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Il-6 In Osteoarthritis: Expression and Research Progress

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Abstract

Osteoarthritis (OA) is a degenerative joint disease characterized by cartilage degradation, synovial inflammation, and subchondral bone changes. Interleukin-6 (IL-6) is a multifunctional cytokine that plays a significant role in immune responses, inflammation, and hematopoiesis. This review aims to provide a comprehensive overview of IL-6, it signaling pathways, and its role in OA. We will discuss the current understanding of IL-6 signaling and function, the specific signaling pathways related to IL-6 in OA, and the immunohistochemical expression of IL-6 in OA tissues. Despite extensive research, the precise mechanisms by which IL-6 contributes to OA pathogenesis remain unclear, and further investigation is necessary to elucidate its potential as a therapeutic target. This review will summarize the latest findings and highlight areas requiring further exploration to better understand the complex role of IL-6 in OA.

Keywords: interleukin-6; osteoarthritis; cytokine; inflammation; signal transduction; immunohistochemistry

Introduction

Osteoarthritis (OA) is a prevalent degenerative joint disease characterized by the progressive erosion of cartilage, subchondral bone remodeling, and synovial inflammation. Among the various cytokines implicated in the pathogenesis of OA, interleukin-6 (IL-6) has garnered significant attention due to its multifaceted roles in inflammation and joint degradation. Elevated levels of IL-6 have been consistently observed in the synovial fluid and serum of OA patients, correlating with disease severity and progression [1]. This review aims to provide a comprehensive overview of IL-6's expression, signaling pathways, and functional roles in OA, as well as its immunohistochemical characteristics in the disease context

Overview of IL-6

IL-6 is a multifunctional cytokine that plays a crucial role in the immune response, inflammation, and hematopoiesis. It is produced by various cell types, including T cells, B cells, monocytes, fibroblasts, and endothelial cells, in response to infections, tissue injuries, and other inflammatory stimuli [2]. IL-6 exerts its effects through binding to its receptor complex, which consists of the IL-6 receptor (IL-6R) and the signal-transducing component gp130. This binding activates intracellular signaling pathways such as the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, the mitogen-activated protein kinase (MAPK) pathway, and the phosphatidylinositol-3-kinase (PI3K)/Akt pathway [3]. These pathways mediate various biological functions, including the acute phase response, immune cell differentiation, and regulation of metabolic, regenerative, and neural processes [4].

IL-6 is also implicated in the pathogenesis of several chronic inflammatory diseases, including rheumatoid arthritis, inflammatory bowel disease, and, notably, OA [5]. In OA, IL-6 is found in elevated levels in the synovial fluid and serum of patients, correlating with disease severity and progression [6]. The cytokine contributes to OA pathophysiology by promoting the expression of matrix metalloproteinases (MMPs) and other catabolic enzymes that degrade cartilage extracellular matrix components [7]. Additionally, IL-6 can induce the production of other pro-inflammatory cytokines and mediators, creating a feedback loop that exacerbates joint inflammation and damage [8]. Recent studies have highlighted the dual role of IL-6 in OA, where it can also upregulate anti-catabolic factors, suggesting a complex regulatory function that is not yet fully understood [9]. This duality may be attributed to the differential effects of IL-6 classic signaling versus trans-signaling. Classic signaling involves the membrane-bound IL-6R and is typically associated with regenerative and anti-inflammatory responses, whereas trans-signaling, which involves the soluble form of IL-6R, is linked to pro-inflammatory effects [10].

Given its significant role in OA, IL-6 has become a target for therapeutic intervention. Strategies to

inhibit IL-6 signaling, such as the use of monoclonal antibodies against IL-6 or IL-6R, have shown promise in preclinical models and clinical trials [11]. These therapies aim to reduce inflammation, slow disease progression, and alleviate pain, offering new hope for patients with OA [12]. IL-6 is a pivotal cytokine in the inflammatory cascade of OA, influencing both catabolic and anabolic processes within the joint. Understanding the precise mechanisms of IL-6 signaling and its dual roles in OA pathogenesis is crucial for developing effective therapeutic strategies to manage this debilitating disease [13].

IL-6 Signaling and Function

IL-6 is a multifunctional cytokine that plays a critical role in immune responses, inflammation, and hematopoiesis. The signaling pathway of IL-6 involves the binding of IL-6 to its receptor, IL-6R, which then associates with the signal-transducing component gp130. This complex formation triggers the activation of the JAK/STAT pathway, particularly STAT3, which is a significant signaling molecule in regulating IL-6/gp130 signaling and is highly implicated in various pathological conditions [14]. The activation of STAT3 leads to the transcription of various genes involved in cell survival, proliferation, and differentiation. Additionally, IL-6 can signal through classic signaling (cis-signaling) or trans-signaling, where the latter involves the soluble form of IL-6R (sIL-6R) and is associated with chronic inflammation and cancer [15].

IL-6 is known to have both pro-inflammatory and anti-inflammatory effects, depending on the context of the immune response. For instance, IL-6 promotes the differentiation of naïve T cells into Th17 cells in the presence of transforming growth factor-beta (TGF-β), which is crucial in autoimmune diseases [16]. Moreover, IL-6 is involved in the acute phase response by inducing the production of acute-phase proteins such as C-reactive protein (CRP) from the liver [17]. The dual role of IL-6 in inflammation and immune regulation makes it a critical target for therapeutic interventions in various diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, and cytokine release syndrome [18].

The regulation of IL-6 signaling is tightly controlled by various mechanisms, including the expression of suppressors of cytokine signaling (SOCS) proteins and protein inhibitors of activated STAT (PIAS), which act as negative regulators of the JAK/STAT pathway [19]. Dysregulation of IL-6 signaling can lead to chronic inflammatory conditions and has been implicated in the pathogenesis of several cancers, including prostate cancer and esophageal adenocarcinoma [20-21].

In the context of OA, IL-6 has been shown to play a pivotal role in disease progression by promoting the production of matrix-degrading enzymes and inflammatory cytokines [22]. IL-6 can also induce the expression of anti-catabolic factors, suggesting a protective role in certain contexts [23]. The complex role of IL-6 in OA highlights the need for a nuanced understanding of it signaling pathways to develop effective therapeutic strategies. Understanding the intricacies of IL-6 signaling and its regulation is essential for developing targeted therapies for diseases characterized by chronic inflammation and immune dysregulation.

IL-6 Related Signaling Pathways in OA

The role of IL-6 in OA is primarily realized through its complex signaling mechanisms, which involve various cellular and molecular pathways. IL-6 exerts its effects through both classical signaling and trans-signaling. Classical signaling mainly occurs in immune cells, while trans-signaling takes place in various cell types, including fibroblasts and endothelial cells [24]. In OA, IL-6 activates signaling pathways such as JAK/STAT, PI3K/Akt, and MAPK by binding to its receptor, thereby regulating gene expression, promoting inflammatory responses, and matrix degradation [25]. For example, IL-6 promotes the production of inflammatory factors and the expression of hypertrophic markers in chondrocytes through the JAK2/STAT3 pathway [26]. Additionally, IL-6 enhances the inflammatory response and matrix degradation in chondrocytes via the PI3K/Akt/NF-κB pathway [27]. The activation of these signaling pathways not only exacerbates the pathological process of OA but also provides potential targets for treatment.

In the pathological process of OA, IL-6 promotes inflammation and matrix degradation through various mechanisms. Firstly, IL-6 activates the JAK/STAT pathway, promoting the production of inflammatory factors such as TNF-α and IL-1β, which further intensify the inflammatory response [28]. Secondly, IL-6 regulates the expression of MMPs and ADAMTS through the PI3K/Akt pathway, which play a crucial role in cartilage matrix degradation [29]. Furthermore, IL-6 promotes the expression of inflammatory factors and the apoptosis of chondrocytes through the NF-κB pathway [30]. These mechanisms work together to lead to cartilage

degradation and joint destruction, ultimately triggering the clinical symptoms of OA.

Research has shown that blocking the IL-6 signaling pathway can effectively slow the progression of OA. For instance, the use of JAK2 inhibitors can significantly alleviate cartilage degeneration and joint pain [31]. Additionally, inhibitors of the PI3K/Akt/NF-κB pathway have also demonstrated good therapeutic effects [32]. These findings indicate that IL-6 and its related signaling pathways are potential targets for OA treatment. Future research should further explore the specific mechanisms of these signaling pathways and develop specific inhibitors targeting these pathways, aiming to provide more effective treatment options for OA patients.

Immunohistochemical Expression of IL-6 in OA

Immunohistochemical (IHC) analysis has been instrumental in elucidating the role of IL-6 in OA. IL-6 is a pro-inflammatory cytokine that has been implicated in the pathogenesis of OA, contributing to both inflammation and cartilage degradation. Studies have shown that IL-6 levels are significantly elevated in the synovial fluid and synovium of OA patients compared to healthy controls [33]. Immunohistochemical staining techniques have allowed for the visualization and quantification of IL-6 expression in various tissues affected by OA, including cartilage, synovium, and subchondral bone. In OA, IL-6 is predominantly expressed in the synovial lining cells, chondrocytes, and subchondral bone osteoblasts. The increased expression of IL-6 in these tissues correlates with the severity of synovitis and cartilage degradation [34]. For instance, studies have demonstrated that IL-6 expression is markedly higher in the synovium of OA patients with severe synovitis compared to those with mild or no synovitis [35]. This suggests that IL-6 may play a crucial role in the inflammatory processes that exacerbate OA progression. Moreover, IL-6 has been shown to interact with other cytokines and signaling pathways involved in OA. For example, IL-6 can induce the production of MMPs, which are enzymes that degrade cartilage extracellular matrix [36]. Immunohistochemical studies have revealed that IL-6 co-localizes with MMPs in the synovium and cartilage of OA patients, indicating a synergistic role in cartilage breakdown [37]. Additionally, IL-6 can activate the JAK/STAT pathway, further promoting inflammatory responses and cartilage degradation [38].

The role of IL-6 in OA is not limited to its pro-inflammatory effects. IL-6 also influences the metabolic activity of chondrocytes and osteoblasts. Immunohistochemical studies have shown that IL-6 can modulate the expression of anabolic and catabolic genes in these cells, thereby affecting cartilage homeostasis and subchondral bone remodeling [39]. For example, IL-6 has been found to upregulate the expression of catabolic factors such as MMP-13 and downregulate anabolic factors like collagen type II in chondrocytes [40]. This dual role of IL-6 underscores its importance in the pathophysiology of OA. immunohistochemical studies have provided valuable insights into the expression and role of IL-6 in OA. The elevated levels of IL-6 in the synovium, cartilage, and subchondral bone of OA patients highlight its contribution to inflammation and tissue degradation. Understanding the immunohistochemical expression of IL-6 in OA can aid in the development of targeted therapies aimed at modulating IL-6 activity to alleviate OA symptoms and slow disease progression.

Conclusion

IL-6 is a multifunctional cytokine that plays a critical role in the pathogenesis of OA. Its expression in OA has been extensively studied, revealing its involvement in various pathological processes, including inflammation, cartilage degradation, and subchondral bone remodeling. Elevated levels of IL-6 have been detected in the synovial fluid, serum, and cartilage of OA patients, indicating its systemic and local contributions to disease progression [41].

The expression of IL-6 in OA is regulated by several factors, including mechanical stress, hypoxia, and other pro-inflammatory cytokines such as TNF-α and IL-1β. Mechanical stress, a significant factor in OA, induces the production of IL-6 in chondrocytes and synovial cells, contributing to the inflammatory milieu of the joint [42]. Hypoxia, commonly observed in the OA joint environment, also upregulates IL-6 expression through hypoxia-inducible factors (HIFs), further exacerbating inflammation and cartilage degradation [43].

IL-6 mediates its effects through classic signaling and trans-signaling pathways. In classic signaling, IL-6 binds to its membrane-bound receptor (IL-6R), which then associates with the gp130 receptor to initiate intracellular signaling cascades. This pathway is primarily involved in regenerative and anti-inflammatory processes. In contrast, IL-6 trans-

signaling, which involves the binding of IL-6 to a soluble form of IL-6R (sIL-6R), can activate cells that do not express membrane-bound IL-6R, leading to pro-inflammatory responses [44]. This dual mode of action allows IL-6 to have a broad impact on various cell types within the joint, including chondrocytes, cnidocytes, and immune cells.

Research has shown that IL-6 contributes to cartilage degradation by upregulating MMPs and aggrecans, enzymes responsible for the breakdown of cartilage extracellular matrix [45]. Additionally, IL-6 promotes the production of other pro-inflammatory cytokines and chemokines, creating a feedback loop that sustains and amplifies joint inflammation [46]. This cytokine also influences subchondral bone remodeling by affecting the balance between osteoclast and osteoblast activity, leading to bone sclerosis and osteophyte formation [47].

Therapeutic strategies targeting IL-6 signaling have shown promise in preclinical and clinical studies. IL-6 inhibitors, such as tocilizumab, have been evaluated for their efficacy in reducing OA symptoms and slowing disease progression. These inhibitors work by blocking IL-6 from binding to its receptor, thereby preventing the downstream inflammatory effects [48]. Clinical trials have demonstrated that IL-6 blockade can reduce pain and improve joint function in OA patients, although long-term benefits and safety profiles require further investigation [49].

From an expert perspective, the advancements in understanding IL-6's role in OA offer potential therapeutic avenues. Targeting IL-6 or it signaling pathways holds promise for developing novel treatments aimed at mitigating inflammation and slowing disease progression. However, balancing the therapeutic benefits with potential side effects, especially given IL-6's role in normal immune function, remains a critical challenge. Future research should aim to refine these therapeutic strategies, perhaps through more targeted delivery systems or combination therapies that minimize adverse effects while maximizing therapeutic efficacy.

Furthermore, the heterogeneity observed in OA patients suggests that IL-6's role may vary across different stages of the disease and patient populations. Personalized medicine approaches, incorporating genetic, molecular, and clinical data, could enhance the effectiveness of IL-6-targeted therapies. Continued interdisciplinary research, integrating insights from molecular biology, immunology, and clinical studies, will be essential in translating these findings into practical, patient-centered treatments.

In conclusion, IL-6 plays a pivotal role in the pathogenesis of OA through its involvement in inflammation, cartilage degradation, and bone remodeling. Understanding the mechanisms regulating IL-6 expression and it signaling pathways provides valuable insights into potential therapeutic targets for OA management. Future research should focus on elucidating the precise molecular interactions of IL-6 in OA and developing targeted therapies that can effectively modulate its activity without adverse effects [50].

In summary, IL-6 represents a pivotal component in the pathogenesis of OA, with significant implications for disease management and therapy. While considerable progress has been made in elucidating its mechanisms and potential as a therapeutic target, ongoing research is essential to fully harness its potential in improving outcomes for OA patients.

Declarations

Ethics approval and consent to participate

These paper and accompanying images have been published with the consent of the Hospital and Animal Ethics.

Consent for publication

The publication of this paper has been approved by Guangxi Bone Injury Hospital.

Availability of data and materials

The data and materials are authentic and available.

Competing interests

None.

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