

Fetal Wound Healing and Translational Applications for Scarless Skin Repair

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Abstract

Fetal wound healing represents a unique model of scarless tissue repair and provides an important biological framework for developing regenerative therapies for adult skin wounds. Unlike adult wound healing, which often results in fibrosis and permanent scar formation, early-gestation fetal wounds can restore normal skin architecture with minimal inflammation, rapid re-epithelialization, organized extracellular matrix deposition, and reduced myofibroblast activation. This review summarizes the cellular, molecular, immunological, and biomechanical mechanisms underlying fetal scarless wound healing and discusses their translational relevance for tissue engineering and regenerative medicine. Key features of fetal repair include a hyaluronic acid-rich extracellular matrix, a higher collagen III/I ratio, increased TGF- β 3 activity relative to TGF- β 1 and TGF- β 2, attenuated inflammatory cytokine signaling, fetal-specific fibroblast phenotypes, and a mechanically compliant wound environment. Particular attention is given to mechanotransduction pathways, including integrin-mediated signaling, FAK, Rho/ROCK, and YAP/TAZ, which link matrix stiffness and tissue tension to fibroblast activation and scar formation. The review further examines fetal-inspired therapeutic strategies, including hyaluronic acid-based hydrogels, immunomodulatory biomaterials, stem cell-derived secretomes, controlled growth factor delivery, anti-fibrotic agents, RNA-based therapies, and bioengineered skin substitutes. Although these approaches have shown promising preclinical and early clinical potential, true scarless regeneration in adult human skin remains challenging due to the complexity of the fetal wound microenvironment, differences in immune maturity, delivery timing, safety concerns, and regulatory barriers. Understanding fetal wound healing as an integrated and dynamically regulated process may guide the design of multi-cue regenerative therapies aimed not only at reducing scar formation but also at restoring functional skin architecture.

1. Introduction

Scarless wound healing remains one of the most persistent challenges in tissue engineering and regenerative medicine. Although considerable advances have been achieved in the development of skin substitutes, bioactive wound dressings, and cell-based therapies, complete structural and functional restoration of adult skin after injury remains clinically unattained⁽¹⁾. In adult mammals, wound healing typically culminates in fibrotic scar formation, a reparative process characterized by excessive extracellular matrix (ECM) deposition, altered collagen architecture, and the permanent loss of skin append-

ages such as hair follicles and sweat glands⁽²⁾. Beyond aesthetic concerns, scar tissue exhibits reduced mechanical elasticity, impaired thermoregulation, and diminished sensory function, highlighting the fundamental limitations of current therapeutic approaches⁽³⁾. In contrast, early-gestation fetal skin demonstrates a remarkable capacity for scarless healing. This phenomenon is driven by a distinct cellular and molecular microenvironment that differs fundamentally from adult wound healing⁽⁴⁾. Hallmarks of fetal repair include a hyaluronic acid-rich ECM, differential transforming growth factor (TGF) signaling, particularly a higher TGF- β 3 to TGF- β 1 ratio⁽⁵⁾,

In humans, scarless fetal wound healing is generally observed during early and mid-gestation and is typically maintained until approximately 24 weeks of gestation. Thereafter, wound repair gradually transitions toward an adult-like fibrotic phenotype rather than shifting at a sharply defined developmental stage⁽⁷⁾. This transition is associated with progressive immune maturation, increased mechanical tension within the developing skin, and changes in extracellular matrix composition and remodeling⁽⁴⁾. Accordingly, scarless healing should be considered a temporally restricted developmental phenotype that progressively declines as fetal skin acquires the structural, mechanical, and immunological properties of postnatal tissue⁽⁸⁾.

Recent advances in biomaterials and biofabrication have facilitated the translation of fetal developmental principles into engineered therapeutic strategies. Approaches including extracellular matrix-mimetic scaffolds, immunomodulatory biomaterials, controlled delivery of morphogens and growth factors, and mechanically tunable hydrogels aim to recreate key features of the fetal regenerative microenvironment in adult wounds. Emerging technologies, such as three-dimensional bioprinting⁽⁹⁾ and stimulus-responsive biomaterials⁽¹⁾, enable spatial and temporal control of cellular behavior during tissue repair.

Despite these advances, important translational barriers remain. Reproducing the fetal wound-healing niche requires coordinated biochemical, immunological, and biomechanical control, while challenges in growth factor delivery, signal stability, biomaterial reproducibility, scalable manufacturing, and regulatory translation continue to limit clinical application⁽¹⁰⁾. As a result, most fetal-inspired strategies remain preclinical.

This review examines fetal wound healing as a model for scarless healing and its translational relevance to tissue engineering. We summarize the biological mechanisms underlying scarless healing and evaluate engineering approaches, including ECM-mimetic biomaterials, controlled delivery of regenerative signals, and biomechanical modulation, to outline a framework for advancing scarless skin regeneration toward clinically viable therapies.

2. Unique Features of Fetal Scarless Wound Healing

Fetal skin possesses a remarkable healing capacity that enables rapid repair with minimal to no visible scar formation. This phenomenon, known as scarless wound healing, occurs primarily during early gestation and differs fundamentally from adult wound repair. Unlike the fibrotic healing seen in postnatal tissues, fetal wound repair can largely restore skin architecture, including relatively normal dermal organization and preservation of key functional characteristics⁽¹⁾.

Several features contribute to this capacity. Fetal wounds exhibit minimal inflammation, reduced neutrophil and macrophage infiltration, and a cytokine profile favoring anti-inflammatory signaling. The ECM also differs from adult skin, particularly in its high hyaluronic acid (HA) content and higher collagen type III to type I ratio. In addition, fetal fibroblasts display enhanced migratory capacity and a reduced tendency toward myofibroblast differentiation, limiting excessive matrix deposition and contraction⁽¹¹⁾. The fetal biomechanical environment is also softer and less tension-driven, supporting signaling pathways associated with tissue remodeling. Together, these features create a pro-regenerative microenvironment that supports scarless wound healing⁽¹²⁾.

For conceptual clarity, this review distinguishes between “regenerative” and “scarless” healing. “Regenerative healing” refers to structural and functional restoration of native skin architecture, including orderly collagen assembly and re-establishment of skin appendages⁽¹³⁾. By contrast, “scarless healing” refers to the clinical or macroscopic absence of visible scar tissue. Although these phenotypes overlap in early-gestation fetal repair, a scarless outcome does not necessarily indicate complete functional regeneration, as subtle extracellular matrix and biomechanical differences may persist⁽¹⁰⁾.

2.1 Developmental Stages of Fetal Skin Healing

The scarless wound healing potential of fetal skin is strongly dependent on gestational age. Early-gestation fetal wounds typically heal in a scarless manner, whereas wounds occurring during later stages of development gradually transition toward a repair process more similar to that observed in adults⁽¹⁴⁾.

During early fetal development, wound closure occurs rapidly through coordinated cell migration and proliferation. Keratinocytes migrate efficiently to re-epithelialize the wound surface, while fetal fibroblasts contribute to matrix remodeling without inducing excessive fibrosis. The inflammatory phase, which plays a prominent role in adult wound healing, is markedly attenuated during this stage⁽¹¹⁾.

As gestation progresses, changes in the immune system, ECM composition, and fibroblast phenotype gradually alter the healing response. Increased inflammatory activity, changes in collagen deposition, and enhanced differentiation of fibroblasts into contractile myofibroblasts contribute to the progressive loss of scarless regenerative capacity. This developmental transition suggests that the mechanisms responsible for fetal scarless healing are tightly linked to the maturation of skin structure and immune regulation⁽⁴⁾.

Understanding the temporal regulation of these developmental processes is essential for identifying biological cues that could potentially be harnessed in regenerative medicine and tissue engineering strategies.

2.2 Structural Characteristics of Fetal Skin

The structural organization of fetal skin differs substantially from that of adult skin and plays an important role in enabling scarless wound healing. These differences are particularly evident in the architecture of the dermis and the composition of the ECM.

Organization of Dermis

The fetal dermis exhibits a loosely organized and highly cellular structure compared with adult dermis. Collagen fibers in fetal skin are typically thin, uniformly distributed, and arranged in a reticular pattern rather than the dense, parallel bundles commonly seen in adult tissue. This organization facilitates rapid matrix remodeling and allows cells to migrate efficiently during the wound healing process⁽¹⁵⁾.

Fetal fibroblasts also display distinct functional characteristics⁽¹⁶⁾. They produce ECM components in a controlled and balanced manner and show reduced differentiation into myofibroblasts, which are largely responsible for wound contraction and fibrotic scar formation in adult tissues. As a result, the structural integrity of the dermis can be restored without excessive matrix deposition or tissue contraction⁽¹⁷⁾.

ECM Composition

The ECM of fetal skin is characterized by features that favor regenerative healing, including high levels of hyaluronic acid (HA) and a higher collagen type III-to-type I ratio^(5, 18). These ECM components create a dynamic microenviron-

ment that supports controlled tissue remodeling and limits fibrotic responses during wound healing. The mechanistic roles of HA and collagen composition in fetal repair are discussed in Sections 4.1 and 4.2, respectively.

2.3 Differences Between Fetal and Adult Wound Healing

Although fetal and adult wound healing share the same general phases (hemostasis, inflammation, proliferation, and remodeling) the magnitude and regulation of these processes differ substantially.

One of the most significant differences is the degree of inflammation. Adult wounds are characterized by a pronounced inflammatory response involving the recruitment of neutrophils, macrophages, and pro-inflammatory cytokines. In contrast, fetal wounds display a markedly reduced inflammatory reaction, and increased expression of anti-inflammatory mediators (see Section 5.2)⁽¹¹⁾.

Feature	Fetal wound healing	Adult wound healing
Inflammation	Low	High
Fibroblast phenotype	Migratory, less myofibroblastic	α -SMA+ myofibroblast-rich
ECM	HA-rich, collagen	Collagen I-rich,
TGF-β profile	Higher TGF- β 3/ TGF- β 1	Higher TGF- β 1/2
Mechanical tension	Low	High
Outcome	Regeneration	Fibrosis/Scar

Fetal wound healing (scarless)	Adult wound healing (scar-forming)
 Inflammation Low, brief, controlled	 Strong, prolonged
 Fibroblast / Myofibroblast Activity - Regenerative fibroblasts - Limited myofibroblasts	 Activated fibroblasts Abundant myofibroblasts Contraction
 Hyaluronic acid-rich Organized matrix	 Dense provisional matrix Fibrotic remodeling
 Fine reticular, Collagen III-dominant Organized tissue	 Thick, parallel Collagen I-rich
 Cytokine / Growth Factor Profile - Low TGF-β1/β2 - Higher TGF-β3 - Pro-regenerative signaling	 High TGF- β 1/ β 2 Pro-fibrotic signaling
 Reduced neutrophils Macrophage activity ↓	 Robust inflammatory cell infiltration
 Low tension / Compliant tissue	 High tension / Stiff matrix
 Complete regeneration With skin appendages	 Scar with reduced appendages

Figure 1: Comparison of fetal and adult wound healing

Another key difference lies in fibroblast behavior and ECM deposition. In adult wound healing, fibroblasts differentiate into myofibroblasts that produce large amounts of collagen and contribute to wound contraction and scar formation. Fetal fibroblasts, however, produce matrix components in a more regulated manner and exhibit reduced myofibroblast differentiation, thereby preventing excessive fibrosis⁽¹²⁾.

Differences also exist in growth factor signaling, particularly in the balance of TGF- β isoforms. Adult wounds typically show increased expression of TGF- β 1 and TGF- β 2, whereas fetal wounds exhibit higher levels of TGF- β 3⁽¹⁷⁾ (see Section 5.1).

Finally, the mechanical environment of adult skin, which experiences greater tension and mechanical stress, further promotes scar formation. In contrast, the relatively low-tension environment of fetal skin contributes to more organized tissue remodeling⁽¹⁹⁾. These differences have shown in table 1, and figure 1.

Table 1: Comparison of fetal and adult wound healing

3. Cellular Mechanisms of Scarless Healing

Scarless fetal wound healing is driven by distinct cellular mechanisms that differ fundamentally from those observed in adult tissue repair. In fetal skin, the coordinated activity of fibroblasts, keratinocytes, and immune cells creates a microenvironment that favors regeneration rather than fibrosis. These cells interact dynamically with the ECM and signaling molecules to regulate cell migration, proliferation, and matrix remodeling. Unlike adult wound healing, where prolonged inflammation and excessive fibroblast activation lead to scar formation, fetal wounds exhibit a tightly controlled cellular response that enables rapid tissue restoration while maintaining normal skin architecture.

Understanding these cellular behaviors is critical for tissue engineering approaches aimed at recreating a regenerative microenvironment in adult wounds. These mechanisms are illustrated in Figure 2.

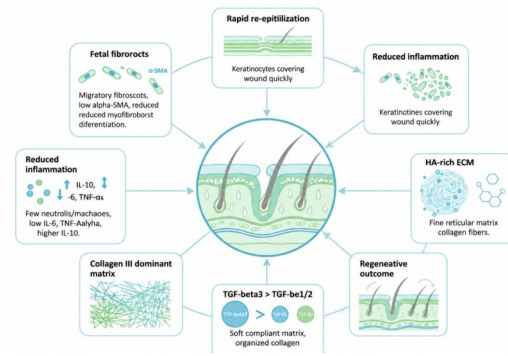


Figure 2: Mechanism of scarless fetal wound healing

3.1 Fetal Fibroblast Phenotypes

Fibroblasts play a central role in wound healing through the synthesis and remodeling of ECM components. However, fetal fibroblasts exhibit phenotypic and functional characteristics that differ significantly from adult fibroblasts, which contribute to their scarless healing capacity⁽¹⁷⁾.

One of the defining features of fetal fibroblasts is their reduced tendency to differentiate into myofibroblasts. In adult wound healing, fibroblasts commonly differentiate into α -smooth muscle actin (α -SMA)—expressing myofibroblasts, which generate contractile forces and produce large amounts of collagen, ultimately leading to fibrotic scar formation. In contrast, fetal fibroblasts maintain a more migratory and proliferative phenotype and produce ECM in a balanced manner, preventing excessive collagen accumulation⁽⁴⁾.

Additionally, fetal fibroblasts exhibit distinct gene expression profiles associated with scarless healing processes⁽²⁰⁾. These cells show increased expression of factors that promote matrix remodeling and reduced expression of pro-fibrotic mediators. Their ability to migrate efficiently and organize collagen deposition contributes to the restoration of normal dermal architecture during healing⁽¹¹⁾.

3.2 Keratinocyte Behavior and Re-epithelialization

Keratinocytes are essential for the rapid restoration of the epidermal barrier following injury. In fetal wounds, re-epithelialization occurs more rapidly and efficiently than in adult wounds, largely due to enhanced keratinocyte migration and proliferation. Fetal keratinocytes exhibit a highly coordinated migratory response that allows them to rapidly cover the wound surface. These cells interact closely with the underlying ECM and fibroblasts to facilitate tissue repair. Growth factors and signaling

molecules within the fetal wound environment promote keratinocyte activation while minimizing inflammatory signaling pathways. Moreover, fetal epidermal cells contribute to the restoration of normal skin structure without inducing the hyperproliferative responses often observed in adult wounds. This controlled re-epithelialization process helps maintain epidermal integrity and prevents abnormal tissue remodeling⁽²¹⁾.

3.3 Immune Cell Profile and Reduced Inflammation

Fetal wounds exhibit a markedly attenuated inflammatory response compared with adult wounds (see Section 5.2). In addition, macrophages in fetal wounds appear to adopt a more reparative phenotype, supporting tissue remodeling rather than prolonged inflammation. These observations suggest that the immune microenvironment is a key determinant of scarless fetal repair⁽²²⁾.

4. ECM and Biomechanical Environment

ECM plays a fundamental role in regulating cell behavior during wound healing. In fetal skin, the ECM provides a dynamic and permissive microenvironment that supports rapid tissue scarless healing. In addition to its biochemical composition, the biomechanical properties of the matrix, such as stiffness and mechanical tension, significantly influence cellular responses.

Compared with adult skin, fetal tissue exhibits a softer and more hydrated ECM that facilitates cell migration and matrix remodeling. These structural and mechanical properties help regulate fibroblast activity, reduce myofibroblast differentiation, and maintain balanced collagen deposition. Consequently, the ECM in fetal wounds functions not only as a structural scaffold but also as an active regulator of regenerative signaling pathways.

4.1 HA-Rich Microenvironment

One of the most distinctive features of fetal skin is the high abundance of HA within the ECM. HA is a glycosaminoglycan that contributes to tissue hydration, matrix viscoelasticity, cell migration, and ECM organization⁽²³⁾.

Elevated HA levels create a highly hydrated and permissive microenvironment that facilitates the migration of fibroblasts and keratinocytes during wound repair. In fetal wounds, this HA-rich matrix is associated with rapid tissue restoration and reduced formation of dense, disorganized collagen bundles characteristic of scar tissue. Through interactions with cell-surface receptors, particularly CD44, HA can modulate signaling pathways involved in cell adhesion, proliferation, migration, and matrix remodeling⁽²⁴⁾.

Furthermore, HA contributes to the regulation of the wound inflammatory response by influencing cytokine activity and immune-cell recruitment⁽²³⁾. Collectively, these biochemical and biophysical effects support a regenerative wound niche and help limit excessive fibroblast activation and fibrotic matrix deposition. However, the biological effects of HA depend on factors such as its molecular weight, concentration, and local inflammatory context. Thus, HA represents a key, but context-dependent, component of the fetal regenerative microenvironment.

4.2 Collagen Type III Dominance

Another characteristic feature of fetal wound healing is the predominance of collagen type III within the ECM. In adult wounds, collagen type I is the dominant structural protein and is typically deposited in thick, densely packed bundles that contribute to scar formation. In contrast, fetal skin contains a higher ratio of collagen type III to collagen type I. Collagen type III forms a more flexible and loosely organized network, allowing for greater tissue elasticity and more controlled matrix remodeling. This structural arrangement supports the restoration of normal dermal architecture rather than the formation of rigid scar tissue⁽²⁵⁾.

The balanced deposition and subsequent remodeling of collagen fibers in fetal wounds therefore play a critical role in maintaining tissue integrity while preventing fibrotic responses.

4.3 Matrix Remodeling and Mechanical Tension

Matrix remodeling is an essential process during wound healing, involving the synthesis, degradation, and reorganization of ECM components. In fetal skin, this process is highly regulated and occurs in a manner that preserves tissue architecture⁽²⁶⁾.

Enzymes such as matrix metalloproteinases (MMPs) and their inhibitors coordinate the controlled degradation and remodeling of collagen and other matrix proteins⁽²⁷⁾. This balanced activity prevents excessive matrix accumulation and supports the orderly reconstruction of the dermis⁽²⁶⁾.

In addition to biochemical factors, mechanical tension plays a critical role in determining wound healing outcomes⁽²⁸⁾. Adult skin is subjected to considerable mechanical stress, which can stimulate fibroblast activation and promote myofibroblast differentiation, ultimately contributing to scar formation⁽²⁹⁾. In contrast, fetal skin experiences lower mechanical tension, which reduces mechanotransduction signals associated with fibrosis⁽³⁰⁾.

The combination of controlled matrix remodeling and reduced mechanical stress creates a biomechanical environment that favors scarless healing. These insights have important implications for tissue engineering strategies aimed at designing biomaterials and scaffolds that replicate the scarless characteristics of the fetal skin microenvironment.

5. Molecular and Signaling Pathways in Fetal Scarless Repair

Scarless wound healing in fetal skin is regulated by a complex network of molecular signals and intracellular pathways that coordinate cellular behavior and ECM remodeling. Unlike adult wound repair, which often involves excessive activation of pro-fibrotic signaling cascades, fetal healing is characterized by a tightly controlled molecular environment that promotes scarless healing. Several signaling pathways play key roles in orchestrating this scarless healing process. Understanding these pathways is essential for identifying potential therapeutic targets that may help replicate fetal-like healing responses in adult tissues.

5.1 TGF- β Isoform Balance (TGF- β 3 vs TGF- β 1/2)

Among the molecular regulators of wound healing, the TGF- β family plays a pivotal role in determining whether tissue repair results in scarless healing or fibrosis. In adult wound healing, the isoforms TGF- β 1 and TGF- β 2 are typically upregulated and promote fibroblast activation, myofibroblast differentiation, and excessive collagen deposition. These processes contribute significantly to scar formation. In contrast, fetal wound healing is characterized by a distinct balance of TGF- β isoforms, with higher levels of TGF- β 3 relative to TGF- β 1 and TGF- β 2. TGF- β 3 has been associated with reduced fibrotic activity and more organized ECM deposition. This shift in isoform expression appears to suppress the pathways that drive fibrosis while promoting scarless tissue remodeling⁽³¹⁾. Experimental studies have demonstrated that modulation of the TGF- β signaling pathway, particularly increasing TGF- β 3 activity or reducing TGF- β 1/2 signaling, can reduce scar formation in adult wounds. Consequently, the TGF- β isoform balance has become an important target in the development of anti-scarring therapies and regenerative medicine strategies^(32, 33).

5.2 Cytokine and Growth Factor Regulation

Cytokines and growth factors play critical roles in regulating cellular communication during wound healing. In fetal skin, the expression profile of these signaling molecules differs markedly from that observed in adult wounds, contributing to a scarless healing.

Fetal wounds typically exhibit a cytokine profile that favors anti-inflammatory and regenerative signaling, characterized by lower levels of pro-inflammatory cytokines, including IL-6 and TNF- α , and relatively greater prominence of anti-inflammatory mediators such as IL-10 (22). This balanced cytokine milieu limits the recruitment and activation of inflammatory cells, suppresses excessive immune activation, and attenuates the activation of pro-fibrotic pathways^(22, 34, 35). Consequently, it helps maintain a scarless wound microenvironment and reduces the likelihood of fibrosis that commonly characterizes adult wound healing.

Several growth factors are also involved in fetal wound repair. Factors such as fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) regulate processes including angiogenesis, cell proliferation, and matrix remodeling. However, the temporal and spatial regulation of these growth factors in fetal tissue appears to be more tightly controlled, allowing for coordinated tissue regeneration without excessive fibrosis⁽³⁶⁾.

5.3 Wnt, Notch, and Hedgehog Signaling

Developmental signaling pathways play important roles in regulating tissue growth, differentiation, and regeneration. Among these pathways, Wnt, Notch, and Hedgehog signaling have been implicated in the regulation of fetal skin regeneration.

The Wnt signaling pathway is involved in the regulation of stem cell activity, cell proliferation, and hair follicle development. Activation of Wnt signaling during wound healing has been associated with improved tissue regeneration and the restoration of skin appendages. In fetal wounds, balanced Wnt signaling contributes to coordinated cellular responses that support scarless healing⁽³⁷⁾.

The Notch signaling pathway regulates cell fate determination and differentiation within the epidermis and dermis. Through interactions between neighboring cells, Notch signaling influences keratinocyte differentiation and tissue organization during skin development and repair⁽³⁸⁾.

Moreover, the Hedgehog signaling pathway plays a role in embryonic development and tissue patterning. Its activity has been linked to hair follicle regeneration, dermal cell proliferation, and the regulation of ECM production. Together, these developmental signaling pathways help maintain a regenerative environment in fetal wounds and represent potential targets for regenerative therapies⁽³⁹⁾.

5.4 Role of microRNAs and Epigenetic Regulation

In addition to classical signaling pathways, epigenetic regulation plays a significant role in controlling gene expression during fetal wound healing. Epigenetic mechanisms, including DNA methylation, histone modification, and non-coding RNAs, enable dynamic regulation of genes involved in inflammation, cell proliferation, and matrix remodeling⁽⁴⁰⁾.

Among these regulators, microRNAs (miRNAs) have attracted particular attention. These small molecules regulate gene expression by inhibiting the translation of target messenger RNAs. Several miRNAs have been implicated in the regulation of fibroblast activity, collagen synthesis, and inflammatory responses during wound healing⁽⁴¹⁾.

In fetal tissues, specific miRNA expression patterns contribute to the suppression of pro-fibrotic pathways and the promotion of scarless healing processes. By modulating key signaling molecules and transcription factors, miRNAs help maintain the balance between matrix production and degradation⁽⁴²⁾.

Because epigenetic modifications are potentially reversible, targeting miRNAs and other epigenetic regulators represents a promising strategy for developing therapies aimed at reducing fibrosis and promoting scarless healing.

5.5 Mechanotransduction Pathways

Table 2: Translational fetal-inspired strategies

Strategy	Fetal principle mimicked	Example	Developmental stage	Limitation
HA hydrogel	HA-rich ECM	HA-CS hydrogels	Preclinical	degradation, delivery
TGF- β modulation	TGF- β 3 dominance	TGF- β 3 delivery	preclinical/clinical	failed trials, dosing
MSC therapy	immunomodulation	MSC-CM, exosomes	preclinical/clinical	Heterogeneity
Smart Hydrogel	Dynamic niche	light-responsive VEGF	Preclinical	Scalability

HA: Hyaluronic acid; MSC: Mesenchymal Stem Cell; CM: Conditioned Medium

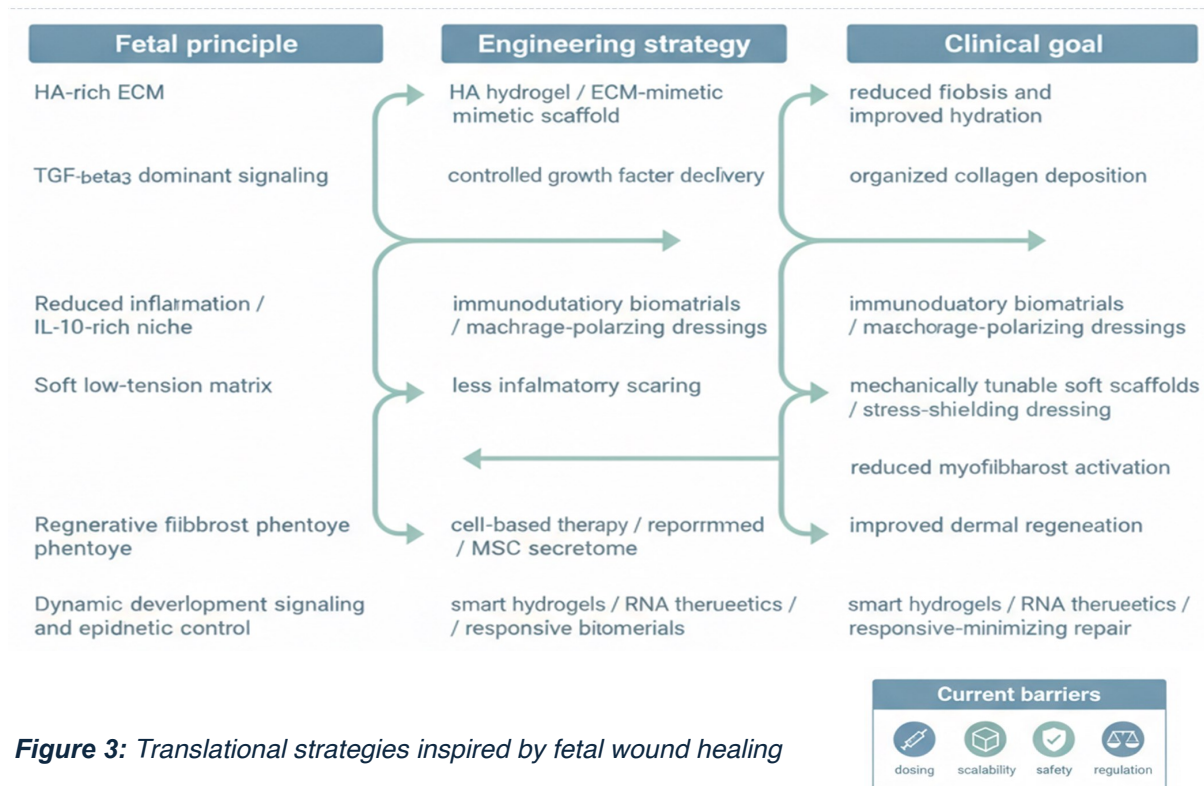


Figure 3: Translational strategies inspired by fetal wound healing

Mechanical cues strongly influence whether wound healing proceeds toward regeneration or fibrosis. In adult wounds, increased matrix stiffness and tissue tension activate integrin-mediated signaling, focal adhesion kinase (FAK)⁽⁴³⁾, Rho-associated coiled-coil-containing protein kinase (ROCK) pathways⁽⁴⁴⁾, and YAP/TAZ nuclear translocation⁽⁴⁵⁾, promoting fibroblast activation and myofibroblast differentiation⁽⁴⁶⁾. In contrast, the softer fetal matrix may attenuate these mechanotransductive signals, thereby limiting α -SMA expression and excessive collagen deposition⁽¹²⁾. Targeting mechanotransduction pathways has therefore emerged as a promising strategy for recapitulating fetal-like healing in adult wounds⁽⁴⁷⁾.

6. Immunological Basis of Scarless Wound Healing

The immune system plays a critical role in determining the outcome of wound healing. In adult tissues, inflammation is an essential early response to injury, but excessive or prolonged inflammatory activity often promotes fibrosis and scar formation⁽⁴⁸⁾. In contrast, fetal wound healing is characterized by a distinct immunological environment that supports scarless healing while minimizing inflammatory damage⁽⁴⁷⁾.

6.1 Attenuated Inflammatory Response

The immunological environment of fetal wounds differs fundamentally from that of adult wounds and is a major contributor to scarless repair. Early fetal healing occurs in the context of an immature immune system, resulting in reduced leukocyte infiltration, limited inflammatory amplification, and rapid resolution of tissue injury. Compared with adult wounds, fetal wounds show lower levels of pro-inflammatory cytokines.

Macrophages also play an important role in this process. Rather than sustaining prolonged inflammatory signaling, fetal wound macrophages appear to support tissue remodeling and regenerative repair. However, macrophage phenotype alone does not fully determine healing outcome, and the timing and balance of immune responses are likely more important than the presence of any single reparative cell type^(22, 49).

These immunological features have inspired translational approaches aimed at modulating inflammation in adult wounds. Biomaterials, stem cell-derived secretomes, and cytokine-targeted therapies are being developed to reduce excessive inflammation and create a fetal-like pro-regenerative immune environment. Nevertheless, reproducing the tightly regulated fetal immune niche in adult tissue remains a major challenge.

6.2 Cytokine Balance

As discussed previously, balance of cytokines within the wound environment plays a crucial role in regulating immune responses and tissue repair (see Section 5.2).

7. Translational Strategies Toward Scarless Skin Repair

Insights gained from fetal wound healing have inspired numerous translational strategies aimed at reducing fibrosis and promoting scarless healing in adult skin. In tissue engineering and regenerative medicine, the goal is to recreate aspects of the fetal wound microenvironment, such as balanced cytokine signaling, reduced inflammation, and regenerative ECM organization. Several approaches have been explored, including biomaterial-based scaffolds, cell-based therapies, molecular interventions, and advanced skin substitutes. These strategies attempt to integrate biological knowledge with engineering technologies to guide adult wound healing toward a more regenerative outcome⁽⁵⁰⁾. A summary of these approaches is presented in Table 2 and Figure 3.

7.1 Biomaterial-Based Approaches

Biomaterials have become central tools in regenerative medicine for modulating the wound environment and supporting tissue repair. In the context of scarless healing, biomaterial design increasingly focuses on replicating the structural and biochemical features of fetal skin⁽¹⁰⁾.

ECM-mimicking scaffolds are engineered to reproduce the architecture and composition of the native ECM. These scaffolds often incorporate collagen, gelatin, elastin, or synthetic polymers arranged in nanofibrous structures that resemble the dermal matrix. By providing appropriate mechanical support and cell-adhesion cues, ECM-like scaffolds can regulate fibroblast activity, promote organized collagen deposition, and facilitate cell migration. In this regard, Gansevoort et al. developed a collagen scaffold functionalized with heparin, FGF2, and VEGF. In a fetal sheep wound model, this scaffold induced a regenerative gene expression profile with features of scarless healing, including tight control over cell signaling and organized ECM deposition⁽⁵¹⁾.

Another promising strategy involves HA-based matrices designed to mimic the transiently hydrated, HA-rich microenvironment characteristic of fetal skin (the biological and cellular mechanisms of HA in fetal healing are detailed in Section 4.1). Rather than re-establishing the underlying signaling pathways, translational applications focus on utilizing HA-based hydrogels and composite biomaterials for their biocompatibility, tunable mechanical properties, and capacity to limit fibrotic progression in adult wounds. For instance, Rong et al. re-

ported that an HA-chondroitin sulfate hydrogel designed to mimic the fetal ECM promoted rapid wound closure, neovascularization, and hair follicle regeneration while supporting organized tissue remodeling⁽⁵²⁾. Similarly, Avila-Martinez et al. incorporated HA into collagen-based scaffolds to recapitulate this fetal microenvironment. This platform successfully modulated the immune response by inducing an anti-inflammatory M2c-like macrophage phenotype (CD206-high, CD163-high, IL-10-high) and significantly downregulated key scarring-related markers, including TGFB1, COL10A1, and ACTA2, in myofibroblast-like cells⁽⁵³⁾. These findings highlight the translation of fetal ECM characteristics into bioactive scaffolds to guide adult tissue repair away from fibrotic scarring.

7.2 Cell-Based Therapies

Cell-based therapies represent another important avenue for promoting scarless wound healing. By introducing cells with regenerative potential into the wound environment, these strategies aim to restore tissue architecture and modulate inflammatory responses⁽⁵⁴⁾.

Stem cells, including mesenchymal stem cells (MSCs), and induced pluripotent stem cells have shown considerable promise in enhancing wound healing. These cells secrete a wide range of paracrine factors that regulate inflammation, stimulate angiogenesis, and promote ECM remodeling^(54, 55). Their immunomodulatory properties also contribute to the reduction of fibrotic responses. For instance, conditioned medium derived from adipose-derived MSCs has been shown to accelerate wound closure in diabetic models by upregulating pro-angiogenic factors such as VEGF, bFGF, and EGF, while simultaneously downregulating pro-inflammatory mediators including TNF- α , IL-1 β , and IL-6 through the inhibition of TNF and chemokine signaling cascades⁽⁵⁶⁾.

Another emerging concept involves the use of fetal-like fibroblasts or fibroblasts reprogrammed to exhibit regenerative phenotypes. Since fetal fibroblasts demonstrate reduced myofibroblast differentiation and more organized matrix deposition, replicating these characteristics in adult fibroblasts may help shift wound healing toward a regenerative pathway—for example, by modulating TGF- β signaling or optimizing the biophysical properties of the scaffold environment. This concept is supported by experimental lineage-tracing studies demonstrating that Engrailed-1 lineage-negative fibroblasts (ENFs), which predominate in early fetal skin, drive dermal development and regeneration⁽⁵⁷⁾. As development progresses, however, these cells are replaced by Engrailed-1 lineage-positive fibroblasts (EPFs), which are the principal contributors to fibrotic matrix deposition and scar formation following injury. Importantly, this phenotypic shift from regeneration to scarring can be reversed locally by transplanting ENFs into adult wounds, provid-

ing direct evidence that fibroblast identity is a key determinant of regenerative versus fibrotic outcomes⁽⁵⁸⁾.

7.3 Growth Factor Modulation and Anti-Fibrotic Therapies

The role of TGF isoforms and their balance were discussed previously (see Section 5.1).

The conducted studies⁽⁵⁹⁻⁶¹⁾ have motivated efforts to develop anti-fibrotic therapies that modulate TGF- β signaling or target related mediators such as connective tissue growth factor. Additional strategies include the use of plant-derived compounds, matrix-modulating agents, and small molecules that suppress fibroblast activation and collagen overproduction. RNA-based approaches, including small interfering RNAs and microRNA-targeted therapies, have also emerged as promising tools for regulating profibrotic pathways⁽⁶²⁻⁶⁴⁾.

Despite strong biological rationale, clinical translation has been inconsistent. In particular, therapies based on single growth factors such as TGF- β 3 have not consistently reproduced fetal-like scarless healing in adult patients. This limitation suggests that successful scarless healing will likely require combinatorial approaches that integrate growth factor control with immune modulation, ECM engineering, and mechanical regulation.

7.4 Tissue Engineering and Skin Substitutes

In parallel with cell-based and pharmacological strategies, tissue engineering approaches aim to develop bioengineered skin substitutes capable of restoring both the structural and functional properties of native skin. These constructs often combine biomaterials, living cells, and bioactive molecules to recreate the architecture of the dermis and epidermis. Modern skin substitutes are designed not only to provide temporary wound coverage but also to actively guide tissue regeneration. Advances in 3D bioprinting, nanofibrous scaffolds, and bioactive hydrogels have enabled the development of more sophisticated constructs that support vascularization, epithelialization, and matrix remodeling.

For instance, in the realm of 3D bioprinting, a recent study developed an epidermal-dermal skin construct using an alginate-gelatin-diethylaminoethyl cellulose-fibrinogen bioink, which, when implanted in a rat full-thickness wound model, promoted faster wound closure and enhanced angiogenesis compared to dermal-only or acellular constructs⁽⁶⁵⁾. In another innovative approach, nanofibrous scaffolds were engineered as a 3D anisotropic sponge loaded with black phosphorus and VEGF. This scaffold enabled the controlled release of VEGF under near-infrared light, effectively guiding cell growth along oriented fibers and significantly enhancing skin flap survival in vivo through improved angiogenesis⁽⁶⁶⁾. Fur-

thermore, bioactive hydrogels have been designed as injectable, photo-crosslinkable systems based on methacrylated silk fibroin (SilMA) that provide a biphasic release of botulinum toxin type A (BTXA) and 5-fluorouracil (5-Fu). This system accelerated wound closure while suppressing fibrotic proliferation in a rabbit ear scar model, demonstrating the potential of smart hydrogels for scarless healing⁽⁶⁶⁾.

By integrating biomaterials with cellular and molecular components, tissue engineering approaches offer a promising platform for translating the principles of fetal scarless healing into clinically applicable therapies to recapitulate the regenerative microenvironment. Furthermore, the convergence of bioprinting technologies with patient-derived cells opens the door to personalized skin grafts that may ultimately achieve scarless repair.

8. Current Clinical Applications and Emerging Therapies

Although complete scarless healing has not yet been achieved in adult humans, several therapeutic strategies inspired by fetal wound biology are currently being explored in clinical and preclinical settings.

Various anti-scarring treatments have been developed to reduce fibrosis and improve the cosmetic and functional outcomes of wound healing. These include topical agents^(67, 68), growth factor therapies⁽⁶⁹⁾, and pharmacological inhibitors targeting fibrotic signaling pathways^(70, 71). For instance, in a comparative split-face clinical study evaluating treatments for atrophic post-acne scars, microneedling combined with either topical insulin or non-cross-linked HA demonstrated comparable efficacy. Both therapeutic approaches yielded significant improvements in qualitative and quantitative scar grading scales, with no statistically significant difference in clinical outcomes between the two interventions. These findings suggest that incorporating either topical insulin or HA into microneedling protocols can effectively stimulate tissue remodeling and reduce scar severity, offering viable clinical options for promoting skin repair and improving the appearance of atrophic scars⁽⁶⁸⁾. A prospective randomized controlled trial evaluated topical bFGF administration via injection or irrigation in patients following skin incisions. Key findings demonstrated that no hypertrophic scars were observed in bFGF-treated groups, whereas significant hypertrophic or widened scars developed in controls. The proportion of minimal scars was significantly higher in treated groups, confirming superior cosmetic outcomes. Postoperative bFGF administration effectively prevented scar spreading and hypertrophy without serious adverse effects. These findings support bFGF as a safe and effective intervention for improving scar quality in surgical patients, particularly those at high

risk for keloid or hypertrophic scar formation⁽⁶⁹⁾. In another example, a preclinical study using a rat burn wound model demonstrated that butorphanol significantly accelerates wound healing and reduces pathological scarring by suppressing the IL-6/p38/JNK signaling pathway. The drug promoted M2 macrophage polarization (increased CD206, decreased CD86), reduced pro-inflammatory cytokines in early stages, and temporally regulated fibrosis-associated markers to prevent excessive late-stage scarring⁽⁷⁰⁾.

In addition, regenerative skin grafts and bioengineered skin substitutes are increasingly used in the treatment of burns, chronic wounds, and extensive skin injuries. Some of these constructs incorporate biomaterials, cultured cells, or bioactive molecules designed to reduce scar formation^(72, 73). Among bioengineered skin substitutes, denovoSkin™, an autologous, bilayered dermo-epidermal graft, has demonstrated superior outcomes compared to conventional split-thickness skin grafts (STSG) in a prospective randomized controlled phase IIb trial. Key findings demonstrated that denovoSkin™ grafts resulted in minimal to no clinically relevant scarring at follow-up, whereas STSG areas predominantly developed hypertrophic scars. Additionally, the bioengineered construct offered a substantially higher expansion ratio, significantly reducing donor-site morbidity. These primary clinical data support the potential of advanced tissue-engineered constructs to achieve superior functional and aesthetic outcomes in burn wound management⁽⁷²⁾.

Furthermore, clinical trials targeting fibrosis and scar formation are investigating new molecular therapies, including growth factor modulation, cytokine inhibitors, and RNA-based treatments. These studies aim to translate insights from developmental biology and regenerative medicine into practical therapeutic interventions. In this regard, Preclinical studies in keloid xenograft models demonstrated reduced dermal fibrosis and attenuated scar volume. Based on these findings, 9MW3811 (anti-IL-11 monoclonal antibody) has entered Phase II trials for hypertrophic scars and keloids. With an extended half-life, this approach represents a shift toward precisely targeted anti-fibrotic therapy⁽⁷⁴⁾. In another example, a study was conducted in line with the emerging field of RNA-based therapeutics for fibrotic disorders. In this study, SRN001 was evaluated as a small interfering RNA designed to downregulate amphiregulin (AREG), a downstream growth factor in the TGF- β pathway that promotes fibroblast proliferation and myofibroblast conversion. Using the self-assembled micelle inhibitory RNA (SAMiRNA™) delivery platform, SRN001 enables sustained AREG knockdown at the wound site. Currently in Phase I trials, this RNA-based therapy highlights the growing role of

biomarker-driven patient selection in anti-fibrotic drug development, with patient stratification based on baseline serum AREG levels⁽⁷⁵⁾.

9. Challenges in Translating Fetal Healing to Adult Skin

Despite significant advances in understanding fetal wound healing, translating these mechanisms into effective clinical therapies remains challenging. Several biological and practical barriers limit the direct application of fetal regenerative principles to adult tissues.

One major challenge arises from the intrinsic biological differences between fetal and adult skin. Fetal tissues possess unique cellular properties, ECM composition, and developmental signaling patterns that are difficult to replicate in adult wound environments.

Another important factor is the immune and mechanical environment of adult skin. Adult wounds typically experience stronger inflammatory responses and greater mechanical tension, both of which promote fibrotic healing. Replicating the low-inflammation and low-tension conditions characteristic of fetal wounds remains a significant challenge.

Additionally, regulatory and ethical considerations influence the development and clinical implementation of advanced regenerative therapies. Cell-based treatments, gene therapies, and biomaterial implants must undergo extensive safety and efficacy evaluations before clinical approval, which can slow the translation of promising laboratory findings into clinical practice.

Although TGF- β 3-based therapy was strongly supported by fetal wound biology and early clinical findings, later-stage clinical trials failed to demonstrate consistent efficacy in scar reduction. This discrepancy highlights a major translational challenge: a single fetal-associated signaling molecule may be insufficient to recreate the complex, temporally regulated fetal wound microenvironment in adult skin. Therefore, future strategies may require combinatorial delivery systems that integrate TGF- β modulation with immune regulation, ECM remodeling, and mechanical control.

10. Conclusion

Fetal wound healing provides a powerful biological model for understanding how skin can heal without scar formation. Unlike adult wound repair, which is commonly associated with prolonged inflammation, excessive fibroblast activation, myofibroblast differentiation, and disorganized collagen deposition, fetal scarless healing occurs through a highly coordinated interaction among cells, ECM components, immune responses, and molecular signaling pathways. These features create a regenerative microenvironment that supports rapid re-epithelialization, balanced ma-

trix remodeling, and restoration of normal skin architecture.

The key mechanisms underlying fetal scarless repair include the unique behavior of fetal fibroblasts and keratinocytes, reduced inflammatory cell infiltration, a HA-rich ECM, predominance of collagen type III, balanced TGF- β isoform expression, and tightly regulated developmental signaling pathways. Together, these mechanisms prevent the activation of fibrotic cascades and preserve tissue organization during repair.

From a translational perspective, fetal wound healing offers valuable design principles for tissue engineering and regenerative medicine. Biomimetic scaffolds, HA-based hydrogels, bioengineered skin substitutes, stem cell therapies, anti-fibrotic agents, TGF- β 3-based interventions, and miRNA-targeted strategies all represent promising approaches for guiding adult wound healing toward a more regenerative outcome. However, achieving true scarless healing in adult skin remains challenging due to fundamental differences between fetal and adult tissues, including immune maturity, mechanical tension, cellular phenotype, and ECM composition.

Future progress will depend on the integration of developmental biology, biomaterials science, immunomodulation, and precision medicine. Rather than relying on a single therapeutic target, successful scarless skin regeneration will likely require multifactorial strategies that recreate the fetal-like regenerative niche in a controlled and clinically applicable manner. Continued advances in smart biomaterials, controlled delivery systems, cell-based technologies, and molecular therapies may ultimately enable the development of effective treatments that minimize fibrosis, restore skin function, and improve both aesthetic and functional outcomes for patients.

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Conflict of interest

The authors declare that they have no conflict of interest

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