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SCIENTIFIC SEMINAR

Tess Dierckx, Ph.D.

Department of Psychiatry and Behavioral Sciences,
Stanford University

„„Timing matters for remyelination: circadian control of oligodendroglial metabolic and lipid function"

The age-associated failure to produce myelinating oligodendrocytes from oligodendrocyte precursor cells (OPCs) underlies the progressive nature of multiple sclerosis (MS). Our lab was the first to demonstrate the importance of the circadian transcription factor BMAL1 in modulating oligodendroglial cell cycle, morphology, migration, and differentiation during myelination and remyelination. The circadian system is a hierarchical network of biological clocks originating at the molecular level with a transcriptional-translational feedback loop that regulates processes such as cellular metabolism and cell cycle, and undergoes significant changes with aging. However, a critical gap remains in our understanding of the exact mechanisms by which BMAL1 regulates oligodendroglial dynamics and myelination. Here we show that BMAL1 regulates mitochondrial energy homeostasis in OPCs and that BMAL1-mediated circadian disruption alters mitochondrial energy homeostasis, increases oxidative stress, and induces a premature senescence phenotype. Furthermore, preliminary findings indicate that *Bmal1* dysfunction disrupts sirtuin activation and that strategically targeting this metabolic sirtuin pathway downstream of *Bmal1* (i.e., chronotherapy) can rescue *in vitro* proliferation and differentiation in *Bmal1*-disrupted OPCs. Analysis of publicly available MS and aging single-nucleus RNA sequencing studies reveals circadian changes in OPCs, raising the question of whether circadian disruption in OPCs may contribute to the remyelination failure observed in MS progression, a topic currently under investigation in ongoing research. Our study garners novel mechanistic insights into how BMAL1 regulation affects chronic demyelinating diseases and identifies new targets for the development of therapeutic strategies aimed at promoting remyelination. We expect our study to serve as a foundation for more advanced research into circadian-related myelin dynamics. For instance, it is highly relevant to investigate how the circadian machinery regulates oligodendrocyte myelination, how sleep affects de- and remyelination, and how the timing of drug administration impacts their efficacy.

Wednesday, 02.10.2024, 10:00 AM

Host: Gesine Saher, Department of Neurogenetics, City-Campus

Seminar room 4th floor, City-Campus

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