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Effects of Immunopotentiation and Demyelination on Microglial Activation and Neuronal Injury in Two Genetic Mouse Models

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Keywords

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Abstract

Multiple Sclerosis is an inflammatory demyelinating disease of the central nervous system (CNS) in which the degeneration of axons causes cumulative disability. The relative contribution of myelin loss and inflammation to axonal degeneration was studied in in a novel transgenic mouse model of demyelination. Myrf, a gene necessary for myelin production, was knocked out from mature oligodendrocytes. The density of activated microglia in the optic nerve was measured during acute demyelination, following remyelination, and in aged mice. A sustained inflammatory reaction was seen at all time points following demyelination relative to wild-type mice. Inducible nitric oxide synthase (iNOS) was not noted to be strongly expressed in the knockout mice, contrary to existing autoimmune models and pathologic analyses of human multiple sclerosis tissue. Immune boosting with intraperitoneal lipopolysaccharide (LPS) injections was used to induce to microglial activation within the CNS as demonstrated by the upregulation of genes encoding known pro-inflammatory cytokines and iNOS. To assess if the additive insults of a heightened microglial cytokine response and demyelination could cause neurodegeneration, immune boosting was then used in a second mouse model in which remyelination is prevented following demyelination by knocking Myrf out of both mature oligodendrocytes and oligodendrocyte precursors. No statistically significant differences in neuronal injury, indicated by the activation of the stress pathway culminating in the phosphorylation of C-Jun, or outright neuronal loss indicated by the density of RBPMS-positive retinal ganglion cells (RGCs) were seen following LPS injection. However, demyelination coupled with impaired remyelination was sufficient to phosphorylate C-Jun suggestive of damage to these neurons with demyelination. Although microglial activation is intensified by both demyelination and LPS injection independently, together they were not enough to cause neurodegeneration within the visual system in this model.