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REVIEW ARTICLE

Epigenetic memory in periodontal healing: mechanisms, evidence, and emerging therapeutic perspectives

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Abstract

Periodontitis is a chronic inflammatory disease characterized by progressive connective tissue and alveolar bone destruction, with recurrence frequently observed despite conventional therapy. Emerging evidence indicates that periodontal cells—including gingival fibroblasts, osteoblast progenitors, and immune cells—may acquire persistent epigenetic modifications that sustain an exaggerated inflammatory phenotype even after apparent clinical resolution. This narrative review summarizes recent evidence (2020–2025) regarding the role of epigenetic mechanisms in periodontal inflammation, wound healing, and regenerative responses, with emphasis on their biological relevance and emerging therapeutic implications. A focused narrative search of PubMed and Scopus was performed to identify representative English-language studies published between 2020 and 2025 using combinations of the terms 'periodontitis,' 'epigenetic regulation,' 'DNA methylation,' 'histone modification,' 'epigenetic memory,' and 'trained immunity.' Original experimental, molecular, translational, and selected review articles were screened based on title, abstract, and full-text relevance. Because this article was designed as a narrative review, the literature was synthesized interpretively rather than appraised systematically. Altered DNA methylation patterns in inflammatory gene promoters (e.g., IL6, TNFA) and histone modifications such as H3K27ac and H3K4me3 contribute to sustained pro-inflammatory signaling and impaired regenerative capacity. These epigenetic changes may lower the inflammatory response threshold and influence post-treatment tissue stability. Experimental evidence suggests that pharmacologic modulators (HDAC and DNMT inhibitors) and biologic agents (e.g., PRF, EMD, hyaluronic acid) may partially restore regenerative gene expression and improve cellular homeostasis. Epigenetic remodeling represents a plausible biological mechanism that may contribute to disease persistence and interindividual variability in healing outcomes. Improved understanding of epigenetic memory may help generate testable hypotheses for future host-modulation strategies and individualized periodontal care; however, current biomarker and therapeutic applications remain investigational.

Keywords Epigenetics · Periodontitis · DNA methylation · Histone modification · Gingival fibroblasts · Regeneration

Introduction

Periodontitis is a multifactorial disease characterized by irreversible destruction of the tooth-supporting tissues, initiated by microbial dysbiosis and sustained by an exaggerated host immune response. Disease progression cannot be explained solely by the direct effects of the bacterial biofilm, as persistent immune activation, incomplete resolution of inflammation, and disturbances in tissue homeostasis also play central roles [1]. Clinically, recurrence in some patients despite apparent inflammatory resolution after therapy has encouraged the exploration of biological models that extend beyond conventional concepts of periodontal pathogenesis. Within this context, epigenetic mechanisms have attracted increasing attention as a potential explanation for the persistence of inflammation-associated cellular alterations.

Epigenetic regulation controls gene expression without altering the DNA sequence and involves mechanisms such as DNA methylation, histone modifications, and RNA-mediated regulation [2]. Because these processes respond to

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environmental cues, microbial products, and inflammatory signals, prolonged immune activation in chronic periodontitis may induce persistent transcriptional reprogramming in host cells [3]. This reprogramming is not limited to immune cells but can also stably modify gene expression profiles in structural cells such as gingival fibroblasts, periodontal ligament cells, and osteoblast progenitors. Consequently, even after apparent clinical healing, these cells may retain features of an 'inflammatory memory.' This may contribute to exaggerated cytokine responses upon re-stimulation and may increase tissue vulnerability over time (Fig. 1).

Recent studies have suggested that alterations in DNA methylation profiles within periodontal tissues may contribute to sustained changes in the expression of immune response genes [4]. These epigenetic modifications are proposed to facilitate sustained inflammatory activity, particularly along the interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and nuclear factor kappa-B (NF-κB) axes, thereby compromising tissue stability even after therapy [5]. Furthermore, epigenetic alterations associated with mitochondrial dysfunction have been reported to influence cellular energy metabolism, potentially modulating

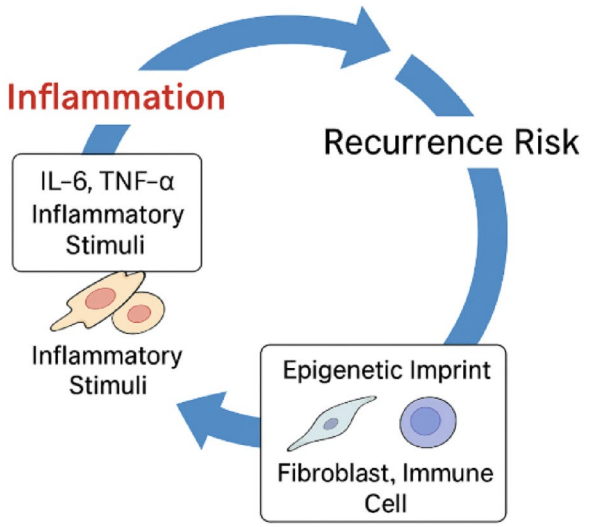

Fig. 1 The cycle of "epigenetic memory" in periodontal inflammation. Schematic and hypothesis-generating illustration summarizing literature-based concepts linking inflammation, epigenetic alterations, and potential post-treatment vulnerability in periodontal tissues. Persistent inflammatory stimuli (e.g., IL-6, TNF-α) may be associated with stable DNA methylation changes and histone modifications in fibroblasts and immune cells, potentially contributing to a sustained pro-inflammatory state. This figure is intended as a conceptual synthesis and should not be interpreted as a definitive causal pathway. Relevant evidence informing this conceptual model is summarized in representative studies on periodontal DNA methylation, persistent post-treatment methylation patterns, and fibroblast-associated inflammatory memory [14–16, 28]. IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha. .Created by the authors using Inkscape (open-source vector illustration software) for conceptual visualization

fibroblast and osteoblast activity during the healing phase [4]. Collectively, these findings suggest that epigenetic regulation may contribute both to the persistence of inflammation and to variation in regenerative responses.

Epigenetic mechanisms are also being increasingly investigated in the diagnosis and prognosis of periodontal diseases. DNA methylation signatures and histone modification patterns have been explored as potential biomarkers of disease activity and therapeutic responsiveness [6]. In this context, epigenetic research expands current biological understanding of pathogenesis, although its implications for personalized periodontal therapy remain investigational [7]. Integrating the epigenetic perspective into the understanding of the recurrent nature of periodontitis opens new avenues for research at both the basic science and clinical application levels.

This review aims to examine the evidence for persistent epigenetic marks in post-inflammatory periodontal tissues and to discuss how this form of 'biological memory' may influence host responses, tissue stability, and regenerative capacity. Accordingly, it considers periodontitis not only as an inflammatory disease but also as a condition in which persistent epigenetic alterations may contribute to long-term cellular responses.

Search strategy

Because this article was designed as a narrative review, the search strategy was intended to identify representative and mechanistically informative studies rather than to conduct a formal systematic review or meta-analysis. PubMed and Scopus were searched for English-language publications published between 2020 and 2025 using combinations of the terms 'periodontitis,' 'epigenetic regulation,' 'DNA methylation,' 'histone modification,' 'epigenetic memory,' and 'trained immunity.' The search was last updated on 1 February 2026. Original experimental, molecular, translational, and selected review articles were considered if they addressed periodontal inflammation, post-treatment tissue stability, wound healing, regeneration, or epigenetically relevant biomarkers. Records were screened according to title, abstract, and full-text relevance in order to construct an interpretive overview of the field. Because the aim of this review was hypothesis-generating and interpretive rather than systematic, no PRISMA flow diagram, formal study-counting procedure, or risk-of-bias assessment was performed.

The concept of epigenetic memory: "trained response" at the level of immunity and fibroblasts

The immune system has long been categorized into two distinct branches: innate and adaptive. However, recent evidence indicates that this traditional dichotomy is not absolute, as innate immune cells are also capable of developing a lasting "learning capacity" in response to previous stimuli. Monocytes, macrophages, and natural killer cells, upon pathogen exposure, undergo metabolic and epigenetic reprogramming, enabling them to mount faster and stronger responses upon subsequent encounters. This process is termed "trained immunity," whereas the reduced responsiveness induced by excessive or prolonged stimulation—known as "tolerant immunity"—functions as a regulatory mechanism preventing pathological inflammation [8].

The hallmark of trained immunity is that this "learned" phenotype arises not through genetic mutation but via epigenetic remodeling. At the cellular level, this involves alterations in DNA methylation, histone modifications (particularly H3K4me3 and H3K27ac), and chromatin reorganization. These changes render promoter regions of specific genes persistently more open or closed. Once established in the nucleus, these epigenetic marks maintain inflammatory response genes in a "primed" state, allowing the cell to initiate a rapid transcriptional response upon renewed stimulation [9]. This reprogramming is not limited to genetic regulation but is also supported by metabolic reorientation. Trained cells exhibit increased activity in the mevalonate pathway, altered glycolysis–oxidative phosphorylation balance, and elevated reactive oxygen species production. These metabolic adaptations provide substrates for histone acetylation and methylation, thereby reinforcing epigenetic modifications. Thus, a bidirectional relationship arises between cellular energy metabolism and transcriptional regulation. This mechanism may explain why host cells in chronic inflammatory diseases such as periodontitis retain a long-lasting "proinflammatory memory" [10].

The periodontal microenvironment provides a prototypical model of this epigenetic learning process. Gingival tissues are constantly exposed to pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS), peptidoglycan, and bacterial DNA. These repetitive stimuli chronically activate signaling cascades involving Toll-like receptors (TLR2, TLR4) and NF-κB. Even after the acute phase subsides, chromatin regions governed by these pathways may remain "open," resulting in incomplete resolution of cellular activation. Under such conditions, gingival fibroblasts and epithelial cells may exhibit exaggerated cytokine responses even to relatively mild stimuli, potentially contributing to subclinical inflammatory persistence after therapy [11].

Periodontal fibroblasts are central to this process. Once considered merely structural cells, they are now recognized as active modulators of long-term immune regulation. In epigenetically reprogrammed fibroblasts, persistent activation of IL-6, TNF-α, and NF-κB pathways may sustain an inflammatory tone within the tissue microenvironment [11, 12]. This mechanism may underlie interindividual variability in post-treatment stability. While maintaining a "primed" defense state may confer short-term protection, it can ultimately compromise tissue homeostasis over time [13].

The clinical relevance of these mechanisms is supported by molecular analyses. Genome-wide DNA methylation studies of gingival tissues reveal pronounced hypomethylation in inflammation-associated gene regions, correlating with persistent gene activation [14]. Similarly, methylation differences identified in cyclooxygenase-2 (COX-2), interferon-gamma (IFN-γ), and TNF-α genes may influence not only local tissue destruction but also systemic inflammatory activity [15]. These findings indicate that periodontal inflammation is shaped not merely by microbial burden but also by the epigenetic background of host cells.

Epigenetic reprogramming is not limited to the periodontium. In chronic inflammatory tissues such as periapical granulomas, overexpression of DNA methyltransferase (DNMT1, DNMT3A) and ten-eleven translocation hydroxymethylase (TET1) genes has revealed that epigenetic activity operates similarly across oral tissues [16]. This suggests that oral tissues develop a shared "epigenetic defense memory" in response to chronic inflammation. The concept of epigenetic memory adds an important mechanistic dimension to current models of periodontitis. At the molecular level, the ability of cells to "remember" prior inflammatory events may accelerate immune responses and confer short-term defensive advantages. However, it may also delay inflammatory resolution and sustain tissue vulnerability. Taken together, the available data suggest that periodontitis may involve not only microbial dysbiosis but also persistent epigenetic and immunologic reprogramming in immune and connective tissue cells. At present, these observations should be interpreted primarily as mechanistic and conceptual evidence, because their direct contribution to clinical recurrence has not yet been established.

Periodontitis and epigenetic reprogramming

Although periodontitis has traditionally been defined as a connective tissue destruction disease triggered by bacterial dysbiosis, recent studies have revealed the central role of

epigenetic remodeling in this process [17]. Gingival and periodontal ligament cells, following repeated exposure to microbial products and host-derived inflammatory signals, can exhibit persistent epigenetic reprogramming of gene expression profiles without any alteration in genetic sequence [18]. This indicates that periodontitis represents not merely an infection but also a chronic inflammatory condition in which epigenetic regulatory mechanisms contribute to sustained host responses [19].

Biological significance of epigenetic alterations

Epigenetic mechanisms — DNA methylation, histone modifications, and chromatin remodeling — regulate gene expression without altering the DNA sequence [20]. In the periodontal microenvironment, these regulatory systems induce persistent changes particularly in inflammatory genes such as IL-6, TNF-α, interleukin-17 (IL-17), and Toll-like receptors (TLR2, TLR4) [21]. DNA hypomethylation observed in gingival fibroblasts and immune cells has been associated with sustained activity of these genes and may contribute to incomplete resolution of the host response [22]. This process is not restricted to transcriptional regulation alone. Overexpression of DNA methyltransferase 1 and 3 A (DNMT1, DNMT3A) has been prominently detected in tissues of periodontitis patients [16, 23]. This suggests that DNA methylation acts as a "stabilizing" mechanism of cellular memory. The "primed" state of periodontal fibroblasts in response to environmental stimuli may explain why low-grade inflammation persists even after clinical healing [18].

Histone modifications and the persistence of chronic inflammation

Chemical modifications of histone proteins serve as key regulators determining whether genes remain transcriptionally active or silenced [19]. In periodontal diseases, stimuli such as lipopolysaccharide (LPS) and reactive oxygen species (ROS) disrupt the balance between histone acetyltransferase (HAT) and histone deacetylase (HDAC) enzymes, leading to persistent alterations in chromatin architecture [24]. In particular, elevated histone H3 lysine-27 acetylation (H3K27ac) facilitates transcription of IL-6 and IL-8 genes, perpetuating inflammatory activity [25]. These findings suggest that histone modifications are not merely passive byproducts but may act as active regulators contributing to the chronic nature of periodontitis. Clinically, this epigenetic "open chromatin" state may account for the incomplete shutdown of inflammatory responses following therapy. Experimental studies have shown that HDAC inhibitors can partially reverse this epigenetic persistence and promote the phenotypic normalization of fibroblasts [20].

Pro-inflammatory memory in fibroblasts

Gingival fibroblasts not only form the structural scaffold of periodontal tissue but may also retain features consistent with inflammation-associated cellular memory [21]. After repeated inflammatory stimulation, these cells develop stable epigenetic marks within IL-6, TNF-α, and NF-κB pathways [26]. As a result, even low-intensity bacterial signals can elicit exaggerated proinflammatory responses. This mechanism may explain interindividual differences in clinical stability after periodontal therapy [18]. Furthermore, systemic factors such as aging, oxidative stress, and hyperglycemia have been reported to alter histone acetylation patterns and lower the activation threshold of fibroblasts [24]. This epigenetic sensitivity may help explain the more severe and treatment-resistant course of periodontitis observed in diabetic patients [27].

Persistent marks in gingival and systemic cells

Epigenetic remodeling is not confined to local periodontal tissues. DNA hypomethylation and accumulation of histone H3 lysine-4 trimethylation (H3K4me3) have also been detected in peripheral monocytes and macrophage precursors [23]. The occurrence of these changes across various cell types is summarized in Table 1. Even after resolution of periodontitis, these cells may preserve their potential for inflammatory gene expression, contributing to sustained systemic inflammation. These findings suggest that the association between periodontal and systemic diseases—such as cardiovascular and metabolic disorders—may be mediated not only by cytokine dissemination but also by shared epigenetic reprogramming mechanisms [19].

Clinical implications and future perspectives

The persistence of epigenetic marks has been proposed as one of the molecular mechanisms that may contribute to post-treatment inflammatory persistence in periodontitis. DNA methylation profiles, histone modification patterns, and chromatin accessibility maps are being explored as potential biomarkers for monitoring disease activity and estimating interindividual treatment responses [17]. Findings from clinical studies utilizing these biomarker-based approaches are summarized in Table 2.

The potential reversibility of epigenetic mechanisms also supports further therapeutic investigation. Agents such as HDAC inhibitors, BET protein modulators, and DNA methyltransferase inhibitors have shown the capacity to modulate persistent inflammatory programs in fibroblasts and immune cells in experimental settings, with possible implications for tissue healing [17, 20, 27]. The experimental

Table 1 Epigenetic mechanisms in periodontitis and cellular memory

Author (Year)	Model/Cell Type	Epigenetic Target	Key Findings
Liu J et al. (2024) [28]	Human gingival fibroblasts	DNA methylation (IL-6 promoter)	Sustained inflammatory gene activation and trained fibroblast memory
Cao J et al. (2023) [25]	Periodontal ligament stem cells	H3K27ac/H3K4me3	HDAC inhibition enhances osteogenic differentiation
Ge W et al. (2023) [26]	Human PDLSCs	HDAC9	Regulates autophagy and TNF-α response under inflammatory stress
Rasperini G et al. (2025) [15]	Human gingival tissues (post-therapy)	COX-2, IFN-γ, TNF-α promoter methylation	Persistent methylation pattern after therapy
Ahmed M et al. (2025) [16]	Periapical granuloma tissue	DNMT1, DNMT3A, TET1	Aberrant methylation machinery linked to impaired healing
Larsson L et al. (2025) [3]	Gingival and peri-implant tissues	Global DNA/RNA methylation	Distinct methylation profiles between health and disease
Lagosz-Cwik KB et al. (2023) [8]	Human gingival fibroblasts	Global DNA methylation	Increased methylation sensitivity under chronic inflammation
Jurdziński KT et al. (2020) [1]	Experimental periodontitis model	Histone acetylation/methylation	Epigenetic modulation governs chronic inflammatory response

Representative studies on DNA methylation, histone modification, and inflammation-associated cellular memory in periodontitis

PDLSCs, periodontal ligament stem cells; IL-6, interleukin-6; HDAC9, histone deacetylase 9; TNF-α, tumor necrosis factor-alpha; COX-2, cyclooxygenase-2; IFN-γ, interferon-gamma; DNMT1, DNA methyltransferase 1; DNMT3A, DNA methyltransferase 3A; TET1, ten-eleven translocation methylcytosine dioxygenase 1; RNA, ribonucleic acid.

Table 2 Epigenetic modulation and regenerative pathways

Author (Year)	Model/Cell Type	Epigenetic Target	Key Findings
Iwata T et al. (2023) [22]	Bone marrow-derived MSCs and fibroblasts	HDAC1/2	Co-culture enhances osteogenesis through HDAC-dependent signaling
Hu M & Fan Z (2025) [19]	Dental mesenchymal stem cells	H3K9me3, H3K27me3	Histone methylation controls lineage commitment
Shi ZJ & Liu W (2025) [18]	Dental stem cells	Post-translational modifications	Epigenetic regulation drives osteogenic differentiation
Lu W et al. (2023) [20]	Adipose-derived stem cells	HDAC inhibition (MI192)	HDAC inhibitor promotes osteogenic gene expression
Quigley RM et al. (2024) [37]	Tissue engineering models	DNMT and HDAC inhibitors	Combined pharmacologic modulation enhances regeneration
Asa'ad F et al. (2020) [47]	Biomaterial–cell interactions	Epigenetic functionalization	Biomaterials influence cell differentiation via epigenetic cues
Pilloni A et al. (2025) [38]	Gingival fibroblasts	HA-mediated chromatin remodeling	Hyaluronic acid modulates epigenetic landscape during healing
Nieboga E et al. (2025) [31]	Gingival fibroblasts	OPG/RANKL regulatory network	Epigenetic regulation of osteoclastogenesis during repair

Representative studies on pharmacologic and biomaterial-based strategies that modulate epigenetic mechanisms during periodontal regeneration

MSCs, mesenchymal stem cells; HDAC, histone deacetylase; H3K9me3, histone H3 lysine-9 trimethylation; H3K27me3, histone H3 lysine-27 trimethylation; DNMT, DNA methyltransferase; HA, hyaluronic acid; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor kappa-B ligand.

effects of these epigenetic modulators on periodontal regeneration are presented in Table 3. Epigenetic reprogramming in periodontitis has been associated particularly with persistent alterations in inflammatory genes such as IL-6 and TLR2/4, whereas similar patterns reported along the TNF-α, IL-17, and NF-κB axes remain largely indirect or limited to in vitro evidence [28]. Importantly, the current literature is still dominated by mechanistic, in vitro, and preclinical studies, with limited direct clinical validation. Accordingly, epigenetic-based diagnostic and therapeutic approaches should currently be regarded as an emerging research direction in periodontal medicine rather than an established clinical framework [19]. Translational and systems biology studies integrating epigenetic regulation with immunological and systemic responses in periodontitis are summarized in Table 4.

Table 3 Translational and systems biology insights

Author (Year)	Model/Cell Type	Epigenetic Target	Key Findings
Men B et al. (2024) [5]	Human cohort (periodontitis–CVD)	Global DNA methylation	Shared epigenetic signatures link periodontitis to cardiovascular disease
Ding J et al. (2025) [21]	Macrophages/fibroblasts	Protein acylation/acetylation	Epigenetic acylation modulates inflammatory signaling
Liaw A et al. (2022) [2]	Review of oral tissues	Histone acetylation/methylation	Overview of histone modification and gene regulation
Hussain A et al. (2022) [32]	Dental stem cells	Global chromatin remodeling	Epigenetic networks coordinate differentiation and immune control
Almiñana-Pastor PJ et al. (2023) [48]	Gingival crevicular fluid	miRNA profile	Altered miRNA networks regulate inflammatory and regenerative genes
Tong T et al. (2025) [43]	hPDLSCs	lncRNA–miR-181a–SPP1 axis	Noncoding RNA network controls osteogenic regeneration

Representative studies linking epigenetic regulation with inflammatory, immunologic, and systemic responses in periodontal disease

CVD, cardiovascular disease; miRNA, microRNA; hPDLSCs, human periodontal ligament stem cells; lncRNA, long non-coding RNA; miR-181a, microRNA-181a; SPP1, secreted phosphoprotein 1

Table 4 Clinical and biomarker-oriented evidence

Author (Year)	Model/Cell Type	Epigenetic Target	Key Findings
Akdeniz T et al. (2023) [49]	Human saliva	miRNA-155	Elevated levels correlate with periodontal inflammation
Guzeldemir-Akcakanat E et al. (2023) [33]	Gingival tissues	miRNA network	Dysregulated miRNAs associated with tissue destruction
Han P et al. (2025) [40]	Human saliva	circRNA expression	circRNAs may serve as biomarkers for disease activity
Rasperini G et al. (2025) [15]	Human gingival tissue (post-therapy)	COX-2, TNF-α promoter methylation	Residual methylation marks influence healing outcomes
Almiñana-Pastor PJ et al. (2023) [48]	GCF samples	miRNA profile	miRNAs as potential diagnostic biomarkers for periodontitis
Ahmed M et al. (2025) [16]	Granulomatous tissue	DNMT1, TET1	Aberrant methylation pattern linked with poor regeneration

Representative clinical and biomarker-based findings related to the diagnostic and prognostic relevance of epigenetic regulation in periodontitis

miRNA, microRNA; circRNA, circular RNA; COX-2, cyclooxygenase-2; TNF-α, tumor necrosis factor-alpha; GCF, gingival crevicular fluid; DNMT1, DNA methyltransferase 1; TET1, ten-eleven translocation methylcytosine dioxygenase 1

Epigenetic signature of post-treatment tissue stability

The clinical resolution of inflammation following periodontal therapy does not necessarily indicate that the tissues have been completely "reset" at the molecular level. Recent multilayered epigenomic analyses have demonstrated that even after mechanical debridement or regenerative surgery, fibroblasts, cementoblasts, and osteoblast progenitors retain persistent epigenetic marks — "epigenetic scars" — that reflect the molecular memory of prior inflammation [29]. These marks induce lasting chromatin remodeling within the nucleus, lowering the threshold for response to environmental stimuli. Therefore, clinical healing observed on the surface does not always correspond to complete biological resolution.

Epigenetic remodeling is most prominently reflected in DNA methylation patterns. Persistent hypomethylation in the promoter regions of inflammatory signaling genes such as IL6, TNFA, and NF-κB has been associated with sustained cytokine expression even under low-grade inflammatory conditions [28]. These stable open chromatin configurations may represent a plausible molecular contributor to inflammatory persistence, although a direct causal link to clinical relapse has not been established. Conversely, hypermethylation observed in the promoter regions of osteogenic genes such as runt-related transcription factor 2 (RUNX2) suppresses bone formation, thereby limiting regenerative capacity [15]. Epigenetic modifications associated with mitochondrial stress also play a key role in this process. Decreased energy metabolism — particularly reduced acetyl-CoA levels — disrupts histone acetylation balance and decreases chromatin accessibility [30]. As a result, fibroblasts and cementoblasts exhibit suppression of regenerative gene expression and a reduced healing rate. Such mitochondria-associated epigenetic remodeling has been described as a state of prolonged "biochemical silence" in post-treatment tissues.

Gingival fibroblasts appear to play a central role in epigenetic remodeling after periodontitis. These cells may

retain inflammation-associated memory as a relatively stable form of functional reprogramming [3]. Even after therapy, open chromatin configurations have been reported in promoter regions regulating IL-6 and CXCL8 expression. These observations suggest that fibroblasts may retain features analogous to inflammatory memory, even after apparent clinical resolution. This phenomenon may be one of several mechanisms underlying why similar clinical protocols result in more stable healing in some individuals but persistent inflammatory vulnerability in others.

Comparable epigenetic persistence has also been observed in cementoblasts and osteoblast progenitors. Modifications such as histone H3 lysine-27 acetylation (H3K27ac) and H3 lysine-4 trimethylation (H3K4me3) form stable silencing islands in osteogenic gene promoters, restricting the regenerative response [31]. This epigenetic barrier is regarded as one of the key biological factors limiting the effectiveness of regenerative materials. Moreover, epigenetic silencing of the Wnt/β-catenin and bone morphogenetic protein (BMP) signaling pathways inhibits osteoblast differentiation and slows bone formation [32]. In diabetic or metabolically stressed individuals, these epigenetic marks appear more resistant. Elevated DNMT and HDAC activity in hyperglycemic environments suppresses the expression of healing-related genes while maintaining the open chromatin state of inflammatory genes [33]. This mechanism may contribute to the treatment-resistant and recurrent clinical course often observed in diabetic patients.

Cross-talk between macrophages and fibroblasts is also epigenetically reprogrammed. Post-translational modifications such as protein acylation stabilize the inflammatory tone of macrophages, while transforming growth factor-β1 (TGF-β1) and platelet-derived growth factor (PDGF) signals released from fibroblasts further reinforce this memory [21]. This bidirectional interaction delays inflammatory resolution and sustains subclinical activation. Even in the absence of overt external stimuli, prior inflammatory exposure may leave persistent transcriptional tendencies that resemble a form of molecular persistence rather than complete biologic reset.

Multi-omic studies have shown that these epigenetic marks are not confined to local tissues but correlate with systemic inflammatory biomarkers [34]. Hypomethylation profiles detected in peripheral blood monocytes resemble the epigenetic signatures found in periodontal fibroblasts, suggesting that local inflammation generates a systemic "epigenetic echo." This finding supports the hypothesis that the link between periodontitis and cardiometabolic diseases may involve not only cytokine circulation but also shared epigenetic reprogramming patterns. Recent advanced bioinformatic analyses have reported that the regression rate of epigenetic marks varies greatly among individuals and is more strongly influenced by environmental factors than by genetics [35]. Factors such as smoking, hypoxia, aging, and oxidative stress prolong the "closure" period of these marks by disrupting histone acetylation balance. Therefore, each individual's periodontal healing potential depends not only on genetic predisposition but also on the cumulative burden of environmental epigenetic stress.

Collectively, these findings suggest that post-treatment tissue stability may be influenced by each individual's epigenetic history. Even under identical treatment protocols, the degree of epigenetic memory within fibroblasts, cementoblasts, and immune cells may vary [36]. This supports the view that healing is a biologically heterogeneous process and justifies further investigation into whether epigenetic profiling may eventually assist more individualized treatment planning. Tissue stability may therefore depend not only on surgical success but also on the extent of cellular epigenetic reprogramming. In this context, the concept of the "epigenetic scar" may be viewed as a biological trace of prior inflammation that could influence the boundaries of future regenerative responses.

Epigenetic modulation potential in regenerative therapies

In recent years, periodontal regeneration has been discussed not only in terms of tissue formation but also in relation to molecular programs that regulate cellular behavior during healing. Accumulating evidence suggests that prior inflammatory exposure may leave durable epigenetic marks that influence fibroblast, immune-cell, and osteogenic responses, thereby affecting post-treatment tissue stability [37]. A schematic model summarizing a proposed transition from an inflammation-associated to a more regenerative fibroblast phenotype after periodontal therapy is presented in Fig. 2. Epigenetic modulation should therefore be regarded as an emerging conceptual framework rather than an established therapeutic principle. Pharmacological agents such as histone deacetylase inhibitors (HDACi) and DNA methyltransferase inhibitors (DNMTi), particularly when studied together with biological materials such as platelet-rich fibrin (PRF), enamel matrix derivative (EMD), and hyaluronic acid (HA), have shown experimental potential to influence regenerative processes at tissue, transcriptional, and epigenomic levels (Table 5).

Pharmacological epigenetic modulators

Pharmacological manipulation of epigenetic regulators has emerged as an experimental approach for modulating

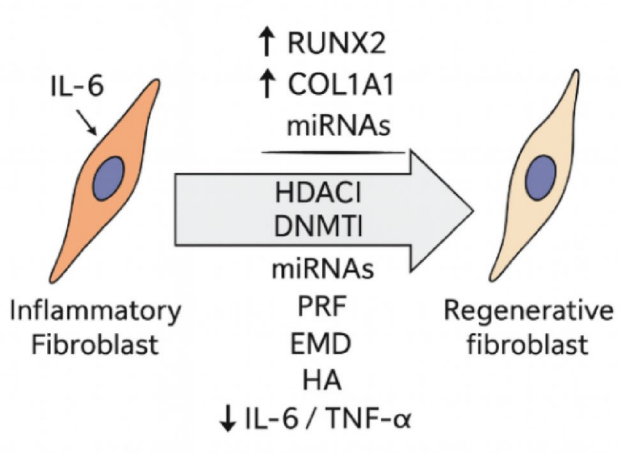

Fig. 2 Model of epigenetic reprogramming after periodontal therapy. Schematic and hypothesis-generating illustration summarizing a proposed transition from an inflammation-associated fibroblast phenotype toward a more regenerative phenotype after periodontal therapy. Epigenetic modulators, including histone deacetylase (HDAC) inhibitors, DNA methyltransferase (DNMT) inhibitors, microRNAs (miRNAs), and biologic agents such as platelet-rich fibrin (PRF), enamel matrix derivative (EMD), and hyaluronic acid (HA), have been investigated in experimental settings for their potential to influence chromatin structure, regenerative gene expression, and inflammatory signaling. This figure is intended as a conceptual synthesis and should not be interpreted as a validated therapeutic sequence. Representative experimental evidence informing this conceptual model is summarized in studies on HDAC/DNMT modulation and biologic agents such as PRF and EMD [20, 37, 44, 45]. HDAC, histone deacetylase; DNMT, DNA methyltransferase; miRNAs, microRNAs; PRF, platelet-rich fibrin; EMD, enamel matrix derivative; HA, hyaluronic acid. Credit: Created by the authors using Inkscape (open-source vector illustration software) for conceptual visualization.

inflammation-associated cellular memory and fibroblast behavior. HDACi prevent the removal of acetyl groups from histone tails, leading to chromatin relaxation and enhanced gene transcription. Well-known examples such as trichostatin A (TSA) and vorinostat reduce IL-6 and TNF-α production in periodontal fibroblasts while enhancing the activation of osteogenic genes such as RUNX2 and collagen type I (COL1A1) [38]. This shift in epigenetic balance may support a transition of fibroblasts toward a less inflammatory and potentially more regenerative phenotype.

DNMTi remove methyl groups accumulated on CpG islands of DNA, reactivating previously "silenced" gene regions. In particular, treatment with 5-azacytidine has been shown to reopen BMP and Wnt/β-catenin signaling pathways, enhancing osteogenic potential [2]. This reactivation supports the early differentiation of osteoblast progenitors during the initial phase of periodontal regeneration. The impact of epigenetic inhibitors extends beyond gene expression and also affects cellular energy metabolism. HDAC inhibition increases the accumulation of acetyl-CoA, sustaining histone acetylation and stabilizing open chromatin architecture [39]. Consequently, fibroblasts may maintain matrix synthesis activity over a more prolonged period under experimental conditions.

Furthermore, pharmacological epigenetic modulators have been shown to reverse "chromatin stiffening" associated with aging. Administration of DNMTi and HDACi reduces the accumulation of ROS, activates DNA repair genes, and balances the p53/p21 axis, thereby slowing cellular senescence [40]. This observation may be relevant for future translational investigation aimed at preserving regenerative capacity in elderly individuals.

Recent studies further suggest that these inhibitors may enhance the differentiation potential of dental-derived stem cells (DDSCs), supporting their experimental relevance in tissue engineering. When epigenetically reprogrammed, these cells acquire a "rejuvenated" phenotype and show enhanced osteogenic differentiation capacity [41]. Thus, pharmacological epigenetic modulation may represent an experimental strategy not only for influencing inflammatory

Table 5 Epigenetic modulators and their cellular mechanisms in periodontal regeneration

Modulator Type	Representative Agent(s)	Target Mechanism	Effect on Periodontal Cells	Reference
HDAC inhibitors	Trichostatin A, Vorinostat	Histone deacetylase blockade → ↑H3K27ac	↓ IL-6 and TNF-α expression, ↑ RUNX2 and COL1A1	Lu et al. (2023) [20]
DNMT inhibitors	5-Azacytidine, Decitabine	DNA demethylation (reversal of methylation)	↑ Osteogenic gene activation (RUNX2, BMP2)	Lai et al. (2024) [57]
BET protein modulators	JQ1	Gene expression control via histone acetylation	↓ Inflammatory activity in gingival fibroblasts	Maksylewicz et al. (2019) [27]
microRNAs	miR-146a, miR-155, miR-181a-5p	mRNA silencing/translational repression	↓ NF-κB and IL-1β activity, ↑ osteoclastogenesis balance	Tong et al. (2025) [43]
Biological agents (PRF, EMD, HA)	TGF-β1, PDGF, SMAD, miR-21	Indirect epigenetic activation (↑HAT activity)	Chromatin relaxation and ↑ collagen synthesis	Cores Ziskoven et al. (2025) [44]

Representative epigenetic modulators and their reported cellular effects in periodontal regeneration

HDAC, histone deacetylase; DNMT, DNA methyltransferase; BET, bromodomain and extra-terminal domain protein; PRF, platelet-rich fibrin; EMD, enamel matrix derivative; HA, hyaluronic acid; TGF-β1, transforming growth factor beta-1; PDGF, platelet-derived growth factor; SMAD, small mothers against decapentaplegic; miR-21, microRNA-21; H3K27ac, histone H3 lysine-27 acetylation; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; RUNX2, runt-related transcription factor 2; COL1A1, type I collagen alpha-1 chain; BMP2, bone morphogenetic protein-2; NF-κB, nuclear factor kappa-B; IL-1β, interleukin-1 beta; HAT, histone acetyltransferase

pathways but also for exploring aging-related regenerative decline.

Epigenetic effects of biological agents

Biological agents modulate epigenetic mechanisms indirectly through natural growth factors and extracellular matrix components. These materials may support tissue repair and may also influence how cells regulate gene expression, potentially contributing to longer-term biological reprogramming. TGF-β1 and PDGF within PRF enhance histone acetyltransferase (HAT) activity, facilitating chromatin relaxation in fibroblasts. Consequently, collagen synthesis, fibroblast proliferation, and angiogenesis may be enhanced [42]. Simultaneously, PRF suppresses DNA methyltransferase activity, thereby limiting the expression of inflammatory genes and stabilizing the NF-κB signaling pathway [35].

EMD reactivates the RUNX2 promoter in cementoblasts and osteoblast progenitors, prolonging the expression period of genes associated with bone formation. This effect is mediated by increased histone H3 lysine-27 acetylation (H3K27ac) and SMAD-dependent signaling activation [20]. HA modulates cellular stress responses at the epigenetic level. Specifically, it upregulates microRNA-21 (miR-21) and microRNA-146a (miR-146a) expression, leading to the silencing of IL-1β and TNF-α genes. This microRNA-based epigenetic regulation contributes to the long-term rebalancing of the inflammatory microenvironment [43, 44].

PRF and EMD, on the other hand, not only provide transient tissue repair but also promote wound healing by enhancing fibroblast migration and proliferation. PRF further upregulates genes such as VEGF and BMP-2, thereby stimulating connective tissue and bone regeneration. Through the modulation of cellular signaling pathways and gene regulatory networks, these biological agents may indirectly contribute to epigenetic remodeling and enhance long-term tissue stability [44, 45].

Combined strategies for epigenetic modulation in regenerative contexts

The integration of pharmacological and biological approaches has supported the emerging concept that epigenetic modulation may be relevant to regenerative therapies. The conceptual aim of this strategy is not only to restore tissue integrity but also to explore whether cellular phenotypes can be influenced at the epigenetic level. Epigenetic regulators such as HDACi and DNMTi have demonstrated the potential to modulate gene expression by altering chromatin architecture in various cellular models. HDACi have been shown to influence differentiation and proliferation in stem cells, whereas DNMTi modulate DNA methylation profiles, thereby affecting cell fate determination. When incorporated into biomaterials with controlled-release systems, these molecules may help modulate cellular behavior and regenerative responses [32, 46].

Advances in surface engineering and controlled drug delivery now allow pharmacological agents to be incorporated into biomaterial carriers with prolonged and spatially targeted effects. Consequently, these strategies may improve the ability to modulate both cellular processes and epigenetic mechanisms in tissue engineering applications [47]. Conceptually, epigenetic modulation in regenerative contexts views tissue repair as a process shaped by dynamic regulation of gene expression. In this model, regenerated tissues are not only morphologically restored but also develop within a microenvironment in which detrimental molecular imprints—such as those associated with chronic inflammation—may be reduced, thereby guiding cellular phenotypes toward more stable regenerative profiles [30].

In the future, combining epigenetic modulators with biomaterial carriers such as HA, PRF, and polymeric scaffolds may provide a basis for investigating localized epigenetic reprogramming strategies in preclinical and, ultimately, clinical settings. Such approaches may contribute not only to morphological restoration but also to more stable regulation of healing-related molecular pathways [37]. Therefore, epigenetic modulation in regenerative contexts should be considered an emerging conceptual framework that links tissue repair with molecular plasticity. At present, these approaches remain investigational and require rigorous validation, including safety profiling and clinically relevant outcome assessment, before routine clinical implementation can be considered [35].

Clinical and translational perspective: toward personalized periodontal therapy through "epigenetic profiling"

Epigenetic regulation has emerged as a potentially relevant host-related factor in both periodontal pathogenesis and variability in treatment response. In addition to genetic susceptibility, stable epigenetic imprints left by prior inflammatory exposure may influence disease course and healing dynamics [3]. This form of 'cellular memory' may alter gene expression in fibroblasts and immune cells, such that some cells retain a primed pro-inflammatory phenotype even after apparent clinical resolution. These observations support the hypothesis that epigenetic memory may contribute to persistent inflammatory vulnerability in periodontitis; however, its direct role in clinical recurrence remains unproven.

Conventional periodontal therapy primarily aims to reduce microbial burden, whereas epigenetic research

provides an additional framework for understanding host-cell memory and biologic variability in healing. Accordingly, epigenetic profiling may eventually contribute to more individualized treatment planning, although such applications remain investigational and are not part of routine periodontal care.

Diagnostic and prognostic value of epigenetic biomarkers

Beyond its association with bacterial biofilm, periodontitis may also involve an epigenetically reprogrammed inflammatory state. DNA-methylation patterns, microRNAs (miRNAs), and long non-coding RNAs (lncRNAs) are increasingly being investigated as candidate biomarkers of disease activity [19]. Persistent hypomethylation within the promoters of IL6, TNFA, TLR4, and NF-κB has been associated with a lower inflammatory-response threshold in periodontal fibroblasts, potentially sustaining subclinical inflammation after therapy. These 'open chromatin' configurations may represent one of the molecular features linked to inflammation-associated persistence, but they should not be interpreted as definitive evidence of epigenetic relapse.

Among epigenetic biomarkers, miRNAs are particularly promising due to their non-invasive detectability in saliva:

- **miR-146a-5p** has been proposed as a potential marker associated with periodontitis progression [48].
- **miR-155** levels are elevated in both periodontitis and plaque-induced gingivitis, limiting the repression of inflammatory genes [49].
- **miR-199a-5p** increases in early gingivitis, suggesting potential diagnostic relevance in the preclinical phase [50].
- The **miR-181a-5p/SPP1** axis modulates osteoclastic activity and may influence the rate of alveolar bone resorption [43].

Recent discoveries of lncRNA–miRNA interaction networks in fibroblasts and immune cells suggest that epigenetic regulation may operate at a broader systemic level [21]. These networks form "epigenetic hubs" that explain inter-individual differences in inflammatory thresholds. Moreover, multi-marker salivary panels have been investigated for their ability to reflect not only disease presence but also disease activity, and some reports suggest that they may complement traditional clinical parameters (CAL, PPD, BOP) in the detection of early activity [34].

Epigenetic risk profiling in treatment planning

Epigenetic profiling may have both diagnostic and prognostic relevance. IL6 promoter hypomethylation and miR-155 overexpression have been reported in association with residual inflammation and recurrent disease activity after treatment [19]. These observations suggest that biological heterogeneity among patients may influence treatment response. Proposed epigenetic risk models aim to integrate DNA-methylation signatures, histone-modification patterns, and miRNA/lncRNA-expression ratios into multilayered analytical frameworks that may help estimate inflammatory vulnerability and recurrence-related risk [51].

More recently, integrative approaches that combine molecular datasets with clinical parameters have been proposed to support more individualized treatment frameworks; however, these models remain investigational and are not yet suitable for routine clinical decision-making [52].

Epigenetic reprogramming as an experimental therapeutic concept

Epigenetic reprogramming has been proposed as a concept that extends regenerative thinking from morphological repair toward molecular remodeling. In experimental settings, epigenetic modulators, including BET-related and other chromatin-targeting approaches, have been investigated for their potential to modulate pro-inflammatory gene expression in periodontal cells [27, 53]. Owing to safety concerns, the clinical translation of these approaches requires careful evaluation of delivery strategy and tissue specificity [54]. In this approach, biological matrices such as PRF and HA serve as controlled-release platforms for epigenetic drugs. Biological matrices such as PRF may support fibroblast activity and wound-healing responses through bioactive signaling mechanisms relevant to tissue repair [55, 56].

Studies combining DNMTi with PRF formulations have reported enhanced collagen synthesis and osteogenic differentiation in fibroblasts, supporting the view that epigenetic regulators may influence tissue regeneration. More broadly, the role of DNA methylation in cell differentiation and tissue repair suggests that epigenetic modifications may shape longer-term cellular response patterns. Inhibition of DNMT activity alters the expression of osteogenic transcription factors, particularly RUNX2 and related osteogenic genes, thereby supporting osteogenic differentiation (e.g., the effects of DNA methylation on the osteogenic differentiation of mesenchymal stem cells have been well documented) [57].

Within this framework, epigenetics in regenerative therapy should be viewed as an experimental approach to modulating inflammation-related and healing-related

gene-expression programs rather than as an established clinical intervention. In this context, healing may be interpreted not only as wound closure but also as a biologically regulated cellular response. Current evidence suggests that DNMT inhibitors combined with biological constituents such as PRF may provide an experimental platform for exploring collagen synthesis and osteogenic differentiation [57, 58].

Ethical, clinical, and technical limitations

Epigenetic manipulation presents substantial ethical and technical challenges in its transition to clinical application. Tissue heterogeneity, sampling time, and cell subtype variations may result in divergent epigenetic signatures [21]. Moreover, environmental factors—particularly oxidative stress and tobacco exposure—can rapidly alter methylation patterns, thereby limiting the temporal reliability of these epigenetic markers [59]. Pharmacological epigenetic agents have also been reported to cause off-target transcriptional activation, potentially increasing the risk of tumorigenesis [60]. Hence, the boundary between *biological repair* and *biological manipulation* remains exceptionally delicate.

Before clinical implementation, combination strategies involving DNMT inhibitors and other epigenetic regulators should be evaluated comprehensively in multicenter preclinical studies to define long-term toxicity profiles, germline safety, and persistent epigenomic effects. Current evidence on the systemic impact and potential adverse effects of epigenetic modifications remains limited, and the field is still at an early investigative stage. Because some interventions may induce permanent epigenomic alterations, especially in germline cells through heritable "epigenetic memory" modifications, dedicated safety assessments beyond conventional genotoxicity assays will be required, including the development of an epigenotoxicity testing framework [61].

From a technical perspective, the high cost of comprehensive epigenomic and multi-omic analyses—such as methylome and miRNome profiling—remains a major limitation for widespread preclinical or clinical adoption. These techniques require high-throughput sequencing and complex bioinformatics pipelines, which increase laboratory and analytical expenses. However, technological advances such as lab-on-a-chip microfluidic platforms and AI-assisted epigenetic prediction algorithms offer promising improvements in data-processing efficiency, accelerating analysis workflows and potentially enhancing clinical accessibility. Machine learning and artificial intelligence are increasingly employed to identify molecular patterns and infer functional relationships from large-scale epigenomic datasets [62, 63].

Future outlook

The future of periodontal therapy may extend beyond microbial control to include closer consideration of host epigenetic responses. A better understanding of cellular memory may eventually help refine treatment planning and improve interpretation of interindividual variability in tissue stability and recurrence. However, integration of epigenetic profiling into routine clinical practice remains a future possibility that will require substantial validation, standardization, and safety assessment [3, 64].

Conclusions and future directions

Epigenetic memory suggests that periodontal tissue stability may depend not only on suppression of inflammation but also on longer-term changes in cellular regulatory states. After repeated inflammatory stimulation, gingival fibroblasts, periodontal ligament cells, and macrophages may acquire a form of molecular memory that results in lasting transcriptional remodeling and altered cytokine production, even after clinical resolution [1, 65]. This phenomenon may offer one biologically plausible explanation for why recurrence is observed in some individuals despite similar treatment protocols.

Post-treatment persistence of epigenetic scars—such as stable DNA methylation and histone-modification patterns—may contribute to tissue homeostasis and variation in healing responses. Hypomethylation of IL6, TNFA, and NF-κB promoters has been associated with increased fibroblast inflammatory propensity, whereas hypermethylation of osteogenic genes such as RUNX2 and BMP2 limits regenerative capacity [16, 28, 66]. This bidirectional regulation indicates that epigenetic control influences not only pathological progression but also the *quality of healing*.

Recent studies suggest that epigenetic reprogramming of fibroblasts and mesenchymal stem cells may influence tissue regeneration [6, 11, 67]. These findings suggest that research combining epigenetic regulators—such as DNMT or HDAC inhibitors—with PRF or biomaterial-based carrier systems is still in the early preclinical phase, and the clinical translatability of these strategies has yet to be experimentally validated [68, 69]. Future research should focus on single-cell epigenomic mapping and longitudinal methylation tracking to identify cell populations predisposed to recurrence [52, 70]. Such approaches could form the conceptual foundation of a "periodontal memory clock," a biological timeline in which aging, inflammation, and healing dynamics can be quantified through epigenetic signatures [66]. Additionally, AI-based "epigenetic dashboard" systems integrating DNA methylation, histone modification,

and miRNA profiles with clinical parameters may provide a conceptual framework for personalized periodontal treatment planning; however, these models have not yet undergone clinical validation [51, 62, 71]. It is increasingly being considered that treatment success may depend not only on infection control but also on the host cell's capacity for adaptive epigenetic regulation. This conceptual framework may contribute to expanding current host-modulation strategies by integrating epigenetic perspectives into periodontal research and clinical investigation [1, 16, 68].

This integrative perspective suggests that long-term periodontal health may depend not only on the reduction of pathogenic burden and suppression of inflammation but also on longer-term regulation of host-cell epigenetic memory. Healing should be regarded as an adaptive biological process in which prior inflammatory imprints may persist to varying degrees across individuals, potentially influencing regenerative performance and relapse susceptibility. From a translational perspective, future research should aim to identify reproducible epigenetic signatures associated with clinical outcomes and evaluate whether targeted host-modulatory strategies can safely enhance tissue stability.

Limitations and future perspectives

Despite integrating recent advances in molecular and translational aspects of epigenetic memory, several limitations should be acknowledged:

- **Model heterogeneity**: Most available data derive from animal or in-vitro fibroblast studies, which may not fully represent human clinical conditions.
- **Temporal variability**: Epigenetic markers such as DNA methylation and histone acetylation exhibit dynamic changes that are rarely tracked longitudinally.
- **Lack of standardized methodology**: Differences in sequencing platforms, normalization pipelines, and bioinformatic criteria hinder cross-study comparisons.
- **Clinical translation gap**: Pharmacologic or biomaterial-based epigenetic interventions (e.g., DNMT or HDAC inhibitors) remain at the preclinical stage and require validation in human models.

Future research should focus on single-cell epigenomic mapping, time-course methylation profiling, and integrative AI-based "epigenetic dashboards" to predict regenerative outcomes and personalize therapy.

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Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval Not applicable (narrative review).

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