position, and circuit integration in *Satb2* null mice carrying the Satb2:Cre^{ERT2} allele: Satb2:Cre-expressing neurons are now found in an aberrant lateral position closer to the termination zone of CGRP+ peptidergic nociceptive afferents, they lose input from proprioceptive neurons, and they make a sparse number of aberrant output contacts on cells dorsal to the V2a interneuron population. In addition, transcription factor expression in these neurons is altered: while there is no change in Ptf1a and Lbx1 expression, there is altered expression in Pax2, Bhlhb5, and Ctip2 (Figure 1B), suggesting that these cells are not just aberrantly localized, but also changed in aspects of their molecular identity. Future studies will help clarify the molecular mechanisms by which Satb2 expression instructs cell fate and position. How the lateral "move" of the Satb2-expressing cells contributes to the behavioral phenotypes is still unclear. Do the phenotypes arise from new circuitry or from the loss of the wild-type ISR^{Satb2} cells? Experiments aimed at silencing ISR^{Satb2} neurons might help distinguish these possibilities.

Summary

While the study of the nociceptive withdrawal reflex has a long history in neuroscience, the questions raised by this most recent contribution are as contemporary as ever. How much variation can be found in a pool of developmentally related interneurons, and how is this diversity established? Is circuit connectivity determined by the lineage and molecular profile of a neuron, or does it more reflect the neuron's position relative to a projection target zone? How are multiple sensory streams coordinated into singular behavioral outputs, and how do single interneurons or microcircuits contribute to multiple behavioral outputs? And what are the computational strategies at the level of single cells that support such convergence of input or divergence of output? The work of Hilde et al. (2016) simultaneously advances our understanding and raises fascinating questions. With Satb2 as a genetic handle for an involved population of interneurons, we now have an entry point for modern circuit cracking of the nociceptive flexor withdrawal reflex.

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Myelin Avoids the JAM

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In this issue of *Neuron*, Redmond et al. (2016) identify junction adhesion molecule 2 (JAM2) as an inhibitor of somatodendritic myelination in spinal cord neurons, thereby elucidating how myelin forms on axons but avoids dendrites and cell bodies.

During the development of the central nervous system (CNS), oligodendrocyte precursor cells (OPCs) undergo a highly coordinated maturation process resulting in the ensheathment of multiple axons in compact multi-lamellar structures, termed myelin. The segmental wrapping of axons facilitates enhanced propagation of action potentials by providing increased interaxonal resistance, decreased membrane capacitance, and ordered segregation of ion channels at Nodes of Ranvier. In addition, recent work suggests that oligodendrocytes serve as key sources of metabolic support for axons (Simons and Nave, 2016). As a result, disruption or malformation of myelin is highly relevant to many neuropathologies, such as multiple sclerosis (Hughes and Appel, 2016). While recent strides have been made in understanding factors involved in OPC

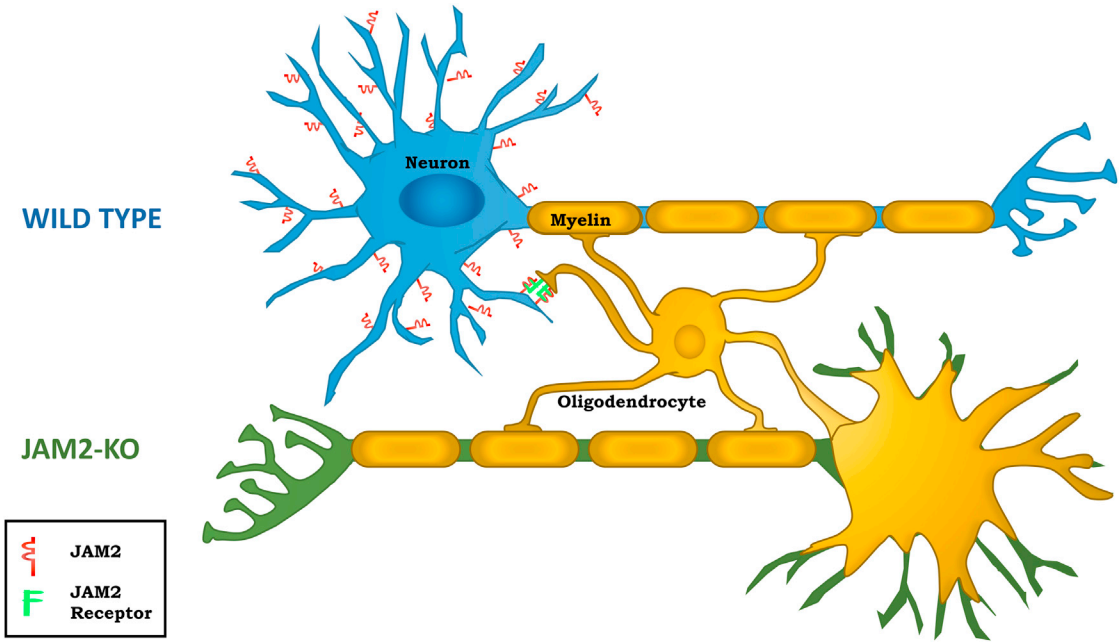

Figure 1. JAM2 Inhibits CNS Myelin Formation
During myelination, high-level expression of JAM2 (red) in the somatodendritic compartment inhibits the local formation of myelin through interaction with an unknown JAM2 receptor (green) expressed by oligodendrocytes. In neurons from JAM2 knockout mice (JAM2-KO), aberrant ensheathment of the somatodendritic compartment by oligodendrocytes occurs more frequently.

migration and differentiation, one fundamental unanswered question is how oligodendrocytes discriminate their axonal targets from other structures. For example, why don't oligodentrocytes ensheath dendrites or somata? Are there myelin-inducing signals on axons, repulsive signals expressed by the somatodendritic compartment, or is there a combination?

In this issue of *Neuron*, Redmond et al. (2016) tackle these questions and reveal a novel role for junction adhesion molecule 2 (JAM2) as a myelin repulsion molecule. They provide evidence for a model in which JAM2 surface expression in the somatodendritic compartment of spinal cord neurons (SCNs) inhibits the local formation of myelin through interaction with an unidentified receptor on oligodendrocytes (Figure 1).

Historically, oligodendrocytes have been known as eager myelinators that will readily form myelin sheets in culture, even on glass coverslips, and can myelinate inert objects such as polystyrene nanofibers (Hughes and Appel, 2016). Therefore, oligodendrocytes do not appear to require inductive signaling from axons to commence myelination. However, when cultured with neurons, and in vivo, myelin is strictly segregated to axons, suggesting that while myelin genesis is an intrinsic feature of oligodendrocytes, extrinsic myelin guidance cues must exist to prevent improper somatodendritic ensheathment. Redmond et al. (2016) explored the nature of these potential guidance cues by co-culturing rat primary SCNs with OPCs. Normally, when co-cultured, OPCs differentiate and exclusively myelinate axons. However, when the authors pre-treated the neurons with the cross-linker paraformaldehyde (PFA) to disrupt neuron-oligodendrocyte signaling, not only were axons myelinated, but dendrites and even some SCN somata were ensheathed. These results suggested that an inhibitory signal on the somatodendritic compartment may have been interrupted by the cross-linker.

To identity somatodendritic-specific myelin inhibitory signals, they conducted next-generation RNA-sequencing of cultured SCN and dorsal root ganglion (DRG) neurons, looking for genes differentially expressed by the SCNs. They reasoned that since DRG neurons lack true dendrites, they would be unlikely hosts to a somatodendritic inhibitor. Among the candidate inhibitory proteins that they identified, JAM2 caught their attention due to its low expression in DRG cell bodies and high expression in SCN somatodendritic compartments. JAM2 is a member of the JAM family, which are transmembrane proteins involved in the formation of tight junctions. JAM2 has also been reported to have a role in cell adhesion, migration, and metastasis in tumor cells (Zhao et al., 2016). Intriguingly, when the extracellular portion of JAM2, fused to the Fc region of an immunoglobulin (JAM2-Fc), was introduced into cultured oligodendrocytes, they found markedly higher JAM2-Fc binding to myelin basic protein-positive (MBP+), myelinating oligodendrocytes relative to OPCs. This result suggests that the surface expression of a JAM2 receptor could be upregulated during OPC maturation, as would be expected from a regulator of myelination.

Redmond et al. also provide compelling evidence for JAM2 modulation of oligodendrocyte myelination in vitro. When OPCs were plated onto an array of micropillars, they formed myelin; however, when the micropillars were coated with JAM2-Fc, myelination was reduced by 86%. Importantly, there were no changes