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Neurofascin as a novel target for autoantibody-mediated axonal injury

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Axonal injury is considered the major cause of disability in patients with multiple sclerosis (MS), but the underlying effector mechanisms are poorly understood. Starting with a proteomics-based approach, we identified neurofascin-specific autoantibodies in patients with MS. These autoantibodies recognize the native form of the extracellular domains of both neurofascin 186 (NF186), a neuronal protein concentrated in myelinated fibers at nodes of Ranvier, and NF155, the oligodendrocyte-specific isoform of neurofascin. Our in vitro studies with hippocampal slice cultures indicate that neurofascin antibodies inhibit axonal conduction in a complement-dependent manner. To evaluate whether circulating antineurofascin antibodies mediate a pathogenic effect in vivo, we cotransferred these antibodies with myelin oligodendrocyte glycoprotein–specific encephalitogenic T cells to mimic the inflammatory pathology of MS and breach the blood–brain barrier. In this animal model, antibodies to neurofascin selectively targeted nodes of Ranvier, resulting in deposition of complement, axonal injury, and disease exacerbation. Collectively, these results identify a novel mechanism of immune-mediated axonal injury that can contribute to axonal pathology in MS.