids (Kumar et al., 2018). Soon after came the realization that Vps13 and Atg2 are structurally related, marking them as founding members of a larger protein family (Osawa et al., 2019; Valverde et al., 2019). Another key development here, and everywhere else, was when AlphaFold allowed us to see the bridge-forming structures of the entire family (10 in humans, seven in yeast, and six in flowering plants), many of which can bridge gaps between organelles (15–30 nm) (Jumper et al., 2021). To celebrate these advances, this journal put together a collection of new work on VPS13 and other bridge-like transfer proteins, which includes six original research articles and four reviews.

Starting with original research (see Table 1), Amos et al. showed that VPS13A interacts with XK, its known partner at the plasma membrane, only in cells at the right stage of differentiation, explaining why this was missed using standard approaches (Amos et al., 2023). Levine showed how domains, particularly the repeating beta-groove (RBG) domains characteristic of bridge-like lipid transfer proteins, are distributed across eukaryotes (Levine, 2022). Leterme et al. used bioinformatics to show the complex evolution of VPS13 in photosynthetic organisms, producing the groundwork for functional studies (Leterme et al., 2023). Du et al. showed that VPS13B, previously linked to the Golgi apparatus, has a positive role in promoting Golgi-LD contact, a cellular phenomenon hardly reported on before (Du et al., 2023). Chen et al. showed that both VPS13A and VPS13C, two proteins in this group that can target lipid droplets, are functionally linked to this compartment, being required for normal lipid accumulation (Chen et al., 2022). Lei et al. showed that in addition to the known role of ATG2 in supplying lipids to the growing autophagosome, Vps13 in yeast contributes at the late stages, with some selectivity for the type of autophagic cargo (Lei et al., 2022).

Among the reviews, Walker et al. described the “core neuroacanthocytosis syndromes,” which indicate a shared

pathway for VPS13A and XK, so that diseases of each, previously called chorea-acanthocytosis and McLeod syndrome, respectively, are currently recognized as highly similar (Walker et al., 2023). Kumar et al. described the AsmA-like protein family in Gram-negative bacteria. These descendants of the likely prokaryotic ancestor of RBG proteins are one of two large protein assemblies recently shown to transfer phospholipids from the inner membrane to the outer membrane (Kumar and Ruiz, 2023). Pandey et al. described the superfamily of bridge-like lipid transfer proteins in *C. elegans*, in particular focusing on their own work on LPD-3, the ortholog of BLTP1/Tweek/Fmp27, which provides a useful model for the BLTP1-associated hereditary neurodevelopmental disorder Alkuraya-Kučinskis syndrome (Pandey et al., 2023). Finally, Vargas Duarte and Reggiori described the key AuTophagy (ATG) proteins for lipid traffic to growing autophagosome membranes: the RBG protein ATG2 and its partners on autophagosomes ATG18/WIPI4 and ATG9, which act as an adaptor and lipid scramblase, respectively, (Vargas Duarte and Reggiori, 2023).

The discovery that these large proteins are direct conduits for lipid flow between organelles has upended our ideas about eukaryotic lipid transport. The papers in this special collection have outlined new roles for bridge-like transfer proteins and emphasized general principles. They also highlighted fundamental open questions (e.g., What powers lipid traffic and what regulates it?) which will no doubt prove fascinating areas for future research.

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Table 1. Articles in Special Collection on VPS13 and Bridge-Like Lipid Transfer Proteins.

Lead Author	Topic	
	Original Research	Reference
Pietro De Camilli	VPS13A interaction with XK	Amos et al. (2023)
Tim Levine	Structural elements in bridge-like LTP superfamily	Levine (2022)
Morgane Michaud	Phylogeny of VPS13 in plants	Leterme et al. (2023)
Weike Ji and Juan Xiong	VPS13B at Golgi-lipid droplet contacts	Du et al. (2023)
James Olzmann and Susan Ferro-Novick	VPS13A/VPS13C and lipid droplet abundance	Chen et al. (2022)
Dan Klionsky	Vps13 in autophagy in yeast	Lei et al. (2022)
Reviews		
Ruth Walker	Neuroacanthocytosis syndromes: clinical perspective	Walker et al. (2023)
Natasha Ruiz	Bridge-like LTP antecedents in bacteria	Kumar and Ruiz (2023)
Dengke Ma	Bridge-like LTPs in <i>C. elegans</i>	Pandey et al. (2023)
Fulvio Reggiori	Phagophore-ER contacts	Vargas Duarte and Reggiori (2023)


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