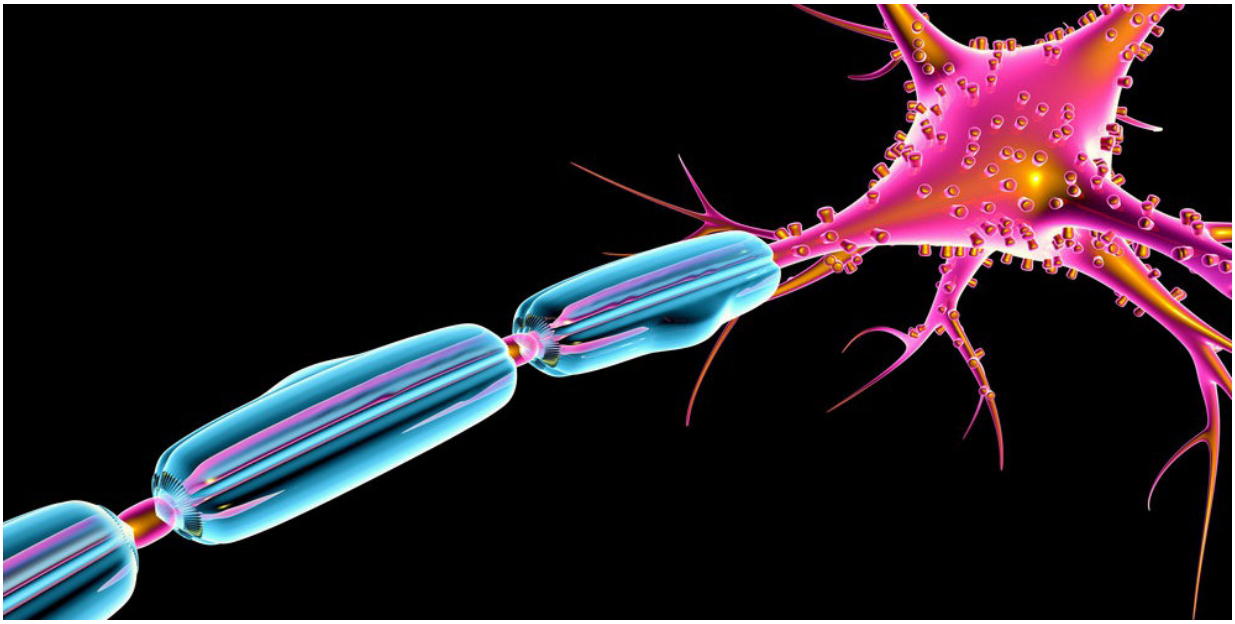
Enzyme ensures thick insulation

March 8 2018, by Peter Rüegg



Schwann cells build up the blue insulation layer of a nerve fibre. If these cells lack a certain enzyme, the isolation is inadequate. Credit: Alfred Pasieka / Science Photo Library / Keystone

ETH researchers have revealed that Schwann cells in the peripheral nervous system largely produce their own fatty acids in order to create electrical insulation for nerve fibres. This process relies on an enzyme whose absence leads to defective insulation and impaired motor function.

Axons, the long projections of neural cells which form the nerves of our

peripheral nervous system, are like electrical cables: they have thick electrical insulation so that they can quickly relay stimuli from the body and signals from the brain to a toe, for example.

This insulation, called myelin, is made up of numerous layers of cellular membranes – seen in cross section, an axon insulated in this way resembles the rings of a tree. These myelin sheaths have constrictions (or nodes) at regular intervals, and nerve impulses jump from one node to the next in order to propagate quickly.

Defective insulation

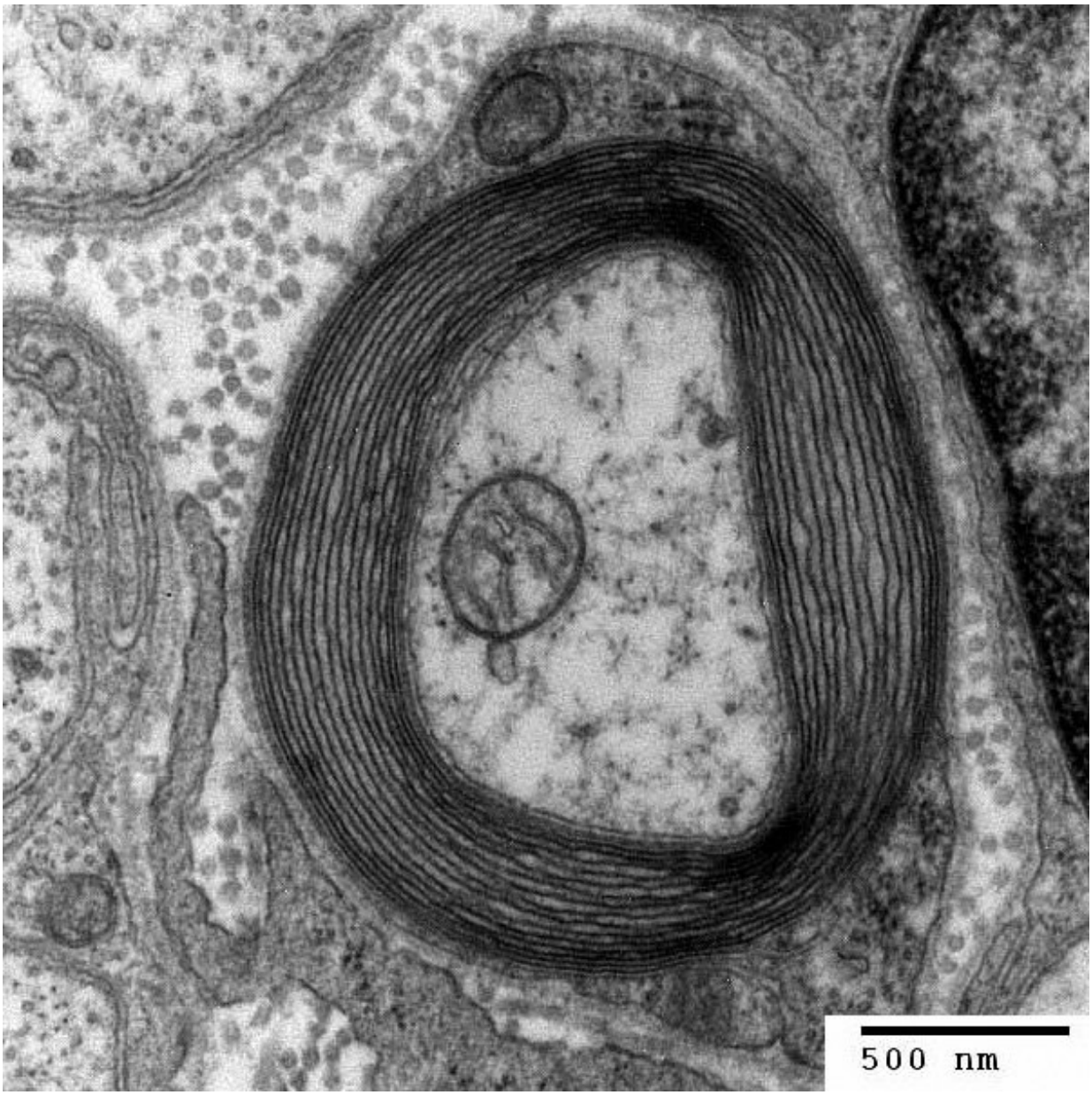
In some neurodegenerative diseases, the myelin sheaths of axons in the peripheral nervous system degrade, meaning they can no longer relay signals and commands efficiently. One example of these diseases is Charcot-Marie-Tooth disease (CMT), which is an inherited condition. Over time, the breakdown of the insulation leads to degeneration of the nerves and ultimately also of the muscles that are cut off from nerve impulses as a result. As the disease progresses, patients lose the ability to control their motor functions and can barely walk properly, as well as suffering from pain.

Building up the axons' insulation is the responsibility of the surrounding Schwann cells. These use large quantities of various fat molecules (lipids) in a short time, mostly in the first years after birth, to encase axons in myelin. Until now, it was not known how they satisfied their huge need for lipids. Scientists debated if they obtained these molecules from food or produced them themselves.

Central enzyme for synthesis

Researchers at ETH Zurich, led by Laura Montani from the group of

Ueli Suter at the Institute of Molecular Health Sciences, have now used a mouse model to demonstrate that the Schwann cells synthesise around half of the lipids needed for building up the insulation from scratch – that is, they produce them themselves. The cells obtain the other half of the lipids they need from food.



Like tree rings: layers of myelin coat a nerve fibre. Credit: wikimedia commons

Sitting inside the Schwann cells, an enzyme known as fatty acid synthase (FASN) acts as a central "switch" in the process of synthesising lipids. The team found that this enzyme is essential for the correct composition of lipids in the insulating layers, for the cells to start myelination, and for the healthy growth of myelin layers. Via the fat molecules produced, called fatty acids, FASN also regulates an entire signal network that plays an important role in myelination.

Once this enzyme is missing, the cells can no longer produce critical lipids for the myelin layers. The Schwann cells then rely more heavily on obtaining dietary lipids from blood vessels that pass through nerve fibres . However, Schwann cells laying more far away from the bloodstream can neither synthesise their own lipids nor obtain them well from the blood and therefore cannot insulate the axons sufficiently – if at all.

In addition, the researcher and her colleagues from various universities, including the Universities of Graz (Austria), Washington-St. Louis (USA) and Zurich, found that even a high-fat diet failed to reverse the process in mice that lacked the enzyme FASN: the axons' insulation remained defective. This shows that intrinsic lipid production by Schwann cells is essential for the formation of myelin sheaths in the nerves.

Montani and her colleagues conducted their experiments using animals with a specific mutation that meant they lacked the enzyme FASN. Her study compared the myelination of these mice with that of mice in which FASN did occur. The study examined animals in their "childhood", from birth onwards, as this is the critical stage of life in which axons receive their myelin insulation. After adolescence, myelination is more or less complete. The insulation will still be thickened if need be, but the phase of rapid build-up is over.

Connection with rare neurological diseases?

It remains unclear what implications the results have for different diseases. Montani is now studying if the enzyme is also crucial for the cells which myelinate the brain during postnatal development and if it plays a role in repairing myelin after a lesion, as the ones present in multiple sclerosis patients.

A large number of rare childhood diseases stem from mutations in genes that play an essential role in lipid synthesis. Little research exists into these diseases, as they occur very rarely. The patients typically die at a very young age due to severe degeneration of the nervous system.

Montani suspects that the breakdown of neurons could be caused by reduced synthesis of lipids in the myelinating cells of the nervous system, among other factors. "Knowing how reduced lipid synthesis affects myelination during development is an important step towards gaining a better understanding of how these kinds of diseases progress," she says.

Moreover, although very few people suffer from each of these disorders, she says rare disorders as a whole are one of today's biggest causes of death in babies and infants in the industrialised nations. They are responsible for around a third of deaths in the first year of life. Montani therefore wants to continue her research in this direction in the future. As the fruit of six years of hard work, her project is now complete and will provide the foundation for this future research.

More information: Laura Montani et al. De novo fatty acid synthesis by Schwann cells is essential for peripheral nervous system myelination, *The Journal of Cell Biology* (2018). DOI: 10.1083/jcb.201706010

Provided by ETH Zurich