

P002 The human OSBP-related proteins (ORPs) – sterol sensors that coordinate lipid metabolism?

Vesa Olkkonen¹, Christoph Thiele², Marie Johansson¹,
Monika Suchanek², Riikka Hynynen¹, Daoguang Yan¹,
Matti Jauhiainen¹, and Markku Lehto¹

¹*Department of Molecular Medicine, National Public Health Institute, Biomedicum, Helsinki, Finland;* ²*Max-Planck-Institute for Molecular Cell Biology and Genetics, Dresden, Germany*

Oxysterol binding protein homologues, ORPs, are characterized by an OSBP-related ligand binding domain (ORD). Some proteins (short ORPs) consist of an ORD only, while others (long ORPs) carry an N-terminal extension with a pleckstrin homology domain (PHD) and other membrane targeting signals. A majority of human ORPs bind oxysterols with their ORD and associate via a FFAT motif with VAMP-associated proteins of the ER. The N-terminal PHDs bind phosphoinositides and are involved in targeting ORPs to non-ER membranes. We have proposed a model in which long ORPs either shuttle between the ER and other organelles or bind simultaneously to both. The latter scheme suggests that long ORPs could facilitate or regulate the formation of membrane contact sites (MCS) involved for example in inter-organelle lipid transport. We favour a model in which ORPs act as oxysterol sensors that set the stage for other protein machineries responsible for bulk lipid transport. The mode of action of the short ORPs is likely to differ substantially from that of the long ORPs. Our latest results show that over-expression of OSBP in mouse liver induces distinct alterations in serum lipoproteins, supporting a role of this protein as a regulator of lipid metabolism. Further, we have shown that ORP1L interacts with Rab7, impacting on the Rab7 functional cycle and the microtubule-dependent localization of LE. This suggests that (i) ORP1L is involved in sterol regulation of late endocytic membrane trafficking or (ii) the ORP1L interaction reveals a new function of Rab7, possibly in non-vesicular transport of lipids.