

Generally Physiological

Of lipid transfer, resistance to F^- , and stimulus-dependent channel conformations



This month's installment of *Generally Physiological* considers the non-vesicular transfer of lipids between membranes, channels and transporters that enable microorganisms to resist the toxic effects of F^- , and alternative, stimulus-dependent open channel conformations of a pannexin channel.

Transferring lipids to target membranes

The endoplasmic reticulum (ER) comes into close proximity with the plasma membrane and the membranes of other organelles, forming contact sites that enable signaling between cellular compartments and the nonvesicular exchange of lipids between the apposed membranes. Proteins in the extended synaptotagmin (E-SYT) family, which act as tethers between the ER and the plasma membrane, contain an N-terminal ER membrane anchor domain, C2 membrane-targeting domains, and a region identified by

bioinformatics analyses as a potential lipid-binding module (the SMP domain). Schauder et al. (2014) determined the 2.44-Å-resolution crystal structure of a fragment of human E-SYT2 (residues 163–634) that included the SMP domain and two of

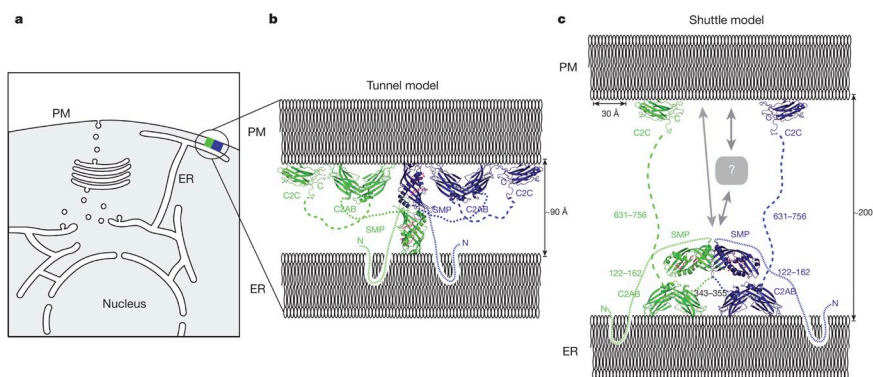
Nonvesicular transfer of lipids between membranes, channels and transporters that enable microorganisms to resist the toxic effects of F^- , and stimulus-dependent open channel conformations of a pannexin channel

its three C2 domains (C2A and C2B) and found that the SMP domain dimerized to form a cylinder. A 10-Å-wide channel lined with hydrophobic residues spanned the 90-Å-long cylinder, connecting to

solvent at both ends and through a longitudinal seam. A combination of electron density mapping and mass spectrometric analysis indicated that E-SYT2 binds lipids; each monomer can bind two lipid molecules, with the fatty acid moiety lying in the hydrophobic SMP channel and the polar head group protruding through the seam. The authors thus conclude that E-SYTs, and perhaps other SMP domain-containing proteins present at ER membrane contact sites, play a role in lipid transport, proposing “bridge” or “shuttle” models, whereby SMP dimers, perhaps in conjunction with other lipid transfer proteins, could transfer lipids from sites of synthesis in the ER to target membranes.

Fighting against fluoride

Fluoride (F^-) is ubiquitous in soil and in water, posing an existential threat to unicellular microorganisms through its inhibition of crucial enzymes. Two distinct families of F^- exporters that help combat F^- toxicity have recently been identified, the bacterial CLC^F -type F^-/H^+ antiporters (a subset of the CLC superfamily of anion transport proteins) and the Fluc family of F^- channels. Noting that Cl^- is far more abundant in the environment than F^- , Brammer et al. (2014) investigated the basis of CLC^F selectivity for F^- over Cl^- . Sequence analysis showed that the CLC^F s lacked a serine implicated in coordinating Cl^- in canonical CLCs; moreover, two phylogenetically distinct CLC^F subclades showed distinct amino acid signatures, with one subclade



(a) E-SYT2 at a contact site between the ER and the plasma membrane. The C2C domain binds to the plasma membrane, and the N-terminal domain region provides an anchor to the ER. (b) If the two membranes are ~90 Å apart, SMP dimers may provide a lipid transfer tunnel. (c) If the two membranes are closer than 200 Å, the SMP dimer may act as a shuttle. (Reprinted by permission from Macmillan Publishers, Ltd. C.M. Schauder. 2014. *Nature*. <http://dx.doi.org/10.1038/nature13269>, copyright 2014.)

