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Review Article

Genes involved in chronic wound healing and their therapeutic potential

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ABSTRACT

Chronic wounds are wounds that fail to progress through the normal stages of healing and remain open for an extended period of time. These wounds often require specialized treatment approaches. While the genes involved in wound healing play important roles in chronic wound treatment as well, the specific genetic factors contributing to chronic wounds are still being studied. Some of the genes and genetic factors that have been implicated in chronic wound healing and their potential for treatment include Transforming Growth Factor-Beta (TGF-β) Family, Matrix Metalloproteinases (MMPs), Transforming Growth Factor-Alpha (TGF-α), Hypoxia-Inducible Factor-1 (HIF-1), Vascular Endothelial Growth Factor (VEGF), Nitric Oxide Synthase (NOS) and Wound-Healing-Associated microRNAs. It's important to note that chronic wounds are multifactorial, and their treatment requires a comprehensive approach addressing various factors beyond genetic factors alone. Other aspects such as underlying medical conditions, infection, local wound environment, and patient-specific factors also play crucial roles in chronic wound management.

1. Introduction

A chronic non-healing wound is a wound that fails to progress through the normal stages of healing within an expected timeframe, typically around 4 weeks.[1] These types of wounds pose a significant challenge in clinical practice and require specialized management. Several factors can contribute to the development of chronic non-healing wounds, including:

1. Impaired Microcirculation: Poor blood supply to the wound area due to conditions such as peripheral artery disease or diabetes can result in inadequate oxygen and nutrient delivery, hampering the healing process.[2]
2. Infection: Persistent bacterial or fungal infections in the wound can lead to chronic inflammation and delayed healing. Biofilm formation, where microorganisms form protective communities within the wound, can further complicate the healing process.[3]
3. Persistent Inflammation: Chronic wounds often have elevated levels of pro-inflammatory cytokines that can disrupt the healing process. Excessive inflammation can impair the formation of new blood vessels and impair the recruitment and function of healing cells.[4]
4. Tissue Necrosis: Dead or necrotic tissue within the wound bed hinders healing. Necrotic tissue provides a favorable environment for bacterial growth and impedes the growth of new tissue.[5]
5. Protease Imbalance: An imbalance between proteases and their inhibitors can result in excessive degradation of the extracellular matrix, leading to delayed wound closure.[6]
6. Cellular Senescence: Cellular senescence, the state of irreversible growth arrest, can occur in chronic

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wounds. Senescent cells secrete pro-inflammatory factors and can impair tissue repair and regeneration.[7]

7. Systemic Factors: Underlying conditions such as diabetes, vascular diseases, malnutrition, immunodeficiency, and certain medications can contribute to impaired wound healing and the development of chronic non-healing wounds.[8]

Gene therapy holds promise as a potential treatment approach for chronic non-healing wounds. It involves the delivery of genetic material into cells to correct underlying genetic defects, enhance wound healing processes, or modulate specific pathways involved in wound repair[9]. While gene therapy for chronic wounds is still in the early stages of development, several strategies are being explored and we have summarized them in this review article.

2. TGF-β Signaling Pathway

Modulating the TGF-β (Transforming Growth Factor-Beta) signaling pathway represents a promising approach for chronic wound treatment. TGF-β is a multifunctional cytokine that plays a crucial role in wound healing, regulating various aspects of the process, including inflammation, cell proliferation, extracellular matrix production, and tissue remodeling. However, dysregulation of TGF-β signaling can contribute to impaired wound healing and the development of chronic wounds[9,10]. Here are some strategies that aim to modulate TGF-β signaling for chronic wound treatment:

1. TGF-β Inhibitors: Small molecule inhibitors or blocking antibodies can be used to specifically target and inhibit the activity of TGF-β. These inhibitors can reduce excessive TGF-β signaling, which is associated with fibrosis and delayed wound healing. By blocking TGF-β activity, the inhibitors may help to promote a more favorable wound healing environment.[11]
2. TGF-β Receptor Modulators: Modulating the activity of TGF-β receptors can be an alternative strategy to regulate TGF-β signaling. This can be achieved through the use of receptor agonists or antagonists, which can influence TGF-β receptor activation and downstream signaling pathways. By selectively modulating the activity of TGF-β receptors, it is possible to fine-tune TGF-β signaling and promote appropriate wound healing responses.[12]
3. TGF-β Gene Therapy: Gene therapy approaches can be employed to manipulate TGF-β signaling in chronic wounds. For example, introducing genes encoding soluble TGF-β receptors or TGF-β antagonists into the wound site can act as a local "sink" for TGF-β ligands, effectively reducing their availability and downstream signaling. This approach aims to limit excessive TGF-β activity and promote a more balanced wound healing response.[13]
4. Targeting TGF-β Signaling Pathway Components: Specific components of the TGF-β signaling pathway can be targeted to modulate its activity. For example, downstream signaling molecules like SMAD proteins, which mediate TGF-β signaling, can be targeted for modulation. By selectively modulating the activity of these components, it is possible to influence the downstream effects of TGF-β signaling and promote enhanced wound healing.[14,15]

It's important to note that the modulation of TGF-β signaling for chronic wound treatment requires careful consideration. TGF-β plays diverse roles in wound healing, and its signaling is finely regulated. Therefore, achieving the appropriate balance in TGF-β activity is crucial to ensure optimal healing outcomes. Additionally, the specific approach for modulating TGF-β signaling may vary depending on the characteristics of the wound, patient factors, and the stage of wound healing. Further research and clinical trials are necessary to evaluate the efficacy, safety, and long-term effects of these strategies in the context of chronic wound treatment.

3. Regulating the activity of MMPs

Regulating matrix metalloproteinase (MMP) activity is an important aspect of chronic wound treatment. MMPs are enzymes involved in tissue remodeling and degradation of the extracellular matrix. Imbalances in MMP activity can contribute to delayed wound healing and the development of chronic wounds. Here are some strategies and therapies that aim to regulate MMP activity for chronic wound treatment:

1. MMP Inhibitors: Small molecule inhibitors can be used to directly target and inhibit the activity of specific MMPs. These inhibitors bind to the active site of the enzyme, preventing it from degrading the extracellular matrix excessively. Various synthetic MMP inhibitors have been developed, and some have shown potential in preclinical and clinical studies.[16] However, the challenge lies in achieving specific inhibition of the desired MMPs without interfering with other essential matrix remodeling processes.
2. TIMPs (Tissue Inhibitors of Metalloproteinases): TIMPs are endogenous proteins that naturally regulate MMP activity. They act as inhibitors by binding to active MMPs, thereby controlling their proteolytic activity.[17] In chronic wounds, the balance between MMPs and TIMPs is disrupted, leading to excessive matrix degradation. Strategies that promote the expression or delivery of TIMPs may help restore this balance and regulate MMP activity.
3. Growth Factors and Cytokines: Certain growth factors and cytokines, such as TGF-β, can influence MMP activity. Modulating these factors can indirectly regulate MMP activity. For instance, TGF-β can

promote the expression of TIMPs, leading to decreased MMP activity. By using growth factors or cytokines that influence MMP-TIMP balance, it may be possible to regulate MMP activity and promote proper wound healing.[18]

4. Cellular Therapies: Cell-based therapies, such as the application of mesenchymal stem cells (MSCs), have shown potential in regulating MMP activity. MSCs have been observed to modulate MMP expression and secretion, favoring a more balanced MMP-TIMP ratio. MSC-based therapies may contribute to the regulation of MMP activity and facilitate the healing of chronic wounds.[19]
5. Topical Agents: Various topical agents have been investigated for their ability to regulate MMP activity. Examples include dressings or ointments containing substances such as silver, honey, or plant-based compounds. These agents may modulate MMP activity indirectly by influencing wound environment factors such as inflammation, bacterial load, or oxidative stress.[20]

It is worth noting that the regulation of MMP activity should be carefully balanced because MMPs also play important roles in wound healing processes, such as cell migration and tissue remodeling. Achieving the right balance between MMPs and TIMPs is crucial to promote appropriate tissue remodeling while avoiding excessive matrix degradation. Further research is needed to optimize strategies for regulating MMP activity and determine their efficacy and safety in chronic wound treatment.

4. TGF-α and its Analogs

Transforming Growth Factor-Alpha (TGF-α) is a growth factor that belongs to the epidermal growth factor (EGF) family. It has been studied for its potential role in chronic wound healing treatment. TGF-α is primarily involved in stimulating cell proliferation, migration, and the formation of new tissue.[21] Here are some ways TGF-α can be utilized for chronic wound healing treatment:

1. Topical Application: TGF-α can be administered topically as a part of wound dressings or gels. It promotes re-epithelialization, the process by which new skin cells migrate and cover the wound bed. By stimulating the proliferation and migration of epithelial cells, TGF-α aids in the closure of chronic wounds.[22]
2. Gene Therapy: Gene therapy approaches can be employed to deliver TGF-α genes directly to the wound site. This involves the introduction of genetic material encoding TGF-α into cells at the wound bed. By continuously producing TGF-α locally, gene therapy aims to enhance the healing process by stimulating cell growth and tissue regeneration.[23]
3. Combination Therapies: TGF-α can be used in combination with other growth factors or cytokines to augment its effects on chronic wound healing. For example, TGF-α has been studied in combination with platelet-derived growth factor (PDGF) to promote angiogenesis and tissue remodeling. Combining TGF-α with other growth factors may enhance their overall effectiveness in wound healing.[24]
4. TGF-α Receptor Agonists: TGF-α binds to specific receptors, such as the epidermal growth factor receptor (EGFR), to mediate its effects. The administration of TGF-α receptor agonists can activate these receptors and stimulate wound healing processes. By directly targeting the receptors, these agonists can promote cell proliferation, migration, and tissue regeneration.[25]

It's important to note that while TGF-α shows potential for chronic wound healing treatment, its application must be carefully controlled. Excessive TGF-α activity can lead to abnormal tissue growth or fibrosis. Moreover, individual patient characteristics and wound conditions may influence the response to TGF-α therapy. Therefore, further research and clinical trials are necessary to determine the optimal dosage, delivery method, and combination therapies for utilizing TGF-α effectively in chronic wound healing treatment.

5. Stimulating HIF-1 Activity

Hypoxia-Inducible Factor-1 (HIF-1) is a transcription factor that plays a crucial role in cellular response to low oxygen levels (hypoxia). It regulates the expression of genes involved in various aspects of wound healing, including angiogenesis, cell survival, and metabolism. Modulating HIF-1 activity has shown potential as a therapeutic strategy for chronic wound healing.[26] Here are some ways to stimulate HIF-1 for chronic wound healing therapy:

1. Topical Oxygen Therapies: One approach is to provide supplemental oxygen to the wound bed using methods such as hyperbaric oxygen therapy (HBOT) or topical oxygen therapy. These therapies increase oxygen availability, which can stabilize HIF-1 and promote its activity in hypoxic wound environments. Enhanced HIF-1 activity, in turn, can drive angiogenesis, enhance tissue repair, and accelerate wound healing.[27]
2. Pharmacological HIF-1 Activators: Small molecules and drugs that can directly activate HIF-1 are being investigated as potential therapies for chronic wounds. These activators can stabilize the HIF-1 protein or enhance its transcriptional activity, even in normoxic conditions. Examples of HIF-1 activators include prolyl hydroxylase inhibitors (PHIs), which prevent the degradation of HIF-1α, and histone deacetylase inhibitors (HDACis), which enhance HIF-1 activity indirectly.[28,29]

3. Growth Factors and Cytokines: Certain growth factors and cytokines can induce HIF-1 activity, either directly or indirectly, through their signaling pathways. For instance, vascular endothelial growth factor (VEGF) can activate HIF-1 and promote angiogenesis. By using growth factors or cytokines that can stimulate HIF-1, it may be possible to enhance wound healing processes, particularly in hypoxic wound environments.[30]
4. Gene Therapy: Gene therapy approaches can be utilized to deliver genes encoding components of the HIF-1 pathway to the wound site. For example, introducing genes encoding HIF-1α or other HIF-1-regulated factors can enhance HIF-1 activity and promote the expression of downstream target genes. This approach aims to overcome the impaired HIF-1 response often observed in chronic wounds and promote efficient wound healing.[31]

It's important to consider that HIF-1 activation should be carefully regulated to avoid potential side effects, such as excessive angiogenesis or tissue fibrosis. Additionally, the optimal timing, dosage, and combination therapies for HIF-1 stimulation in chronic wound healing require further research and clinical evaluation. Individual patient factors, wound characteristics, and underlying health conditions should also be taken into account when considering HIF-1 stimulant therapies for chronic wound treatment.

6. Enhancing VEGF Expression

Enhancing vascular endothelial growth factor (VEGF) expression or administering VEGF directly can be effective strategies to improve chronic wound healing. VEGF is a key regulator of angiogenesis, which is essential for proper wound healing. Here are some strategies to enhance VEGF expression or administer VEGF for chronic wound healing:

1. Topical Application of VEGF: VEGF can be applied topically to the wound bed in the form of gels, ointments, or dressings. This approach delivers VEGF directly to the wound site, promoting angiogenesis and stimulating blood vessel formation. Controlled release systems can be used to sustain the delivery of VEGF over time, maximizing its effect on wound healing.[22]
2. Gene Therapy: Gene therapy can be employed to introduce VEGF genes directly into the cells at the wound site. This approach involves the use of viral or non-viral vectors to deliver the VEGF genes, leading to local production of VEGF protein. Gene therapy allows for sustained VEGF expression, which can enhance angiogenesis and promote efficient wound healing.[23,32]
3. Growth Factor Combinations: Combining VEGF with other growth factors or cytokines can enhance its effectiveness in promoting chronic wound healing. For instance, combining VEGF with platelet-derived growth factor (PDGF) or fibroblast growth factor (FGF) has shown synergistic effects on wound healing by promoting angiogenesis, cell proliferation, and tissue regeneration.[33]
4. Stem Cell Therapy: Stem cell-based therapies, such as the use of mesenchymal stem cells (MSCs), can enhance VEGF expression and secretion. MSCs have been shown to secrete VEGF and other growth factors, creating a pro-angiogenic environment at the wound site. The administration of MSCs or their derivatives can stimulate VEGF production, promoting angiogenesis and facilitating chronic wound healing.[19]
5. Oxygen Therapies: Increasing oxygen availability to the wound site through hyperbaric oxygen therapy (HBOT) or topical oxygen therapy can stimulate VEGF expression. Oxygen-rich environments promote HIF-1α stabilization, leading to increased VEGF production. By enhancing VEGF expression, oxygen therapies can promote angiogenesis and improve wound healing outcomes.[27]

It's important to note that the optimal dosage, timing, and delivery methods for VEGF administration or enhancement vary depending on the specific wound characteristics and patient factors. Careful consideration should be given to potential side effects, such as excessive angiogenesis or the risk of promoting abnormal blood vessel growth. Further research and clinical trials are necessary to establish the safety, efficacy, and long-term effects of these strategies for enhancing VEGF expression or administering VEGF in chronic wound healing.

7. Targeting NO Production

Targeting nitric oxide (NO) production can be a therapeutic approach to treat chronic wound healing. No is a small molecule that plays a critical role in wound healing by regulating various processes, including vasodilation, angiogenesis, inflammation, and antimicrobial activity. Here are some therapeutic approaches that target NO production for chronic wound healing:

1. Nitric Oxide Donors: Nitric oxide donors are compounds that release NO upon administration. Topical application of NO donors to chronic wounds can directly increase NO levels in the wound bed. This promotes vasodilation, enhances blood flow, and improves tissue oxygenation, which are essential for wound healing. Examples of NO donors include nitroglycerin, sodium nitroprusside, and S-nitrosothiols.[34]
2. Nitric Oxide Synthase (NOS) Modulators: NOS is the enzyme responsible for the production of NO in the body. Modulating NOS activity can influence NO production and wound healing outcomes. NOS inhibitors can be used to regulate excessive NO

production, which can be detrimental to wound healing. Conversely, NOS substrates or cofactors, such as L-arginine or tetrahydrobiopterin (BH4), can enhance NOS activity and NO production, potentially improving chronic wound healing.[35]

3. Nitric Oxide-Releasing Dressings: Specialized wound dressings can be designed to release NO directly into the wound bed. These dressings are coated or infused with NO-releasing compounds or nanoparticles, which gradually release NO over time. The sustained release of NO from the dressings promotes wound healing by enhancing vasodilation, reducing bacterial load, and modulating inflammatory responses.[36]
4. Physical Modalities: Certain physical modalities, such as low-level laser therapy (LLLT) or photodynamic therapy (PDT), can stimulate NO production in the wound area. These therapies involve the application of specific wavelengths of light, which trigger biochemical reactions that result in increased NO production. The enhanced NO levels promote wound healing by stimulating angiogenesis, reducing inflammation, and enhancing tissue repair.[37,38]
5. Antioxidant Therapies: Excessive reactive oxygen species (ROS) can disrupt NO signaling and impair wound healing. Antioxidant therapies can help restore the balance between NO and ROS by reducing oxidative stress. Antioxidants, such as vitamins C and E, can scavenge ROS and prevent their detrimental effects on NO availability. By preserving NO levels, antioxidant therapies can support the healing process in chronic wounds.[39]

It is important to note that the regulation of NO production must be carefully balanced, as both too little and too much NO can have adverse effects on wound healing. Individual patient factors, wound characteristics, and underlying health conditions should be considered when implementing therapeutic approaches targeting NO production for chronic wound healing. Further research is needed to optimize these approaches and determine their efficacy and safety in clinical practice.

8. MicroRNA-based Therapies

MicroRNAs (miRNAs) are small non-coding RNA molecules that play a critical role in gene expression regulation. Certain miRNAs have been identified as important regulators of the wound healing process and have potential therapeutic applications for treating chronic non-healing wounds.[40] Here are some wound-healing-associated miRNAs that have been studied for the treatment of chronic non-healing wounds:

1. miR-21: miR-21 is one of the most widely studied miRNAs associated with wound healing. It promotes fibroblast migration, angiogenesis, and extracellular matrix remodeling. Increased expression of miR-21 has been found to enhance wound healing in both animal models and in vitro studies.[41]
2. miR-210: miR-210 is induced by hypoxia and regulates angiogenesis, cell survival, and extracellular matrix deposition. It promotes the formation of new blood vessels and can improve wound healing in ischemic or hypoxic conditions.[42]
3. miR-146a: miR-146a plays a role in regulating inflammation and immune responses during wound healing. It modulates the expression of pro-inflammatory cytokines and chemokines, and its dysregulation has been associated with chronic inflammation. Modulating miR-146a expression may help reduce chronic inflammation and promote proper wound healing.[43]
4. miR-155: miR-155 is involved in regulating immune responses and inflammatory processes. It affects the expression of cytokines, growth factors, and extracellular matrix components. Dysregulation of miR-155 has been observed in chronic wounds, and its modulation may aid in restoring proper wound healing.[44]
5. Let-7 family: The Let-7 miRNA family members are involved in tissue repair and regeneration. They regulate cell proliferation, differentiation, and migration. Alterations in Let-7 expression have been associated with impaired wound healing. Modulating Let-7 family members may help promote wound healing processes.[45]
6. miR-192: miR-192 is involved in regulating fibrosis and extracellular matrix remodeling. It modulates the expression of key factors involved in fibrotic responses, such as TGF-β and collagen genes. Modulating miR-192 may help prevent excessive fibrosis and promote proper tissue remodeling in chronic wounds.[46]

These miRNAs represent just a few examples of the many miRNAs implicated in wound healing. Therapeutic strategies targeting these miRNAs may involve the use of miRNA mimics, inhibitors, or delivery systems to modulate their expression in chronic non-healing wounds. However, it's important to note that further research is needed to fully understand the mechanisms and potential therapeutic applications of miRNAs in chronic wound healing, as well as to evaluate their safety and efficacy in clinical settings.

9. Conclusion

It's important to note that gene therapy for chronic non-healing wounds is still largely in the experimental stage, and further research and clinical trials are needed to establish its safety and effectiveness. The complexity of chronic wounds and the challenges associated with targeted gene delivery remain areas of active investigation. Nonetheless,

gene therapy holds potential as a future therapeutic option for addressing the underlying molecular and genetic factors contributing to chronic non-healing wounds.

10. Conflicts of Interest

None.

11. Source of Funding

None.

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