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Myelin—More than Insulation

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Myelin is often compared to electrical insulation on nerve fibers. However, nerve impulses are not transmitted through neuronal axons the way electrons are conducted through a copper wire, and the myelin sheath is far more than an insulator. Myelin fundamentally changes the way neural impulses (information) are generated and transmitted, and its damage causes dysfunction in many nervous system disorders including multiple sclerosis, cerebral palsy, stroke, spinal cord injury, and cognitive impairments. A detailed understanding of myelin structure is therefore imperative, but is lacking. On page 319 of this issue, Tomassy *et al.* (1) provide a high-resolution global view of myelin structure spanning the six layers of mammalian cerebral cortex. The findings are likely to spark new concepts about how information is transmitted and integrated in the brain.

New techniques of automating collection of electron microscopic images taken in series through layers of tissue are becoming available to analyze neuron ultrastructure in large volumes (2). Using such methods, Tomassy *et al.* reveal myelin structure in the mouse cerebral cortex along individual nerve fibers, providing a coherent picture.

Myelin is a coating of compacted cell membrane that is wrapped around the axon by non-neuronal cells called oligodendrocytes. These multipolar cells extend slender cellular processes to grip axons and spin up to dozens of layers of membrane around it like electrical tape. Many oligodendrocytes grasp a single axon to span its full length. The tiny space exposed between each grasping “hand” corresponds to a node of Ranvier, where voltage-gated sodium channels are concentrated. When the electrical potential across the axon membrane depolarizes by about 20 mV, these channels allow rapid influx of sodium ions that discharges the transmembrane potential, creating a voltage transient of ~0.1 V—the action potential. Myelin forces the action potential to be generated only at these 1- μ m-long nodes of Ranvier and to leap rapidly in sequence over tens or hundreds of micrometers to excite an action potential in the next node. Rather than spreading down an unmyelinated axon as a slow wave of depolarization, the nodes of Ranvier act as repeaters. The speed at which signals are transmitted is limited by the distance between nodes, the thickness of the myelin wrapping, and the length of the exposed axon in the node.

The common presumption that these features are relatively uniform along a single axon is invalidated by the observations of Tomassy *et al.* in the mouse cerebral cortex. The authors observed long stretches (up to 55 μ m) along an individual axon of pyramidal neurons in layer II/III where there is no myelin sheath interspersed with segments that are myelinated

(see the figure). These unmyelinated regions could be passive internodes or they could have clusters of ion channels to promote action potential propagation. Notably, the critical segment of bare axon extending from the cell body to the first segment of myelin [the axon initial segment (3); referred to as the premyelin axonal segment by Tomassy *et al.*] differs between cortical layers.

Variation in myelination along an axon could adjust transmission speed to optimize the time of arrival of signals from multiple axons at a relay point in a neural circuit. Unusually long nodes of Ranvier (50 μm) may even delay action potential propagation (4), as they increase the electrical capacitance of the axon membrane and consequently increase the time required to charge and discharge it. The as yet unknown ion channel properties in these unmyelinated regions of cortical neurons will also influence conduction velocity. However, the total transmission time across the relatively short distance of the cerebral cortex (about 0.5 mm in a mouse and 2 to 4 mm in humans) may present a negligible delay, suggesting additional reasons for the intermittent myelin. Perhaps unmyelinated axon segments can permit more complex forms of network integration.

The “neuron doctrine” states that information flows through synaptic inputs on dendrites and passes out of the axon as an action potential to excite dendrites of the next neuron in the circuit. However, other modes of communication are becoming apparent. Synapses can form on unmyelinated segments of axons (5), and bare axons can release neurotransmitters, signaling by nonsynaptic communication (6). Action potentials also propagate backward into the cell body, affecting neural integration and synaptic plasticity (7). Oscillations and waves of electrical activity at different frequencies couple neurons into functional assemblies that coordinate and gate information, and the frequency of oscillation differs in layers II/III and V (8). Myelin also can constrain where axons sprout and form synapses with dendrites or with other axons. Indeed, proteins in the myelin sheath, such as Nogo, block axon sprouting, indicating that the myelin wrapping stabilizes axon structure and the pattern of connectivity in neural circuits (9).

The most critical segment of unmyelinated axon is the axon initial segment. The 5- to 80- μm -long unmyelinated section between the cell body and first myelin segment is the decision point where action potentials are triggered. The morphological features of this segment, and types of ion channels present in it, regulate excitability of the neuron. This region also controls the shape of the action potential, which affects the amount of neurotransmitter released from the synapse, the frequency of action potential firing, and other aspects of action potential signaling (3). Action potentials are initiated at the distal end of the axon initial segment (10), and the distance to this trigger point has important functional consequences. Tomassy *et al.* found that this region of the axon was longer in layers III/IV than V/VI.

The length and membrane properties of the axon initial segment influence the capacity of action potentials to propagate back into the cell body and dendrites (3). Back-propagating action potentials in hippocampal neurons develop during slow-wave sleep and quiet periods of wakefulness and are important in memory formation (7).

The length of the myelinated axon between nodes may be determined by neuronal signals, intrinsic properties of the oligodendrocytes, and region-specific factors. Tomassy *et al.* report that the layer-specific pattern of myelination on axons is disrupted in genetically modified mice that have abnormal cortical layering, pointing to a role for neurons in specifying myelination properties. The age of oligodendrocytes can also determine the length of internodal segments, with oligodendrocytes generated later in life producing shorter internodes (11). Internodal length and other properties of myelin differ in different brain regions, with corresponding effects on conduction velocity (12).

There are countless axons in the nervous system that are unmyelinated and they do not “short out.” Myelin organizes the very structure of network connectivity, facilitates modes of nervous system function beyond the neuron doctrine, and regulates the timing of information flow through individual circuits. It is certainly time to set aside the frayed metaphor of myelin as insulation and appreciate the more fascinating reality.

Acknowledgments

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Unusual features of myelin in the mammalian cerebral cortex permit more complex forms of network integration.

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Intermittent myelination

Myelination of layer II/III pyramidal neurons of the cerebral cortex is illustrated, with a long axon initial segment and segments with variable lengths of unmyelinated axon.