P-1.100

Unveiling Ttyh2-apoe Synergy: A Novel Pathway for Lipid Transfer

Birgit Plochberger [1], Andreas Karner [1], Florian Weber [1], Anastasiia Sukalskaia [2], Raimund Dutzler [2]

[1] University of Applied Sciences Upper Austria, Linz, Austria

[2] University Zürich (UZH), Zürich, Switzerland

Brain lipid metabolism is independently regulated, with ApoE playing a key role in lipid homeostasis. The ApoE4 isoform is a major genetic risk factor for Alzheimer's disease, though its mechanisms remain unclear. Tweety homologs (TTYHs), conserved transmembrane proteins, are widely expressed in the brain and involved in neuronal function and immune activation. Recent proteomics studies identified an interaction between ApoE and TTYH2, suggesting a role in lipid transfer from astrocytes to neurons. While ApoE secretion and receptor-mediated uptake are well characterized, post-endocytic processes remain elusive. Using biochemical and biophysical techniques, we identified ApoE as a TTYH2 interaction partner and demonstrated their co-localization in endosomes. Cryo-EM revealed ApoE binding to TTYH2's luminal side. An in vitro assay confirmed TTYH2-mediated lipid transfer, further visualized via atomic force and fluorescence microscopy. Single-molecule force spectroscopy validated the interaction. Our findings suggest TTYH2 facilitates lipid unloading from ApoE-containing lipoproteins, highlighting its role in intracellular lipid trafficking.