This Week in The Journal

JUN Likely Opens Chromatin in Schwann Cells after Injury

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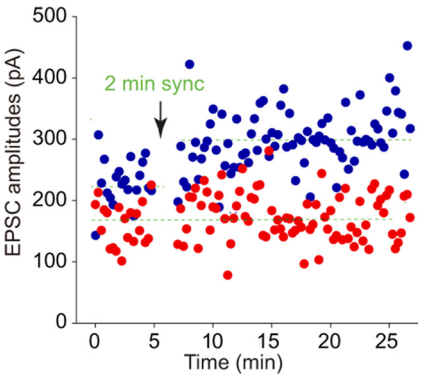
(see pages 6506–6517)

After peripheral nerve injury, Schwann cells undergo dramatic phenotypic changes. They stop producing myelin and rapidly transition into repair cells that clear debris and form tracks to guide regenerating axons. Besides suppressing the expression of myelin genes, repair Schwann cells express many genes that are not expressed during any other stage of Schwann cell development. This change requires modification of epigenetic tags.

Inactive DNA is typically wrapped tightly around histones, making genes and regulatory elements inaccessible to transcription factors and RNA polymerase. Some epigenetic modifications, such as trimethylation of lysine 27 on histone H3 (H3K27me3), promote tight wrapping and gene silencing, whereas others, such as monomethylation of lysine 4 on H3 (H3K4me1) and acetylation of lysine 27 on H3 (H3K27ac) make genes more accessible. After peripheral nerve injury, hundreds of enhancer elements in Schwann cells become newly associated with the permissive marker H3K27ac as the cells transdifferentiate into the repair phenotype.

In stem cells, many enhancers are poised to be activated as the cells differentiate. These enhancers are associated with both the permissive modification H3K4me1 and the repressive modification H3K27me3. Given the pronounced change in gene expression that accompanies transdifferentiation of Schwann cells after nerve injury, Ramesh et al. asked whether injury-induced enhancers (those that acquire H3K27ac only after injury) are likewise poised to be activated before such injury occurs. To answer this, they determined whether injury-induced enhancers were associated with H3K27me3 before injury. A few were, but ~99% were not. In contrast, the transcription factor JUN, which was previously shown to play a pivotal role in reprogramming Schwann cells to the repair phenotype, bound to ~30% of injury-induced enhancers, and most of those were associated with H3K27ac after injury. Moreover, mutating the JUN-binding enhancers of *Sonic Hedgehog*, a gene expressed in Schwann cells only after nerve injury, prevented injury-induced upregulation of this gene.

These results suggest that most injury-induced enhancers are not poised for activation. How then are they accessed after injury? Previous work suggests that JUN, as part of a complex, can bind to closed chromatin and recruit other factors. The fact that JUN is induced quickly after injury and binds to many injury-induced enhancers suggests that it has this role in Schwann cells.



After 2 min synchronous activation of inputs from the BLA and ventral hippocampus to the NAcSh, EPSCs evoked by stimulation of hippocampal fibers (blue) are potentiated whereas those evoked by BLA fibers (red) are not. See Yu et al. for details.

Coactive Amygdala and Hippocampal Inputs Induce LTP in MSNs

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(see pages 6581–6592)

Animals routinely learn to recognize sensory stimuli that predict rewards or threats; those stimuli can then motivate the animal to seek reward or escape danger. The performance of goal-directed behaviors in response to sensory stimuli is driven by medium spiny neurons (MSNs) in the nucleus accumbens shell (NAcSh), which receive information about contextual cues from the ventral hippocampus and information about emotional or valence states from the basolateral amygdala (BLA). Input from these two areas converges on single dendrites of MSNs, and patterned activation of either pathway can induce long-term potentiation (LTP) or depression of the activated synapses. Yu et al. now report that coactivation of BLA and ventral hippocampal projections induces heterosynaptic LTP selectively at hippocampal inputs to MSNs.

The authors expressed different light-activated cation channels in BLA and hippocampal projection neurons. Importantly, the channels could be selectively activated by different wavelengths of light, allowing the authors to activate inputs to individual MSNs independently or simultaneously. Activating both projections simultaneously just eight times over 2 min led to an increase in the amplitude of EPSCs evoked by activating hippocampal inputs alone, but it did not affect the amplitude of EPSCs evoked in the same cell by activating BLA inputs alone. LTP was stronger in MSNs that expressed D_1 dopamine receptors than in those that expressed D_2 receptors, and it was blocked by an antagonist of D_1 receptors, but not by an antagonist of D_2 receptors. LTP was also blocked by silencing dopaminergic projections from the ventral tegmental area, but surprisingly, it was not affected by blocking G-protein signaling downstream of dopamine receptors in recorded MSNs. Finally, LTP was not prevented by blocking NMDA receptors or $GABA_A$ receptors.

These results suggest that coactivation of convergent inputs from BLA and ventral hippocampus to MSNs selectively strengthens the inputs from the hippocampus, but only if dopamine is also present. This plasticity could allow otherwise neutral contextual cues (carried by hippocampal fibers) to acquire the ability to motivate action—a type of learning that requires dopaminergic signaling in the NAc. Future work should determine how coactivation of BLA and hippocampal inputs induces dopamine release and where the dopamine receptors required for LTP are located.

This Week in The Journal was written by Teresa Esch, Ph.D.
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