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Short Talk 6, Mikael B. L. Winkler - STRUCTURAL INSIGHT INTO EUKARYOTIC STEROL TRANSPORT THROUGH NIEMANN-PICK TYPE C PROTEINS

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Niemann-Pick type C (NPC) proteins are essential for sterol homeostasis, believed to drive sterol integration into the vacuolar/lysosomal membrane before redistribution to other cellular membranes. Using a combination of crystallography, cryo-electronmicroscopy, biochemical and in vivo studies on the Saccharomyces cerevisiae NPC system, NCR1/NPC2, we recently generated a framework for sterol membrane integration (Winkler et al., (2019)). Sterols are transferred between hydrophobic pockets of vacuolar NPC2 and membrane-protein NCR1. NCR1 has its N terminal domain (NTD) positioned to deliver a sterol to a tunnel connecting NTD to the luminal membrane leaflet 50 Å away. A sterol is caught inside this tunnel during transport, and a proton-relay network of charged residues in the transmembrane region is linked to this tunnel supporting a proton-driven transport mechanism. We propose a model for sterol integration which clarifies the role of NPC proteins in this essential eukaryotic pathway and which rationalizes mutations in patients with Niemann-Pick disease Type C that I will present at the talk.

Winkler et al, Structural insight into eukaryotic sterol transport through Niemann-Pick Type C proteins, Cell (accepted, 2019)

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