Myelinophagy: Schwann cells dine in

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When nerve injury occurs, the axon and myelin fragments distal to the injury site have to be cleared away before repair. In this issue, Gomez-Sanchez et al. (2015; *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201503019) find that clearance of the damaged myelin within Schwann cells occurs not by phagocytosis but rather via selective autophagy, in a process they term "myelinophagy."

The peripheral nervous system has the considerable ability to regenerate axons after nerve injury. A prerequisite for successful repair is the degradation and clearance of axonal and myelin fragments in areas distal to the injury site, a process known as Wallerian degeneration (Vargas and Barres, 2007; Conforti et al., 2014; Simons et al., 2014). In nerves undergoing Wallerian degeneration, myelin breaks down and fragments into small ovoid-like structures at the Schmidt-Lanterman clefts (funnel-shaped incisures in the myelin). These fragmented pieces of damaged myelin were thought to be cleared away by phagocytosis both by Schwann cells and by invading macrophages.

However, in this issue, Gomez-Sanchez et al. now show that macroautophagy is essential for myelin breakdown and clearance in Schwann cells after nerve injury. Macroautophagy (hereafter autophagy) is a bulk degradation pathway that delivers cytoplasmic substrates to lysosomes for degradation (Choi et al., 2013; Feng et al., 2014). During this process, cytoplasm and superfluous or dysfunctional organelles are sequestered by the phagophore, a double membrane that expands and matures into an autophagosome. Autophagosomes subsequently fuse with lysosomes, which trigger degradation of the autophagic cargo by hydrolases.

Autophagy was initially described as a nonselective process that occurs in response to starvation or during cell differentiation, but it is now clear that there are tightly regulated and highly selective subtypes that require cargo recognition by the autophagy machinery. Several cargo-specific autophagic subtypes have been described: for example, the removal of aggregated proteins (aggrephagy), damaged mitochondria (mitophagy), peroxisomes (pexophagy), ribosomes (ribophagy), endoplasmic reticulum (reticulophagy), lipid droplets (lipophagy), and pathogens (xenophagy; Okamoto, 2014). Now, Gomez-Sanchez et al. (2015) show that in response to nerve injury, autophagy is responsible for clearing away damaged myelin within Schwann cells, a process that they term "myelinophagy." These findings are particular remarkable, as myelinophagy, in contrast to other cargo-selective variants of macroautophagy that degrade damaged intracellular components, describes a process of how a plasma membrane is degraded.

To solve this topological conundrum, a closer look at myelin architecture is necessary. Myelin is formed when the "inner tongue," the leading edge of the myelinating cells, starts to move multiple times around the axon until a multilayered compacted membrane is generated (Bunge et al., 1989; Snaidero et al., 2014). When the process is completed, the Schwann cell engulfs the myelin sheath with its outermost, cytoplasmic-rich myelin layer (Fig. 1 A). Even if myelin is localized within the interior of the Schwann cell, it is continuous with the plasma membrane and therefore not an intracellular structure. However, in nerves undergoing Wallerian degeneration (Fig. 1 B), myelin starts to fragment into ovoid-like structures in an active process that requires actin polymerization at the Schmidt-Lanterman incisures (Jung et al., 2011). During this process, myelin loses its connection with the cell surface (Fig. 1 C). If, now, the outermost layer of the myelin membrane fuses with the plasma membrane—like the closure of a phagocytic cup—fragmented myelin would be internalized into the Schwann cell cytoplasm without using endocytic pathways. Here, the myelin fragments could be selectively recognized by so-far unknown autophagic receptor molecules for the recruitment to the phagophore (Fig. 1 D). Why do Schwann cells use autophagy and not endocytosis for recycling parts of its plasma membrane? One reason could be that fragmented myelin sheaths are too tightly clumped and too bulky for Schwann cells that are not specialized in phagocytosis.

Based on the presented model of myelinophagy, a block of autophagy should result in the accumulation of fragmented myelin within the Schwann cell cytoplasm. Surprisingly, this is not what Gomez-Sanchez et al. (2015) observe; instead, they find intact myelin sheaths after blocking autophagy genetically or pharmacologically. Thus, autophagy must somehow participate in myelin fragmentation. One possibility is that autophagy activates or provides energy for pathways involved in myelin fragmentation. Alternatively, autophagy is required for triggering an intrinsic genetic program in Schwann cells during nerve injury.

Regardless of the mechanisms of myelin fragmentation and internalization, Gomez-Sanchez et al. (2015) describe an important pathway of myelin breakdown in nerve injury. While this pathway is shown in the context of Wallerian degeneration, it is possible that myelinophagy is also activated in hereditary Charcot-Marie-Tooth or inflammatory neuropathies. One important question there is how axonal injury induces myelinoph-

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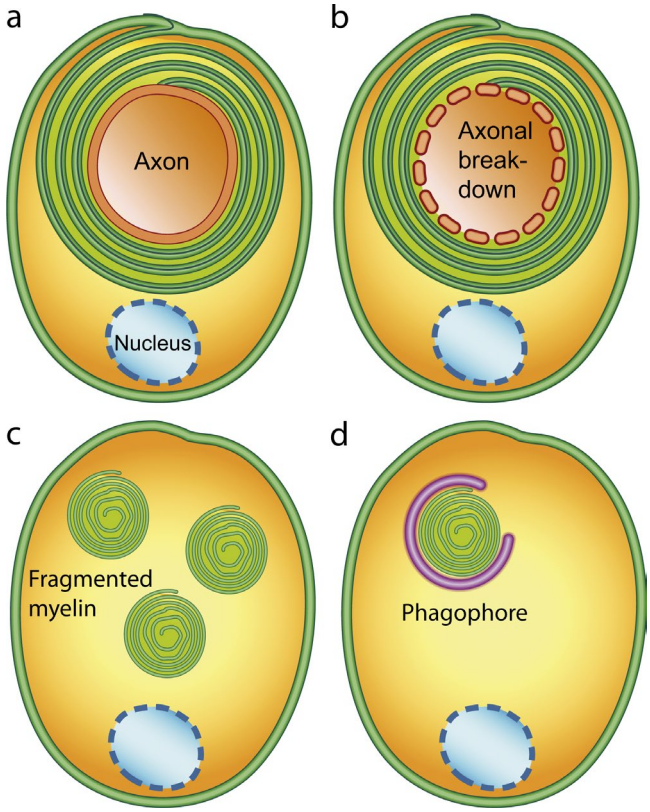

Figure 1. **Myelinophagy.** (A) Graphical illustration of a healthy myelinating Schwann cell. (B) When Wallerian degeneration is initiated, the axon starts to break down into fragments. (C) The Schwann cell then internalizes myelin fragments, possibly by the fusion of the outer "lips" of the Schwann cell plasma membrane. (D) Next, the resulting myelin fragments are taken up into phagophores. Not shown is the following: the sealing of phagophores to form autophagosomes and their fusion with lysosomes, which finally leads to degradation of the myelin fragments.

agy. It is known that Schwann cells are able to sense axon damage and respond by activating multiple signaling pathways, including ERK/MAPK, JNK/c-Jun, Notch, and JAK-STAT (Harrisingh et al., 2004; Arthur-Farraj et al., 2012; Napoli et al., 2012). These signals not only induce cell activation, but also trigger myelin fragmentation. Myelinophagy is positively regulated by the JNK/c-Jun pathway, the central regulator of Schwann cell reprogramming during injury (Arthur-Farraj et al., 2012). Thus, it appears that myelinophagy is part of a genetically controlled response that is triggered upon nerve dissection and coordinates the mutual breakdown of the connected axon–glia unit.

What is the advantage of myelinophagy in Schwann cells as compared with myelin phagocytosis by invading macrophages? If Schwann cells are able to take care of a large part of myelin degradation with only a little help from macrophages, tissue inflammation could be kept to a minimum. In summary, myelinophagy represents a mechanism of how Schwann cells digest their own cell surface upon receiving signals from the associated and degenerating axon. This response must now be considered as an essential pathway of nerve injury in peripheral nerves. If myelinophagy is selective, identification of the cargo receptor will be an important step toward therapeutically modulating myelin turnover.

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References

Arthur-Farraj, P.J., M. Latouche, D.K. Wilton, S. Quintes, E. Chabrol, A. Banerjee, A. Woodhoo, B. Jenkins, M. Rahman, M. Turmaine, et al. 2012. c-Jun reprograms Schwann cells of injured nerves to generate a repair cell essential for regeneration. *Neuron.* 75:633–647. http://dx.doi.org/10.1016/j.neuron.2012.06.021

Bunge, R.P., M.B. Bunge, and M. Bates. 1989. Movements of the Schwann cell nucleus implicate progression of the inner (axon-related) Schwann cell process during myelination. *J. Cell Biol.* 109:273–284. http://dx.doi.org/10.1083/jcb.109.1.273

Choi, A.M., S.W. Ryter, and B. Levine. 2013. Autophagy in human health and disease. *N. Engl. J. Med.* 368:651–662. http://dx.doi.org/10.1056/NEJMra1205406

Conforti, L., J. Gilley, and M.P. Coleman. 2014. Wallerian degeneration: an emerging axon death pathway linking injury and disease. *Nat. Rev. Neurosci.* 15:394–409. http://dx.doi.org/10.1038/nrn3680

Feng, Y., D. He, Z. Yao, and D.J. Klionsky. 2014. The machinery of macroautophagy. *Cell Res.* 24:24–41. http://dx.doi.org/10.1038/cr.2013.168

Gomez-Sanchez, J.A., L. Carty, M. Iruarrizaga-Lejarreta, M. Palomo-Irigoyen, M. Varela-Rey, M. Griffith, J. Hantke, N. Macias-Camara, M. Azkargorta, I. Aurrekoetxea, et al. 2015. Schwann cell autophagy, myelinophagy, initiates myelin clearance from injured nerves. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201503019

Harrisingh, M.C., E. Perez-Nadales, D.B. Parkinson, D.S. Malcolm, A.W. Mudge, and A.C. Lloyd. 2004. The Ras/Raf/ERK signalling pathway drives Schwann cell dedifferentiation. *EMBO J.* 23:3061–3071. http://dx.doi.org/10.1038/sj.emboj.7600309

Jung, J., W. Cai, H.K. Lee, M. Pellegatta, Y.K. Shin, S.Y. Jang, D.J. Suh, L. Wrabetz, M.L. Feltri, and H.T. Park. 2011. Actin polymerization is essential for myelin sheath fragmentation during Wallerian degeneration. *J. Neurosci.* 31:2009–2015. http://dx.doi.org/10.1523/JNEUROSCI.4537-10.2011

Napoli, I., L.A. Noon, S. Ribeiro, A.P. Kerai, S. Parrinello, L.H. Rosenberg, M.J. Collins, M.C. Harrisingh, I.J. White, A. Woodhoo, and A.C. Lloyd. 2012. A central role for the ERK-signaling pathway in controlling Schwann cell plasticity and peripheral nerve regeneration in vivo. *Neuron.* 73:729–742. http://dx.doi.org/10.1016/j.neuron.2011.11.031

Okamoto, K. 2014. Organellophagy: eliminating cellular building blocks via selective autophagy. *J. Cell Biol.* 205:435–445.

Simons, M., T. Misgeld, and M. Kerschensteiner. 2014. A unified cell biological perspective on axon-myelin injury. *J. Cell Biol.* 206:335–345. http://dx.doi.org/10.1083/jcb.201404154

Snaidero, N., W. Möbius, T. Czopka, L.H. Hekking, C. Mathisen, D. Verkleij, S. Goebbels, J. Edgar, D. Merkler, D.A. Lyons, et al. 2014. Myelin membrane wrapping of CNS axons by PI(3,4,5)P3-dependent polarized growth at the inner tongue. *Cell.* 156:277–290. http://dx.doi.org/10.1016/j.cell.2013.11.044

Vargas, M.E., and B.A. Barres. 2007. Why is Wallerian degeneration in the CNS so slow? *Annu. Rev. Neurosci.* 30:153–179. http://dx.doi.org/10.1146/annurev.neuro.30.051606.094354