E-seminar 4 presented by Patricia Garcia Fernandez ESR9 on September 14, 2021

Paper presented: Tumor necrosis factor receptor-1 is selectively sequestered into Schwann cell extracellular vesicles where it functions as a TNF alpha decoy by Sadri et al. published in *Glia*.

E-seminar review by ESR 5 – Zerina Kurtovic

Patricia did an excellent job presenting the paper. The study is about the finding that Schwann cells produce extracellular vesicles which have the capability to sequester TNF alpha. Most of the experiments are done *in vitro* in Schwann cell cultures. This is relevant for models of injury of the peripheral nervous system as these injuries lead to Wallerian degeneration of the injured tissue and Schwann cells play an important role in this process by, for example, producing inflammatory cytokines.

The authors first show that Schwann cells do indeed produce extracellular vesicles (EV). They do this by culturing the cells and analyzing the conditioned media with nanoparticle tracking and electron microscopy. They further analyze the expression of several Schwann cell and EV specific markers and show that their EV fractions are pure. They find that the EVs contain TNFR1 in their membrane, while Schwann cells express TNFR2. The two receptors both bind TNF alpha but TNFR1 has a greater affinity for TNF alpha.

The authors further show that TNF alpha causes activation of the Schwann cells and measured by P-p38 expression. If TNF alpha is introduced together with EVs this activation is reduced. Additionally, the activation is restored with blockage of the TNFR1 on EVs. On the other hand, blocking the TNFR2 decreased the activation. The also show that EVs regulate the effect of TNF alpha on Schwann cells on terms of morphology, cytokine expression and cell death.

Finally, the study complements the *in vitro* experiments with *in vivo* experiments in rats. The animals were injected with TNF alpha at the site of the sciatic nerve. This led to Schwann cell activation, Edema in the nerve and reduced mechanical hypersensitivity thresholds. All the observations were at least partially restored when EVs where co-injected.

The presentation was followed by an interesting discussion session with many questions.