ERMES- and vCLAMP-facilitated intermembrane lipid transport is molecular species-selective

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Sequential steps in membrane lipid biosynthesis can be localized to different organelles, necessitating efficient transport of lipids between organellar membranes. Prime examples are the syntheses of cardiolipin (CL) and phosphatidylethanolamine (PE) in mitochondria that depend on import of the respective metabolic precursors phosphatidic acid and phosphatidylserine (PS) from the ER and/or vacuole.

Transport is thought to occur at regions of close contact between organelles. In the yeast *S. cerevisiae* protein complexes tethering ER to mitochondria, i.e. the ER–mitochondria encounter structure (ERMES) and the ER membrane complex (EMC), as well as a protein complex clamping the vacuole to the mitochondria, the vacuole and mitochondria patch (vCLAMP), have been implicated in mitochondrial lipid import.

By overexpressing the GPAT Sct1p, introducing a metabolic sink for saturated lipid acyl chains and limiting the availability of di-unsaturated phospholipids, we created conditions for investigating the mechanism of lipid transfer including the contribution of each of the tethering complexes. Experiments in mutants showed that both ERMES and vCLAMP mediate the transfer of preferentially di-unsaturated phospholipid molecular species. Based on the results we propose that lipid flow between ER and mitochondria at membrane contact sites is molecular species-selective, rate-limited by lipid efflux from the donor membrane, and facilitated by the lipid species' concentration gradient between donor and acceptor membrane and the presence of tethering complexes.