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EDITORIAL

Advances and future directions in keloid research: Pathogenesis, diagnosis and personalized treatment strategies

Song-Yun Zhao, Dan Wu, Chao Cheng, Jia-Heng Xie

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Abstract

Keloids, which are abnormal manifestations of wound healing, can result in significant functional impairment and aesthetic deformities. The pathogenesis of keloids is multifaceted and complex and influenced by various factors, such as genetics, the environment, and immune responses. The evolution of keloid treatment has progressed from traditional surgical excision to a contemporary combination of therapies including injection and radiation treatments, among others. This article provides a comprehensive review of keloid pathogenesis and treatment, emphasizing the latest advances in the field. Ultimately, this review underscores the necessity for continued research to enhance our understanding of keloid pathogenesis and to devise more effective treatments for this challenging condition.

Key Words: Keloids; Pathogenesis; Diagnosis; Treatment; Personalized therapy

Core Tip: This article provides a comprehensive review of keloids, which are abnormal outcomes of wound healing. Keloids can lead to dysfunction and aesthetic deformities pathogenesis is influenced by genetic, environmental and immune responses. The evolution of keloid treatment has shifted from traditional surgical excision to modern therapies, including injections and radiation therapy. The article emphasizes the need for continued research to better understand keloid development and improve therapeutic strategies for this complex condition.

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INTRODUCTION

Keloids are a common yet challenging type of skin lesion that can cause significant physical and emotional distress[1]. These irregular growths are the result of an overgrowth of fibroblasts and can occur after various skin injuries, such as surgical incisions and acne[2,3]. Although keloids are not life-threatening, their occurrence in vital or functional areas can greatly impact a patient's appearance and functionality and potentially restrict their mobility[4,5].

Over the years, considerable progress has been achieved by both researchers and clinicians in understanding the fundamental mechanisms of keloid formation and developing effective treatment options[6]. Advances in diagnostic imaging and molecular biology have improved our ability to identify and characterize keloids, while innovative therapeutic approaches, including laser therapy and cryotherapy, present promising alternatives to traditional surgical excision[7-10].

This review focuses on recent advancements in the pathogenesis, diagnosis, and treatment of keloids, emphasizing pivotal research that contributes to our understanding of this intricate disorder. By incorporating the latest findings from both basic research and clinical studies, our aim is to offer a comprehensive overview of the current status of keloid management while also highlighting avenues for further investigation and innovation in this critical field.

THE IMMUNE MICROENVIRONMENT OF KELOIDS PROMOTES THEIR GROWTH

Immune cells present within the keloid microenvironment, including macrophages, T cells, and mast cells, play a crucial role in the initiation and persistence of keloids[11-13]. Macrophages, which are key players in the inflammatory response, exhibit an M2-like phenotype in keloids, which is linked to anti-inflammatory reactions and tissue mending[14]. However, these M2-type macrophages also generate substantial levels of transforming growth factor-β1 (TGF-β1) and vascular endothelial growth factor (VEGF), potentially contributing to the excessive deposition of extracellular matrix (ECM) and the observed angiogenesis in keloids[15].

T cells, which are present in the keloid microenvironment, can produce cytokines that contribute to disease development and progression[16]. Research has revealed the presence of CD4+ and CD8+ T cells in keloids, and there is a predominance of CD8+ T cells[16]. These cells produce cytokines such as interferon-γ, tumor necrosis factor-α, and interleukin (IL)-10, which stimulate fibroblast proliferation and collagen synthesis[16].

Mast cells, which are involved in immune responses, can produce a variety of mediators, including histamines, cytokines, and growth factors, that contribute to keloid development. Studies have shown that mast cells in keloids produce high levels of TGF-β1, thereby promoting fibrosis[17].

Within this immune context, keloid fibroblasts also undergo significant alterations. In comparison to normal skin fibroblasts, these cells exhibit heightened antiapoptotic capabilities and faster proliferation rates[18]. Keloid fibroblasts release various cytokines, including IL-6, IL-8, VEGF-A, and basic fibroblast growth factor, which mediate angiogenesis, fibroblast proliferation, and the deposition of ECM[19]. Furthermore, keloid fibroblasts exhibit a more contractile phenotype than fibroblasts in normal tissues, contributing to the excessive deposition of collagen in keloids[20].

The ECM also plays a significant role in the development of keloids[21]. The ECM has a complex composition involving collagen, elastin, and proteoglycans and offers structural support for the skin[21]. Keloids are characterized by excessive deposition of ECM proteins, particularly collagen, leading to increased tension and firmness in keloid tissues [21].

NUMEROUS SIGNALING PATHWAYS CONTRIBUTE TO THE GROWTH AND MAINTENANCE OF KELOIDS

One critical signaling pathway implicated in the development of keloids is the TGF-β pathway[22]. TGF-β cytokines participate in and promote various cellular processes, including growth, differentiation, and the generation of the ECM [23]. In keloids, there is an abnormal increase in TGF-β expression, leading to increased collagen production and reduced degradation. Consequently, excessive deposition of collagen occurs in the keloid tissue, resulting in a raised and thickened scar.

Another signaling pathway involved in keloid formation is the mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway regulates the proliferation, differentiation, and survival of keloid cells[24]. In keloids, the MAPK pathway is activated, contributing to enhanced cell proliferation and collagen production.

The Wnt/β-catenin pathway is also closely associated with keloids[25]. This pathway regulates cell proliferation and differentiation and is activated in keloids, leading to increased cell proliferation and collagen production, which contribute to the growth and maintenance of keloid tissue[25].

Finally, the Notch signaling pathway is involved in keloid formation. Notch, which is a transmembrane receptor, regulates cell fate and differentiation. In keloids, the Notch pathway is activated, leading to increased cell proliferation and collagen production[26].

ADVANCES IN THE DIAGNOSIS AND TREATMENT OF KELOIDS

The diagnosis of keloids primarily relies on clinical presentation and can be confirmed through biopsy. Keloid treatment can be challenging, and no single method is universally applicable. Treatment options include conservative approaches such as pressure therapy, silicone gel sheets, corticosteroid injections, and more invasive methods such as surgery, cryotherapy, laser therapy, and radiation therapy[1-5].

Conservative measures are typically the initial step in treating keloids[27]. Pressure therapy involves applying pressure to keloids using materials such as pressure bands or patches, which can help flatten keloids, reduce tension, and decrease the risk of recurrence[27]. Intralesional corticosteroid injections can help minimize inflammation and slow the growth of keloids[28].

Surgical removal of keloids is another treatment option; however, the risk of recurrence is high[29]. To mitigate the risk of recurrence, postoperative adjuvant therapies, such as intralesional corticosteroid injections, radiotherapy, or cryotherapy, may be used[29]. Cryotherapy involves freezing keloids with liquid nitrogen, while radiotherapy primarily involves exposing keloids to low doses of radiation, thereby inhibiting the growth and secretion of keloid fibroblasts[30]. Laser therapy can also be used to treat keloids[31]. By using high-intensity lasers to break down scar tissue and promote the growth of new, healthy tissue, this method is less invasive than surgery and carries a lower risk of recurrence[31]. It is worth noting that combination therapy may be more suitable for treating keloids in some cases. For instance, a combination of surgery, radiation, and intralesional corticosteroids may be used to treat large or recurrent keloids.

In summary, the diagnosis of keloids relies on the clinical presentation, and treatment selection depends on factors such as the size, location, and severity of the keloid, as well as the patient's medical history. Despite significant advancements in understanding and treating keloids, the overall therapeutic results remain unsatisfactory. Future research in the field of keloids may concentrate on various areas, including identifying new therapeutic targets, developing more effective treatments, and clarifying the underlying mechanisms of keloid formation and growth.

FUTURE RESEARCH DIRECTIONS IN THE KELOID FIELD

Keloids, which are characterized by excessive scar tissue growth, are thought to have a genetic component, and single nucleotide polymorphisms (SNPs) in various genes have been studied for their potential associations with keloid formation[32]. Candidate genes involved in wound healing, inflammation, collagen production, and ECM regulation, such as TGF-β, ILs, matrix metalloproteinases, and collagen genes, have been investigated for SNPs[33]. Genetic variations in immune response genes, cytokines, and growth factors have also been explored. Ethnic and geographic differences in keloid prevalence may be influenced by genetic factors[34]. However, the genetic basis of keloids remains complex and multifactorial, and while specific genetic markers have been associated with keloids in some studies, the precise mechanisms and markers are not fully understood, and genetic testing is not yet a routine diagnostic tool for keloids. Clinical management primarily involves various treatment options.

A prospective focal point in the field might involve the development of innovative therapies for keloids, such as the use of growth factor inhibitors, immunomodulators, or gene therapies targeting specific signaling pathways implicated in keloid formation and growth. Additionally, the advancement of more efficient drug delivery systems, such as nanoparticles, could enhance the effectiveness of existing therapies[35,36].

Another area of potential exploration is the use of tissue engineering techniques to treat keloids. Exploring the use of stem cells, growth factors, and scaffolds to regenerate healthy tissue and facilitate the healing of keloids could yield promising outcomes[37]. Further advancements in tissue engineering may enable the implementation of personalized therapies tailored to individual patients.

The development of novel diagnostic tools and biomarkers may significantly contribute to the diagnosis and treatment of keloids. Incorporating imaging methods such as magnetic resonance imaging or ultrasound could facilitate improved visualization of keloid tissue and the monitoring of treatment progress[38]. The identification of specific biomarkers, such as cytokines or growth factors, could also aid in the diagnosis and monitoring of keloids. Researchers can determine the underlying mechanisms of keloid formation and growth at the molecular and cellular levels. The identification of key genes, proteins, and signaling pathways involved in keloid formation may lead to the creation of innovative therapies and diagnostic tools. Advancements in genomics, proteomics, and other high-throughput technologies might contribute to the discovery of new targets and pathways[35].

CONCLUSION

In conclusion, the field of keloids is poised for significant advancements in the future with the emergence of new treatments, diagnostic tools, and biomarkers. Progress in tissue engineering, genomics, and other technologies may pave the way for personalized, targeted treatments for keloids.

FOOTNOTES

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