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There are some striking parallels between how skin wounds heal and how malignant tumours grow. Cell culture can help us understand the mechanisms involved – but animal testing still has a role to play.

TEXT Fabio Bergamin

HOW WOUNDS HEAL – AND CANCERS GROW

Picture the scene: you're chopping an onion, and suddenly the knife slips, leaving you with a painful cut on your index finger. It's something most of us have probably experienced at one time or another. Fortunately, these kind of wounds usually heal within a week – but sometimes things take a more complicated turn. Wounds can become infected after surgery, for example, and many elderly people suffer from chronic open wounds that won't heal. And even when the healing process runs smoothly, it may still leave an unsightly scar.

Wound healing is the main area of research of ETH professor Sabine Werner. A biochemist by training, her interest lies in the molecular and cellular mechanisms used by cells to heal wounds and form scars. In one of the most significant milestones of her research career, Werner was able to show that activin – a cellular growth factor – is a major orchestrator of wound healing. Moreover, she showed that this factor not only plays a key role in wound healing but also in the development of cancer.

This research had its roots in animal testing. A number of years ago, Werner was conducting experiments with mice to identify genes and proteins that are expressed at higher levels in both wound healing and cancer – and that was when she hit upon activin. Using cell culture models, she went on to study the mechanisms by which this factor acts. By performing further tests on mice, she was able to show that the right level of activin at the right time is vital if a wound is to heal normally. Blocking this factor in mice significantly impairs wound healing. By contrast, when cells produce high levels of activin, wounds heal faster – though too much activin is associated with the formation of larger scars.

"I wanted to stick solely to in vitro testing rather than using animals in my research," she says. But she soon realised that animal testing was essential if she was to have any hope of fully understanding the wound healing process. She also knew that if she wanted the results of her ⟶

research to benefit patients with impaired wound healing, she would need to collaborate closely with clinicians in hospitals.

OUT OF CONTROL In further tests on mice with small skin tumours, Werner was also able to show that increased activin levels stimulate tumour growth and that the cancer cells increasingly invade the surrounding tissue. "We see many of the same biochemical and cellular processes taking place both in wound healing and in the development of multiple types of cancer," she says. "In the case of wound healing, these processes come to a halt once the wound has been repaired. But in cancer, they spiral out of control, and malignant tumours harness the mechanisms involved in wound healing in order to stimulate their own growth."

Through her collaboration with dermatologists at the university hospitals in Zurich and Lausanne, Werner regularly receives biopsies from skin cancer patients for use in her research. Experiments with this tissue showed that tumours that grow aggressively also produce excessive levels of activin, and that this activates the same biochemical processes.

"To get the best results in biomedicine, you have to combine as many techniques as possible," says Werner. "We need to study these mechanisms in human tissue – that is, in biopsies – and in good cell culture systems with human cells, but it's also important to study them in animals."

Scientists all over the world are currently making huge efforts to optimise and improve cell culture models. Werner, too, is involved in this research through Switzerland's interdisciplinary skin research project Skintegrity.ch. She is confident that cell culture will yield even more useful insights over the coming decades. "The balance will tilt more towards cell culture and away from animal testing," she predicts. Scientists already have access to complex and sophisticated cell culture models that consist of both dermal and epidermal layers and that even encompass different skin cell types. "We're already using these advanced methods wherever we can in our research," she says.

But there are still many areas of research in which cell culture is not an appropriate tool. Both wound healing and cancer are characterised by inflammatory responses that involve many different immune cells. Hormones play a role in wound healing and scar formation, as do growth factors, such as those produced by nerve cells embedded in the skin. With cell culture systems, it is impossible to reproduce all these aspects in a way that adequately reflects the complexity of the human body. Equally, cell culture cannot be used to study the formation of metastases in different organs.

"Testing on animals offers certain advantages and is, unfortunately, necessary. However, we still need to do everything we can to alleviate the suffering of laboratory animals and to reduce the amount of animal experimentation," says Werner. Her group is working on improving animal experiments and optimising pain management. In addition, modern biochemical methods of analysing wound material allow scientists to obtain meaningful results using relatively little material. This has enabled Werner's group to reduce the number of invasive animal experiments significantly in recent years.

QUEST FOR NEW DRUGS Werner hopes that her findings on the growth factor activin will lead to the development of potential new therapies. The idea is to create new drugs, particularly for cancer, that prevent activin from interacting with its targets, or that prevent it from activating specific biochemical signalling pathways. Werner is too focused on fundamental research to tackle this step herself, but she's working closely with clinicians to get the ball rolling. Any drugs that make it through this process will also have to be tested on animals before patients can benefit from them.

In Werner's experience, research into cancer always produces crossover benefits for wound healing, and vice versa. So it's perfectly possible that these drugs could also prevent the formation of large, unsightly scars. ○

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→ mhs.biol.ethz.ch/research/werner

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