



Advances in Wound Healing and Skin Regeneration: From Biology to Molecular Mechanisms

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Abstract

Introduction: Wound healing is a highly ordered and regulated physiological process for restoring the integrity of the skin after injury. Chronic wounds, such as diabetic ulcers and burns, still represent a significant clinical problem because of compromised cell reactions and disordered molecular signalling. This review aims to familiarise the readers with aspects of skin biology, wound-healing processes, and basic cellular and molecular regulators of tissue repair and regeneration. **Methods:** This review provides a narrative synthesis of the literature focusing on skin structural organisation, phases of wound healing, cellular dynamics, signalling pathways, growth factors, ECM remodelling, and oxidative stress. **Results and Discussion:** Wound healing occurs in four overlapping phases: hemostasis, inflammation, proliferation, and remodelling. Adjacent to each other, keratinocytes, fibroblasts, endothelial cells, and immune cells communicate to orchestrate re-epithelialization, collagen deposition, angiogenesis, and immune regulation during the healing process. Specific pathways associated with molecular, such as MAPK/ERK, PI3K/Akt, NF- κ B, and TGF- β /Smad, are of great significance for controlling proliferation, survival, inflammation and extracellular matrix synthesis. Growth factors (eg, EGF, VEGF, PDGF) and cytokines add another layer of complexity in modulating healing, whereas oxidative stress and its dual effects, both beneficial and detrimental, are dependent on oxidative stress levels. The deregulation of these mechanisms leads to the occurrence of chronic wounds. **Conclusion:** A detailed knowledge of such integrated mechanisms will aid in designing novel, innovative and personalised therapeutic approaches to improve wound healing and skin regeneration.

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1. Introduction

Wound healing is a natural yet sophisticated biological process required for the restoration of homeostasis through the reconstruction of skin integrity and

functional status. The skin is our first line of defence, protecting us from microbial invasion, temperature changes and maintaining homeostasis. Injury that

exceeds this barrier initiates a series of complex and often compounding biological responses, which have been conventionally categorised into the four sequential phases of haemostasis, inflammation, proliferation, and remodelling[1]. These stages are all tightly regulated by feedback interactions between different cell types, components of the ECM, cytokines and growth factors that facilitate proper tissue repair [2].

Phase I formation of platelet aggregates/clot, which not only stops bleeding but also acts as a temporary tissue scaffold for incoming cells. The next one is the inflammatory phase, in which immune cells, such as neutrophils and macrophages, clean up the debris and pathogens in the injured area, releasing signalling molecules that dictate what will occur next in the process of healing. In the proliferative phase, keratinocyte migration takes place to re-epithelialize the wound, synthesis of collagen and ECM from fibroblasts, and restoration of blood supply via angiogenesis. Lastly, collagen fibres are organised in the remodelling stage, which allows a lot more tensile strength to the tissue and permits a return to function [3].

However, this delicate process can become dysregulated during the time of pathology and is known to result in chronic, or non-healing, wounds. Introduction: Chronic wounds remain a global challenge and are represented by diabetic ulcers, pressure ulcers, and other thermal injuries; they are characterised by defective cellular response, persistent inflammation, increased reactive oxygen species, and aberrant molecular signalling at the wound healing stage. The associated complications not only impact patients' quality of life but also contribute to the healthcare burden [4].

Over the last few years, the scientific community has changed the objective of the latest research from common aspects of wound healing, very gradually shifted into the cellular and molecular mechanisms engaged in the process of wound healing. Novel and specific treatment strategies have emerged thanks to advanced knowledge surrounding keratinocytes, fibroblasts, immunomodulation and key signalling pathways [5].

This review provides an integrated mechanistic perspective on wound healing and skin regeneration by connecting the major phases of wound repair with the cellular and molecular events that regulate their progression. In addition to discussing skin biology and the four overlapping phases of healing, particular insulate and shock absorb, but now also has the added

emphasis is placed on the interaction among keratinocytes, fibroblasts, endothelial cells, and immune cells; major signalling pathways; growth factors and cytokines; extracellular-matrix remodelling; and the dual role of oxidative stress [6]. The review further considers how dysregulation and cross-talk among these mechanisms contribute to chronic wounds and impaired repair. Finally, emerging directions, including advanced wound-healing models, multi-omics, artificial intelligence, biomaterials, tissue engineering, regenerative medicine, and personalised therapeutic strategies, are discussed to connect current mechanistic knowledge with future translational applications.

2. Skin Biology and Structural Organisation

Skin is a bidirectional, very dynamic, redoubtable, multi-functional organ that is essential for ensuring physiological homeostasis of the organism and protecting it against exogenous attacks. It is the body out of the door and outside the architectural barriers, one of the biggest, forms the physical and immunological barriers against pathogens, ultraviolet radiation and mechanical injury (skin), as well as regulating body temperature, carrying out emblematic sensory perception organ principles and participating in metabolic actions, such as vitamin D synthesis [7]. The hierarchy of skin architecture is vital for injury response and effective wound healing. Its layers, cellular components and extracellular matrix are interactive and function together to create tightly coordinated, uniquely structured organ systems to perform normal function and promote tissue repair. Therefore, the target of the investigation of mechanisms of regeneration, as well as the answer to the question of therapy, has to cover a good understanding of skin biology [8].

2.1 Anatomy of Skin

The skin is composed of three primary layers: the epidermis, dermis and hypodermis, each with a specialised contribution to the function of the organ. The epidermis (the outermost layer of skin) is an array of more than 100 µm of keratinocytes assembled into basal, spinous, granular and cornified layers [9]. These cells undergo continuous division and differentiation to develop a tough and cell-resilient layer that forms a barrier against desiccation and environmental insults. Beneath it is the dermis, a thicker layer of dense connective tissue, composed mainly of fibroblasts, collagen and elastin fibres, blood vessels, and nerve endings. It gives structural strength and elasticity to the epidermis and is food for the epidermis. The third layer of skin, called the hypodermis (subcutaneous layer), consists primarily of fat (adipose tissue) to job of anchoring skin to more utopian structures [10].

2.2 Cellular Components

Skin is an organ that contains a very diverse population of specialised cells, which help to maintain the functional integrity of the skin by regulating tissue repair and regeneration. Keratinocytes are important players in re-epithelialization, migrating from the borders of the wound and proliferating to restore the epidermis barrier [11]. Fibroblast cells reside in the dermis and secrete collagen and other extracellular matrix to facilitate granulation tissue formation. Endothelial cells in the formation of new blood vessels grow to form a vascular system by angiogenesis, which provides the supply of oxygen and nutrients required to repair injury. Immune cells such as neutrophils or macrophages play key roles in the early response to tissue injury to instigate and regulate inflammation, clearing potential pathogens and cellular debris, and transition to later phases of the healing process through cytokine signaling [12].

2.3 Extracellular Matrix

The extracellular matrix (ECM) is an organised and dynamic physical framework formed of structural proteins (collagen or elastin), glycosaminoglycans, and proteoglycans. Not only does it serve as a mechanical support and structural function of skin, but it also serves as a depot of growth factors and signalling molecules [13]. During the remodelling phase of wound healing, the ECM undergoes a series of cycles, allowing local spatial and temporal control of cell adhesion, movement, growth and differentiation. The ECM that is gradually modified is a key component in the modulation of the cellular response and thus critical for proper tissue regeneration [14].

3. Phases of Wound Healing

Wound healing is a complex and organised process occurring in four overlapping but separate phases: hemostasis, inflammation, proliferation, and remodelling. Note that these stages are not necessarily linear or sequential but cyclical in the sense that each stage frames and shapes the next stage [15]. The proper coordination of cellular functions, signalling molecules, and extracellular matrix (ECM) components is essential for the successful restoration of tissue integrity. With each of these phases consisting of numerous steps, any disruption in the process will damage healing or result in a chronic wound, so understanding of each stage becomes indispensable [16].

Wound healing comprises four overlapping and interconnected phases: haemostasis, inflammation, proliferation, and remodelling. Haemostasis rapidly controls blood loss and forms a provisional fibrin-rich matrix that initiates subsequent repair. During inflammation, neutrophils and macrophages remove

debris and pathogens while releasing cytokines, chemokines, and growth factors that regulate repair. The proliferative phase involves fibroblast-mediated extracellular-matrix deposition, keratinocyte migration and re-epithelialisation, and endothelial-cell-driven angiogenesis. Remodelling subsequently reorganises and matures the extracellular matrix, increasing tissue strength. These phases are not isolated but depend on continuous communication among platelets, immune cells, keratinocytes, fibroblasts, endothelial cells, cytokines, growth factors, and matrix components. Proper temporal coordination promotes functional repair, whereas persistent inflammation or excessive matrix deposition may result in chronic wounds, fibrosis, or abnormal scar formation (Figure 1) [17, 18].

3.1 Hemostasis Phase

The hemostasis phase is the first step in the repair of tissue damage and is essential to prevent haemorrhage. Immediately following an insult, the blood vessels constrict (vasoconstriction), and platelets aggregate at the site of damage to form a clot [19]. This mass of primarily fibrin, platelets and blood cells literally serves as a scaffold or physical support to provide architectural stability to a wound. In addition to clot's protective role, the clot also acts as a provisional matrix for migrating cells of inflammation and repair [20]. In the inflammatory phase of wound healing, platelets release several growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF- β), which initiate the subsequent stages of repair [21].

3.2 Inflammation Phase

This phase begins immediately after hemostasis and usually lasts 3-5 days. It is recognised for recruiting immune cells-primarily neutrophils and macrophages-to the site of injury [22]. Neutrophils are the first responders that phagocytose bacteria and clear cellular debris. They secrete cytokines, chemokines, and growth factors that modulate inflammation and promote tissue repair by following the trail; they are the ones that jump and become the great regulators of healing [23]. They recruit more cells, induce angiogenesis and prime up the regenerating phase. Inflammation is actually a constructive process of defence and clearance; however, the excess and/or continued presence of inflammatory mediators can impede the wound-healing process and lead to a long-term state of chronicity of the wound [24].

3.3 Proliferation Phase

The proliferative phase of the wound, characterised by the formation of active tissues, usually lasts for days to weeks, depending on injury severity. Re-epithelialization: During this phase, reactive

keratinocytes at the wound edges proliferate and migrate across the wound bed to reform the epidermis [25]. Fibroblasts are also activated to secrete collagen (primarily type III) and other extracellular matrix proteins, resulting in granulation tissue simultaneously. The second phase is when angiogenesis, which is the formation of new blood vessels from previous vasculature, occurs to provide enough oxygen and nutrients to the tissue that is in the process of regeneration. Such processes are then coordinated, leading to the gradual closure of the wound [26].

3.4 Remodeling Phase

Finally, the remodelling phase, or maturation phase, is when the wound itself closes, and may last anywhere from weeks to several months, up to several years. The

first of these phases involves a rearrangement of the collagen that was first deposited into the tissue, which is then replaced by type I collagen, allowing for greater tissue tensile strength [27]. The fibroblasts are then differentiated into myofibroblasts, which will help to contract the wound by also contributing to further size reduction. Moreover, the excess blood vessels that develop in early angiogenesis undergo regression through apoptosis, leading to a refined network of blood vessels [28]. While the tissue gains a large portion of its strength during healing, it usually does not regain the full functional and structural properties of unwounded skin. Scarless Degeneration and Remodelling. It is widely accepted that the most important aspect of post-injury repair is proper remodelling, which is essential for minimising scar formation and restoration of tissue function [29].

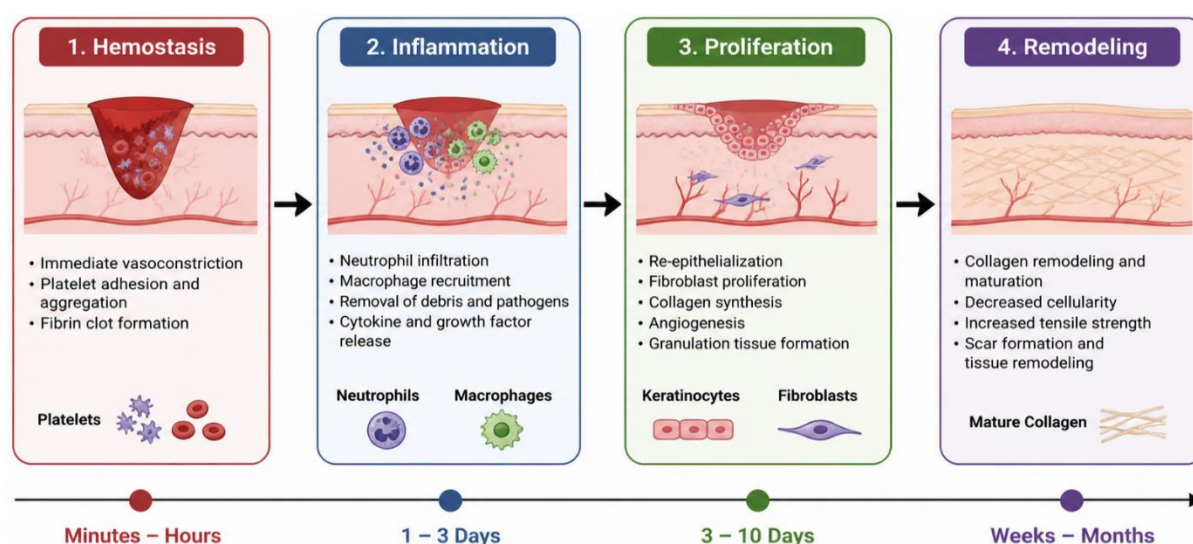


Figure 1: Overview of wound healing phases: hemostasis, inflammation, proliferation, and remodelling, showing key cellular events, biological processes, and time progression from injury to tissue repair.

4. Cellular Mechanisms in Skin Regeneration

Skin regeneration is a highly orchestrated series of cellular events involving keratinocytes, fibroblasts, endothelial cells and immune cells [30]. These cells communicate via biochemical signalling, mechanical signals, and extracellular matrix (ECM) remodelling to restore tissue integrity. These mechanisms need to be tightly regulated in time and space since even small changes from the normal physiology can lead to either impaired healing or fibrosis (Table 1) [31].

4.1 Keratinocyte Dynamics

Keratinocytes are a major cell type of the epidermis and act as the main cells participating in re-epithelialization. In the injured area, basal keratinocytes at the wound edge are activated and exhibit phenotypic changes characterised by loss of cell-cell adhesion (through downregulation of E-cadherin) and increased motility [32]. In the injured further induce proliferation by the activation of

area, basal keratinocytes at the wound edge become activated and exhibit phenotypic changes characterised by reduced cell–cell adhesion and increased motility. These cells migrate over the provisional matrix through coordinated cytoskeletal reorganisation and integrin-mediated adhesion. The rate of keratinocyte migration is highly dependent on the experimental and tissue context; therefore, a single numerical migration rate should not be considered a universal physiological value. Epidermal growth factor (EGF) and keratinocyte growth factor (KGF/FGF-7) can promote keratinocyte proliferation and migration through signalling pathways including MAPK/ERK and PI3K/Akt[33]. The rates of proliferation for keratinocytes are 18–24 hours for doubling in the presence of suitable conditions, and proliferation occurs almost exclusively in the basal layer. Epidermal growth factor (EGF, ~1-10 ng/mL) and keratinocyte growth factor (KGF/FGF-7) can MAPK/ERK and PI3K/Akt pathways, respectively.

Keratinocytes also secrete cytokines (e.g., IL-1, TNF- α) to modulate inflammation and fibroblast activity—an indication of the dual scaffold and signalling roles played by these cells [34].

4.2 Fibroblast Function

Fibroblasts are the primary regulators of dermal repair and ECM deposition. TGF- β signalling promotes fibroblast activation, myofibroblast differentiation, and extracellular-matrix deposition, although its effects are strongly dependent on tissue context, receptor signalling, concentration, and duration of exposure. Fibroblast-mediated collagen deposition also varies considerably with wound stage, tissue type, and experimental conditions; therefore, a fixed deposition rate is not considered representative of all healing wounds [35]. For example, matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), such as MMP-1, -9, and TIMPs, strictly control ECM remodelling. MMP:TIMP ratio (ideally, a ratio of 1:1 in physiologic healing) is essential and frequently, chronic wounds are associated with interface MMP / TIMP dysregulation, with a higher MMP:TIMP ratio correlating with excessive matrix degradation [36].

4.3 Angiogenesis

In order for the regenerated tissue to get oxygen and other nutrients, it is necessary to achieve angiogenesis. Endothelial cells respond to hypoxia and angiogenic growth factors, particularly vascular endothelial growth factor (VEGF), through VEGF receptor signalling. VEGF promotes endothelial-cell survival,

proliferation, migration, and vascular sprouting, while FGF-2 and angiopoietins contribute to vessel maturation and stabilisation. The magnitude and timing of these responses depend on the experimental model, tissue environment, oxygen availability, and local growth-factor concentrations. Thus, specific numerical values for VEGF concentration, endothelial proliferation, vessel-sprouting rate, or tissue oxygen tension should be interpreted as context-dependent experimental observations rather than universal physiological thresholds. [37].

4.4 Immune Modulation

Immune cells, particularly macrophages, play key roles in modulating the wound-healing response via cyclical, phenotypic switching. Macrophages initially contribute to the inflammatory response through the production of mediators such as IL-1, IL-6, and TNF- α . As healing progresses, macrophage phenotypes and functions change in response to the local microenvironment, with reparative macrophage states contributing to resolution of inflammation, angiogenesis, and matrix remodelling. The timing and extent of these phenotypic changes vary with wound type, tissue environment, and experimental model; therefore, macrophage states should not be interpreted as a rigid M1-to-M2 sequence occurring at a fixed time point. Collectively, these cellular mechanisms highlight the complexity of skin regeneration, which necessitates the coordinated orchestration of cellular behaviour, signalling pathways, and microenvironment factors during wound repair [38].

Table 1: Cellular mechanisms and processes driving skin regeneration and wound healing.

S. No.	Cell Type / Process	Features	Mechanism	Role in Skin Regeneration	References
1.	Keratinocyte Dynamics	Migration (~0.5-1 mm/day), proliferation	Cytoskeletal reorganisation, activation of signalling pathways (e.g., MAPK/ERK)	Re-epithelialization and restoration of the epidermal barrier	[39]
2.	Fibroblast Function	Collagen synthesis, ECM production	Secretion of collagen (Type I & III) and regulation via MMPs	Formation of granulation tissue and matrix remodelling	[40]
3.	Angiogenesis	New blood vessel formation	Endothelial cell proliferation and migration mediated by VEGF	Improves oxygen and nutrient supply to healing tissue	[41]
4.	Immune Modulation	Macrophage polarization (M1 $\rightarrow$ M2)	Cytokine signalling (IL-10, TGF- β) and resolution of inflammation	Promotes tissue repair and reduces chronic inflammation	[42]

5. Molecular Mechanisms of Wound Healing

Cell signalling events orchestrating the basic wound

healing process are multimodal, existing as a network of soluble mediators and redox-sensitive processes

that regulate the cellular response that ultimately dictates functional wound healing [43]. During the healing process, each of these mechanisms may be required for proper and precise coordination of inflammation, proliferation, and matrix reorganisation. Dysregulation at the molecular level (e.g., continual inflammatory signalling, defective growth factor activity, oxidative imbalance) can result in chronic wounds or depressed scarring (Table 2) [44].

5.1 Signalling Pathways

Cellular responses necessary for efficient wound healing are intricately regulating the signalling pathways in the cells [45]. Pathways that result from the activation of growth factors, cytokines, and mechanical signals are critical and will require each pathway to be modulated precisely to have the proper regulation of gene expression, cell proliferation, migration, survival, and secretory function and/or ECM production [46]. MAPK/ERK, PI3K/Akt, NF- κ B and TGF- β /Smad are just some of the most important pathways that regulate different but interconnected aspects of tissue repair [47].

The MAPK/ERK pathway is mostly related to cell proliferation and migration. Activation occurs when receptor tyrosine kinases bind growth factors like epidermal growth factor (EGF), triggering a phosphorylation cascade leading through Ras, Raf, MEK, and ERK1/2. ERK is typically induced between 5-15 mins after stimulation and subsequently translocates to the nucleus to influence factors such as Elk-1 and c-Fos[48]. This pathway enhances keratinocyte migration (approximately 0.5-1mm/day) and fibroblast proliferation, which are important aspects of re-epithelization and granulation tissue formation [49].

The PI3K/Aktsignalling pathway is a major upregulator of cell survival and metabolism [50]. Phosphatidylinositol 3-kinase (PI3K) transduces the

signal, resulting in phosphorylation of Akt at Ser473 and Thr308. Activated Akt impedes apoptosis through modulation of proteins such as Bad and caspase-9, whereas it supports protein synthesis by activating mTORsignalling[51]. This pathway is especially crucial for cell survival during stress conditions such as hypoxia (O₂ tension <30 mmHg) and is also important for stimulating angiogenesis [52].

NF- κ Bsignalling Pathways is an important transcription factor that regulates inflammation. In the resting state, it is sequestered in the cytoplasm by inhibitor I κ B. After challenge with pro-inflammatory cytokines such as TNF- α (~10–50 ng/mL) or IL-1 β , I κ B is phosphorylated and degraded, after which NF- κ B can translocate into the nucleus within 15–30 minutes [53]. Then it triggers the secretion of the inflammatory mediators, adhesion molecules, and enzymes like COX-2. The NF- κ B cascade is crucial to initiate the immune response, but continued NF- κ B activation leads to chronic inflammation and impaired healing process [54].

The Smad–nuclear pathway that originates from TGF- β has an essential role in ECM production and tissue remodelling. On the other hand, binding of TGF- β 1 (approximately 0.1–5 ng/mL) to its receptors activates the phosphorylation of Smad2/3, which subsequently binds to Smad4 and translocates to the nucleus [55]. It also promotes transcription of genes encoding collagen (types I and III), fibronectin, and proteoglycans, and it stimulates fibroblast-to-myofibroblast differentiation. TGF- β plays an important role in the repair process, but the excessive TGF- β signalling is deviant and contributes to fibrosis and hypertrophic scar [56].

Collectively, these signalling pathways provide an interlocking signalling network which integrates relevant cues to allow for timely healing of a wound, and they balance inflammation, cell growth and survival, and matrix deposition (Figure 2) [57].

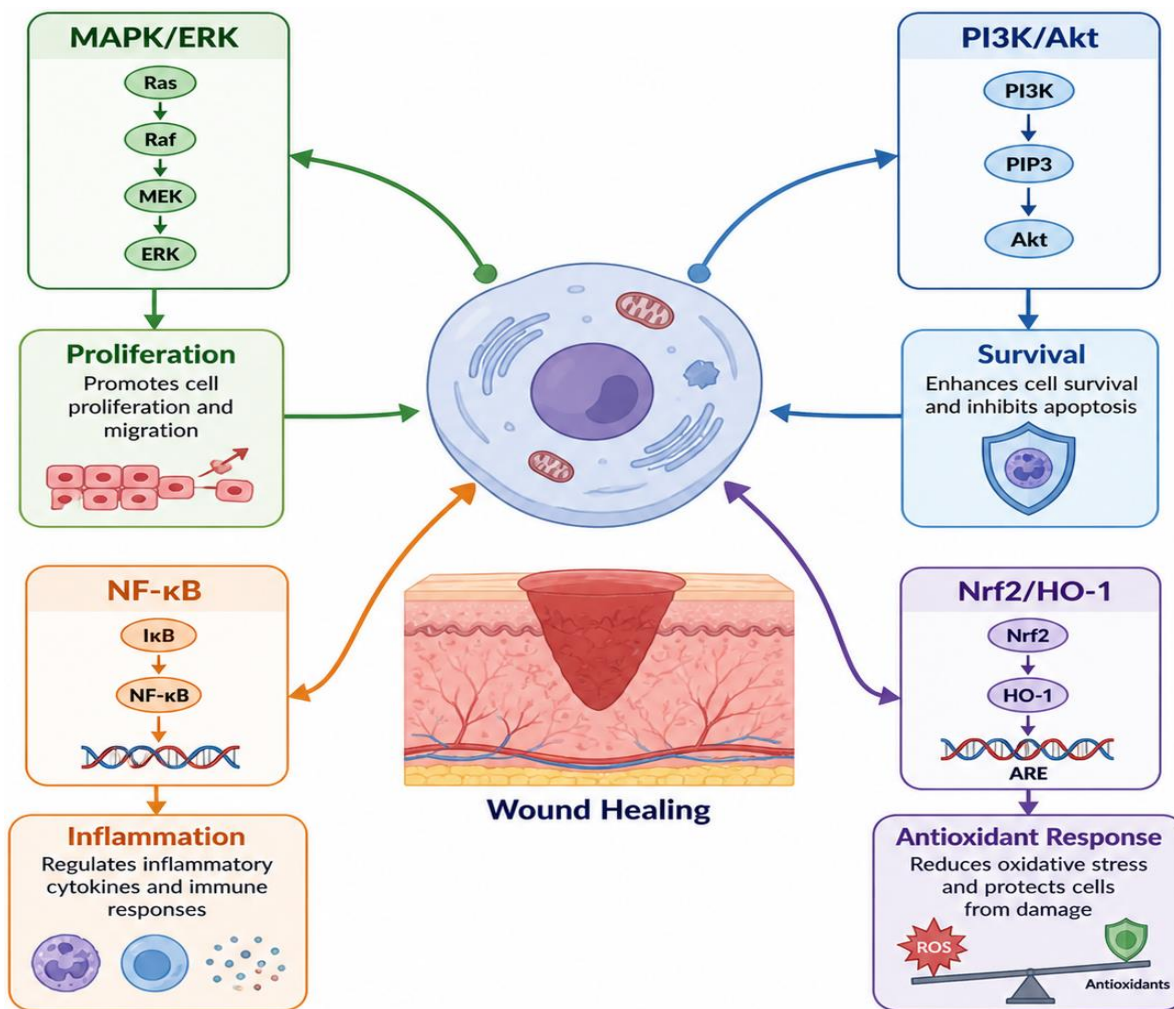


Figure 2: Key signalling pathways (MAPK/ERK, PI3K/Akt, NF-κB, Nrf2/HO-1) regulating proliferation, survival, inflammation, and antioxidant responses during coordinated wound healing and tissue regeneration processes.

The signalling pathways involved in wound healing should not be considered as independent linear cascades, because extensive cross-talk among them coordinates the transition from inflammation to tissue repair. Growth-factor and cytokine stimulation can activate MAPK/ERK and PI3K/Akt signalling, thereby promoting cell survival, proliferation, migration, and other reparative responses. In parallel, inflammatory stimuli activate NF-κB, which regulates the expression of inflammatory mediators and can influence the cellular responses required for subsequent repair. TGF-β/Smad signalling provides an important link between inflammatory resolution, fibroblast activation, extracellular-matrix synthesis, and tissue remodeling [58].

These pathways are also closely connected with cellular redox regulation. Nrf2/HO-1 signalling contributes to antioxidant and cytoprotective responses and can modulate the effects of reactive oxygen species on inflammatory and reparative signalling. Conversely, excessive oxidative stress may sustain inflammatory signalling and disturb pathways involved in cell survival and matrix regulation. Thus, be interpreted as context-dependent experimental

the biological outcome of wound healing depends not on activation of a single pathway, but on the coordinated balance and temporal interaction of MAPK/ERK, PI3K/Akt, NF-κB, TGF-β/Smad, and Nrf2/HO-1 signalling. Dysregulation of this network may contribute to persistent inflammation, impaired proliferation, abnormal extracellular-matrix deposition, and delayed or chronic wound healing [59].

5.2 Growth Factors and Cytokines

Growth factors and cytokines function as important mediators of communication among cells during wound repair. VEGF promotes endothelial-cell responses and angiogenesis, whereas PDGF contributes to fibroblast recruitment, proliferation, and matrix formation. Pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α participate in early immune responses, while anti-inflammatory and pro-resolving mediators contribute to the transition toward tissue repair. The concentration, duration, and cellular source of these mediators vary substantially among wound types and experimental models. Therefore, reported numerical concentrations should be interpreted as context-dependent experimental measurements rather than universal physiological

ranges [60]. Platelet-derived growth factor (PDGF, 5–20 ng/mL): PDGF mobilises fibroblasts and smooth muscle cells to migrate toward the wound. Pro-inflammatory cytokines (e.g. IL-1, IL-6, TNF- α) play a major role in the regulation of inflammatory responses and recruitment of immune cells, whereas anti-inflammatory cytokines (e.g. IL-10) function to resolve the inflammation. Cytokines exist in temporal equilibrium wherein prolonged stimulation of TGIF- α (>50 ng/mL locally) promotes chronic wounds [61].

5.3 ECM Remodelling

Extracellular matrix (ECM) remodelling is a process characterised by degradation and de novo synthesis of ECM components. Matrix metalloproteinases (MMPs), such as MMP-1 (collagenase) and MMP-9 (gelatinase), can degrade damaged ECM, allowing cells to migrate [62]. Their activity is strictly regulated by tissue inhibitors of metalloproteinases (TIMPs). MMP activity is regulated by endogenous tissue inhibitors of metalloproteinases (TIMPs), and the balance between proteolytic activity and inhibition is important for appropriate ECM turnover. Altered MMP and TIMP expression and activity have been associated with chronic wounds and excessive matrix degradation. However, the MMP:TIMP relationship is dependent on the specific MMP or TIMP measured, wound type, tissue compartment, disease state, and analytical method; therefore, a single numerical MMP:TIMP ratio should not be considered a universal physiological or pathological threshold [63]. Whereas turnover rates can be indicative of a rapid matrix remodelling rate of work (~10–15% per day) during this phase of maturation [64].

5.4 Oxidative Stress

Reactive oxygen species (ROS) are either decisive in

postinjury healing processes, e. g., superoxide (O_2^-) and hydrogen peroxide (H_2O_2), but can also exert a deleterious action in many pathological processes [65]. ROS function as important signalling mediators during wound repair, but their biological effects depend on the species involved, cellular source, concentration, duration of exposure, and antioxidant capacity of the tissue. Transient and controlled ROS production can participate in cell signalling, migration, angiogenesis, and host defence, whereas sustained or excessive oxidative stress can damage lipids, proteins, and nucleic acids and impair healing. Accordingly, fixed concentration thresholds should not be interpreted as universal boundaries between beneficial and detrimental ROS activity. The Nrf2/HO-1 pathway provides an important cytoprotective response by inducing antioxidant and stress-response genes following oxidative challenge.[66]. On the other hand, a very high concentration of ROS ($>10^{-6}$ M) exerts typical oxidative injury on lipids, proteins, and DNA, hindering the mending process. The Nrf2/HO-1 pathway is one of the main antioxidant defence systems [67]. In the presence of oxidative stress, Nrf2 detaches from Keap1 and enters the nucleus after 30–60 minutes, and initiates the transcription of antioxidant enzymes like heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and catalase. Thus, this ensures cellular protection against mtDNA leakage and the correct implementation of the repair process [68].

Cumulatively, these mechanisms emphasise the uniqueness of the wound-healing process, in which exquisitely regulated signalling networks and biochemical mediators determine whether treatment of a tissue achieves regeneration or not [69].

Table 2: Overview of signalling pathways, growth factors, and molecular mechanisms involved in wound healing and tissue regeneration.

S. No.	Category	Key Components	Primary Function	Role in Wound Healing	References
1.	Signalling Pathways	MAPK/ERK	Cell proliferation and migration	Promotes keratinocyte movement and re-epithelialization	[70]
		PI3K/Akt	Cell survival and anti-apoptosis	Enhances cell viability under stress conditions	[71]
		NF- κ B	Inflammatory regulation	Controls cytokine production and immune responses	[72]
		TGF- β /Smad	ECM synthesis and remodelling	Stimulates collagen production and tissue repair	[73]
2.	Growth Factors & Cytokines	EGF, VEGF, PDGF	Cell growth and angiogenesis	Promote proliferation, vascularisation, and	[74]

				tissue regeneration	
		IL-1, IL-6, TNF- α	Immune modulation	Regulate inflammation and healing progression	[75]
3.	ECM Remodeling	MMPs	ECM degradation	Remove damaged matrix and facilitate cell migration	[76]
4.		TIMPs	MMP regulation	Maintain balance in matrix remodelling	[77]
5.	Oxidative Stress	ROS	Cellular signaling	Low levels promote healing; excess causes tissue damage	[78]
		Nrf2/HO-1 pathway	Antioxidant defense	Protects cells from oxidative stress and supports repair	[79]

6. Challenges and Future Perspectives

Conventional in vitro systems are often unable to recapitulate the high human skin architecture, including complex 3D tissue microenvironment, cellular heterogeneity, and dynamic microenvironment. Similarly, animal modelling often does not fully recapitulate human wound healing and is also ineffective in treating non-healing chronic wounds (for example, diabetic ulcers) [80]. Another challenge is our incomplete insight into the complex signalling networks and their temporally controlled regulation. Highly context-dependent interaction among pathways, including MAPK/ERK, PI3K/Akt, NF- κ B and TGF- β /Smad, with disorganized signaling favouring either impaired healing or fibrosis, eliminate selective modulation of signalling pathways [81].

Future directions in research on wound healing are now focused on integrative and precision-based strategies. Multi-omics technologies (including genomics, proteomics and metabolomics) are employed to generate a systematic perspective of the wound-related molecular profiles at different stages of the wound. Artificial Intelligence and Machine Learning also offer capabilities for predictive modelling, biomarker discovery and treatment strategy optimisation [82]. This would seem to have therapeutic relevance for personalised medicine approaches based on patient profiles and comorbidities. It can also be hoped that improvements in biomaterials, tissue engineering, and regenerative medicine (including stem-cell-based therapies) will also revolutionise wound healing. The Unifying-DIET Approach to Person-Centred Precision in Wound Healing. The same strategies, together with the objective of filling in recognised gaps in the discipline for designed, targeted, and patient-oriented wound healing therapies [83].

Despite major advances in understanding wound-molecules, and cellular states that cannot be

healing biology, several limitations continue to restrict the translation of experimental findings into effective clinical therapies. A major challenge is the limited ability of conventional experimental models to reproduce the complexity of human skin and the dynamic wound microenvironment. Two-dimensional in vitro cultures generally lack the three-dimensional architecture, extracellular-matrix organisation, cellular heterogeneity, vascular interactions, and immune-cell communication present in native skin. Animal models provide greater biological complexity but may differ from humans in skin structure, wound contraction, immune responses, and the kinetics of repair. These differences can contribute to inconsistent translation of preclinical findings, particularly in chronic and difficult-to-heal wounds [84].

6.1. Organoids and reconstructed skin models:

Three-dimensional skin organoids and reconstructed human skin models provide opportunities to study wound repair in systems that more closely reproduce aspects of human tissue organisation than conventional monolayer cultures. These models can incorporate multiple skin cell populations and can be used to investigate epithelial regeneration, cellular communication, extracellular-matrix responses, and selected disease-associated phenotypes under controlled conditions. Their use may therefore help bridge the gap between simplified in vitro systems and more complex in vivo models. Nevertheless, current organoid and reconstructed-skin systems do not completely reproduce the vascular, neural, immune, mechanical, and systemic components of a living wound, and further standardisation and validation are required before they can fully replace animal models [85].

6.2. Multi-omics approaches

Wound healing involves coordinated changes in gene expression, proteins, metabolites, signalling adequately characterised using a single analytical

approach. Integration of genomics, transcriptomics, proteomics, metabolomics, and other omics-based approaches can provide a more comprehensive understanding of the molecular changes occurring at different stages of wound repair. Such approaches may help identify biomarkers associated with delayed healing, distinguish regenerative from pathological repair responses, and reveal molecular networks that could serve as therapeutic targets. Integration of multi-omics data with spatial and single-cell approaches may further improve understanding of cellular heterogeneity and pathway interactions within the wound microenvironment [86].

6.3. Artificial intelligence and machine learning

The increasing availability of complex clinical and molecular datasets also creates opportunities for artificial intelligence and machine-learning approaches. These methods may assist in identifying patterns associated with wound progression, predicting healing outcomes, classifying wound characteristics, discovering potential biomarkers, and supporting treatment selection. When combined with imaging, clinical parameters, and molecular data, AI-based approaches may contribute to more objective and personalised assessment of wound status. However, their clinical usefulness depends on the quality, representativeness, and standardisation of the underlying datasets. Issues related to model interpretability, external validation, bias, data privacy, and integration into clinical workflows must therefore be addressed before widespread clinical implementation [87].

7. Future perspectives: Future wound-healing research is likely to benefit from combining physiologically relevant experimental models with multi-omics and computational approaches. Integration of organoids or reconstructed skin with advanced biomaterials, controlled mechanical and biochemical environments, and relevant immune or vascular components may provide increasingly representative platforms for studying wound repair and testing therapeutic interventions. At the same time, integration of molecular and clinical datasets through AI and machine learning may facilitate biomarker discovery and patient stratification. Such multidisciplinary approaches could help move wound-healing research from descriptive characterisation toward mechanistically informed and personalised therapeutic strategies[88].

Conclusion

Wound healing is governed by a dynamic and highly interconnected network in which inflammatory responses, cellular proliferation and survival, redox

regulation, angiogenesis, and extracellular-matrix remodelling must remain appropriately coordinated. A key mechanistic insight is that the outcome of repair depends not on the activation of individual signalling pathways alone, but on their temporal and functional cross-talk. Dysregulation of MAPK/ERK, PI3K/Akt, NF- κ B, TGF- β /Smad, and Nrf2/HO-1 signalling can shift the healing response toward persistent inflammation, oxidative stress, impaired regeneration, or excessive fibrosis.

Despite advances in understanding these regulatory networks, translation into effective therapies remains constrained by the inability of conventional in vitro and animal models to fully reproduce the complexity of the human wound microenvironment. Current organoid and reconstructed-skin models offer improved physiological relevance but still require greater standardisation and incorporation of vascular, immune, neural, mechanical, and systemic components. Future progress should therefore focus on integrating multi-omics, spatial and single-cell profiling with artificial intelligence and machine learning to identify clinically meaningful biomarkers, stratify patients according to their underlying wound biology, and guide treatment selection. Coupling these approaches with human-relevant tissue models and advanced biomaterials could enable more precise interventions tailored to the molecular and clinical characteristics of individual wounds. Such a multidisciplinary, mechanism-driven framework offers a promising route toward personalized wound-healing therapies that improve functional regeneration while minimizing chronicity and pathological scarring.

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Authors contribution

AKP: Study Conception and Design, NS: Data Collection; **MK, PRS:** Draft Manuscript; **MK, AKP:** reviewing and editing; **DK, LPS:** All authors reviewed the results and approved the final version of the manuscript.

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