

The Immune System That Mistakes Repair for Infection

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The proposition we defend

Not every inflammatory alarm signifies infection. We argue that sterile tissue damage can create a self-replenishing immune stimulus, allowing repair pathology to continue without microorganisms. Once activated, the inflammatory response can injure tissue further and thereby manufacture the signals that call it back.

The immune system does not respond only to pathogens. Damaged host tissue can release signals that recruit inflammatory responses even in sterile conditions. A potentially self-sustaining disease state can arise if the consequences of inflammation continually generate more of those signals.

Why the mechanism deserves to be taken seriously

Extracellular ATP, mitochondrial DNA, uric acid crystals and damaged matrix fragments can function as danger-associated signals under defined conditions. Mitochondrial DNA released into the cytosol can activate cGAS-STING signaling; damaged cells recruit innate immune clearance. The plausible feedback loop is damage, innate activation, secondary injury and further danger signal release.

The causal argument

Dying cells release danger-associated molecules and altered extracellular structures; innate receptors and recruited immune cells interpret these as evidence that the local environment requires attention. Initially this is protective: debris is cleared and reconstruction begins. The pathological transition occurs when immune activity produces new microdamage, local hypoxia or fibrotic stiffness that perpetuates danger signaling. The causal architecture is a loop from tissue stress to alarm, from alarm to additional tissue stress and back. If the loop persists independently of the original injury, simply removing that injury may not restore homeostasis.

Causal architecture under closer examination

The immune system receives signals about damage as well as signals about microbes. A ruptured cell, altered matrix or disturbed barrier can recruit defense pathways even in a sterile environment. This is necessary for clearing debris and enabling regeneration. The pathology emerges when responding to tissue damage creates more damage of the type that initiated the response. To demonstrate self-sustaining sterile inflammation one needs more than a negative culture and an elevated cytokine. Researchers should identify an endogenous activating ligand, its sensing pathway, downstream immune activity and the new tissue stress produced as a consequence. For example, excessive protease release or oxidative injury may damage extracellular structures and generate additional alarm signals. Alternatively, matrix stiffness could alter local cell behavior and maintain inflammation mechanically. These loops are not interchangeable: they imply different cellular sources, spatial distributions and intervention windows. One pathway may dominate in a healing skin wound; another may matter in chronic fibrotic lung tissue. An integrated theory should honor organ-specific ecology.

A concrete physiological case

Imagine a sterile inflammatory lesion with repeated macrophage activation and progressive fibrosis after the initiating physical insult has ceased. Pathogen assays remain negative and tissue still releases host-derived alarm

signals. An experimental interruption of the danger-signal pathway reduces inflammation and preserves architecture. That result would support a self-sustaining sterile loop; repeated occult infection would call for a different interpretation.

Original conceptual illustration

Mitochondrial DNA found in the wrong cellular compartment can activate a DNA-sensing immune pathway. That mechanism is much more specific than saying mitochondria are “toxic” or the body has failed to detoxify. The cause may be oxidative injury, apoptosis-related membrane permeabilization or other stress. A theory must show how the nucleic acid leaves its usual location, which cell senses it, and whether this response is necessary for pathology.

What established physiology already supports

Sterile inflammation, danger signaling and innate immune sensing of tissue injury are established mechanisms. The provocative extension is the claim that some chronic disease is organized around *mistaking ongoing repair damage for renewed external attack*. The metaphor is useful only if host-derived ligands and their receptors can be identified.

The strongest counterargument—and the answer

The main alternative is an unseen driver—microbial persistence, autoimmunity or recurring mechanical injury. These are plausible and often clinically important. The thesis has to show that a host-generated loop continues even when those drivers are held constant. Blanket suppression of inflammation would be a poor experiment because inflammation also clears debris and enables repair.

An activated inflammatory pathway does not mean immunity is “confused.” Many sterile responses are appropriate and terminate normally. Ongoing disease may instead reflect infection, ischemia, autoimmune antigen recognition or mechanical injury. Calling all inflammation mistaken ignores necessary wound defense.

The discriminating experiment

In a sterile injury model, follow the time sequence from initial tissue damage to danger-ligand release and inflammatory-cell recruitment. After the initiating insult ends, selectively interrupt a proposed positive-feedback link and monitor both tissue architecture and function. Demonstration of a sustained loop and its collapse under targeted interruption would be stronger than correlations between C-reactive protein and symptoms.

The discriminating evidence is a causally important endogenous ligand whose reduction alters inflammation despite no change in microbial burden or primary damage. The model weakens if inflammation requires an untreated infectious or structural trigger.

Decisive comparisons and limits of inference

The decisive intervention occurs after the original sterile insult has ended. If a targeted blockade of the sustaining danger-signal loop reduces ongoing inflammation and improves tissue architecture without renewed injury, the model gains causal force. If inflammation continues because occult pathogens or mechanical insults remain, disabling one sterile pathway may provide limited benefit or compromise defense. It is also essential to distinguish resolution from generalized immunosuppression. A broad drug that reduces inflammatory markers can make histology appear calmer while impairing actual wound closure. Research must therefore measure barrier integrity, functional repair and susceptibility to infection alongside inflammatory activity. A useful prediction is spatial: persistent host-derived danger signals should co-localize with sites of tissue stress, and the loop may spread as damage extends. The thesis is most provocative when it argues that some chronic disease no longer requires its original cause to remain active. The immune response can manufacture sufficient evidence of danger to reactivate itself. Demonstrating such a circuit would shift therapy toward specific feedback interruption rather than a perpetual search for absent microbes or the indiscriminate suppression of every inflammatory signal.

A second prediction from the original model

A sterile immune feedback loop should persist without a replicating pathogen and weaken when its identified self-derived danger signal is removed. Without that discriminating observation, inflammation could simply be responding appropriately to continuing injury.

Why the hypothesis matters if correct

The argument matters when an immune response persists after the initial insult but continues to receive activating signals generated by its own effects on tissue. Such a feedback loop can make inflammation self-maintaining even without infection. To establish it, the paper must identify a host-derived danger signal, the sensing pathway and the new damage produced by activation. If a targeted intervention breaks the cycle and restores tissue architecture after the original injury is gone, the causal claim becomes strong. Yet a tissue may also remain inflamed because infection or ongoing mechanical injury has not been removed; in that case the feedback model is secondary. The scientific payoff is a distinction between fighting an external trigger and terminating an internally sustained response. This could influence research on chronic sterile inflammation and fibrosis. It does not make indiscriminate immune suppression desirable, because many inflammatory activities remain essential for debris removal and recovery.

The clinical and conceptual consequence

The controversial idea is that the immune system can help perpetuate an environment it is trying to repair. Disease may then require breaking a feedback circuit rather than suppressing all immunity or searching indefinitely for an undetected pathogen.

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Source bibliography: verification pending

- Kim J et al. Molecular mechanisms of mitochondrial DNA release and activation of the cGAS-STING pathway. *Exp Mol Med*. 2023.
- de Laval B et al. C/EBP β -dependent epigenetic memory induces trained immunity in hematopoietic stem cells. *Cell Stem Cell*. 2020.

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.