HUMAN BIOLOGY
2025, VOL. 95, ISSUE 3
ORIGINAL ARTICLE

OPEN ACCESS

The Role Of IL-6 In Osteoarthritis: A Comprehensive Analysis of Inflammation and Signaling Pathways

Chao Ge[1], Jia Yao[2], LiPeng Gao[1], Yin Shen[1], ChaoXin Liang[3]**

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.

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 Wiegertjes et al. (2020). 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 Wiegertjes et al. (2020)]. 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 Mima et al. 2022. These pathways mediate various biological functions, including the acute phase response, immune cell differentiation, and regulation of metabolic, regenerative, and neural processes Hou et al. 2021.

IL-6 is also implicated in the pathogenesis of several chronic inflammatory diseases, including rheumatoid arthritis, inflammatory bowel disease, and, notably, OA Udomsinprasert et al. 2020. In OA, IL-6 is found in elevated levels in the synovial fluid and serum of patients, correlating with disease severity and progression Nummenmaa et al. 2020. The cytokine contributes to OA pathophysiology by promoting the expression of matrix metalloproteinases (MMPs) and other catabolic enzymes that degrade cartilage extracellular matrix components Chen et al. 2021. Additionally, IL-6 can induce the production of other pro-inflammatory cytokines and mediators, creating a feedback loop that exacerbates joint inflammation and damage Keller et al. 2023.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 Miao et al. 2022. This duality may be attributed to the differential effects of IL-6 classic signaling versus trans-

[1]Guangxi Orthopedic Hospital, Nanning, Guangxi 530012.
[2]The second affiliate hospital of Guangxi medicine university, Nanning, Guangxi 530000
[3]Guangxi Hydroelectric Hospital,Nanning, Guangxi 530219

Corresponding to: ChaoXin Liang[1*,] Guangxi Orthopedic Hospital, Nanning, Guangxi 530012, China. E-mail Address: 969398318@qq.com

Keywords : Interleukin-6 ; Osteoarthritis ; Cytokine, Inflammation ; Signal Transduction ; Immunohistochemistry

signalling. Classic signalling involves the membrane-bound IL-6R and is typically associated with regenerative and anti-inflammatory responses, whereas trans-signalling, which involves the soluble form of IL-6R, is linked to pro-inflammatory effects Liu et al. 2021.

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 Liao et al.2022. These therapies aim to reduce inflammation, slow disease progression, and alleviate pain, offering new hope for patients with OA Gruol et al. 2021. 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 Mihailova et al. 2022.

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 Matsuda et al. 2023. 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 Wiegertjes et al. 2020.

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 Aliyu et al. 2022. 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 Ridker et al. 2021. 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 Zhang et al. 2020.

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 Morris et al. 2021. 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 Culig et al. 2021, Chen et al..2020.

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 Wiegertjes et al. 2020. IL-6 can also induce the expression of anti-catabolic factors, suggesting a protective role in certain contexts Hou et al. 2021. The complex role of IL-6 in OA highlights the need for a nuanced understanding of it signalling pathways to develop effective therapeutic strategies. Understanding the intricacies of IL-6 signalling 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 Wiegertjes et al. 2020. 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 Mima et al. 2022. For example, IL-6 promotes the production of inflammatory factors and the expression of hypertrophic markers in chondrocytes through the JAK2/STAT3 pathway Miao et al. 2022. Additionally, IL-6 enhances the inflammatory response and matrix degradation in chondrocytes via the PI3K/Akt/NF-κB pathway Hou et al. 2021. 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 Liu et al. 2021. Secondly, IL-6 regulates the expression of MMPs and ADAMTS through the PI3K/Akt pathway, which play a crucial role in cartilage matrix degradation Jiang et al. 2021. Furthermore, IL-6 promotes the expression of inflammatory factors and the apoptosis of chondrocytes through the NF-κB pathway Chen et al. 2021. 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 He et al. 2021. Additionally, inhibitors of the PI3K/Akt/NF-κB pathway have also demonstrated good therapeutic effects Chen et al. 2023. 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 Li et al. 2024. 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 Li et al.2021. 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 Choi et al. 2020. 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 Yi et al. 2021. 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 Idota et al. 2021. Additionally, IL-6 can activate the JAK/STAT pathway, further promoting inflammatory responses and cartilage degradation Mével et al. 2022.

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 Lee et al. 2022. 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 Udomsinprasert et al. 2020. 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.

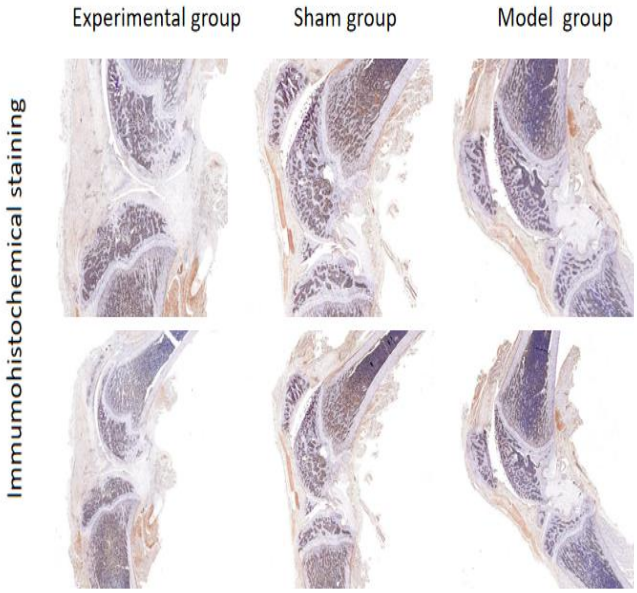
To determine the immunohistochemical expression of IL-6 in osteoarthritis, 30 male SD rats aged 8.5 weeks were selected from the Animal Experiment Center of Guangxi Medical University (License No: SYXK Gui 2020-0004, Ethical Approval No: 202105004). The experimental group (10 rats) underwent no surgical intervention. Twenty SD male rats were anesthetized with 10% chloral hydrate (3 ml/kg) via intraperitoneal injection, and once satisfactory anesthesia was achieved, the rats were placed in a supine position and fixed to the surgical table, followed by routine disinfection and draping. The skin of the left and right hind limbs was shaved with a surgical razor, and the hind limbs were cleaned with gauze soaked in new chlorhexidine, followed by disinfection with iodine. In the model group (10 rats), a 2 cm incision was made parallel to the medial collateral ligament at the left and right knees, with the skin, muscle, and fascia separated in sequence, the joint capsule incised, and the patella displaced at a 90° flexion to open the joint cavity. The anterior cruciate ligament was located and cut with scissors, and a drawer test was performed to ensure complete transection of the anterior cruciate ligament. The joint cavity was flushed

with 0.9% sodium chloride solution, and the joint capsule and skin were sutured. In the sham surgery group (10 rats), only the joint capsule was incised without any further treatment, and then sutured. After all rats recovered, they were returned to their cages. One month later, the articular cartilage tissues from each group of rats were dewaxed and activated for enzyme assays, followed by routine paraffin embedding and sectioning.

Knee joint immunohistochemical staining: The paraffin sections were dewaxed to water, followed by antigen retrieval, and placed in a 3% hydrogen peroxide solution for 25 minutes at room temperature in the dark. The slides were washed 3-5 times in PBS (pH 7.4) on a decolorizing shaker, with each wash lasting 5 minutes, and then blocked with serum for 30 minutes. After removing the blocking solution, the prepared primary antibody was added to the sections, which were then incubated in a humid box at 4°C for 12 hours. The corresponding secondary antibody was applied at room temperature for 50 minutes. The slides were washed 3 times in PBS, with each wash lasting 5 minutes. DAB chromogenic solution was added, and the chromogenic time was controlled under a microscope; a brown-yellow color indicated a positive result, after which the slides were rinsed with running water to stop the reaction. The cell nuclei were stained with hematoxylin, dehydrated, and mounted. The expression of IL-6 related antibodies was detected.

In this study, in the control group, IL-6 antibody showed positive expression in immunohistochemical staining.See Figure 1.

Figure 1: Immunohistochemical manifestations of osteoarthritis pathology in SD rats.



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 Kreimendahl et al. 2020.

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 Ferreira et al. 2020. Hypoxia, commonly observed in the OA joint environment, also upregulates IL-6 expression through hypoxia-inducible factors (HIFs), further exacerbating inflammation and cartilage degradation Liang et al. 2020.

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 Scherger et al. 2020. This dual mode of action allows IL-6 to have a broad impact on various cell types within the joint, including chondrocytes, synoviocytes, and immune cells.

Research has shown that IL-6 contributes to cartilage degradation by upregulating MMPs and aggrecanases, enzymes responsible for the breakdown of cartilage extracellular matrix Santacroce et al. 2020. Additionally, IL-6 promotes the production of other pro-inflammatory cytokines and chemokines, creating a feedback loop that sustains and amplifies joint inflammation Robea et al. 2020. This cytokine also influences subchondral bone remodeling by affecting the balance between osteoclast and osteoblast activity, leading to bone sclerosis and osteophyte formation Iseselo et al. 2020.

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 Kciuk et al. 2020. 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 Seong et al. 2020.

From an expert perspective, the advancements in understanding IL-6's role in OA offer potential therapeutic avenues. Targeting IL-6 or its 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 Jacintho et al. 2020.

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

This 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 Orthopedic Hospital.

Availability of data and materials

The data and materials are authentic and available.

Competing interests

None.

Funding

None.

Authors' contributions

Study concept/design: all.

Data collection: all.

Writing the paper: all.

Critical revision: all.

Acknowledgements

Thanks to Guangxi Orthopedic Hospital for providing the research platform.

Authors' information

Guangxi Orthopedic Hospita, Department director, deputy chief physician.

REFERENCES

1. Wiegertjes R, van de Loo FAJ, Blaney Davidson EN. 2020. A roadmap to target interleukin-6 in osteoarthritis. Rheumatology (Oxford).59(10):2681-94.

2.Wiegertjes R, van de Loo FAJ, Blaney Davidson EN. A roadmap to target interleukin-6 in osteoarthritis. Rheumatology (Oxford). 2020 Oct 1;59(10):2681-2694.

3.Mima Z, Wang K, Liang M, et al. 2022. Blockade of JAK2 retards cartilage degeneration and IL-6-induced pain amplification in osteoarthritis. Int Immunopharmacol. 113(Pt A):109340.

4.Hou CH, Tang CH, Chen PC, et al. 2021. Thrombospondin 2 Promotes IL-6 Production in Osteoarthritis Synovial Fibroblasts via the PI3K/AKT/NF-κB Pathway. J Inflamm Res. 13; 14:5955-67.

5.Udomsinprasert W, Manoy P, Yuktanandana P, et **al.**

2020. Decreased Serum Adiponectin Reflects Low Vitamin D, High Interleukin 6, and Poor Physical Performance in Knee Osteoarthritis. Arch Immunol Ther Exp (Warsz). 24;68(3):16.

6.Nummenmaa E, Hämäläinen M, Pemmari A, et al. 2020. Transient Receptor Potential Ankyrin 1 (TRPA1) Is Involved in Upregulating Interleukin-6 Expression in Osteoarthritic Chondrocyte Models. Int J Mol Sci. 23;22(1):87.

7.Chen X, Li Z, Hong H, et al. 2021. Xanthohumol suppresses inflammation in chondrocytes and ameliorates osteoarthritis in mice. Biomed Pharmacother. 137:111238.

8.Keller LE, Tait Wojno ED, Begum L, et al. 2023. Interleukin-6 neutralization and regulatory T cells are additive in chondroprotection from IL-1β-induced inflammation. J Orthop Res. 41(5):942-50.

9.Miao Z, Dong M, Wang Z, et al. 2022. Linalool inhibits the progression of osteoarthritis via the Nrf2/HO-1 signal pathway both in vitro and in vivo. Int Immunopharmacol. 113(Pt A):109338.

10.Liu JF, Chi MC, Lin CY, et al. 2021. PM2.5 facilitates IL-6 production in human osteoarthritis synovial fibroblasts via ASK1 activation. J Cell Physiol. 236(3):2205-13.

11.Liao Y, Ren Y, Luo X, et al. 2022. Interleukin-6 signaling mediates cartilage degradation and pain in posttraumatic osteoarthritis in a sex-specific manner. Sci Signal. 26;15(744): eabn7082.

12.Gruol DL, Melkonian C, Huitron-Resendiz S, et al. 2021. Alcohol alters IL-6 Signal Transduction in the CNS of Transgenic Mice with Increased Astrocyte Expression of IL-6. Cell Mol Neurobiol. 41(4):733-50.

13.Mihailova A. 2022. Interleukin 6 Concentration in Synovial Fluid of Patients with Inflammatory and Degenerative Arthritis. Curr Rheumatol Rev. 18(3):230-33.

14.Matsuda T. 2023. The Physiological and Pathophysiological Role of IL-6/STAT3-Mediated Signal Transduction and STAT3 Binding Partners in Therapeutic Applications. Biol Pharm Bull. 46(3):364-78.

15. Wiegertjes R, van de Loo FAJ, Blaney Davidson EN. 2020. A roadmap to target interleukin-6 in osteoarthritis. Rheumatology (Oxford).59(10):2681-94.

16.Aliyu M, Zohora FT, Anka AU, et al. 2022. Interleukin-6 cytokine: An overview of the immune regulation, immune dysregulation, and therapeutic approach. Int Immunopharmacol. 111:109130.

17.Ridker PM, Rane M. 2021. Interleukin-6 Signaling and Anti-Interleukin-6 Therapeutics in Cardiovascular Disease. Circ Res. 28;128(11):1728-46.

18.Zhang C, Wu Z, Li JW, et al. 2020. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 55(5):105954.

19.Morris R, Hilton DJ, Jarratt A, et al. 2021. Dissecting the molecular control of Interleukin 6 signaling using the M1 cell line. Cytokine. 146:155624.

20.Culig Z. 2021. Interleukin-6 Function and Targeting in Prostate Cancer. Adv Exp Med Biol. 1290:1-8.

21.Chen M, Ye A, Wei J, et al. 2020. Deoxycholic Acid Upregulates the Reprogramming Factors KFL4 and OCT4 Through the IL-6/STAT3 Pathway in Esophageal Adenocarcinoma Cells. Technol Cancer Res Treat. 19:1533033820945302.

22. Wiegertjes R, van de Loo FAJ, Blaney Davidson EN. 2020. A roadmap to target interleukin-6 in osteoarthritis. Rheumatology (Oxford).59(10):2681-94.

23.Hou CH, Tang CH, Chen PC, et al. 2021. Thrombospondin 2 Promotes IL-6 Production in Osteoarthritis Synovial Fibroblasts via the PI3K/AKT/NF-κB Pathway. J Inflamm Res. 13; 14:5955-67.

24. Wiegertjes R, van de Loo FAJ, Blaney Davidson EN. 2020. A roadmap to target interleukin-6 in osteoarthritis. Rheumatology (Oxford).59(10):2681-94.

25.Mima Z, Wang K, et al. 2022. Blockade of JAK2 retards cartilage degeneration and IL-6-induced pain amplification in osteoarthritis. Int Immunopharmacol. 113(Pt A):109340.

26.Miao Z, Dong M, Wang Z, et al. 2022. Linalool inhibits the progression of osteoarthritis via the Nrf2/HO-1 signal pathway both in vitro and in vivo. Int Immunopharmacol. 113(Pt A):109338.

27. CH, Tang CH, Chen PC, et al. 2021. Thrombospondin 2 Promotes IL-6 Production in Osteoarthritis Synovial Fibroblasts via the PI3K/AKT/NF-κB Pathway. J Inflamm Res. 13; 14:5955-67.

28. Liu JF, Chi MC, Lin CY, et al. 2021. PM2.5 facilitates IL-6 production in human osteoarthritis synovial fibroblasts via ASK1 activation. J Cell Physiol. 236(3):2205-13.

29. Jiang RH, Xu JJ, Zhu DC, et al. 2021. Glycyrrhizin inhibits osteoarthritis development through suppressing the PI3K/AKT/NF-κB signaling pathway in vivo and in vitro. Food Funct. 11(3):2126-36.

30. Chen X, Li Z, Hong H, et al. 2021. Xanthohumol suppresses inflammation in chondrocytes and ameliorates osteoarthritis in mice. Biomed Pharmacother. 137:111238.

31. He L, Pan Y, Yu J, et al. 2021. Decursin alleviates the aggravation of osteoarthritis via inhibiting PI3K-Akt and NF-kB signal pathway. Int Immunopharmacol. 97:107657.

32. Chen Y, Guo W, Lu W, et al. 2023. SNIP1 reduces extracellular matrix degradation and inflammation via inhibiting the NF-κB signaling pathway in osteoarthritis. Arch Biochem Biophys. 747:109764.

33. Li B, Shen E, Wu Z, et al. 2024. BMSC-Derived Exosomes Attenuate Rat Osteoarthritis by Regulating Macrophage Polarization through PINK1/Parkin Signaling Pathway. Cartilage. 19476035241245805.

34. Li M, Li H, Ran X, et al. 2021. Effects of adenovirus-mediated knockdown of IRAK4 on synovitis in the osteoarthritis rabbit model. Arthritis Res Ther. 23(1):294.

35. Choi C, Jeong W, Ghang B, et al. 2020. Cyr61 synthesis is induced by interleukin-6 and promotes migration and invasion of fibroblast-like synoviocytes in rheumatoid arthritis. Arthritis Res Ther. 22(1):275.

36. Yi X, Liu J, Cheng MS, et al. 2021. Low-intensity pulsed ultrasound inhibits IL-6 in subchondral bone of temporomandibular joint osteoarthritis by suppressing the TGF-β1/Smad3 pathway. Arch Oral Biol. 125:105110.

37. Idota M, Ishizuka S, Hiraiwa H, et al. 2021. 4-Methylumbelliferone suppresses catabolic activation in anterior cruciate ligament-derived cells via a mechanism independent of hyaluronan inhibition. J Orthop Surg Res. 16(1):507.

38. Mével E, Shutter JA, Ding X, et al. 2022. Systemic inhibition or global deletion of CaMKK2 protects against post-traumatic osteoarthritis. Osteoarthritis Cartilage. 30(1):124-36.

39. Lee HR, Lee S, Yoo IS, et al. 2022. CD14+ monocytesand soluble CD14 of synovial fluid are associated with osteoarthritis progression. Arch Rheumatol. (3):335-343.

40. Udomsinprasert W, Jinawath A, Teerawattanapong N, et al. 2020. Interleukin-34 overexpression mediated through tumor necrosis factor-alpha reflects severity of synovitis in knee osteoarthritis. Sci Rep. 10(1):7987.

41. Kreimendahl S, Rassow J. 2020. The Mitochondrial Outer Membrane Protein Tom70-Mediator in Protein Traffic, Membrane Contact Sites and Innate Immunity. Int J Mol Sci. 1;21(19):7262.

42. Ferreira C, Viana SD, Reis F. 2020. Gut Microbiota Dysbiosis-Immune Hyperresponse-Inflammation Triad in Coronavirus Disease 2019 (COVID-19): Impact of Pharmacological and Nutraceutical Approaches. Microorganisms. 8(10):1514.

43. Liang Y, Meng Z, Chen Y, et al. 2020. A Data Fusion Orientation Algorithm Based on the Weighted Histogram Statistics for Vector Hydrophone Vertical Array. Sensors (Basel). 20(19):5619.

44. Scherger M, Bolli E, Antunes ARP, et al. 2020. Transient Multivalent Nanobody Targeting to CD206-Expressing Cells via PH-Degradable Nanogels. Cells. 9(10):2222.

45. Santacroce L, Charitos IA, Ballini A, et al. 2020. The Human Respiratory System and its Microbiome at a Glimpse. Biology (Basel). 9(10):318.

46. Robea MA, Jijie R, Nicoara M, et al. 2020. Vitamin C Attenuates Oxidative Stress and Behavioral Abnormalities Triggered by Fipronil and Pyriproxyfen Insecticide Chronic Exposure on Zebrafish Juvenile. Antioxidants (Basel). 9(10):944.

47. Iseselo MK, Tarimo EAM, Sandstrom E, et al. 2020. Sexual Behaviours and Practices before and after Phase I/II HIV Vaccine Trial: A Qualitative Study among Volunteers in Dar es Salaam Tanzania. Int J Environ Res Public Health. 17(19):7193.

48. Kciuk M, Marciniak B, Mojzych M, et al. 2020. Focus on UV-Induced DNA Damage and Repair-Disease Relevance and Protective Strategies. Int J Mol Sci. 21(19):7264.

49. Seong SY, Shim JS, Bang SW, et al. 2020. Overexpression of OsC3H10, a CCCH-Zinc Finger, Improves Drought Tolerance in Rice by Regulating Stress-Related Genes. Plants (Basel). 9(10):1298.

50. Jacintho AEPGA, Cavaliere ISG, Pimentel LL, et al. 2020. Modulus and Strength of Concretes with Alternative Materials. Materials (Basel). 13(19):4378.

