acetyl-CoA, is found on histone proteins. Second, ACSS2 is readily observed in the nucleus of tumor cells, as evidenced by histological staining. And third, as noted above, ACSS2 knockdown in human patient tumor cell lines, grown in media devoid of acetate, is growth inhibitory. These finding suggest that the major role of ACSS2 is to capture acetate released from deacetylated proteins and to reincorporate that into the acetyl-CoA pool for epigenetic regulation. As Comerford et al. (2014) point out, the half-life of histone acetylation is on the order of minutes, and a considerable fraction of acetate could be produced in vivo by the turnover of histone acetylation. ACSS2 in the nucleus provides a rapid way to reconvert this acetate to acetyl-CoA for use in reacetylating histones and thereby maintaining the epigenetic code. Although ACSS2 is not essential for this function in normal tissues, as evidenced by the viable *ACSS2* knockout mouse, it is possible that certain cancer cells require this function to maintain gene expression profiles optimized for rapid growth. Exogenous acetate, in this case, is treated equivalently to that generated by deacetylation. Regardless of the mechanism(s) by which cancer cells utilize acetate, the insights provided by these studies position acetate metabolism as a potentially exploitable vulnerability in cancer metabolism.

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A New "Spin" on Recovery after Spinal Cord Injury

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Functional recovery can occur after incomplete spinal cord injury. Takeoka et al. now report that such recovery relies on muscle spindle feedback that is necessary for neuronal circuit remodeling, suggesting novel targets to restore motor functions following spinal cord injuries.

Following incomplete lesions of the spinal cord, substantial recovery of sensory motor functions is observed (Curt et al., 2008; Martinez et al., 2012). Previous work has shown that such a recovery correlates with the formation of intraspinal circuits that bypass the injury (Bareyre et al., 2004; Courtine et al., 2008). Although sensory afferents are known to play a key role in the recovery process (Helgren and Goldberger, 1993), the sensory modality that allows the injured nervous system to re-establish functional connections has remained elusive. In this issue, Takeoka et al. (2014) provide evidence for the role of muscle spindle feedback in promoting neuroplasticity and motor recovery following spinal cord injury (SCI).

Muscle spindles are sensory mechanoreceptors specialized for proprioception. They are located in skeletal muscles, and consist of several specialized intrafusal muscle fibers surrounded by a capsule of connective tissue (Figure 1A). Muscle spindles are innervated by specialized motor and sensory axons. Deformation of intrafusal muscle fibers generates action potentials by activating stretch-sensitive ion channels expressed along the sensory axons that are coiled around the central part of the spindle. These axons connect to spinal motorneurons and different classes of interneurons that control muscle activity necessary for accurate body movements.

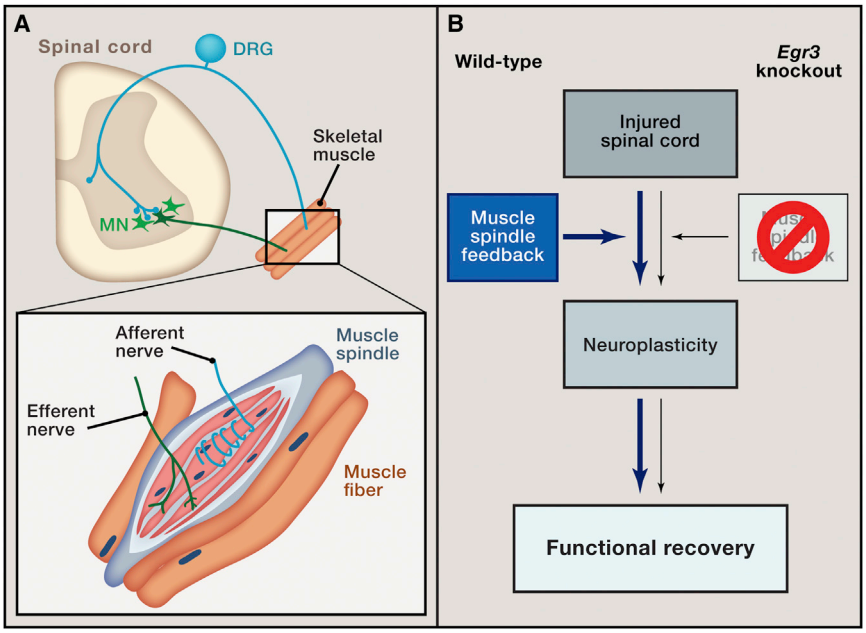

Figure 1. Promoting Neuroplasticity and Recovery after Spinal Cord Injury

(A) Muscle spindles are sensory organs located in skeletal muscles that receive innervation by specialized motor (efferent) and sensory (afferent) axons. Proprioceptive sensory axons originating from dorsal root ganglia (DRG) neurons spiral around the central region of the intrafusal fibers and respond to fiber stretch. The contractile regions of intrafusal fibers receive innervation by gamma motor neurons.

(B) Muscle spindle feedback promotes neuroplasticity and functional recovery after incomplete spinal cord injury. Absence of muscle spindle inputs in *Egr3* mutant mice results in impaired neuroplasticity and lack of recovery.

Previous studies demonstrated progressive postnatal degeneration of muscle spindles in mice lacking the zinc-finger transcription factor early growth response 3 (*Egr3*) (Tourtellotte and Milbrandt, 1998). While these mice are known to develop gait ataxia, resting tremors, and scoliosis (Tourtellotte and Milbrandt, 1998), the authors demonstrated with a sophisticated behavior/kinematic analysis combined with electromyogram recording that adult *Egr3* mutants have no major defects in walking when compared to wild-type mice. This provides a genetic entry point to study the contribution of muscle spindle feedback during motor recovery after SCI.

To study this process, the authors used thoracic lateral hemisection as a model of incomplete SCI. While control mice gradually recovered basic locomotor functions over time, *Egr3* mutants exhibited severe impairments on the ipsilateral side, providing evidence for a key contribution of muscle spindle feedback during the recovery phase and indicating that absence of physiological inputs from muscle spindles may prevent engagement of spinal circuits. However, daily administration of monoaminergic receptor agonists, a pharmacological approach known to increase the activity of local spinal circuits (van den Brand et al., 2012), was not sufficient to promote locomotor recovery in *Egr3* mutants. This further supports the hypothesis that muscle spindle feedback directs motor recovery after incomplete SCI.

As recovery progresses, neuroplasticity occurs within the injured spinal cord. Several studies have shown that neuroplasticity can promote functional recovery in the absence of long-distance regeneration (Bareyre et al., 2004; Courtine et al., 2008). To investigate whether muscle spindle feedback contributes to this process, Takeoka et al. used state-of-the-art transsynaptic tracing techniques to determine changes in neuronal connectivity associated with recovery. To start off, the authors found no difference in the topographic organization of supraspinal pathways in wild-type versus *Egr3* mutant mice prior to injury. Several weeks after incomplete SCI, however, substantial reorganization of supraspinal pathways and the formation of midline-crossing detour circuits were found in wild-type but not in *Egr3* mutant mice (Figure 1B), thereby providing anatomical evidence that muscle spindle feedback promotes plasticity of neuronal circuits. It is important to note that motor skills that require fine control of body movements were also severely compromised in wild-type mice several weeks after injury, suggesting that muscle spindle feedback alone may not be sufficient to restore complex motor skills. This also highlights the importance of combinatorial strategies including the promotion of axon regeneration, task-specific rehabilitation, and/or electrical stimulation to refine connectivity of supraspinal pathways following SCI.

The work of Takeoka et al. clearly represents an important step forward for the field, once again underscoring the key role of muscle spindle feedback in directing locomotor recovery and circuit reorganization after injury (Figure 1B). However, a number of intriguing questions remain open. Earlier work demonstrated that absence of neurotrophin-3 (NT-3) in mutant spindles might be responsible for the lack of synaptic connectivity between sensory and motor neurons in *Egr3* mutants (Chen et al., 2002). Thus, an interesting experiment would be to test whether lack of substantial recovery in *Egr3* mutants could be restored by intramuscular viral delivery of NT-3. Furthermore, because *Egr3* mutant mice lack dual midline-crossing axons, it would be important to define whether a causal relationship exists between anatomical and functional outcomes. What happens after ablation of dual midline-crossing axons in wild-type mice? While this is an important experiment, it is worth mentioning that there are major difficulties hindering its execution. One major limitation is the absence of genetic markers to specifically select and manipulate the neurons from which midline-crossing axons originate. Future studies will be required to fully understand the molecular mechanism for muscle spindle feedback-mediated recovery after a variety of CNS trauma, including incomplete SCI.

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