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Mechanisms underlying structural and functional plasticity in mouse spinal cord in chronic pain states

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Although acute pain is an important physiological function of the body, chronic pain resulting from inflammation or nerve injury is a debilitating disease itself. Chronic pain cannot be currently adequately treated and clinical translation has remained problematic owing to the gaps in understanding underlying mechanisms. Although pain is perceived in the brain, there is evidence showing that structural and functional changes both in neurons and glial cells in the spinal cord can contribute to induction of long-lasting changes in pain sensitivity. Hence, understanding the molecular mechanisms underlying these activity-dependent alterations in nociceptive circuits in the spinal cord is important.

Persistent nociceptive activity evokes synaptic potentiation at nociceptive synapses in the superficial spinal dorsal horn, comprising both pre- and post-synaptic contributions downstream of glutamatergic signaling mechanisms. However, mechanisms linking synaptic glutamatergic receptors to structural and functional changes in spinal neurons remain unclear. One goal of this thesis was to address the contributions of a family of proteins that are capable of linking glutamate receptors to rapid changes in the actin cytoskeleton. Kalirin7, a splice variant of the *Kalrn* gene, is a multifunctional guanine-nucleotide-exchange factor (GEF) for Rho GTPases and is characterized by its localization at excitatory synapses in the brain. Kalirin7 interacts with glutamate receptors and can dynamically modulate the neuronal cytoskeleton in neurons in the brain. Although misregulation of Kalirin7 was found to be involved in several neurological diseases, little is known whether it also contributes in chronic pain. In the study, we show that spinally-expressed Kalirin7 is required for nociceptive activity-dependent synaptic long-term potentiation as well as activity-dependent remodeling of synaptic spines in the spinal dorsal horn. In addition, we found the spine morphogenesis in spinal neurons was tightly regulated by Rac1, a substrate for Kalirin7. Depletion of spinal Kalirin7 or Rac1 suppressed the development of inflammatory nociceptive hypersensitivity as well as the remodeling of spinal synaptic spines.

Conversely, overexpression of Rac1 enhanced nociceptive sensitivity and enhanced spine density in spinal neurons. Therefore, we postulate that nociceptive activity utilizes postsynaptic Kalirin7-Rac1 signaling to modulate spinal synapses structurally as well as functionally during the course of inflammatory pain.

A second goal of this thesis was to study pain in the pathological context of multiple sclerosis (MS). MS, one of the most common neurological diseases mostly affecting young adults, is an incurable, chronic neuroinflammatory and neurodegenerative disease with unknown etiology. Chronic pain is one of the debilitating symptoms of MS, albeit with heterogeneous prevalence and temporal course; yet little is known about the mechanisms underlying MS-related pain and its treatment remains difficult, largely due to a lack of mechanistic studies. Experimental autoimmune encephalomyelitis (EAE), an animal model, which closely resembles MS, provides us the possibility to address the mechanism underlying MS-related pain. In this study, by comparing two distinct EAE mouse models directly, we found differences in pain behavior throughout the disease course, which may reflect the heterogeneity in MS. We observed different activation patterns for spinal microglia and astrocytes in a distinct spatiotemporal manner across the two models. By matching these with behavioral changes in nociceptive sensitivity, we found that the degrees of glial activation are temporally correlated with the development of mechanical hypersensitivity. Therefore, we suggest that the signaling molecules that are released from activated glia cells in the spinal cord during the disease can facilitate the development of pathological pain. These and further mechanistic studies will provide a basis for future possible treatments in MS patients.

Taken together, our studies indicate structural and functional plasticity of neurons as well as changes in the activation pattern of glia cells in the spinal dorsal horn are pivotal in chronic pain modulation. These results deliver insights into molecular and cellular mechanisms in the spinal dorsal horn that are specific to particular types of pathological pain.