

Genetic & epigenetic regulation of scar formation

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Abstract

Pathological scar formation, encompassing hypertrophic scars and keloids, remains a significant therapeutic challenge because of its intricate pathophysiology, considerable cosmetic and functional impact, and frequent recurrence following treatment. This review synthesizes the current evidence regarding the genetic and epigenetic factors that contribute to pathological scar formation, with a particular emphasis on the molecular mechanisms responsible for fibroblast dysfunction, excessive extracellular matrix (ECM) accumulation, and chronic inflammatory responses. Existing studies demonstrate that the development of pathological scars is driven by a complex interaction between genetic predisposition and epigenetic regulatory processes. Genetic contributors, such as susceptibility loci, gene polymorphisms, and aberrant activation of signaling pathways—particularly those mediated by transforming growth factor-beta (TGF- β)—play fundamental roles in disease progression. Moreover, epigenetic alterations, including DNA methylation, histone modifications, and the regulation of gene expression by non-coding RNAs, are critically involved in controlling fibroblast proliferation, collagen biosynthesis, angiogenesis, and tissue remodeling throughout the wound-healing process. A deeper understanding of these molecular pathways may facilitate the discovery of novel diagnostic biomarkers and accelerate the development of targeted, mechanism-based therapeutic interventions aimed at improving the prevention and treatment of pathological scars.

Keywords: Epigenetic Regulation, Hypertrophic scars, Non-coding RNAs, Pathological scar.

1. Introduction

1.1. Overview of scar formation (cutaneous wound healing, fibrosis)

Inflammation is essential in the process leading to scar formation. Following tissue injury, an inflammatory response is initiated, marked by the secretion of many cytokines and growth factors. These signaling molecules attract inflammatory cells to the site of injury, where they orchestrate tissue repair. Dysregulated inflammation might result in considerable scarring. Scar prevention techniques that mitigate inflammation are promising. Fibroblasts, the primary cells involved in wound healing, generate scars. Upon activation, fibroblasts proliferate and move to the wound site to regenerate the ECM. Abnormal fibroblast activity can lead to

ECM deposition, hypertrophic scars, and keloids. Regulating fibroblast activation and behavior to modify scarring is compelling (1).

1.2. Clinical significance of abnormal scarring (hypertrophic scars, keloids)

The two main types of scars, hypertrophic scars (HS) and keloids, are classified by their pathological characteristics and clinical presentations. Keloid or hypertrophic scarring is equally common in men and women, 20–30-year-olds, and Fitzpatrick skin types IV–VI. Since bulgy hypertrophic and keloid scarring are signs of oxidative stress, the role of reactive oxygen species (ROS) in dysregulated wound healing is noteworthy (2). Keloids and hypertrophic scars are fibroproliferative wound-healing disorders that cause exces-

skin disorders. The disease load is higher in people with darker skin and in high-tension anatomical regions, including the chest, shoulders, and earlobes, implying biological and mechanical stresses (3).

1.3. Scope: Genetic vs. epigenetic mechanisms

Epigenetics distinguishes diseases by examining how an individual's external environment affects gene expression, particularly the production of proteins, without altering the DNA itself (4). The genomic sequence constitutes the hardware, but epigenetics functions as the software, modulating gene expression via methods like DNA methylation and histone modification without modifying the DNA sequence (5).

2.1. Genetic Basis of Scar Formation

Chronic fibroproliferative keloid scarring disrupts wound healing. Keloids, unlike hypertrophic scars, invade healthy tissue beyond wound boundaries, recur post-surgery, and cause severe pain and pruritus. The effects go beyond the body. Its emotional toll and quality of life make it a clinical priority over aesthetics. The pathophysiology begins with overactive dermal fibroblasts that emit dysregulated cytokine signals and produce too much type I and III collagen. Given that our treatment options are mostly empirical, understanding the genetic framework behind these molecular abnormalities is crucial (6). High genetic susceptibility to keloid disease (KD) is evident. Inherited disease risk is called 'genetic susceptibility' or 'genetic predisposition'. KD incidence in diverse ethnic groups, family history, and twin prevalence shows genetic susceptibility. Afro-Caribbeans are more likely than Caucasians of northern European ancestry to develop aggressive keloids, or 'morbid' keloids. A strong family history of KD increases the likelihood of multiple lesions. Better clinical descriptions of KD and HS, and an understanding of their differential etiologies, will lead to more effective treatments (7).

2.2. Heritability and familial predisposition to abnormal scarring

Researchers used a genomic technique to find genes involved in keloid development and predisposing to this scarring disorder. They analyzed families with a high occurrence of keloids. In the examined families, researchers discovered autosomal dominant inheritance of keloid formation. The inheritance pattern of keloid development in these families suggests a genetic linkage strategy to find susceptibility loci, with mutations in single genes predisposing to scarring con-

ditions. Keloid formation is affected by various factors, including age, ethnicity, anatomical location, and type of trauma (8). Genetic variations that induce keloids have been identified in families of African-American, Japanese, and Chinese descent. Alterations in the genetic expression of specific proteins may modify an individual's physical and physiological traits, referred to as phenotype. The Fitzpatrick skin types exemplify interindividual variances in phenotype.(4) In addition to monogenic illnesses, wound healing in the general population exhibits a complex polygenic structure, influenced by the cumulative and interacting effects of multiple genetic loci. Genome-wide association studies (GWAS) and pathway analyses have identified variants that influence angiogenesis, immune modulation, oxidative stress, and extracellular matrix turnover. Polygenic factors contribute to the diverse healing abilities seen in illnesses, including diabetes, peripheral artery disease, and chronic kidney disease, where the aggregate hereditary risk interacts with metabolic and environmental elements to affect wound healing results (9).

2.3. Candidate genes associated with scar formation

Keloid development mechanisms encompass changes in growth hormones, collagen metabolism, and tension alignment, with genetic and immunological variables. Trauma, foreign-body reactions, infections, and endocrine dysfunctions have been identified as risk factors for keloid formation post-surgery in genetically predisposed individuals. Keloid illness impacts both genders equally and can manifest at any age, although it is most common between the ages of 10 and 30 (10).

2.4. Genetic susceptibility and profibrotic signaling pathways in keloid pathogenesis

Examination focuses on genes linked to TGF β , TP53, and HLA. Failure is attributed to hyperactivation of profibrotic pathways, including TGF- β , SMAD family proteins (SMAD), and bone morphogenetic protein (BMP) signaling, as well as inflammatory cascades like nuclear factor kappa B (NF- κ B) and interleukin-17 (IL-17). This molecular convergence causes ECM accumulation in keloid formation. Cell hyperproliferation is regulated by this convergence. Integrative molecular studies increasingly suggest that genetic predisposition and dysregulated wound healing pathways cause keloid formation. Extracellular vesicles and exosomes facilitate intercellular communication, which transmits profibrotic signals between fibroblasts and their surrounding

cells in the keloid microenvironment (9). No gene locus for familial keloid development has been identified. After conducting a genome-wide linkage search, we found keloid susceptibility loci on chromosomes 2q23 and 7p11 in two big families (8). Many family keloid studies have sought chromosomal connections. Researchers found keloid susceptibility loci on chromosome 2q23 in a Japanese family and on 7p11 in an African-American family, with likelihood ratios (LOD) of 3.01 and 3.16, respectively. The authors suggested locus heterogeneity in familial keloids based on a Chinese pedigree's 7p11 keloid connection, which could not be substantiated. Two genes linked to keloids include epidermal growth factor receptor (EGFR) at 7p11 and tumor necrosis factor alpha-induced protein 6 (TNFAIP6) at 2q23. TNFAIP6 gene and protein expression were significantly higher in keloid tissues than in internal control skin. Keloids proliferated more than normal fibroblasts in response to epidermal growth factor (EGF). Despite having 82% EGFR, they were less susceptible to EGF-stimulated cell migration. Genome sequencing of exons, intron/exon junctions, and promoter regions did not reveal mutations or disease-associated polymorphisms in relevant families. The team found that mutations in other genes at the loci likely cause keloid formation (11).

2.5. Genome-wide association studies (GWAS) in keloids and hypertrophic scars

While severe scarring (including keloids and hypertrophic scars) affects many races, earlier large-scale GWASs focused on Asian individuals, identifying 5 genetic susceptibility loci. Combined East Asian and European ancestry keloid data from a recent cross-phenotype investigation were presented (12). The inaugural GWAS of hypertrophic scarring reveals that rs11136645, a prevalent mutation in the CSMD1 gene, is substantially correlated with reduced scar height. Our findings illustrate the viability of utilizing the GWAS methodology in the investigation of hypertrophic scarring (HTS) and endorse more research in populations with heightened susceptibility to HTS. This variant allele would not directly replace amino acids, as rs11136645 is in the intronic region of the CSMD1 gene. Intronic SNPs can affect messenger RNA (mRNA) splicing, translation, and other gene-product functions. A functional effect on CSMD1 or one or more ungenotyped variant(s) in linkage disequilibrium with rs11136645 may explain the connection between rs11136645 and lower scar height (13).

2.6. Single nucleotide polymorphisms (SNPs) in fibrotic pathways

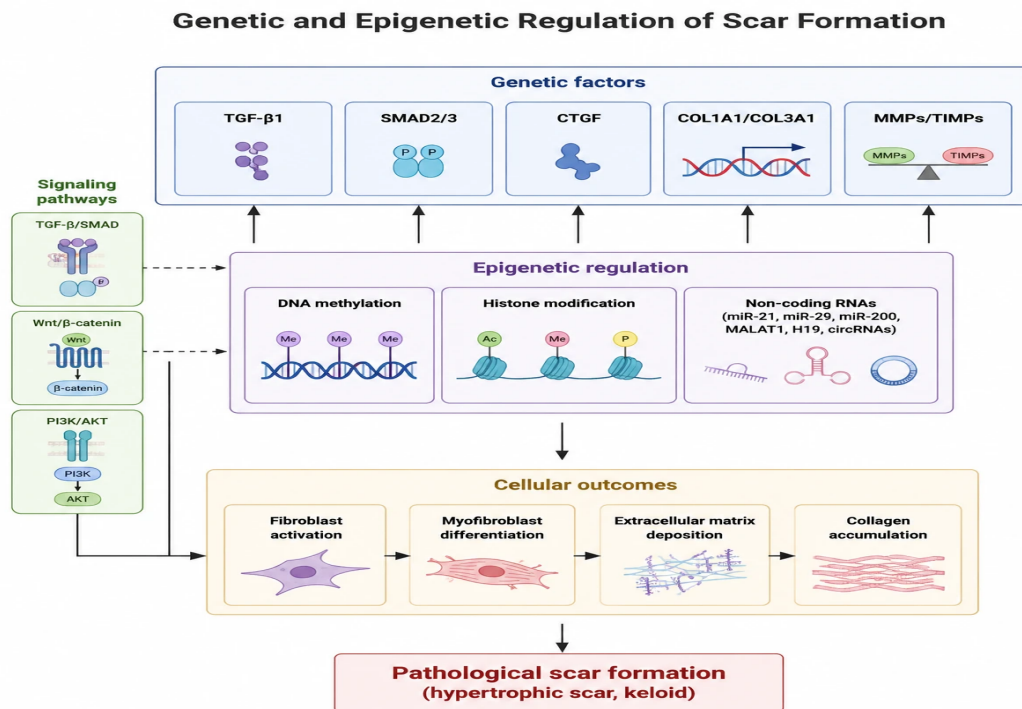


Figure 1. Genetic and epigenetic regulation of scar formation. Key signaling pathways engage with epigenetic mechanisms, such as DNA methylation, histone modifications, and non-coding RNAs, to regulate the expression of genes linked to fibrosis. These interactions activate fibroblasts, induce myofibroblast differentiation, promote extracellular matrix deposition, and facili-

There is a significant amount of variation in scar formation that can be attributed to single nucleotide polymorphisms (SNPs) that are found in fibrotic pathways. There is a possibility that individuals who possess variations in genes that encode essential components of fibrotic signaling, including TGF- β , SMADs, and extracellular matrix proteins, may be more prone to experiencing substantial scarring. When it comes to developing targeted genetic strategies for scar prevention and treatment, having a solid understanding of these SNP associations is absolutely necessary. With the help of this information, we will be able to determine which populations are at risk.(14)

2.7. Ethnic and population differences in scar-related genetic variants

Gene expression and phenotype are determined by epigenetic modifications like DNA methylation, histone modification, and non-coding RNA regulation. Alternative DNA methylation in keloid tissue and fibroblasts, as well as differential expression of epigenetic modifying enzymes and non-coding RNAs (e.g., miRNA and lincRNA), can inhibit or promote gene expression by affecting transcription factor or repressor complex binding. Moreover, non-coding RNA sequences regulate mRNA transcriptionally and post-transcriptionally. The functional effects of keloids' epigenetic changes are unknown. The study found that modified processes were linked to TGF β , WNT, fibroblast proliferation, and ECM formation (15).

3.1. Epigenetic regulation of scar formation

Epigenetic regulation dictates the activation or deactivation of genes, thereby influencing the phenotypic plasticity of individual cells, organs, or entire organisms. Epigenetic regulatory mechanisms in the skin are crucial for maintaining homeostasis, facilitating wound healing, and contributing to the pathogenesis of various skin diseases. The nucleus orchestrates gene expression through epigenetic regulatory mechanisms that depend on specific chromatin structural states and their remodeling. These encompass DNA methylation, histone modifications, and non-coding RNAs (16). Which collectively govern the cellular mechanisms that lead to fibrotic outcomes (Figure 1)

3.2. DNA methylation

Epigenetic DNA methylation is required for gene and transposon silencing, imprinting, and X chromosome inactivation. Over two decades ago, DNA methylation was found to be post-replicative. Most DNA alterations' biological signifi-

cance is emerging. A large body of experimental data links DNA methylation to gene activity and restriction modification mechanisms in bacteria and eukaryotic systems. This link requires understanding cell-specific methylation patterns during development (17).

3.3. Methylation patterns in fibrotic genes

When DNA methyltransferase (DNMT) enzymes methylate the cytosine ring's carbon 5, 5-methylcytosine (5MeC) is formed. This is DNA methylation. DNA methylation usually occurs on cytosine residues before guanosine. Cytosine-phosphate-guanine dinucleotide (CpG) islands are proximal promoter CpGs. CpG island promoters are often unmethylated, promoting transcription. In the cell cycle, daughter cells inherit methylation, which inhibits gene transcription. One of two methods represses transcription after methylation and 5MeC. First, transcription factor binding to promoter recognition sites is directly affected by 5MeC production. Methylation prevents cAMP response element-binding protein (CREB), E2 promoter binding factor (E2F), hypoxia-inducible factor (HIF), and NF- κ B from binding to CpG residues. Second, some transcriptional repressors directly silence methylated DNA genes. These methyl-CpG-binding proteins regulate gene expression with methylated DNA and histone-modifying enzymes. Methyl-CpG-binding protein 1 / 2 (MeCP1 and MeCP2) were the first protein complexes. Additional proteins like methyl-CpG-binding domain protein 1 / 2 / 4 (MBD1, MBD2, and MBD4) were described. The MBD motif of most repressor protein complexes binds methylated DNA (18).

3.4. Role of DNA methyltransferases (DNMTs) in myofibroblast persistence

Tissues with acute and chronic inflammation had myofibroblasts. In all cases, tissue cells produced stimulatory chemicals after injury. Epigenetic processes may limit fibroblast quiescence and preserve healing response in chronic injuries. Constant stimulation causes fibrosis, a pathological process that forms fibrous tissue (18). DNA methylation controls gene transcription on chromosomes. Hypermethylated human DNA with cytosine and guanine levels over 50% silences transcription. The main enzymes that transfer methyl groups from S-adenosylmethionine (SAM) to cytosine residues at CpG dinucleotides are DNA methyltransferases (DNMTs). Maintenance of symmetrical cytosine methylation at double-stranded hemimethylated CpG and de novo methylation of unmethylated CpG dinucleotides during DNA replication are known (19).

3.5. Histone modifications

Epigenetic mechanisms include histone changes, which comprise the molecular basis of the “histone code” theory. Histone N-terminals are methylated, acetylated, and phosphorylated. These changes restructure chromatin and recruit transcription-regulating effector proteins. Unlike DNA methylation, histone changes are dynamic and reversible. They react quickly to nutrition, temperature, and pathogens due to their flexibility. Therefore, histone modifications are essential for integrating the production environment, the animal genome, and the phenotype (20).

3.6. Acetylation (HATs/HDACs) and deacetylation in scar-related gene expression

histone acetyltransferases (HATs) transfer acetyl groups from acetyl-CoA to histone tail lysine residues. The positive charge of lysines is neutralized, lowering histone-DNA electrostatic interaction. The relaxation of chromatin makes genetic loci more accessible to transcription factors and RNA polymerase II. Because HATs need acetyl-CoA, histone acetylation is linked to energy metabolism. Histone deacetylases (HDACs) remove acetyl groups from lysines, restoring histones' positive charge and compacting chromatin. This action neutralizes acetylation and represses transcription. Epigenetic maintenance is carried out by zinc-dependent Classes I, II, and IV. Sirtuins 1–7 (SIRT1–SIRT7) are a distinct class III member. They need nicotinamide adenine dinucleotide (oxidized/reduced) NAD^+ instead of zinc. Sirtuin activity is critically linked to the cellular NAD^+/NADH ratio, which indicates energy status and metabolic stress. Sirtuins are epigenetic sensors that detect changes in deacetylation and gene expression due to fasting, heat stress, or dietary limitation (21).

3.7. Methylation of histones (H3K4me3, H3K27me3) in fibroblast activation

Among the over 100 distinct histone modifications, histone H3 lysine 27 trimethylation (H3K27me3) and histone H3 lysine 4 trimethylation (H3K4me3) are prominent histone marks linked to inactive and active promoters, respectively (22). H3K4me3, an active histone mark linked with transcriptionally active/poised chromatin, has two unique distribution patterns in yeast, plants, worms, flies, and mammals. H3K4me3-enriched nucleosomes are typically identified as small peaks (<1 kb) near transcription start sites (TSSs) in ChIP-seq research. For several genes, large H3K4me3 domains (>4 kb) extend downstream into the body and have

lower signal intensity than acute peaks. Since sharp and broad H3K4me3 peaks do not coincide, distinct processes may regulate the two distribution patterns. Different transcription factors, chromatin remodelers, and super-enhancers may bind differently. Nucleosomes in the broad H3K4me3 domain have multiple histone post-translational modifications PTMs). We'll call this chromatin feature of expressed genes the broad epigenetic domain (23).

3.8. Non-coding RNAs

In recent years, non-coding RNAs (ncRNAs) have been identified as crucial regulators of gene expression and cellular homeostasis, significantly influencing several biological and pathological processes. The primary categories of non-coding RNAs (ncRNAs) comprise microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), which modulate gene expression via transcriptional, post-transcriptional, and epigenetic mechanisms. Non-coding RNAs modulate several biochemical pathways, including cell proliferation, inflammatory responses, apoptosis, and fibrotic processes, all of which are essential (24).

3.9. MicroRNAs (e.g., miR-29, miR-21, miR-200 family) in collagen deposition and TGF- β signaling.

Gene regulation and extracellular transport make miRNAs powerful disease biomarkers and targeted therapies. Some call them molecular medicine's “crown jewel”. Technological advances boost translational medicine miRNA use. The majority of miRNA treatments use chemically modified antisense inhibitors (anti-miRs) or synthetic mimics. Exosome membrane structure guides miRNA distribution; miRNA mimics or antagonists heal wounds. Technology improves science with lncRNA research. Recent sequencing advances have made lncRNAs gene expression regulators, not “transcriptional noise.” lncRNAs over 200 nucleotides affect cell proliferation, differentiation, and gene network control via epigenetics, chromatin remodeling, and post-transcriptional mechanisms. By interacting with DNA, chromatin-modifying complexes, transcriptional regulators, mRNA stability, and translation efficiency, lncRNAs reduce miRNA targeting to mRNAs as ceRNAs as miRNA “sponges,” and affect epigenetic, transcriptional, and post-transcription. Increasing evidence suggests lncRNAs control chronic wounds. The main chemicals were H19, MALAT1, GAS5, XIST, and WAKMAR. HG-cultured HDF had 7 increased and 7 decreased angiogenesis-related lncRNAs. These findings suggest lncRNAs predict diabetic wound DFU (25).

3.10. Long non-coding RNAs (lncRNAs) as regulators of fibrosis (e.g., MALAT1, H19)

Single-stranded RNAs longer than 200 bases, called lncRNAs (TP53TG1, LINC00342, H19, MALAT1, DNMT3OS, MEG3), are being explored for their roles in organ fibrosis. lncRNAs compartmentalize the nucleus, regulate splicing, and influence gene activity by suppressing transcription factor active sites or maintaining euchromatin and producing heterochromatin regions. lncRNAs compete with miRNAs as ceRNAs in the cytoplasm, avoiding mRNA repression. They regulate post-translational protein modifications, scaffold signaling pathway proteins, and communicate amongst cells. MALAT1 on chromosome 11q13.1 regulates neurological, muscular, and vascular growth in various organs. It induces cancer via MAPK/ERK, PI3K/AKT, β -catenin/Wnt, Hippo, VEGF, and yes-associated protein signaling. MALAT1 promotes lung, liver, heart, and kidney fibrosis via increasing cytokines, fibroblast proliferation, migration, and EMT (26).

3.1.1 Circular RNAs (circRNAs) in scar pathogenesis

When compared to linear RNAs, circRNAs are more abundant due to their superior stability, longer half-life, and resistance to exonucleases such as RNase R. An increasing number of circRNAs with translational potential have been found, encouraging research into whether their coding and non-coding roles can co-exist in the same cell and how they may contribute to chronic wound repair. Circular RNAs encode proteins through cap-independent processes, such as internal ribosome entry site (IRES) or N⁶-methyladenosine (m⁶A)-mediated translation initiation, unlike canonical mRNA translation. After studying circRNA expression in various phases of human skin wound healing, CircGLIS3 became a promising option. Transiently increased in dermal fibroblasts during the acute wound phase, this circRNA is expected to have both regulatory and protein-coding potential (27).

4.1. Interaction Between Genetic and Epigenetic Mechanisms

Epigenetics governs gene expression and is crucial to various disorders. Epigenetics and non-genetic factors, including aging, nutrition, and physical activity, affect phenotypes. Epigenetic biomarkers, therapeutics, and editing methodologies can enhance the diagnosis and treatment of metabolic disorders in clinical environments (28).

4.2. SNPs affecting epigenetic modifications (epialleles)

Single-nucleotide changes in the genome, such as insertions, deletions, transversions, and single-base transitions, produce

SNPs, which have an allelic variation frequency greater than 1%. These polymorphisms are widespread, with one SNP per 700 bp in *B. taurus* and 300 bp in *B. indicus* in both the coding and non-coding areas. They are usually biallelic since a single base pair has very low mutation rate, and two-point mutations at the same site are unlikely. Transition seems to be preferred over transversion. SNPs are ubiquitous, biallelic, and easily assayable by automated methods, making them one of the most commonly genotyped genetic markers (29).

4.3. Epigenetic regulation of scar-associated risk genes

Beyond DNA methylation, post-translational modification of histone tails and chromatin accessibility provide a dynamic and responsive epigenetic control layer in cutaneous fibrosis. These alterations directly regulate transcriptional apparatus access to genes regulating fibroblast proliferation, differentiation, and collagen synthesis, locking transformed cells into a pro-fibrotic state. Recent results have shown multiple but converging methods by which scar-forming fibroblasts' histone marks and chromatin architecture are reprogrammed to be pro-fibrotic (30).

4.4. Gene–environment interactions in scar formation via epigenetic modifications

The local microenvironment of keloids includes fibroblasts, immunological cells, vascular-associated cells, and metabolic changes that may affect lesion growth. Endothelial dysfunction and hypoxia can help remodel local tissue, and upregulation of HIF-1 α is linked to angiogenesis, fibroblast proliferation, and collagen synthesis, and may synergize with TGF- β /Smad and NF- κ B to promote fibrotic responses. Metabolic stress, such as increased glycolysis and aberrant fatty acid metabolism, may help keloid cells synthesize and regulate associated fibrotic programs (31).

5.1. Translational and Therapeutic Implications

DNA methylation affects skin cell proliferation and differentiation, affecting wound healing. mRNA methylation controls epidermal cell renewal. A complex interaction of genetic factors, wound characteristics, individual differences, and dysregulated inflammatory responses during wound healing causes pathological scarring, a common sign of abnormal wound healing. Collagen production and degradation abnormalities affect scar formation, while genetics and epigenetic regulation affect keloid development. Thus, understanding wound healing's complex regulatory networks and exploring novel treatments like targeting histone methylation enzymes, modulating

RNA methylation, and regulating non-coding RNAs may improve tissue regeneration and reduce scarring (32).

5.2 Genetic biomarkers for predicting scar risk

Engineered exosomes constitute a promising approach; mesenchymal stem cell-derived exosomes infused with miR-578 or miR-3646 may inhibit TGF- β 1/Smad3 signaling within the fibrotic microenvironment. Circulating miRNA panels, such as miR-1273d for heart failure risk classification and miR-4539 as a biomarker for keloid protection, may facilitate noninvasive scar subtyping. Incorporating these indicators with machine learning methods, such as convolutional neural networks, may enhance prognosis models for malignant transformation of scars. Simultaneously, immune cell dynamics were assessed by flow cytometry for CD66b++ myeloid cells or BAFF-R+ B cells (33).

5.3. Epigenetic therapies

A fundamental aim of the clinical translation of epigenetic therapy is to create tools that achieve a precise and lasting gene expression state, which endures through mitosis and cellular differentiation long after the editor has been eliminated. Although initial "hit-and-run" strategies employing multi-component editor cocktails showcased the viability of this method, recent studies have produced significant progress in the development of compact, effective, and safe single-protein systems capable of encoding and deleting heritable epigenetic memory (34).

5.4. HDAC inhibitors, DNMT inhibitors

DNMTs epigenetically methylate cytosine. DNA methylation begins with DNMT3A and DNMT3B. Newly synthesized DNA is methylated by DNMT1 after pattern setting. Activity is affected by DNA methyltransferase enzyme components or process participants. The enzyme's active site, which binds cytidine and SAM simultaneously, is the most intriguing target because its locations are well-studied. Off-target effects should be considered when designing active site inhibitors since cytidine and SAM are not DNMT substrates. An inhibitor targeting SAM- and cytidine-binding sites may solve this problem and improve efficacy. DNMT inhibitors mainly bind to the active site. However, the search for allosteric inhibitors continues, and developing more selective inhibitors that interact with unique structural aspects beyond the active site of DNMT family enzymes seems intriguing. DNA is a target for inhibitors because CpG dinucleotides affect catalytic complex formation. All nucleoside analogues and non-nucleoside chemicals inhibit DNMT. Synthetic and natural non-

nucleoside chemicals exist (35). Histone acetylation regulates gene expression. Deacetylated histones inhibit genes, while acetylation increases transcription. Histone deacetylases (HDACs) remove the acetyl group from histones to regulate gene expression (36). HDAC enzymes remove acetyl groups from ϵ -N-acetylated lysine side chains in histones and nonhistones. 18 human HDACs found. HDACs are zinc-dependent (classes I, II, and IV) and sirtuin in class III. Sirtuins regulate gene expression and act as "metabolic sensors" in response to cellular redox status by targeting cytoplasm, mitochondria, and nucleus proteins. Sirtuins and zinc-dependent HDACs remove acetyl groups from histone and nonhistone proteins, but "HDAC" usually means the latter (37).

5.5. miRNA mimics/antagomirs

MiRNAs play a function in fibrosis development, according to recent studies. miRNAs influence gene expression by binding to target mRNAs' 3'UTR complementary regions. This binding inhibits protein synthesis by degrading or inhibiting mRNA translation. Conserved noncoding small molecules control oncogenic processes, tumor suppression, alveolar EMT, and epithelial cell shape. In addition, the miR-200 family, the first discovered oncogenic miRNAs (OncoMiR), increases TGF- β -induced EMT. Research indicates that miR-200 family members (miR-200a/200b/200c/141/429) inhibit invasion, cell migration, and EMT by targeting ZEB1 and ZEB mRNA via two E-cadherin repressor levels. Reports indicate that miR-200 family suppression occurs when the DNA region is hypermethylated. Conversely, miR-200c decreases metastasis in A549 NSCLC cell lines (38).

5.6. Targeting lncRNAs

Pathological fibrosis can be treated by carefully regulating lncRNA expression or functional connections. Current treatments use gene silencing to target and eliminate out-of-balance lncRNAs that cause fibroblast activation and excessive extracellular matrix deposition. To disrupt scarring-causing regulatory processes, small-molecule inhibitors or specific oligonucleotide decoys can prevent lncRNAs from chemically interacting with their target proteins or signaling molecules. The activity of miRNA is controlled by epigenetic regulation, specifically the ceRNA process made possible by long non-coding RNAs. These lncRNAs grab miRNAs and stop them from attaching to target mRNAs. This makes it easier for gene expression to go up (39).

5.7. Current challenges and future directions in precision medicine for scarring

The effectiveness, applicability, and long-term sustainability of surgical excision, compression therapy, silicone sheeting, laser treatments, and pharmaceutical interventions are all severely lacking. Multifunctional hydrogel-based wound dressings show great promise as a treatment option because of their biocompatibility, controlled drug-release, inherent antimicrobial and anti-inflammatory properties, and so on. According to recent studies, hydrogel dressings can shorten the time it takes for wounds to heal by 30% to 40%, which means less medical care and fewer secondary interventions are needed. These advancements tackle the main shortcomings of traditional treatment, allowing for scar-free healing (40).

6. Conclusion and Future Perspectives

A complex network of interrelated biological and molecular processes allows skin to regenerate during wound healing. But, when there are any disruptions in the normal healing process, the body's reparative responses take over, and the usual repair procedure ends up producing thick, itchy scars that are unsightly and functionally problematic. Scar therapy methods as they stand are not very targeted or effective. A thorough familiarity with the regulatory systems controlling scarring and wound healing is necessary to achieve this goal. We highlighted the heterogeneity of genes influencing susceptibility to scar formation to elucidate scar management techniques via the formulation of prognostic and preventive strategies, ultimately leading to personalized medicine, taking into consideration the significance of genetic and epigenetic variations in normal or abnormal wound healing. Achieving this goal will require future robust research, readily available techniques and technologies for genetic screening to detect polymorphisms and understand their roles in wound healing. In addition, the study of gene dysregulations linked to inflammation, granulation tissue growth, apoptosis, and ECM remodeling yielded crucial insights, suggesting that genetic therapies could improve wound healing and prevent skin fibrosis. Safe, focused, and effective gene delivery is a difficulty, as is determining the right amount of modification, regulating the spatiotemporal activity of mediators with dual functions, and selecting the right cells to target. Epigenetic alterations, such as DNA methylation, histone abnormalities, and noncoding ribonucleic acids like microRNAs and lncRNAs, play a crucial role in wound healing. More research into the precise mechanisms by which regulatory epigenetic molecules may alleviate scars due to putative gene dysregulation is necessary before recommending them as a treatment option. However, advancements in the methods and tools for finding, delivering, and precisely modifying genetic and epigenetic regulators are necessary for the success-

ful application of these new approaches. This opens up new possibilities for the control of scar formation and makes it easier to resolve related problems (41).

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