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Review Article

The Role of Cytokines in Wound Healing: Insights into Mechanisms, Therapy, and Innovations

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Abstract:

Wound healing, a multifaceted and dynamic process that is essential for restoring tissue structure and function after an injury. This process requires a well-coordinated interplay of multiple cellular and molecular systems to renovate damaged tissue and restore homeostasis. A complex network of cytokines and growth factors lies at the heart of this orchestration, regulating cellular responses at various stages of healing such as inflammation, proliferation, and tissue remodeling. Disruptions to these signaling molecules can result in persistent wounds or excessive scarring, thus their delicate balance and precise timing are critical for optimal healing outcomes. This review article presents a detailed assessment of major cytokines TNF-α, IL-1, IL-6, and TGF-β involved in wound healing, focusing on their cellular mechanisms and therapeutic potential in both animal models and human patients. Moreover, we highlight research gaps, such as the need for more targeted and sustained cytokine-modulating therapies and bioengineering strategies. These insights aim to inform future innovations, optimizing healing outcomes and addressing unmet clinical needs.

Keywords: Wound healing, cytokines, inflammation, fibrosis, angiogenesis, skin repair

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1. Introduction

The skin, which serves as the human body's initial barrier, is especially vulnerable to external assaults.[1] Physicians often encounter skin wounds, such as acute burns and persistent non-healing ulcers, which pose significant challenges in clinical management and patient care. Skin wound healing is a complex and intricate biological process essential for restoring tissue integrity after injury .[2]

This process involves a dynamic interplay of cellular, molecular, and biochemical events, which can be divided into four stages: hemostasis, inflammation, proliferation, and tissue remodeling that are the cornerstones of

Trans. Health Sci. Feb 2025, Vol (1), Issue (1), 25 - 39
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rebuilding skin integrity and functionality.[3] Central to the orchestration of these stages are cytokines and growth factors, pivotal molecules that influence critical cellular behaviors such as migration, proliferation, differentiation, and apoptosis. Through their actions, these mediators play a vital role in promoting effective tissue repair and regeneration.[4]

The body's inflammatory and immunological responses, as well as tissue repair, depend on a diverse group of signaling proteins called cytokines. These proteins can be categorized into two main types: pro-inflammatory cytokines, which trigger and maintain inflammation, and anti-inflammatory cytokines, which aid in the resolution of inflammation and encourage healing. The delicate equilibrium between these cytokines is vital for effective wound healing; any disruption in this balance may result in chronic inflammation, hindered recovery, or excessive scarring.[5]

The effect of cytokines is vital for the wound healing process and carries significant implications for both acute and chronic wounds. Understanding the roles of cytokines in the wound healing process holds great promise for the development of innovative therapeutic strategies that can expedite healing, minimize scar formation, and effectively manage chronic wounds. This paper describes several key cytokines, their relation with wound healing in animals and human patients, possible mechanisms behind them, and the potential they present for therapeutic advancements.

2. Cytokines in Wound Healing

Cytokines are proteins released by cells that specifically influence cell functions and communication. They can have different modes of action: an autocrine effect, where they act on the same cells that release them; a paracrine effect, where they affect nearby cells; or, in some cases, an endocrine effect, where they impact distant cells .[6]

2.1. Necrosis Factor-alpha in Wound Healing

Tumor Necrosis Factor-alpha (TNF-α) is a cytokine that plays a key role in the wound healing milieu. Its functions involve various stages of healing, including inflammation, tissue repair, and remodeling. Understanding the dual nature of TNF-α—both beneficial and potentially detrimental—can illuminate its therapeutic applications in wound management.

The first role of TNF- α is initiating the inflammatory phase of wound healing. It promotes the recruitment and activation of immune cells, such as macrophages and neutrophils, which are responsible for clearing debris and pathogens from the wound site.[7]

TNF-α stimulates fibroblast proliferation and migration, which are critical for collagen deposition and granulation tissue formation.[8] TNF-α interacts with TNF receptors (TNFR1 and TNFR2), triggering signaling cascades that activate nuclear factor-kappa B (NF-κB) and c-Jun N-terminal kinase (JNK) pathways.[9] This leads to amplified production of adhesion molecules on endothelial cells, promoting leukocyte migration into tissues.[10] TNF-α also influences keratinocyte activity, aiding in re-epithelialization, not only by promoting their proliferation but also through inducing matrix metalloproteinases (MMPs), enzymes that break down extracellular matrixes to allow re-modelling.[11] Additionally, it enhances angiogenesis, the formation of new blood vessels, by increasing the expression of

Trans. Health Sci. Feb 2025, Vol (1), Issue (1), 25 - 39
DOI: 10.21608/ths.2025.344997.1002

vascular endothelial growth factor (VEGF), a vital factor for providing nutrients and oxygen to healing tissues for effective wound repair.[9]

In cases of impaired healing characterized by excessive inflammation such as chronic wounds, inhibiting TNF-α can be beneficial. Studies demonstrated using the anti-TNF-α neutralizing antibodies such as infliximab can enhance wound healing by reducing inflammation and promoting a favorable equilibrium between M1 (pro-inflammatory) and M2 (anti-inflammatory) macrophages.[12,13]

2.2. Interleukin-1 in Wound Healing

Interleukin-1 (IL-1) is one of the first cytokines produced in response to injury, by neutrophils, keratinocytes, and macrophages.[14] Its role in wound healing is promoting inflammation and recruiting fibroblasts and keratinocytes. IL-1 binds to its receptor (IL-1R), activating the MyD88-dependent signaling cascade, which consequently activates NF-κB and mitogen-activated protein kinases (MAPK) pathways.[15]

IL-1 promotes the recruitment of neutrophils and macrophages to the wound site, facilitates the synthesis of other cytokines, and helps regulate fever.[16] It also plays a key role in the activation of NF-κB, a transcription factor essential for the expression of genes involved in inflammation and tissue repair. This results in the expression of various inflammatory chemokines, enhancing the inflammatory response and promoting fibroblast activation for tissue repair.[17]

Therapeutic strategies targeting the IL-1 cytokine family have garnered attention due to its dual roles in encouraging healing and contributing to pathological fibrosis. The use of IL-1 Receptor antagonist (IL-1Ra) has shown significant promise in modulating inflammatory responses during wound healing.[8] Experimental studies demonstrate that administering IL-1Ra reduces pro-inflammatory cytokine levels and enhances tissue regeneration without compromising mechanical properties, indicating its potential for early intervention in acute injury settings.[18] To enhance its therapeutic efficacy, controlled delivery systems are being explored to sustain IL-1Ra's anti-inflammatory effects throughout the critical phases of wound healing.[19] Furthermore, combining IL-1 inhibitors with other therapeutic compounds, including growth factors or modulators of pathways like TGF-beta, may provide synergistic benefits, optimizing healing outcomes while minimizing the risk of excessive scarring.[20]

2.3. Interleukin-6 in Wound Healing

Interleukin-6 (IL-6) is a cytokine with several distinct functions that plays a key part in wound healing, particularly during the inflammatory and proliferative phases, through various channels with prospective therapeutic applications.[21] Following tissue injury, IL-6 is rapidly upregulated, peaking around 12 hours post-injury, and plays a crucial role in initiating the inflammatory response by recruiting neutrophils and monocytes to the wound site.[22] These immune cells clear debris and secrete additional cytokines and growth factors to facilitate healing. The formation of IL-6 ligand-receptor complex triggers the activation of multiple intracellular signaling pathways, such as the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway, the Mitogen-activated protein kinase/ extracellular signal-regulated kinases

Trans. Health Sci. Feb 2025, Vol (1), Issue (1), 25 - 39
DOI: 10.21608/ths.2025.344997.1002

(MAPK/ERK) pathway, and the Phosphoinositide 3-kinase/ Protein kinase B (PI3K/Akt) pathway. Recent studies indicate classic signaling is crucial for the anti-inflammatory and regenerative effects of IL-6, whereas trans-signaling is more associated with promoting pro-inflammatory responses.[23]

As the process transitions from inflammation to repair, IL-6 enhances macrophage polarization from a pro-inflammatory (M1) to a reparative (M2) phenotype, a critical step for tissue regeneration. Additionally, IL-6 influences fibroblast migration to injury sites and enhances collagen synthesis, essential for extracellular matrix (ECM) deposition and structural support during healing.[24] It also contributes to angiogenesis by regulating factors that drive new blood vessel formation, ensuring sufficient nutrient and oxygen supply to the regenerating tissue.[25]

Despite these benefits, dysregulated IL-6 activity can lead to excessive fibrosis or scarring, disrupting normal tissue architecture and function through binding to IL-6R, activating the JAK/STAT signaling pathway, particularly STAT3.[26] JAK-STAT activity was reported to be associated with proliferation, and differentiation of fibroblasts within human cutaneous scar tissues.[27] To harness IL-6's positive effects while mitigating adverse outcomes, therapeutic strategies such as monoclonal antibodies targeting IL-6 or its receptor (IL-6R) have shown promise in reducing excessive inflammation, enhancing re-epithelialization, and minimizing scarring.[28] Gene therapy approaches aimed at modulating IL-6 expression offer potential to balance its roles in acute healing while reducing chronic inflammation and fibrosis risks.[29]

Furthermore, personalized medicine strategies leveraging insights into individual genetic variations in IL-6 signaling pathways could optimize treatment for conditions like keloids or hypertrophic scars by disrupting the JAK-STAT pathway and its subsequent pathway signaling on cell proliferation and collagen production.[29]

Overall, while IL-6 is integral to wound healing through its roles in inflammation, macrophage polarization, fibroblast activation, and angiogenesis, precise modulation of its activity is essential to maximize therapeutic outcomes and prevent fibrotic complications as keloids.[30]

2.4. Transforming growth factor-beta in Wound Healing

One of the several cytokines and growth factors essential for efficient wound healing is transforming growth factor (TGF-β). The three isoforms of the TGF-β family—TGF-β1, TGF-β2, and TGF-β3—have active domains that are roughly 80% structurally identical.[31]

The TGF-β signaling stream is critical for a wide range of cellular processes and is believed to have evolved with the emergence of multicellular organisms.[32] When TGF-β attaches to its receptors (TGF-βRI and TGF-βRII), phosphorylating SMAD proteins (SMAD2 and SMAD3) initiates the signaling cascade.[33] These phosphorylated SMADs create a complex with SMAD4 and translocate into the nucleus, where they regulate the transcription of target genes involved in ECM synthesis and fibroblast activation.[34] TGF-β has important roles during development, including promoting the endocardial cells' epithelial-to-mesenchymal transition (EMT), which is necessary for the proper the development of the heart.[35] TGF-β is also responsible for modulating cellular

Trans. Health Sci. Feb 2025, Vol (1), Issue (1), 25 - 39
DOI: 10.21608/ths.2025.344997.1002

differentiation, death, cell-cycle arrest, ECM synthesis, and cell migration to maintain tissue homeostasis after development.[36]

In wounds, TGF-β facilitates the closure and tissue repair by promoting ECM protein synthesis and suppressing the activity of MMPs.[37] A study aimed to evaluate the role of TGF-β3 in murine excisional wound healing, demonstrated that TGF-β3 deficiency delays epithelialization and granulation tissue maturation.[38] However, due to its diverse functions across different cells, excessive TGF-β activity is characteristic of fibrotic diseases and causes aberrant tissue fibrosis, which can disrupt normal tissue function.[39]

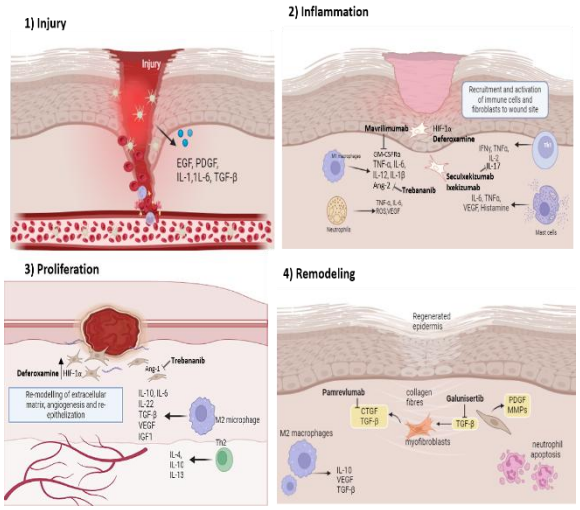

Fig. 1: Cytokine roles and drugs acting in the four stages of wound healing. "Created with Biorender". EGF: Epidermal growth factor; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HIF-α: Hypoxia-inducible factor-1-α; Ang: Angiopoietin; PDGF: platelet-derived growth factor; TGF-β: transforming growth factor; VEGF: vascular endothelial growth factor; IGF-1: Insulin-like growth factor 1, MMP: Matrix metalloproteinase; CTGF: Connective tissue growth factor; ROS: reactive oxygen species; IFN-γ: Interferon gamma; IL: Interleukin.

Novel Cytokine-Modulating Drugs

While many cytokine-modulating therapies have already shown promise, newer approaches are being explored that could address unmet needs in wound management. Recent advancements in immunology and molecular biology have catalyzed the development of innovative therapies that target specific cytokine pathways, offering new strategies to enhance wound healing. These novel approaches hold particular promise for addressing chronic and non-healing wounds, where conventional treatments often fail.

2.5. Inflammatory Cytokine Inhibitors

Among the pro-inflammatory cytokines, IL-17 has emerged as a key target due to its role in sustaining chronic inflammation and contributing to delayed wound healing and excessive scarring. Drugs like Secukinumab and Ixekizumab, currently approved for autoimmune conditions such as psoriasis, are now being considered for their potential to reduce inflammation and improve outcomes in wound management.[40] Similarly, granulocyte-macrophage colony-stimulating factor (GM-CSF), while essential for immune cell recruitment, can exacerbate inflammation when overexpressed. GM-CSF inhibitors like Mavrilimumab could offer a way to modulate excessive inflammation, promoting a more favorable environment for wound repair while maintaining necessary immune defenses.[41] by reducing T cell activation, Th1 differentiation (interferon-γ), and pro-inflammatory cytokines IL-6, TNFα, and IL-1β.[42] In contrast, other studies report that in diabetic foot ulcers (DFUs), GM-CSF activity is only partially activated compared to healthy wounds, resulting in a weakened inflammatory response. This situation suggests administering exogenous GM-CSF to rectify macrophage immune dysfunction could play

Trans. Health Sci. Feb 2025, Vol (1), Issue (1), 25 - 39
DOI: 10.21608/ths.2025.344997.1002

a pivotal role in restoring equilibrium within the wound ecosystem, thereby invigorating the wound healing cascade.[43]

2.6. Anti-inflammatory response enhancers

In addition to reducing inflammation, enhancing anti-inflammatory responses is a critical area of focus. Interleukin-22 (IL-22), a cytokine known for its regenerative and epithelial repair properties, has shown promise in experimental models of tissue injury.[44] Recombinant IL-22 agonists like F-652 have demonstrated their ability to promote epithelial regeneration and barrier repair, suggesting a potential role in accelerating wound re-epithelialization by JAK/STAT and PI3K/Akt downstream signaling.[45] Similarly, Interleukin-37 (IL-37), a newly characterized anti-inflammatory cytokine, holds great potential for wound healing through suppressing activated MAPK signaling pathway, reducing TNF-α, IL-1β, and nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome expression in diabetic wounds in mice .[46] Recombinant IL-37 or gene-based delivery of IL-37 could offer innovative approaches to control inflammation and enhance repair in wounds prone to chronicity.[47]

2.7. Scar prevention therapies

Fibrosis and scarring, common complications of wound healing, present another therapeutic challenge. Connective tissue growth factor (CTGF), a downstream effector of TGF-β signaling, is a key player in cellular events such as skeletogenesis, angiogenesis, wound healing and scar formation. Anti-CTGF agents like Pamrevlumab have shown efficacy in fibrotic diseases, successfully halting the progression of idiopathic pulmonary fibrosis in clinical trials and holds potential for preventing pathological scarring in wounds.[48] Similarly, Galunisertib blocks the phosphorylation of the intracellular unit of the TGF-βR-1/ Activin receptor-like kinase-5 (ALK5) serine-threonine kinase, inhibiting downstream SMAD 2/3 signaling and nuclear transcription of fibrotic gene expression. It demonstrated a twofold advantage in in-vitro studies of fibroproliferative dermal fibroblasts. They suppressed the excessive dermal fibroblast activity, without hindering their normal homeostatic proliferation, and expedited cell migration leading to a higher rate of wound closure as quantified by scratch tests.[49]

2.8. Angiogenesis promoting therapies

Angiogenesis is necessary for delivering vital nutrients and oxygen to healing tissues, hence. targeting angiogenic cytokines and pathways has become a promising strategy.[50] CXCL12, a chemokine critical for angiogenesis and stem cell recruitment, has been investigated in relation to wound healing.[51] Angiopoietins, particularly Ang-1 and Ang-2, play a central role in vascular stability and angiogenesis. Modulating these pathways through agents such as Trebananib could improve vascularization and enhance the healing process in wounds with impaired blood supply.[52]

Deferoxamine (DFO), an iron chelator, has been shown to enhance neovascularization and modulate gene expression in diabetic wound healing. Hou et al. demonstrated that DFO treatment accelerated wound closure at 7, 10, and 14 days compared to vehicle and VEGF-A treatments. Histological analysis revealed increased micro-vessel formation in granulation tissue by day 7.[53] Another study

Trans. Health Sci. Feb 2025, Vol (1), Issue (1), 25 - 39
DOI: 10.21608/ths.2025.344997.1002

by Ram et al. indicated that DFO ointment (0.1%) application significantly upregulated Hypoxia-inducible factor-1-α (HIF-1α), VEGF-A, stromal cell-derived factor 1-α (SDF-1α), TGF-β1, and IL-10 expression from days 3 to 14, while reducing pro-inflammatory markers TNF-α, MMP-9, and IL-1β at days 7 and 14. Furthermore, DFO decreased TNF-α protein levels and increased IL-10 protein levels from day 3 onward, suggesting its potential to promote anti-inflammatory and regenerative processes in wound healing.[54]

Over the previous decade, researchers have discovered that, in addition to their lipid-lowering effects, statins exhibit pro-angiogenic qualities *via* activating Akt/PI3K pathway by inhibiting the formation of HMG-CoA reductase and mevalonate, in turn, promoting endothelial cell proliferation and capillary morphogenesis, as well as the production of VEGF.[55] Studies have explored the effects of simvastatin on wound healing in diabetic mice. Bitto et al. revealed that intraperitoneal simvastatin (5 mg/kg) enhanced VEGF-A expression, improved wound closure, and increased angiogenesis.[56] Similarly, Asai et al. found that topical simvastatin (50 μg/wound) enhanced neovascularization and lymph-angiogenesis, achieving over 90% re-epithelization and accelerated wound closure by day 7.[57]

2.9. Bioengineering strategies

Emerging platforms for cytokine modulation have added precision and innovation to wound healing strategies. Nanotechnology-based delivery systems are being developed for the controlled release of cytokines or cytokine inhibitors directly at the wound site.[58] This approach minimizes systemic side effects while ensuring localized and sustained action. For example, nanoparticles loaded with IL-10 or TGF-β3 have shown promise in promoting wound healing while preventing excessive fibrosis.[59,60] Gene therapy approaches, such as CRISPR-Cas9-mediated modulation of cytokine expression, offer a cutting-edge method for achieving scarless healing by selectively downregulating TGF-β1 or enhancing TGF-β3 activity.[61] Furthermore, engineered cytokines or "muteins" – modified versions of cytokines with enhanced specificity and efficacy – are being developed for various applications, including cancer immunotherapy, and could be adapted for wound healing.[62,63]

Discussion

Cytokine modulation performs a focal role in orchestrating balanced wound healing by regulating inflammation, fibroblast activity, and keratinocyte function. In the early stages of inflammation, pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 serve a vital function as they attract neutrophils and macrophages to remove debris and stop infection. For example, because of decreased immune cell infiltration, IL-1β knockout animals show delayed recovery [64] while TNF-α inhibitors like infliximab have demonstrated efficacy in reducing inflammation and promoting healing in chronic diabetic ulcers.[65] Anti-inflammatory cytokines, including IL-10 and TGF-β3, facilitate the resolution of inflammation and transition to tissue repair [66] recombinant TGF-β3 has shown promise in reducing scarring and improving collagen organization in both preclinical and clinical studies.[26] Fibroblast activity, regulated by cytokines like TGF-β isoforms and PDGF, is essential for ECM deposition and tissue remodeling.[67] While TGF-β1 and TGF-β2 promote fibroblast proliferation, leading to hypertrophic scars,[68] TGF-β3 balances these

Trans. Health Sci. Feb 2025, Vol (1), Issue (1), 25 - 39
DOI: 10.21608/ths.2025.344997.1002

effects by enhancing collagen alignment and reducing inflammatory responses, as observed in studies using neutralizing antibodies and recombinant proteins.[69] Keratinocyte function, crucial for re-epithelialization, is similarly influenced by cytokines like IL-6, which enhances proliferation and migration at moderate levels but delays healing at excessive concentrations.[70]

Table 1: Comparison between drugs and their therapeutic outcomes in modulating repair.

Drug/Approach	Target	Therapeutic Outcome
Secukinumab, Ixekizumab	IL-17	Reduces chronic inflammation, improves outcomes in wound management.
Mavrilimumab	GM-CSFα receptor	Reduces excessive inflammation and destructive effects of macrophages.
Exogenous GM-CSF	GM-CSF receptors	Induces immunological tolerance, stimulates keratinocytes and fibroblasts proliferation, upregulates angiogenic factors (VEGF) in endothelial cells and M2 macrophages.
F-652	IL-22	Promotes epithelial regeneration and accelerates wound re-epithelialization.
Recombinant IL-37 or Gene-based Delivery	IL-37	Controls inflammation, fosters tissue homeostasis, enhances repair in chronic wounds.
Pamrevlumab	CTGF	Prevents pathological scarring and fibrosis.
Galunisertib	TGF-β	Reduces fibroblast activity, minimizes scarring, and supports ECM formation for tissue regeneration.
Trebananib	Angiopoietins (Ang-1, Ang-2)	Enhances vascular stability, promotes angiogenesis, and improves healing in wounds with impaired blood supply.
Deferoxamine	HIF-1α	Stimulates new blood vessel formation and modulates gene expression to accelerate wound closure and reduce inflammation.
Simvastatin	VEGF, Akt/PI3K pathway	Promotes angiogenesis, endothelial cell proliferation, increases NO production
Nanotechnology-based Delivery Systems	Cytokines/Cytokine Inhibitors (e.g., IL-10, TGF-β3)	Provides localized, sustained release, promoting wound healing and minimizing fibrosis.
CRISPR-Cas9 Gene Therapy	TGF-β1, TGF-β3	Enables scarless healing by downregulating TGF-β1 or enhancing TGF-β3 activity.

Trans. Health Sci. Feb 2025, Vol (1), Issue (1), 25 - 39
DOI: 10.21608/ths.2025.344997.1002

Cytokine Muteins	Respective cytokine target but with altered specificity	Increases efficacy and bioactivity of cytokines; adaptable for wound healing applications.

Upon IL-6R activation, the JAK/STAT signaling pathway is triggered, specifically activating STAT3. This activation enhances collagen production and drives the differentiation of fibroblasts into myofibroblasts, which are essential for wound contraction and scar formation. Myofibroblasts exhibit contractile properties that facilitate wound closure by drawing the edges together. However, prolonged or excessive STAT3 activation can lead to overproduction of collagen, potentially causing pathological fibrosis .[71]

Moreover, fibroblasts also produce the ECM that supports cell migration and tissue scaffold formation. Controlled delivery of IL-6 has improved wound closure in preclinical models, [25] while recombinant epidermal growth factor (EGF) has shown efficacy in accelerating re-epithelialization in diabetic foot ulcers. EGF helps counteract the impaired cellular responses and chronic inflammation typical in diabetic wounds by modulating inflammatory cytokine levels, reducing oxidative stress, and fostering a more conducive environment for healing [72] EGF activates intracellular signaling pathways such the PI3K-Akt and Ras-Raf-MEK-ERK cascades by binding to its high-affinity receptor, EGFR, on the surface of keratinocytes and fibroblasts.[73] Cell-based treatments, biologics, and corticosteroids are examples of therapeutic interventions that further demonstrate the potential of cytokine regulation.[74] Corticosteroids reduce pro-inflammatory cytokines and fibroblast activity, effectively managing hypertrophic scars, whereas biologics targeting TGF-β and TNF-α pathways minimize fibrosis and inflammation, improving healing outcomes.[75] Cell-based approaches, such as adipose-derived stem cells secreting IL-10 and TGF-β3, have demonstrated accelerated healing and reduced scarring in animal models.[76]

While these findings emphasize the critical role of cytokine modulation in optimizing wound repair and minimizing pathological scarring, several research gaps persist. For instance, the synergistic effects and crosstalk between cytokines in the wound-healing cascade remain underexplored, limiting the ability to fully leverage their therapeutic potential. Furthermore, cytokine dynamics in unique populations with comorbid conditions such as diabetes, autoimmune diseases, or aging-related impairments warrant further investigation.

Another significant gap lies in understanding the long-term effects of cytokine therapies. Current data on safety and efficacy is limited, necessitating longitudinal studies to validate these interventions across diverse patient populations. Advanced research integrating molecular biology, immunology, and bioengineering holds the promise of overcoming these challenges. For example, adaptive delivery systems and engineered cytokines could enhance therapeutic precision and efficacy.

Cytokine-modulating treatments for wound healing have a bright future, with ongoing innovations poised to address unmet clinical needs. Exploring these research gaps will

Trans. Health Sci. Feb 2025, Vol (1), Issue (1), 25 - 39
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pave the way for transformative advancements in wound care and tissue regeneration.

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Trans. Health Sci. Feb 2025, Vol (1), Issue (1), 25 - 39
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