

The Wound That Never Received the Message to Stop

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The proposition we defend

Repair is a timed program with an off-switch, not a permanently virtuous activity. We argue that selected chronic inflammatory and fibrotic disorders arise when repair signaling continues after its constructive work should have ended. The defining lesion may be a failure of termination rather than a failure of initiation.

Tissue repair requires as much termination as initiation. A wound might close visibly while persistent fibroblast, macrophage or neural signaling sustains abnormal physiology. The hypothesis is that in some disorders the missing step is not initiation of repair, but successful exit from the repair program.

Why the mechanism deserves to be taken seriously

In healing tissue, leukocyte recruitment should give way to resolution, myofibroblast activity should decline, and matrix remodeling should reach an appropriate balance. Stiff extracellular matrix can reinforce YAP/TAZ-dependent fibroblast activation; persistent damage-associated signals may recruit innate immune cells. An initial scar can become an input to ongoing fibrogenesis. This is a physically plausible feedback loop rather than merely a metaphor.

The causal argument

Inflammatory recruitment, fibroblast activation, matrix deposition and angiogenesis help a wound close. Resolution requires clearance of dead cells, changes in macrophage signaling, fibroblast deactivation or removal, and matrix remodeling. If stiff matrix keeps activating fibroblasts, or hypoxic tissue repeatedly releases danger signals, the termination signal cannot prevail. The disease then becomes self-maintaining: tissue distortion creates more of the cues that normally initiate repair. This is why visible closure of a wound cannot be equated with completion of its underlying biological program.

Causal architecture under closer examination

The difficult problem in wound biology is not simply getting cells to divide; it is making them cease dividing, deactivate and reorganize after a defect has been sealed. In a successful repair sequence, an inflammatory landscape gives way to matrix synthesis and then to remodeling. Fibroblasts that once produced contractile force must reduce activity or disappear, while macrophage populations change their tasks and excess vascular structures regress. A failure at any step could leave a tissue structurally closed but biologically stuck in an active repair state. The cleanest mechanistic candidate is a positive-feedback circuit. For example, a stiffened matrix promotes cellular tension, tension sustains profibrotic signals, and those signals deposit additional stiff matrix. The original wound may have healed but the circuit now has its own inputs. A similar loop could involve local hypoxia and angiogenic signaling or persisting damage-associated ligands and innate immunity. These pathways should not all be invoked at once; each condition requires a specific circuit and measurements showing that it remains active when the original injury has ended.

A concrete physiological case

Consider a healed operation site that gradually becomes tighter and more painful without infection. Repeated tissue sampling or imaging may reveal progressive matrix deposition and persistent contractile fibroblast activity. The thesis predicts that a persistent local feedback system exists despite absence of an open wound. A similar framework applies to internal organ fibrosis, although the trigger, cellular composition and reversibility vary greatly among organs.

Original conceptual illustration

A healed skin wound provides a useful thought experiment: the epithelium has closed, but fibroblast activation may remain abnormal beneath it. If tissue stiffness keeps driving matrix synthesis, then manipulating the original inflammatory trigger may not reverse the new mechanical loop. If the tissue is simply a mature, inactive scar, the mechanism is different. The essay must therefore distinguish ongoing pathology from permanent but biologically quiet structural change.

What established physiology already supports

Fibrosis, sustained myofibroblast signaling and chronic inflammatory repair are documented phenomena. The proposed conceptual advance is to treat exit from the repair state as an active, vulnerable process that can fail independently of the original injury. That directs attention to the switch between deposition and remodeling rather than only to how much inflammation remains.

The strongest counterargument—and the answer

The main rival explanation is an unrecognized persistent insult—reflux, autoimmunity, repeated injury or infection. Those causes must be assessed. The off-switch hypothesis is strongest when the initiating injury is objectively absent or controlled but self-sustaining profibrotic signaling continues. If ongoing exposure explains the trajectory fully, no separate program-failure model is needed.

Continued inflammation may reflect a real ongoing insult such as infection, mechanical stress or autoimmunity. Fibrosis can also be an irreversible consequence rather than an active self-sustaining process. A visible scar does not prove pathological signaling is still occurring.

The discriminating experiment

Follow a healing tissue through expected resolution while measuring macrophage states, fibroblast phenotypes, matrix stiffness and vascular supply. Perturb the sustaining loop after closure without re-opening the wound. A genuine termination defect predicts that restoring a resolution signal reverses excessive matrix activity even when the initial trigger has already ended. The endpoint must be tissue function and architecture, not a single molecular marker.

The model predicts persistent molecular or mechanical activation after the initiating lesion is controlled, and responsiveness to interruption of the feedback circuit rather than repeated removal of triggers. If signaling ends promptly yet dysfunction remains due solely to fixed architecture, the model needs revision.

Decisive comparisons and limits of inference

One important prediction is that the chronology of repair and dysfunction will diverge. Skin closure, falling infection markers or absence of an obvious lesion could occur before fibroblast activation returns to baseline. Histological and imaging measurements might then show a prolonged active state that forecasts later stiffness or loss of mobility. Researchers should compare patients with similar initial wounds but different resolution patterns, controlling infection, diabetes, medication and repeated trauma. A targeted perturbation that changes the predicted feedback link after closure and improves architecture would strengthen the claim that termination is independently defective. The alternative is persistent injury or occult infection, which may be the actual reason repair remains active. That

possibility is not an editorial nuisance: it determines whether a treatment should address infection, eliminate repeated mechanical stress, or interrupt fibrotic reinforcement. The counterintuitive lesson is that interventions designed to stimulate repair may become harmful after a phase transition. A wound that appears slow to finish may not need more stimulation; it may need restoration of the signals that specify completion. Yet clinical treatment decisions must remain disease-specific, because suppressing necessary healing can also be dangerous.

A second prediction from the original model

The most distinctive sign would be pathological fibroblast activation that persists after the primary inflammatory stimulus is controlled but decreases when a specific matrix-feedback pathway is interrupted. An inactive mature scar would not meet this definition.

Why the hypothesis matters if correct

If the hypothesis is correct, some therapies intended to promote healing may intensify disease because the tissue has already completed the constructive work and failed only to terminate the program. A persistently activated fibroblast or macrophage circuit can convert repair into architecture-distorting fibrosis. The implication is a need to recognize the transition from necessary activity to self-maintaining overactivity. Measures of wound closure alone are insufficient: a scar can be closed while internal remodeling remains dysfunctional. Researchers should seek the earliest point at which a sustaining circuit becomes independent of the initial insult, then determine whether a targeted intervention reverses that circuit without impairing remaining constructive repair. This approach can distinguish failure of termination from ongoing injury that continues to demand a legitimate repair response. The most useful contribution is the idea that the off-switch is as biologically important as the on-switch. Repair is successful when it reconstructs and then relinquishes control, not when it remains indefinitely active.

The clinical and conceptual consequence

The provocative treatment question is whether some chronic disease requires teaching a tissue to stop repairing. More repair stimulation could make the disorder worse. That inversion is worth testing rigorously because it challenges the assumption that regenerative signaling is always desirable.

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Source bibliography: verification pending

- Liu F et al. Mechanosignaling through YAP and TAZ drives fibroblast activation and fibrosis. *Am J Physiol Lung Cell Mol Physiol*. 2015.
- Fibroblast Yap/Taz Signaling in Extracellular Matrix Homeostasis and Tissue Fibrosis. *Int J Mol Sci*. 2024.

Editorial and clinical boundaries

This paper advances a causal thesis and identifies observations that would support or defeat it. It does not establish a new diagnosis or treatment, and it should not be used to discontinue medically indicated care. Bibliographic entries inherited from the original edition have not all been independently verified.