**Nonvesicular lipid transport drives myelin growth in the central nervous system**

Wu, J., Kislinger, G., Duschek, J. *et al.* *Nat Commun* **15**, 9756 (2024).

**Presenter**: Wei-Hsiang Hsu **Date/Time**: 2025/06/06, 16:20-17:10

**Commentator**: Dr. Chun-Hsien Chu **Location**: Room 601, Med College Building

**Background**: Oligodendrocytes are known to produce the myelin sheaths that enwrap CNS neuron axons to provide electrical insulation and enable saltatory conduction. From a nascent state, an oligodendrocyte has to go through an evident morphology change (from arborous to membranous) before it is able to myelinate axons. Underlying this change is the production of galactocerebrosides (GalCer) in their ER, which is the main constituent of the myelin membrane layers, providing its compactness through the interactions between sugar residues. It has been postulated that vesicular lipid transport dominates the mechanism in which myelin inner tongue receives the GalCer and other lipids to keep growing. On the other hand, mechanisms of non-vesicular transport are becoming more popular where there are contact sites between ER, Golgi, organelles & plasma membrane, and direct lipid transfer via a tether or transport protein is possible.

**Objective/Hypothesis**: Because the vesicular transport theory of lipid delivery to the myelin inner tongue is seriously contested, where through-hole channels are supposed to exist on myelin membranes to enable vesicular passage, the alternative hypothesis is considered where lipids are delivered in bulk by nonvesicular mechanisms.

**Results**: P14 myelinating-age mice were studied for their growing myelin sheaths. For volume EM, automated tape-fed ultramicrotomy (ATUM, 50nm) slices of optic nerve and spinal cord samples were imaged, and the 3D tomography was reconstructed to demonstrate that tubular ER runs along the length of the myelin inner tongue. This tubular organelle has been observed in 1928 by Río-Hortega, whose drawings indicate subtle sheaths and fine reticula with turns and coils.[1] In the century since then, it was also described in various names, from *tubular reticulum* to *myelinic channel system*. Despite that, its identity as tubular ER was not revealed. Here, several ER-specific markers were selected from the RNA-seq data (Zhang et al. 2014), including reticulons (RTN1, RTN4) and receptor expression-enhancing protein 5 (REEP5). It is shown that these ER markers highly (~80%) coincide with myelin basic protein (MBP), therefore the tubular organelle identifies as ER. Based on the close proximity of the tubular ER to the plasma membrane, contact sites for direct lipid transfer are likely to develop. Hence the RNA-seq data was consulted again for nonvesicular-lipid-transport protein candidates in myelinating oligodendrocytes, where GLTP by itself showed very high expression. The authors then establish that GLTP-cKO mice develop hypomyelinated axons, with thinner myelin layers and a higher g-ratio. By EM imaging, they show that the tubular ER in GLTP-cKO mice are either flat, lumenless or rolled-up and thickened, resulting from non-delivery of GalCer to destination myelin membranes, thus excessive GalCer on ER membrane causes ER self-adhesion. Lipidomic changes are also noted in the GLTP-cKO mice, showing decrease of Hex(=Glu/Gal)Cer with normal fatty acid (NFA) residue, but interpretation of lipidomics requires further study.

**Conclusion**: GLTP plays a major role in CNS myelin development, transferring ER-made GalCer to the myelin membrane, an example of nonvesicular lipid transport.

**References**:
1. Edgar, J.M., McGowan, E., Chapple, K.J., Möbius, W., Lemgruber, L., Insall, R.H., *et al* (2021) Río-Hortega's drawings revisited with fluorescent protein defines a cytoplasm-filled channel system of CNS myelin. *Journal of Anatomy*, **239**, 1241–1255.