

Cellular and Molecular Mechanisms of Scarless vs. Fibrotic Wound Healing: A Comprehensive Review

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Abstract

Wound healing restores tissue integrity through overlapping phases of hemostasis, inflammation, proliferation, and remodeling. While adult wounds typically heal via fibrotic repair with excessive extracellular matrix deposition and scarring, early gestation fetal skin demonstrates scarless regenerative healing with complete architectural restoration. Understanding mechanisms distinguishing these outcomes is critical given the clinical burden of pathological fibrosis and chronic wounds.

This review synthesizes recent advances from single-cell and spatial transcriptomics to present a comprehensive framework comparing fibrotic and regenerative healing. We evaluate cellular heterogeneity, molecular signaling networks, and environmental drivers determining healing phenotype.

Healing outcome appears to emerge from three interconnected regulatory axes: fibroblast lineage specification, where distinct developmental subpopulations (POSTN+, CD26+) may carry predispositions toward fibrotic or regenerative responses; mechanical signaling, wherein YAP/TAZ mechano-transduction appears to integrate matrix stiffness and tension to amplify fibroblast programs; and immune modulation, with prolonged neutrophil persistence and macrophage activation driving fibrosis through NET release and pro-fibrotic crosstalk. Critical molecular determinants include the TGF- β 3/TGF- β 1 ratio with isoform-specific Smad activation, inflammatory dynamics, and extracellular matrix composition, particularly high molecular weight hyaluronic acid and collagen organization. Cell-cell communication networks, notably POSTN-SPP1 positive feedback loops between profibrotic fibroblasts and macrophages, establish self-reinforcing fibrotic cycles.

Therapeutic strategies targeting multiple pathways sequentially or simultaneously may hold greater promise than isolated pathway inhibition. However, significant challenges remain in achieving spatiotemporal delivery control, addressing patient heterogeneity, and translating rodent findings to humans. Future progress requires biomarker-stratified approaches, validated predictive markers, and clinical trials with scar quality endpoints to redirect adult wound healing toward regeneration.

Keywords: Wound healing, Fibrosis, Myofibroblasts, Macrophage Activation, Extracellular matrix

1. Introduction

Wound healing enables organismal survival by restoring tissue integrity following injury. This highly orchestrated process involves overlapping phases: hemostasis, inflammation, proliferation, and remodeling (1). While this

programmed response effectively closes wounds and prevents infection, healing quality varies dramatically depending on developmental stage, tissue type, environmental factors, and patient-specific variables (2).

In contrast, adult wounds typically heal through a fibrotic process characterized by excessive extracellular matrix (ECM) deposition, wound contraction, and permanent scar formation (4,5). This scarring represents not merely a cosmetic concern but frequently leads to functional impairment, particularly in vital organs including the heart, lungs, liver, and skin (6).

Chronic wounds and fibrotic disorders remain major clinical and economic burdens. Moreover, pathological fibrosis contributes to a high percentage of all deaths in the developed world when considering diseases such as idiopathic pulmonary fibrosis, liver cirrhosis, and heart failure (5,6). Understanding the mechanisms that distinguish scarless regeneration from fibrotic repair is therefore of great importance for the development of effective therapeutic interventions.

Recent advances in single-cell and spatial transcriptomics, advanced imaging, and systems biology have improved understanding of the cellular and molecular regulation of wound healing outcomes (7). This review synthesizes these discoveries, to present a comprehensive theoretical framework comparing fibrotic and regenerative wound healing. We critically evaluate the roles of specific cell populations, molecular signaling pathways, and environmental drivers that determine healing phenotype, ultimately identifying promising targets for therapeutic intervention.

This narrative review was conducted following literature search principles to ensure comprehensive coverage and transparency. We searched PubMed, Web of Science, and Embase databases for peer-reviewed articles published between January 2010 and July 2026. The search strategy employed combinations of the following keywords and MeSH terms: wound healing, fibrosis, scarless healing, fetal wound healing, regenerative healing, myofibroblast, macrophage polarization, TGF-beta, YAP/TAZ, mechano-transduction, extracellular matrix, single-cell transcriptomics, and spatial transcriptomics.

Inclusion criteria encompassed: (1) original research articles examining cellular and molecular mechanisms of wound healing in mammalian systems; (2) review articles providing comprehensive synthesis of wound healing biology; (3) studies comparing fibrotic and regenerative healing paradigms; (4) articles investigating therapeutic interventions targeting wound healing pathways; and (5) publications utilizing advanced methodologies including single-cell sequencing, spatial transcriptomics, and imaging mass cytometry. Exclusion criteria included: non-mammalian studies without direct translational relevance, case reports, conference ab-

stracts without peer review, and articles not available in English.

2. Background and Conceptual Framework

2.1 The Classical Model of Wound Healing

The classical model of adult wound healing describes four overlapping phases that progress from injury to tissue restoration (1). The hemostasis phase initiates immediately upon injury, involving platelet activation, clot formation, and release of pro-inflammatory mediators. The subsequent inflammatory phase, lasting approximately 3–5 days, recruits neutrophils and macrophages to clear debris and pathogens (8).

The proliferative phase, beginning 3–5 days post-injury and extending for several weeks, involves fibroblast activation, granulation tissue formation, angiogenesis, and epithelialization (9). Finally, the remodeling phase can persist for months to years, during which the provisional matrix is replaced by mature collagenous scar tissue (10). This extended remodeling phase is characterized by collagen cross-linking and tissue contraction, ultimately producing a scar that lacks the architectural and functional properties of uninjured tissue.

2.2 Refinements to the Classical Wound Healing Model

Recent research has revealed important refinements and controversies to this classical model that challenge this simplified framework.

Rather than discrete sequential phases, contemporary studies demonstrate that cellular events exhibit substantial spatiotemporal heterogeneity (7). Neutrophils, traditionally considered exclusive to the early inflammatory phase, persist in chronic wounds for weeks (11). Conversely, proliferative events begin within 24 hours in regenerative healing, challenging the notion of strict phase boundaries (12).

Single-cell transcriptomics has revealed that macrophages and fibroblasts exist along continuous activation spectra rather than discrete phenotypic states (M1/M2, fibroblast/myofibroblast) (13,14). This plasticity enables dynamic responses to changing microenvironmental cues that the classical model does not capture.

The four-phase model derives primarily from cutaneous wound studies (1). However, healing in mucosal tissues, bone, and cardiac muscle exhibits distinct cellular and molecular signatures that warrant tissue-specific frameworks (5).

These refinements indicate the need for more nuanced models that incorporate cellular heterogeneity, spatiotemporal dynamics, and context-dependent regulation,

2.3 The Paradigm of Scarless Fetal Wound Healing

Fetal wound healing represents a fundamentally different paradigm. In early gestation (before approximately 24 weeks in humans), fetal skin heals rapidly without scar formation while restoring normal skin architecture including adnexal structures such as hair follicles and sweat glands (2,3). This scarless healing capability is intrinsic to fetal tissues and does not depend on the sterile intrauterine environment, fetal wounds heal scarlessly even when transplanted to adult animals (15).

The transition from scarless to scar-forming wound healing occurs during a defined developmental window. In

mice, this transition coincides with embryonic day 16.5 (E16.5), while in humans, scarless healing is observed before the second trimester (2,16). This transition is tissue-autonomous and correlates with changes in inflammatory response, growth factor expression profiles, and ECM composition (2).

While the fetal-adult comparison provides a powerful experimental framework, several caveats merit consideration (15). First, fetal wound healing occurs in a fundamentally different physiological context (sterile, hydrated, low-tension environment) that may independently influence outcomes (16). Second, the rapid growth of fetal tissues creates distinct cellular dynamics that may not

Table 1: Comparative characteristics of fibrotic versus regenerative wound healing

Feature	Fibrotic Healing (Adult)	Regenerative Healing (Fetal)	Clinical Implications
Inflammatory response	Prolonged, intense neutrophil and macrophage infiltration (days 1–14+) (8)	Minimal, transient inflammation (days 1–3) (2)	Early anti-inflammatory intervention may reduce fibrosis
Growth factor profile	High TGF- β 1, PDGF, FGF2 (17)	High TGF- β 3, low TGF- β 1 (3)	TGF- β 3 supplementation or TGF- β 1 inhibition are therapeutic targets
ECM composition	Collagen I predominant, disorganized fibers (10)	Collagen III predominant, organized network (2)	Modulating collagen I/III ratio may improve scar quality
Cellular phenotype	Myofibroblast differentiation (α -SMA+) (4)	Fibroblast proliferation without differentiation (3)	Preventing myofibroblast differentiation preserves tissue architecture
Wound contraction	Significant, mediated by myofibroblasts (4)	Minimal contraction (2)	Mechanical offloading reduces contraction and scarring (18)
Adnexal restoration	Absent	Complete hair follicle and gland regeneration (3)	Reprogramming strategies to restore adnexal structures (19)
Scar formation	Prominent, permanent (10)	None (3)	Goal: redirect adult healing toward regenerative phenotype
Mechanical strength	Often exceeds native tissue (10)	Matches native tissue properties (2)	Excessive strength may indicate pathological cross-linking
Neutrophil persistence	Persistent NET release (chronic wounds) (11)	Rapid neutrophil clearance (2)	Targeting NETs may improve chronic wound outcomes
Microbiome influence	Dysbiosis promotes fibrosis (20)	Minimal microbial exposure (16)	Microbiome modulation as therapeutic strategy

3. Cellular Mechanisms

3.1 Fibroblast Heterogeneity and Lineage Plasticity

Fibroblasts are the principal cellular mediators of wound healing, responsible for synthesizing and remodeling the ECM (4,9). Recent advances in single-cell transcriptomics have revealed that fibroblasts represent a heterogeneous

population with distinct subtypes exhibiting specialized functions during wound healing and fibrosis (13).

3.1.1 Fibroblast-to-Myofibroblast Transition

The transition of fibroblasts to myofibroblasts represents a critical event in fibrotic wound healing (4,21). Myofibroblasts are characterized by expression of α -smooth muscle actin (α -SMA), which confers contractile properties

translate to adult quiescent tissues (2). Third, most mechanistic studies rely on rodent models, and species-specific differences in immune system maturation complicate direct translation to humans (16).

2.4 Defining Characteristics of Fibrotic vs. Regenerative Healing

As summarized in Table 1, fibrotic and regenerative healing differ fundamentally across multiple dimensions. Understanding the molecular and cellular bases of these differences is essential for developing strategies that promote regenerative healing in adult tissues.

Recent evidence demonstrates that direct physical contact between fibroblasts and myofibroblasts is sufficient to induce myofibroblast differentiation, even in the absence of biochemical cues such as TGF- β or mechanical signals from stiff matrices (22). This contact-mediated transition involves Gq/11/14 signaling and may explain persistent myofibroblast activation observed in chronic fibrotic conditions despite therapeutic interventions (22).

While the contact-mediated transition represents an important advancement, the relative contribution of this mechanism compared to TGF- β and mechanical signaling in vivo remains unclear. Additionally, most studies have used two-dimensional culture systems that may not recapitulate the complex three-dimensional microenvironment of healing wounds (4).

3.1.2 Fibroblast Lineage Switching and Scarring Origins

Emerging research has identified fibroblast lineage switching as a developmental origin of scarring. Different fibroblast lineages exhibit distinct capacities for regenerative versus fibrotic responses. POSTN+ fibroblasts have been identified as key contributors to dermal fibrosis, whereas other fibroblast populations promote regenerative healing (5,13).

This lineage specificity appears to arise during development and persists into adulthood. Understanding the transcriptional programs that define pro-regenerative versus pro-fibrotic fibroblast lineages offers opportunities for targeted therapeutic interventions that selectively modulate specific fibroblast populations (13).

The field currently lacks consensus on the precise markers that define fibroblast lineages across different tissues and species (13). Additionally, the degree of lineage plasticity versus fixed fate commitment remains debated (22). Some studies suggest substantial interconversion between fibroblast states, while others support more rigid lineage restriction (13).

3.2 Macrophage Polarization and Immune Regulation

Macrophages play central roles in orchestrating wound healing outcomes through their remarkable functional plasticity (8,23). These cells exhibit a spectrum of activation states, traditionally classified as pro-inflammatory M1 and anti-inflammatory M2 phenotypes, though this binary model is now recognized as an oversimplification (24,25).

3.2.1 M1 Macrophages and Inflammation

M1 macrophages, classically activated by interferon- γ and lipopolysaccharide, dominate the early inflammatory phase of wound healing (23). These cells produce pro-inflammatory cytokines including TNF- α , IL-1 β , and IL-6, which are necessary for pathogen clearance and debris removal but can promote fibrosis when inflammation persists (8,26).

In regenerative fetal wound healing, the inflammatory response is markedly attenuated, with reduced M1 activation and macrophage infiltration compared to adult wounds (2). This diminished inflammation correlates with reduced scarring and may represent a therapeutic target for promoting regenerative healing (2).

3.2.2 M2 Macrophages and Tissue Resolution

M2 macrophages, activated by IL-4 and IL-13, promote tissue repair through production of anti-inflammatory cytokines, growth factors, and ECM components (23,24). The timely transition from M1 to M2 phenotype is critical for proper wound healing, with delayed polarization contributing to chronic wounds and premature M2 activation potentially promoting fibrosis (25).

Recent research using zebrafish models has revealed distinct morpho-kinetic behaviors of M1 and M2 macrophages during wound healing (27). M1 macrophages exhibit reduced shape elongation and more directed movement compared to M2 macrophages, suggesting that behavioral phenotyping may enable precise monitoring of macrophage activation states during healing (27).

3.2.3 Macrophage-Fibroblast Crosstalk

The interaction between macrophages and fibroblasts is crucial for determining healing outcomes (8,25). Pro-fibrotic macrophages have been identified as key regulators of scar formation, coordinating fibroblast activation and ECM deposition (5). Conversely, appropriate macrophage polarization can promote fibroblast quiescence and prevent excessive fibrosis (24).

Recent single-cell analyses have revealed cell type-specific communication patterns (5). POSTN+ fibroblasts and SPP1+ macrophages form positive feedback loops that may drive scar formation, while other cell-type pairings promote regenerative responses (5,13,28). Under-

standing these communication networks provides a framework for designing interventions that interrupt pathological signaling while preserving necessary repair functions.

3.3 Neutrophil Biology and Early Inflammatory Programming

Neutrophils, traditionally overlooked in fibrosis research, have emerged as critical determinants of healing outcomes (11). As the first responders to tissue injury, neutrophils arrive within minutes to hours and establish the initial inflammatory milieu that programs subsequent healing responses (8).

3.3.1 Neutrophil Extracellular Traps (NETs)

Neutrophils release chromatin structures decorated with antimicrobial proteins called NETs, which are essential for pathogen capture. Dysregulated NET formation (NETosis) contributes to fibrosis in multiple organs (11). NET-derived DNA and proteins activate fibroblasts directly and sustain inflammatory signaling (11). Elevated NET markers correlate with poor wound healing outcomes in diabetic patients (26).

3.3.2 Neutrophil-Macrophage Crosstalk

Neutrophils actively program macrophage phenotype through multiple mechanisms (8). Neutrophil-derived IL-1 β and CXCL8 promote pro-inflammatory macrophage polarization, while neutrophil clearance by macrophages (efferocytosis) triggers anti-inflammatory programming (23). Impaired efferocytosis in chronic wounds prolongs inflammation and delays healing (26).

3.3.3 Neutrophil-Lymphocyte Ratio (NLR)

The NLR serves as a clinically accessible biomarker for wound healing prognosis (8). Elevated NLR predicts poor outcomes in chronic wounds, surgical incisions, and burn injuries (8). This ratio reflects both neutrophil-driven inflammation and lymphocyte-mediated immune regulation, providing a systems-level view of immune status.

While NETs are implicated in fibrosis, therapeutic targeting remains challenging. DNase I, which digests NETs, has shown promise in preclinical models but may interfere with physiological NET functions in infection control (11). The optimal timing and duration of NET-targeted interventions require further investigation.

3.4 Keratinocyte and Epithelial Dynamics

Re-epithelialization is essential for wound closure and restoration of barrier function (1). Keratinocytes exhibit distinct behaviors in scarless versus fibrotic healing that extend beyond simple migration speed (2).

3.4.1 Keratinocyte Migration and Integrin Profiles

In scarless healing, keratinocytes migrate rapidly and express different integrin profiles compared to adult wound healing (2). Fetal keratinocytes predominantly express $\alpha 3\beta 1$ and $\alpha 6\beta 4$ integrins that interact with laminin-rich basement membranes, facilitating organized epithelial sheet migration (2). Adult keratinocytes upregulate $\alpha 5\beta 1$ and αv integrins that bind fibronectin and vitronectin in the provisional matrix, enabling faster but less organized migration (1).

3.4.2 Epithelial-Mesenchymal Transition (EMT) in Wound Healing

The epithelial-mesenchymal transition (EMT) that occurs at the wound edge in adult healing contributes to fibroblast activation and scarring (4). Keratinocytes undergoing EMT lose epithelial markers (E-cadherin, cytokeratins) and gain mesenchymal markers (vimentin, α -SMA, N-cadherin) (4). These transitioned cells acquire migratory and secretory capacities, producing TGF- $\beta 1$ and matrix metalloproteinases that stimulate underlying fibroblasts (4,21).

Fetal keratinocytes exhibit markedly lower EMT (2). Maintenance of epithelial identity in fetal wounds may prevent paracrine activation of fibroblasts and contribute to scarless outcomes. The transcription factors Snail, Slug, and Twist, which drive EMT, are expressed at lower levels in fetal compared to adult wound keratinocytes (2,29).

3.4.3 Keratinocyte-Fibroblast Paracrine Signaling

Keratinocytes regulate fibroblast behavior through secreted factors. In adult wounds, keratinocyte-derived IL-1 α and TGF- α stimulate fibroblast proliferation and matrix synthesis (4). Keratinocytes also produce granulocyte-macrophage colony-stimulating factor (GM-CSF) that recruits and activates inflammatory cells (8).

In scarless healing, keratinocytes secrete distinct factor profiles including higher levels of fibroblast growth factor 7 (FGF7/KGF), which promotes fibroblast proliferation without myofibroblast differentiation (2). The keratinocyte secretome thus guides the fibrotic or regenerative phenotype of underlying dermal cells.

Most studies of keratinocyte-fibroblast interactions have used in vitro co-culture systems that may not recapitulate the spatial organization and kinetics of in vivo wound healing (4). Additionally, the relative contribution of keratinocyte EMT-derived cells versus resident fibroblasts to scar formation remains debated (4,13).

3.5 Stem and Progenitor Cells

Adult skin contains multiple stem cell populations that contribute to wound healing (19). Hair follicle stem cells, interfollicular epidermal stem cells, and dermal stem cells all participate in tissue repair (30). In scarless healing, these progenitor cells more effectively integrate into regenerating tissue architecture, including restoration of adnexal structures (19,30).

Recent advances in cell reprogramming have demonstrated that delivery of specific transcription factors can promote scarless wound healing with hair follicle regeneration (19). These findings support the feasibility of redirecting adult wound healing toward a regenerative phenotype through targeted manipulation of cellular programs.

4. Molecular Mechanisms and Signaling Pathways

4.1 Transforming Growth Factor- β Signaling

The TGF- β superfamily appears to play a central role in wound healing and fibrosis (17,21). Three isoforms (TGF- β 1, TGF- β 2, and TGF- β 3) exhibit distinct expression patterns and functional roles during wound repair (17).

4.1.1 Isoform-Specific Functions and Receptor Signaling

TGF- β 1 is the predominant isoform in adult wound healing and strongly promotes fibroblast activation, myofibroblast differentiation, and ECM synthesis (17,21). High levels of TGF- β 1 correlate with fibrotic outcomes, and targeted inhibition of TGF- β 1 signaling decreases scarring in multiple models (31–33).

In contrast, TGF- β 3 is enriched in fetal wounds and promotes scarless healing (17). The relative ratio of TGF- β 3 to TGF- β 1 appears to be a determinant of healing phenotype, with higher ratios favoring regeneration over fibrosis (17).

Mechanistic basis for isoform-specific effects:

TGF- β isoforms signal through the same receptor complex (TGF- β RI and TGF- β RII) but exhibit differences in receptor affinity and downstream signaling kinetics. TGF- β 3 appears to bind TGF- β RII with higher affinity than TGF- β 1, leading to distinct receptor occupancy dynamics. Additionally, TGF- β 3 preferentially activates Smad2 over Smad3, whereas TGF- β 1 activates both equally. Since Smad3 drives fibrotic gene expression while Smad2 can antagonize this response, the differential Smad activation may contribute to isoform-specific outcomes (17).

Therefore, these TGF- β isoforms have been recognized as important targets for anti-fibrotic therapy. This approach may enable selective modulation of fibrotic responses while preserving necessary tissue repair functions (17).

4.1.2 Smad-Dependent and Independent Signaling

TGF- β signals through canonical Smad-dependent pathways as well as non-canonical Smad-independent pathways including MAPK, PI3K/Akt, and RhoA/ROCK signaling (17,21). The balance between these pathways influences cell fate and ECM production (17).

Smad3 appears to be the principal mediator of TGF- β -induced fibrosis (17). Smad3 knockout mice exhibit reduced scar formation, and pharmacologic Smad3 inhibition attenuates fibrosis in multiple models (5). In contrast, Smad2 may have protective effects, as some studies demonstrate that Smad2 knockdown exacerbates fibrosis (17). This differential role of highly related Smad proteins presents opportunities for selective therapeutic targeting.

Non-canonical TGF- β signaling through TAK1, p38 MAPK, and JNK contributes to fibroblast activation and may operate independently of Smad pathways (21). The relative contribution of canonical versus non-canonical signaling varies by cell type, complicating efforts to predict therapeutic outcomes based on pathway inhibition alone (17).

4.2 Wnt/ β -Catenin Signaling

Wnt/ β -catenin signaling plays complex and context-dependent roles in wound healing and fibrosis (34,35). This pathway is essential for tissue development and regeneration but can also promote fibrosis when dysregulated (34).

4.2.1 Dual Roles in Regeneration and Fibrosis

Canonical Wnt signaling promotes fibroblast proliferation and myofibroblast differentiation through β -catenin-dependent transcription (34). In fibrotic conditions, elevated Wnt/ β -catenin signaling drives excessive ECM production and tissue remodeling (34,35). Nuclear β -catenin forms complexes with TCF/LEF transcription factors to activate target genes including collagen type I, fibronectin, and α -SMA (35,36).

However, Wnt signaling is also required for tissue regeneration (34). Studies have shown that sequential treatment with Wnt agonists and antagonists has a positive effect on tissue repair while minimizing fibrosis (37). This temporal regulation reflects the complex dynamics of Wnt signaling during normal wound healing.

The dual role of Wnt signaling creates challenges for therapeutic targeting (35). Constitutive Wnt activation promotes fibrosis, while complete Wnt inhibition impairs healing (34). The success of sequential agonist/antagonist approaches suggests that precise temporal control, rather than simple pathway modulation, may be necessary for optimal outcomes (34).

4.2.2 Cross-Talk with TGF- β Pathway

Wnt and TGF- β signaling pathways exhibit extensive cross-talk during wound healing (34). Wnt/ β -catenin can form negative feedback loops during TGF- β 1-induced myofibroblast transition, suggesting that coordinated modulation of both pathways may be necessary for optimal therapeutic outcomes (34).

Recent studies have revealed physical interactions between Smad and β -catenin proteins (34). TGF- β signaling can phosphorylate β -catenin at distinct sites, resulting in a change in its stability and transcriptional activity (34). Conversely, β -catenin can influence Smad nuclear localization and transcriptional complex formation (35). These molecular interactions provide mechanistic bases for pathway cross-talk.

4.3 Inflammatory Signaling Networks

4.3.1 Cytokine Cascades

The inflammatory response involves complex cytokine networks that influence healing outcomes (8,23). Pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α) promote initial healing responses but can potentially drive fibrosis when chronically elevated (8,25). Anti-inflammatory cytokines (IL-10, IL-4) promote tissue resolution but may impair pathogen clearance if prematurely expressed (24).

The balance between these cytokine networks determines healing phenotype (25). In scarless fetal healing, pro-inflammatory cytokines are transiently expressed at lower levels compared to adult wounds (2). The mechanisms underlying this differential cytokine expression include epigenetic modifications, distinct transcription factor profiles, and differences in cellular composition (24).

4.3.2 Inflammasome Activation

NLRP3 inflammasome activation contributes to pyroptosis and IL-1 β release during wound healing (24). Dysregulated inflammasome activity has been implicated in chronic wounds and excessive scarring, representing a potential therapeutic target (5).

Inflammasome activation occurs in response to danger-associated molecular patterns (DAMPs) released from damaged cells, including ATP, uric acid, and mitochondrial DNA (24). In fibrotic healing, sustained DAMP release induces inflammasome activation and chronic inflammation (8). Targeting upstream DAMP signaling or downstream IL-1 β may interrupt this cycle (5).

4.4 Epigenetic Regulation

Epigenetic mechanisms including DNA methylation, histone modifications, and non-coding RNAs regulate gene expression during wound healing (24). These modifica-

tions can stabilize fibrotic or regenerative cellular phenotypes and may explain why certain cell populations maintain their healing characteristics (24).

MicroRNAs have emerged as key regulators of wound healing (24). miR-133a inhibits myofibroblast differentiation and pulmonary fibrosis, while other microRNAs promote fibrotic responses (24,38). Long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) have also been implicated in wound healing regulation, though their mechanisms are less well characterized (24).

Understanding the epigenetic aspect of wound healing offers opportunities for targeted intervention (24). However, the challenges of achieving cell-type-specific epigenetic modification in vivo have limited clinical translation to date.

4.5 Microbiome and Metabolic Signaling

The wound microbiome has emerged as a critical but underappreciated determinant of healing outcome (39). Recent advances in 16S rRNA sequencing and metagenomics have revealed complex microbial communities within wounds that actively influence host healing responses (40).

4.5.1 Microbial Dysbiosis and Healing Outcomes

Chronic wounds exhibit characteristic dysbiosis characterized by decreased microbial diversity and dominance of specific taxa (39). *Staphylococcus aureus* and *Pseudomonas aeruginosa* are frequently enriched in non-healing wounds and produce virulence factors that impair healing. These pathogens secrete proteases that degrade growth factors and ECM components, effectively "hijacking" the healing process (39,41).

While associations between specific microbes and poor healing are well-established, causality remains difficult to prove. Most studies are observational, and the directionality of microbe-healing relationships is unclear; poor healing may create environments that select for pathogenic organisms rather than pathogens causing poor healing.

4.5.2 Biofilm Formation and Immune Evasion

Bacterial biofilms, which are structured in extracellular polymeric substances (EPS), form in the most chronic wounds. Biofilms lead to antimicrobial resistance and enable immune evasion, sustained inflammation and delaying healing. Biofilm-encased bacteria exhibit altered metabolism and reduced susceptibility to both antibiotics and host immune mechanisms (42).

Biofilm disruption strategies, including topical surfactants, quorum sensing inhibitors, and bacteriophage therapy, represent promising approaches to chronic wound management (42). However, clinical evidence supporting these strategies remains limited.

4.5.3 Microbial Metabolite Signaling

Microbial metabolites directly influence host cell behavior. Short-chain fatty acids (SCFAs) produced by commensal bacteria modulate immune responses and can promote anti-inflammatory macrophage polarization (43). In contrast, phenazines and pyocyanin produced by *P. aeruginosa* generate oxidative stress and activate fibrotic signaling pathways (44).

The host-microbe metabolite exchange represents a potential therapeutic target. Prebiotics and metabolite-based interventions may promote beneficial microbial communities and improve healing outcomes.

5. Extracellular Matrix Dynamics

5.1 ECM Composition in Scarless vs. Fibrotic Healing

The extracellular matrix provides structural support and biochemical cues that regulate cellular behavior during wound healing (9,10). Qualitative and quantitative differences in ECM composition distinguish scarless from fibrotic healing (2,10).

5.1.1 Collagen Subtype Distribution

Adult fibrotic wounds are characterized by predominance of collagen I, which forms thick, disorganized bundles that create visible scars (10). In contrast, fetal scarless wounds contain higher proportions of collagen III, which forms finer, more organized fibrils that better replicate normal tissue architecture (2).

The collagen I/III ratio has been proposed as a biomarker for fibrosis (10). Therapeutic strategies that promote collagen III synthesis or inhibit collagen I deposition may reduce scarring while maintaining wound strength (10,45). However, the relationship between collagen subtype and mechanical properties is complex, and optimal ratios likely vary by tissue type and wound characteristics (45).

While the collagen I/III ratio is widely cited (46), recent studies have challenged its universality (45). Some regenerative healing models show normal collagen I deposition without fibrosis, suggesting that collagen organization and cross-linking may be more important than subtype composition (45). Additionally, collagen V and VI have emerged as important regulators of fibrillogenesis that may be more predictive of scar quality than the I/III ratio (46,47).

5.1.2 Proteoglycan and Glycosaminoglycan Content

Hyaluronic acid (HA) is markedly elevated in fetal wounds compared to adult wounds and plays important roles in facilitating cell migration, modulating inflammation, and promoting regenerative healing (2,48). High molecular weight HA exhibits anti-inflammatory properties, while HA fragments can promote inflammation and fibrosis (48,49).

The balance between HA synthesis (by hyaluronan synthases, HAS1-3) and degradation (by hyaluronidases, HYAL1-2) determines HA molecular weight distribution and biological activity (50,51). Fetal fibroblasts express higher HAS2 levels and lower HYAL activity, contributing to elevated high molecular weight HA (48,52).

5.2 Matrix Remodeling and Metalloproteinases

Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) regulate ECM turnover during wound healing (10,45). The balance between MMP-mediated degradation and TIMP-mediated preservation of ECM components determines matrix composition and organization (53).

In fibrotic healing, dysregulated MMP activity leads to excessive collagen accumulation and abnormal matrix cross-linking (54,55). CD44-dependent regulation of MMP activity has been identified as a key mechanism controlling ECM remodeling and tensile strength during cutaneous wound healing (45).

5.3 Mechanobiology of Matrix Remodeling

Mechanical forces profoundly influence wound healing outcomes (18,56). Matrix stiffness and mechanical tension regulate fibroblast activation and promote myofibroblast differentiation in fibrotic healing (4,18). This mechanobiological feedback loop can result in chronic fibrotic responses even after the initial injury has resolved (56).

Mechanical tension stimulates fibroblast-to-myofibroblast transition in human burn scars (57). Clinical strategies that reduce mechanical tension on healing wounds, such as silicone gel sheeting and tension-reducing sutures, have demonstrated efficacy in reducing scar formation (58,59).

5.4 YAP/TAZ Mechano-transduction

The Hippo pathway effectors Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) have emerged as central mediators linking mechanical signals to fibrotic gene expression (60,61). These transcriptional coactivators shuttle between cytoplasm and nucleus in response to mechanical cues, translating physical forces into transcriptional programs (62).

5.4.1 Mechano-sensing and Nuclear Translocation

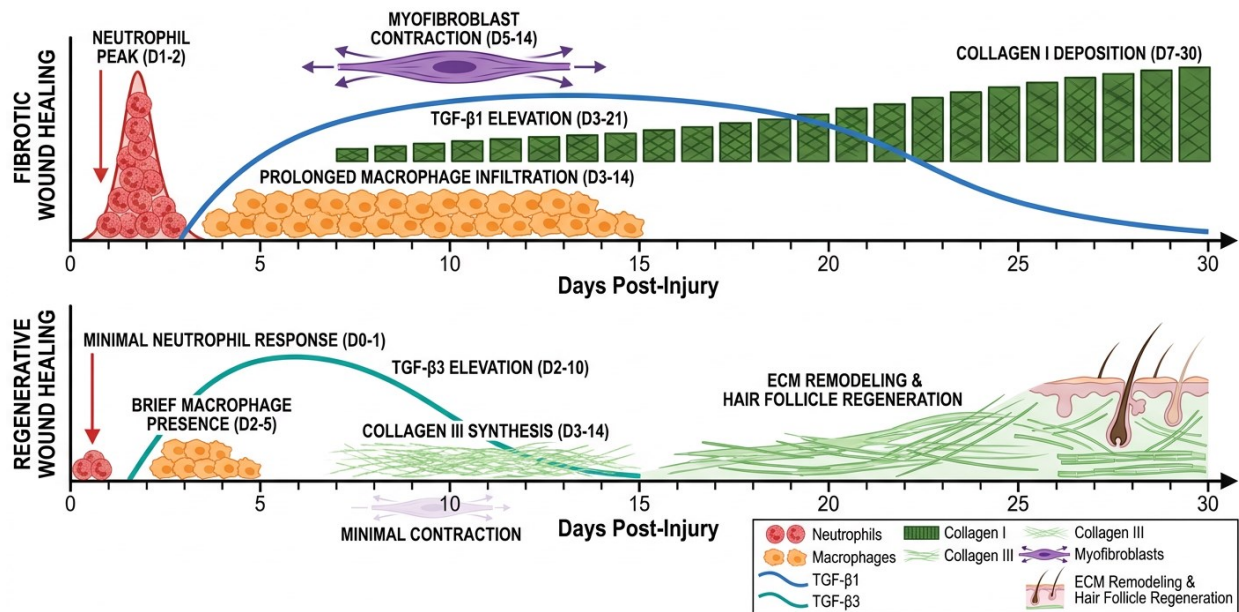


Figure 1. Temporal dynamics of fibrotic versus regenerative wound healing. (A) Fibrotic healing (adult) is characterized by prolonged neutrophil infiltration (days 1–3), sustained macrophage presence (days 3–14), elevated TGF- β 1 (days 3–21), collagen I deposition (days 7–30), and myofibroblast-mediated contraction (days 5–14). (B) Regenerative healing (fetal) exhibits minimal neutrophil response (days 0–1), brief macrophage infiltration (days 2–5), TGF- β 3 predominance (days 2–10), collagen III synthesis (days 3–14), minimal contraction, and restoration of adnexal structures including hair follicles.

YAP/TAZ are regulated by the core Hippo kinase cascade (MST1/2 and LATS1/2). When Hippo signaling is active, LATS1/2 phosphorylates YAP/TAZ, promoting cytoplasmic retention and degradation. When Hippo signaling is inhibited, such as upon exposure to stiff matrices or high cell density, YAP/TAZ translocate to the nucleus and activate transcription (62,63).

Mechanical cues regulate YAP/TAZ through multiple interconnected mechanisms. The polymerization of F-actin and the formation of stress fibers promote the nuclear translocation of YAP/TAZ, enhancing their transcriptional activity (64). Cell morphology also plays a critical role, as spread cells tend to maintain YAP/TAZ within the nucleus, whereas rounded cells typically exhibit cytoplasmic localization (61). In addition, the engagement of integrins with the extracellular matrix transmits mechanical signals that modulate the Hippo signaling pathway (65). Cell–cell contact further influences YAP/TAZ regulation through cadherin-mediated adhesions, which activate Hippo signaling and consequently restrict the nuclear localization and activity of YAP/TAZ (66).

5.4.2 Cross-Talk with TGF- β and Wnt Pathways

YAP/TAZ physically and functionally interact with major fibrotic signaling pathways. TGF- β 1 promotes YAP/TAZ nuclear accumulation and transcriptional activity, creating a positive feedback loop that amplifies fibrotic responses

(67,68). Smad and YAP/TAZ form transcriptional complexes that synergistically activate fibrotic genes including CTGF, CYR61, and collagen isoforms (69).

Wnt/ β -catenin and YAP/TAZ pathways also exhibit cross-talk. Both pathways share common target genes and can stabilize each other's transcriptional effects (70). Co-activation of Wnt and YAP/TAZ signaling produces potent fibrotic responses (71).

5.4.3 Therapeutic Targeting of YAP/TAZ

Given their central role in mechano-transduction and fibrosis, YAP/TAZ represent attractive therapeutic targets. Statins, which inhibit mevalonate synthesis and thereby block YAP/TAZ geranylgeranylation, show anti-fibrotic effects in preclinical models (72). Verteporfin, a photosensitizer that disrupts YAP-TEAD interactions, also attenuates fibrosis (73).

However, YAP/TAZ are essential for normal tissue homeostasis and regeneration. Complete YAP/TAZ inhibition impairs liver and intestinal regeneration, raising concerns about safety in wound healing applications (74,75). Developing context-specific or temporally controlled YAP/TAZ modulators represents an important challenge.

6. Comparative Analysis: Integrating Cellular and Molecular Mechanisms

6.1 Spatiotemporal Dynamics

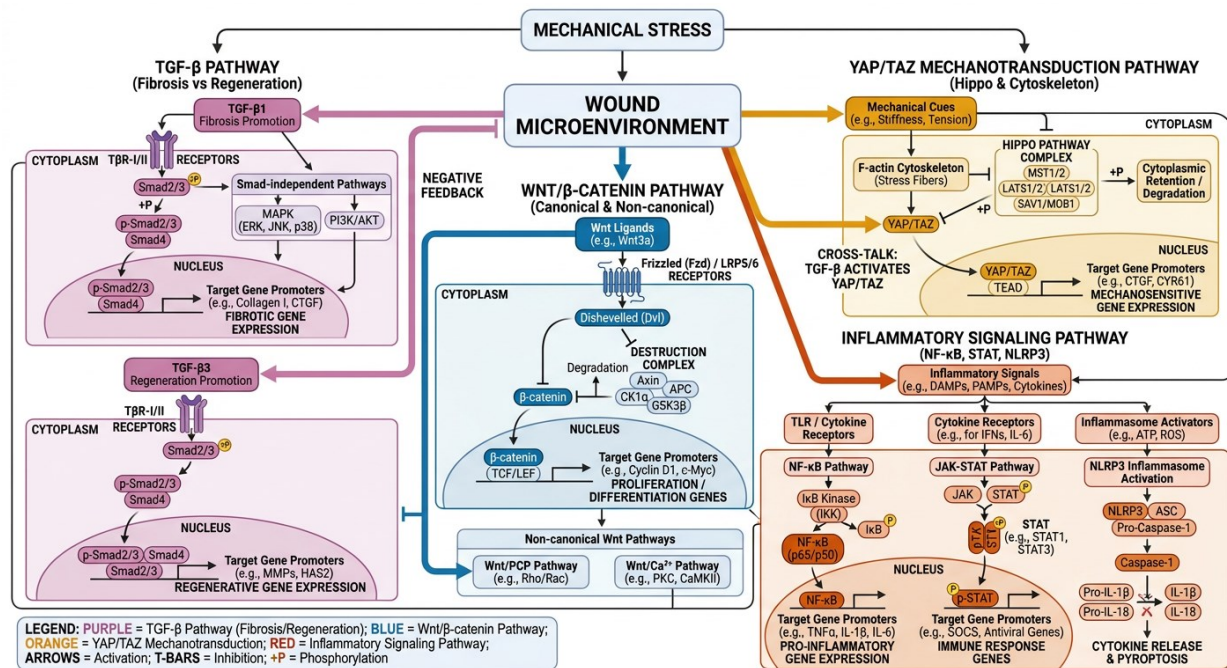


Figure 2. Integrated signaling network governing wound healing phenotype. The wound microenvironment integrates mechanical, biochemical, and inflammatory signals through four major pathways: (1) TGF-β signaling with isoform-specific effects (TGF-β1 promoting fibrosis vs. TGF-β3 promoting regeneration) acting through Smad-dependent and independent routes; (2) Wnt/β-catenin signaling with context-dependent roles in regeneration and fibrosis; (3) YAP/TAZ mechano-transduction linking matrix stiffness to transcriptional programs via the Hippo pathway; (4) Inflammatory signaling through NF-κB, STAT, and inflammasome activation. Extensive cross-talk occurs between pathways: TGF-β activates YAP/TAZ, Wnt provides negative feedback to TGF-β, and mechanical stress influences all pathways.

Recent advances in imaging and spatial transcriptomics have revealed the spatiotemporal dynamics of mammalian wound healing (7). These studies demonstrate that healing involves coordinated waves of cellular activation and molecular signaling that propagate across the wound bed in defined temporal sequences (7).

As illustrated in Figure 1, the temporal organization of healing events differs significantly between fibrotic and regenerative paradigms (2). In fibrotic healing, the inflammatory phase is prolonged, creating an environment that promotes myofibroblast differentiation and ECM deposition (4,8). In regenerative healing, rapid resolution of inflammation and distinct growth factor profiles enable tissue restoration without fibrosis (2,3).

6.2 Integrated Signaling Networks

Wound healing involves complex networks of interacting signaling pathways (34). Systems biology approaches have begun to map these networks and identify key nodes that determine healing outcomes (Figure 2).

6.3 Cell-Cell Communication Networks

Beyond individual signaling pathways, cell-cell communication networks determine healing outcomes (Figure 3). Paracrine signaling between macrophages, fibro-

blasts, keratinocytes, and neutrophils creates feedback loops that either induce fibrosis or promote resolution (11,25).

Recent single-cell analyses have revealed cell type-specific communication patterns. POSTN+ fibroblasts and SPP1+ macrophages form positive feedback loops that may drive scar formation, while other cell-type pairings promote regenerative responses (28,76).

Understanding these communication networks provides a framework for designing interventions that interrupt pathological signaling while preserving necessary repair.

8. Discussion

This review has examined the cellular and molecular mechanisms distinguishing scarless regenerative healing from fibrotic repair. Rather than isolated processes, the evidence points toward three interconnected regulatory axes whose combined activity shapes healing outcome: fibroblast lineage specification, mechanical signaling, and immune modulation.

Fibroblasts are not uniform. Different lineages exist, established during development and marked by distinct molecular signatures such as POSTN and CD26, carrying different predispositions toward fibrotic or regenerative responses (13). This heterogeneity provides the

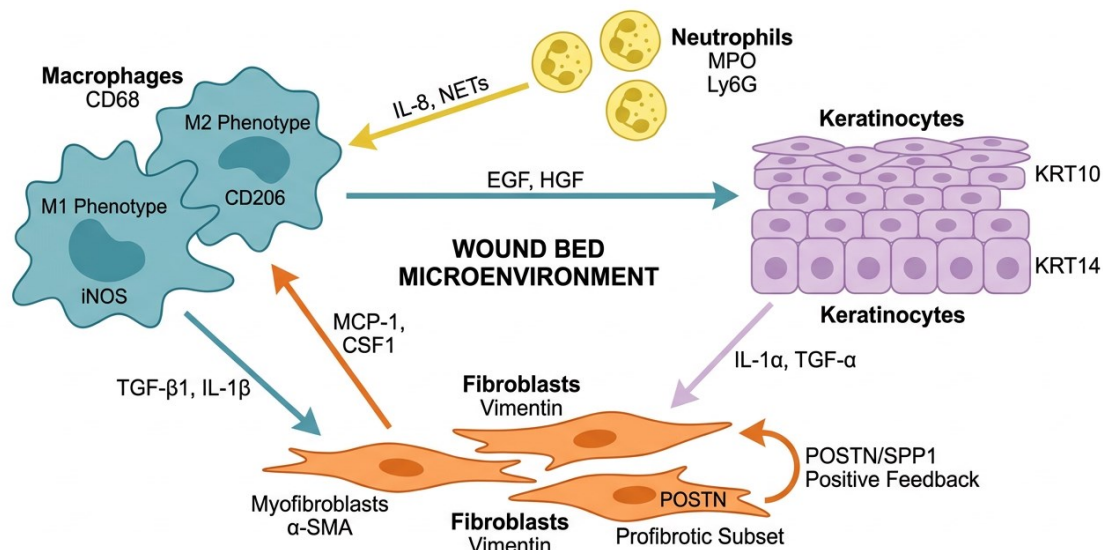


Figure 3. Cell-cell communication networks in wound healing. The wound microenvironment comprises interacting cell populations with characteristic markers: macrophages (CD68, CD206, iNOS), fibroblasts (Vimentin, α -SMA, POSTN), keratinocytes (KRT14, KRT10), and neutrophils (MPO, Ly6G). Directional paracrine signaling includes: macrophage-to-fibroblast (TGF- β 1, IL-1 β), fibroblast-to-macrophage (MCP-1, CSF1), keratinocyte-to-fibroblast (IL-1 α , TGF- α), neutrophil-to-macrophage (IL-8, NETs), and macrophage-to-keratinocyte (EGF, HGF). The POSTN-SPP1 positive feedback loop between profibrotic fibroblasts and macrophages may drive scar formation. Abbreviations: M1, pro-inflammatory macrophages; M2, anti-inflammatory macrophages; NETs, neutrophil extracellular traps; POSTN, periostin; SPP1, osteopontin; α -SMA, alpha-smooth muscle actin; KRT, keratin; iNOS, inducible nitric oxide synthase; EGF, epidermal growth factor; HGF, hepatocyte growth factor; CSF1, colony-stimulating factor 1; MCP-1, monocyte chemoattractant protein-1; IL, interleukin; TGF, transforming growth factor.

cellular substrate upon which other signals act. What remains unclear is how permanently these identities are fixed. Some evidence suggests contact-mediated transitions between states can occur without classical TGF- β or mechanical cues (22), while other data support more rigid restriction (13). This matters for therapy because reversible identity enables reprogramming strategies, whereas fixed fate requires different approaches.

Mechanical forces amplify whatever program fibroblasts are already running. YAP/TAZ mechano-transduction and integrin signaling respond to matrix stiffness and tissue tension, driving fibroblast activation. In pro-fibrotic lineages, mechanical stress drives myofibroblast differentiation and excessive matrix production (4). The same environment may trigger different responses in pro-regenerative lineages (2). Clinical observations support this, as tension-reducing strategies demonstrably reduce scar formation across diverse patients (58,59). YAP/TAZ sit at the center of this response, forming complexes with Smad proteins and β -catenin where mechanical, TGF- β , and Wnt inputs converge (67–71). Complete YAP/TAZ inhibition carries risks because these pathways are essential for normal tissue homeostasis (74,75), so temporally controlled modulation will likely be necessary.

The immune response provides contextual signals determining which fibroblast programs engage and how mechanical inputs are interpreted. This is perhaps the best-supported principle, with converging evidence from fetal wounds, genetic models, and clinical observations (8). Scarless fetal healing occurs with brief, attenuated inflammation that fails to trigger fibrotic programs (2). Fibrotic adult healing involves sustained inflammatory signaling from macrophages and neutrophils that activates and amplifies pro-fibrotic responses (8,25). Neutrophils have emerged as more important than previously appreciated, with their extracellular traps directly activating fibroblasts and sustaining inflammation (11). POSTN+ fibroblasts and SPP1+ macrophages form positive feedback loops driving scar formation, while other cell pairings promote regenerative outcomes (5,13,28). Breaking pathological communication while preserving necessary repair signaling represents a major challenge, particularly because inflammation cannot be eliminated entirely given its essential roles in debris clearance and infection control (23).

Several conclusions emerge with confidence. Inflammatory duration and intensity genuinely influence outcome (2,8). The TGF- β 3/TGF- β 1 ratio appears important, with TGF- β 3 associating with regeneration and TGF- β 1 driving fibrosis through differential receptor affinity and

Smad activation patterns (3). Mechanobiological feedback loops are self-reinforcing, as stiffer matrix activates fibroblasts producing more matrix (18,56). The widely cited collagen I/III ratio as a fibrosis biomarker has been challenged, with collagen organization and cross-linking potentially more important than subtype composition (45,47). Hyaluronic acid is elevated in fetal wounds, with high molecular weight HA exhibiting anti-inflammatory properties while fragments promote fibrosis (48,49).

Several areas deserve more attention. The wound microbiome influences healing quality, but causality remains unclear (39). Chronic wounds show dysbiosis with pathogenic enrichment (39,41), yet whether poor healing selects for pathogens or pathogens cause poor healing is unresolved. Sex differences are real and likely clinically relevant but systematically underexplored. Epigenetic mechanisms stabilize fibrotic or regenerative phenotypes (24), but achieving cell-type-specific modification *in vivo* has limited translation.

Fundamental questions remain unresolved. The developmental origins of fibroblast lineages and whether identities are fixed or plastic are incompletely understood (13,22). The temporal boundaries for meaningful intervention are poorly defined. The mechanisms of acute-to-chronic wound transition are unclear (26). How local wound biology integrates with systemic factors such as aging and diabetes needs better characterization (26). We also need to be clear about how well animal research actually carries over to human wound healing. While studies on rodents have been essential for uncovering the underlying biology, there are several biological differences that prevent us from applying those results directly to human. For instance, rodents have a thin muscle layer beneath their skin, the panniculus carnosus, that allows wounds to close quickly through contraction. Human wounds, by contrast, depend much more on the regrowth of epithelial tissue and the formation of granulation tissue, which means the roles played by myofibroblasts, extracellular matrix production, and the inflammatory response are correspondingly quite different (77). Variations in how neutrophils and macrophages behave, as well as how quickly inflammation declines, can also cause animal models to inadequately reflect the prolonged inflammatory state that often leads to scar formation in humans (78).

Fetal wound-healing studies come with their own challenges. Healing in the fetus takes place in a uniquely sterile, fluid-filled, low-tension environment inside the uterus, and the exact developmental moment when scarless repair shifts to scar-forming repair is not consistent across species (17). Moreover, the genetic uniformity common to inbred laboratory strains, combined with metabolic differences between species, means these models may miss the wide variability seen in how humans actually heal (79,80).

None of this reduces the importance of animal research for pinpointing promising mechanisms and drug targets. Still,

we should be careful not to overstate how broadly those findings will apply to human patients. Results from preclinical work need to be confirmed using systems that better mirror human biology, such as *ex vivo* wound models, three-dimensional skin cultures, and organ-on-a-chip technologies, before moving into well-designed clinical trials that use standardized scar-assessment criteria and classify patients by relevant biomarkers. These limitations should be considered when interpreting mechanistic evidence throughout this review, particularly when proposed therapeutic strategies are based primarily on rodent studies.

Based on this framework, several hypotheses need to be investigated. Sequential targeting of inflammation early then mechano-transduction late may outperform either alone. Patient stratification by lineage markers could identify responders to specific therapies. Early microbiome modulation might shift immune recruitment beneficially. Sex-specific approaches targeting hormonal signaling may improve outcomes in relevant populations. YAP/TAZ inhibition during remodeling rather than early healing might reduce scarring without compromising closure. The field needs validated biomarkers predicting response, and standardized outcome measures for scar quality.

Clinical translation also requires consideration of patient heterogeneity. Age, diabetes, vascular disease, medications, immune status, genetics, wound location, and mechanical environment can all influence healing. Therapeutic strategies that target a single pathway may therefore have variable effects among patients.

The ultimate clinical endpoint should extend beyond rapid wound closure. A therapy that accelerates closure but produces excessive fibrosis may not represent a meaningful improvement. Future trials should therefore incorporate validated measures of scar quality, tissue architecture, mechanical properties, and functional outcomes.

Overall, the evidence supports an integrated rather than reductionist model of wound healing. Fibroblast state, immune context, extracellular matrix properties, and mechanical signaling appear to interact dynamically. However, the proposition that simultaneous or sequential targeting of multiple regulatory axes will consistently outperform single-pathway interventions remains a testable hypothesis rather than an established therapeutic principle.

7. Conclusion

The distinction between scarless regenerative healing and fibrotic repair reflects fundamental differences in how tissues respond to injury. This review has demonstrated that healing outcome emerges from the integrated activity of fibroblast lineage specification, mechanical signaling, and immune modulation rather than any single dominant pathway. Scarless fetal healing is characterized by minimal inflammation, favorable TGF- β 3/TGF- β 1 ratios, organized

collagen III deposition, and absence of sustained myofibroblast activation. Fibrotic adult healing involves prolonged inflammatory responses, TGF- β 1 predominance, excessive collagen I deposition, and self-reinforcing mechanobiological feedback loops mediated by YAP/TAZ signaling. These mechanistic differences have identified promising therapeutic targets including isoform-selective TGF- β modulation, mechanical offloading, temporally controlled immune intervention, and fibroblast lineage-specific approaches. However, substantial obstacles separate mechanistic insight from clinical benefit. Key knowledge gaps persist regarding fibroblast lineage plasticity, optimal therapeutic windows, integration of local and systemic factors, and translation from rodent models to human biology. The field lacks validated biomarkers for predicting healing trajectories and standardized outcome measures for scar quality beyond simple wound closure.

The ultimate goal is not simply faster closure but restoration of tissue architecture and function without pathological scarring. Achieving this will likely require combination strategies addressing multiple regulatory axes in appropriate temporal sequence rather than single pathway interventions. The transition from scarless fetal healing to fibrotic adult repair demonstrates that mammalian tissues possess the biological capacity for regeneration. The challenge now is unlocking that capacity therapeutically through rigorous experimental validation, human-relevant model systems, biomarker-stratified clinical trial designs, and regulatory frameworks that prioritize long-term functional outcomes. As our understanding of fibroblast heterogeneity, mechanotransduction, and immune regulation deepens, personalized approaches based on patient-specific profiles become increasingly feasible, offering hope for the millions whose lives are diminished by chronic wounds and pathological scarring.

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