

Why Inflammation Does Not Stop

Paper 11 · Editorial concept paper · Created 15 October 2026

Abstract. Acute inflammation is usually terminated by active processes, not merely exhaustion of its initiating signal. Failure of resolution may be one maintaining mechanism in selected chronic inflammatory conditions, with crucial distinctions between unresolved infection, dysregulated immunity and structural injury.

Beginning and ending are different programs

The inflammatory response recruits cells and mediators to contain a threat and initiate repair. Successful recovery does not simply mean the disappearance of the initial pathogen-associated signal. Neutrophil influx must decline, dying cells must be cleared, macrophage programs must change, and tissue architecture must be rebuilt. Lipid mediators including lipoxins, resolvins, protectins and maresins have been implicated in regulation of resolution. Their existence supports an active-resolution model; it does not show that supplementation with their precursors cures chronic inflammatory disease.

Persistence may have several distinct meanings

A patient can remain inflamed because an antigen or microorganism persists, because an autoimmune process is maintained, because tissue continues releasing damage-associated signals, or because the terminating machinery is ineffective. These possibilities overlap but are not interchangeable. For example, treating uncontrolled infection as purely failed resolution could be dangerous; suppressing immunity without recognizing a pathogen can worsen the underlying illness.

The termination checkpoint

An important cellular event is efficient efferocytosis, the uptake of apoptotic cells before they undergo secondary necrosis. Failure can leave inflammatory material within tissue and help sustain recruitment. In atherosclerotic plaque, evidence links defective macrophage corpse clearance to necrotic core development and lesion progression. This is a focused example where termination failure contributes to a clinically consequential disease pathway.

An original explanatory framework

We propose distinguishing four phases: recognition, amplification, containment and resolution/remodeling. Chronic disease can emerge because amplification exceeds control, containment fails, the threatening stimulus remains, or resolution/remodeling is incomplete. This prevents the phrase 'chronic inflammation' from functioning as if it named a unique cause. It also encourages asking why apparently successful control of an upstream variable does not necessarily restore tissue function.

Discriminating the possibilities

The model would gain value if phase-specific measurements predict outcomes beyond circulating inflammatory markers. Demonstrations of persistent pathogen, altered efferocytosis, impaired pro-resolving signaling or irreversible fibrosis demand different interpretations. Randomly lowering an inflammatory laboratory value does not establish that resolution has occurred.

Safety and scope

This is not a recommendation to abandon anti-inflammatory medication. Such drugs can preserve organs and lives when used for the right disease. Conversely, attempts to 'stimulate resolution' without understanding infection or autoimmunity remain experimental. The strongest contribution is causal clarity: stopping an inflammatory process and rebuilding the injured tissue are linked but distinct tasks.

A resolution failure is not the same as immune deficiency

An immune system can be vigorous yet poorly coordinated. A tissue may recruit effector cells effectively but fail to remove them promptly, or it may clear dying cells poorly and prolong inflammatory exposure. The resulting process is not well described by either 'weak immunity' or 'strong immunity.' It is a failure of sequence and regulation. This distinction matters because treatments marketed as immune stimulation can be inappropriate in a disorder with excessive or misdirected immune activity.

Specific mediators and the danger of therapeutic extrapolation

Specialized pro-resolving lipid mediators have provided important mechanistic insight into how inflammatory programs terminate. They do not simply reproduce the effects of indiscriminate immunosuppression. Some promote the clearing of apoptotic cells and influence the trafficking of immune populations. Yet a compound's ability to stimulate resolution in an animal model is not proof of benefit in patients with rheumatoid arthritis, postviral symptoms or autoimmune thyroid disease. Drug formulation, pharmacokinetics, target tissue and unintended effects all matter.

Reading the phase of disease

In an early infection, vigorous microbial containment may be indispensable. After the threat is controlled, the unresolved inflammatory response may become relatively more important. In advanced fibrosis, structural injury may dominate even after inflammation subsides. These temporal distinctions suggest different questions for different clinical stages. The model is falsifiable when phase and outcome are defined, and dangerously vague when 'inflammation' is invoked as both cause and symptom without identifying the process.

Selected scientific reading

1. [Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. Nature. 2014;510:92–101.](#)
2. [Tabas I. Macrophage death and defective inflammation resolution in atherosclerosis. Nat Rev Immunol. 2010;10:36–46.](#)

3. [Netea MG et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol. 2020;20:375–388.](#)

Editorial status: Conceptual scientific essay, not peer reviewed. Not original clinical data, a treatment protocol or medical advice. Selected readings are not a systematic review. Evidence and interpretation should be assessed independently.