SPP 1757

Functional heterogeneity of oligodendrocytes with aging

Speaker:

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Project description:

Myelination of long axons is a key feature of the vertebrate brain, and it is generally thought that myelin is maintained throughout life. However, the aging brain white matter tracts show characteristic ultrastructural changes, including myelin delamination and outfoldings. By proof-of-principle analysis we show here that the molecular composition of myelin changes significantly with aging. Interestingly, the most strongly down-regulated myelin-specific protein in the aging brain is CNP1, partial loss-of-function genotypes of which are causative of a unique catatonia-depression syndrome in mouse and man when combined with aging. Similarly, the abundance of several alpha- and beta-tubulins, the major constituents of microtubules (MT), were decreased in aged myelin. CNP1 and MT localize to non-compact myelin, i.e. the cytosolic channels. These findings prompt our first working hypothesis that an intact system of cytoplasmic channels allowing vesicular transport is necessary for normal oligodendrocyte function with consequences on both the maintenance of myelin and other oligodendroglial support mechanisms for axons. We propose that channel integrity is dependent on microtubule tracks, motor protein function and CNP1 and further suggest that changed abundances of the respective proteins with aging have consequences for the functionality of cytosolic channels and overall myelin integrity. Cre-mediated cell lineage analyses in transgenic mice have revealed a continued recruitment of oligodendrocyte precursor cells (OPC) in adult life. The differentiation of OPC to adult-born oligodendrocytes is associated with the incorporation of new myelin sheaths within existing white matter tracts. Whether mature oligodendrocytes have a specific half-life in the adult brain and whether myelin undergoes regular turnover is under current investigation. Thus, in a second project, we aim at genetically preventing the generation of new oligodendrocytes from adult OPC. By this approach we want to investigate the functional consequences of the lack of adult-born oligodendrocytes and myelin turnover in white matter tracts at the histological and behavioral level. To this end we will exploit a novel mouse mutant harboring a floxed allele of the Sip1 (Smad-interacting protein, Zfhx1b) gene, encoding a transcription factor that is essential for oligodendrocyte differentiation and myelination. This mouse is already available in my lab. By conditional ablation of Sip1 in adult OPC we will interfere with the generation of adult-born myelin forming oligodendrocytes at different ages throughout lifetime. Mice will be analyzed at the molecular, morphological and behavioral level.

Quelle:
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