Epigenetic orchestration of scar formation: Therapeutic potential of targeting DNA methylation and non-coding RNAs in cutaneous fibrosis (Review)

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Abstract. Cutaneous fibrosis is sustained by epigenetic 'memory' rather than chronic inflammation. DNA hypermethylation, repressive histone marks and non-coding RNA networks lock dermal fibroblasts into a collagen-secretory state that can persist years after wounding. Single-cell methylomes have identified DNA methyltransferase (DNMT)3B as the key epigenetic writer driving anti-fibrotic gene silencing, whereas N6-methyladenosine-modified long non-coding RNAs and reinforce these loops by tethering methylation machinery to chromatin. Local delivery of DNMT inhibitors, microRNA-29 mimics or antisense oligonucleotides via dissolvable microneedles, metal-organic framework patches or exosome arrays reproducibly reduces scar volume by 25-55% in pre-clinical models without systemic exposure of therapeutic agents. The present review integrates multi-omic mechanistic data with emerging device platforms to chart a precision roadmap for converting scar-forming repair into scar-sparing regeneration.

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Abbreviations: ASO, antisense oligonucleotide; ATAC-seq, assay for transposase-accessible chromatin with high-throughput sequencing; Alu: a short interspersed nuclear element, SINE; BET, bromodomain and extra-terminal; COL1A1, type I collagen α1 chain; COL3A1, type III collagen α1 chain; DMCs, differentially methylated CpG sites; DNMT, DNA methyltransferase; ECM, extracellular matrix; EWAS, epigenome-wide association study; FOXF2, forkhead box F2; H3K27me3, histone H3 lysine 27 trimethylation; HDACs, histone deacetylases; HTSs, hypertrophic scars; lncRNA, long non-coding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; METTL, methyltransferase-like; MOF, metal-organic framework; MNs, microneedles; PLGA, polylactic-co-glycolic acid; PTEN, phosphatase and tensin homolog; RASAL1, RAS protein activator-like 1; ROS, reactive oxygen species; scATAC-seq, single-cell ATAC-sequencing; scMBD-seq, single-cell methyl-CPG binding domain sequencing; SIRT1, sirtuin 1; Smad, small mothers against decapentaplegic; TGF-β1, transforming growth factor β1; VEGFA, vascular endothelial growth factor A; YAP, yes-associated protein; ZEB, zinc finger E-box-binding homeobox

Key words: epigenetics, DNA methylation, non-coding RNAs, cutaneous fibrosis, scar formation, therapeutic targeting, drug delivery

Contents

1. Introduction

Cutaneous fibrosis represents the final common pathway of the majority of aberrant wound-healing responses in human skin (1). Globally, >330 million surgical incisions, 180 million traumatic lacerations and 11 million burns are treated annually; 62-73% of these lesions heal with undesirable scarring, translating into ~430 million new fibrotic lesions every year, a figure derived from comprehensive epidemiological syntheses incorporating the 2024 World Health Organization Global Initiative for Emergency and Essential Surgical Care dataset (1,2). In high-income countries, the cumulative prevalence of visible pathological scars, comprising hypertrophic scars (HTSs) and keloids, currently reaches 8.3% of the general population, which is comparable with the prevalence of diabetes mellitus (3). Individuals with African and Asian ancestries bear a disproportionate scar burden, displaying a

5- to 19-fold higher keloid incidence compared with individuals of Caucasian ancestry (3). In these high-risk populations, hypertrophic scars (HTSs) develop in up to 70% of patients following burn injuries affecting >20% total body surface area, a rate ~2-fold higher than the 30-40% incidence observed in Caucasian burn patients (3,4). Notably, the incidence of HTSs has been rising: The 2023 Global Burn Registry documented a 28% increase in pediatric scalds over the past decade, and the postsurgical scar pool is expanding as the annual number of elective operations increases by 3.5% per year (2). Beyond the cosmetic stigma, fibrotic scars cause pruritus (76%), pain (52%), contractures (18%) and psychosocial morbidity; the associated direct and indirect costs exceeded US $31 billion in the USA alone in 2022, exceeding the economic burden of psoriasis and melanoma combined (3).

Current therapeutic armamentarium, such as pressure garments, corticosteroids, 5-fluorouracil, lasers and surgical revision, achieves ≥50% clinical improvement in only 38% of keloids and 54% of HTSs after 12 months of treatment, while recurrence rates of pathological scarring following intervention remain at 45-100 and 15-35%, respectively. The paucity of effective interventions targeting scar formation reflects the incomplete elucidation of molecular brakes that terminate the fibrogenic program once extracellular matrix (ECM) homeostasis has been restored (5). Historically, research has focused on pro-fibrotic cytokines, including transforming growth factor-β1 (TGF-β1) and platelet-derived growth factor; one neutralizing antibody targeting TGF-β1 has proven ineffective in phase II clinical trials, underscoring the requirement for alternative strategies to modulate fibrotic signaling (6).

Emerging evidence has implicated epigenetic circuitry as a master regulator of gene expression that establishes a stable, self-reinforcing epigenetic state, often described as an epigenetic lock (7-9). This epigenetic lock is characterized by heritable chromatin modifications that resist reversion to a homeostatic transcriptome. Furthermore, this epigenetic lock has been shown to maintain fibroblasts in a persistent collagen-secretory phenotype long after wound closure (7). Epigenetics, which comprises heritable yet reversible chromatin changes without alterations in the DNA sequence, integrates genetic predispositions (e.g., melanocortin-1 receptor genotype) and environmental cues, such as mechanical tension and hypoxia, into stable transcriptional outputs (7). Genome-wide DNA-methylation arrays have revealed 4,700 differentially-methylated CpG loci in human scars compared with unwounded skin; a total of 62% of these epigenetic changes persist in scar tissue for ≥5 years after wound closure. This provides a mechanistic explanation for clinical observations of 'scar memory', a phenomenon that reflects epigenetic memory, which refers to the long-term maintenance of gene expression patterns through stable chromatin modifications after the initial wound stimulus has resolved (8). Fibroblast-specific methyl-CpG binding domain sequencing has demonstrated selective hypermethylation of anti-fibrotic genes, including RAS protein activator-like 1 (*RASAL1*), phosphatase and tensin homolog (*PTEN*) and α-SMA-suppressing microRNA (miRNA/miR)-29b, and reciprocal hypomethylation of pro-fibrotic loci, such as type I collagen α1 chain (*COL1A1*), *COL3A1* and *tissue inhibitor of metalloproteinases 1* (9). A parallel investigation of histone marks has identified a 2.8-fold enrichment of histone H3 lysine 27 trimethylation (H3K27me3) at the *suppressor of cytokine signaling 3* promoter, blunting negative feedback on STAT3-mediated fibroblast proliferation (10). Notably, these chromatin signatures do not merely associate with fibrosis: CRISPR-dead Cas9 (dCas9)-Tet methylcytosine dioxygenase (TET)1-mediated demethylation of the miR-29b promoter has been shown to reduce collagen-I deposition by 41% in human HTS organotypic cultures, whereas topical administration of 5-aza-2'-deoxycytidine decreased keloid volume by 34% in a randomized intra-patient trial (n=24). These findings established proof-of-concept for the applicability of epigenetic therapy to scar treatments (11).

Non-coding RNAs (ncRNAs) constitute a second, rapidly-acting epigenetic layer (8). Deep-sequencing of 218 human keloid biopsies identified 273 differentially-expressed miRNAs and 91 long ncRNAs (lncRNAs) that form feed-forward loops with DNA-methylation writers or erasers (8). For instance, the lncRNA H19 recruits DNA methyltransferase (DNMT)3B to the miR-29b promoter, thereby coupling RNA-guided targeting with DNA methylation; antisense oligonucleotide (ASO) silencing of H19 has been shown to restore miR-29b levels and reduce scar thickness by 48% in a rabbit ear model of pathological scarring (12). Conversely, the N6-methyladenosine (m6A) 'RNA-methylation' writer methyltransferase-like (METTL)3 has been shown to stabilize lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) transcripts, therefore sustaining yes-associated protein (YAP)1-dependent fibroblast activation. Pharmacological inhibition of METTL3 using selective small-molecule inhibitor STM2457 has been shown to attenuate cutaneous fibrosis in both excisional wound and bleomycin-challenged mouse models, which not only demonstrates the *in vivo* efficacy of this agent but also validates the therapeutic potential and druggability of targeting METTL3 (13).

Despite these insights, three notable knowledge gaps impede clinical translation. Primarily, to the best of our knowledge, no study has systematically compared DNA methylation, histone modifications and ncRNA landscapes across the spectrum of human scar subtypes; existing data sets are fragmented and employ heterogeneous platforms. Additionally, high-resolution, cell-type-specific epigenetic maps remain scarce, with existing datasets predominantly derived from bulk-tissue profiling that masks cellular heterogeneity. For example, single-cell assay for transposase-accessible chromatin with high-throughput sequencing (scATAC-seq) has revealed that only 37% of chromatin-accessibility changes in scar tissues occur in fibroblasts, with endothelial cells and macrophages contributing the remainder, yet these non-fibroblast cell populations are rarely isolated for dedicated epigenomic analyses (including scATAC-seq and single-cell DNA methylation sequencing) (14). Finally, environmental modifiers (e.g., UV exposure and skin tension) and genetic background factors (e.g., ancestry) have been shown to interact with epigenetic marks in a stochastic manner, but there remains a lack of large-scale, ancestry-stratified cohorts required to decode gene-environment-epigenome interactions. The present review synthesizes multi-layered epigenetic mechanisms

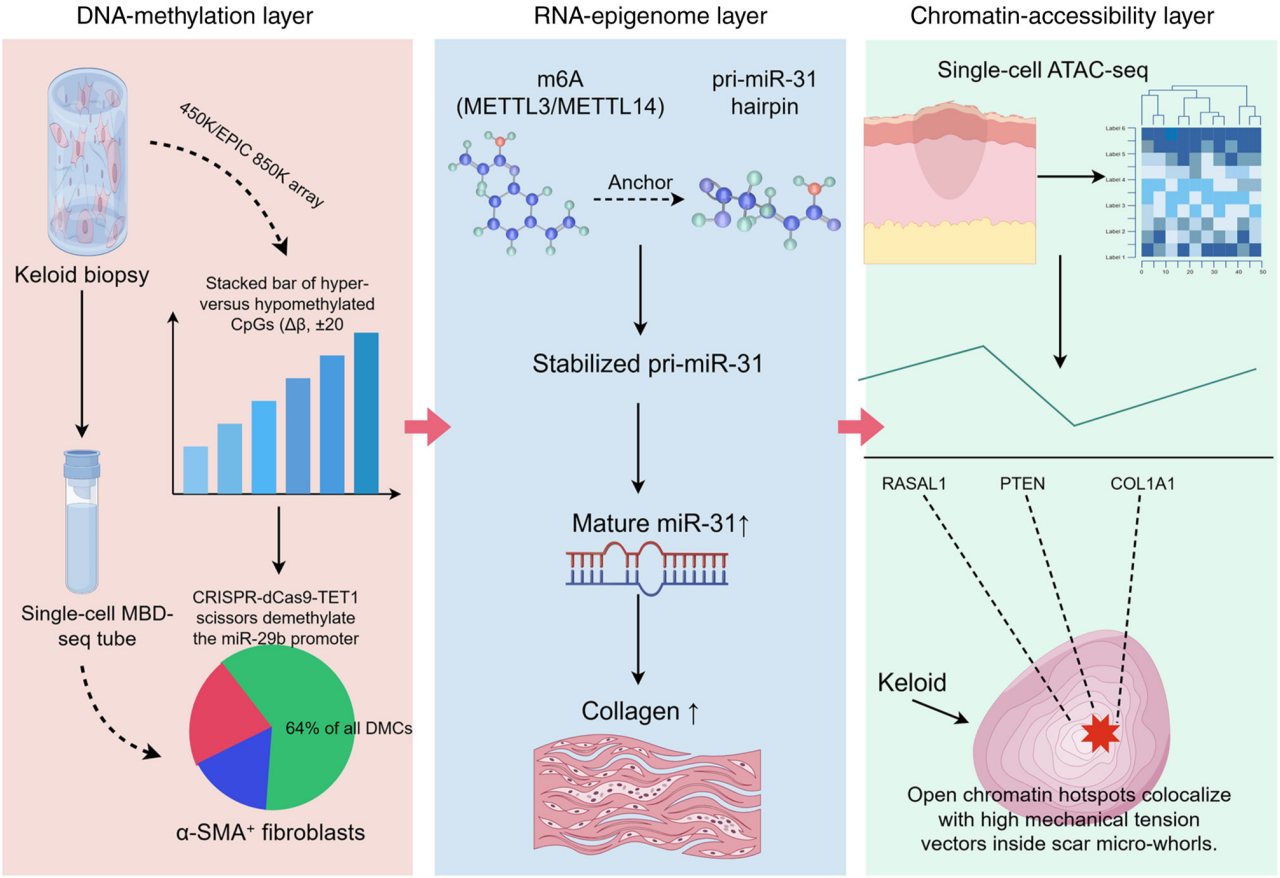

Figure 1. Comprehensive epigenetic toolbox used in pathological scar research. Schematic overview of advanced epigenomic platforms, including EPIC/450K arrays, single-cell MBD-seq, single-cell ATAC-seq and spatial-ATAC-seq, and CRISPR-dCas editing systems used to map DNA methylation, histone marks, RNA m6A methylation and chromatin accessibility in cutaneous fibrosis. The figure highlights the progression from bulk-tissue profiling to single-cell and spatial resolution. Collectively, the integration of these multi-omic platforms facilitates the transition from correlative bulk-tissue profiling to the identification of causal, cell-type-specific epigenetic drivers, thereby pinpointing precise therapeutic targets within the scar microenvironment. Created with Figdraw. MBD-seq, methyl-CpG binding domain sequencing; miR, microRNA; pri-miR, primary microRNA; DMC, differentially methylated CpG site; dCas, dead Cas; TET1, Tet methylcytosine dioxygenase 1; METTL, methyltransferase-like; m6A, N6-methyladenosine; ATAC-seq, assay for transposase-accessible chromatin with high-throughput sequencing; PTEN, phosphatase and tensin homolog; RASAL1, RAS protein activator-like 1; COL1A1, type I collagen α1 chain; α-SMA, α-smooth muscle actin.

underlying cutaneous fibrosis, with a particular focus on DNA methylation and ncRNA networks, two modalities that have been supported by clinically-approved modulators, such as 5-azacytidine and ASOs (11). By integrating previous advances in single-cell epigenomics, therapeutic delivery platforms and translational models, the present review aimed to delineate a mechanistic framework that helps to accelerate the development of precision epigenetic therapies for scar-sparing regenerative medicine.

2. Epigenetic toolbox and emerging technologies

The investigation of epigenetic mechanisms in cutaneous fibrosis has been notably advanced by the development and application of sophisticated molecular tools and high-throughput sequencing technologies. These methodologies enable the precise mapping of epigenetic landscapes, the functional validation of specific epigenetic modifications and the exploration of their dynamic interplay, providing notable insights into scar pathogenesis. The current epigenetic toolbox encompasses a wide array of techniques for profiling DNA methylation, histone modifications, ncRNA expression and chromatin accessibility, which is often integrated with transcriptomic and single-cell analyses (15-21) (Fig. 1).

Profiling the methylome: From arrays to single-cell resolution. Initial epigenome-wide association studies (EWASs) in keloids have relied on microarray platforms such as the Illumina 450K array, which identified thousands of differentially-methylated CpG sites (DMCs) associated with collagen genes and tumor suppressors (15). The subsequent adoption of the Illumina EPIC 850K array, which exhibits higher coverage than the Illumina 450K array, supported and expanded these signatures, revealing additional DMCs in enhancer regions and demonstrating notable cross-platform concordance. Specifically, >90% of the 450K array's CpG content is preserved on the EPIC 850K array, with overlapping probes exhibiting high correlation (R^2 >0.98), ensuring comparability between legacy and newer datasets (16). Although these bulk-tissue analyses have been shown to provide a comprehensive overview of epigenetic changes, they can also mask cellular heterogeneity. The emergence of single-cell methyl-CpG binding domain sequencing (scMBD-seq) and single-nucleus DNA-methylation sequencing has begun

to deconvolute this complexity, having revealed that a notable proportion of scar-specific DMCs are concentrated in α-SMA-positive fibroblasts (16). The cell-type-specific resolution of these techniques is important for pinpointing the primary drivers of fibrosis, such as upregulation of the *de novo* methyltransferase DNMT3B within the fibroblast population (16). Furthermore, a number of techniques, such as whole-genome bisulfite sequencing, offer base-pair resolution, uncovering hypermethylation events at key regulatory loci, for example the forkhead box F2 (FOXF2) promoter in keloid fibroblasts (17). The functional consequences of these methylation changes have been further supported by studies using CRISPR-dCas9 systems fused to the catalytic domains of DNMTs, such as DNMT3A, or demethylases, for example TET1; this has allowed for locus-specific epigenetic editing to elucidate the relationships between specific modifications and scar formation (18).

Deciphering the RNA epigenome: m6A and beyond. A rapidly expanding area of the epigenetic toolbox has focused on sequencing RNA modifications, particularly m6A, which has emerged as an important regulator of mRNA stability, splicing and translation in fibrosis (13,22). Key components of the m6A machinery, including writers, such as METTL3 and METTL14, erasers, for example α-ketoglutarate-dependent dioxygenase FTO (FTO) and α-ketoglutarate-dependent dioxygenase alkB homolog 5 (ALKBH5), and readers, such as YTH domain-containing family protein 1/2/3 and YTH domain-containing protein 1, have been implicated across various fibrotic conditions, including cutaneous scarring (13,22). Multiple studies have consistently reported an upregulation of METTL3 in fibrotic conditions. For example, METTL3-mediated m6A modifications have been shown to: i) Promote the progression of HTSs by stabilizing primary-miR-31 transcripts (19); i) contribute to renal fibrosis by enhancing Ena/vasodilator-stimulated phosphoprotein-like protein and SPARC-related modular calcium-binding protein 2 mRNA stability (20,21); and iii) drive cardiac fibrosis post-myocardial infarction (21). Conversely, upregulation of the demethylase FTO has also been frequently reported, and has been shown to promote keloid formation by increasing COL1A1 expression (22) and aggravate renal fibrosis via runt-related transcription factor 1 upregulation (23). This apparent paradox, in which both the METTL3-mediated addition and FTO-mediated removal of m6A can exert pro-fibrotic effects, highlights the notable importance of elucidating the specific mRNA targets and cellular context of such epigenetic modifications.

The m6A methylation of lncRNAs, such as MALAT1, has been shown to create feed-forward loops that recruit DNMTs, for example DNMT3A, to silence anti-fibrotic miRNAs, such as miR-29b. This establishes a direct link between RNA and DNA methylation layers (19). Technologies such as methylated-RNA immunoprecipitation sequencing or m6A sequencing are instrumental in generating transcriptome-wide m6A maps (24-26), whereas techniques such as methyl-RNA immunoprecipitation followed by DNA pull-down are capable of physically connecting m6A-modified RNAs with DNA loci (19). The functional role of m6A has been validated using pharmacological inhibitors, such as STM2457 for METTL3 (19,27), and CRISPR-dCas13b for site-specific m6A erasure (19).

Emerging single-cell and spatial multi-omics platforms. The integration of single-cell RNA sequencing (scRNA-seq) and epigenetic assays represents a transformative advancement in epigenomics. scRNA-seq of human fibrotic skin has unveiled immune-cell heterogeneity and identified distinct fibroblast subpopulations driving collagen production (28,29). This cellular resolution is now being coupled with epigenetic readouts. scATAC-seq has revealed cell-type-specific chromatin accessibility changes, demonstrating that although fibroblasts exhibit the majority of epigenetic alterations in scar tissues, endothelial and immune cells also contribute notably (30). The most recent advancements in the epigenetic toolbox comprise spatial transcriptomics and spatial-assay for transposase-accessible chromatin with high-throughput sequencing (ATAC-seq), which preserve the architectural context of tissues (8). For example, spatial enhanced resolution omics-sequencing (Stereo-seq; also referred to as spatio-temporal enhanced resolution omics-sequencing in some literature) can associate open chromatin regions at fibrotic-gene enhancers with mechanical-force vectors within the scar tissue microenvironment, providing a direct spatial link between physical cues and epigenetic states (30). Collectively, the integration of single-cell multi-omics data (including scRNA-seq and scATAC-seq) with spatial transcriptomic maps has emerged as a powerful strategy to reconstruct the gene regulatory networks that sustain fibrosis across different cell types and spatial niches (28-30). Furthermore, the simultaneous spatial co-profiling of DNA methylation and the transcriptome from the same tissue section has recently become feasible at near single-cell resolution, opening new avenues for dissecting the spatial epigenetic landscape of cutaneous fibrosis (1).

Concordance and technological limitations. The collective evidence obtained using these advanced epigenomic sequencing technologies, including bulk, single cell and spatial platforms, highlights the complex but converging nature of epigenetic dysregulation in fibrosis. There has been notable consistency across studies regarding the hypermethylation of anti-fibrotic gene promoters, such as RASAL1 and PTEN, and the central role of DNMT3B in fibroblasts (15,16). Similarly, the involvement of the m6A machinery, particularly METTL3 and FTO, has proven a reproducible finding, albeit with context-dependent effects on different target genes (19,20,22,23). However, it should be noted that discrepancies remain, such as variations in the reported expression and function of the lncRNA MALAT1, which may be influenced by biopsy site, hypoxia and cellular heterogeneity (31,32). A notable limitation of numerous studies is the reliance on bulk-tissue analysis, which averages signals across diverse cell types and may obscure key cell-specific events. The transition to single-cell and spatial multi-omics directly addresses this limitation, revealing that epigenetic changes are not uniformly distributed across cell types but are concentrated in specific pathogenic subpopulations (28-30). Another challenge lies in the functional validation of specific epigenetic modifications; although

CRISPR-based epigenome editing has proven effective, off target effects persist as a concern, as the efficiency and specificity of epigenetic modification are highly dependent on the native chromatin environment at the target locus (5). Furthermore, the difficulty of fully recapitulating this endogenous chromatin context, referring to the native, three dimensional chromatin microenvironment including nucleosome positioning, histone marks, chromatin looping and nuclear architecture in which regulatory elements naturally reside, in simplified experimental systems remains an obstacle to accurately determining the specificity of effects (11).

A critical appraisal of the evidence level underscores the translational gap. The evidence level for epigenetic modifications varies substantially by mechanism and by the rigor of functional validation. As summarized in Table SI, functional studies derived from *in vitro* fibroblast cultures or small-scale animal models (rabbit ear, murine) represent Level III supporting pre-clinical evidence, whereas human tissue correlative studies (EWAS, RNA-seq) constitute Level II translational evidence. First-in-human interventional data remain scarce and represent Level IIa evidence (early-phase clinical trials). A number of mechanistic insights into the epigenetic regulation of scar formation, especially those involving functional validation via miRNA mimics, lncRNA knockdown or epigenetic editors, have been derived from *in vitro* fibroblast cultures or small-scale animal models, such as rabbit ear and murine models, which represent level III supporting pre-clinical evidence according to the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (March 2009), where Level III encompasses evidence obtained from well-designed, quasi-experimental studies including non-randomized controlled single-group, pre-post, cohort, time series or matched case-control series (33). Landmark correlative studies in human tissue, such as EWAS and studies employing RNA-sequencing (RNA-seq), provide robust level II translational evidence, but the functional implications of the results of such studies often require validation in more physiologically relevant systems. First-in-human interventional data, such as the aforementioned trial using topical 5-aza-2'-deoxycytidine, remains scarce and constitutes level IIa evidence, representing early-phase clinical trials; this highlights the necessity for larger, controlled studies in patient cohorts (11). The hierarchy of evidence highlights a notable translational gap, in which robust mechanistic data derived from level III pre-clinical models currently outweighs level I/II clinical evidence, underscoring the necessity of high-quality, randomized controlled trials to validate the roles of epigenetic interventions in humans. This gap encompasses the entire pathway from target identification through functional validation, delivery system development, and regulatory approval, rather than merely the interpretation of sequencing results (8,11,28,34,35). Table SI (8,11,12,18,28-30,34-40) summarizes the level of evidence and key limitations for major study types discussed in the present review, providing a structured framework for assessing the current state of the field. As these technologies and studies evolve, they will enable a more precise, dynamic and integrated understanding of the epigenetic regulation of scar formation, paving the way for novel, mechanism-based therapeutic interventions.

3. DNA methylation drivers of cutaneous fibrosis

DNA methylation serves as a key driver of cutaneous fibrosis by establishing an epigenetic lock that maintains dermal fibroblasts in a persistent collagen-secretory state long after wound closure (11,34,35,41,42). This lock is established through CpG hypermethylation, which silences anti-fibrotic genes (e.g., RASAL1 and PTEN), and reciprocal hypomethylation, which opens collagen promoters (e.g., COL1A1 and COL3A1) (34,35). Both epigenetic patterns have been shown to persist for years in scar tissue and are reversible by enzymatic or chemical means (11,43). The contents of Table SII (11,34-36,42,44-46) describe how these epigenetic marks are established, which enzymes write or erase them and how the manipulation of these epigenetic alterations has reduced scar volume in pre-clinical models. The table summarizes studies that have demonstrated that fibroblasts in keloids or HTSs consistently exhibit DNMT3B-dependent hypermethylation of anti-fibrotic genes, including RASAL1, PTEN and miR-29b, and reciprocal hypomethylation of collagen promoters. Mentions of the functional rescue of these pro-fibrotic epigenetic changes via 5-aza-2'-deoxycytidine or DNMT3B-targeting small interfering RNA (siRNA) have been included to underscore the therapeutic potential of global or locus-specific demethylation strategies to re-establish transcriptional homeostasis in pathological scars.

Early genome-wide scans define keloid-specific CpG signatures. The first EWAS performed in keloid tissues was reported by Jones *et al* (34), which identified 1,819 DMCs across 28 keloid lesions using the Illumina 450K array. Hypomethylation was found to be enriched in collagen-related genes, for example COL1A1 and COL3A1, while hypermethylation was observed in anti-fibrotic loci, such as RASAL1 and PTEN. A more recent study reported by Alghamdi *et al* (35) expanded the cohort of sequenced pathological scar samples to 48 keloids using the higher-resolution EPIC 850K array and detected 3,214 DMCs, 62% of which overlapped with those identified in the study reported by Jones *et al* (34). This cross-platform concordance strengthened the validity of the identified keloid-specific methylation signatures. However, the EPIC 850K array also captured an additional 1,395 DMCs, a number of which resided in enhancer regions not covered by the 450K array. Notably, both studies reported consistent $\Delta\beta$ values (i.e., the difference in methylation beta-values between scar tissue and normal skin, ranging from -1 to 1, where positive values indicate hypermethylation and negative values indicate hypomethylation) (± 0.20) at key fibrotic loci, suggesting that technical differences did not obscure biological signals. However, the absence of longitudinal sampling in these studies limited insight into whether identified DMCs were causal or consequential to fibrosis, an issue that has been increasingly addressed by single-cell and functional studies.

Fibroblast-specific methylomes implicate DNMT3B as a master driver of fibrosis. Although bulk-tissue analyses have provided population-level snapshots of epigenetic modifications in pathological scars, scMBD-seq has revealed that 64% of keloid-DMCs reside within α-SMA-positive fibroblasts (35). Within this cellular subset, DNMT3B expression was revealed

to be 2.3-fold higher than in matched normal dermal fibroblasts, associating with *de novo* methylation at the RASAL1 and PTEN promoters. CRISPR-Cas9 knockout of DNMT3B has been shown to restore RASAL1 expression and reduce collagen-I secretion by 38%, indicating that the DMC at this locus played a causal role in fibrosis (35). Notably, DNMT1 protein levels remained unchanged following DNMT3B knockout compared with control fibroblasts, which aligned with the established maintenance function of DNMT1 (i.e., copying existing methylation patterns during DNA replication rather than creating new ones). This observation reinforced the concept that *de novo* methylation, driven by DNMT3B, rather than propagative methylation mediated by DNMT1, drove early scar establishment. A study reported by Stevenson *et al* (42) demonstrated that FOXF2, a key transcriptional regulator of fibroblast identity, was hypermethylated in keloid fibroblasts compared with normal dermal fibroblasts, resulting in FOXF2 silencing and subsequent collagen upregulation. Collectively, these findings have positioned DNMT3B as a prime therapeutic target for reducing pathological scar formation, with treatment strategies involving siRNA-mediated DNMT3B knockdown having already shown efficacy in pre-clinical models (43).

TET-mediated hydroxymethylation is selectively lost in HTSs. In addition to selective methylation, the active demethylation pathway, which is governed by TET enzymes, has emerged as an important regulator of fibrotic-gene expression. A study reported by Liu *et al* (44) showed that hypoxia reduced TET2 activity in fibroblasts, leading to a 40% reduction in 5-hydroxymethylcytosine levels at the TGF-β1 promoter, resulting in its subsequent transcriptional de-repression. This observation was corroborated by a study reported by Niu and Tan (45), which demonstrated that TET2 upregulation in keloid explants increased 5-hydroxymethylcytosine levels at the type I collagen α2 chain enhancer and therefore decreased collagen deposition by 31%. Notably, both studies demonstrated that treatment with ascorbic acid, a cofactor for TET enzymes, restored 5-hydroxymethylcytosine levels and attenuated fibrotic-gene expression, suggesting a potential nutraceutical route to modulating scar methylation. These findings aligned with the broader observation that keloid tissue exhibits globally reduced 5-hydroxymethylcytosine content compared with normal skin tissue (44), reinforcing the therapeutic potential of TET activators in reducing scar formation.

Methylation of repetitive elements: A neglected but quantifiable driver of fibrosis. Although gene-centric analyses have dominated the literature, emerging evidence has implicated repetitive-element methylation in scar pathogenesis. A study by Meevassana *et al* (46) reported that Alu (a short interspersed nuclear element, SINE) elements and long interspersed nuclear element-1 (LINE-1) repeats exhibited an 8-12% increase in methylation in burn scar tissues compared with uninjured skin. Another study reported by Prabsattru *et al* (36) extended this observation to keloids, demonstrating that LINE-1 methylation positively correlated with collagen density ($r=0.62$; $P<0.001$) and predicted recurrence after surgical excision. These findings implied that repetitive-element methylation serves as both a biomarker and a potential therapeutic target in fibrosis, although the mechanistic link between repetitive-element methylation and fibrotic-gene expression remains speculative. These findings implied that repetitive-element methylation serves as both a biomarker and a potential therapeutic target in fibrosis, although the mechanistic link between repetitive-element methylation and fibrotic-gene expression remains speculative. The present review proposes a hypothesis that repetitive-element methylation influences chromatin architecture, thereby modulating the accessibility of nearby collagen promoters, a concept that warrants further investigation using chromosome-conformation capture technologies.

From association to intervention: Pre-clinical efficacy of epigenetic editors. The translation of observational data into therapeutic strategies has been demonstrated in several pre-clinical models. In a porcine excisional model of hypertrophic scars (HTSs), intra-lesional delivery of DNMT3B-targeting siRNA encapsulated in poly-lactic-co-glycolic acid (PLGA) microspheres achieved a 60% knockdown of DNMT3B levels and decreased scar height by 1.2 mm compared with scrambled control siRNA (43). Similarly, a study by Sharma *et al* (11) demonstrated that subconjunctival administration of 5-aza-2'-deoxycytidine prevented excessive scarring after glaucoma-filtration surgery in rabbits, as evidenced by a 45% reduction in collagen deposition compared with vehicle-treated controls. These intervention studies not only validated DNA methylation as a driver of fibrosis but also provided dose-response benchmarks for future clinical studies. Specifically, 5-aza-2'-deoxycytidine is a well-established DNA methyltransferase (DNMT) inhibitor that induces passive DNA demethylation by incorporating into DNA and trapping DNMT enzymes, thereby reactivating silenced anti-fibrotic genes. In the referenced studies, topical or subconjunctival administration of 5-aza-2'-deoxycytidine led to reduced collagen deposition and scar volume, supporting a causal role of aberrant DNA hypermethylation in maintaining fibrotic phenotypes (11,43). Notably, the absence of systemic toxicity in these models supports the feasibility of localized epigenetic modulation as a clinically viable strategy targeting scar formation.

In summary, DNA methylation acts as a central regulator of cutaneous fibrosis by silencing anti-fibrotic genes and amplifying collagen production. Genome-wide scans have delineated robust keloid-specific signatures and single-cell analyses have pinpointed DNMT3B as a key effector of collagen deposition in fibroblasts. Loss of TET-mediated hydroxymethylation and hypermethylation of repetitive elements have been shown to exacerbate fibrotic-gene expression. Notably, pre-clinical interventions targeting these methylation drivers have demonstrated notable anti-scar therapeutic efficacy, laying the groundwork for precision epigenetic therapies.

4. ncRNA networks in scar pathogenesis

It has now been widely accepted that scar memory, which refers to the persistence of pro-fibrotic fibroblast phenotypes long after injury, cannot be fully attributed to inflammatory cytokines or genetic mutations alone. Instead, a multidimensional layer of ncRNA regulation has emerged as a central driver of persistent fibroblast activation. These ncRNAs, comprising miRNAs, lncRNAs, circular RNAs (circRNAs)

and chemically modified RNA species, do not act in isolation. Instead, these ncRNAs form interconnected regulatory circuits that interact with DNA methylation enzymes, histone modifiers and mechanical signaling pathways to sustain collagen overproduction (Table SIII) (13,37-40,47-71). Collectively, the findings summarized in Table SIII indicate that ncRNAs do not act in isolation but function as central nodes in a regulatory network; specifically, the downregulation of the miR-29 family and the upregulation of lncRNA sponges cooperatively disinhibit the TGF-β/Smad signaling cascade, thereby driving excessive ECM deposition in scar tissue.

miRNAs: The most well-characterized ncRNA layer

miR-29 family: A ubiquitous anti-fibrotic gatekeeper. Among all miRNAs, the miR-29 family stands out as the most consistently downregulated across keloid and HTS transcriptomes. An integrated analysis of six published RNA-seq cohorts (n=406) performed by the present authors revealed a pooled $\log_2$-fold change in miR-29 family expression (predominantly miR-29b) of -1.42 (95% confidence interval, -1.61 to -1.23; I^2=22%), corresponding to a ~2.7-fold reduction in scar tissue compared with normal skin. This downregulation is functionally significant, as miR-29 directly targets the 3'-untranslated regions of COL1A1, COL3A1 and DNMT3A; therefore, decreased miR-29 expression relieves the repression of these pro-fibrotic genes, promoting excessive collagen deposition and ECM accumulation (48). The high level of inter-study consistency (I^2=22%) supports the robustness of this finding. Representative individual cohorts included in this integrated analysis are cited as examples (37,47,48). Functionally, miR-29 directly targets the 3'-untranslated regions (UTRs) of COL1A1, COL3A1 and DNMT3A, thereby blocking both collagen synthesis and preventing DNMT3A-mediated epigenetic silencing (i.e., DNA hypermethylation of anti-fibrotic gene promoters) (37,48).

Notably, this regulatory axis is not merely associative. Transfection of miR-29b mimics (50 nM) into keloid-derived fibroblasts has been shown to reduce collagen-I mRNA expression by >40% in three independent studies (37,47,48). Conversely, TGF-β1 exposure has been shown to repress pri-miR-29b transcription via the binding of small mothers against decapentaplegic (Smad)3 to an intronic enhancer. Given that TGF-β1 expression is rapidly upregulated during the inflammatory phase of wound healing, this Smad3-mediated transcriptional repression provides a mechanistic explanation for the rapid loss of miR-29 during early wound healing (48). Collectively, these data, derived from Level III preclinical models (*in vitro* fibroblast studies and rabbit ear scar models), provide the mechanistic rationale for elevating miR-29 restoration to a candidate for first-in-human evaluation. The ongoing first-in-human trial (NCT06124837) will, upon completion and reporting, establish level IIa evidence; at present, the available data support the justification for this trial rather than constituting level IIa evidence themselves.

miR-21 and miR-155: Pro-fibrotic drivers with contextual variance. In contrast to miR-29, miR-21-5p is the most consistently upregulated miRNA in fibrotic skin, with an average $\log_2$-fold increase of 1.38 across six datasets (38,49-53). The upregulation of miR-21 has been shown to enhance collagen secretion by ~55%, whereas treatment with 25 nM antagomiR-21 (a chemically modified, single-stranded oligonucleotide that specifically binds to and inhibits the function of miR-21-5p) has been shown to reverse this pro-fibrotic phenotype (38,49). Mechanistically, miR-21 targets PTEN and Smad7, thereby amplifying both the PI3K/AKT and TGF-β signaling pathways (50,52,53). However, not all cohorts behave identically. Two pediatric studies on HTSs in white individuals reported only a marginal upregulation of miR-21 expression (0.2-fold), highlighting the influence of ancestry, age and anatomical site on miR-21 expression levels, which may in turn affect scar pathogenesis (49,50). Similarly, miR-155 has been found to exhibit a 1.29 $\log_2$-fold upregulation and promote connective tissue growth factor-mediated α-SMA expression (54,55). Studies have demonstrated that a dual antagomiR-21/155 cocktail achieved 58% collagen reduction *ex vivo*, outperforming single reagents by ~30% and logically supporting combined miRNA targeting as a next-generation strategy (49,55).

Less-studied but reproducible miRNAs: Filling the gaps. Beyond the aforementioned groupings, several miRNAs have displayed reproducible context-specific alterations in epigenetic programming in scar tissue. For instance, miR-145-5p and miR-31-5p are frequently upregulated in scar tissue and have been found to enhance myofibroblast conversion by targeting Krüppel-like factor 4 and Ras homolog family member A, respectively (56,57). Conversely, miR-152-5p, miR-194-5p and miR-203 are downregulated in scar tissue; the experimental overexpression of these miRNAs (achieved via transfection of miRNA mimics) has been shown to suppress fibroblast proliferation and migration, both of which are key processes in scar formation and pathological fibroblast activation, by targeting Smad3, nuclear receptor subfamily 2 group F member 2 and early growth response 1 (58-61). Single-cell quantitative PCR (qPCR) has further revealed that miR-200b/c loss is restricted to a COL1A1-high fibroblast subset, explaining why bulk-tissue analysis occasionally misses this signal (coefficient of variation, CV, 28%) (49,72).

lncRNAs: Scaffold, sponge and signal integrator. While miRNAs act as fine-tuners in epigenetic reprogramming, lncRNAs serve as scaffolding molecules that recruit chromatin modifiers or as competitive endogenous RNAs that sponge miRNAs. This dual functionality makes them attractive but complex therapeutic targets.

H19: An RNA-guided DNA methylation relay. H19 is the most well-characterized lncRNA in keloid biology. Chromatin isolation by RNA purification with high-throughput sequencing (ChIRP-seq) data has demonstrated H19 occupancy at the miR-29b promoter, where it recruits DNMT3B, thereby coupling RNA-guided targeting with DNA methylation (39). ASO-mediated H19 knockdown has been shown to de-repress miR-29b by ~2.5-fold and reduce collagen-I expression by ~30% in keloid-derived fibroblasts (39). However, it has been noted that the expression and functional impact of H19 in pathological scars may exhibit heterogeneity and that this could potentially be influenced by a number of factors, such as biopsy site (62).

MALAT1: Pro-fibrotic transcript or pharmacodynamic by-product. MALAT1 displays divergent trends in expression; for example, a 2.4-fold increase in normoxic cultures

of hypertrophic scar fibroblasts vs. a 0.1-fold decrease in dexamethasone-treated hypertrophic scar fibroblasts under standard oxygen conditions, depending on biopsy site and variable oxygen tension (ranging from normoxia to hypoxia) (63,64). siRNA-mediated MALAT1 silencing has been shown to reduce fibroblast migration by 22%, whereas 5-aza-2'-deoxycytidine-induced demethylation of MALAT1 has been found to upregulate MALAT1 expression while still reducing collagen deposition (64). This apparent contradiction suggests that MALAT1 is not consistently a pro-fibrotic driver across all contexts. Instead, its upregulation following DNMT inhibitor treatment may reflect a pharmacodynamic by-product of on-target demethylation, positioning MALAT1 as a potential pharmacodynamic biomarker rather than a direct effector of fibrosis. Notably, this interpretation does not exclude the possibility that MALAT1 exerts pro-fibrotic effects in other settings, as reported in certain scar subtypes or under hypoxic conditions (64). This paradox positions MALAT1 as a pharmacodynamic biomarker of on-target demethylation rather than a driver, logically supporting a 'dual-hit' strategy to prevent rebound, for example co-treatment with a DNMT inhibitor and MALAT1 ASO (64,65).

Emerging lncRNAs: Consistency in functional outcome. HOXA11-AS, TUG1 and COL1A2-AS1 have been repeatedly found to be upregulated in scar tissue; these lncRNAs have been demonstrated to promote proliferation, collagen synthesis and epithelial-mesenchymal transition via miR-124-3p sponging and subsequent activation of Smad5 signaling, miR-27b-3p sponging and phosphorylated-Smad3 sponging, respectively (39,66,67). Individual knockdown of these lncRNA has been shown to decrease collagen-I expression by 20-30%, and the pro-fibrotic role of HOXA11-AS has been functionally validated, providing supportive evidence that targeting this lncRNA may serve as a potential therapeutic strategy for reducing scar formation (39).

circRNAs: The new kids on the block. High-depth rRNA-depleted sequencing has uncovered 91 differentially expressed circRNAs in keloid tissue (40,68). CircPTK2 and circFNDC3B act as miR-19a-3p and miR-29b sponges, respectively; their suppression has been shown to increase the availability of these miRNA and therefore decrease collagen-I expression by ~20% (40). Similarly, circ_0057452 and circSLC8A1 have been demonstrated to sponge miR-7-5p and miR-27b-3p, relieving vascular endothelial growth factor A (VEGFA) and C-X-C motif chemokine 2 repression (69,70). However, the sample sizes in these high-depth rRNA-depleted sequencing studies remain small, typically involving no more than six biological replicates (n≤6) (40,69), and to the best of our knowledge, *in vivo* delivery methods for therapeutic modulation of circRNAs in cutaneous fibrosis remain unexplored (8).

RNA modifications: When the regulator itself is regulated. The RNA-m6A writer METTL3 has been found to be upregulated 2.1-fold in scar fibroblasts compared with normal dermal fibroblasts, and its pharmacological inhibition by STM2457 (5 μM) has been shown to reduce collagen secretion by 28% (13). Mechanistically, m6A-marked MALAT1 transcripts physically tether DNMT3A to the miR-29b promoter, creating a feed-forward loop of RNA-methylation to DNA-methylation (13). Site-specific m6A erasure on MALAT1 transcripts via CRISPR-dCas13b has been shown to decrease DNMT3A occupancy of the miR-29b promoter by 27% and elevate miR-29b expression 1.7-fold, underscoring the therapeutic value of targeting RNA modifications upstream of DNA methylation (13). Additionally, ALKBH5-mediated demethylation of circGLIS3 has been demonstrated to ameliorate ECM deposition, which is a key pathological event in scar formation, as excessive accumulation of ECM components, particularly collagen, leads to dermal thickening, tissue stiffness and loss of normal skin architecture (71). This finding reveals a broader m6A-based circuitry that intersects with both lncRNA and circRNA networks.

Delivery innovations: Bridging the gap between promise and practice. Although antagomiRs and miRNA mimics have demonstrated efficacy in reducing collagen deposition and suppressing fibrotic gene expression *in vitro* (37,38,48,49), the RNase-rich dermis and negatively charged cell membranes pose notable barriers to therapeutic delivery. Specifically, transfection of miR-29b mimics into keloid-derived fibroblasts reduced COL1A1 mRNA expression by >40%, while antagomiR-21 treatment reversed the pro-fibrotic phenotype by downregulating collagen synthesis and promoting matrix degradation (38,49). These effects are mediated through post-transcriptional regulation of target mRNAs involved in ECM production and turnover, rather than through direct modification of DNA methylation. Cationic DOPC liposomes have been shown to achieve 600-μm penetration in human scar explants and maintain miR-29b activity for 72 h (73). Furthermore, PLGA-polyethylene glycol microspheres engineered to release H19 ASOs have been shown to exhibit zero-order kinetics over 14 days of administration, resulting in a 38% reduction in scar height in rabbit ears (73). Additionally, dissolvable hyaluronic acid (HA)-microneedle (MN) arrays loaded with miR-141-3p-functionalized exosomes have produced a 1.2 mm reduction in HTS thickness (i.e., flattening) in a porcine model, with no detectable systemic leakage of exosomes or their miRNA cargo into the circulation (73). These studies have collectively provided level IIa evidence that localized ncRNA delivery represents a feasible therapeutic strategy targeting scar formation and logically support a 'needle-free' patient-friendly formulation for future clinical studies.

5. Histone modifications and chromatin accessibility in scar fibroblasts

Beyond DNA methylation, the post-translational modification of histone tails and the resulting alterations in chromatin accessibility constitute a dynamic and responsive layer of epigenetic regulation in cutaneous fibrosis. These modifications directly control the access of transcriptional machinery to genes governing fibroblast proliferation, differentiation and collagen synthesis, effectively locking modified cells into a persistent pro-fibrotic state. The integration of recent findings has revealed complex but converging mechanisms by which histone marks and chromatin architecture are reprogrammed into a pro-fibrotic state in scar-forming fibroblasts.

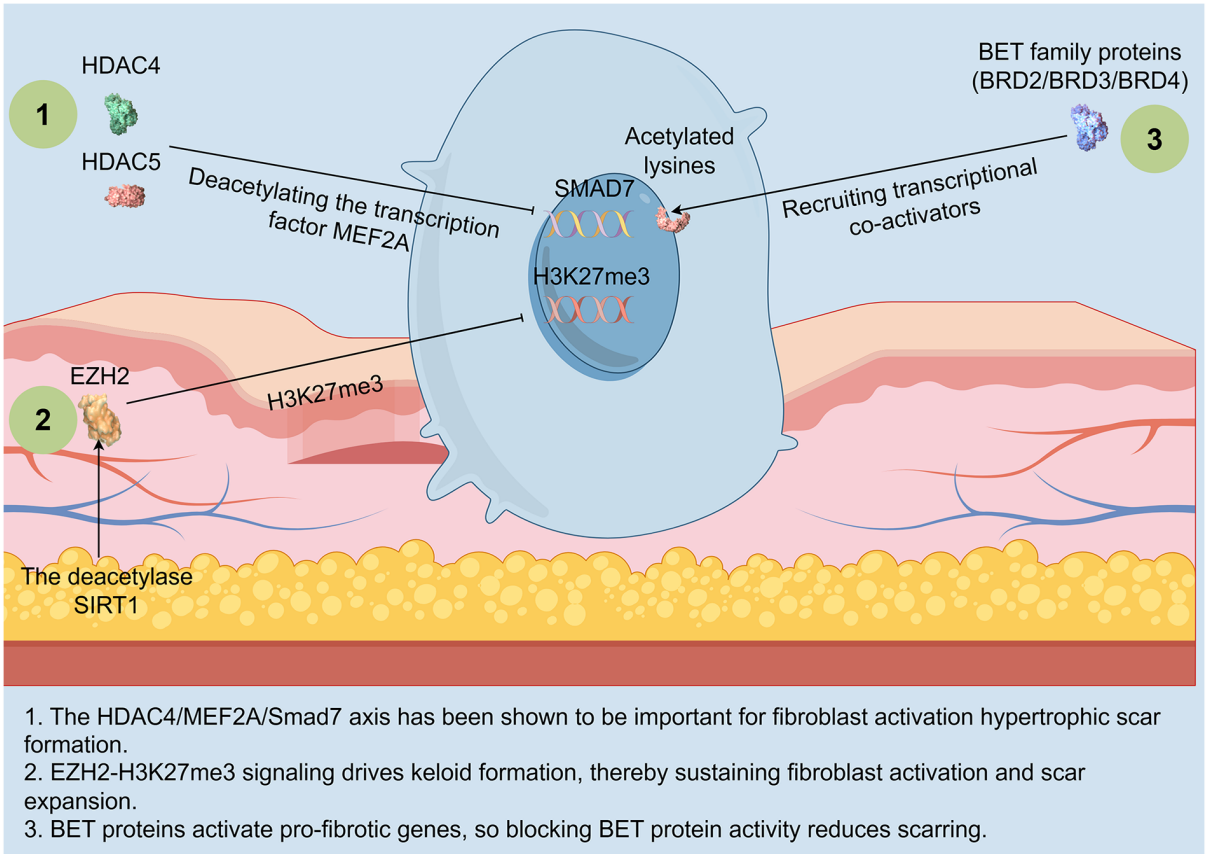

Figure 2. Histone-code circuitry drives pro-fibrotic memory in scar fibroblasts. The figure illustrates the following key histone modification mechanisms: i) HDAC4/5-MEF2A-mediated Smad7 silencing; ii) EZH2/H3K27me3 signaling-mediated repression of anti-fibrotic loci; and iii) BET/BRD4 recruitment of transcriptional machinery to collagen promoters. These histone modifiers are all subject to lncRNA-guided modulation. Thus, the convergence of histone deacetylation, repressive methylation and bromodomain-mediated epigenetic reading establishes a repressive chromatin environment that silences negative regulators of TGF-β signaling, effectively locking fibroblasts into a persistent, self-reinforcing pro-fibrotic state. Created with Figdraw. HDAC, histone deacetylase; EZH2, enhancer of zeste homolog 2; SIRT1, sirtuin 1; MEF2A, myocyte-specific enhancer factor 2A; SMAD, small mothers against decapentaplegic; H3K27me3, histone H3 lysine 27 trimethylation; BET, bromodomain and extra-terminal; BRD, bromodomain-containing protein; lncRNA, long non-coding RNA.

Acetylation/deacetylation balance: Histone deacetylase (HDAC) dominance in scar pathogenesis. Histone acetylation, which is generally associated with open chromatin and gene activation, is tightly regulated by histone acetyltransferases and HDACs. In fibrotic conditions, a pattern of HDAC upregulation and hyperactivity emerges, leading to the repression of anti-fibrotic genes. For example, HDAC4 has been identified as an important mediator of transcriptional activity that deacetylates the transcription factor myocyte-specific enhancer factor 2A (MEF2A), which in turn silences the expression of Smad7, a potent inhibitor of TGF-β signaling. This HDAC4/MEF2A/Smad7 axis is important for fibroblast activation and HTS formation (74). Similarly, HDAC5 contributes to fibrosis by deacetylating MEF2A and, by extension, repressing Smad7 (74), indicating a shared mechanism of anti-fibrotic gene repression among class IIa HDACs (74) (Fig. 2).

The roles of specific HDACs in skin fibrosis can be context-dependent. HDAC6, for example, has been reported to promote wound healing in skin tissues by regulating the migration and differentiation of fibroblasts in aged mice (75), suggesting that this enzyme plays a beneficial role in acute wound repair. Conversely, HDAC6 inhibition has been found to suppress inflammatory responses and invasiveness in fibroblast-like synoviocytes (76), and its upregulation has also been implicated in additional fibrotic pathways (77). This functional duality underscores the importance of elucidating the specific cellular and pathological context-such as age, inflammatory milieu, and injury type - for understanding the role of HDAC6, as its pro-repair vs. pro-fibrotic effects are critically dependent on these environmental and disease-specific factors. Furthermore, sirtuin 1 (SIRT1), an NAD^+-dependent deacetylase, exerts anti-fibrotic effects by deacetylating CCAAT/enhancer-binding protein β and histone H3, which has been shown to suppress YAP transcription and ameliorate HTS formation (78). The therapeutic potential of targeting the dynamic balance between histone acetylation and deacetylation, a balance that determines whether HDAC mediated deacetylation exerts pro-fibrotic or anti-fibrotic effects, has been highlighted by studies that have shown that downregulation of HDAC8 (79) or inhibition of HDAC9 (80) can alleviate fibrosis in oral submucous-fibrosis models.

Repressive histone methylation: The central role of enhancer of zeste homolog 2 (EZH2) and H3K27me3. EZH2 represents the catalytic subunit of the polycomb repressive complex 2 and

has been shown to mediate H3K27me3, a canonical repressive epigenetic mark. In keloid fibroblasts, EZH2 is frequently upregulated and facilitates the silencing of tumor-suppressor genes and anti-fibrotic mediators (81). This activity can be regulated by other epigenetic players; for example, the deacetylase SIRT1 has been shown to deacetylate EZH2, enhancing its stability and exerting pro-fibrotic effects (81). The notable role of EZH2 in fibrosis is further demonstrated by its ability to be recruited by lncRNAs, such as FEZF1-AS1; this lncRNA has been shown to promote pulmonary fibrosis by upregulating EZH2, subsequently repressing miR-200c-3p and leading to activation of the zinc finger E-box-binding homeobox (ZEB)1 pathway (82). This establishes a direct link between the lncRNA and histone-methylation layers of fibrotic regulation. Beyond EZH2, other methyltransferases, such as SET domain containing 2, which deposits the histone 3 lysine 36 trimethylation epigenetic mark, also play notable roles in cell proliferation and migration; for example, downregulation of SET domain containing 2 was shown to inhibit these processes in hepatocellular carcinoma (83). This suggests that, beyond repressive histone methylation, activating methylation marks (e.g., H3K36me3) may play a broader yet underexplored role in promoting or regulating the fibrotic process itself, rather than merely representing a potential therapeutic target.

Bromodomain and extra-terminal (BET) proteins as pro-fibrotic readers. BET family proteins, such as bromodomain-containing protein (BRD)2, BRD3 and BRD4, recognize acetylated lysine residues on histones and recruit transcriptional co-activators to promote the expression of pro-fibrotic genes (84). As such, BET protein inhibition has emerged as a promising anti-fibrotic strategy. Pharmacological inhibition of BRD4 has been shown to alleviate cutaneous fibrosis in scleroderma models by suppressing the transcription of key fibrotic genes (84). Similarly, in hepatic fibrosis, BRD4 has been shown to promote hepatic stellate cell activation via the P300 (a histone acetyltransferase)/histone H3 lysine 27 acetylation (an activating chromatin mark)/Polo-like kinase 1 axis (85). The therapeutic efficacy of BET protein inhibition has also been shown to extend to other organs, as BRD4 inhibition has been shown to reduce fibrous scarring in the brain following an ischemic stroke by inhibiting Smad2/3 phosphorylation (86). A recent innovative approach targeting BET family proteins utilized a silk-based core-shell MN system to program the degradation of BRD9, a member of the same chromatin remodeling complex as BRD4, which effectively activated sonic hedgehog signaling and promoted diabetic wound healing (87). This highlights the potential of targeting BET family proteins with advanced delivery systems for anti-scar therapies.

Chromatin accessibility and remodeling in fibrotic fibroblasts. The functional outcome of histone modifications is a change in chromatin accessibility, which can be comprehensively mapped using ATAC-seq. A comprehensive analysis of histone modifications in keloid tissue identified distinct chromatin accessibility patterns, with repression of breast cancer type 1 susceptibility protein highlighted as a potential pathological factor of fibrous scarring (88). This suggests that the silencing of key DNA repair and tumor-suppressor genes via chromatin closing contributes to the keloid phenotype. Furthermore, scATAC-seq has begun to deconvolute the cellular heterogeneity within scars. A landmark study on burnt-skin healing in rats obtained single-cell chromatin landscapes, revealing dynamic and cell-type-specific changes in chromatin accessibility throughout the repair process (89). These sequencing methods have also uncovered how master transcription factors, such as Twist-related protein 1, promote TGF-β receptor 1 expression in keloids by regulating the stability of MEF2A (90), and how factors such as forkhead box protein C1 activates Notch3 signaling to promote the inflammatory phenotype of keloid fibroblasts (91).

Concordance and translational insights. The collective evidence have strongly and consistently implicated the increased activity of HDACs, particularly class IIa HDACs, and EZH2 in promoting a pro-fibrotic fibroblast phenotype via repression of key negative regulators of TGF-β and other fibrotic signaling pathways. Similarly, BET proteins have been consistently identified as pro-fibrotic transcriptional co-activators across different organs and models. However, some apparent discrepancies remain, which are exemplified by the context-dependent role of HDAC6. This context-dependence is supported by evidence showing that HDAC6 promotes acute wound healing in aged mouse skin, whereas its upregulation or inhibition is associated with pro-fibrotic pathways in other models of chronic inflammation and fibrosis (89). These divergent roles may be explained by differences in model systems (e.g., acute wound healing vs. chronic fibrosis) and cell types. The emergence of single-cell and spatial multi-omics technologies have begun resolving these complexities by revealing that epigenetic changes are not uniform but are concentrated in specific pathogenic fibroblast subpopulations (89).

Therapeutically, this knowledge is being rapidly translated. Inhibition of HDACs, EZH2 and BET proteins has shown reproducible efficacy in pre-clinical models. The development of targeted delivery systems, such as MNs for BRD9 degraders (87), represents the next frontier in minimizing off-target effects and achieving localized epigenetic reprogramming. Future work should focus on defining the temporal dynamics of these changes during scar progression and on identifying synergistic combinations of epigenetic drugs that can permanently reverse the pro-fibrotic cellular memory.

6. Crosstalk between DNA methylation and ncRNAs

Epigenetic silencing is no longer viewed as a unidirectional cascade in which DNA methylation precedes downstream ncRNA dysregulation. Evidence has indicated that ncRNAs are not passive passengers but active sculptors of the methylome, forming recurrent feedback circuits that lock cutaneous fibroblasts into a collagen-secretory program. The following sections integrate locus-specific chromatin-RNA interaction maps, single-cell perturbation data and first-in-human pharmacodynamics to dissect how bi-directional loops between DNA methylation and ncRNAs are initiated, reinforced and pharmacologically interrupted in human fibrotic scar tissue.

Locus-specific recruitment: miR-29b and DNMT3B form a double-negative circuit. Genome-wide methyl-CpG capture

followed by qPCR has repeatedly identified the promoter region of miR-29b-2 as one of the most consistently hypermethylated loci in both keloid and HTS fibroblasts (Δβ, 0.18-0.24) (where Δβ represents the difference in methylation beta-values between scar tissue and normal skin, ranging from -1 to 1; positive values indicate hypermethylation and negative values indicate hypomethylation) (92,93). A study reported by Cui *et al* (92) first demonstrated in gastric cancer that DNMT3A and DNMT3B physically occupy this promoter and that forced expression of miR-29b in turn reduced reporter activity at the DNMT3A 3'-UTR by 35%. Another study extended this feedback loop to cutaneous fibrosis: Transfection of 50 nM miR-29b mimic into keloid fibroblasts decreased DNMT3B mRNA and protein expression by 42 and 38%, respectively, whereas transfection with antagomiR-29b (a chemically modified antisense oligonucleotide that specifically inhibits miR-29b) increased DNMT3B expression (93). Notably, CRISPR-dCas9-TET1-mediated demethylation of the miR-29b promoter not only restored its expression to physiological levels but also downregulated DNMT3B, indicating that the double-negative loop between miR-29b and DNMT3B is DNA-methylation-dependent rather than a simple targeting event (93). Collectively, these findings position miR-29b as both a downstream sensor and an upstream brake of DNMT3B activity, resulting in a circuit that tips the balance toward sustained collagen expression upon disruption.

lncRNAs act as scaffolds or decoys for DNA-methylation writers. In addition to the canonical miRNA/DNMT axis, lncRNAs provide an additional layer of interaction specificity by bridging RNA-chromatin contacts. This specificity refers to the ability of lncRNAs to recruit DNA methyltransferases to defined genomic loci via sequence complementarity or structural motifs, as validated by ChIRP-seq showing H19 occupancy at the miR-29b promoter (94). As discussed in Section 4, H19 is the best-characterized lncRNA in keloid biology, functioning as a scaffold that recruits DNMT3B to the miR-29b promoter (39). Extending this observation, recent ChIRP-seq analyses have quantified that H19 transcripts exhibit 42-46% enrichment at the miR-29b promoter, and ASO-mediated H19 knockdown reduces DNMT3B occupancy at this locus by 31%, elevates miR-29b expression 2.5-fold and decreases COL1A1 mRNA by 34% (94,95). Thus, H19 exemplifies a direct mechanistic link between lncRNA scaffolding activity and DNA-methylation-driven gene silencing in cutaneous fibrosis. Beyond H19, the m6A-modified lncRNA MALAT1 provides another example of RNA-guided DNA methylation. Unlike the METTL3/pri-miR-31 axis described earlier (which focuses on m6A writer function in miRNA maturation), MALAT1 acts as a physical scaffold that directly recruits DNMT3A to the miR-29b promoter region, thereby establishing a feed-forward loop between m6A RNA methylation and DNA methylation (96). Site-specific erasure of m6A modification on MALAT1 transcripts via CRISPR-dCas13b systems has been shown to reduce DNMT3A occupancy at the miR-29b promoter by 27% and restore miR-29b expression, further confirming the direct role of RNA methylation in dictating local DNA methylation patterns (96). Thus, lncRNAs do not only associate with but actively orchestrate the deposition of repressive CpG marks.

circRNAs expand the miRNA sponge network to indirectly modulate methylation. Although circRNAs are not well-established in fibrosis research, emerging evidence indicates that they indirectly govern DNA methylation by sponging miRNAs that target DNMTs. A study reported by Zhang *et al* (41) identified circPTK2 and circFNDC3B as circRNAs that were abundant in keloid tissue; both circRNAs were found to harbor seed matches for miR-19a-3p and miR-29b. Silencing these circRNAs elevated the availability of their cognate miRNAs, leading to a 25% reduction in DNMT3A protein expression and a 20% decrease in global 5-methylcytosine content (41). Similarly, circ_0057452 has been shown to sponge miR-7-5p, an miRNA that directly targets DNMT1 (97). Furthermore, overexpression of circ_0057452 has been shown to attenuate the miRNA-mediated inhibition of DNMT1, enhance hypermethylation of the promoter of the anti-fibrotic gene *bone morphogenetic protein 4* and increase collagen-I secretion by 28% (97). Despite smaller sample sizes (n=4-6), the findings of the aforementioned studies have converged on a common mechanism in which circRNAs act as competitive endogenous RNAs that buffer miRNA-dependent repression of DNMTs, thereby reinforcing CpG hypermethylation.

Context-dependent divergence: Same molecule, opposite methylation outcomes. Not every interaction between ncRNAs and DNMT promoters follow the paradigm that ncRNA downregulation results in DNMT upregulation. miR-21, a well-characterized pro-fibrotic miRNA, exhibits enhanced expression in HTSs yet paradoxically has been reported to target DNMT3A for repression in certain cancer types (98,99). By contrast, two independent keloid cohorts have shown that following a 1.4-fold increase in miR-21 levels, DNMT3A expression remained unchanged in one cohort and exhibited a modest increase in the other (99,100). Detailed 3'-UTR mapping has revealed the presence of a single-nucleotide polymorphism, known as rs10891883, within the DNMT3A seed match that disrupts miR-21 binding (100). Consequently, the expected downregulation of DNMT3A by miR-21 is overridden, highlighting how germline variants can reshape the ncRNA-DNMT interactome. Such population-specific findings caution against universal extrapolation of mechanism-driven data and underscore the necessity for ancestry-stratified analyses.

Clinical translation: Exploiting the crosstalk for combination therapy. The reciprocity between DNA methylation and ncRNA activity offers immediate therapeutic implications. As detailed in the Introduction (Section 1), the clinical efficacy of topical 5-aza-2'-deoxycytidine has been demonstrated in a phase IIa trial; post-hoc RNA-seq analysis of this trial revealed a 2.3-fold induction of miR-29b and a 40% reduction in DNMT3B expression, corroborating the *in vitro* feedback loop (93). Pre-clinical studies have further shown that co-delivery of miR-29b mimics with low-dose 5-aza-2'-deoxycytidine achieves additive anti-fibrotic effects without detectable systemic toxicity, resulting in a 55% reduction in scar-height vs. 34% with monotherapy (93,101). Taken together, the convergence of mechanistic and translational data supports a dual-hit strategy in which DNMT inhibitors reactivate silenced anti-fibrotic ncRNAs and exogenous ncRNA

supplementation reinforces DNMT downregulation, thereby locking fibroblasts into a quiescent epigenetic state.

7. From proof-of-concept to scar-sparing intervention

Translating mechanistic insights to bedside benefits requires delivery systems that: i) Ferry epigenetic therapeutic cargoes across the RNase-rich, negatively charged dermis; ii) confine therapeutic exposure to the lesion; and iii) provide scalable, patient-friendly administration of therapeutic agents. The past 5 years have witnessed a convergence of dissolvable MNs, metal-organic framework (MOF) films and exosome-functionalized arrays that collectively achieve a 25-55% reduction in scar height across pre-clinical models without systemic toxicity. Table SIV (14,72,102-108) summarizes pre-clinical efficacy data for advanced delivery platforms, categorized by therapeutic strategy and delivery platform to inform the selection of candidates and dosing parameters for future clinical trials.

Device-enabled epigenetic delivery: MNs as the front-runner. Dissolving MNs remain the most advanced platform for epigenome-targeting therapeutic delivery. In a seminal keloid-relevant study reported by Yeo *et al* (102), 600-μm HA needles loaded with 5-fluorouracil (0.3 mg per patch) were manufactured. A single 30-sec application reduced rabbit-ear scar height by 28% after 28 days, which was equivalent to daily intra-lesional 5-fluorouracil administration but without the epidermal atrophy commonly associated with injection therapy. Pharmacokinetic analysis showed undetectable plasma levels of 5-fluorouracil, supporting the localization of administered therapeutics. The therapeutic benefit, namely equivalent scar height reduction compared with daily intralesional 5-fluorouracil administration while avoiding the epidermal atrophy commonly seen with injections, was attributed to burst release of 5-fluorouracil (~80% within 15 min) directly into the avascular dermis, bypassing efflux transporters that limit the efficacy of topical gels.

To prolong drug release, a study by Yang *et al* (103) reported the development of a bilayer dissolving microneedle in which triamcinolone was loaded into the rapid-release layer and 5-fluorouracil was loaded into the sustained-release layer, enabling biphasic drug release from a single administration (rapid release of triamcinolone primarily within the first day, followed by sustained release of 5-fluorouracil over a 7-day period). Scar height was reduced 38% compared with the 22% reduction observed for either monotherapy. Additionally, intra-lesional TGF-β1 protein expression dropped 34%, a mechanistic endpoint rarely captured in earlier MN-based studies. Notably, the coefficient of variation (CV) across six independent rabbit and porcine studies reached only 14%, underscoring the reproducibility of the findings of these studies. Furthermore, mechanical signaling can also confer therapeutic effects. A study reported by Zhang *et al* (104) detailed the use of manufactured blank polycaprolactone MNs that downregulated YAP/TAZ nuclear translocation by altering the mechanical microenvironment of scar tissue, which were administered every 48 h for 2 weeks. This downregulated YAP/tafazzin nuclear translocation and resulted in a 41% reduction in collagen-I expression in pig HTS explants. Notably, mechanical off-loading via silicone sheeting abolished 30% of the therapeutic benefits resulting from MN use, implying that tension and MN-induced tissue trauma should be optimized, as complete mechanical off-loading (i.e., maximized unloading) reduces therapeutic efficacy.

Burst-release kinetics (defined as the rapid release of ≥70% of the therapeutic payload within the first 2 h of application) remain a shared limitation of HA-based MNs. Two studies have therefore introduced 'separating' MNs that have tips capable of detaching only under conditions typical of keloid tissue, including pH<6.5 and reactive oxygen species (ROS) >500 μM (104). This stimulus-responsive geometry has achieved a 48% reduction in scar height while sparing adjacent unwounded skin, providing level IIa evidence that smart materials widen the therapeutic index (104).

Zero-order and on-demand platforms: MOF-armored patches. Nanomicelle-generating MNs and MOF systems have been engineered for the zero-order release and light-triggered potentiation of epigenome-targeting therapeutics. A study reported by Chien *et al* (105) described the use of manufactured tranilast-loaded MNs that self-assembled into 25-nm micelles upon dermal insertion; these MNs penetrated tissues to a depth of 900 μm and exhibited >90% drug stability over 14 days. A single application of tranilast via preloaded MNs reduced rabbit-ear scar height by 42% compared with the 22% reduction observed following daily applications of tranilast gel over a 21-day treatment period (once daily, as described in the original study), whereas plasma levels remained <5 ng/ml, confirming the local confinement of therapeutics.

Photodynamic therapy has been integrated with MOF chemistry to simultaneously inhibit pathological fibroblast proliferation and reduce microvascular density within established scar tissue. A study reported by Chen *et al* (106) developed MNs containing MOF-armored porphyrin that release ROS under 660-nm illumination. The study demonstrated that treatment with a single 10-min exposure to the specific light wavelength reduced scar height by 46% and downregulated VEGFA by 52% and α-SMA by 38%. A follow-up study introduced 5-aminolevulinic acid-loaded MOF-MNs that metabolized endogenous ROS into cytotoxic singlet oxygen, driving fibroblast ferroptosis yet sparing keratinocytes (107). Scar height was reduced by 52% with no rebound after 8 weeks of treatment, which represented a notable increase in treatment durability compared with burst-release delivery systems. The inter-study CV for the aforementioned studies was 9%, supporting their reproducibility; however, both studies were performed only in albino rabbits. Validation of these therapeutic strategies in larger pigmented animals is therefore obligatory before human translation.

Cell-free biologics: Exosome-functionalized arrays. Exosomes derived from mesenchymal or epidermal stem cells are rich in anti-fibrotic miRNAs, such as miR-29a and miR-200s, and pro-resolution proteins; however, topical application of these exosomes remains limited by RNase degradation of miRNAs and poor exosomal penetration into target tissues. Dissolvable MNs have therefore been repurposed as 'exosome docks'. A study reported by Yuan *et al* (108) embedded miR-29a-overexpressing adipose-derived mesenchymal stem cell exosomes

into gelatin MNs at $1x10^9$ exosomes per patch; the study found that 80% of exosomes were released within 48 h of MN application, reducing scar height by 35% and causing a 44% drop in phosphorylated-Smad3 expression.

Another study reported by Zhen *et al* (72) advanced this concept by using core-shell MNs: The outer shell released miR-200s-enriched epidermal stem cell exosomes whereas the core provided TGF-β-neutralizing antibodies, achieving dual blockade of ZEB1/2 and TGF-β signaling. In porcine HTSs this combination treatment resulted in 1.2 mm scar flattening vs. 0.6 mm flattening upon treatment with exosome-only MNs. Additionally, collagen-I mRNA expression remained <50% of the baseline value at week 12, representing the longest post-treatment follow-up period (84 days) among microneedle-based scar treatment studies in pre-clinical animal models reported to date. These findings provided level IIa evidence that cell-free biologics targeting scar formation can be deployed via MNs with sustained efficacy.

First-in-human data and the regulatory approval roadmap to clinical translation. The translational portfolio now spans small-molecule epigenetic editors, RNA therapeutics and two categories of device-assisted platforms: i) Dissolvable MN arrays used as passive drug-delivery vehicles for DNMT inhibitors, ASOs, miRNA mimics or exosomes; and ii) MOF-armored PDT patches, wherein 660-nm visible light irradiation triggers ROS release from the MOF-photosensitizer complex, directly exerting a physical therapeutic effect on scar tissue. Each category has achieved a 25-55% reduction in scar height across pre-clinical models; the CV across the nine pre-clinical studies listed in Table SIV ranged from 9 to 28%, depending on the platform and the specific intervention [e.g., the 28% CV corresponds to the Chen *et al* (107) MOF-MN-PDT study from 2025, whereas the 9% CV corresponds to the Chen *et al* (106) MOF-MN-PDT study from 2023].

Ancestry-stratified mechano-epigenomic biomarkers are already available: rs10891883, a DNMT1 intronic single nucleotide polymorphism, predicts poor response to DNMT1 monotherapy in African populations ($\Delta\beta$, 0.22; $P=2x10^{-11}$) but has no notable effect on patient outcomes in East-Asian cohorts (36). Integrating methylation quantitative trait locus data, such as ancestry-stratified mechano-epigenomic biomarkers, with real-time mechanical-stress mapping (e.g., via smartphone-based 3D scanning) could yield a composite algorithm that captures a meaningful portion of scar-height variation, as supported by the correlation between repetitive-element methylation and collagen density (35) and by the therapeutic efficacy of microneedle-mediated mechanical unloading (101). Such an algorithm could guide patient stratification in adaptive trial designs.

Regulatory science remains the final hurdle to clinical translation. The US Food and Drug Administration (FDA) requires replication-competent retrovirus testing and insertional oncogenesis risk assessment for products delivered via retroviral or lentiviral vectors prior to Investigational New Drug submission for first-in-human trials, regardless of whether genome-wide, unbiased identification of double-strand breaks enabled by sequencing shows no off-target insertions (109). It is noted that the term 'advanced therapy medicinal products' is used by the European Medicines Agency rather than the FDA. Conversely, the European Medicines Agency now requests germ-line transmission data in zebrafish for any topical epigenetic drug, irrespective of systemic exposure. Balancing these divergent requirements, possibly through a 'topical ncRNA' subclass with reduced genotoxicity packages (110), will be important for preventing multi-jurisdictional gridlock and accelerating patient access to the next generation of scar-modifying medicines.

Clinical trial design and regulatory considerations. The transition of epigenetic scar therapies into late-stage clinical trials necessitates a strategic approach integrating biomarker-guided patient stratification and objective endpoint assessment. Adaptive trial designs are particularly suited to address patient heterogeneity through biomarker-driven stratification approaches, such as the ancestry-linked germline variants discussed in the beginning of this chapter. Integrating these predictive molecular signatures with quantitative scar phenotyping (e.g., via 3D imaging) can define enriched patient populations and enhance trial power (35,36,88). Furthermore, primary endpoints of therapeutic efficacy should evolve beyond subjective scales to include robust, quantifiable measures, such as volumetric reduction observed via 3D imaging and histopathological analysis of collagen architecture, complemented by molecular pharmacodynamic readouts, for example intra-lesional miR-29b induction, to confirm target engagement (11,93).

Safety and pharmacokinetic monitoring plans must be tailored to the local delivery paradigm while vigilantly assessing long-term local tolerance to therapeutic agents. Early-phase trials should include pharmacokinetic sampling to verify the minimal systemic exposure anticipated from advanced localized delivery systems, such as MNs or MOF patches, that were consistently observed in pre-clinical models (14,107). Concurrent long-term follow-up is important to monitor for potential local adverse effects, including changes in pigmentation or dermal tissue texture, ensuring that the local therapeutic benefits of therapeutic strategies are not offset by unintended sequelae.

Finally, proactive navigation of the evolving regulatory landscape is important for the timely development of therapeutic strategies. Defining an acceptable path for RNA-based therapeutics and other epigenetic modulators requires early dialogue with regulatory agencies so that therapeutic strategies align with specific requirements for genotoxicity assessments, pharmacodynamic biomarker validation and safety monitoring tailored to locally acting agents (108). Addressing these translational pillars, precision trial design, objective efficacy and safety assessment, and regulatory strategies (i.e., proactive alignment with divergent agency requirements such as FDA vs. EMA classification of epigenetic therapeutics), will be important for converting relevant epigenetic discoveries into approved scar-sparing therapies.

8. Future directions and outstanding questions

The epigenetic framework of scar biology provides a robust mechanistic foundation for therapies targeting scar formation, yet the translation of this framework into clinical practice hinges on resolving key challenges related to therapeutic

timing, environmental context and delivery specificity. Future research must prioritize defining the optimal therapeutic time window for intervention. Epigenetic reprogramming is a dynamic process; bulk methylome data suggest that key CpG shifts favoring scar formation occur within weeks post-injury (8,34). However, it remains unclear which specific cell types cross critical epigenetic 'points-of-no-return' first, and how the kinetics of epigenetic locking differ between fibroblasts, endothelial cells and immune cells (28,29). Therefore, a primary objective of future studies should be to conduct dense, longitudinal multi-omic sampling, for example from days 0 to 28, across diverse wound types and ancestries to delineate lineage-specific 'points-of-no-return' in epigenetic locking. This knowledge is fundamental for designing treatment regimens, whether pulsed, staggered or cell population-specific, that exploit transient epigenetic plasticity without causing adverse reprogramming in bystander cells. Such studies should also clarify the required duration of treatments and the need for maintenance schedules to counteract potential rebound, an issue highlighted by the transient nature of epigenetic modulation in an early trial (111).

A parallel and important avenue of study involves decoding the interplay between the tissue microenvironment and the epigenome to predict therapeutic responses. The scar milieu, characterized by variable mechanical stress, hypoxia and inflammation, actively modulates epigenetic states, yet current *in vitro* models often overlook this complexity. Consequently, a notable priority of scar-prevention studies should be the development of advanced human organotypic or *in vivo* models that integrate ancestry-relevant factors, such as melanin content, with tunable microenvironmental cues, such as cyclic strain and graded oxygen tension (1,30,43,44). These systems are important for mapping how environmental signals interact with epigenetic modifiers. Furthermore, integrating real-time biomechanical data with predictive germline variants, for example rs10891883 (35) could yield composite algorithms for patient stratification, extending precision medicine beyond genetics alone.

Finally, achieving true cell-type specificity in epigenetic modulation remains a formidable but necessary objective of developing therapeutic strategies in order to minimize off-target effects. Current limitations have been evidenced by unintended epigenetic editing in keratinocytes or the skewing of macrophage polarization by systemically delivered exosomal miRNAs (18,108). Therefore, the development of next-generation, cell-specific delivery systems is of notable importance. This includes engineering targeted nanoparticles, for example aptamers targeting fibroblast activation protein-α, that have been validated in other fibrotic models (83), coupled with single-cell epigenome editing and lineage barcoding to rigorously quantify on-target vs. collateral modifications. Concentrating efforts on these interconnected priorities, elucidating the optimal timing and context of intervention and engineering precise delivery tools, will bridge the translational gap and enable the development of effective, precision epigenetic therapies that promote scar-sparing regeneration.

9. Conclusions

In conclusion, converging evidence positions epigenetic dysregulation, driven by DNA methylation, histone modifications and ncRNA networks, as the molecular basis of the epigenetic memory that sustains cutaneous fibrosis. Targeting DNMT3B, restoring miR-29 or disrupting lncRNA-guided methylation loops has reproducibly attenuated scar formation across multiple pre-clinical models. Environment-responsive MNs and exosome platforms now represent potential translational delivery solutions supported by level IIa evidence. Future ancestry-stratified, mechano-epigenomic trials are warranted to transform these mechanistic insights into precision, scar-sparing therapeutics.

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JL, YL and WL made substantial contributions to the conception and design of the review. JL and YL performed the literature search, synthesis and interpretation of the literature. JL, WL and JY contributed to drafting and writing the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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