Much more **than Glue**

To function properly, our nervous system needs a substance called myelin, which surrounds and protects nerve fibers. If this myelin sheath is destroyed, as in multiple sclerosis (MS), the consequences are severe. Prof. Mikael Simons is researching how this protective insulating layer is formed – with the aim of improving treatment for MS patients.

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Claudia Doyle

Mehr als nur Leim

Die meisten Neurologen erforschen Nervenzellen, Neuronen genannt. Nur wenige Wissenschaftler widmen sich dem anderen Zelltyp im Gehirn, den sogenannten Gliazellen. „Früher war man als Neurologe, der an Gliazellen forscht, schon ein Exot“, sagt Mikael Simons, Professor für Molekulare Neurobiologie an der TUM und Wissenschaftler am Deutschen Zentrum für Neurodegenerative Erkrankungen (DZNE). „Aber das ist längst nicht mehr so.“

Simons hat eher als andere damit angefangen, sich für eine ganz bestimmte Art von Gliazellen zu interessieren. Er untersucht sogenannte Oligodendrozyten, die aus ihrer Zellmembran eine isolierende Myelinscheide um Nervenfasern herum ausbilden. Die Myelinscheide beschleunigt die Signalweiterleitung, sie schützt die Axone und versorgt sie mit Energie.

Die Myelinisierung des Gehirns beginnt kurz nach der Geburt, findet aber auch im Erwachsenenalter noch statt. Damit hat Myelin auch einen Anteil an der Plastizität unseres Gehirns.

Dass unser Gehirn plastisch ist, sich also je nach Gebrauch in seiner Anatomie verändert, das weiß man schon seit fast 20 Jahren. Je nachdem, welchen Umwelteinflüssen wir ausgesetzt sind, welchen Sport wir treiben oder welches Musikinstrument wir üben, verändert sich die Struktur unseres Denkapparats. Gehirnareale wachsen oder übernehmen neue Aufgaben.

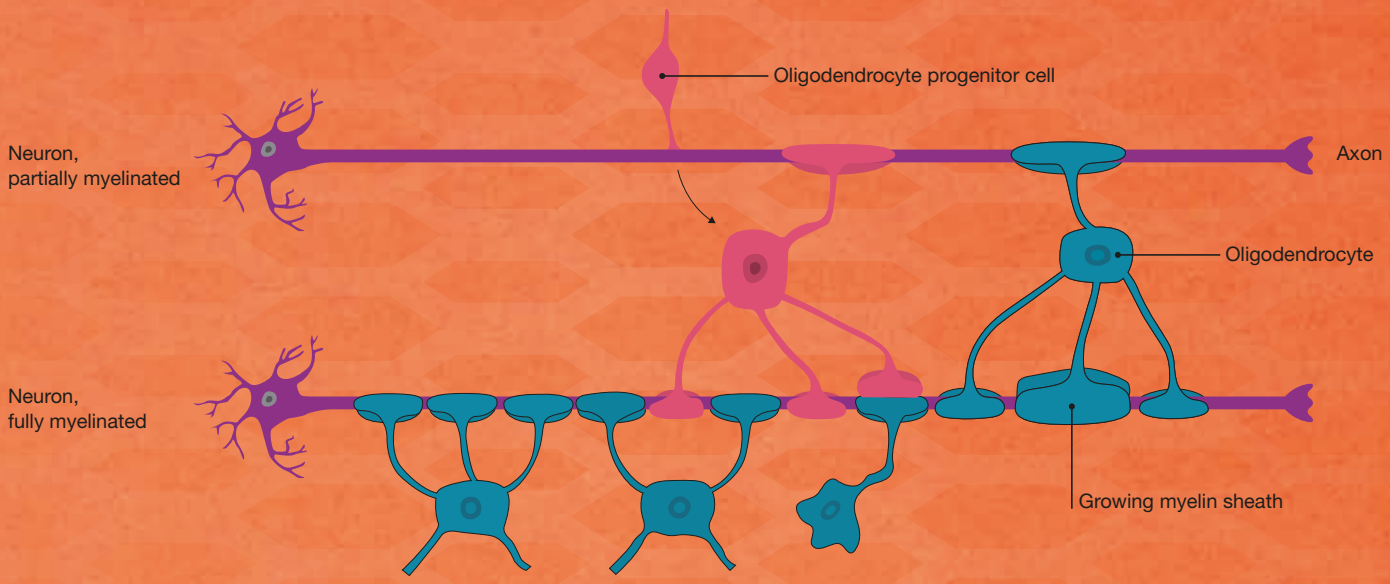
Bisher dachte man jedoch, dass einzig die Neuronen dafür verantwortlich sind. Dass sie in viel benutzten Bereichen neue Synapsen ausbilden und Datenautobahnen bauen. Doch das ist nur die halbe Wahrheit. Das Myelin ist ebenfalls beteiligt, es übernimmt die Feinabstimmung.

Das konnte schon in zahlreichen Experimenten gezeigt werden. Trainierten Probanden einen komplexen Bewegungsablauf oder lernten sie eine neue Sprache, dann sahen die Forscher im Magnetresonanztomographen, dass sich in bestimmten Gehirnarealen mehr Myelin gebildet hatte.

Simons hat mithilfe von modernsten Mikroskopiemethoden herausgefunden, dass für die korrekte Ausbildung der Myelinscheide ein Protein ganz entscheidend ist: das Myelin-Basische Protein (MBP). Fehlt MBP, dann degeneriert die Myelinscheide. Sie verliert ihre Stabilität und wird schließlich von Fresszellen abgebaut.

Solche grundlegenden Erkenntnisse über den Auf- und Abbau von Myelin sind essentiell für die Entwicklung neuer Therapien, zum Beispiel für Multiple Sklerose (MS). Bei MS-Patienten wird die Myelinscheide während eines Schubs zerstört. Dann wächst sie nach, jedoch selten vollständig. Einige Schäden bleiben, die Krankheit schreitet voran. Im Mausmodell hat Simons vor kurzem einen Stoff identifiziert, der bei der Regeneration der Myelinscheide hilft. Wenn zukünftige klinische Studien diesen Erfolg beim Menschen bestätigen können, wäre das ein großer Schritt hin zu einer besseren Therapie von MS. □

Picture credit: ediundsepp



A cell cautiously feels its way along a nerve fiber. Luckily, it is the first one to make it to its chosen spot, with no other oligodendrocytes in sight. And so it gets going, slowly winding its membrane around the nerve fiber, or axon. Once, twice, again and again – it only stops when the axon is surrounded by dozens of membrane layers. This is known as the myelin sheath, and is itself still shrouded in mystery. Physicians are only now starting to understand how many different functions it fulfills in a healthy brain – and the role played by damaged myelin in neural disorders.

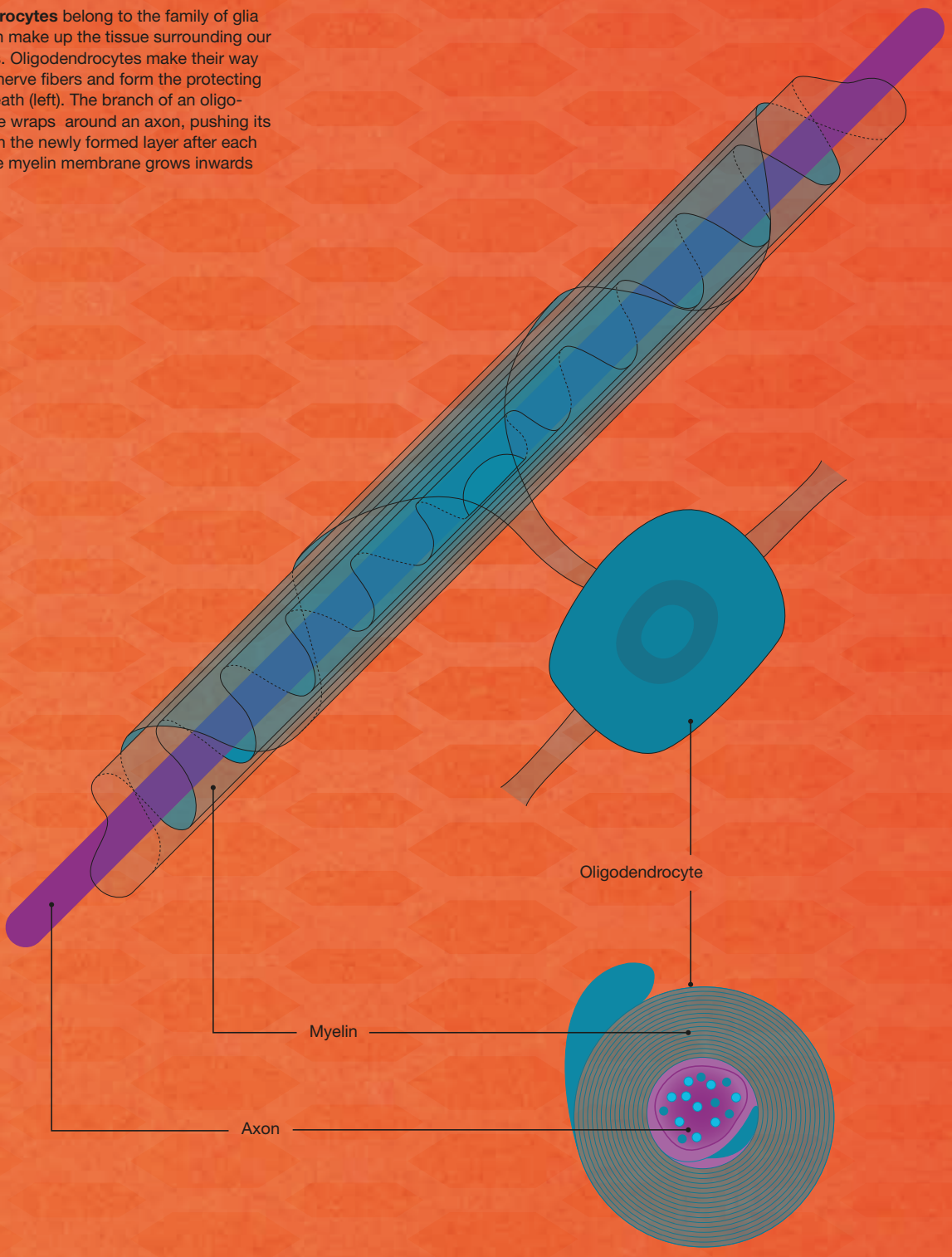
Most neurologists conduct their research into nerve cells, known as neurons. Only a few scientists devote themselves to the other type of cell in the brain, called glial cells or neuroglia. The word “glia” comes from the Greek for “glue”. And for a long time, this was the way most scientists viewed these cells – as a type of adhesive, connecting and supporting the neurons. Now, though, this definition is obsolete; as every neurologist knows, the glia cells do far more than that. In fact, without them, the neurons would not be able to function. “In the past, a neurologist researching glial cells was certainly a rarity,” agrees Mikael Simons, “but that has long since changed.” Simons is Professor of Molecular Neurobiology at TUM and an associate member of the German Center for Neurodegenerative Diseases (DZNE). He is interested in a particular type of glial cell – the oligodendrocytes, which coat the nerve fibers with an insulating myelin layer formed from their cell membranes. This myelin sheath accelerates nerve impulse conduction, protects the axons and supplies them with metabolites, which it transports from the blood vessels.

Immature brains at birth

When we are born, our brains are not yet mature. The neural pathways lie bare, and signals from one cell to another are relatively slow. Then myelination begins around birth in earnest. Oligodendrocytes make their way along the nerve fibers and set about forming a myelin sheath. This process also occurs in the peripheral nervous system, outside the brain. Here, the myelin is supplied by Schwann cells instead of oligodendrocytes. The principle, however, remains the same.

The myelin membrane grows inwards in the immediate vicinity of the axon. After each circuit of the axon, the tip of the oligodendrocyte pushes beneath the newly formed myelin layer and wraps itself around the axon again. “So possibly the opposite of what you might expect,” acknowledges Simons. Some neural pathways are fully myelinated, while others receive little to no myelin. There does appear to be an underlying system at work, but no scientist has yet succeeded in decoding it.

Oligodentrocytes belong to the family of glia cells which make up the tissue surrounding our nerve cells. Oligodendrocytes make their way along the nerve fibers and form the protecting myelin sheath (left). The branch of an oligo-dendrocyte wraps around an axon, pushing its tip beneath the newly formed layer after each circuit: The myelin membrane grows inwards (right).



Graphics: ediundsepp (source: TUM)

"Here at TUM, basic and clinical research are already interwoven at the highest level. This really is a dream come true."

Mikael Simons

Prof. Mikael Simons

Mikael Simons studied medicine at Heidelberg University, pursuing his doctorate in the laboratory of Konrad Beyreuther, a distinguished Alzheimer's researcher. However, this field was already very popular with scientists, and Simons wanted to explore completely unknown territory – such as the myelin sheath.
After periods of study abroad in Yale and Harvard, Simons then returned to Germany. He initially worked at Tübingen and Heidelberg universities, before taking up the position of Junior Group Leader at the University of Göttingen's Center for Biochemistry and Molecular Cell Biology in 2004. In 2007, he was then also appointed head of the Neurology department in Tübingen.
In 2008, Simons received a grant from the European Research Council, enabling him to set up a working group at the Max Planck Institute for Experimental Medicine. He was then made Full Professor of Molecular Neurobiology at the University of Göttingen in 2009, transferring to TUM at the start of 2016.
Simons is now engaged in basic research, but clinical issues remain of interest. His hope is that patients will eventually benefit from his research findings. TUM and its new MS center, currently in the planning stages, offer the ideal environment for him to achieve this. Awarded 25 million euros in funding from the Klaus Tschira Foundation (KTS), the MS center will open in 2020 and focus entirely on multiple sclerosis research. "Here at TUM, basic and clinical research are already interwoven at the highest level," reports Simons, adding that such close collaboration is a rarity in Germany. "This really is a dream come true."

What we do know is that the process follows some sort of hierarchical order. The very first neural pathways to be myelinated help conduct signals for vital functions, such as breathing. Then come neurons involved in more complex tasks such as coordinating movement. Finally, myelin is applied to axons in the cerebral cortex: the seat of our higher, intellectual functions.

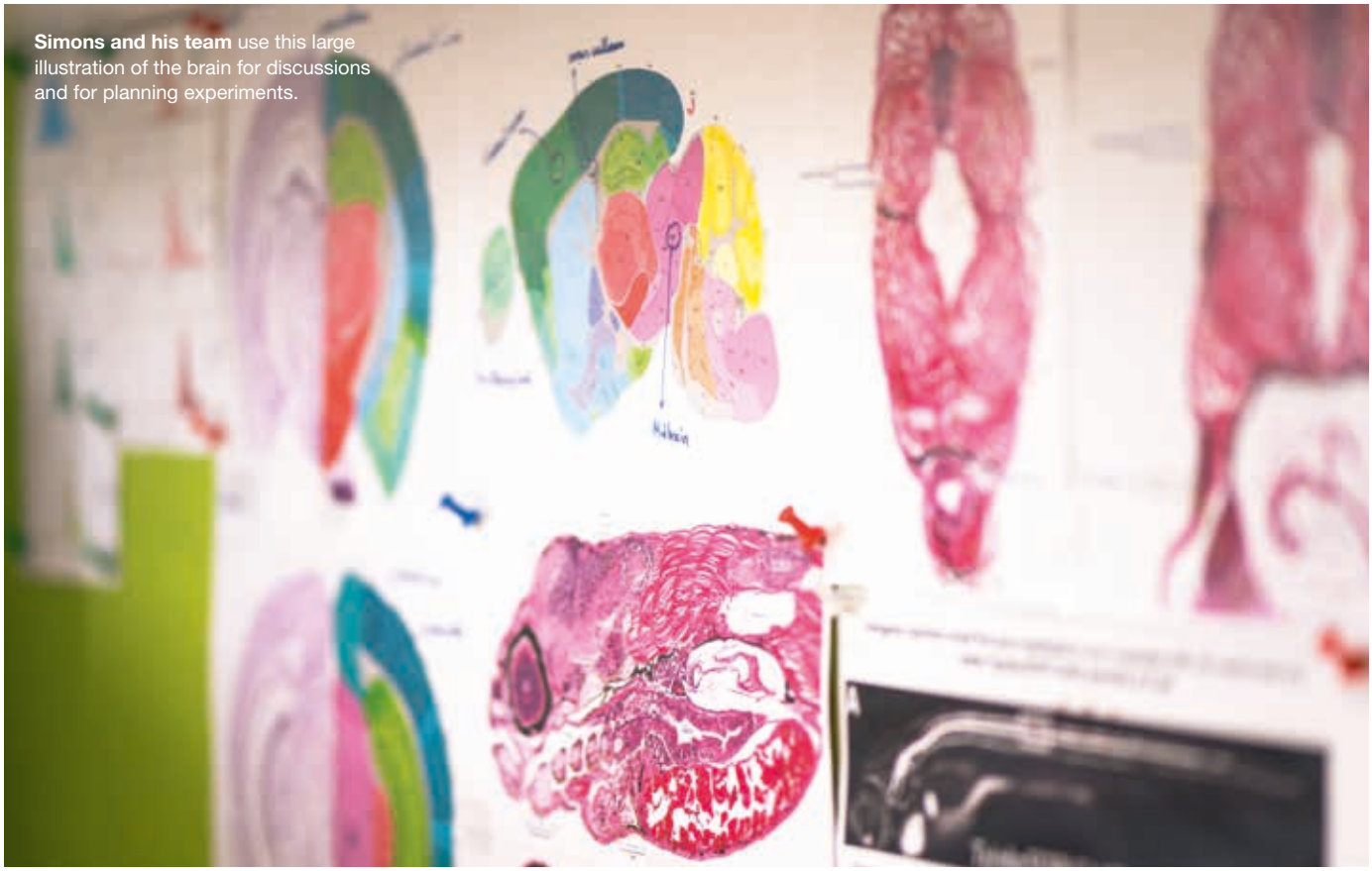
Myelin promotes brain plasticity

Rather than taking place once and for all as part of childhood development, myelination also continues into adulthood. So the brain's plasticity also extends to myelin production.
We have long since known that the brain is plastic – that is, its anatomy changes according to use. The structure of our thinking apparatus is capable of adapting in line with our exposure to environmental factors, what sport we play or what musical instrument we practice, for instance. Brain areas grow or perform new roles. And if an area is no longer in use, it can be freed up to take on other tasks.
Previously, though, it was thought that the neurons were solely responsible for this, forming new synapses and building information highways in heavily used areas. It now turns out that this is only half the story. Myelin also has its role to play in brain plasticity, taking care of the fine-tuning.
This has already been demonstrated in numerous experiments. When test subjects practiced a complex sequence of movements or learned a new language, researchers were then able to see increased myelin formation in specific brain areas on MRI scans.
Oligodendrocytes appear to increase myelination of axons that are particularly active and conduct a lot of signals. However, as yet we have no idea how the oligodendrocytes can actually determine what is happening inside the axons. "The two cell types seem to communicate in some way, but we don't know how," Simons confirms.
In the central nervous system, at least, myelin is thus subject to constant changes. But researchers are still puzzled as to how this functions in such an inert, inaccessible membrane. How is it constructed? And can it disappear again too?

How is myelin depleted by disease?

To get to the bottom of this question, we must first take a closer look at the construction of the myelin sheath.
When the branch of an oligodendrocyte first wraps itself around an axon, there is still plenty of room between the superimposed cell membranes. As is customary in other cells, this space teems with protein factories, cellular powerhouses and all sorts of other vital molecules. But then the contraction process begins. The individual layers constrict and together form thick membrane stacks. Recently, Simons and his team were able to demonstrate the essential role of a specific protein in this process. Using various microscope imaging techniques, such as electron microscopy, they were able to ▷

Picture credit: Eckert



Simons and his team use this large illustration of the brain for discussions and for planning experiments.

Mikael Simons and two postdocs, Ioannis Alexopoulos and Minou Djannatian, discuss and analyze data generated by convocal microscopy experiments.

Maria Cunha, a Ph.D. student in Simons' laboratory, uses a convocal microscope to observe myelination in a living but sedated zebrafish (inside the petri dish in the lower image).

Picture credits: Eckert

observe how loss of myelin basic protein (MBP) in the mouse brain goes hand in hand with destruction of the myelin sheath. MBP can best be pictured as long, untidy strands of protein, swimming in the cytoplasm of oligodendrocytes. Once both ends of one of these protein fibers come into contact with superimposed areas of cell membrane, the protein folds itself tightly, pulling the membranes towards each other.
Like a zipper mechanism, this process continues until the entire myelin sheath has contracted into an extremely compact stack of cell membranes. Only the innermost and outermost layers of the membrane stack are exempt from this activity.
Without MBP, the myelin sheath loses its stability, and is eventually destroyed by scavenger cells. This appears to be the case in many myelin diseases.

Improving regeneration in MS

What happens when the myelin sheath is damaged – however this occurs – can be seen in numerous diseases. Psychiatric disorders such as schizophrenia and depression are associated with changes in the myelin sheath. What has not yet been established is how these changes are triggered.
In multiple sclerosis, the situation is clearer. An inflammatory response in the brain leads the patient's own immune system to attack and destroy the myelin sheath. This causes various symptoms, including weakness and loss of sensation. The disease usually occurs in episodes, with demyelination attacks followed by periods in which the myelin sheath partly regenerates.
However, this regeneration in MS patients is not complete. In the early stages of the disease, it still seems to work well, but as the disease progresses, the capacity for regeneration steadily declines.
"The most promising window for myelin regeneration is probably when inflammation is still active," explains Simons. Once the inflammation has completely subsided, scar tissue (sclerosis) forms at the edges of the damaged myelin sheaths. While Simons does not rule out new myelin growing at these sites, he considers it a great deal more difficult.
Against this backdrop, he is searching for a drug to actively support patients in myelin sheath regeneration – and has already identified a promising candidate. "The good thing is that the molecule in question is already known," he reveals. "Which might mean we can go straight into clinical trials."
This entire field of research seems to hold many more questions than answers to date. But Mikael Simons relishes that – in fact, it is why he chose it. "In many branches of neurology, you have so many people on the case, at some point you might run out of questions entirely," he muses. As far as the myelin sheath is concerned, that certainly does not look likely to happen any time soon. *Claudia Doyle*

Physicians are only now starting to understand how many different functions the myelin sheath fulfills in the brain – and the role played by damaged myelin in neural disorders.

Picture credit: Eckert