This Week in The Journal

RNA Modification as a Novel Target for Neuropathic Pain

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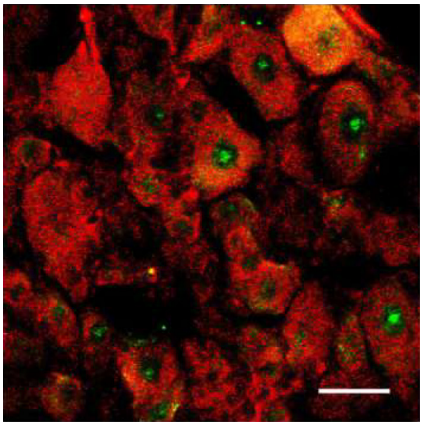
(see pages 3009–3027)

Chronic neuropathic pain—the type caused by nerve damage—is known to involve long-term changes in gene transcription and translation, but little research has yet investigated the influence of epigenetic changes. This week, Zhang et al. explore the role of the N4-acetylcytidine (ac4C) post-transcriptional RNA modification, which occurs universally across all organisms and had not been examined before in pain regulation. The researchers began by looking at the only known ac4C "writer" protein, N-acetyltransferase 10 (NAT10). Sciatic nerve chronic constriction injury (CCI), a model of neuropathic pain in mice, increased ac4C modification and *Nat10* mRNA and NAT10 protein levels in dorsal root ganglion (DRG) neurons, which transmit nociceptive sensation. The researchers traced the NAT10 upregulation to the upstream transcription factor 1 (USF1). Knockdown of USF1 alleviated the thermal and mechanical hypersensitivity in CCI mice but had no effect on behaviors in sham-operated mice. Remarkably, injection of *Usf1* lentivirus in naive mice led to increased USF1 and NAT10 expression and to induction of neuropathic pain-like behaviors. Knockdown of NAT10 in CCI mice reduced CCI-induced heat and mechanical hypersensitivity whereas injection of Nat10 lentivirus increased NAT10 expression and increased heat and mechanical sensitivity, suggesting that USF1-mediated upregulation of NAT10 contributes to neuropathic pain-like symptoms. Further experiments showed that CCI led to increased NAT10 expression, enhanced ac4C modification, and increased *de novo* protein synthesis. Downstream of NAT10, synaptotagmin 9 (SYT9) emerged as a target of NAT10. SYT proteins regulate exocytosis and neurotransmitter release by sensing calcium levels; SYT1 and SYT2 had been previously implicated in neuropathic pain, but a role for SYT9 had not yet been studied. Upregulation of NAT10 in DRGs dramatically increased SYT9 protein expression but not *Syt9* mRNA, indicating that NAT10 regulated SYT9 post-transcriptionally. The increase was mediated by NAT10-controlled ac4C modification of *Syt9* mRNA. Finally, knockdown of SYT9 alleviated mechanical and thermal hypersensitivity in CCI mice, whereas upregulation of SYT9 in naive mice led to neuropathic pain-like behaviors, demonstrating that NAT10 plays a key role in inducing nerve injury-induced pain by targeting SYT9 for ac4C modification and suggesting NAT10 as a potential target for neuropathic pain therapeutics.



Coexpression of SYT9 (red) with NAT10 (green) in dorsal root ganglion neurons. Scale bar, 30 μm.

Assessing the Role of the Cerebellum in Perceived Fatigue

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(see pages 3094–3106)

Fatigue, or the perception of weariness or exhaustion, is a debilitating symptom of many neurological and neuropsychiatric disorders. Despite its pervasiveness, little is understood about fatigue, and no treatments exist. This week, Casamento-Moran et al. explore the role of the cerebellum, a brain region that is primarily associated with learning and motor control but also perceptual processes such as pain. Participants performed a pinch task with their thumb and index finger, exerting 80% of maximum voluntary capacity. Participants reported the sensation of fatigue after the fatiguing but not the control task, and they demonstrated fatigability, an objective decrement in performance over time, which is a distinct phenomenon from fatigue perception. The researchers applied transcranial magnetic stimulation and measured motor evoked potentials from primary motor cortex (M1) and cerebellar inhibition (CBI), reflecting the connectivity between the cerebellum and M1. CBI was significantly reduced both immediately and 30 min after the fatiguing but not the control task. Cerebellar excitability was reduced after the fatiguing task, and participants with lower cerebellar activity reported milder fatigue perception independent from fatigability. In contrast, corticomotor activity was not correlated with fatigue or fatigability, nor did fatigue have an effect on intracortical inhibition or facilitation. In a second experiment with a separate cohort of participants, the researchers measured CBI before and after the fatiguing and control tasks and also after tasks that require significant cerebellar function. Motor control was impaired after the fatiguing but not the control task, lower CBI was correlated with greater motor error, suggesting that the cerebellum minimized fatigue perception at the expense of performance. Finally, the authors presented participants with a proprioceptive task, demonstrating that proprioception was not impaired by fatigue. The authors concluded that deactivation of cortical and subcortical areas maintain homeostasis by calibrating the sensorimotor state, and that the cerebellum integrates internal representations and external stimuli to help maintain this homeostasis, which, when upset, results in fatigue. The results supported the idea that the cerebellum optimizes performance under rested conditions, but that under lower energetic circumstances, resources are prioritized toward fatigue-related processes. The work advances our understanding of this still mysterious perception.

This Week in The Journal was written by Stephani Sutherland

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