Effect of neuronal sphingolipid accumulation on mitochondrial mobility and function as contributor to peripheral denervation and pain in Fabry disease

Aim:
To investigate mitochondrial mobility and function in human-derived sensory neurons as potential contributor to denervation and pain in Fabry disease.

Background:
Fabry disease (FD) is an X-linked multiorgan disorder caused by various mutations in the alpha-galactosidase A gene. Due to enzyme deficiency, the sphingolipid globotriaosylceramide accumulates in diverse cell types, including sensory neurons. FD patients suffer from triggerable pain and thermal hyposensitivity, and skin punch biopsies show peripheral denervation. Previous studies have pointed out that mitochondrial mobility and function might be affected in FD and we observed mitochondrial blockage by sphinganine in sensory neurites derived from FD patients. We hypothesize that disturbance in mitochondrial mobility and function results in mitochondrial dysfunction contributing to pain and peripheral denervation in FD. In this project, we will apply live *in vitro* imaging of mitochondria in sensory neurons to understand the potential mechanism linking mitochondrial mobility with pain in FD patients.

Tasks:
- Cultivation of 2 FD patient-derived sensory neuron cell lines and characterization of an isogenic cell line
- Determination of mitochondrial mobility and function in sensory neurites
- In vitro treatment of mitochondrial dysfunction associated with globotriaosylceramide depositions

Techniques:
iPSC culture, Immunofluorescence, confocal microscopy, real time PCR (RT-PCR), Seahorse assay

Publications:
1) Klein, T., Grüner, J., Breyer, M., Schlegel, J., Schottmann, N. M., Hofmann, L., Gauss, K., Mease, R., Erbacher, C., Finke, L., Klein, A., Klug, K., Karl-Schöller, F., Vignolo, B., Reinhard, S., Schneider, T., Günther, K., Fink, J., Dudek, J., … Üçeyler, N. (2023). Small fibre neuropathy in Fabry disease: a human-derived neuronal in vitro disease model. BioRxiv, 2023.08.09.552621. https://doi.org/10.1101/2023.08.09.552621.
2) Klug, K., Spitzel, M., Hans, C., Klein, A., Schottmann, N. M., Erbacher, C., & Üçeyler, N. (2023). Endothelial Cell Dysfunction and Hypoxia as Potential Mediators of Pain in Fabry Disease: A Human-Murine Translational Approach. International Journal of Molecular Sciences, 24(20), 15422. MDPI AG. Retrieved from http://dx.doi.org/10.3390/ijms242015422.
3) Spitzel, M., Wagner, E., Breyer, M., Henniger, D., Bayin, M., Hofmann, L., Mauceri, D., Sommer, C., & Üçeyler, N. (2022). Dysregulation of Immune Response Mediators and Pain-Related Ion Channels Is Associated with Pain-like Behavior in the GLA KO Mouse Model of Fabry Disease. Cells, 11(11), 1730. https://doi.org/10.3390/cells11111730

Contact:
Application documents (CV and motivation letter) to
Prof. Dr. N. Üçeyler: ueceyler_n@ukw.de