Multiple Sclerosis: Sustaining Care, Seeking a Cure
June 2-5, 2010 * San Antonio, Texas

Platform Presentations
Friday, June 4 (1:00 pm - 3:00 pm)

(P08) MAXIMIZING THE MYELINOGENIC POTENTIAL OF OLIGODENDROCYTES FOR REPAIR
S. Chong,1 S.S. Rosenberg,1 Y.A. Shen,1 B. Zheng,2 A.W. McGee,1 R.Q. Lu,4 L.I. Zhang,5 J.R. Chan1

1Biochemistry and Molecular Biology, University of Southern California, Los Angeles, CA; 2Neurosciences, University of California San Diego, San Diego, CA; 3Pediatrics, University of Southern California, Los Angeles, CA; 4Developmental Biology, University of Texas Southwestern Medical Center, Dallas, TX; 5Physiology and Biophysics, University of Southern California, Los Angeles, CA

Background: Current efforts have focused on identifying global determinants (transcription and growth factors) that promote differentiation of oligodendrocyte precursor cells into myelinating oligodendrocytes during development. Based on this view, myelination is an all-or-none event that is controlled in part by the transcriptional program responsible for differentiation. However, it is evident that the central nervous system (CNS) is composed of heterogeneous microenvironments that shape the unique architecture and relationship between neurons and glia. As an alternative approach, myelination can also be viewed as a graded process, and maximizing the capacity of an oligodendrocyte to form numerous myelin segments with varying internode lengths (myelinogenic potential) may offer an effective strategy for future therapies. Objectives: The objective of our work is to ascertain the nature of this myelinogenic potential and identify the molecular cues that promote the formation of myelin internodes. Methods: Generation of a transgenic mouse line with sparsely labeled oligodendrocytes (0.1–0.5%) and biochemically and genetically manipulating the microenvironment of the oligodendrocyte in both in vivo and in vitro paradigms. Results: We establish that individual oligodendrocytes within the same local brain region and along the same axon tracts can form from 10 to 60 myelin internodes with lengths that vary from 100 to 400 μm. Here we show that inhibitory cues expressed by oligodendroglia modulate the myelinogenic potential of individual oligodendrocytes within a dynamic and complex environment. We identify the amino-terminal region of Nogo-A expressed by oligodendroglia as necessary and sufficient to inhibit the number and length of myelin internodes. Conclusions: Together, these findings suggest that myelination is a graded process, subject to competition within the microenvironment, and identify a novel physiologic role for Nogo-A in the precise myelination of the developing CNS. Maximizing the myelinogenic potential of oligodendrocytes may offer an effective strategy for repair in future therapies for demyelination.

Supported by: National Multiple Sclerosis Society

Disclosure: Nothing to disclose

Keywords: glial biology, CNS repair