Here, I want to discuss how advances in in vivo microscopy together with mouse genetics can improve our understanding of the cellular, subcellular and molecular mechanisms that mediate neuroinflammatory tissue damage.

To illustrate this approach I will use 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), 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 an in vivo imaging approach 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 intermediated stages that can persist for several days and progress either to the degeneration or full recovery of the affected axons.

In vivo imaging approaches now allow us to address the following key aspects of the axon degeneration process: First, to identify the molecular mechanisms that drive axonal degeneration, we can now reveal the actions of key damage mediators, in particular the influx of calcium and the release of reactive species, in vivo. Second, to better understand the relation between structural and functional axon damage in neuroinflammatory lesions, we can directly measure axonal transport in neuroinflammatory lesions. Using these examples, I hope to illustrate how recent advances in light microscopy can help us to reveal and mechanistically dissect neuroinflammatory tissue damage as it happens in the living CNS.

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