(P09) THE NF1-RAS SIGNALING PATHWAY REGULATES OLIGODENDROCYTE MYELINATION

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Background: Myelination by brain oligodendrocytes is affected by kinases activated by the Ras family of small G-proteins, yet effects of Ras signaling on the oligodendrocyte lineage are poorly understood. Significant brain defects and magnetic resonance imaging (MRI) abnormalities occur in patients with mutations in Ras pathway genes, including neurofibromatosis type 1 and Costello syndrome. Similar MRI abnormalities are found in patients with multiple sclerosis (MS); these are thought to be due to changes in myelination within the brain. Objectives: Define the role of the Nf1-Ras pathway in oligodendrocyte myelination.

Methods: Nf1+/− mutant, PLP-CreERT; Nf1 fl/fl, and CNP-HaRasV12 mice were generated to examine the role of Nf1 and Ras in oligodendrocyte myelination and remyelination. Electron microscopy and immunohistochemistry were performed on the brains of control, Nf1 mutant, and CNP-HaRasV12 mice after cuprizone-induced demyelination in order to examine the Ras-GAP function of Nf1 in myelination and remyelination. Electron microscopy and MRI abnormalities were confirmed in PLP-CreERT; Nf1 fl/fl mice—indicating that these defects in myelination are cell autonomous to oligodendrocytes. Results: We show that activation of Ras-GTP through loss of Nf1 results in failure to myelinate large-diameter axons in adult mouse corpus callosum, which is mimicked by cell autonomous transgenic expression of constitutively active CNP-HaRasV12 or loss of Nf1 specifically in oligodendrocytes. This myelination defect is specific to large-caliber, not small- or medium-caliber, axons. Electron microscopic analysis of all three mouse models showed frequent splitting of lamellae within the myelin. The PLP-Cre; Nf1 fl/fl model mimics MRI abnormalities found in patients with MS and neurofibromatosis type 1. After cuprizone injury, remyelination is accelerated in Nf1 mutants, but demyelination and remyelination are delayed in HaRasV12 mutants. Conclusions: Results from this study indicate an important role for the Nf1-Ras signaling pathways in control of oligodendrocyte myelination and may be relevant to aspects of brain dysfunction in patients with MS, neurofibromatosis, and Costello syndrome.

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