



When cancer cells migrate

How metastases develop in the brain

By Anja Störiko

Although many types of cancer can be treated very successfully nowadays, fatal metastases often develop in the brain. How cancer cells manage to overcome the blood-brain barrier, survive in such a well-protected organ as the brain and continue to divide is something that Lisa Sevenich's research group at the Institute for Tumour Biology and Experimental Therapy, Georg-Speyer-Haus, is investigating.

Using tissue cultures from the brains of mice, the cancer research team in Frankfurt monitors via video how cancer cells migrate into the brain: a cell from the brain tissue stretches further and further towards the blood vessel, literally snuggles up to the cancer cell washed up in the bloodstream and ultimately allows it to enter the brain tissue – through the normally more or less insurmountable blood-brain barrier. Cancer cells, as the video shows, evidently manipulate brain cells across the blood-brain barrier for their own benefit.

Observations such as these allow far-reaching insights into how cancer spreads. "We're interested in this fascinating interaction between cancer cells and brain cells," explains Lisa Sevenich. Her research group has taken on a difficult topic: metastases.

Although it is often possible nowadays to combat tumours at the initial site through surgery, radiation or chemotherapy, in many cases cells have already broken away from the original (primary) tumour beforehand and travelled to other organs. This is why metastases, that is, secondary tumours in organs other than the primary site of the tumour, are meanwhile the most common cause of death among cancer patients. "In the past, patients died from the primary tumour or undetected metastases. Today, thanks to earlier diagnosis and better treatment, they survive – but all too many die from secondary brain tumours," says Sevenich. Until now, it has been difficult to treat brain tumours because surgery is risky, but also because insufficient research has been conducted on the cellular and molecular principles of how brain metastases develop.

Brain metastases are frequent, but research is scarce

Metastases often develop in the brain above all in breast, skin and lung cancer – according to the German Cancer Society in 20 to 45 percent of patients. "When and why single cancer cells dislodge from the primary tumour is still not entirely clear," says Sevenich. As they spread through the body, the cancer cells are at the mercy of the immune system, which identifies and destroys most of them. Less than one percent of the cells that spread through the body via the bloodstream survive the immune system's attacks and manage to colonise elsewhere. However, scientific knowledge about this journey and the colonisation of metastatic cells is still in its infancy. There are cells that break away very early in the cancer process and colonise other organs, but often "hibernate" there – until one day they "wake up" and start reproducing: a dangerous development.

Cancer cells penetrate the protected brain

Lisa Sevenich and her team are exploring questions related to metastasis: "How does an organ, in our case the brain, react to the incoming cancer cells? And how must the cancer cells adapt in order to survive there?" After all, the brain is a very special and well-protected organ. Its blood vessels are more or less impermeable, and this is what shields it from the rest of the body. This blood-brain barrier restricts and regulates both the exchange of soluble factors as well as cell penetration, meaning that the brain is also shielded from the body's immune system. It has its own immune cells that protect it from life-threatening inflammation with great effect.

Beautiful but dangerous: in a metastatic brain tumour, the cancer cells are densely packed together (cell nuclei: turquoise). The microglia (green and red), the brain's defence cells, cannot fight the tumour effectively.

Immune system vs. cancer cells Disguise, hide-and-seek and misunderstandings



Illustration: Lisa Sevenich

To protect sensitive neurons (N) from inflammation, the brain normally suppresses immune reactions. Cancer cells that colonise the brain (BM) exploit this. Although the microglia (MG), the brain's immune cells, recognise these invaders, they are not particularly specialised and therefore unable to efficiently fight off the very versatile cancer cells. They require the help of T cells, which have learned to attack cancer cells systematically. Cancer cells, however, use camouflage to resemble neurons. In this way, they can hide from the immune system and feed on the nutrients actually intended for the neurons. In addition, the cancer cells make it possible for other immune cells to enter the tumour and prevent the T-cells there from attacking it. Through the cancer cells' deception, misunderstandings between the T cells and the microglia arise – they launch processes designed to repair tissue, but the cancer cells disguised as neurons take advantage of this: they multiply.

Yet cancer cells manage to break through the blood-brain barrier – and even to manipulate the brain cells across this barrier, as described in the scenario above. This is because the cancer cells bring along certain protein-degrading enzymes and have specific tumour factors that make the brain, actually a closed system, mechanically permeable and reprogramme it with the help of soluble factors. Although immune cells from the blood can pursue the invading cancer cells, the cancer cells make sure that these immune cells remain inactive in the brain. "We've discovered that cancer cells literally block the body's defences and even use them for their own benefit," says Sevenich. The cancer cells switch off the brain's defence mechanisms and actively reprogramme the immune cells for their own reproduction.

Like a gripping film

First, Sevenich's team attempted to block the immune cells exploited by the tumour. But it proved very difficult to interrupt the interaction between cancer cells and normal cells. "In the process, we found everything you need for an exciting film script: disguise, hide-and-seek, misunderstandings!" she says. For example, tumours can disguise themselves as neurons and in this way confuse the brain's defence cells (see box). Recently, Sevenich's research team succeeded in luring more anti-tumour immune cells (T cells) into the tumour with the help of radiation therapy. At the same time, they inhibited a signal that usually blocks T cells, thus making them attack the tumour. Unfortunately, however, this only works for a limited period, meaning that the tumour still wins in the end. "It was frustrating to see that certain blockades work for a short time, but after a few days or weeks, the cancer cells are back in the director's chair – if anything more potently than before." The goal must therefore be to understand the entire chain of effects and only then intervene in a targeted way.

This is, however, not quite so easy: the group conducts most of its research on mouse models, combined with cell cultures (which, however, only ever allow the study of a single aspect). In both experiments, the cancer cells enter the mouse's bloodstream; a few colonise the brain. From there, the cancer cells can be isolated, grown in cell cultures and analysed. To obtain sufficient cancer cells that manage to enter the brain, this cycle is repeated so that the cancer cells accumulate there. In this way, the researchers can detect changes in cell, protein and effect patterns.

"We want to understand how the cancer cells 'train' their environment to serve their purpose – and sooner or later we want to succeed in blocking this process," Sevenich hopes.

ABOUT LISA SEVENICH

Lisa Sevenich, 41, studied biology with a focus on immunology. After her doctoral degree in Freiburg, she discovered her fascination for brain metastases during her postdoctoral work in New York. Particularly important for her is the relevance of her research to the disease itself, with the goal of one day being able to contribute to a cure. In 2019, she was awarded the Beug Foundation's Prize for Metastasis Research for her work, which is funded by the Max Eder Junior Research Group Programme of German Cancer Aid.

sevenich@gsh.uni-frankfurt.de





Dr Lisa Sevenich and doctoral candidate Dominic Menger with a Petri dish containing a thin section of a mouse brain. The tissue is first made transparent before the cells are stained and analysed under the microscope.

Photo: Uwe Dettmar

“Expressed in human terms: the immune cells are trying very hard, but misunderstandings between the different types of immune cell arise again and again. Although they want to protect the brain cells and destroy the cancer cells, tricks performed by the latter make them confuse these tasks. We want to help them do their job.” To this end, the researchers will continue to search for strategies to keep immune cells in brain metastases awake until they know how to attack and ultimately conquer just the tumour and not the brain cells.

Useful findings for many pathologies

The route to healing patients is still a long way off. But Sevenich, a keen athlete, likes such difficult challenges. Only a few research groups are working in the field of brain metastases because, firstly, brain surgery is risky, and, secondly, patients usually survive only a few months once brain metastases have been detected, so the time available for treatment is extremely limited.

“In my opinion, the body’s reaction to the tumour is not particularly specific, but instead resembles more a stress response,” explains Sevenich. “If we understand the process of who is manipulating whom here, then we can presumably transfer this to other diseases too – because neurological diseases such as Alzheimer’s trigger similar responses in immune cells.”

The worrying thing is that cancer cells often set off on their journey to new tissue early on – sometimes even before the original tumour has been detected. They often “hibernate” there and then begin one day, often decades later, to divide. The reasons for this are unknown. One of the goals of Sevenich’s research group is to understand these mechanisms and possibly find ways to sustain the harmless dormancy stage of cancer cells.

Sevenich herself finds many of her research findings exciting but also frightening: “Unfortunately, the path from our still very fundamental knowledge of brain tumours to therapeutic approaches is still very long,” she says. “But the worry that it could happen to us or someone close to us is naturally also our motivation for understanding the ecosystem of tumours.” ●



The author

Dr Anja Störiko, 56, holds a doctoral degree in microbiology. She works as a freelance journalist for general interest magazines, is editor of “BIOspektrum”, a biosciences journal, and has written books on health topics. Sevenich’s findings on metastases aroused mixed feelings in her: she found them alarming, but also admired the researchers’ courage in taking on the challenge of brain metastases.

anja@stoeriko.de
<http://stoeriko.de>