Review Article

Iranian Journal of Immunology

December 2025; 22(4):344-356.

Advances in Understanding Immune Dysregulation and Therapeutic Strategies Targeting Epidermal and Dermal Cells in Keloids

Yuan Xia#, Jing Niu#, Hengheng Fan, Lin Liu, Yuan Zhou, Yuyun Xiong, Yumei Li*

Department of Dermatology, Institute of Regenerative Medicine, Affiliated Hospital of Jiangsu University, Jiangsu University, Zhenjiang 212001, China
#These authors contributed equally to this work.

ABSTRACT

Keloid, as a skin fibrotic proliferative disorder, have a complex pathogenesis that remains incompletely understood. It is characterized by abnormal and excessive scar formation following skin injury. The occurrence and development of keloids are closely associated with immune dysregulation. Immune cells, such as T cells, macrophages, mast cells, and Langerhans cells, play crucial roles in the formation of keloids. These immune cells contribute to keloid initiation and progression through mechanisms including cytokine secretion, promotion of inflammatory responses, and regulation of fibroblast proliferation and collagen synthesis. With advances in immunological research, the roles of fibroblasts, keratinocytes and melanocytes in the immunological dysregulation underlying keloids have received increasing attention. This paper aims to review recent progress on the abnormal immunological regulation involving these three epidermal cell types, in order to provide new insights and theoretical foundations for the treatment of this disease.

Keywords: Hypertrophic scar, Immunological regulation, Fibroblast, Keratinocyte, Melanocyte

*Corresponding author:
Yumei Li,
Department of Dermatology, Institute of Regenerative Medicine, Affiliated Hospital of Jiangsu University, Jiangsu University, Zhenjiang 212001, China
Email: yumeili@ujs.edu.cn

Cite this article as:
Xia Y, Niu J, Fan H, Liu L, Zhou Y, Xiong Y, Li Y. Advances in Understanding Immune Dysregulation and Therapeutic Strategies Targeting Epidermal and Dermal Cells in Keloids. *Iran J Immunol.* 2025; 22(4): 344-356, doi: 10.22034/iji.2025.107262.3048.

Received: 2025-05-25
Revised: 2025-07-18
Accepted: 2025-07-21

INTRODUCTION

As a skin fibroproliferative disease, the pathogenesis of keloid is complex and not yet fully understood. It is characterized by abnormal and excessive scar formation after skin injury. These scars frequently extend beyond the boundaries of the original wound and present as firm, raised nodules or plaques that rarely regress spontaneously. Unlike hypertrophic scars, keloids exhibit: Invasive growth beyond wound margins; Th17-skewed inflammation (IL-17+ cell density: 3.2-fold higher); and persistent TGF-β3 downregulation (1). Keloids occur with higher incidence in specific populations, particularly in individuals of African and Asian descent and those with family history of the condition, and are marked by both high incidence and recurrence rate (2). In addition, cutaneous injury events such as trauma, surgery, and burns are triggers for keloid, keloid formation, significantly affecting both the physical and psychological well-being of patients (3).

The occurrence and progression of keloids are closely associated with immune dysregulation. Immune cells, including T cells, macrophages, mast cells, and Langerhans cells, play crucial roles in keloid pathogenesis. These cells contribute through mechanisms such as cytokine secretion, promotion of inflammatory responses, and regulation of fibroblast proliferation and collagen synthesis. Immunological assessments, such as quantifying the number and functional status of T cells, may aid in developing targeted treatment strategies and serve as prognostic markers in keloid patients. With technological advances and increasing clinical demand, research on the immunological mechanisms in underlying keloid development has expanded considerably.

Single-cell sequencing has provided detailed insights into the cellular composition and heterogeneity of keloid tissues (4). Key cell types identified include vascular endothelial cells, fibroblasts; keratinocytes; sweat gland cells, while dysregulated pathways involve TGFβ/Eph-ephrin signaling and TGF-β/Smad cascade. These findings highlight the complexity of cellular interactions and molecular mechanisms in keloid formation, pointing toward novel therapeutic targets (5, 6). In recent years, increasing attention has been directed toward the role of fibroblasts, keratinocytes and melanocytes in the immune dysregulation underlying keloid pathogenesis (7, 8).

Fibroblasts are the principal cellular components of keloid dermis, and their abnormal proliferation together with excessive extracellular matrix (ECM) deposition is considered central to keloid formation. Interactions between keratinocytes and fibroblasts are also critical, as keratinocyte-derived factors can markedly influence fibroblast-driven collagen deposition. In addition, melanocytes and their associated genetic and environmental influences have been implicated in keloid susceptibility. The main cell types in the epidermis include keratinocytes and melanocytes, while fibroblasts are the predominant cells in the dermis. Increasing evidence indicates that epidermal cells play an important role in keloid development.

Therefore, this paper focuses on these three key cell types in the epidermis and dermis, discussing their contributions to immune dysregulation and how these processes drive keloid pathogenesis. By clarifying the role of these cells, we aim to provide a deeper understanding of the immunological mechanisms underlying keloid formation.

THE ROLE OF EPIDERMAL AND DERMAL CELLS IN THE NORMAL SCAR FORMATION PROCESS

The normal wound healing process is generally divided into four stages: hemostasis, inflammation, proliferation, and dermal remodeling. Each stage requires the coordinated involvement of different cells and molecular factors.

Hemostasis

Immediately after injury, platelets are rapidly activated, aggregate at the wound site, and release coagulation factors. These factors promote clot formation and facilitate the activation and migration of inflammatory cells, keratinocytes, and fibroblasts (9, 10). Keratinocytes help establish a protective barrier by re-forming the stratum corneum, which reduces blood loss and supports hemostasis.

Inflammation

During the inflammatory phase, resident immune cells, including mast cells, Langerhans cells, T cells, and macrophages, are activated via pattern recognition receptors (PRRs) recognizing damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) (11). Activated immune cells release pro-inflammatory cytokines and chemokines which recruit neutrophils from circulation into the wound site (12).

Neutrophils contribute to wound repair, by producing reactive oxygen species and various types of proteases to eliminate pathogens and necrotic tissue, while also secreting inflammatory mediators and cytokines that further attract inflammatory cells, endothelial cells, and fibroblasts (13). Fibroblasts at the wound site secrete ECM components and growth factors that support the clearance of inflammatory cells (such as macrophages) and wound stabilization. They also participate in immune regulation by secreting cytokines and chemokines that recruit and activate additional immune cells (14, 15). Damaged or stimulated keratinocytes release cytokines and chemokines such as TNF-α and IL-1α, which further attract and activate neutrophils and macrophages, thereby promoting pathogen clearance and tissues debridement (16).

Proliferation

During the proliferative phase, growth factors such as platelet-derived growth factor (PDGF), TGF-β, fibroblast growth factor (FGF), stimulate fibroblasts to proliferate and differentiate into myofibroblasts. These cells secrete collagen, elastin, and other ECM components to form granulation tissue, which fills the wound (17). Fibroblasts also degrade the temporary matrix via matrix metalloproteinases, replacing it with granulation tissue enriched in fibronectin, immature collagen, and proteoglycans (18). This provisional matrix provide structural support and serves as a scaffold for cell migration, angiogenesis, and epithelialization (19).

At the wound edge, epithelial-ECM interactions promote the proliferation and migration of keratinocytes. Once migration ceases, keratinocytes establish a new epithelial layer, and reform the basement membrane and undergo terminal differentiation to regenerate the epidermis (19). Melanocytes contribute by synthesizing and secreting melanin, which protects the newly formed skin from ultraviolet radiation. Melanin has also been shown to stimulate fibroblast proliferation, accelerate wound closure, and support barrier (20).

Dermal Remodeling

Scar formation occurs primarily during dermal remodeling. Following normal wound healing, scar formation and degradation reach a dynamic equilibrium (21). In this phase, fibroblasts orchestrate ECM remodeling by replacing the fibrin clot with hyaluronic acid, fibronectin, and proteoglycans, followed by deposition of mature collagen fibers (22). Proteoglycans facilitate collagen crosslinking and serve as conduits for cell migration (23). As healing progresses, type III collagen is gradually replaced by type I collagen, increasing tensile strength (24).

Myofibroblasts contribute to wound contraction through pseudopodia extension and cytoplasmic actin binding to fibronectin within the matrix (17). Muscle fibroblasts adhere to one another via desmosomes, and to matrix fibers, generating contractile forces that pull the wound margins together (25). Keratinocytes maintain epidermal integrity and promote barrier maturation, while melanocytes provide long-term protection via sustained melanin synthesis. Melanocytes may also modulate immune responses by attenuating local inflammation, thereby reducing tissue redness, pain, and swelling (26). Finally, as macrophages, endothelial cells, and fibroblasts undergo apoptosis or leave the wound site, wound healing gradually subsides, leaving behind a stable scar (27).

THE MECHANISM OF IMMUNE REGULATION DISORDERS INVOLVED IN KELOID

Imbalance of Immune Cell Function

Immune dysregulation initiates keloid pathogenesis. In early wounds, M2 macrophages dominate and secrete IL-10, priming fibroblast activation (28). Depletion of CD8+ T cell reduces cytotoxic pressure, allowing fibroblast survival (29). Keloid tissue contains abundant lymphocytes and dendritic cells, and alterations in their number are associated with scar development.

Lymphocytes: Comparative analyses show that infiltration of T follicular helper cells and monocytes is significantly higher in scar tissue than in normal skin (30). Downregulation of cytotoxic $CD8^+$T cells is consistently observed in both peripheral blood and scar lesions (29). Several studies have reported that both direct and indirect cultures of $CD8^+$T cells with fibroblasts exert significant inhibitory effects on fibroblasts (31). Their immunomodulatory activity positions $CD8^+$ T cells as a pivotal target for developing new immunotherapeutic strategies against keloids. Although monocytes differentiate into M2 macrophages during early wound healing in both normal and keloid-prone individuals, this process appears to be dysregulated in the latter. In keloid pathogenesis, the M2 macrophage response is exaggerated and prolonged, resulting in sustained release of profibrotic factors such as IL-10 and TGF-β, which continually activate fibroblasts and drive excessive ECM deposition (28). Thus, the key difference may lie not in the initial differentiation of monocytes into M2 macrophages, but in the heightened and prolonged nature of this pro-repair immune response and its failure to resolve, ultimately contributing to pathological fibrosis in susceptible individuals.

Neutrophils: Neutrophils are the first immune cells recruited to the site of injury. Beyond antimicrobial defense, they secrete cytokines including IL-1, IL-17, vascular endothelial growth factor (VEGF), and TNF-α (32), which recruit other immune cells, promote fibroblast proliferation, and facilitate wound healing (33). However, excessive neutrophil activity can be detrimental, as their depletion accelerate wound healing without significant scar formation, highlighting their dual role in fibrosis (34).

Langerhans cells: Langerhans cells are located in the granular layer of the epidermis and migrate to wound sites following trauma. Their density is significantly higher in keloid tissue compared with normal skin, implicating them in scar progression (35). Interaction among Langerhans cells, keratinocytes, and the deep dermis may influence the formation of scar tissue by modulating the release of cytokines such as IL-1α and IL-4.

Mast cells: Mast cells are increased in both number and activity in keloid tissue. Upon IgE-mediated activation,, they degranulate and release mediators such as histamine, which which amplify inflammation and stimulate fibroblasts to increase collagen synthesis, acting as potent pro fibrotic mediators (36). Changes in the activity of the glycosphingolipid (GSL) metabolic pathway in fibroblasts were analyzed using pseudo time trajectory, revealing that increased GSL metabolic pathway activity is associated with fibroblast differentiation (37).

Immune-stromal crosstalk: Crosstalk between immune and stromal cells is central to keloid development. M2 macrophages are predominant in keloid tissues and secrete IL-10, sustaining TGF-β/Smad3 activation in fibroblasts. Concurrently, infiltrating Th17 cells produce IL-17A, which amplifies fibroblast proliferation through the STAT3-HIF-1α axis (38).

Collectively, immune dysregulation alters immune–fibroblast interactions, resulting in abnormal fibroblast activation and excessive ECM synthesis that drive keloid formation.

Abnormal Production of Cytokines

Scar tissue formation is characterized by abnormal expression of multiple cytokines and growth factors, including TGF-β, VEGF, PDGF, FGF, all of which are markedly upregulated in scar tissue. These mediators drive keloid progression by promoting fibroblast proliferation and collagen synthesis. Plasma analyses from patients with keloid revealed persistently elevated concentrations of inflammatory cytokines, underscoring in the central role of chronic inflammation in keloid pathogenesis (39). Notably, IL-17 significantly upregulate the expression of SDF-1 in fibroblasts, enhancing directed migration and infiltration of Th17 cells from the circulation, amplifying the complexity

of the immune microenvironment in keloid (40). These findings suggest that, therapeutic strategies aimed at interleukin blockade and suppression of inflammatory responses may be effective for keloid treatment (41). In addition, the expression of the chemokine CCL2 and its receptor CCR2 is significantly increased in keloid tissue. Their interaction directly stimulates fibroblast proliferation, identifying the CCL2–CCR2 axis as a potential therapeutic target (42). In summary, a deeper understanding of cytokine-driven mechanisms in keloid development will provide a stronger theoretical foundation for designing precise and effective therapeutic approaches.

Fibroblasts themselves secrete a range of cytokines that promote cell proliferation and collagen synthesis (43, 44). Immune dysregulation can result in abnormal expression of these cytokines, thereby exacerbating the formation of keloid. Stimulated keratinocytes release various cytokines such as IL-1 and IL-6, which promote inflammation and cell proliferation (45). In melanocytes, immune dysregulation can disrupt pigment metabolism, altering scar pigmentation. While this does not directly lead to the formation of scars, it significantly affects scar visibility and cosmetic appearance.In summary, the formation of a keloid is a complex pathological process involving interactions of multiple immune and non-immune cells and cytokines. Immune dysregulation disrupts the balance of these pathways, promoting pathological scar formation.

THE ROLE OF EPIDERMAL AND DERMAL CELLS IN THE DEVELOPMENT OF KELOID

Fibroblasts

Fibroblasts contribute to scar tissue primarily through excessive proliferation, collagen synthesis and deposition, ECM remodeling, dysregulated inflammatory responses, altered immune regulation, and angiogenesis. Scar formation represents a complex pathological process in which fibroblasts interact with their surrounding immune cells, thereby amplifying abnormal tissue repair and hyperproliferation (46). TGF-β is one of the most important fibrosis-promoting mediators, regulating collagen formation in fibroblasts and myofibroblasts. By activating canonical (Smad2/3) and non-canonical (NF-κB, p38 MAPK) signaling pathways, TGF-β TGF-β drives overactivation of fibroblasts and myofibroblasts, resulting in excessive collagen formation and keloid formation (43). Crosstalk with mast cell-derived histamine further amplifies TGF-β signaling, reinforcing fibroblast-driven collagen overproduction (36). Upon trauma or inflammation, fibroblasts: secrete PDGF which recruits immune cells and upregulates collagen synthesis via the ERK1/2 pathway. In scar tissue, overexpression of PDGF may lead to excessive fibroblasts proliferation and aberrant ECM deposition (44). Fibroblasts also secrete fibroblast growth factor (FGF), which promotes fibroblast proliferation and collagen synthesis, thereby contributing to scar tissue formation and progression (47). When stimulated by trauma or inflammation, Fibroblasts release inflammatory factors such as IL-6, which participate in the formation and development of scar tissue by enhancing the activation and proliferation of fibroblasts, and the synthesis of collagen and other ECM components (48). Additionally, fibroblasts may secrete TNF-α under certain conditions, which can promote fibroblast proliferation and activates downstream signaling cascades, including NF-κB, JNK and p38 MAPK, further contributing to the pathological remodeling processes observed in scar tissue (49). Research has shown that inhibition of the heme synthesis pathway significantly reduces the expression of cellular hemoglobin, a process closely associated with the abnormal viability and proliferative capacity of fibroblasts in keloid tissue (50). Keloid fibroblasts demonstrate tumor-like properties: Proliferation: a 2.1-fold increase in EdU+ cells compared with

normal fibroblasts (51); anti-apoptosis: a 60% reduction in caspase-3 activity under TNF-α stimulation (49). Furthermore, significant changes in lipid metabolism have been observed in keloid fibroblasts and are strongly associated with keloid progression. This highlighs the potential therapeutic relevance of targeting metabolic pathways in the treatment of keloids (52). Notably, the activity of bacteria and specific enzymes such as catalase has been identified as an important factor in triggering or exacerbating scar tissue formation. This finding underscores the need for therapeutic strategies that target inflammation and restore microbial balance in scar treatment (53). From a drug development perspective, Dilatinib has shown significant inhibitory effects on fibroblast proliferation, migration, invasion, and collagen production in in vitro experiments. These results highlight its potential as a promising candidate pharmacological agent for the treatment of scar tissue disorders (54). In addition, microRNAs (miRNAs) such as miR-214 regulate scar tissue pathology by targeting A2AR expression, which alters TGF-β levels. This process not only enhances the proliferation of scar tissue fibroblasts, but also inhibits apoptosis, underscoring the critical regulatory role of miRNAs in scar formation (55). Research on signaling pathways indicates that both p38 inhibitors and 2ME2 effectively suppress the proliferation of scar tissue fibroblasts (56). Notably, 2ME2 may exert its anti-proliferative effects by directly targeting the p38 signaling pathway, providing a theoretical basis for the development of novel anti-fibrotic agents. Microbiome analysis further reveals Staphylococcus aureus enrichment in keloid tissues, which may contribute to fibrosis through catalase-mediated oxidative stress (53). These findings highlight the importance of the host–microbe interaction in scar pathology and warrant further mechanistic investigation.

Keratinocytes

Keratinocytes secrete various factors that regulate fibroblasts activity and extracellular matrix (ECM) synthesis, thereby affecting the formation and development of scars. For example, TGF-β activates fibroblasts via the TGF/Smad signaling pathway, promoting their proliferation, differentiation, and ECM deposition (57). Platelet derived growth factor (PDGF), secreted by keratinocytes, also enhances fibroblast activity (1). Similarly, FGF, produced by keratinocytes and other cells, supports the proliferation and differentiation of fibroblasts. In scar tissue, FGF contributes to regulating fibroblasts function (54). Keratinocytes can also undergo partial epithelial-mesenchymal transition (EMT), characterized by a reduction in epithelial markers and an increase in mesenchymal markers. In keloid keratinocytes, EMT-related genes are significantly upregulated, including the decreased expression of epithelial markers such as E-cadherin (↓60%) and β- catenin, alongside increased expression of the mesenchymal marker vimentin (↑3-fold) (58, 59). These changes blur the boundary between the epidermis and dermis, enhance cellular migration and invasion, and facilitate the expansion and invasion of keloids into surrounding normal tissues (60).

Melanocytes

A study has found that melanocyte secretions can activate TGF-β signaling in fibroblasts, which may represent an important mechanism for promoting scar formation (61). Under specific conditions, melanocytes release exosomes carrying specific microRNAs (miRNAs), such as kmiR-7704. These exosomes are internalized by fibroblasts, transferring bioactive molecules such as miRNAs into the fibroblast cells. The transferred miRNAs, inhibit Smurf1 within the fibroblasts, leading to abnormal activation of the TGF-β/Smad pathway. This dysregulation results in excessive proliferation, differentiation, and migration of fibroblasts, ultimately contributing to keloid formation. Such findings highlight

the critical role of melanocyte-fibroblast interactions in the pathogenesis of keloids and suggest potential molecular targets for therapeutic interventions (61). In addition, Taylor et al. found that α-melanocyte-stimulating hormone (α-MSH), secreted by melanocytes in the skin, can increase the production of TGF-β by activating T cells, suppress the production of INF-α, and stimulate the proliferation of fibroblasts. This further promotes the development of keloids (62, 63).

Interactions among Fibroblasts, Keratinocytes and Melanocytes

In keloid tissue, the key cytokine TGF-β, secreted by keratinocytes, activates the TGF-β/Smad signaling pathway, leading to excessive activation of fibroblasts and myofibroblasts. This leads to an overproduction of collagen and ultimately the development of keloids. .Following skin injury or inflammatory stimuli, fibroblasts and keratinocytes secrete excessive amounts of PDGF and FGF further enhancing fibroblast activity. Fibroblasts also produce IL-6, which promotes their activation and proliferation, while also secreting TNF-α, which further stimulates fibroblast proliferation through activation of the NF-κB, JNK, and p38 MAPK signaling pathways. Additionally, inhibition of heme synthesis (e.g., by ALA dehydratase knockdown) has been shown to decrease cytoglobin expression, directly enhancing fibroblast proliferation (50). Fig. 1 summarizes these key interactions: Keratinocyte → Fibroblast: TGF-β/PDGF; melanocyte → Fibroblast: kmiR-7704 exosomes; shared loops: IL-6/STAT3.

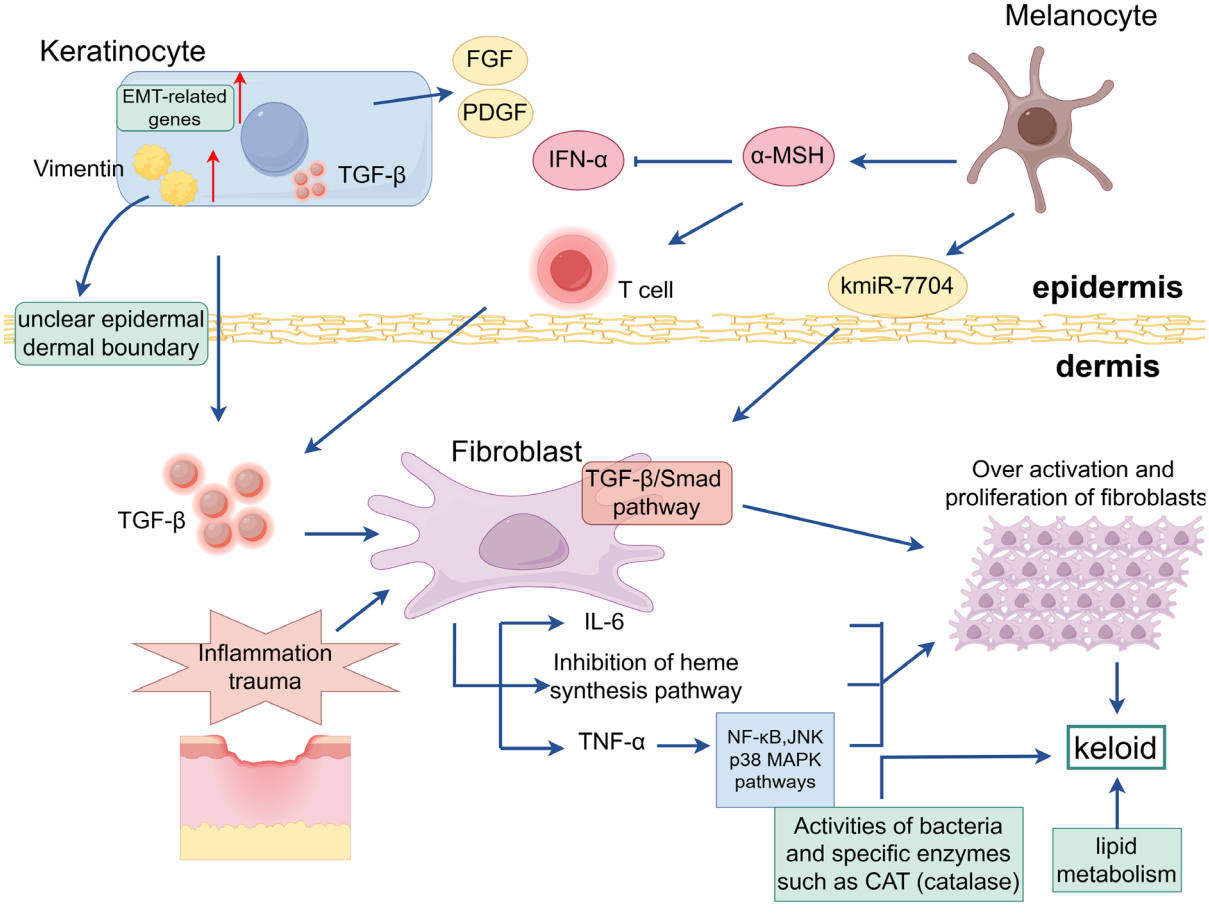

Fig. 1. Cross-talk among keloid cells. (1) Keratinocytes secrete TGF-β and PDGF to activate fibroblasts. (2) Melanocyte-derived exosomes deliver kmiR-7704, which suppresses Smurf1 in fibroblasts. (3) Shared cytokines (IL-6, TNF-α) establish a pro-fibrotic feedback loop. Red inhibitors indicate potential therapeutic targets (e.g., STAT3, RhoA/ROCK1).

NOVEL THERAPEUTIC TARGETS AND INNOVATIVE APPROACHES IN KELOID TREATMENT

Although classified as benign hyperplasia of the skin, keloids exhibit biological characteristics similar to malignant tumors, such as excessive cell proliferation, resistance to apoptosis, and invasive growth. These properties impose significant physical and psychological burdens on patients, manifesting as pain, pruritus, and tissue contracture. However, the precise pathogenesis of keloids remains incompletely understood. As a result, current clinical interventions, such as surgical excision and corticosteroid therapy, are limited by of high recurrence rates and the absence of effective long-term pharmacological options, making keloid management a persistent clinical challenge. In recent years, researchers have conducted extensive studies at the cellular and molecular levels to clarify the mechanisms underlying keloid formation and identify novel and effective therapeutic targets.

Potential Therapeutic Targets for Keloid

The formation of keloids is a complex and dynamic biological process, with abnormal differentiation of fibroblasts into myofibroblasts at its core. This process significantly promotes the accumulation of excess collagen, leading to an exacerbation of scar tissue formation. Cytokines, as key mediators of intra- and intercellular information communication, play a pivotal role in keloid pathogenesis. Regulating cytokine balance offers therapeutic potential: inhibiting pro-inflammatory cytokines (e.g., IL-6 and IL-8) while enhancing anti-inflammatory cytokines (e.g., IL-10) can suppress fibrosis. Clinical evidence shows that IL-6 blockade reduces collagen density by approximately 40%. Inflammatory cells, including macrophages, T cells, and mast cells, also contribute significantly to keloid progression, making reduction of the inflammatory cascade a central therapeutic strategy (64). HMGB1, a key mediator of the inflammatory and cellular stress response, represents a novel therapeutic target (65). Similarly, transcriptional regulators such as Runx2 and PKM2 play crucial roles in the pathogenesis of keloid and may serve as future therapeutic targets (66). The upregulation of HIF-1 α in scar tissue suggests its potential role in driving pathological scar formation, offering new insights into the underlying disease mechanism (67). The transcription factor HOXC9 has emerged as both a potential biomarker and therapeutic target (68). Moreover, inhibition of STAT3 has been shown to significantly alleviate fibroblasts dysfunction, underscoring the critical role of molecular targeted therapies in managing scar tissue pathology (51).

In addition to cytokines and transcription factors, dysregulated signaling pathways are central to in scar formation. Impaired autophagy scar tissue is associated not only with necrotic cell death, but also with fibrosis progression. Therapeutic interventions targeting the TGF-β/Smad pathway remain fundamental, while emerging regulators such as HMGB1, Runx2, and PKM2, which uniquely regulate keloid fibroblast metabolism, offer novel avenues to modulate fibroblast activity and metabolism (69). Collectively, these insights suggest that interventions focusing on these signaling pathways may revolutionize treatment strategies for keloids (58).

In summary, advancing our understanding of keloid pathogenesis, continues to unveil novel therapeutic targets and strategies, offering renewed hope for affected patients.

Exploration of Innovative Treatment for Keloid

This review highlights the potential of several innovative drugs, such as dasatinib, microRNA-29 mimetics (Remlarsen), and the PARP1 inhibitor Rucaparib, in the treatment of keloids. Dasatinib, a tyrosine kinase inhibitor, has demonstrated anti-fibrotic activity and holds promise as a therapeutic

option for keloid management (70). Remlarsen, a synthetic miR-29 mimic, has shown significant potential in preventing fibrotic scar formation by effectively suppressing collagen overexpression and inhibiting fibrosis at skin incision sites, thereby offering a novel strategy for early keloid intervention (71). In addition, this review discusses the potential of the PARP 1 inhibitor rucaparib as a novel therapeutic option keloid. Its distinct pharmacological profile introduces a new dimension to keloid treatment strategies, underscoring the diversification of future treatment approaches (72). Paclitaxel (PTX) has also attracted attention as a promising anti-keloid agent; however, its precise therapeutic mechanism remains incompletely understood. Therefore, in-depth investigation of the specific mechanism by which PTX influences keloid pathogenesis is crucial for advancing its clinical application, with the potential to yield more precise and effective therapeutic options for keloid patients (73). The strong association between asporin (ASPN) and keloid pathogenesis has inspired innovative therapeutic approaches, notably the use of ASPN siRNA-loaded nanoparticles to precisely modulate the expression of ASPN. In xenograft models, PEI-coated ASPN siRNA nanoparticles reduced collagen deposition by 35% (74). However, the low transfection efficiency (<50% in fibroblasts) remains a barrier to clinical translation. As a multi-targeted agent, nintedanib demonstrates considerable therapeutic potential for the treatment of keloid by effectively suppressing cell proliferation, migration and excessive production of collagen, positioning it as a promising candidate drug for clinical intervention (75). Pirfenidone, a novel antifibrotic agent, has demonstrated promising potential in keloid treatment. It can not only block the epithelial-mesenchymal transition in keratinocytes, but also modulate the gene expression profiles, and suppressing cell migration and proliferation, collectively contributing to the attenuation of keloid progression and recurrence (76). Adipose derived stem cells (ADSCs), as a form of biological therapy, have shown notable promise in the treatment of keloid by significantly inhibiting the proliferation and invasion of keloid fibroblasts. However, their specific role in regulating apoptosis remains to be elucidated (77). Notably, emerging molecular therapies have shown encouraging progress; for instance, growth factors and cytokines present in human Wharton's jelly stem cell-conditioned medium (hWJSC-CM) promote the repair and regeneration of scar tissue by stimulating the proliferation and differentiation of skin cells, thereby accelerating scar maturation and softening (78). Modulating the expression of Circ-PDE7B influences the gene regulatory network involved in scar formation, thereby suppressing excessive scar hyperplasia and enhancing scar texture. Its anti-keloid activity highlights the potential for novel therapeutic strategies (79). Ongoing efforts to develop pharmacological agents, further expand the horizon of treatment options, offering renewed hope for patients with keloid.

CONCLUSION AND OUTLOOK

Fibroblasts, keratinocytes and melanocytes play pivotal roles in the dysregulated immune responses underlying keloid pathogenesis. Among them, fibroblasts serve as the principal effector cells. Their abnormal activation and proliferation drive excessive deposition of ECM, a hallmark of keloid formation. Keratinocytes contribute to disease progression by disrupting the epidermal–dermal interface, through downregulation of EMT-related genes and intercellular adhesion proteins such as E-cadherin, thereby exacerbating the pathological remodeling of keloid tissue. Melanocytes contribute significantly to the formation of keloid by delivering specific miRNAs that modulate the TGF-β/Smad signaling pathway in fibroblasts, thereby promoting fibrotic activity. In conclusion, fibroblasts,

keratinocytes and melanocytes interact within the dysregulated immune microenvironment of keloid, jointly influencing its initiation and progression. Among these, fibroblasts are the primary effector cells driving keloid formation. Given their their distinct roles in keloid pathogenesis, targeting fibroblast proliferation and promoting their apoptosis represents a promising therapeutic strategy. Further elucidation of the immunomodulatory functions of cytokines secreted by keratinocytes, such as IL-6 and TGF-β, and their crosstalk with fibroblasts, may uncover novel therapeutic targets and strategies for the prevention and treatment of keloids.

Furthermore, investigating the mechanisms by which melanocytes contribute to keloid development offers promising therapeutic avenues, particularly for individuals with darker skin tones, who exhibit increased susceptibility to keloid formation. Advancing tailored treatment strategies for these specific groups represents a critical direction for future research. When combined with a deeper insights into cell-cell interactions within keloid tissue, these approaches hold substantial potential to improve prevention and clinical management of keloids.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to colleagues at Department of Dermatology, Institute of Regenerative Medicine, Affiliated Hospital of Jiangsu University, Jiangsu University for their valuable support. This study received no financial support and the authors declare no conflicts of interest.

AUTHOR'S CONTRIBUTION

Y. X., J. N.; conceived the study and drafted the manuscript. H.F.; conducted the literature review. L.L., Y.Z.: Reviewed and edited the manuscript. Y. X., Y. L.; oversaw the overall supervision and edited and approved the final version. All authors have read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Siotos C, Uzosike A C, Hong H, Seal S M, Rosson G D, Cooney C M, et al. Keloid Excision and Adjuvant Treatments: A Network Meta-analysis. Ann Plast Surg. 2019; 83(2): 154-162.
2. Limandjaja G C, Niessen F B, Scheper R J,Gibbs S. The Keloid Disorder: Heterogeneity, Histopathology, Mechanisms and Models. Front Cell Dev Biol. 2020; 8(360.
3. Liu X, Chen W, Zeng Q, Ma B, Li Z, Meng T, et al. Single-Cell RNA-Sequencing Reveals Lineage-Specific Regulatory Changes of Fibroblasts and Vascular Endothelial Cells in Keloids. J Invest Dermatol. 2022; 142(1): 124-135.e111.
4. Feng C, Shan M, Xia Y, Zheng Z, He K, Wei Y, et al. Single-cell RNA sequencing reveals distinct immunology profiles in human keloid. Front Immunol. 2022; 13(940645.
5. Shim J, Oh S J, Yeo E, Park J H, Bae J H, Kim S H, et al. Integrated Analysis of Single-Cell and Spatial Transcriptomics in Keloids: Highlights on Fibrovascular Interactions in Keloid Pathogenesis. J Invest Dermatol. 2022; 142(8): 2128-2139.e2111.
6. Andrews J P, Marttala J, Macarak E, Rosenbloom J,Uitto J. Keloids: The paradigm of skin fibrosis - Pathomechanisms and treatment. Matrix Biol. 2016; 51(37-46.
7. Wang L, Wang B, Kou E, Du L,Zhu Y. New insight into the role of fibroblasts in the epithelial immune microenvironment in the single-cell era. Front Immunol. 2023; 14(1259515.
8. Clark R A. Fibrin and wound healing. Ann N Y Acad Sci. 2001; 936(355-367.
9. Scully D, Sfyri P, Wilkinson H N, Acebes-Huerta A, Verpoorten S, Muñoz-Turrillas M C, et al. Optimising platelet secretomes to deliver robust tissue-specific regeneration. J Tissue Eng Regen Med. 2020; 14(1): 82-98.
10. Chen L,DiPietro L A. Toll-Like Receptor Function in Acute Wounds. Adv Wound Care (New Rochelle). 2017; 6(10): 344-355.
11. Golebiewska E M,Poole A W. Platelet secretion: From haemostasis to wound healing and beyond. Blood Rev. 2015; 29(3): 153-162.

12. Martin P,Leibovich S J. Inflammatory cells during wound repair: the good, the bad and the ugly. Trends Cell Biol. 2005; 15(11): 599-607.
13. Cavagnero K J,Gallo R L. Essential immune functions of fibroblasts in innate host defense. Front Immunol. 2022; 13(1058862.
14. Correa-Gallegos D, Jiang D,Rinkevich Y. Fibroblasts as confederates of the immune system. Immunol Rev. 2021; 302(1): 147-162.
15. Spiekstra S W, Breetveld M, Rustemeyer T, Scheper R J,Gibbs S. Wound-healing factors secreted by epidermal keratinocytes and dermal fibroblasts in skin substitutes. Wound Repair Regen. 2007; 15(5): 708-717.
16. Li J, Chen J,Kirsner R. Pathophysiology of acute wound healing. Clin Dermatol. 2007; 25(1): 9-18.
17. Xue M,Jackson C J. Extracellular Matrix Reorganization During Wound Healing and Its Impact on Abnormal Scarring. Adv Wound Care (New Rochelle). 2015; 4(3): 119-136.
18. Baum C L,Arpey C J. Normal cutaneous wound healing: clinical correlation with cellular and molecular events. Dermatol Surg. 2005; 31(6): 674-686; discussion 686.
19. Cui H S, Joo S Y, Cho Y S, Lee Y R, Ro Y M, Kwak I S, et al. Exosomes Derived from Hypertrophic Scar Fibroblasts Suppress Melanogenesis in Normal Human Epidermal Melanocytes. Int J Mol Sci. 2024; 25(13).
20. Takeo M, Lee W,Ito M. Wound healing and skin regeneration. Cold Spring Harb Perspect Med. 2015; 5(1): a023267.
21. Darby I A, Laverdet B, Bonté F,Desmoulière A. Fibroblasts and myofibroblasts in wound healing. Clin Cosmet Investig Dermatol. 2014; 7(301-311.
22. Schultz G S,Wysocki A. Interactions between extracellular matrix and growth factors in wound healing. Wound Repair Regen. 2009; 17(2): 153-162.
23. Diegelmann R F,Evans M C. Wound healing: an overview of acute, fibrotic and delayed healing. Front Biosci. 2004; 9(283-289.
24. Stadelmann W K, Digenis A G,Tobin G R. Physiology and healing dynamics of chronic cutaneous wounds. Am J Surg. 1998; 176(2A Suppl): 26s-38s.
25. Alkhalil A, Carney B C, Travis T E, Muhie S, Miller S A, Ramella-Roman J C, et al. Dyspigmented hypertrophic scars: Beyond skin color. Pigment Cell Melanoma Res. 2019; 32(5): 643-656.
26. Larouche J, Sheoran S, Maruyama K,Martino M M. Immune Regulation of Skin Wound Healing: Mechanisms and Novel Therapeutic Targets. Adv Wound Care (New Rochelle). 2018; 7(7): 209-231.
27. Yin X, Bu W, Fang F, Ren K,Zhou B. Keloid Biomarkers and Their Correlation With Immune Infiltration. Front Genet. 2022; 13(784073.
28. Xu H, Zhu Z, Hu J, Sun J, Wo Y, Wang X, et al. Downregulated cytotoxic CD8(+) T-cell identifies with the NKG2A-soluble HLA-E axis as a predictive biomarker and potential therapeutic target in keloids. Cell Mol Immunol. 2022; 19(4): 527-539.
29. Shan M, Liu H, Hao Y, Song K, Feng C,Wang Y. The Role of CD28 and CD8(+) T Cells in Keloid Development. Int J Mol Sci. 2022; 23(16).
30. Limandjaja G C, Waaijman T, Roffel S, Niessen F B,Gibbs S. Monocytes co-cultured with reconstructed keloid and normal skin models skew towards M2 macrophage phenotype. Arch Dermatol Res. 2019; 311(8): 615-627.
31. Chen D, Tang T X, Deng H, Yang X P,Tang Z H. Interleukin-7 Biology and Its Effects on Immune Cells: Mediator of Generation, Differentiation, Survival, and Homeostasis. Front Immunol. 2021; 12(747324.
32. Li Y, Li M, Qu C, Li Y, Tang Z, Zhou Z, et al. The Polygenic Map of Keloid Fibroblasts Reveals Fibrosis-Associated Gene Alterations in Inflammation and Immune Responses. Front Immunol. 2021; 12(810290.
33. Brubaker A L, Schneider D F,Kovacs E J. Neutrophils and natural killer T cells as negative regulators of wound healing. Expert Rev Dermatol. 2011; 6(1): 5-8.
34. Jiao H, Fan J, Cai J, Pan B, Yan L, Dong P, et al. Analysis of Characteristics Similar to Autoimmune Disease in Keloid Patients. Aesthetic Plast Surg. 2015; 39(5): 818-825.
35. Lee C C, Tsai C H, Chen C H, Yeh Y C, Chung W H,Chen C B. An updated review of the immunological mechanisms of keloid scars. Front Immunol. 2023; 14(1117630.
36. Song B, Zheng Y, Chi H, Zhu Y, Cui Z, Chen L, et al. Revealing the roles of glycosphingolipid metabolism pathway in the development of keloid: a conjoint analysis of single-cell and machine learning. Front Immunol. 2023; 14(1139775.
37. Nangole F W, Ouyang K, Anzala O, Ogengo J,Agak G W. Multiple Cytokines Elevated in Patients with Keloids: Is It an Indication of Auto-Inflammatory Disease? J Inflamm Res. 2021; 14(2465-2470.
38. Lee S Y, Kim E K, Seo H B, Choi J W, Yoo J H, Jung K A, et al. IL-17 Induced Stromal Cell-Derived Factor-1 and Profibrotic Factor in Keloid-Derived Skin Fibroblasts via the STAT3 Pathway. Inflammation. 2020; 43(2): 664-672.
39. Zhang D, Li B,Zhao M. Therapeutic Strategies by Regulating Interleukin Family to Suppress Inflammation in Hypertrophic Scar and Keloid. Front Pharmacol. 2021; 12(667763.
40. Lee A R, Lee S Y, Choi J W, Um I G, Na H S,

Lee J H, et al. Establishment of a humanized mouse model of keloid diseases following the migration of patient immune cells to the lesion: Patient-derived keloid xenograft (PDKX) model. Exp Mol Med. 2023; 55(8): 1713-1719.
41. Chen J, Zhao S, Liu Y, Cen Y,Nicolas C. Effect of captopril on collagen metabolisms in keloid fibroblast cells. ANZ J Surg. 2016; 86(12): 1046-1051.
42. Zhang T, Wang X F, Wang Z C, Lou D, Fang Q Q, Hu Y Y, et al. Current potential therapeutic strategies targeting the TGF-β/Smad signaling pathway to attenuate keloid and hypertrophic scar formation. Biomed Pharmacother. 2020; 129(110287.
43. Johnson B Z, Stevenson A W, Prêle C M, Fear M W,Wood F M. The Role of IL-6 in Skin Fibrosis and Cutaneous Wound Healing. Biomedicines. 2020; 8(5).
44. Zhang X, Wu X,Li D. The Communication from Immune Cells to the Fibroblasts in Keloids: Implications for Immunotherapy. Int J Mol Sci. 2023; 24(20).
45. Yang J, Deng P, Qi Y, Feng X, Wen H,Chen F. NEAT1 Knockdown Inhibits Keloid Fibroblast Progression by miR-196b-5p/FGF2 Axis. J Surg Res. 2021; 259(261-270.
46. Xue H, McCauley R L,Zhang W. Elevated interleukin-6 expression in keloid fibroblasts. J Surg Res. 2000; 89(1): 74-77.
47. Li Q, Cheng F, Zhou K, Fang L, Wu J, Xia Q, et al. Increased sensitivity to TNF-α promotes keloid fibroblast hyperproliferation by activating the NF-κB, JNK and p38 MAPK pathways. Exp Ther Med. 2021; 21(5): 502.
48. Nauli R, Wanandi S I, Sadikin M, Antarianto R D,Jusman S W A. Inhibition of ALA dehydratase activity in heme biosynthesis reduces cytoglobin expression which is related to the proliferation and viability of keloid fibroblasts. J Clin Biochem Nutr. 2023; 73(3): 185-190.
49. Li C Y, Xie R X, Zhang S W, Yun J, Zhong A, Cen Y, et al. Metabolism, fibrosis, and apoptosis: The effect of lipids and their derivatives on keloid formation. Int Wound J. 2024; 21(2): e14733.
50. Shan M, Xiao M, Xu J, Sun W, Wang Z, Du W, et al. Multi-omics analyses reveal bacteria and catalase associated with keloid disease. EBioMedicine. 2024; 99(104904.
51. Xu S, Zhu Y, Wang P, Qi S,Shu B. Derazantinib Inhibits the Bioactivity of Keloid Fibroblasts via FGFR Signaling. Biomedicines. 2023; 11(12).
52. Du Y, Liu J, Hao Q, Wang S, Zhang A, Li Y, et al. Effects of miR-214 on adenosine A2A receptor and carboxymethyl chitosan nanoparticles on the function of keloid fibroblasts and their mechanisms. Sci Rep. 2024; 14(1): 4896.
53. Zhang M Z, Liu Y F, Ding L, Li Z J, Li Y Z, Si L B, et al. 2-Methoxyestradiol inhibits the proliferation level in keloid fibroblasts through p38 in the MAPK/Erk signaling pathway. J Cosmet Dermatol. 2023; 22(11): 3135-3142.
54. Funayama E, Chodon T, Oyama A,Sugihara T. Keratinocytes promote proliferation and inhibit apoptosis of the underlying fibroblasts: an important role in the pathogenesis of keloid. J Invest Dermatol. 2003; 121(6): 1326-1331.
55. Butler P D, Longaker M T,Yang G P. Current progress in keloid research and treatment. J Am Coll Surg. 2008; 206(4): 731-741.
56. Hahn J M, McFarland K L, Combs K A,Supp D M. Partial epithelial-mesenchymal transition in keloid scars: regulation of keloid keratinocyte gene expression by transforming growth factor-β1. Burns Trauma. 2016; 4(1): 30.
57. Kuwahara H, Tosa M, Egawa S, Murakami M, Mohammad G,Ogawa R. Examination of Epithelial Mesenchymal Transition in Keloid Tissues and Possibility of Keloid Therapy Target. Plast Reconstr Surg Glob Open. 2016; 4(11): e1138.
58. Yan L, Cao R, Wang L, Liu Y, Pan B, Yin Y, et al. Epithelial-mesenchymal transition in keloid tissues and TGF-β1-induced hair follicle outer root sheath keratinocytes. Wound Repair Regen. 2015; 23(4): 601-610.
59. Shen Z, Shao J, Sun J,Xu J. Exosomes released by melanocytes modulate fibroblasts to promote keloid formation: a pilot study. J Zhejiang Univ Sci B. 2022; 23(8): 699-704.
60. Slominski A, Tobin D J, Shibahara S,Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. Physiol Rev. 2004; 84(4): 1155-1228.
61. Taylor A W, Yee D G, Nishida T,Namba K. Neuropeptide regulation of immunity. The immunosuppressive activity of alpha-melanocyte-stimulating hormone (alpha-MSH). Ann N Y Acad Sci. 2000; 917(239-247.
62. Liu Y X, Sun J M, Ho C K, Gao Y, Wen D S, Liu Y D, et al. Advancements in adipose-derived stem cell therapy for skin fibrosis. World J Stem Cells. 2023; 15(5): 342-353.
63. Jeon Y R, Roh H, Jung J H, Ahn H M, Lee J H, Yun C O, et al. Antifibrotic Effects of High-Mobility Group Box 1 Protein Inhibitor (Glycyrrhizin) on Keloid Fibroblasts and Keloid Spheroids through Reduction of Autophagy and Induction of Apoptosis. Int J Mol Sci. 2019; 20(17).
64. Lv W, Wu M, Ren Y, Luo X, Hu W, Zhang Q, et al. Treatment of keloids through Runx2 siRNA-induced inhibition of the PI3K/AKT signaling pathway. Mol Med Rep. 2021; 23(1).
65. Lei R, Zhang S, Wang Y, Dai S, Sun J,Zhu C. Metformin Inhibits Epithelial-to-Mesenchymal

Transition of Keloid Fibroblasts via the HIF-1α/PKM2 Signaling Pathway. Int J Med Sci. 2019; 16(7): 960-966.
66. Li Z, Zhang C, Zhang Q, Dong Y, Sha X, Jiang M, et al. Identification of a potential bioinformatics-based biomarker in keloids and its correlation with immune infiltration. Eur J Med Res. 2023; 28(1): 476.
67. Zhou Y, Sun Y, Hou W, Ma L, Tao Y, Li D, et al. The JAK2/STAT3 pathway inhibitor, AG490, suppresses the abnormal behavior of keloid fibroblasts in vitro. Int J Mol Med. 2020; 46(1): 191-200.
68. Lee S Y, Lee A R, Choi J W, Lee C R, Cho K H, Lee J H, et al. IL-17 Induces Autophagy Dysfunction to Promote Inflammatory Cell Death and Fibrosis in Keloid Fibroblasts via the STAT3 and HIF-1α Dependent Signaling Pathways. Front Immunol. 2022; 13(888719.
69. Liu T, Ma X, Ouyang T, Chen H, Xiao Y, Huang Y, et al. Efficacy of 5-aminolevulinic acid-based photodynamic therapy against keloid compromised by downregulation of SIRT1-SIRT3-SOD2-mROS dependent autophagy pathway. Redox Biol. 2019; 20(195-203.
70. Tian Y, Jin L, Zhang W, Ya Z, Cheng Y,Zhao H. AMF siRNA treatment of keloid through inhibition signaling pathway of RhoA/ROCK1. Genes Dis. 2019; 6(2): 185-192.
71. Wang B, Yin H, Zhang H,Wang T. circNRIP1 facilitates keloid progression via FXR1-mediated upregulation of miR-503-3p and miR-503-5p. Int J Mol Med. 2021; 47(5).
72. Darmawan C C, Hur K, Kusumaningrum N, Chung J H, Lee S H,Mun J H. Dasatinib Attenuates Fibrosis in Keloids by Decreasing Senescent Cell Burden. Acta Derm Venereol. 2023; 103(adv4475.
73. Gallant-Behm C L, Piper J, Lynch J M, Seto A G, Hong S J, Mustoe T A, et al. A MicroRNA-29 Mimic (Remlarsen) Represses Extracellular Matrix Expression and Fibroplasia in the Skin. J Invest Dermatol. 2019; 139(5): 1073-1081.
74. Park T H, Kim C W, Choi J S, Park Y J, Chong Y, Park M J, et al. PARP1 Inhibition as a Novel Therapeutic Target for Keloid Disease. Adv Wound Care (New Rochelle). 2019; 8(5): 186-194.
75. Wang M, Chen L, Huang W, Jin M, Wang Q, Gao Z, et al. Improving the anti-keloid outcomes through liposomes loading paclitaxel-cholesterol complexes. Int J Nanomedicine. 2019; 14(1385-1400.
76. Dong Y, Zhang C, Zhang Q, Li Z, Wang Y, Yan J, et al. Identification of nanoparticle-mediated siRNA-ASPN as a key gene target in the treatment of keloids. Front Bioeng Biotechnol. 2022; 10(1025546.
77. Zhou B Y, Wang W B, Wu X L, Zhang W J, Zhou G D, Gao Z, et al. Nintedanib inhibits keloid fibroblast functions by blocking the phosphorylation of multiple kinases and enhancing receptor internalization. Acta Pharmacol Sin. 2020; 41(9): 1234-1245.
78. Satish L, Evdokiou A, Geletu E, Hahn J M,Supp D M. Pirfenidone inhibits epithelial-mesenchymal transition in keloid keratinocytes. Burns Trauma. 2020; 8(tkz007.
79. Zhou J, Shen J Y, Tao L E,Chen H. The Inhibition of Adipose-Derived Stem Cells on the Invasion of Keloid Fibroblasts. Int J Med Sci. 2022; 19(12): 1796-1805.
80. Arjunan S, Gan S U, Choolani M, Raj V, Lim J, Biswas A, et al. Inhibition of growth of Asian keloid cells with human umbilical cord Wharton's jelly stem cell-conditioned medium. Stem Cell Res Ther. 2020; 11(1): 78.
81. Tang Y,Li X. Role and mechanism of Circ-PDE7B in the formation of keloid. Int Wound J. 2023; 20(9): 3738-3749.