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Multiple Sclerosis: **How Immune Cells Attack the Brain**

This is an article about immune cells that issue the wrong instructions. Instead of calling for assistance, they order destruction. It is also an article about the researcher who wants to track down these misguided cells. If he succeeds, we will be a step closer to finding better treatment options for multiple sclerosis and other autoimmune diseases.

Most of the time, multiple sclerosis is invisible. And when it does suddenly reveal itself, it remains disguised behind a variety of masks. No two patients present exactly the same symptoms. Some suffer from vision problems. Others lose their sense of balance, develop a feeling of paralysis or numbness in their arms and legs, or constantly feel tired and weak. The symptoms can often disappear by themselves, only to return with full force months later. Living with multiple sclerosis is unpredictable. And the cause of all this is nothing other than the patient's own immune system.

Many medical scientists believe that it can start with a harmless infection. A head cold, perhaps. Nothing too tricky for the immune system to handle. In the lymph node, a type of immune cell called a T cell identifies the intruder. Using its antenna-like receptor, it binds to an insidious virus protein. The T cell is activated.

Some immune cells, which should be protecting us against harmful viruses or bacteria, suddenly attack the body's own tissue. Instead of coming to the rescue, they go into destructive mode. They do this because they do not just recognize virus antigens, but also cross-react with the body's own molecules. The cells are autoreactive. Thomas Korn, Heisenberg Professor of Experimental Neuroimmunology at TUM's Department of Neurology, wants to track down these misguided or autoreactive cells as part of his EXODUS project. He aims to find out where they are activated, why they send incorrect signals, and how they can be stopped. Armed with this information, medical scientists will be able to develop more effective therapies for multiple sclerosis (MS) and other autoimmune diseases. Worldwide, around 2.3 million people are living with multiple sclerosis. The incidence of the disease is two to three times higher in women than in men. Geography also determines the likelihood of contracting MS: relatively few people suffer from the disease in equatorial regions, but the rate increases the further north or south one travels. No one knows the exact reason for this.

The activated T cells multiply at a rapid rate. They also release signaling substances that attract macrophages – the virus-destroying cells. While traveling through the bloodstream, the activated T cells also pass by the brain. And something that could not happen before suddenly becomes possible. ▷

Graphics: ediundsepp

Claudia Steinert

Multiple Sklerose: Wie Immunzellen das Gehirn angreifen

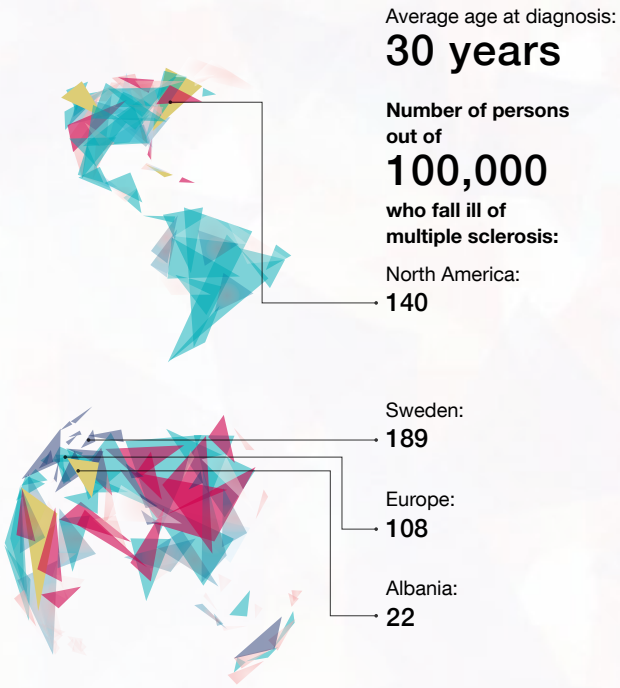
Weltweit sind etwa 2,3 Millionen Menschen an Multipler Sklerose (MS) erkrankt. Die Krankheit tritt vor allem bei jungen Leuten auf und betrifft das Zentralnervensystem. „Dabei ist das Gehirn eigentlich gesund, das Immunsystem ist krank“, erklärt Thomas Korn, Heisenberg-Professor für experimentelle Neuroimmunologie an der Neurologischen Klinik der TUM.

Bei MS erkennen sogenannte autoreaktive Zellen des Immunsystems nicht nur körperfremde Antigene (zum Beispiel Virus-Antigene) – wie es eigentlich sein sollte – sondern auch körpereigene Moleküle. Das hat fatale Folgen. Deswegen fressen bei MS-Patienten Immunzellen im Gehirn die Myelinscheide ab, die die Nervenfasern umhüllt und schützt. Ohne Myelinscheide aber können die Nervenzellen nicht mehr so gut miteinander kommunizieren. Thomas Korn interessiert sich vor allem für eine Sorte Immunzellen: die T-Zellen. Wenn das Immunsystem eine Verteidigungsarmee ist, dann sind die T-Zellen die Generäle. Das Problem: Wenn sie einmal aktiviert sind, schnappen sie nach allem, was ihren T-Zell-Rezeptoren präsentiert wird. Bei MS ist das die Myelinscheide im Gehirn. Dorthin gelangen autoreaktive T-Zellen jedoch nur im aktivierten Zustand. Experten vermuten, dass diese Aktivierung außerhalb des Gehirns stattfindet, zum Beispiel durch einen harmlosen Schnupfenvirus. Um diese Theorie zu prüfen, will Korn in seinem Projekt EXODUS den Weg der T-Zellen nachverfolgen. Dafür hat er Fördergelder vom Europäischen Forschungsrat (ERC) erhalten. Er markiert bei Mäusen T-Zellen, die sich in peripheren Lymphknoten oder in lymphatischem Gewebe im Bereich von Schleimhautoberflächen aufhalten, wie denen des Magen-Darm-Traktes. Wochen später schaut er nach, wohin die markierten Zellen gewandert sind.

Bei Mäusen, die an einer MS-ähnlichen Krankheit leiden, hofft Korn, solche markierten Zellen auch im Gehirn zu finden. Das könnte der Beweis dafür sein, dass die aktivierten, autoreaktiven T-Zellen tatsächlich von der Peripherie ins Gehirn einwandern. Damit wäre endlich klar, dass harmlose Infektionen sozusagen als Spätfolge einen MS-Schub auslösen können. In einem späteren Schritt will Korn auch den umgekehrten Weg testen: Immunzellen im Gehirn markieren und dann ihren Weg nachverfolgen. „Wenn diese Zellen das Gehirn tatsächlich wieder verlassen, dann könnten wir sie isolieren und genauer analysieren“, erklärt Korn. Vielleicht ließen sie sich sogar so manipulieren, dass zukünftige Schübe verhindert werden können. □

Graphics: ediundsepp

Picture credit: Jooss
Graphics: edlundsepp (Source: Atlas of MS 2013, Multiple Sclerosis International Federation)



Worldwide, around 2.3 million people suffer from multiple sclerosis (MS). The disease affects twice as many women as men. The likelihood of contracting MS is highest in North America and Europe, lowest in the equatorial regions.

At this stage, scientists do have a relatively good understanding of what causes the symptoms of multiple sclerosis. The disease wages war on the patient's nervous system. But instead of targeting the nerve cells themselves, it attacks the cells that surround them. The oligodendrocytes. These cells with their tricky name have an extremely important task. They wrap themselves around the projections of the nerve cells (axons), thus insulating them. In this way, they prevent short-circuits from happening in the brain. Information in the form of electrical signals is constantly dashing between our millions of nerve cells. It shoots through the axons at speeds of up to 200 meters per second. The axon can be compared to a power cable, with the myelin sheath formed by the oligodendrocytes corresponding to the insulating rubber jacket. It is the myelin sheath that enables fast and clear communication between the nerve cells. So it is a prerequisite for every deliberate movement and mental process.

The brain is a sensitive organ and must at all costs be defended against invaders. That is why we have the blood-brain barrier. It functions somewhat like a close-mesh mosquito net. Water and nutrients can pass through, but not much else. Activated T cells have a special type of anchor protein, however, which helps them cling on to the blood-brain barrier. They do, after all, want to check whether the brain also needs to be rid of viruses.

In multiple sclerosis patients, the myelin sheath becomes inflamed. Or rather: it comes under attack. "The central nervous system itself is healthy; the problem lies in the immune system," explains Thomas Korn. The immune cells destroy the protective insulation layer and expose the nerve fibers. Electrical signals are then only conveyed slowly or not at all. The fact that this occurs simultaneously at multiple locations in the brain means that a large variety of neurological deficits will become apparent. Problems with speech, distorted vision, numbness. The symptoms are often ambiguous. What is more, they usually disappear again, even without treatment. After a few days or weeks, the myelin sheath in the brain regenerates itself. However, the oligodendrocytes do not always succeed in remyelinating all of the nerve fibers. In such cases, some symptoms linger even after the attack has passed.

In healthy people, the immune cells turn back around halfway through the blood-brain barrier. Only the T cells that are activated and autoreactive make it as far as the brain tissue. Once there, they seek out insidious virus antigens using their receptors. There is a possibility, however, that as well as virus proteins, their receptors will also surround similar-looking myelin proteins. That is a serious mistake. But the cells do not notice this. They are activated and deploy macrophages to the brain. The autoimmune reaction begins.

Everyone has autoreactive T cells to a certain extent, even though this should not be the case. Precursors of T cells are formed in the bone marrow, but T cells only mature in the thymus, an organ of our lymphatic system. A kind of quality assurance takes place there. The thymus is supposed to prevent the creation of T cells capable of attacking the body. Self-antigens are presented to every new T cell in the thymus. If the cell recognizes it and binds to it, then it has pronounced its own death sentence. It cannot leave the thymus and dies in situ. This "quality assurance" is not 100% effective, however. Some autoreactive T cells escape the thymus. When a medic is explaining the immune system to a layperson, they often use war metaphors. Good guys versus bad guys, ▷

"Without funding from the ERC, I would not have been able to carry out this research."

Thomas Korn

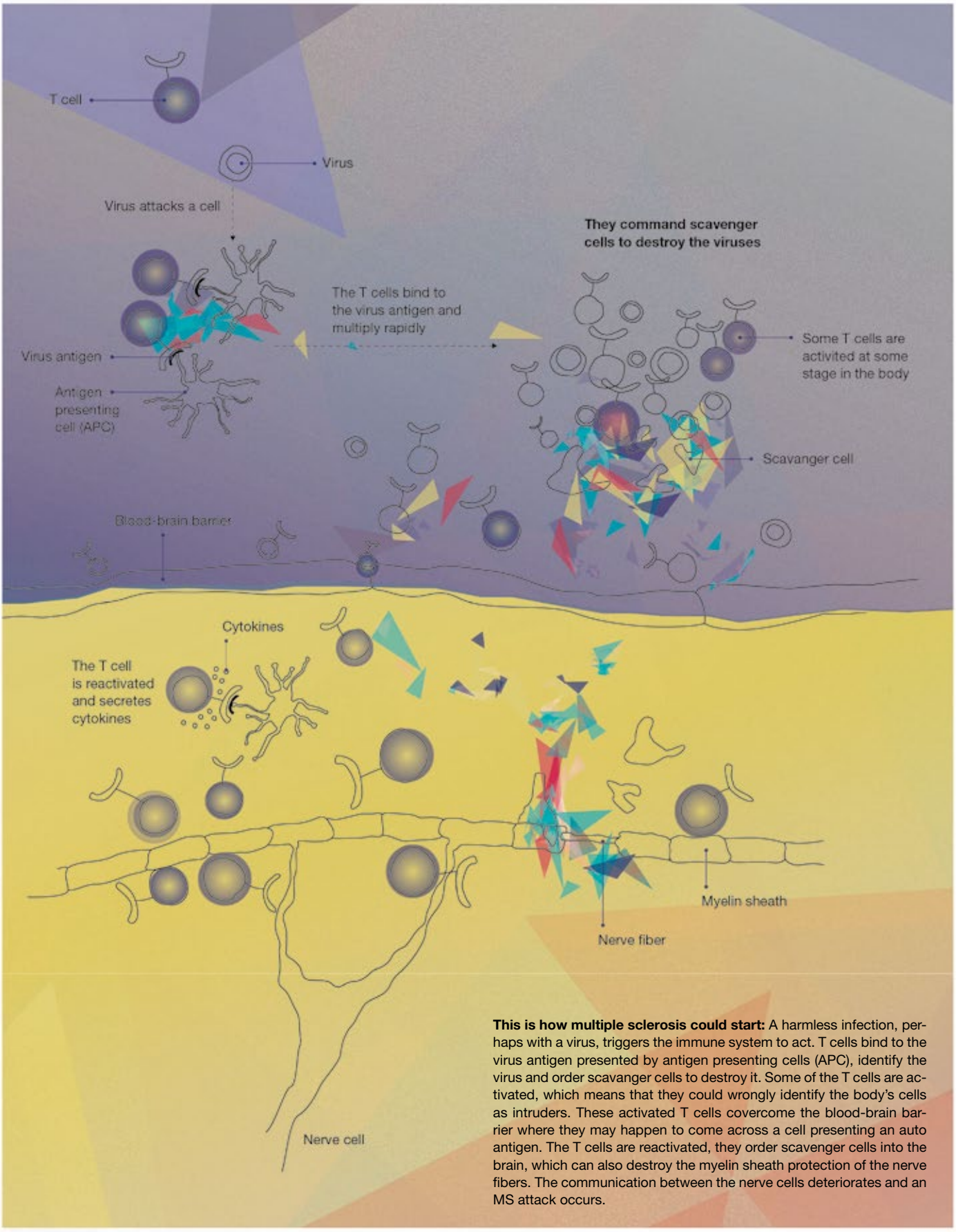
“There are many different immune cells in our immune system’s army. The T cells are like generals, directing the attack.”

Thomas Korn

Klaus Tschira Foundation donates 25 million euros for multiple sclerosis research

A new treatment and research center for multiple sclerosis will be established within the grounds of the TUM Klinikum rechts der Isar. The center will be unique in Germany with medics and scientists in areas ranging from clinical practice to basic research working under a single roof. Thomas Korn is one of currently four TUM scientists involved in the center. “The center provides us with the necessary infrastructure to efficiently drive our research forward,” he says. The project has been enabled thanks to a 25 million euro donation by the Klaus Tschira Foundation. The associated contract was signed on September 23, 2015.

Graphics: ediundsepp



This is how multiple sclerosis could start: A harmless infection, perhaps with a virus, triggers the immune system to act. T cells bind to the virus antigen presented by antigen presenting cells (APC), identify the virus and order scavanger cells to destroy it. Some of the T cells are activated, which means that they could wrongly identify the body's cells as intruders. These activated T cells covercome the blood-brain barrier where they may happen to come across a cell presenting an auto antigen. The T cells are reactivated, they order scavenger cells into the brain, which can also destroy the myelin sheath protection of the nerve fibers. The communication between the nerve cells deteriorates and an MS attack occurs.

immune cells fighting pathogens. Thomas Korn is also fond of these vivid comparisons, but he takes a slightly more detailed approach. He points out that there are at least as many different immune cells as subunits in the army. “The T cells are like generals, directing the attack,” he explains.

Macrophages migrate to the brain. They destroy the myelin sheath protecting the nerve fibers. The exposed axons start to lose their ability to conduct electrical signals. Communication between the nerve cells comes to a halt.

Korn wants to track down these generals. His objective as part of his EXODUS project is to discover the paths taken by T cells within the body and prove the theory that they are first activated at a peripheral location and only then migrate to the brain. This has only been a plausible but unproven assumption up to now. His work will be funded by the European Research Council, which is not afraid to back projects with a certain level of risk attached. “While our preliminary experiments have been promising, I still cannot rule out unforeseen problems,” admits Korn.
In order to trace the presumed path of the T cells to the brain from peripheral lymph nodes or lymphatic tissue, which are associated with mucosal surfaces like the gastrointestinal tract, Thomas Korn uses a very particular marking method. He makes genetically modified T cells glow with a red fluorescence. They will only do this, however, if they have been illuminated by blue light. The scientists push a blue light into the gastrointestinal tract of mice carrying these T cells, which suddenly glow like red lanterns.
The migration of the T cells from the gut to the brain is of particular interest because of indications that it is not just virus proteins, but also our own gut bacteria that could activate the T cells. Each individual’s microbiome, or the entire community of bacteria in the gastrointestinal tract, could therefore play a significant role in determining whether or not we are susceptible to autoimmune diseases like multiple sclerosis.
A few weeks after the light exposure, Korn intends to examine the mouse’s organs to locate the red-glowing T cells. This will make it clear that every red cell originated from the gut, or at least that the ancestral cells came from there. “In healthy mice, we will not find any red T cells in the brain – or at any rate, they will only have migrated as far as the blood-brain barrier,” explains Korn. The first step for the scientists, therefore, is to examine whether the system actually works in healthy animals. Only then will they turn to mice suffering from a disease similar to multiple sclerosis. These animals have a particularly large number of autoreactive T cells, which when activated pass into the brain and attack the myelin sheaths of nerve cells. If Korn does find glowing red T cells in the brains of these animals, he will have demonstrated that the activated T cells do indeed migrate from the periphery to the brain. This would finally prove that harmless infections can trigger an MS attack, as a delayed effect so to speak.

After a while, the activated immune cells slowly die off in the brain. Or they leave the brain. And migrate somewhere else. No one knows for sure. The only thing that is clear is that the MS attacks do come to an end at some stage. Just like that. Because the immune reaction ceases and the myelin sheath is repaired. Until the immune system is again mobilized and triggers the next attack.

A major problem when treating multiple sclerosis is that damaged brain tissue does not regenerate as easily as other organs. In the case of hepatitis, the immune response in the liver is so powerful that the response itself causes pronounced damage to the tissue. This is not a problem, however, because the liver is easily regenerated. But the brain does not have this ability. That is why all of the drugs used to treat multiple sclerosis up to now work outside the brain, and try to prevent a serious immune reaction from taking place within.
At a later stage, Korn intends to examine the opposite pathway by light-activating immune cells in the brain and tracking their progress. “If these cells do indeed exit the brain again, we will be able to isolate them and study them more closely,” confirms Korn. It might even be possible to manipulate them and prevent future attacks in MS sufferers. The first task at hand though, is to verify whether the generals do indeed behave as our theory predicts. *Claudia Steinert*

Prof. Thomas Korn

The courage to take risks

“Without funding from the ERC, I would not have been able to carry out this research,” declares Thomas Korn. So he is fortunate that the European Research Council (ERC) is not afraid to back riskier projects such as EXODUS. The majority of funding programs are risk-averse. “With other donors, there would have been no point in even applying with my idea,” Korn is convinced.

Thomas Korn studied human medicine in Würzburg and London and obtained his doctorate in cell biology at the University of Würzburg. During his specialist training in Würzburg and Homburg, he was already eager to discover how the immune system influences neurological disorders like multiple sclerosis. “In Würzburg, I spent six months per year caring for patients and the other six months working in the lab, which proved to be a very good balance,” recalls Korn. In 2005, he received a grant from the German Research Foundation (DFG) to spend three years conducting research at the Harvard Medical School in Boston.

On his return to Germany in 2008, he was appointed senior physician at the University Neurology Clinic of TUM, praising Munich for “offering a very good research environment for immunologists”. Just two years later, he was appointed to the DFG-funded Heisenberg Professorship of Experimental Neuroimmunology, also at TUM. He has received numerous prizes for his research, including the 2008 Sobek Young Investigator Award and the 2010 Heinrich Pette Award from the German Neurological Society (DGN).

Picture credit: Jooss