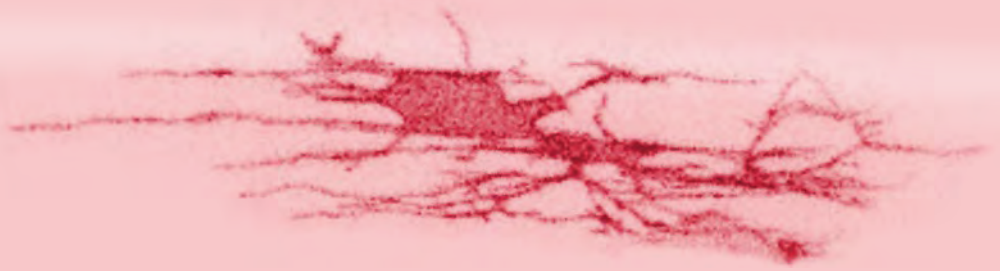
00:00 [hh:mm]

10 µm

00:30 [hh:mm]

01:35 [hh:mm]

02:45 [hh:mm]



Oligodendrocytes ensheath the axons of nerve cells by iteratively 'wrapping' them with their cell membranes. The images show an oligodentrocyte precursor cell observed with a confocal laser scanning microscope in a living zebrafish. At the beginning of the myelination process, the precursor cell makes its way along the nerve fibers (not pictured above), modifying its extensions in minute intervals.

Neuroplasticity – a Matter of White Matter

When adults learn a new skill – whether it be juggling or piano playing – this process modifies not only their gray matter, that is their neurons and synapses. It also changes what is known as white matter, areas of the brain where the nerve fibers are wrapped in a protective membrane called myelin. Tim Czopka is looking to better understand how this happens by investigating the cells that produce the myelin.

Karoline Stürmer

Neuroplastizität – neuer Blick auf die weiße Substanz

Jonglieren oder Klavierspielen – wenn Erwachsene neue Fähigkeiten erlernen, passen sich nicht nur die „grauen Zellen" an, also die Nervenzellen und Synapsen. Auch die weiße Substanz unseres Gehirns verändert sich. So werden die mit einer weißen Myelinschicht umhüllten Nervenfasern bezeichnet, die Reize zwischen den Nervenzellen weiterleiten. Zuständig für die Bildung der schützenden Myelinschicht sind Oligodendrozyten, die zu den Helferzellen im Gehirn gehören. Dr. Tim Czopka untersucht, wie sich diese Zellen entwickeln, um die weiße Substanz zu bilden, diese plastisch zu verändern und sie nach einer Schädigung zu regenerieren. Der 37-jährige Biologe leitet eine Forschungsgruppe am Institut für Zellbiologie des Nervensystems der TUM.

Bisher konnte er zeigen, dass jeder einzelne Oligodendrozyt nur ein Zeitfenster von wenigen Stunden hat, um festzulegen, wie viele Myelinsegmente er an einer oder mehreren Nervenfasern ausbildet. Danach verliert er diese Fähigkeit und verändert sich kaum noch. Daraus folgert Czopka: Defektes Myelin kann nur durch neue Oligodendrozyten ersetzt werden, die sich aus sogenannten Vorläuferzellen entwickeln. Das sind Abkömmlinge von Stammzellen, die schon auf einen künftigen Funktionsbereich festgelegt sind. Czopkas Ziel ist es, die Vorläuferzellen der Oligodendrozyten über ihren gesamten Lebenszyklus zu verfolgen. Er untersucht, wie die Zellumgebung und die Gene darüber entscheiden, ob sich eine Vorläuferzelle weiter teilt oder stattdessen zu einem Oligodendrozyten entwickelt, und wie diese dann die Struktur und Funktion von Nervenzellen verändern.

Czopka arbeitet mit gentechnisch veränderten Zebrafischen als Tiermodell und mit hochauflösenden Mikroskopieverfahren. Weil die Larven der Fische durchscheinend sind, kann der Biologe in das Nervensystem der lebenden Tiere – also in vivo – blicken und Veränderungen einzelner Zellen im selben Tier verfolgen.

„Letztlich wollen wir die Stellschrauben der Myelinregulation identifizieren", sagt Czopka. □

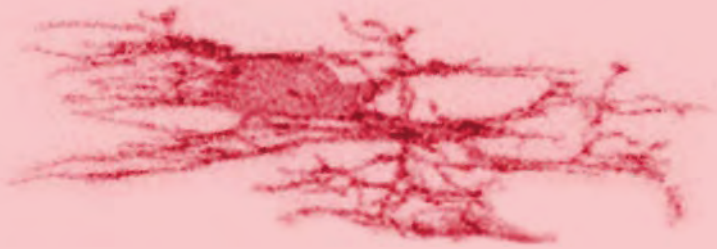
Tim Czopka's research group at TUM's Institute of Neuronal Cell Biology

www.neuroscience.med.tum.de
www.czopka-lab.de

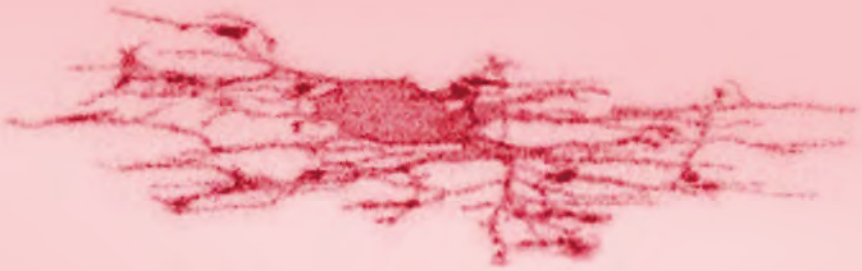
Picture credits: Tim Czopka/TUM

03:55 [hh:mm]

10 µm

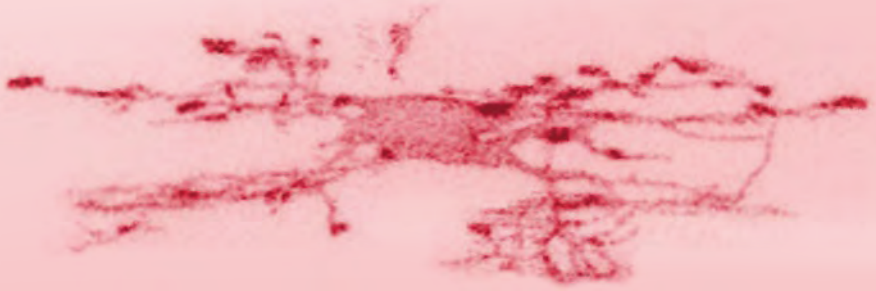


04:40 [hh:mm]



08:00 [hh:mm]

11:05 [hh:mm]



At a certain point in time, the cell starts forming myelin segments, also called internodes, recognizable as small horizontal tubes. Surplus extensions are also drawn back to the cell and eliminated at this time. As myelination progresses, the oligodendrocyte becomes less dynamic and loses the ability to form new myelin segments.

A cell slowly moves its fine extensions, which gradually grow in size and length. As soon as it comes into contact with a fiber of a neuron, called an axon, the cell begins to wrap itself around the axon.
Observed by Dr. Tim Czopka through his microscope, this process is known as myelination – the formation of a myelin layer around the connecting processes between neurons to protect and insulate them. The myelin layer surrounding the axons in the neural pathways is referred to as the white matter of the central nervous system. The cells responsible for myelination are called oligodendrocytes – a type of glial cell, which are helper cells in the brain. Czopka is investigating how these cells develop and what role they play in the formation, the remodeling and the regeneration of myelin. The 37-year-old biologist is a Junior Fellow at TUM's Institute of Neuronal Cell Biology, where he leads a junior research group funded by the German Research Foundation (DFG).

Myelination contributes to neuroplasticity

It is well established that neurons and synapses dynamically adapt to new challenges. New studies show that the role of myelination in this process was previously underestimated. Myelin is a biomembrane that provides electrical insulation, allowing signals between nerve cells to be transmitted quickly and efficiently. This is crucial when it comes to the timing of information processing within neural networks that is needed in the process of learning.
We now know that myelination can adaptively change in response to new experiences. For example, white matter changes occur when test subjects learn new motor skills such as juggling and piano playing. Another recent study showed that genetically modified mice incapable of forming new myelin were not able to perform complex learning tasks.
On the other hand, myelin is selectively attacked and degraded in autoimmune diseases such as multiple sclerosis, which leads to malfunction of the nervous system and varying rates of neurodegeneration.

Variability of precursor cells

The principles underlying the formation and repair of myelin are precisely what Tim Czopka is investigating. To date, he has been able to show that each individual oligodendrocyte has a time span of just a few hours to determine how many myelin segments it will form on one or several nerve fibers. It then loses this ability to form new myelin segments and barely changes any further. From this finding, Czopka concludes that defective myelin, as well as new myelin generated during adaptive processes, can only be produced by newly formed oligodendrocytes from their precursor cells. ▷

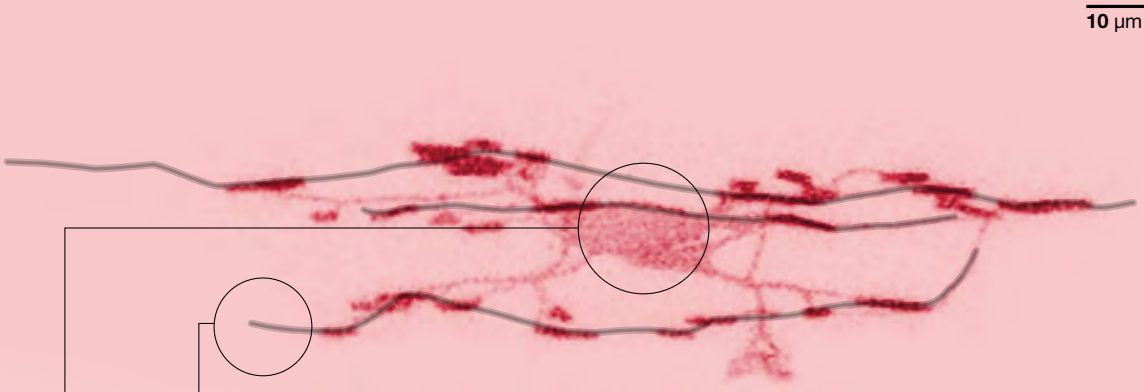
Picture credits: Tim Czopka/TUM; Magdalena Jooss/TUM

Dr. Tim Czopka

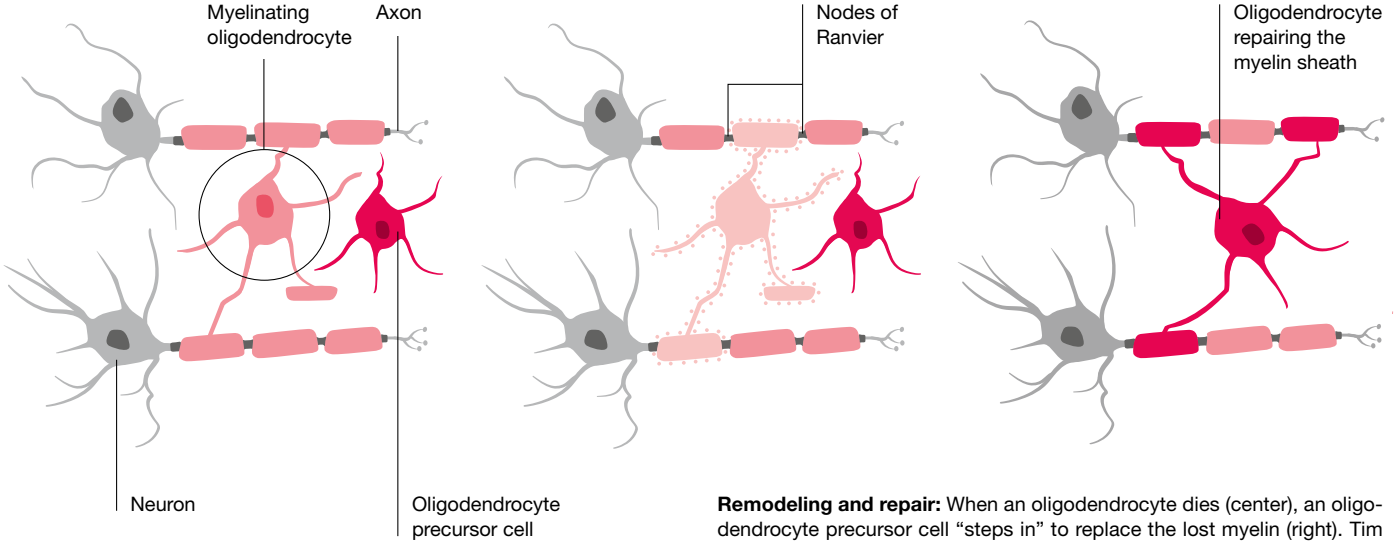
Combining molecular biology and neuroscience

Tim Czopka studied biology at Germany's Ruhr-Universität Bochum, graduating in 2005 and completing his PhD in neuroscience in 2009. He then went on to the University of Edinburgh (UK) for postdoctoral training until 2014. The 37-year-old has been an Emmy Noether group leader at the TUM Institute of Neuronal Cell Biology since 2015. He was one of fourteen early-career scientists in the German state of Bavaria to receive a prestigious Starting Grant from the European Research Council in 2016. He is an associate of the Munich Cluster for Systems Neurology (SyNergy) and the Collaborative Research Center (Sonderforschungsbereich) 870 on the assembly and function of neuronal circuits.

Czopka investigates myelination mechanisms in the central nervous system, using young tropical zebrafish as a model organism. These are particularly well suited to genetic manipulation and in vivo live imaging using high-resolution microscopy.



Axons, or nerve fibers, transmit impulses to other nerve cells and to muscle cells. Each axon (visualized as grey lines above) is covered by consecutive myelin segments – also referred to as internodes – arranged one after the other like beads on a string. Some internodes originate from the same oligodendrocyte and some from different ones. The gaps between the internodes, known as the nodes of Ranvier, are unmyelinated.



Remodeling and repair: When an oligodendrocyte dies (center), an oligodendrocyte precursor cell "steps in" to replace the lost myelin (right). Tim Czopka wants to understand why the repair process is often less efficient than the original formation of myelin.

Oligodendrocyte precursor cells are found in the bodies of humans and other vertebrates in all stages of life. They are descendants of stem cells committed to form myelin. They divide swiftly and migrate through the tissue. Once they turn into oligodendrocytes, they lose this ability and begin forming dense layers of cell membrane around various neurons – the myelin. Because biomembranes have a high fat content, their tight stacking in heavily myelinated areas of the nervous system is even visible to the naked eye as white matter, standing out from the gray matter that contains less myelin. "The coating of neurons with myelin is an evolutionary adaptation in the brain of vertebrates," explains Czopka. "It is probably this that enabled the development of larger and increasingly complex nervous systems in the first place."

A glimpse of the living brain

In order to gain insights into mechanisms of myelin regulation, Czopka observes oligodendrocytes as they develop and interact with neurons – using zebrafish as the animal model and high-resolution imaging procedures. Zebrafish make ideal

Confocal laser scanning microscope: Tim Czopka and his team investigate interactions between neurons and glia using a combination of high resolution microscopy methods, genetics and modern data analysis.

"Our aim is to identify key success factors in the myelination process." *Tim Czopka*

model organisms for neurobiology. Many basic principles that apply to them can be directly transferred to humans. "The problem is, we can't see directly into the human brain," Czopka remarks. But he can see into the brain of a living zebrafish: In genetically modified zebrafish, cells can bear fluorescent tags such as green fluorescent protein (GFP). Since the fish larvae are transparent, researchers can look inside their nervous system – live and in vivo – and track changes to individual cells in the same fish with the aid of high-resolution imaging procedures.

Accompanying the "life cycle" of cells

In 2016 Tim Czopka was awarded a Starting Grant from the European Research Council (ERC) that will help him to pursue this goal: He intends to use this grant to accompany oligodendrocytes and their precursor cells in the nervous system throughout the entire development of an individual organism for the first time. To begin with, he is currently investigating what happens when he destroys individual myelin producing oligodendrocytes. "We see that the immune system clears away the cell debris, and other oligodendrocytes attempt to compensate for the loss," says Czopka. What is not yet clear is why the repair process is often substantially inferior to the original myelination. A general lack of oligodendrocyte precursor cells is not the issue, since they are present in large quantities in the nervous system of vertebrates.

Czopka suspects that various oligodendrocyte populations exist, not all of which are suitable for myelin repair. He is keen to understand what factors determine whether a precursor cell continues to divide or instead develops into an oligodendrocyte. To achieve this, his next step will be to explore the variables that may have an influence in the cellular environment, as well as various oligodendrocyte genes. "Our ultimate aim here is to identify key success factors in the myelination process," Czopka confirms. If he manages to do this, it would open up new insights into neuroplasticity as well as new strategies for treatment of myelin damage, which occurs in diseases like multiple sclerosis. *Karoline Stürmer*

Graphics: ediundsepp (source: TUM), Picture credits: Tim Czopka/TUM; Magdalena Jooss/TUM