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Final Narrative Report

New Jersey Commission on Spinal Cord Research

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Project aims

Functional recovery from neural injuries requires guided growth of regenerating axons across the lesion site to re-establish synaptic connections with the appropriate target. In the vertebrate central nervous system (CNS), axon regeneration and recovery is limited due to many factors, including inhibitory/repulsive molecules that present a major obstacle for regenerating axons to grow across the damaged area. It is thus pivotal to understand the signal transduction mechanisms underlying axon inhibition by these extracellular molecules, from which strategies may be developed to disrupt inhibitory signaling, leading to enhanced axonal growth. This research grant has three specific aims: (1) to establish the role of lipid rafts in axon inhibition by myelin-associated molecules, (2) to determine the raft association of receptors for myelin inhibitors, and (3) to investigate the raft-dependent downstream signaling of myelin-associated inhibitor molecules. The long-term goal of this research project is to elucidate signaling and cytoskeletal mechanisms that control and regulate the axonal responses to inhibitory environment.

Progress summary

The project was funded from 2004-2006 and was granted with no cost extension until June 2008. During the funding period of this grant, we have engaged in many experiments that were proposed in the application and progress has been made in all three aims. We have further modified our experimental approaches for analysis and have obtained additional evidence to support the central hypothesis that membrane rafts are essential for inhibitory signaling in developing axons. First, we have found that axon inhibition and repulsion depend on lipid rafts. We have established growth cone repulsion induced by diffusible gradients of Sema3A, MAG, and Nogo. Second, we have developed an exciting live imaging method to visualize rafts on the growth cone surface, including live imaging of raft constituents GM1 and cholesterol molecules. Importantly, we have found that a number of extracellular molecules could affect the distribution of lipid rafts on the growth cone. These data demonstrate that lipid rafts are dynamic and cell signaling can modify their distribution. We are currently applying this exciting imaging technique to study rafts dynamics in response to inhibitory molecules. Finally, we have started to investigate the raft association of inhibitory receptors. For example, we have identified the raft association of the Sema3A receptor neuropilin-1, which can be increased by Sema3A application. We are currently examining several other receptors and co-receptors for inhibitory cues, including NogoR for MAG and Nogo, co-receptor p75NTR for Nogo. Although these biochemical and imaging analyses are time-consuming, they are moving along well. While no publication has yet been generated from this part of study, we are continuing this part of research and have been accumulating a large body of data, which will lead to a manuscript for future publication.

The lack of axon regeneration of the adult central nervous system is in part due to the presence of inhibitory molecules at the injury site, including myelin associated proteins (e.g. MAG and Nogo). In our effort to elucidate the signaling pathways and cytoskeletal mechanisms underlying axon inhibition, we have come across two important projects that were not proposed in the initial application but are within the central theme of this research – axon inhibition