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Axonal Neuregulin Signaling to Schwann Cells and Oligodendrocytes: Significance for Demyelinating Diseases such as Multiple Sclerosis

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A central question in neurobiology is how axons and glial cells communicate both during myelination and maintenance of the myelin internode. This question is important both to our understanding of neural and glial development and to diseases of the nervous system where interference with normal signaling may influence specific pathophysiologic processes. The present data try to contribute to these problems by showing that the growth factor neuregulin influences both growth and differentiation of Schwann cells, and oligodendrocytes respectively via specific signal transduction pathways and its' expression is downregulated in diseases such as Multiple Sclerosis.
Furthermore the findings indicate that Schwann cells express the neuregulin receptors HER 2 and HER 3 but little HER 4, whereas both oligodendrocyte progenitor cells and oligodendrocytes express HER 2 and HER 4 but no HER 3 After binding to their cell surface receptors, recombinant neuregulin induces the tyrosine phosphorylation of HER 2 and HER 3 in Schwann cells and of only HER 4 in oligodendrocytes and their precursors. Although no phosphorylation of the tyrosine kinase domain of HER 2 was detected in oligodendrocytes, an interaction between HER 2 and HER 4 was discovered in co-immunoprecipitation experiments. Phosphorylation of HER 2, HER 3 and HER 4 is known to occur after receptors form hetero-and/or homodimers upon ligand binding. These phosphotyrosine residues bear binding sites for intracellular signaling proteins such as Shc, Grb2 and indirectly SOS which signal downstream via the ras/MAPK pathway to the nucleus. SOS becomes associated with the activated receptor HER 2 and HER 3 in Schwann cells via the small adapter protein Grb2. In the cells of the oligodendrocyte lineage neuregulin stimulates the association of Shc and Grb2 to tyrosine phosphorylated HER 4. Neuregulin is localized on dorsal root ganglion (DRG) neurites and neuregulin derived from DRG neuron conditioned medium is biologically active.
Eventually, neuregulin and their receptors, HER 2/3/4, are expressed in astrocytes the major nonmyelinating CNS glial cell. Postmortem human brains with MS lesions from several patients were examined for neuregulin expression. Astrocytes were identified in

unaffected white matter and in MS lesions as determined by astrocyte specific GFAP staining. Neuregulin expression by astrocytes is significantly reduced within MS lesions compared with unaffected white matter, as shown by immunocytochemistry and Western blot analysis. Thus neuregulin may play an important role in the development of Multiple Sclerosis, that is its absence would prevent complete remyelination and its presence would enhance the important process of remyelination. Understanding of these molecular mechanisms and functions will further characterize this disease and may help finding therapeutic agents.