Neuroprotective approaches in the animal model

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Our aim is to use modern *in vivo* microscopy techniques to reveal the cellular, subcellular and molecular mechanisms that mediate neuroinflammatory tissue damage *in vivo*. This approach can be illustrated using our recent insights into the *in vivo* pathogenesis of immune-mediated axon damage as an example. Immune-mediated axon damage plays a crucial role in inflammatory diseases of the central nervous system (CNS) like multiple sclerosis (MS) [1], as we know by now that the number of axons damaged by immune cells critically determines the clinical disability of MS patients. However we still understand very little about the process that leads to axon damage. Recently, we have used a spinal *in vivo* imaging approach [2,3] to investigate the pathogenesis of immune-mediated axon damage in an animal model of multiple sclerosis. By time-lapse imaging of fluorescently labeled axons we could follow the slow and spatially restricted degeneration of axons in inflammatory CNS lesions. This "focal axonal degeneration" appears to be a novel type of axonal degeneration that is characterized by intermediate stages that can persist for several days and progress either to the degeneration or full recovery of the affected axons [4].

We are currently addressing the following key aspects of the axon degeneration process using *in vivo* microscopy: First, to identify the molecular mechanisms that drive axonal degeneration, we now reveal the actions of key damage mediators, in particular the influx of calcium and the release of reactive species, *in vivo*. This allows us to study which molecular effector pathways are activated in neuroinflammatory lesions and determine how their activation is regulated. Second, to better understand the relation between structural and functional axon damage in neuroinflammatory lesions, we directly measure axonal transport in neuroinflammatory lesions. Our results identify an early stage of axonal dysfunction that precedes the structural manifestations of axon damage and might help to explain the often short-lasting deficits observed during the relapsing-remitting phase of multiple sclerosis.

Using these examples, I hope to illustrate how recent advances in light microscopy can help us to reveal and mechanistically dissect nervous system damage as it happens in the living CNS. We believe that these insights will help us to develop targeted strategies to prevent nerve cell damage in neuroinflammatory conditions like multiple sclerosis.

Conflict of Interest: No conflicts of interest exist with regards to this presentation.

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