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Review Paper - Derleme Makalesi

THE MOLECULAR MECHANISM, TYPES AND TREATMENT OF SCAR FORMATION

SKAR OLUŞUMUNUN MOLEKÜLER MEKANİZMASİ, TÜRLERİ VE TEDAVİSİ

Enver TEKİN[1]

Özet

Yara iyileşmesi ve skar oluşumu, hasara yanıt olarak hücre dışı matris bileşenlerinin birikmesi ve fibroblastların çoğalmasıyla karakterize karmaşık bir biyolojik süreçtir. Yara iyileşmesinin ve sonrasında oluşan skar oluşumunun altında yatan mekanizmaları, hipertrofik skar ve keloid gibi skar tiplerine bağlı olarak önemli ölçüde değişebilmekte ve çeşitli hücresel ve moleküler faktörlerden etkilenmektedir. Fibroblastların farklılaşmış bir formu olan miyofibroblastlar, kasılma özellikleri ve büyük miktarda kolajen ve diğer hücre dışı matris bileşenleri üretme kabiliyetleri nedeniyle yara iyileşmesinde ve skar oluşumunda önemli bir rol oynarlar. Skar oluşum süreci fibroblastlar, makrofajlar ve endotel hücreleri gibi çeşitli hücre tipleri ile hücre dışı matris bileşenleri arasındaki karmaşık etkileşimleri içerir. Bu mekanizmaların anlaşılması, hipertrofik skar ve keloid gibi patolojik skarları en aza indirmeye yönelik tedavi stratejileri geliştirmek için çok önemlidir. Skar oluşumunun ilk evresinde, iyileşme sürecinin ilk aşaması olan inflamasyon mekanizması başlar. Özellikle makrofajlar olmak üzere inflamatuar hücreler, yara iyileşmesinin düzenlenmesinde önemli bir rol oynarlar. Fibroblastlar, kollajen de dahil olmak üzere ekstraselüler matriks bileşenlerinin sentezlenmesinden sorumlu olan, skar oluşumunda birincil etkili hücrelerdir. Skarlar, özelliklerine, altta yatan mekanizmalarına ve klinik görünümlerine göre çeşitli türlere ayrılabilir. En sık tartışılan iki tür hipertrofik skar ve keloiddir, ancak atrofik skar, kontraktür skar ve akne skarı da görülebilir ve her biri tedavi için farklı özelliklere sahiptir. Bu çalışmanın amacı skar oluşumunun moleküler mekanizmasını, tiplerini ve tedavisini açıklamaktır.

Anahtar Kelimeler: Yara İyileşmesi, Skar, Fibroblast, İnflamasyon, Keloid, Hipertrofik Skar

Abstract

Wound healing and scar formation is a complex biological process that occurs as a response to injury, characterized by the deposition of extracellular matrix components and the proliferation of fibroblasts. The mechanisms underlying wound healing and following scar formation can vary significantly depending on the type of scar, such as hypertrophic scars and keloids, and are influenced by various cellular and molecular factors. Myofibroblasts, a differentiated form of fibroblasts, play a pivotal role in wound healing and scar formation due to their contractile properties and ability to produce large amounts of collagen and other extracellular matrix components. Scar formation process involves complex interactions among various cell types, including fibroblasts, macrophages, and endothelial cells, as well as the extracellular matrix components. Understanding these mechanisms is crucial for developing therapeutic strategies to minimize pathological scarring, such as hypertrophic scars and keloids. The initial phase of scar formation is dominated by inflammation, which is essential for initiating the healing process. Inflammatory cells, particularly macrophages, play a pivotal role in orchestrating the wound healing response. Fibroblasts are the primary effector cells in scar formation, responsible for synthesizing extracellular matrix components, including collagen. Scars can be classified into several types based on their characteristics, underlying mechanisms, and clinical presentations. The two most commonly discussed types of scars are hypertrophic scars and keloids, but there are also atrophic scars, contracture scars, and acne scars, each with distinct features and implications for treatment. The aim of this study is to explain the molecular mechanism, types and treatment of scar formation.

Keywords: Wound Healing, Scar, Fibroblast, Inflammation, Keloid, Hypertrophic Scar

Geliş Tarihi (Received Date): 23.11.2024, Kabul Tarihi (Accepted Date): 12.12.2024, Basım Tarihi (Published Date): 31.12.2024. [1] Health Sciences University, Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital, İzmir, Türkiye. **E-mail:** envertekinmd@gmail.com **ORCID ID's:** E.T; https:/orcid.org/0009-0009-9056-0311

1. INTRODUCTION

Wound healing is a multifaceted biological process that involves a series of complex interactions among various cell types, growth factors, cytokines, and the extracellular matrix (ECM). The process can be broadly categorized into four overlapping phases:

-hemostasis,
-inflammation,
-proliferation,
-remodeling.

Each phase is crucial for the successful repair of damaged tissue, and disruptions at any stage can lead to chronic wounds or impaired healing, particularly in populations with underlying conditions such as diabetes mellitus (Walther et al., 2022, pp.241-254; Moura et al., 2019, pp.1-11; Wei et al., 2022, pp. 1-27).

The initial phase of wound healing, **hemostasis**, involves the constriction of blood vessels and the aggregation of platelets to form a clot, which serves as a temporary matrix for incoming cells. This is followed by the **inflammatory phase**, characterized by the recruitment of immune cells to the wound site, which helps to clear debris and pathogens. Key growth factors such as Platelet-Derived Growth Factor (PDGF) and Transforming Growth Factor-beta (TGF-β) play significant roles in this phase by promoting chemotaxis and proliferation of fibroblasts and endothelial cells (Zhang et al., 2014, pp. 1-8; Noh et al., 2018, pp. 240-247). The presence of these growth factors is essential for the transition from inflammation to the **proliferative phase**, where new tissue formation occurs through angiogenesis, collagen deposition, and re-epithelialization (Sun et al., 2017, pp. 1-11; Wei et al., 2022, pp. 1-27). During the proliferative phase, fibroblasts are activated and migrate to the wound site, where they synthesize collagen and other ECM components. This phase is also marked by the formation of granulation tissue, which is rich in new blood vessels and provides a scaffold for further tissue regeneration. Growth factors such as Fibroblast Growth Factor (FGF) and Vascular Endothelial Growth Factor (VEGF) are crucial for stimulating fibroblast activity and promoting angiogenesis (Wei et al., 2022, pp. 1-27; Zhang et al., 2014, pp. 1-8). Studies have shown that the application of exogenous growth factors can enhance fibroblast proliferation and migration, thereby accelerating wound healing (Walther et al., 2022, pp. 241-254; Wei et al., 2022, pp. 1-27; Noh et al., 2018, pp. 240-247). The **remodeling phase** is the final stage of wound healing, where the newly formed tissue undergoes maturation and reorganization. This phase can last for months to years, during which collagen fibers are remodeled, and the tensile strength of the wound increases. The balance between matrix metalloproteinases (MMPs) and their inhibitors is critical during this phase, as it regulates ECM degradation and remodeling (Masi et al., 2016, pp. 512-521; Qi et al., 2014, pp. 1407-1419). Disruptions in this balance can lead to hypertrophic scars or keloids, which are common complications in wound healing (Walther et al., 2022, pp.241-254; Moura et al., 2019, pp.1-11; Wei et al., 2022, pp. 1-27).

In diabetic patients, wound healing is often impaired due to a combination of factors, including reduced blood flow, neuropathy, and altered immune responses. The presence of high levels of reactive oxygen species (ROS) can also contribute to the dysfunction of growth factor signaling pathways, further complicating the healing process (Bitar and Al-Mulla, 2012, pp. 375-388). Research has indicated that diabetic wounds exhibit lower levels of key growth factors such as VEGF and FGF, which are essential for angiogenesis and fibroblast function

(Moura et al., 2019, pp. 1-11; Zhang et al., 2014, pp. 1-8; Qi et al., 2014, pp. 1407-1419). Consequently, therapeutic strategies aimed at enhancing the local concentration of these growth factors have been explored as potential interventions to improve healing outcomes in diabetic patients (Yuniati et al., 2021, pp. 1-21; Wei et al., 2022, pp. 1-27).

Recent advancements in wound care technologies have focused on the development of bioactive dressings that incorporate growth factors, antimicrobial agents, and other therapeutic compounds to enhance healing. For instance, **electrospun wound dressings** loaded with insulin and growth factors have shown promise in promoting protein expression associated with wound healing (Walther et al., 2022, pp.241-254). Similarly, **hydrogels** containing gold nanoparticles have demonstrated enhanced microbicidal properties and improved healing potential in vivo (Batool et al., 2022, pp. 1-10).

These innovative approaches aim to create a conducive environment for healing by addressing both the biological and mechanical aspects of wound repair. Moreover, the use of platelet-rich plasma (PRP) has gained attention as a regenerative therapy for chronic wounds. PRP is rich in growth factors such as PDGF, TGF-β, and VEGF, which can significantly enhance fibroblast proliferation and migration, thereby accelerating the healing process (Palumbo et al., 2021; Noh et al., 2018, pp. 240-247). Clinical studies have reported positive outcomes with PRP application in various types of wounds, including diabetic ulcers and surgical incisions (Suryanarayan et al., 2014, pp. 65-69; İnan, 2013, pp. 1-8). The combination of PRP with other modalities, such as low-level laser therapy or topical growth factor application, has also been investigated to further enhance healing efficacy (Ebrahiminaseri et al., 2021, pp. 1-23).

In addition to growth factors, the role of the ECM in wound healing cannot be overstated. The ECM provides structural support and biochemical signals that are crucial for cell migration, proliferation, and differentiation. Advances in tissue engineering have led to the development of scaffolds that mimic the natural ECM, facilitating better integration and function of the cells involved in wound healing (Dwivedi et al., 2019, pp. 1-19; Zhang et al., 2018). For example, biodegradable scaffolds that release growth factors in a controlled manner have shown promise in enhancing tissue regeneration and accelerating wound closure (Dwivedi et al., 2019, pp. 1-19; Zhang et al., 2018, pp. 1-12). Furthermore, the application of stem cell therapy in wound healing is an emerging area of research. Stem cells possess the ability to differentiate into various cell types and secrete a range of growth factors and cytokines that can modulate the healing process (Natallya et al., 2019, pp. 1-4; Prakoeswa et al., 2020, pp. 1159-1160). Studies have demonstrated that the use of stem cell-derived secretomes can promote angiogenesis and enhance the proliferation of fibroblasts and keratinocytes, thereby improving wound healing outcomes (Natallya et al., 2019, pp. 1-4; Prakoeswa et al., 2020, pp. 1159-1160). The integration of stem cell therapy with traditional wound care approaches may offer a novel strategy for managing chronic wounds.

2. MOLECULAR MECHANISM OF WOUND HEALING

Wound healing is a complex biological process that involves a series of tightly regulated molecular mechanisms. Each phase of wound healing is characterized by specific cellular activities and signaling pathways that are crucial for effective tissue repair.

Understanding the molecular mechanisms underlying wound healing is essential for developing therapeutic strategies to enhance healing, particularly in chronic wounds associated with conditions such as diabetes and aging.

The initial phase of wound healing, hemostasis, is critical for preventing blood loss and initiating the healing process. Upon injury, platelets aggregate at the site, releasing growth factors such as PDGF and TGF-β, which play pivotal roles in recruiting inflammatory cells and fibroblasts to the wound site (Donovan et al., 2013, pp. 1-9; Yang et al., 2020, pp. 1995-2002). The activation of these growth factors triggers various signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway, which is essential for cell proliferation and migration during subsequent phases of healing (Guan et al., 2021, pp. 1-14). Additionally, the ECM components, such as fibronectin, provide a scaffold for cell attachment and migration, facilitating the transition from hemostasis to inflammation (Hsiao et al., 2017, pp. 70653-70668).

The inflammatory phase is characterized by the recruitment of immune cells, including neutrophils and macrophages, to the wound site. These cells release pro-inflammatory cytokines and growth factors that further promote the healing process. For instance, interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) are critical for activating signaling pathways that enhance keratinocyte migration and proliferation (Vukelic et al., 2011, pp. 10265-10275; Choi et al., 2014, pp. 210-216). The resolution of inflammation is equally important, as excessive inflammation can lead to chronic wounds. The balance between pro-inflammatory and anti-inflammatory signals is mediated by various pathways, including the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, which has been shown to be essential for wound healing (Qin et al., 2017, pp. 465-473).

During the proliferative phase, fibroblasts play a central role in synthesizing collagen and other ECM components, which are necessary for tissue repair. The activation of fibroblasts is influenced by various growth factors, including FGF and VEGF, which promote angiogenesis and the formation of granulation tissue (Li et al., 2015, pp. 65-73). The signaling pathways involved in this phase include the phosphoinositide 3-kinase (PI3K)/Akt pathway, which is crucial for cell survival and proliferation (Wang et al., 2021, pp. 1-13). Additionally, the Notch signaling pathway has been implicated in regulating the behavior of epidermal stem cells, enhancing their ability to contribute to re-epithelialization during wound healing (Yang et al., 2016, pp. 1-7).

The remodeling phase is characterized by the maturation and reorganization of the newly formed tissue. This phase can last for months to years and involves the remodeling of collagen fibers and the restoration of tissue architecture. The balance between MMPs and their inhibitors is critical during this phase, as MMPs degrade the ECM to allow for tissue remodeling (Wang et al., 2018, pp. 1627-1638). Furthermore, the hypoxia-inducible factor (HIF) signaling pathway plays a significant role in regulating cellular responses to low oxygen levels, which are common in wounds. HIF activation promotes angiogenesis, and the expression of genes involved in ECM remodeling, thereby facilitating wound healing (Ruthenborg et al., 2014, pp. 637-643).

In diabetic wounds, the healing process is often impaired due to a combination of factors, including reduced blood flow, neuropathy, and altered immune responses. The presence of high levels of ROS can disrupt normal signaling pathways, leading to impaired fibroblast function and reduced angiogenesis (Süntar et al., 2021, pp. 2424; Li et al., 2021, pp. 509-520). Studies have shown that diabetic wounds exhibit altered expression of key growth factors, such

as VEGF and PDGF, which are essential for promoting angiogenesis and fibroblast activity (Moura et al., 2019, pp. 1-11; Zhang et al., 2014, pp. 1-8; Li et al., 2021 pp. 509-520). The activation of the Nrf2 signaling pathway has been suggested as a potential therapeutic target to enhance wound healing in diabetic patients by modulating oxidative stress and inflammation (Süntar et al., 2021, pp. 2424).

Recent advancements in wound healing therapies have focused on harnessing the molecular mechanisms involved in the healing process. For instance, the application of bioactive dressings that release growth factors in a controlled manner has shown promise in enhancing healing outcomes (Dwivedi et al., 2019, pp. 1-19; Zhang et al., 2018, pp. 1-12). Additionally, stem cell therapies have emerged as a potential strategy for promoting wound healing by providing a source of growth factors and facilitating tissue regeneration (Natallya et al., 2019, pp. 1-4; Prakoeswa et al., 2020, pp. 1159-1160). The use of PRP has also gained attention for its ability to accelerate healing through the release of various growth factors that stimulate fibroblast proliferation and migration (Palumbo et al., 2021, pp. 1-7; Suryanarayan et al., 2014, pp. 65-69). Moreover, understanding the role of microRNAs in wound healing has opened new avenues for therapeutic interventions. MicroRNAs such as miR-129 and miR-335 have been shown to promote diabetic wound healing by inhibiting the expression of MMP-9, which is associated with impaired healing (Wang et al., 2018, pp. 1627-1638). The regulation of these microRNAs may provide a novel approach to enhance the healing process in chronic wounds.

3. SCAR FORMATION

Scar formation is a complex biological process that occurs as a response to injury, characterized by the deposition of extracellular matrix (ECM) components and the proliferation of fibroblasts. The mechanisms underlying scar formation can vary significantly depending on the type of scar, such as hypertrophic scars and keloids, and are influenced by various cellular and molecular factors. This response is not merely a reparative process but can lead to pathological outcomes that affect both the physical and psychological well-being of individuals.

The initial phase of scar formation involves the activation of fibroblasts, which are crucial for synthesizing ECM proteins, including collagen. **Myofibroblasts, a differentiated form of fibroblasts,** play a pivotal role in wound healing and scar formation due to their contractile properties and ability to produce large amounts of collagen and other ECM components. Research has shown that the persistence of myofibroblasts in the wound site, due to inadequate apoptosis, is a significant contributor to excessive scarring (Darby and Desmoulière, 2020, pp. 19-26; , He et al., 2015, pp. 666-676). The TGF-β signaling pathway is particularly important in this context, as it promotes fibroblast activation and myofibroblast differentiation, leading to increased collagen deposition (Ren et al., 2014, pp. 1607-1612; , Ma et al., 2014, pp. 76-83).

Mechanical forces also significantly influence scar formation. Studies have demonstrated that mechanical stretch can activate specific ion channels, such as Piezo1, which mediates calcium signaling pathways that promote hypertrophic scar formation (He et al., 2021, pp. 1-13; Ogawa et al., 2012, pp. 149-157). The application of mechanical tension has been shown to prolong the inflammatory phase of wound healing, which correlates with increased scar formation (Wong et al., 2011, pp. 4498-4510). Furthermore, the interaction between fibroblasts and endothelial cells under mechanical strain has been suggested to drive the fibrotic

response, highlighting the importance of the biomechanical environment in scar development (Tan et al., 2023, pp. 1-15).

Hypertrophic scars are characterized by excessive collagen deposition and a thickened dermis, often resulting from an exaggerated wound healing response. The pathogenesis of hypertrophic scars involves a dysregulated inflammatory response, where pro-inflammatory cytokines and growth factors, such as TGF-β1, play crucial roles in modulating fibroblast activity and ECM synthesis (Wang et al., 2020, pp. 1-10; Pradhan, 2023, pp. 549-563). In contrast, **keloids** represent an even more severe form of scarring, where the scar tissue extends beyond the original wound margins. Genetic predisposition, along with environmental factors, contributes to the development of keloids, making them a significant clinical challenge (Ong et al., 2010, pp. 1302-1315; Williams et al., 2014, pp. 811-812).

The role of inflammation in scar formation cannot be overstated. Inflammatory cells, including macrophages and T-lymphocytes, are recruited to the wound site and secrete various cytokines that modulate fibroblast behavior and ECM remodeling (Feng et al., 2019, pp. 1-7). The intensity and duration of the inflammatory response have been correlated with the final scar size, suggesting that controlling inflammation could be a therapeutic target for minimizing scar formation (Wang et al., 2020, pp. 1-10; Zhao et al., 2023, pp. 3643-3662). Moreover, the interplay between different cell types, including endothelial cells and fibroblasts, is essential for orchestrating the healing process and determining the quality of the resulting scar (Tan et al., 2023, pp. 1-15; , Wong et al., 2011, pp. 4498-4510).

Recent advances in understanding the molecular mechanisms of scar formation have highlighted the potential for therapeutic interventions. For instance, targeting specific signaling pathways, such as the TGF-β pathway or mechanotransduction pathways, may offer strategies to mitigate excessive scarring (He et al., 2015, pp. 666-676; Pradhan, 2023, pp. 549-563). Additionally, the use of biomaterials and devices designed to modulate mechanical forces at the wound site has shown promise in reducing scar formation (Wong et al., 2013, pp. 185-194; Gurtner et al., 2011, pp. 217-225).

4. MOLECULAR MECHANISM OF SCAR FORMATION

Scar formation is a multifaceted biological process that occurs following skin injury, characterized by a series of cellular and molecular events aimed at restoring tissue integrity.

The mechanisms underlying scar formation involve complex interactions among various cell types, including fibroblasts, macrophages, and endothelial cells, as well as the ECM components. Understanding these mechanisms is crucial for developing therapeutic strategies to minimize pathological scarring, such as hypertrophic scars and keloids.

The initial phase of scar formation is dominated by inflammation, which is essential for initiating the healing process. Inflammatory cells, particularly macrophages, play a pivotal role in orchestrating the wound healing response. Macrophages can adopt different phenotypes, with M1 macrophages promoting inflammation and M2 macrophages facilitating tissue repair and remodeling (Feng et al., 2019, pp. 1-7). The balance between these macrophage populations is critical; prolonged activation of M2 macrophages can lead to excessive collagen deposition and scarring (Feng et al., 2019, pp. 1-7; Hesketh et al., 2017, pp. 1-10). Furthermore, the secretion of pro-inflammatory cytokines, such as interleukin-10 (IL-10), has been shown to modulate the

inflammatory response and influence scar formation. Increased IL-10 levels can attenuate the inflammatory response, leading to improved wound healing and reduced scarring (Morris et al., 2014, pp. 406-4146; Kieran et al., 2013, pp. 428-436).

Fibroblasts are the primary effector cells in scar formation, responsible for synthesizing ECM components, including collagen. The transition of fibroblasts to myofibroblasts is a key event in this process, driven by TGF-β signaling. TGF-β promotes the differentiation of fibroblasts into myofibroblasts, which exhibit enhanced contractile properties and increased collagen production (Volk et al., 2011, pp. 25-37; Xu et al., 2020, pp. 1-6). The dysregulation of TGF-β signaling is often implicated in pathological scarring, as excessive TGF-β activity can lead to hypertrophic scars and keloids (Takaya et al., 2022, pp. 4245; Xu et al., 2020, pp. 1-6). Moreover, the balance between collagen types I and III is crucial; while type III collagen is associated with early wound healing, excessive type I collagen deposition can result in disorganized scar tissue (Shi et al., 2013, pp. 1-10).

The ECM plays a significant role in scar formation, providing structural support and regulating cellular behavior. Decorin, a small leucine-rich proteoglycan, has been shown to inhibit fibroblast migration and promote scar formation by modulating TGF-β signaling (Takaya et al., 2022, pp. 4245). Additionally, the composition and organization of the ECM can influence the mechanical properties of the scar tissue, affecting its tensile strength and elasticity. Mechanical forces, such as tension and compression, can alter fibroblast behavior and contribute to the development of hypertrophic scars (Gurtner et al., 2011, pp. 217-225; Yannas et al., 2017, pp. 177-191). The mechanotransduction pathways that mediate these responses are critical for understanding how mechanical stimuli can lead to pathological scarring.

The remodeling phase of wound healing is characterized by the degradation of excess ECM components and the reorganization of collagen fibers. MMPs are key enzymes involved in ECM remodeling, and their activity is tightly regulated by tissue inhibitors of metalloproteinases (TIMPs) (Li et al., 2019, pp. 99-106). An imbalance between MMPs and TIMPs can lead to excessive collagen accumulation and scarring. For instance, TGF-β1 has been shown to induce MMP-1 expression, which is involved in collagen degradation, but excessive TGF-β signaling can also lead to increased collagen synthesis, resulting in hypertrophic scars (Li et al., 2019, pp. 99-106). Recent studies have highlighted the potential of targeting specific molecular pathways to mitigate scar formation. For example, the use of basic fibroblast growth factor (bFGF) has been shown to promote wound healing while reducing scar formation by inhibiting the differentiation of fibroblasts into myofibroblasts (Wang et al., 2017, pp. 1-13; , Shi et al., 2013, pp. 1-10). Additionally, the application of small molecular inhibitors targeting TGF-β signaling has shown promise in preventing hypertrophic scars by modulating fibroblast activity and ECM composition (Wang et al., 2017, pp. 1-13). Furthermore, the use of stem cell therapies and exosomes derived from stem cells has emerged as a novel approach to enhance wound healing and reduce scarring by promoting tissue regeneration and modulating inflammatory responses (Duan et al., 2020, pp. 1-11; Rong et al., 2020, pp. 1-8).

5. SCAR TYPES

Scar formation is a complex biological process that results from the body's healing response to injury. Scars can be classified into several types based on their characteristics, underlying mechanisms, and clinical presentations. The two most commonly discussed types

of scars are **hypertrophic scars and keloids**, but there are also **atrophic scars, contracture scars**, and **acne scars**, each with distinct features and implications for treatment.

Hypertrophic Scars are characterized by raised, thickened areas of skin that **remain within the boundaries of the original wound**. They often develop following surgical procedures, trauma, or burns, and are a result of an overproduction of collagen during the healing process. The **collagen fibers in hypertrophic scars are typically disorganized and densely packed**, leading to a firm texture (Tripathi et al., 2020, pp. 1-11; Gisquet et al., 2011, pp. 160-166).

The prevalence of hypertrophic scars can be notably high in certain populations, particularly among individuals with darker skin types, where the incidence can reach up to 70% following burns (Finnerty et al., 2016, pp. 1427-1436). Hypertrophic scars may improve over time, often flattening and becoming less noticeable, but they can also be associated with symptoms such as itching and discomfort (Limandjaja et al., 2020, pp. 146-161).

Keloids are a more severe form of scarring that extends beyond the original wound margins. They are characterized by an excessive accumulation of collagen and other extracellular matrix components, leading to a raised and often itchy or painful lesion. Keloids can occur after any type of skin injury, including surgical incisions, acne, or even minor injuries.

Histologically, keloids exhibit a dense collagen structure that is disorganized, with a **higher density of fibroblasts and blood vessels compared to hypertrophic scars** (Medyukhina et al., 2011, pp. 627-636; Huang et al., 2013, pp. 1-4). The pathogenesis of keloids is not fully understood, but genetic predisposition plays a significant role, and they are more common in individuals with darker skin (Limandjaja et al., 2020, pp. 146-161; Huang et al., 2013, pp. 1-4). Unlike hypertrophic scars, keloids do not typically regress over time and may require more aggressive treatment options, including corticosteroid injections, laser therapy, or surgical excision (Tripathi et al., 2020, pp. 1-11; Limandjaja et al., 2020, pp. 146-161).

Atrophic scars are another type of scar that results from a loss of tissue, leading to a depressed appearance in the skin. These scars are commonly associated with conditions such as acne, chickenpox, or other forms of skin trauma. Atrophic scars can be further classified into subtypes, including ice pick scars, boxcar scars, and rolling scars, each with distinct shapes and characteristics (Gaur, 2018, pp. 48-50; Fabbrocini et al., 2010, pp. 1-13).

The treatment for atrophic scars often involves methods aimed at stimulating collagen production and skin regeneration, such as microneedling, chemical peels, or dermal fillers (Gaur, 2018, pp. 48-50; Fabbrocini et al., 2010, pp. 1-13).

Contracture scars typically occur after burns or significant skin loss and are characterized by the tightening of the skin, which can restrict movement and function. These scars can affect the underlying muscles and tendons, leading to complications such as joint contractures. The severity of contracture scars often depends on the depth and extent of the initial injury, and they may require surgical intervention to release the tightness and restore function (Finnerty et al., 2016, pp. 1427-1436; Schouten et al., 2023, pp. 810-816).

Acne scars represent a specific subset of atrophic scars that arise from inflammatory acne lesions. They can be classified into hypertrophic and atrophic types, depending on the body's response to inflammation. The management of acne scars is particularly challenging due to their varied presentations and the need for tailored treatment approaches, which may include

laser therapy, chemical peels, or subcision (Kravvas and Al-Niaimi, 2017, pp. 1-17; Fabbrocini et al., 2010, pp. 1-13).

The classification of acne scars is crucial for guiding treatment decisions, as different types respond better to specific interventions (Gaur, 2018, pp. 48-50; Fabbrocini et al., 2010, pp. 1-13).

6. TYPES OF PATHOLOGICAL SCARS

6.1. Hypertrophic Scar Formation

Hypertrophic scar formation is a complex biological process characterized by excessive collagen deposition and fibroblast proliferation following skin injury. This condition is a common outcome of various types of wounds, including surgical incisions, burns, and traumatic injuries. Understanding the molecular mechanisms underlying hypertrophic scar formation is crucial for developing effective therapeutic strategies to prevent or minimize scarring.

The initial phase of hypertrophic scar formation involves an inflammatory response that is critical for wound healing. Inflammatory cytokines, particularly TGF-β, play a pivotal role in this process. TGF-β is secreted by various cell types, including platelets and macrophages, and acts on fibroblasts to promote their proliferation and differentiation into myofibroblasts, which are responsible for collagen synthesis (Deng et al., 2018, pp. 1-12; Xiao et al., 2015, pp. 485-495). The overexpression of TGF-β1 has been closely associated with hypertrophic scar formation, leading to an imbalance in collagen production and degradation (Xiao et al., 2015, pp. 485-495; Li et al., 2016, pp. 326-334). This dysregulation results in excessive deposition of ECM components, particularly collagen types I and III, which are hallmarks of hypertrophic scars (Li et al., 2014, pp.903-911; Li et al., 2016, pp. 326-334).

Fibroblasts are the primary effector cells in hypertrophic scar formation. In response to TGF-β signaling, fibroblasts undergo a phenotypic transformation into myofibroblasts, characterized by increased contractility and collagen production (Xiao et al., 2019, pp. 5989-6000; Deng et al., 2021, pp. 1221-1231). The persistence of myofibroblasts in the wound site is a critical factor contributing to the development of hypertrophic scars. Under normal circumstances, myofibroblasts undergo apoptosis after the wound healing process is complete; however, in hypertrophic scars, their survival is prolonged, leading to continued collagen deposition (Aydoğmuş et al., 2017, pp. 12-17).

The abnormal proliferation and survival of fibroblasts are influenced by various signaling pathways, including the PI3K/AKT and MAPK pathways, which are activated by growth factors such as PDGF and FGF (Ma et al., 2022, pp. 274-284; Wang et al., 2019, pp. 3668-3678). In addition to fibroblast activity, the role of the ECM in hypertrophic scar formation cannot be overlooked. The ECM provides structural support to tissues and regulates cellular behavior. In hypertrophic scars, the ECM is characterized by an abnormal composition and organization, with increased levels of fibronectin and collagen fibers that are densely packed and disorganized (Shibuya et al., 2022, pp. 1-21; Sidgwick and Bayat, 2011, pp. 141-152). This altered ECM environment not only supports fibroblast proliferation but also contributes to the mechanical properties of the scar, affecting its tensile strength and elasticity (Sidgwick and Bayat, 2011, pp. 141-152). The balance between MMPs and their inhibitors (TIMPs) is crucial for ECM remodeling; an imbalance can lead to excessive collagen

accumulation, further exacerbating hypertrophic scar formation (Bikash and Sarkar, 2023, pp. 1191-1196).

The vascular component of hypertrophic scars is also significant. Angiogenesis is often enhanced in hypertrophic scars, contributing to their characteristic redness and swelling (Kwak et al., 2016, pp. 491-497). VEGF is a key mediator of angiogenesis, and its expression is elevated in hypertrophic scars (Kwak et al., 2016, pp. 491-497). The increased vascularity not only supports the metabolic demands of the proliferating fibroblasts but also plays a role in the inflammatory response, perpetuating the cycle of scar formation (Feng et al., 2019, pp. 1-7).

6.2. Keloid Formation

Keloid formation is a complex and multifactorial process characterized by the excessive proliferation of fibroblasts and the abnormal deposition of ECM components, particularly collagen. Keloids typically arise at the site of skin injury, such as surgical incisions, trauma, or burns, and are distinguished from hypertrophic scars by their tendency to extend beyond the original wound margins. Understanding the molecular mechanisms underlying keloid formation is crucial for developing effective therapeutic strategies to manage this condition.

The pathogenesis of keloids involves a dysregulated wound healing response, where the balance between collagen synthesis and degradation is disrupted. One of the key players in this process is TGF-β, which is known to be elevated in keloid tissues. TGF-β promotes fibroblast proliferation and differentiation into myofibroblasts, leading to increased collagen production (Kim et al., 2021, pp. 10765; Zhai et al., 2017, pp. 3467-3472). The TGF-β/SMAD signaling pathway is particularly important in keloid formation, as it regulates the expression of various ECM proteins and modulates fibroblast activity (Kim et al., 2021, pp. 10765; Zhai et al., 2017, pp. 3467-3472).

In keloids, the overexpression of TGF-β1 has been linked to the excessive accumulation of collagen types I and III, contributing to the thick and fibrous nature of keloid scars (He et al., 2017, pp. 1-8; Hunasgi et al., 2013, pp. 116). In addition to TGF-β, other growth factors and cytokines play significant roles in keloid pathogenesis. For instance, insulin-like growth factor-1 (IGF-1) has been shown to enhance fibroblast proliferation and collagen synthesis in keloid fibroblasts (Hu et al., 2014, pp. 822-828). Furthermore, the involvement of inflammatory mediators, such as interleukin-6 (IL-6) and VEGF, has been documented in keloid formation, as they promote angiogenesis and inflammation, further exacerbating the fibrotic response (Seoudy et al., 2022, pp. 38-45; Wu et al., 2020, pp. 1-11).

The ECM composition in keloids is markedly different from that of normal skin and hypertrophic scars. Keloids exhibit a higher density of collagen fibers, particularly type I collagen, which is organized in a disorganized manner compared to the more structured arrangement seen in normal scars (He et al., 2017, pp. 1-8; Jin et al., 2019, pp. 1001-1010). The presence of myofibroblasts, which express alpha-smooth muscle actin (α-SMA), is also a distinguishing feature of keloids, as these cells contribute to the contractile properties of the scar tissue (Hunasgi et al., 2013, pp. 116). The abnormal ECM environment not only supports fibroblast proliferation but also influences the mechanical properties of the keloid, affecting its tensile strength and elasticity (Butzelaar et al., 2017, pp. 758-766; Hahn et al., 2013, pp. 530-544).

Recent research has highlighted the role of non-coding RNAs, particularly miRNAs and long non-coding RNAs (lncRNAs), in the regulation of keloid formation. For example, lncRNA HOXA11-AS has been implicated in promoting type I collagen synthesis and stimulating keloid

formation by sponging miR-124-3p, thereby activating the Smad5 signaling pathway (Jin et al., 2019, pp. 1001-1010). Similarly, miR-200b has been shown to inhibit fibroblast proliferation and promote apoptosis in keloid fibroblasts, suggesting that targeting these non-coding RNAs may offer new therapeutic avenues for keloid management (Yang et al., 2020, pp. 1995-2002; Li, 2023, pp. 1610-1619).

The immune response also plays a critical role in keloid formation. Studies have shown that keloids are associated with an increased presence of inflammatory cells, including macrophages and mast cells, which release cytokines that promote fibroblast activity and collagen deposition (Seoudy et al., 2022, pp. 38-45; Wu et al., 2020, pp. 1-11). The balance between M1 and M2 macrophages is particularly important, as M2 macrophages are known to facilitate tissue repair and fibrosis, while M1 macrophages are associated with inflammation (Seoudy et al., 2022, pp. 38-45). This dysregulation of the immune response can contribute to the chronic inflammation observed in keloid lesions. Mechanical factors, such as tension and stretching of the skin, have also been implicated in keloid formation. Research suggests that mechanical stress can activate signaling pathways that promote fibroblast proliferation and ECM synthesis, leading to the development of keloids (Ogawa et al., 2012, pp. 149-157). This highlights the importance of considering the mechanical environment in the management of keloids, as reducing tension on the scar tissue may help mitigate its progression.

7. POSTOPERATIVE WOUND HEALING AND SCAR FORMATION

Postoperative wound healing and scar formation are critical aspects of surgical recovery that significantly impact patient outcomes and satisfaction. The healing process involves a series of biological events that can lead to various types of scars, including hypertrophic scars and keloids. Understanding the mechanisms of wound healing and the factors influencing scar formation is essential for optimizing surgical techniques and postoperative care.

Several factors can influence the quality of wound healing and scar formation. Surgical techniques, such as the type of incision and closure method, can significantly impact scar outcomes. For instance, the use of intradermal sutures has been shown to reduce the incidence of hypertrophic scars compared to traditional suturing techniques (Wihastyoko and Wuryanjono, 2022, pp. 24-29). Additionally, the tension on the wound edges during healing can affect scar formation; higher tension is associated with an increased risk of hypertrophic scars (Niederstätter et al., 2021, pp. 45).

The timing and type of postoperative interventions also play a crucial role in scar management. Early postoperative treatments, such as the application of silicone gel sheets or the use of fractional laser therapy, have been shown to improve scar outcomes by promoting collagen remodeling and reducing scar thickness (Lee et al., 2013, pp. 1190-1196; Al-Marzouqi et al., 2022, pp. 231-238). For example, fractional carbon dioxide lasers have been effective in treating surgical scars by enhancing collagen remodeling and improving skin texture (Lee et al., 2013, pp. 1190-1196; Al-Marzouqi et al., 2022, pp. 231-238).

Patient-related factors, including age, skin type, and genetic predisposition, can also influence scar formation. Individuals with darker skin types are at a higher risk of developing hypertrophic scars and keloids due to differences in the inflammatory response and collagen metabolism (Surakunprapha et al., 2020, pp. 3883). Furthermore, psychological factors, such

as body image perception and anxiety related to scarring, can impact patient satisfaction with surgical outcomes (Shorka et al., 2021, pp. 2605-2611).

In addition to these factors, the use of adjunctive therapies, such as platelet-rich plasma (PRP) injections and autologous fat grafting, has gained attention in recent years for their potential to enhance wound healing and improve scar appearance (Li et al., 2020, pp. 1-11; Al-Marzouqi et al., 2022, pp. 231-238). PRP, rich in growth factors, can stimulate fibroblast activity and promote collagen synthesis, while fat grafting can provide volume and improve the contour of depressed scars (Li et al., 2020, pp. 1-11; Al-Marzouqi et al., 2022, pp. 231-238).

8. SCAR TREATMENT

Scar treatment is a critical aspect of postoperative care, particularly for patients who undergo surgical procedures that may lead to hypertrophic scars or keloids. The management of scars involves a variety of therapeutic options, including intralesional injections, laser treatments, and topical therapies. Each treatment modality has its own mechanisms of action, efficacy, and indications, which are essential for tailoring interventions to individual patient needs.

8.1. Intralesional Injections

Intralesional injections of corticosteroids, particularly triamcinolone acetonide, have been a cornerstone in the treatment of hypertrophic scars and keloids. These injections work by reducing collagen synthesis and promoting collagen degradation, thereby softening and flattening the scar tissue (Waibel et al., 2013, pp. 135-140; Song et al., 2018, pp. 874-878). Studies have shown that early intervention with intralesional corticosteroids can significantly improve scar outcomes, especially when administered during the early stages of scar formation (Song et al., 2018, pp. 874-878). However, while corticosteroids can effectively reduce scar height and symptoms such as itching and pain, they may not significantly narrow the width of hypertrophic scars (On et al., 2015, pp. 479-484). In addition to corticosteroids, other intralesional agents such as 5-fluorouracil and bleomycin have been explored for their efficacy in treating keloids and hypertrophic scars. These agents can inhibit fibroblast proliferation and collagen production, offering alternative options for patients who may not respond to corticosteroids (Perdanasari et al., 2015, pp. 3; Zhang et al., 2018, pp. 1-12). The combination of intralesional injections with other modalities, such as laser therapy, has also been investigated to enhance treatment outcomes (Krakowski et al., 2014, pp. 1700-1705).

8.2. Laser Therapy

Laser therapy has emerged as a promising treatment for scar management, with various types of lasers being utilized for different scar types. Ablative fractional lasers, such as carbon dioxide (CO_2) lasers, are particularly effective for treating hypertrophic scars and keloids by promoting collagen remodeling and improving skin texture (Tan et al., 2020, pp. 450-457; Kim et al., 2014, pp. 973-978). Fractional laser treatments create micro-injuries in the skin, stimulating the body's natural healing response and leading to the production of new collagen (Tan et al., 2020, pp. 450-457). Studies have demonstrated that early intervention with fractional lasers can improve the appearance of surgical scars, making them a valuable tool in postoperative scar management (Shin et al., 2021, pp. 347-352; Zhang et al., 2019, pp. 137-148).

Non-ablative lasers, such as pulsed dye lasers (PDL), are also used to treat hypertrophic scars by targeting the vascular component of the scar tissue. These lasers can reduce redness and improve the overall appearance of scars without significant downtime (Kim et al., 2014, pp. 973-978; Kauvar et al., 2019, pp. 125-136). The choice between ablative and non-ablative lasers depends on the scar's characteristics, the patient's skin type, and the desired outcomes.

Cryotherapy, particularly when combined with laser treatment, has also been highlighted as an effective approach for managing keloids. The cooling effect of cryotherapy can induce localized tissue destruction and reduce vascularity, which may contribute to scar flattening (Agarwal et al., 2015, pp. 597-604; Choi et al., 2018, pp. 32-37). the CROSS (Chemical Reconstruction of Skin Scars) technique, which employs high concentrations of trichloroacetic acid (TCA), has been effectively used for treating atrophic acne scars, demonstrating significant improvement in scar morphology (Makwana et al., 2022). This method, alongside subcision and microneedling, represents a comprehensive approach to managing various scar types, particularly in patients with complex scar presentations.

8.3. Topical Treatments

Topical treatments are another important aspect of scar management. Silicone gel sheets and silicone ointments have been widely used to prevent and treat hypertrophic scars. These products create a protective barrier over the scar, maintaining hydration and reducing collagen production (Chanprapaph et al., 2012). Studies have shown that silicone therapy can lead to significant improvements in scar appearance, particularly when used early in the healing process (Chanprapaph et al., 2012). Additionally, natural extracts, such as onion extract, have been investigated for their potential benefits in scar treatment, although the evidence supporting their efficacy is less robust compared to silicone products (Chanprapaph et al., 2012).

8.4. Combination Therapies

Combination therapies are increasingly being recognized as effective strategies for scar management. For example, combining laser treatments with intralesional corticosteroids has shown synergistic effects in reducing scar height and improving texture (Krakowski et al., 2014, pp. 1700-1705; Tan et al., 2020, pp. 450-457). Furthermore, the use of pressure therapy in conjunction with other modalities can enhance scar outcomes by applying consistent pressure to the scar tissue, which is known to help flatten hypertrophic scars (Qiu et al., 2015, pp. 2787-2791).

8.5. Surgical Treatment

Surgical intervention remains a viable option for scar treatment, particularly in cases of severe hypertrophic scars or keloids that do not respond to conservative measures. Surgical excision, when combined with postoperative therapies such as corticosteroid injections or laser treatment, can significantly reduce recurrence rates and improve aesthetic outcomes (El-Tahlawi and Mohamed, 2023, pp. 49-55; Park et al., 2011). However, it is crucial to recognize that surgical approaches alone may not suffice, as the recurrence of keloids post-excision is common, necessitating a multimodal treatment strategy (Park et al., 2011; Mohammadi et al., 2018, pp. 326-331).

8.6. Emerging Therapies

Emerging therapies are also being explored for their potential in scar treatment. For instance, the use of PRP has gained attention for its ability to promote healing and reduce scar

formation through the release of growth factors (Li et al., 2020, pp. 1-11). Additionally, novel approaches such as the application of mesenchymal stem cells and gene therapy are being investigated for their potential to improve scar outcomes (Wang et al., 2019, pp. 3668-3678; Yun et al., 2019,).

The CROSS (Chemical Reconstruction of Skin Scars) technique, which employs high concentrations of trichloroacetic acid (TCA), has been effectively used for treating atrophic acne scars, demonstrating significant improvement in scar morphology (Makwana et al., 2022, pp. 34-38). This method, alongside subcision and microneedling, represents a comprehensive approach to managing various scar types, particularly in patients with complex scar presentations.

Recent studies have explored the potential of targeting specific molecular pathways to mitigate hypertrophic scar formation. For instance, the use of anti-VEGF therapies has shown promise in reducing scar formation by inhibiting excessive angiogenesis (Kwak et al., 2016, pp. 491-497). Additionally, agents that modulate TGF-β signaling, such as small molecule inhibitors, have been investigated for their ability to reduce fibroblast activity and collagen deposition (Igarashi et al., 2015, pp. e0125295). Furthermore, the application of topical treatments, such as silicone gel sheets, has been shown to improve scar appearance by providing a moist environment and reducing tension on the scar (Eisendle et al., 2019, pp. 257-260; Gauglitz, 2013, pp. 103).

The psychological impact of scars on patients cannot be overlooked. Scarring can lead to significant emotional distress, affecting self-esteem and quality of life. Therefore, a comprehensive treatment plan should not only focus on the physical aspects of scar management but also consider the psychosocial implications. Counseling and support groups may be beneficial adjuncts to traditional treatment modalities, helping patients cope with the emotional burden of scarring (Sidgwick et al., 2015, pp. 461-477).

9. CONCLUSION

Wound healing is a complex and dynamic process that is influenced by a multitude of factors, including growth factors, cellular interactions, and the extracellular matrix. The molecular mechanisms of wound healing involve a complex interplay of various signaling pathway, each phase of healing is characterized by specific molecular events that are crucial for effective tissue repair.

Scar formation is a complex process involving a dynamic interplay between inflammatory responses, fibroblast activity, ECM remodeling, and mechanical forces. Hypertrophic scars and keloids represent the most common forms of abnormal scarring, while atrophic scars, contracture scars, and acne scars highlight the diverse nature of scar tissue.

Hypertrophic scar formation is a multifactorial process driven by an interplay of inflammatory responses, fibroblast activity, ECM remodeling, and angiogenesis. Keloid formation is also a multifactorial process driven by a combination of genetic, molecular, and environmental factors. The dysregulation of fibroblast activity, abnormal ECM deposition, and the influence of inflammatory and mechanical factors all contribute to the pathogenesis of keloids.

The scar treatment has various treatment choices such as intralesional injections, laser therapy, topical treatments, combination therapies, surgical treatment and emerging therapies. The choice of treatment should be individualized based on the type of scar, the patient's skin characteristics, and the timing of intervention.

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