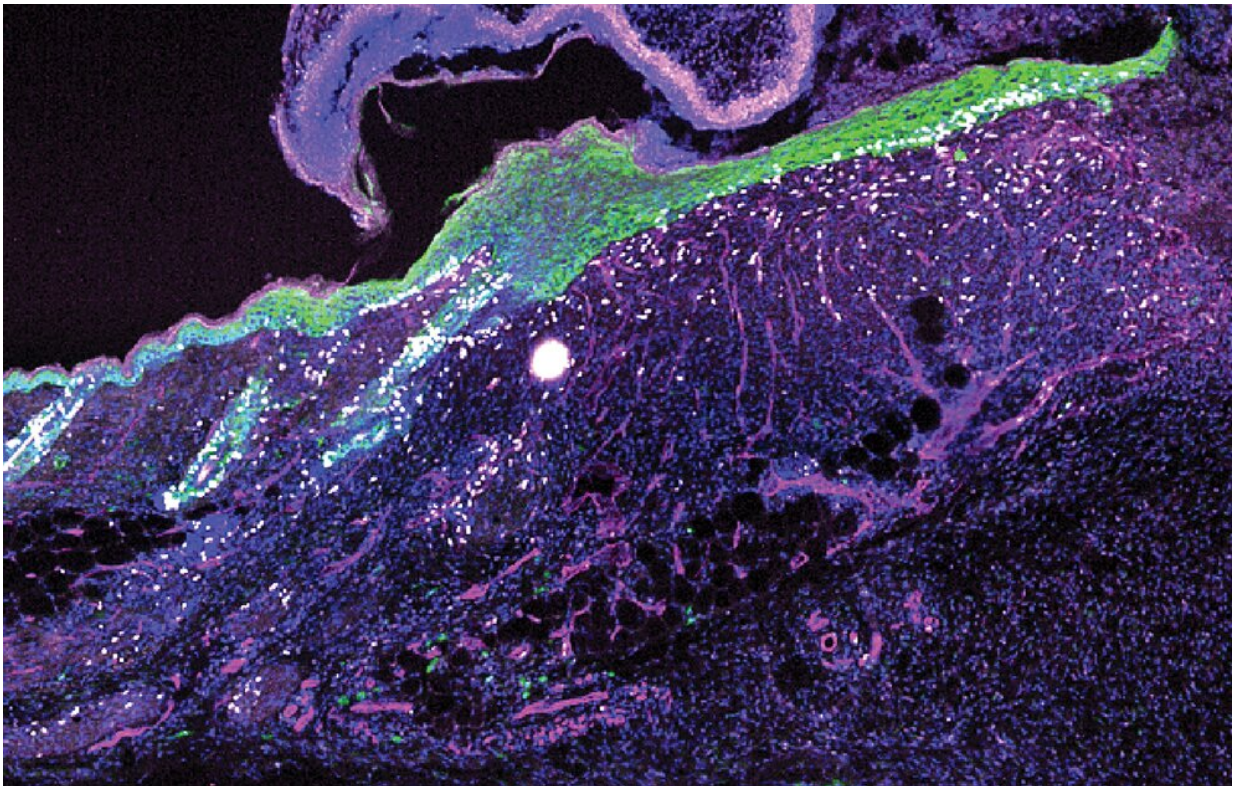


# Researchers reveal an ancient mechanism for wound repair

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A variety of cells (white) proliferate at the ragged edge of a five-day-old wound, including epidermal stem cells (basal layer of epithelium in green), which secrete IL24. Credit: Laboratory of Elaine Fuchs

It's a dangerous world out there. From bacteria and viruses to accidents and injuries, threats surround us all the time. And nothing protects us

more steadfastly than our skin. The barrier between inside and out, the body's largest organ is also its most seamless defense.

And yet the skin is not invincible. It suffers daily the slings and arrows of outrageous fortune, and it tries to keep us safe by sensing and responding to these harms. A primary method is the detection of a pathogen, which kicks the immune system into action. But new research from the lab of Rockefeller's Elaine Fuchs, published in *Cell*, reveals an alternative protective mechanism that responds to injury signals in wounded tissue—including low oxygen levels from blood vessel disruption and scab formation—and it doesn't need an infection to get into gear.

The study is the first to identify a damage response pathway that is distinct from but parallel to the classical pathway triggered by pathogens.

At the helm of the response is interleukin-24 (IL24), whose gene is induced in skin [epithelial stem cells](#) at the wound edge. Once unleashed, this secreted protein begins to marshal a variety of different cells to begin the complex process of healing.

"IL24 is predominately made by the wound-edge epidermal stem cells, but many cells of the skin—the epithelial cells, the fibroblasts, and the endothelial cells—express the IL24 receptor and respond to the signal. IL24 becomes an orchestrator that coordinates [tissue repair](#)," says Fuchs, head of the Robin Chemers Neustein Laboratory of Mammalian Cell Biology and Development.

## **Hints from pathogen-induced signaling**

Scientists have long understood how the host responses protect our body from pathogen-induced threats: Somatic cells recognize invading bacteria or viruses as foreign entities and induce a number of defense

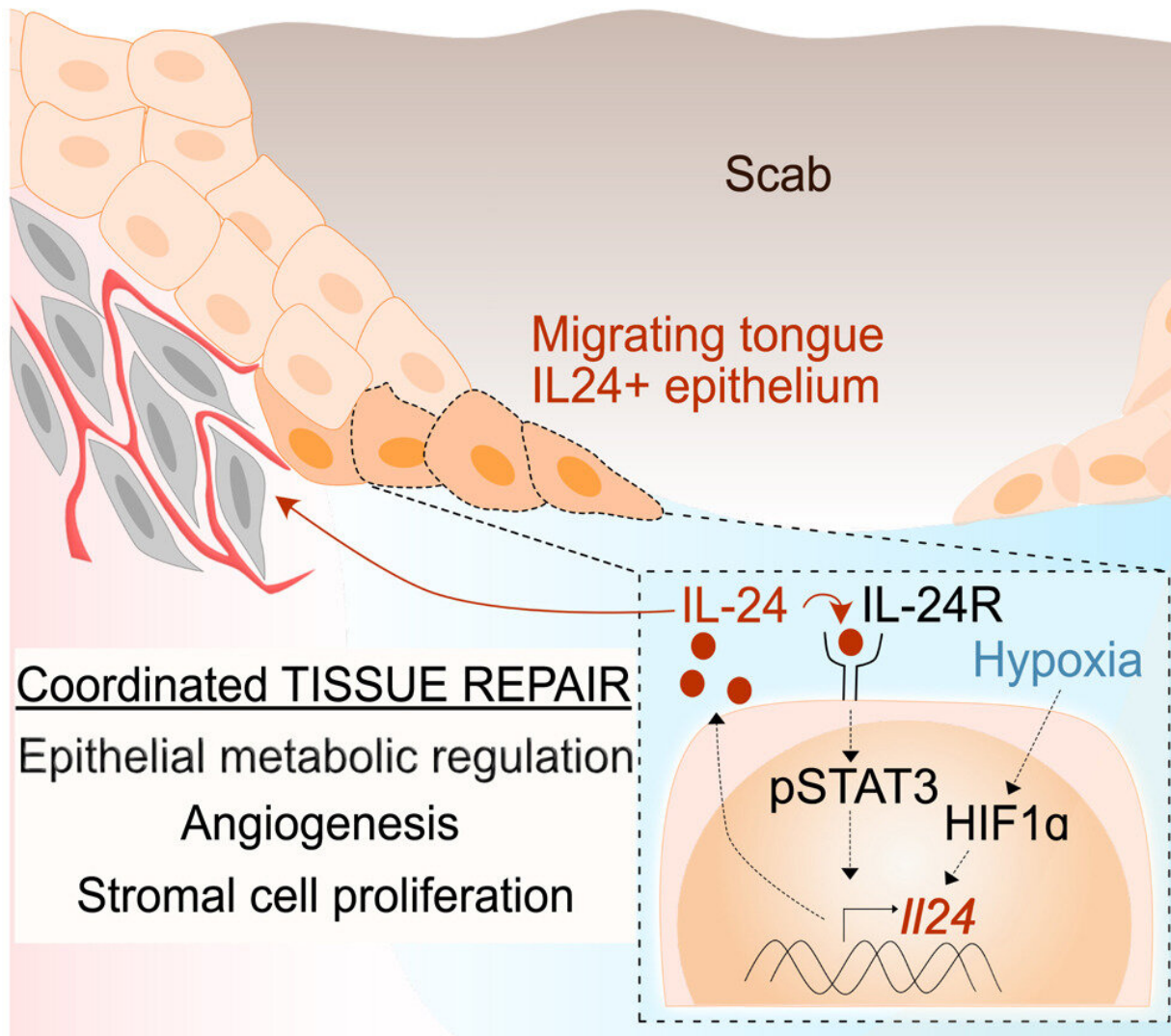
mechanisms with the help of signaling proteins such as type 1 interferons.

But how does the body respond to an injury that may or may not involve foreign invader? If we cut a finger while slicing a cucumber, for example, we know it instantly—there's blood and pain. And yet how the detection of injury leads to healing is poorly understood on a molecular basis.

While type 1 interferons rely on the signaling factors STAT1 and STAT2 to regulate the defense against pathogens, previous research by the Fuchs lab had shown that a similar transcription factor known as STAT3 makes its appearance during wound repair. Siqi Liu, co-first author in both studies, wanted to trace STAT3's pathway back to its origin.

IL24 stood out as a major upstream cytokine that induces STAT3 activation in the wounds.

## Skin Wound Repair



Credit: *Cell* (2023). DOI: 10.1016/j.cell.2023.03.031

### Microbe-independent action

In collaboration with Daniel Mucida's lab at Rockefeller, the researchers worked with mice under germ-free conditions and found that the wound-

induced IL24 signaling cascade is independent of germs.

But what injury signals induced the cascade? Wounds often extend into the skin dermis, where capillaries and blood vessels are located.

"We learned that the epidermal stem cells sense the hypoxic environment of the wound," says Yun Ha Hur, a research fellow in the lab and a co-first author on the paper.

When the blood vessels are severed and a scab forms, epidermal stem cells at the edge of the wound are starved of oxygen. This state of [hypoxia](#) is an alarm bell for cell health, and induced a positive feedback loop involving transcription factors HIF1a and STAT3 to amplify IL24 production at the wound edge. The result was a coordinated effort by a variety of cell types expressing the IL24 receptor to repair the wound by replacing damaged [epithelial cells](#), healing broken capillaries, and generating fibroblasts for new skin cells.

Collaborating with Craig Thompson's group at Memorial Sloan Kettering Cancer Center, the researchers showed that they could regulate IL24 gene expression by changing oxygen levels.

Once the researchers pinpointed the origin of the tissue-repair pathway in epidermal stem cells, they studied the wound repair process in mice that had been genetically modified to lack IL24 functionality. Without this key protein, the healing process was sluggish and delayed, taking days longer than in normal mice to completely restore the skin.

They speculate that IL24 might be involved in the injury response in other body organs featuring epithelial layers, which act as a protective sheath. In recent studies, elevated IL24 activity has been spotted in epithelial lung tissue of patients with severe COVID-19 and in colonic tissue in patients with ulcerative colitis, a chronic inflammatory bowel

disease.

"IL24 could be working as a cue to signal the need for injury repair in many organs," Hur says.

## **Linked by function and evolution**

"Our findings provide insights into an important tissue damage sensing and repair signaling pathway that is independent of infections," explains Fuchs.

An analysis with evolutionary biologist Qian Cong at UT Southwestern Medical Center revealed that IL24 and its receptors share close sequence and structure homology with the interferon family. Though they may not always be working in coordination at every moment, IL24 and interferons are evolutionarily related and bind to receptors sitting near each other on the surface of cells. The researchers suspect that these signaling molecules derive from a common molecular pathway dating far back in our past.

"We think that hundreds of millions of years ago, this ancestor might have diverged into two pathways—one being pathogen defense and the other being tissue injury," Liu says.

Perhaps the split occurred to cope with an explosion of pathogens and injuries that caused a sea of troubles for life on Earth.

**More information:** Siqi Liu et al, A tissue injury sensing and repair pathway distinct from host pathogen defense, *Cell* (2023). [DOI: 10.1016/j.cell.2023.03.031](https://doi.org/10.1016/j.cell.2023.03.031)

Provided by Rockefeller University

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