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Biophysical and Metabolic Cues in the Microenvironment of Skin Wounds: Implications for Stem Cell Behaviour and Epidermal Regeneration

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Abstract: Skin wounds represent a significant challenge in global public health. Successful healing requires not only effective control of infection and inflammation but also a supportive tissue microenvironment that supports stem cell–driven regeneration. Most previous reviews have focused on soluble mediators such as cytokines, growth factors and proteases. However, emerging evidence indicates that biophysical and metabolic cues—including oxygen tension, nutrient availability, tissue mechanics, surface pH, ionic composition and endogenous electric fields—exert profound regulatory effects on the behaviour of resident epidermal and hair follicle stem cells, dermal progenitors and transplanted stem cell products in the wound bed. Gaining a thorough understanding of how skin stem cells perceive and integrate biophysical and metabolic signals is crucial for rationally designing next-generation treatment strategies for burns and other wounds.

1. Introduction

1.1. Clinical burden of skin wounds and burns

Skin wounds represent a significant burden to health-care systems globally. Acute thermal injuries, extensive trauma and surgical wounds coexist with chronic wounds such as diabetic foot ulcers, venous leg ulcers, and pressure ulcers, exhibiting a high incidence and persistent upward trend. These conditions are associated with prolonged hospitalisation, repeated interventions, risk of amputation, increased mortality, and substantial economic costs. Evidence from high-income countries alone suggest that chronic wounds affect between 1 and 2% of the population and account for billions of dollars in annual expenditure. This figure is expected to rise as populations age and metabolic diseases become more common [1-3]. Burn injuries, potentially involving extensive full-thickness tissue loss, complex systemic inflammatory responses and sequelae such as hypertrophic scarring, further heighten the urgent need for effective regenerative therapies [4-6].

1.2. Overview of skin wound healing

Cutaneous wound healing proceeds through overlapping phases of haemostasis, inflammation, proliferation and remodelling [7-9]. Each stage plays a vital role. In uncomplicated acute wounds, these phases are precisely regulated spatially and temporally. However, in cases of chronic wounds, the healing process becomes stalled: inflammation persists, protease activity is excessive, fibroblasts and keratinocytes may enter senescent or non-proliferative states, and biofilms further compromise host responses [10-12]. The resulting microenvironment frequently exhibits characteristics such as hypoxia, alkalinity, and mechanical abnormalities, factors which collectively compromise tissue regenerative capacity.

1.3. Resident stem and progenitor cells in skin repair

The maintenance of the epidermis relies on proliferative keratinocyte stem cells and progenitor cells, which are located in the basal layer of the inter-follicular epidermis and in specific regions of the hair follicle, particularly the follicular bulge [13, 14]. Upon injury, these populations are involved in the process of re-epithelialisation. Hair follicle stem cells can exit their niche, migrate into the wound and transiently adopt an interfollicular fate, thereby accelerating closure but not always regenerating new follicles [15-17]. Within the dermis, heterogeneous fibroblast subsets, perivascular cells and other mesenchymal progenitors participate in matrix deposition, wound contraction and scar formation. Papillary fibroblasts are associated with regenerative, low-scarring outcomes, whereas reticular and pre-adipocyte-like fibroblasts are more strongly linked to fibrosis [18, 19]. The regulation of epidermal and dermal progenitor cells is a complex process that is influenced by signals from various cell types, including immune cells, endothelial cells, adipocytes, and neurons. These cells work together to create a dynamic wound microenvironment [20, 21].

In addition to endogenous cell populations, a variety of exogenous stem cell products, including mesenchymal stromal cells (MSCs) derived from bone marrow, adipose tissue or umbilical cord, epithelial progenitors and cell-derived extracellular vesicles, have been applied in preclinical models and early clinical trials for trauma treatment [22-24]. These therapies must survive and function within the same hostile microenvironment that challenges resident stem cells, underscoring the importance of understanding the underlying biophysical and metabolic constraints.

1.4. From biochemical factors to microenvironmental cues

Most existing reviews focus on biochemical mediators such as cytokines, growth factors, proteases and ECM composition in the processes of wound healing and scar formation [7, 8, 25]. By contrast, less attention has been paid to how “non-classical” dimensions of the wound microenvironment—such as oxygen tension, nutrient and metabolite availability, tissue stiffness, interstitial flow, surface pH, ionic composition and endogenous electric fields—shape the behaviour of stem and progenitor cells. Yet, these dimensions are increasingly recognised as critical regulators in other tissues, including bone marrow and tumour microenvironments, and are likely to be at least as important in cutaneous repair [26-28]. The aim of this review is therefore to synthesise current research on how biophysical and metabolic cues in skin wounds regulate stem cell behaviour and epidermal regeneration, with particular focus on mechanisms relevant to burns and chronic wounds. We first briefly summarise wound biology and stem cell populations, then discuss oxygen and metabolic cues, mechanical cues and pH, ionic, electrical cues in turn. These elements are ultimately integrated into a broader mechanically-metabolic coupling framework, proposing translational therapeutic design principles for the traumatic microenvironment.

2. Main body

2.1. Oxygen and metabolic cues in the wound microenvironment

2.1.1. Oxygen tension and hypoxia

Oxygen tension has been identified as a critical determinant of wound healing outcomes. Acute wounds may experience transient hypoxia; this physiological hypoxia stabilises hypoxia-inducible factors (HIFs) in multiple cell types, inducing transcriptional programmes that promote angiogenesis, cell migration and metabolic adaptation [29, 30]. In contrast, chronic wounds like diabetic foot and venous leg ulcers are characterised by sustained tissue hypoxia due to macro- and microvascular disease, oedema and local inflammation. Such pathological hypoxia often coincides with raised reactive oxygen species (ROS) and impaired antioxidant defences, causing fibroblast senescence, stalled re-epithelialisation and greater infection risk [31, 32].

For stem and progenitor cells, oxygen exerts a dual effect. Many adult stem cells, including MSCs, exhibit a preference for glycolytic metabolism under relatively low oxygen tension in order to maintain stem cell characteristics and minimise oxidative damage. Moderate hypoxia can enhance their proliferation and paracrine factor secretion [33, 34]. However, severe or prolonged hypoxia compromises cell survival and function. Hypoxic preconditioning of MSCs and their exosomes has been explored as a strategy to boost therapeutic efficacy in ischaemic and infected wounds. This approach activates beneficial hypoxia-inducible factor (HIF)-mediated signalling pathways while mitigating the detrimental effects of hypoxia, thereby promoting healing [33, 35].

Clinically, wound oxygen-modulating therapies include hyperbaric oxygen, topical oxygen systems, and oxygen-releasing or -generating dressings. These dressings utilise peroxides, haemoglobin, perfluorocarbons, catalytic nanozymes or photosynthetic microorganisms [29, 36, 37]. However, the challenge in designing these therapeutic strategies lies in alleviating chronic injurious hypoxia while preserving beneficial oxygen concentration gradients.

2.1.2. Metabolic reprogramming of keratinocytes, fibroblasts and immune cells

Cells in the wound bed undergo profound metabolic reprogramming across inflammatory, reparative and remodelling states. Studies reveal how glucose, lipid, and amino acid metabolism supports distinct phases and cell types during skin wound healing [26, 38]. For example, classically activated (M1-like) macrophages rely mainly on glycolysis and truncated tricarboxylic acid (TCA) cycle pathways, producing high levels of pro-inflammatory mediators. Conversely, alternatively activated (M2-like) macrophages, associated with anti-inflammation and tissue repair, shift towards oxidative phosphorylation and fatty-acid oxidation, supporting the reparative process [38, 39].

Keratinocytes and fibroblasts similarly display metabolic plasticity. During active migration and proliferation, keratinocytes upregulate glycolytic pathways in order to provide sufficient ATP and biosynthetic intermediates, thus supporting rapid cell division. As cellular differentiation and stratification progress, mitochondrial metabolism and lipid synthesis gradually become predominant [40]. Fibroblasts in granulation tissue increase glycolytic flux to support ECM production and contractile activity. In chronic wounds, dysregulated metabolism—such as excessive ROS, advanced glycation end products and altered lipid profiles—has been shown to trap cells in maladaptive states, thereby perpetuating inflammatory and fibrotic processes [26, 41, 42].

Recent studies have also highlighted links between immune signals and epithelial metabolism. For instance, interleukin-17 (IL-17) signalling regulates the metabolic programme of keratinocytes during wound healing in mice, coupling inflammatory signals with epithelial proliferation and barrier repair processes [43]. These observations suggest that metabolic reprogramming is not merely a by-product

of wound healing but a key determinant of cellular fate.

2.1.3. Metabolic control of resident and transplanted stem cells

Stem cells are highly sensitive to metabolic environments. Many stem cell populations sustain hypoxic conditions within their native microenvironments and depend on glycolytic pathways, transitioning to oxidative phosphorylation pathways upon initiation of differentiation [33, 44]. In the skin, hair follicle stem cells and basal keratinocyte stem cells inhabit microenvironments that are characterised by distinct oxygen and nutrient properties. These microenvironments promote cellular quiescence while enabling cellular activation during hair growth and wound repair [14, 45].

In the wound setting, altered nutrient gradients and metabolites modify stem cell proliferation, migration and lineage bias. For instance, high glucose and lipid levels in diabetes trigger mitochondrial stress and epigenetic changes in keratinocytes and fibroblasts, altering progenitor cell behaviour [41, 42]. Amino-acid availability, particularly arginine and glutamine, contributes to collagen synthesis and immune cell function, indirectly regulating stem cell–mediated repair [46].

Exogenous stem cell therapies also face metabolic constraints. When MSCs are delivered into chronic wounds, they encounter oxidative stress, nutrient limitation and a complex cytokine milieu. These factors may significantly impact their survival rate and engraftment capacity [32, 33]. To address this challenge, approaches such as hypoxic preconditioning, pharmacological modulation of mitochondrial function, or encapsulation within metabolically protective biomaterials are being developed [35, 47]. Alternatively, cell-free products such as supernants and extracellular vesicles may bypass some of these limitations while still exerting pro-regenerative effects [23, 24, 35].

2.1.4. Therapeutic strategies targeting oxygen and metabolism

A variety of oxygen-modulating dressings are under investigation or in clinical application. These include hydrogels and scaffolds loaded with solid peroxides, and catalytic nanoparticles that decompose endogenous hydrogen peroxide into oxygen [48, 49]. Certain dressing formulations have the capacity to respond to local pH or reactive oxygen species levels, preferentially releasing oxygen in hypoxic or inflammatory areas. Early studies suggest that such dressings can improve epithelialisation, angiogenesis and bacterial control in animal models. Preliminary clinical trials also confirm their ability to enhance healing outcomes in specific chronic wounds [29, 36].

Interventions targeting metabolism encompass systemic glycaemic control, nutritional optimisation, and local delivery of metabolic modulators. Antioxidant-loaded hydrogels, bioactive polymers that re-programme macrophage metabolism and scaffolds that support mitochondrial homeostasis in fibroblasts and keratinocytes are areas of active research [41, 42, 50]. Drawing on insights from tumour metabolism and immunometabolism, there is increasing interest in designing wound therapies that steer local cells towards a “pro-repair” metabolic state. These therapies achieve wound healing by balancing glycolysis and oxidative metabolism, reducing reactive oxygen species production, and supplying substrates required for extracellular matrix synthesis.

From the perspective of stem cell research centres, these strategies aim to create niches supporting stemness, controlled proliferation and appropriate differentiation, not just indiscriminate oxygen or nutrient supply. Integrating metabolic cues with other aspects of the microenvironment, particularly mechanical and electrical signals, is likely to be critical for durable regeneration.

2.2. Mechanical cues and mechanotransduction in skin wounds

2.2.1. Macroscopic mechanical forces

Skin is continuously subjected to mechanical forces, including tension along the lines of Langer,

shear forces from movement and compression from dressings or external devices. These forces undergo alterations during injury, not only influencing wound healing but also potentially increasing the risk of hypertrophic scar development [51, 52]. Clinical observations indicate that tension-relieving devices, precise incision placement, and splinting protocols can all mitigate scar formation, underscoring the significance of mechanical factors in skin healing [51-53].

Negative pressure wound therapy (NPWT) is a widely used modality that applies controlled sub-atmospheric pressure over the wound surface. NPWT changes tissue strain, reduces oedema, improves perfusion and modulates interstitial fluid flow, all of which can influence the behaviour of resident and recruited cells [54-56]. While the direct effects of NPWT on stem cells are not fully understood, it is hypothesised that NPWT exerts therapeutic effects by indirectly influencing mechanotransduction signalling pathways through alterations in the physical microenvironment.

2.2.2. Matrix stiffness and topography

At the microscale, the stiffness and structure of the extracellular matrix evolve significantly during the healing process. Early provisional matrices rich in fibrin and fibronectin are relatively soft, whereas maturing granulation tissue and scar tissue become increasingly rigid due to the deposition of cross-linked collagen and myofibrillar contraction, which is mediated by fibroblasts [57-59]. These changes affect cell spreading, cytoskeletal remodelling, migration and differentiation.

Keratinocytes and epidermal stem cells sense substrate stiffness through integrins and focal adhesions. In vitro studies indicate that stiffness exceeding physiological levels promotes basal keratinocyte proliferation and epidermal growth factor receptor (EGFR) activation, whilst extreme rigidity correlates with abnormal signalling pathways associated with keloid and hypertrophic scar tissue [60]. Fibroblasts respond to stiffness stimuli by differentiating into myofibroblasts, whose increased extracellular matrix production and contractile forces further reinforce tissue, establishing a positive feedback loop that drives fibrotic progression [57, 61, 62].

Work in other stem cell systems has demonstrated that substrate elasticity can direct lineage specification. For example, mesenchymal stem cells commit to neurogenic, myogenic or osteogenic fates when cultured on soft, intermediate or stiff matrices respectively [63]. Although similar systematic studies in skin-resident stem cells are less advanced, the stiffness and viscoelasticity of the matrix are likely to play a crucial role in regulating the quiescent, proliferative, or differentiated states of epidermal and hair follicle progenitor cells.

Topographical features such as fibre alignment, pore size and surface roughness also modulate cell behaviour by guiding migration and influencing focal adhesion distribution [64]. Electrospun scaffolds and patterned hydrogels that mimic aspects of native dermal architecture can promote more organised re-epithelialisation and ECM deposition in experimental models [64-66].

2.2.3. Mechanotransduction pathways in keratinocytes and skin stem cells

Cells convert mechanical information into biochemical signals through mechanotransduction pathways that involve integrins, focal adhesion kinase (FAK), Rho family GTPases, actomyosin contractility and downstream transcriptional regulators including yes-associated protein (YAP), transcriptional co-activator with PDZ-binding motif (TAZ) and myocardin-related transcription factors [67-69]. In keratinocytes, cytoskeletal dynamics and force transmission through desmosomes, hemidesmosomes and adherens junctions influence cell polarity, migratory capacity, and proliferative potential during re-epithelialisation [70].

Mechanical loading has been shown to activate YAP/TAZ signalling in epidermal cells, promoting proliferation and affecting differentiation state. Persistent activation of such pathways in fibroblasts and keratinocytes under high tension conditions is thought to contribute to hypertrophic scarring,

while more compliant environments may favour regenerative responses [59, 61, 62]. Unravelling how epidermal and hair follicle stem cells perceive and interpret specific mechanical signals in vivo represents a crucial avenue for future research, offering potential new therapeutic targets for burn scar and chronic wound management.

2.2.4. Mechanical microenvironment–targeted interventions

Interventions that modulate the mechanical microenvironment operate at multiple scales. At the macroscopic level, these include offloading footwear for diabetic foot ulcers, splints and taping to reduce tension across incisions, and NPWT for complex wounds [52-55]. At the material level, a wide range of hydrogels, foams and adhesive dressings have been engineered with tunable stiffness, viscoelasticity and degradation kinetics to better match or modulate tissue mechanics [71].

For stem cell–based therapies, encapsulating cells in biomaterials with optimised mechanical properties enhances survival and engraftment. Hydrogels mimicking foetal-like soft environments—linked to scarless healing—help maintain pro-regenerative phenotypes in transplanted MSCs or epithelial progenitors [72, 73]. Conversely, scaffolds increasing local stiffness in selected regions constrain pathological remodelling or provide structural support.

Mechanically responsive materials that change stiffness, porosity or drug release in response to strain are an emerging class of wound dressings. Integrating mechanical design with other microenvironmental features, such as oxygen delivery and electrical conductivity, is a promising direction for the development of multifunctional dressings.

2.3. pH, ionic and electrical microenvironment

2.3.1. Wound surface pH and ionic composition

The pH value at the wound surface has been demonstrated to influence a number of factors relevant to wound healing, including protease activity, bacterial growth, haemoglobin oxygen release, and the stability of growth factors and extracellular matrix components. Chronic non-healing wounds often exhibit an alkaline pH, whereas more acidic conditions are associated with improved healing and reduced infection risk [74, 75]. Research has confirmed that objective monitoring of wound pH reflects wound status and therapeutic response, with successful treatment frequently accompanied by a progressive shift towards acidity [74, 76, 77].

Alongside pH, the local ionic environment—including concentrations of calcium, sodium, potassium and trace metal ions such as zinc, copper and iron—modulates cell behaviour and antimicrobial defences [78]. Calcium, for example, is a key regulator of keratinocyte differentiation and intercellular junction formation, while zinc and copper play roles in collagen synthesis and angiogenesis [79-82]. In chronic diabetic wounds, disturbances in pH and ionic homeostasis may exacerbate inflammation and impair matrix deposition [78].

2.3.2. pH and ions as regulators of stem cell behaviour and re-epithelialisation

Experimental work in various stem cell systems indicates that extracellular pH and ionic milieu can influence proliferation, migration and lineage choice by altering the activity of ion channels, transporters and enzymes, as well as affecting ECM assembly and growth factor binding [83, 84]. In skin, keratinocyte stem cells and progenitors experience distinct calcium gradients across the epidermis that help coordinate the transition from proliferation to differentiation [79, 85].

Although direct in vivo data on how wound pH and ionic composition regulate skin stem cells are limited, therapeutic strategies exploiting these factors are emerging. Acidic dressings, including those based on alginate, hydrocolloids and certain honey formulations, have been used to lower wound pH

and improve healing [86, 87]. pH-responsive hydrogels and polysaccharide dressings can preferentially release antimicrobial agents or growth factors at alkaline infected wounds, achieving synergistic effects between pH sensing and drug delivery [88]. Modulating metal ion availability through chelators or ion-releasing materials is also being investigated as a means to fine-tune cellular responses while combating pathogens [78, 89].

The creation of a suitable niche environment for epidermal and mesenchymal progenitor cells necessitates the integration of appropriate pH and ionic conditions, potentially in conjunction with other signals such as oxygen and stiffness. This strategy signifies a highly promising yet under-explored research avenue within the domain of microenvironment engineering for the treatment of burns and chronic wounds.

2.3.3. Endogenous electric fields and exogenous electrical stimulation

Intact skin maintains a transepithelial potential difference generated by ion pumps and channels. Upon epithelial disruption, this potential collapses locally, creating endogenous electric fields that drive the directional migration (galvanotaxis) of keratinocytes and other cells towards the wound centre [90]. In vitro studies have shown that direct current electric fields can accelerate keratinocyte migration and proliferation, and modulate fibroblast, endothelial and immune cell behaviour [91].

Building upon this foundation, exogenous electrical stimulation has been explored as a therapy for acute and chronic wounds. A range of studies, both clinical and preclinical, have employed various forms of electrical stimulation, including low-intensity direct current, pulsed currents, and bioelectric dressings. These studies have reported enhanced wound healing rates and granulation tissue formation across specific indications, despite variations in device parameters and operational protocols [92-94]. Proposed mechanisms include enhanced cell migration and proliferation, improved perfusion, modulation of inflammation and increased antimicrobial activity.

The influence of electrical signals on stem cells is a subject that is attracting increasing attention from the scientific community. Neural and mesenchymal stem cells are known to respond to electric fields with altered proliferation and differentiation patterns, and similar effects may apply to skin-resident stem cell populations. Consequently, conductive scaffolds integrated with electrode dressings provide a dual pathway for the wound microenvironment, offering both structural support and the delivery of electrotherapeutic signals.

2.3.4. Conductive and stimuli-responsive dressings

Conductive hydrogels and other electrically active dressings have emerged as versatile platforms for wound management. These materials combine high water content and tissue-like mechanics with electrical conductivity provided by intrinsically conductive polymers, carbon-based nanomaterials or metallic fillers [95-97]. Conductive dressings can enhance cell migration and proliferation, facilitate controlled electrical stimulation and, in some designs, allow real-time monitoring of physiological signals such as temperature, pH, pressure or metabolite levels [95]. Recent advances have produced multifunctional conductive hydrogels that integrate antibacterial components, anti-inflammatory agents and neuro-immune modulators to orchestrate complex wound microenvironments [96, 97]. Some systems are designed to respond to external triggers (such as electrical or mechanical stimuli) or to internal cues (such as pH or ROS), achieving functional modulation by altering material properties or releasing therapeutic agents.

For stem cell–based therapies, electrically conductive and stimuli-responsive scaffolds support cell survival, guide migration and influence differentiation by combining biophysical signals (electric, mechanical) with biochemical and metabolic cues. Intelligent platforms coupling sensing, feedback control and therapy delivery represent an exciting frontier in personalised wound care.

2.4. Integrative crosstalk between biophysical and metabolic cues

2.4.1. Mechanometabolic coupling in the wound niche

Biophysical and metabolic cues do not operate in isolation; instead, they are intimately interconnected. Mechanical forces can re-programme cellular metabolism—for instance, increased matrix stiffness and cytoskeletal tension have been shown to alter mitochondrial dynamics, glycolytic flux and ROS production in various cell types [98, 99]. Conversely, metabolic state influences cytoskeletal organisation, ECM production and mechanosensitive signalling pathways.

In the wound niche, fibroblast activation and myofibroblast differentiation depend on both mechanical loading and metabolic reprogramming, with glycolysis and glutaminolysis supporting ECM production and contractility [57, 61, 100]. Macrophage metabolic state affects their mechanosensitive responses and cytokine profiles, which in turn shape ECM remodelling and stiffness [38, 100]. These feedback loops can direct wound healing towards either a regenerative or fibrotic outcome. For skin stem cells, mechanometabolic coupling influences decisions between quiescence, transient amplification and terminal differentiation. A niche that is too stiff, hypoxic and oxidatively stressed may push progenitors into senescence or aberrant differentiation, whereas a softer, metabolically balanced environment could favour controlled proliferation and regeneration.

2.4.2. Spatiotemporal dynamics and single-cell insights

The wound microenvironment exhibits high spatial and temporal heterogeneity. Recent spatiotemporal single-cell atlases of human and murine wound healing have begun to map dynamic changes in cell states, signalling pathways and niche interactions across different phases, and to compare acute and chronic wounds [21, 101]. Integrating such single-cell and spatial transcriptomic data with measurements of oxygen, pH, mechanical properties and metabolic state will provide a complete picture of how biophysical and metabolic cues are distributed and sensed by stem cells in vivo. Tools such as intravital microscopy, fluorescent reporters for metabolites and mechanical stress, and wearable sensors for surface pH and temperature are increasingly available and can be combined to capture microenvironmental dynamics in real time [95, 102]. Ultimately, these technologies hold promise for analysing wound mechanics and metabolic characteristics specific to individual patients, thereby providing a basis for developing personalised treatment strategies.

2.4.3. Systems and computational models

Computational models that couple biochemical signalling with tissue mechanics and cell behaviour offer a means to explore mechanobiological principles in wound healing. Recent finite-element and agent-based models have begun to incorporate measured stiffness gradients, fibroblast-ECM interactions and epithelial dynamics to simulate scarring and regeneration [103]. Incorporating metabolic variables, oxygen diffusion, and stem cell compartments into these models would facilitate the generation of testable predictions. This would enable the assessment of interventions targeting specific microenvironments, thereby guiding both experimental and clinical research.

3. Conclusions

Biophysical and metabolic cues form an essential, yet often under-appreciated, dimension of the skin wound microenvironment. Oxygen tension, nutrient and metabolite availability, tissue mechanics, surface pH, ionic composition and endogenous electric fields collectively shape the behaviour of resident epidermal and hair follicle stem cells, dermal progenitors and transplanted stem

cell products. Through complex mechanometabolic coupling, these cues influence whether wounds progress towards timely regeneration or become trapped in chronic, fibrotic states.

For burns and other complex wounds, therapies that focus solely on delivering cells or growth factors without addressing the underlying microenvironmental constraints are unlikely to achieve durable success. Instead, evidence reviewed here supports a shift towards microenvironment-guided strategies that aim to normalise pathological hypoxia, restore pro-repair metabolic programmes, modulate mechanical forces, optimise pH and ionic conditions, and harness electrical cues in an integrated manner. Emerging biomaterials and intelligent dressings—such as oxygen-releasing hydrogels, mechano-tunable scaffolds, conductive and pH-responsive hydrogels and sensor-integrated platforms—offer promising tools to implement these principles. Future work should focus on defining the specific mechanometabolic niches that best support skin stem cell function, developing methods to monitor key parameters in situ and combining microenvironmental modulation with stem cell–based and pharmacological therapies.

Ultimately, gaining a profound understanding of how skin stem cells perceive and integrate biophysical and metabolic signals is paramount for designing next-generation therapeutic approaches. These interventions not only accelerate wound healing but also restore skin structure and function with minimal scar formation, thereby significantly enhancing treatment outcomes for patients suffering from burns and other traumatic or chronic wounds.

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