Inflammatory Restart: A Unified Framework for Resolving Chronic Inflammation Through Epigenetic Rejuvenation

Short title: Inflammatory Restart Paradigm (≤50 characters: 26)

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Summary

Background: Chronic inflammation underlies a broad spectrum of human diseases, yet current therapeutic strategies predominantly rely on immunosuppression, which rarely achieves durable remission and often carries substantial adverse effects.

Methods: We synthesized evidence from immunometabolism, resolution biology, mesenchymal stem cell biology, epigenetic rejuvenation, and geroscience to develop an integrative conceptual framework. References were identified through searches of PubMed, Google Scholar, and Web of Science up to April 2026.

Findings: We introduce the Inflammatory Restart Paradigm—a reconceptualisation of inflammation as an evolutionarily programmed, self-organising cycle of tissue renewal rather than a pathological process to be suppressed. Central to this framework is the quantitative balance between two functionally opposing cytokine subsets operating as a

molecular rheostat governing inflammatory trajectory. When balanced, the system progresses through coordinated phases of clearance, metabolic transition, regeneration, immune re-education, and epigenetic resetting. Rheostat imbalance leads to self-sustaining pathological circuits involving failed resolution, metabolic entrapment, pathological immune memory, and stromal dysregulation. We propose that the physiological purpose of inflammation extends beyond host defence to include periodic resetting of the epigenetic landscape.

Interpretation: This framework reframes chronic inflammatory disease as failure of cycle completion and guides development of therapies designed to restore—rather than suppress—endogenous adaptive resolution capacity. Partial epigenetic reprogramming may represent not an exogenous intervention but an acceleration of natural regenerative mechanisms.

Funding: No specific funding was received for this work.

Research in context

Evidence before this study

Chronic inflammatory diseases remain poorly controlled despite advances in biologic therapies targeting individual cytokines. The classical view of inflammation as a pathology to be suppressed has yielded incremental but not transformative progress. Recent advances in immunometabolism have revealed the intimate coupling between immune cell function and metabolic state, while resolution biology has identified specialized pro-resolving mediators and active pathways for inflammation termination. Separately, the field of geroscience has demonstrated that partial epigenetic reprogramming using Yamanaka factors can reverse cellular hallmarks of ageing in vivo. However, these insights have remained largely disconnected, lacking an integrative framework that explains both the physiology of successful inflammation and the pathogenesis of chronic inflammatory states.

Added value of this study

We synthesize these disparate lines of evidence into a unified conceptual framework—the Inflammatory Restart Paradigm—centered on a quantitative cytokine rheostat that determines whether inflammation progresses to resolution and tissue renewal or becomes self-sustaining and pathological. We extend the classical three-phase model

of inflammation (clearance, resolution, repair) to include a fourth phase of epigenetic resetting, encompassing immune re-education, mesenchymal stem cell activation, and reversal of age-related epigenetic hallmarks. This framework explains how metabolic-epigenetic coupling serves as the mechanistic basis for the resolution switch, and why chronic inflammation represents failure to complete an evolutionarily programmed cycle rather than merely excessive or prolonged inflammation.

Implications of all the available evidence

The paradigm reframes therapeutic strategy from immunosuppression toward precision rebalancing of the cytokine rheostat and, where necessary, direct activation of endogenous epigenetic rejuvenation programmes. It generates testable predictions regarding rheostat position as a predictor of inflammatory trajectory, the requirement of a pro-resolving tissue state for successful partial reprogramming, and the reversibility of the age-related mesenchymal drift. Ongoing clinical trials of partial reprogramming in humans provide an opportunity to test these predictions and may open new avenues for treating chronic inflammatory diseases by restoring—rather than suppressing—the natural cycle of inflammation-driven tissue renewal.

Introduction

Chronic inflammatory diseases—ranging from rheumatoid arthritis and inflammatory bowel disease to metabolic syndrome, neurodegenerative disorders, and age-related frailty—represent one of the greatest therapeutic challenges. Despite remarkable advances in cytokine-targeted biologics and small-molecule immunomodulators, durable remission remains elusive for most patients, and many achieve only partial responses requiring continuous treatment [1-3]. This persistent clinical impasse stems from a fundamental conceptual limitation: inflammation is viewed primarily as a pathology to be suppressed, rather than an evolutionarily programmed, self-organising adaptive cycle for systemic renewal [4,5].

The classical view of inflammation, while enormously productive in identifying molecular mediators and therapeutic targets, has inadvertently fostered a suppressive therapeutic paradigm. Biologics targeting tumour necrosis factor (TNF), interleukin (IL)-6, IL-17, and other pro-inflammatory cytokines have transformed outcomes in autoimmune diseases, yet they rarely induce sustained drug-free remission, and many patients eventually lose response or experience adverse effects [1,2]. This observation suggests that merely

blocking inflammatory mediators fails to restore the homeostatic mechanisms that normally terminate inflammation and initiate tissue repair.

Recent advances across multiple fields have begun to illuminate why this is the case. Immunometabolism has revealed that immune cell function is intimately linked to cellular metabolic states [4,5]. During acute inflammation, immune cells shift from oxidative phosphorylation to glycolysis to support rapid effector functions [6]. This glycolytic burst is not merely a metabolic consequence of activation but an active requirement for inflammatory function—and critically, it must be actively resolved for tissue homeostasis to be restored [7]. Resolution biology has identified specialised pro-resolving mediators (SPMs) derived from polyunsaturated fatty acids that actively terminate inflammation, promote efferocytosis, and initiate tissue repair [1,2]. These discoveries have established that resolution is not passive decay of inflammatory signals but an actively programmed process.

Simultaneously, the field of geroscience has demonstrated that cellular ageing is not irreversible. Partial epigenetic reprogramming using Yamanaka factors (Oct4, Sox2, Klf4—the "OSK" subset) can reverse hallmarks of cellular ageing in vivo without erasing cell identity or inducing teratoma formation [23-26]. This finding has profound implications for inflammation biology: if inflammation serves not only to clear pathogens and damage but also to periodically reset tissue epigenetic landscapes, then chronic inflammation may represent failure of this resetting mechanism.

Here we synthesise these insights into a unified conceptual framework—the **Inflammatory Restart Paradigm**. We propose that successful inflammation follows a programmed cycle culminating in epigenetic rejuvenation, that a quantitative cytokine rheostat determines whether inflammation proceeds through this cycle or becomes self-sustaining, and that chronic disease represents failure to complete this evolutionarily programmed cycle rather than merely excessive inflammation. This framework provides a conceptual foundation for understanding chronic disease pathogenesis and guides development of therapies designed to restore—rather than suppress—endogenous adaptive resolution capacity.

The Inflammatory Cycle: A Four-Phase Programme

We propose that successful inflammation follows a programmed four-phase cycle (Fig. 1a), extending the classical three-phase model to include a final phase of *epigenetic*

resetting that reverses cellular hallmarks of ageing and establishes durable tissue homeostasis.

Phase 1: Clearance

Initiated by tissue damage, pathogen detection, or sterile inflammatory triggers, this phase involves rapid immune cell recruitment, production of pro-inflammatory mediators (TNF, IL-1β, IL-6, prostaglandins, leukotrienes), and elimination of threats. Immune cells—particularly macrophages and neutrophils—shift from oxidative phosphorylation to aerobic glycolysis (the Warburg effect) to support rapid effector functions [5,13]. This metabolic switch, driven by hypoxia-inducible factor (HIF)-1α stabilisation and succinate accumulation, is essential for antimicrobial and cytotoxic functions but generates inflammatory mediators that must later be cleared [6].

Phase 2: Metabolic Transition

The transition from Phase 1 to resolution requires an actively mediated metabolic switch from glycolysis back to oxidative phosphorylation [6,7]. This switch is not passive but is orchestrated by changes in the cytokine milieu, particularly the relative abundance of pro-resolving versus pro-inflammatory signals. Metabolites generated during oxidative metabolism—notably α-ketoglutarate (αKG)—serve dual roles in energy production and epigenetic regulation [9,10]. αKG is a required cofactor for ten-eleven translocation (TET) enzymes that catalyze DNA demethylation and for Jumonji C-domain-containing histone demethylases, directly linking metabolic state to the epigenetic landscape.

Phase 3: Regeneration

Following successful metabolic transition, regenerative programmes are activated. Neurotrophic factors—particularly brain-derived neurotrophic factor (BDNF)—play central roles in tissue remodeling, neurogenesis, synaptogenesis, and restoration of homeostasis [11,12,14]. Importantly, BDNF and related factors are permissive for regeneration only after successful metabolic transition; in the presence of sustained pro-inflammatory signaling, neurotrophic factors may exacerbate pathology rather than promote repair [14].

Phase 4: Epigenetic Resetting

We propose a fourth phase comprising three integrated sub-phases that together establish durable tissue homeostasis and prepare the tissue for future inflammatory challenges:

Immune re-education. The final step in resolution involves active silencing of inflammatory memory in tissue-resident immune cells. Specialized pro-resolving mediators (SPMs) and regulatory T cells (Tregs) create a pro-permissive environment that actively retrains tissue-resident macrophages and dendritic cells to be tolerant to harmless stimuli while remaining vigilant against pathogens [15]. This process involves epigenetic silencing of inflammatory gene loci, preventing inappropriate reactivation.

Mesenchymal stem cell activation. During the resolution phase, mesenchymal stem cells (MSCs) acquire an anti-inflammatory (MSC2) phenotype [8,9]. MSCs are licensed by pro-inflammatory cytokines (IFN-γ, TNF-α, IL-1β) present during the transition from inflammation to resolution; this licensing step is essential, as unlicensed MSCs fail to exert their full immunomodulatory potential [10,11]. Once activated, MSCs secrete immunomodulatory factors—tumour necrosis factor-stimulated gene 6 (TSG-6), IL-1 receptor antagonist (IL-1Ra), prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), and IL-10—that promote tissue repair, polarise macrophages from M1 to M2 phenotypes, expand Treg populations, and establish durable homeostatic states [2,3,12].

Epigenetic rejuvenation. The most profound step in Phase 4 involves resetting the **epigenetic clock** of local cells to a more youthful state. Through transient activation of endogenous or therapeutically delivered reprogramming factors (particularly the OSK subset: Oct4, Sox2, Klf4), cells erase age-associated epigenetic marks without losing their specialized identity or dedifferentiating into a pluripotent state [1,2,4]. This mechanism is directly analogous to the natural epigenetic rejuvenation observed in the developing embryo after fertilization, where the zygote reverses age-related damage inherited from parental gametes. This process reverses the **mesenchymal drift (MD)**—the age-related shift in cellular identity characterized by adoption of a more mesenchymal, fibrotic, and inflammatory gene expression profile [22,24]. Successful epigenetic rejuvenation restores the youthful transcriptome, renews cellular function, and resets tissue structure for the next inflammatory challenge.

The complete progression through all four phases constitutes **Inflammatory Restart**—the evolutionarily programmed cycle that allows tissues to emerge from inflammation renewed rather than damaged [14,20].

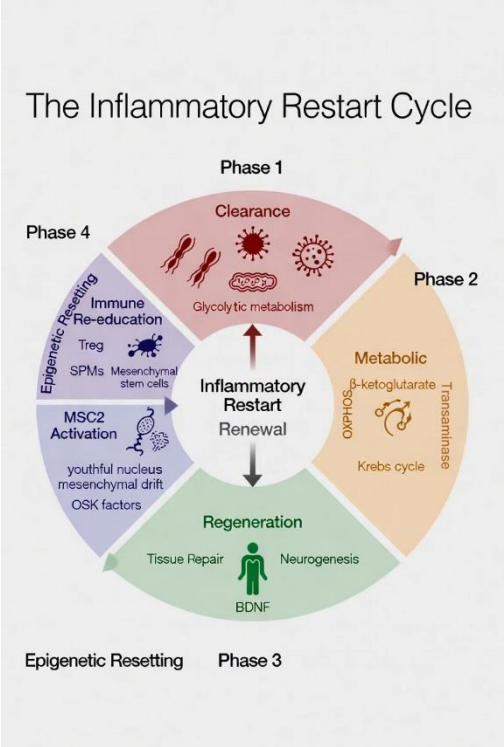

Fig. 1a. The four-phase inflammatory cycle

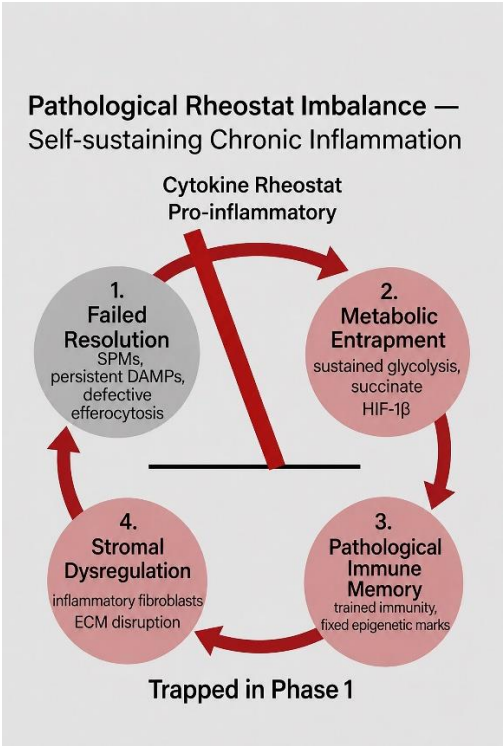

Fig. 1b. Pathological state (rheostat imbalance)

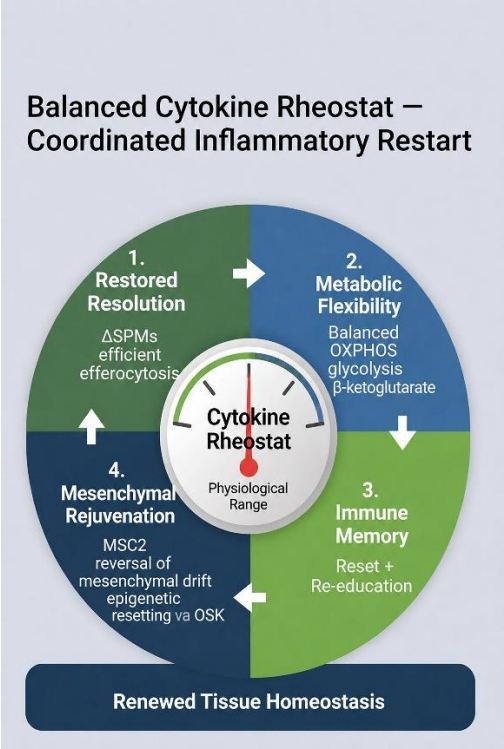

Fig. 1c. Balanced state (rheostat within physiological-homeostatic range)

The Cytokine Rheostat: A Quantitative Determinant of Inflammatory Trajectory

Central to our paradigm is a molecular rheostat—the quantitative balance between two opposing cytokine signals—that dictates inflammatory trajectory (Fig. 1b, c) [8,15]. While the specific cytokine pair may vary across tissues and contexts, the principle is general: immune cells interpret the relative abundance of opposing signals to decide their functional trajectory.

Rheostat Balance Determines Resolution Versus Persistence

When the rheostat is balanced—with pro-inflammatory and anti-inflammatory/pro-resolving signals within a physiological-homeostatic range—the system progresses through the four-phase cycle to successful completion. When the balance favours pro-inflammatory signals beyond a critical threshold, the system becomes trapped in a self-sustaining pathological circuit (Fig. 1b) [16,17].

This imbalanced state generates four interconnected pathological nodes that reinforce one another:

Failed resolution. Impaired SPM production, defective efferocytosis (clearance of apoptotic cells), and persistent damage-associated molecular patterns (DAMPs) perpetuate inflammatory signaling [1,2]. Efferocytosis is actively coupled to pro-resolving pathways; when this coupling is disrupted, uncleared apoptotic cells undergo secondary necrosis, releasing additional DAMPs and amplifying inflammation.

Metabolic entrapment. Sustained glycolysis with succinate accumulation and HIF-1α stabilisation locks immune cells in inflammatory states [5,6]. This metabolic state is self-reinforcing: HIF-1α promotes glycolytic enzyme expression, while succinate inhibits prolyl hydroxylases, further stabilizing HIF-1α. The resulting metabolic configuration is incompatible with the metabolic transition required for resolution.

Pathological immune memory. Trained immunity—the persistence of enhanced inflammatory responses in innate immune cells following initial stimulation—involves fixed epigenetic marks at inflammatory gene loci [7,18]. Unlike adaptive immunological memory, which is antigen-specific and regulated, trained immunity represents a maladaptive epigenetic scarring that predisposes to hyperinflammatory responses to subsequent stimuli.

Stromal dysregulation. Inflammatory fibroblasts and disrupted extracellular matrix create a permissive environment for persistent inflammation [8,19]. Activated fibroblasts produce inflammatory cytokines, chemokines, and matrix metalloproteinases that degrade tissue architecture and perpetuate immune cell recruitment.
These four nodes are not independent but form a self-perpetuating circuit. Failed resolution leads to persistent DAMPs that sustain metabolic entrapment; the latter reinforces pathological immune memory through epigenetic mechanisms; pathological immune memory drives stromal dysregulation; and stromal dysregulation impairs resolution, completing the cycle [3,17].

Metabolic-Epigenetic Coupling: The Resolution Switch

The mechanistic basis for rheostat-controlled resolution lies in metabolic-epigenetic coupling. During oxidative metabolism, Krebs cycle intermediates serve as cofactors for

chromatin-modifying enzymes [9,10]. Most notably, α-ketoglutarate (αKG) is a required cofactor for:

• TET enzymes, which catalyze oxidation of 5-methylcytosine to 5-hydroxymethylcytosine, initiating DNA demethylation
• Jumonji C-domain-containing histone demethylases (KDM2-7 families), which remove repressive histone H3 lysine 9 trimethylation (H3K9me3) and H3K27me3 marks.

When αKG accumulates during oxidative metabolism, these enzymes actively remove repressive epigenetic marks from resolution-associated gene loci, permitting their expression. Conversely, during sustained glycolysis, accumulation of the oncometabolite succinate—structurally similar to αKG but functionally antagonistic—inhibits αKG-dependent dioxygenases, locking inflammatory gene loci in an active chromatin state [5,6].
This metabolic-epigenetic coupling is the molecular switch that determines whether inflammation resolves or persists. The cytokine rheostat governs this switch by regulating the metabolic state of immune cells: balanced cytokine signaling promotes oxidative metabolism and αKG accumulation, while pro-inflammatory bias sustains glycolysis and succinate accumulation.

The Balanced State: Coordinated Resolution, Regeneration, and Epigenetic Resetting

When the cytokine rheostat remains within a physiological-homeostatic range, the system achieves coordinated resolution and regeneration through four corresponding nodes (Fig. 1c):

Restored resolution programmes. Increased SPM production (resolvins, protectins, maresins), efficient efferocytosis, and clearance of DAMPs [1,2]. SPMs actively counter-regulate pro-inflammatory mediator production and promote non-phlogistic recruitment of monocytes for tissue repair.

Metabolic flexibility. Balanced oxidative phosphorylation and glycolysis with α-ketoglutarate accumulation [9,10]. Metabolic flexibility—the ability to switch between metabolic states as required—is a hallmark of cellular health and permits appropriate responses to subsequent challenges.

Immune memory reset. Active epigenetic silencing of inflammatory gene loci and retraining of tissue-resident immune cells to a poised, quasi-homeostatic ground state [7,18]. This resetting involves both removal of activating epigenetic marks (H3K4me3, H3K9ac) and deposition of repressive marks (H3K9me3, H3K27me3) at inflammatory gene loci, preventing inappropriate reactivation.

Mesenchymal rejuvenation. MSC licensing and activation followed by reversal of the age-related mesenchymal drift [8,19,22]. Licensed MSCs promote macrophage polarization from M1 to M2, expansion of Tregs, and protection of epithelial barrier integrity [2,3].

The complete progression through these four nodes constitutes Inflammatory Restart—the evolutionarily programmed cycle that enables tissues to emerge from inflammation renewed rather than damaged [4,14,20].

The Rheostat in Health and Disease

Composite ratios of opposing cytokines have already emerged as superior indices of inflammatory health in ageing and exercise research [18,19]. The Inflammatory Restart Paradigm extends this concept across tissues and disease contexts, incorporating neurotrophic factors such as BDNF, which—only after successful metabolic transition—become permissive for synaptogenesis and neurogenesis [11,12,14].

Chronic Inflammatory Diseases as Rheostat Imbalance

We propose that diverse chronic inflammatory diseases—rheumatoid arthritis, inflammatory bowel disease, metabolic syndrome, atherosclerosis, Alzheimer's disease, and others—share a common pathophysiological feature: failure of Inflammatory Restart due to persistent rheostat imbalance. While the initiating triggers and tissue-specific manifestations differ, the downstream pathological circuit of failed resolution, metabolic entrapment, pathological immune memory, and stromal dysregulation is conserved.

This perspective explains several puzzling clinical observations. First, it accounts for why cytokine-targeted biologics, while often effective in reducing inflammation, rarely induce durable remission: blocking individual cytokines may shift the rheostat but does not restore the coordinated programme of resolution and epigenetic resetting. Second, it

explains why patients frequently relapse upon treatment withdrawal: the underlying epigenetic and stromal changes that perpetuate rheostat imbalance persist even when inflammatory mediators are suppressed. Third, it suggests why combination therapies targeting multiple nodes of the pathological circuit may be more effective than single-agent approaches.

Translational Implications and Convergence with Epigenetic Rejuvenation

The Inflammatory Restart Paradigm reframes chronic disease as failure to complete an evolutionarily programmed cycle—a "metabolic trap" [3,17] from which the system cannot escape without intervention. This reframing has several translational implications.

From Immunosuppression to Rheostat Rebalancing

The paradigm shifts therapeutic strategy from immunosuppression toward precision rebalancing of the cytokine rheostat. Several approaches may achieve this rebalancing:

Lifestyle interventions. Exercise, caloric restriction, and sleep have well-documented effects on inflammatory balance [18,20]. The paradigm provides a mechanistic framework for these effects: lifestyle factors may shift the cytokine rheostat toward balance by promoting metabolic flexibility and resolution programmes.

Biologic and small-molecule therapies. Rather than aiming for complete cytokine blockade, therapeutic strategies might aim for rheostat rebalancing—for example, by combining modest inhibition of pro-inflammatory cytokines with enhancement of pro-resolving pathways (SPM analogues, IL-10 receptor agonists).

Cellular reprogramming. Partial epigenetic reprogramming using Yamanaka factors (OSK) has been shown to reverse ageing hallmarks in multiple tissues and is now entering clinical trials [1,2,4,27]. The Inflammatory Restart Paradigm suggests that the efficacy of partial reprogramming in treating chronic inflammatory diseases will depend on a pre-existing pro-resolving state of the tissue. In other words, the tissue must be primed for resolution before epigenetic rejuvenation can be effective.

Inflammation Resolution as a Trigger for Epigenetic Rejuvenation

A fundamental question unresolved by classical inflammation theory is how termination of inflammation initiates the long-term processes of tissue regeneration and reversal of ageing hallmarks. We propose that a critical link is the activation of cellular reprogramming pathways during the resolution phase.

Natural epigenetic rejuvenation in development. A powerful example of complete "Inflammatory Restarts" occurs in embryogenesis. Parental gametes carry age-related epigenetic marks; after fertilization, the zygote undergoes systematic resetting of the epigenome, reaching a point of maximum developmental potency. This demonstrates that a cell can naturally revert to a youthful, ground state [4].

Partial reprogramming in resolution. During the transition from inflammatory to resolution phases, the changing cytokine milieu (Fig. 2) licenses tissue-resident stem and progenitor cells. When chronic inflammation is resolved, these cells can temporarily activate endogenous repair programmes that mirror the action of Yamanaka factors. This transient activation is sufficient to reverse key hallmarks of ageing, including mesenchymal drift, without triggering uncontrolled proliferation associated with tumour formation [1,2,4,23].

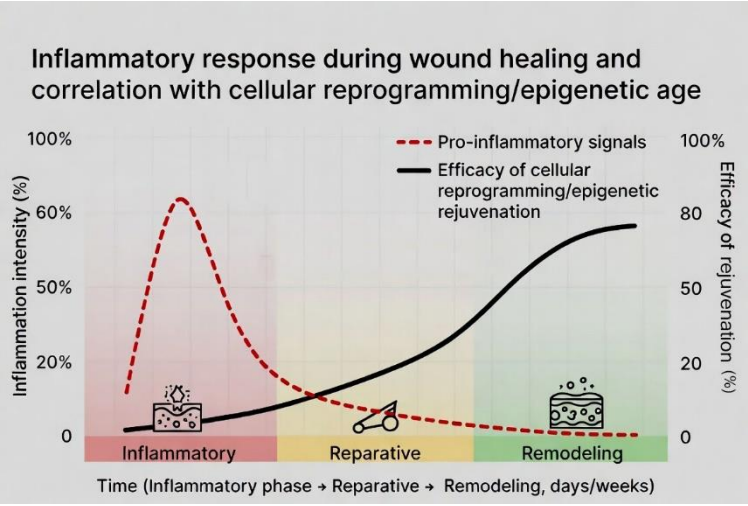

Fig. 2. Dynamics of inflammatory response and cellular reprogramming efficacy during wound healing

Restoring systemic homeostasis. By resetting the epigenome of key stromal and parenchymal cells throughout the body, the cycle returns organs to a state of **allostatic**

youth. This process is not merely about eliminating old cells but about restoring functional youthful identity to existing cells, thereby enabling them to respond adaptively to future metabolic or immune challenges [14].

Testable Predictions

The Inflammatory Restart Paradigm generates several testable predictions:

1. Predictability of inflammatory trajectories. The position of the cytokine rheostat measured as the ratio of opposing cytokines in tissue or circulation and the αKG/succinate ratio will predict whether acute inflammation resolves or becomes chronic, and will correlate with treatment outcomes.

2. Rheostat imbalance in chronic disease. Patients with chronic inflammatory diseases will exhibit rheostat imbalance (excess of pro-inflammatory relative to pro-resolving signals) compared to healthy controls, and successful therapy will restore balance in parallel with clinical improvement [20,21].

3. Genetic and epigenetic modulation of rheostat set points. Genetic polymorphisms in cytokine signalling pathways and epigenetic marks at cytokine gene loci will modulate individual rheostat set points, contributing to differential disease susceptibility and treatment response [7,10].

4. Partial reprogramming requires a pro-resolving state. The efficacy of partial epigenetic reprogramming in treating chronic inflammatory diseases will depend on the presence of a pro-resolving tissue state; reprogramming in a highly inflamed tissue may be ineffective or detrimental.

5. Reversal of mesenchymal drift. Successful Inflammatory Restart, whether achieved spontaneously or therapeutically, will reverse the age-related mesenchymal drift, restoring youthful gene expression profiles in affected tissues [22,24].

Essential mechanisms in the Inflammatory Restart Paradigm are shown in Table 1.

Table 1. Summary of key mechanisms in the Inflammatory Restart Paradigm

Mechanism	Phase	Key mediators	Functional consequence
Glycolytic switch	Phase 1	HIF-1α, succinate	Rapid effector function

Mechanism	Phase	Key mediators	Functional consequence
	(Clearance)		
Metabolic transition	Phase 2	αKG, OXPHOS	Epigenetic reprogramming
Neurotrophic signalling	Phase 3 (Regeneration)	BDNF	Tissue remodelling
Immune re-education	Phase 4	SPMs, Tregs	Silencing of inflammatory memory
MSC licensing	Phase 4	IFN-γ, TNF-α, IL-1β	Immunosuppressive phenotype
Epigenetic rejuvenation	Phase 4	OSK factors	Reversal of mesenchymal drift

Outstanding Questions

Several critical questions remain to be addressed by future research:

1. What are the optimal cytokine pairs defining the rheostat in different tissues and disease contexts, and how should their ratios be measured clinically?
2. Can the rheostat position be used as a predictive biomarker for treatment selection and response monitoring in chronic inflammatory diseases?
3. What are the molecular mechanisms that couple successful resolution to activation of endogenous reprogramming pathways, and can these be therapeutically enhanced?
4. What is the optimal timing, duration, and intensity of partial reprogramming to achieve epigenetic rejuvenation without risking dedifferentiation or malignant transformation?
5. Do all four phases of the Inflammatory Restart cycle occur in all tissues, or are there tissue-specific variations in the programme?
6. Can small molecules that mimic the effects of αKG (inhibiting succinate accumulation or activating αKG-dependent dioxygenases) promote resolution and epigenetic resetting?

Conclusion

The Inflammatory Restart paradigm redefines chronic inflammatory disease as an inability to complete a natural successful inflammation cycle, and it outlines new avenues designed to restore—rather than suppress—endogenous adaptive resolution capacity.

Search Strategy and Selection Criteria

References for this review were identified through searches of PubMed, Google Scholar, and Web of Science up to April 2026, using combinations of search terms including "inflammation resolution", "immunometabolism", "cytokine balance", "rheostat", "epigenetic reprogramming", "partial reprogramming", "Yamanaka factors", "mesenchymal stem cells", "MSC licensing", "trained immunity", "specialised pro-resolving mediators", "α-ketoglutarate", "succinate", and "chronic inflammatory disease". Additional references were identified from the bibliographies of selected articles and from the authors' personal collections. Only articles published in peer-reviewed journals in English were considered. The final reference list was prioritized to include recent reviews and landmark original articles that established key concepts in the field.

Data Sharing Statement

No data were generated or analyzed in this review. Data sharing is not applicable.

Declaration of Interests

The authors declare no competing interests.

Contributors

N.M. conceived the framework, conducted the literature review, and wrote the first draft. C.G. contributed to conceptual development, critical revision, and figure design. All authors approved the final version for submission.

Acknowledgements

The authors thank members of the research community whose foundational work in inflammation resolution, immunometabolism, and epigenetic reprogramming made this synthesis possible. No specific funding was received for this work.

Figures

Figure 1. The Inflammatory Restart Paradigm: Cytokine rheostat control of inflammatory trajectory.

(a) The four-phase inflammatory cycle. **Phase 1 (Clearance)** involves immune activation, pro-inflammatory mediator production, and glycolytic metabolism [5,13]. **Phase 2 (Metabolic Transition)** represents the critical switch from glycolysis to oxidative phosphorylation, governed by the cytokine rheostat and characterized by α-ketoglutarate (αKG) accumulation [4,6,9]. **Phase 3 (Regeneration)** involves neurotrophic factor-mediated tissue remodeling and restoration of homeostasis [11,12,14]. **Phase 4 (Epigenetic Resetting)** comprises immune re-education (epigenetic silencing of inflammatory memory), MSC activation (licensing and MSC2 polarization), and epigenetic rejuvenation (reversal of age-related epigenetic hallmarks including mesenchymal drift), leading to a renewed tissue state prepared for future challenges.

(b) Pathological state (rheostat imbalance). When the balance between opposing cytokine signals exceeds a critical threshold, the system becomes trapped in Phase 1, creating four interconnected self-sustaining nodes: failed resolution (↓ SPMs, persistent DAMPs) [1,2]; metabolic entrapment (sustained glycolysis, succinate accumulation, HIF-1α stabilization) [5,6]; pathological immune memory (trained immunity, fixed epigenetic marks) [7,18]; and stromal dysregulation (inflammatory fibroblasts, disrupted matrix) [8,19]. These nodes reinforce each other, forming a self-perpetuating circuit characteristic of chronic inflammatory diseases [3,17].

(c) Balanced state (rheostat within physiological-homeostatic range). Successful metabolic transition enables coordinated resolution and regeneration through four corresponding nodes: (1) restored resolution programmes (↑ SPMs, effective efferocytosis) [1,2]; (2) metabolic flexibility (balanced OXPHOS/glycolysis, αKG

accumulation) [9,10]; (3) immune memory reset (active epigenetic silencing of inflammatory loci, reinstatement of poised homeostatic state) [7,18]; and (4) mesenchymal rejuvenation (MSC activation, reversal of mesenchymal drift) [8,19,22]. This coordinated progression constitutes Inflammatory Restart—completion of an evolutionarily programmed cycle enabling tissues to emerge renewed rather than damaged [4,14,20].

Figure 2. The inflammatory response during wound healing and its effect on cell maturation and epigenetic age.

The physiological response to tissue damage follows a stereotyped temporal course that can be divided into inflammatory, reparative, and remodelling phases. Pro-inflammatory influences (red dashed line) are dominant in the initial inflammatory phase and diminish progressively thereafter. The efficacy of cellular reprogramming (solid black line) correlates positively with the intensity of resolution-phase signals, indicating that endogenous rejuvenation pathways are activated when appropriate pro-resolution cues are present. This temporal relationship suggests that successful Inflammatory Restart requires not merely reduction of inflammation but active engagement of resolution programmes that license epigenetic rejuvenation.

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