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The Research Progress of LncRNA in Osteoarthritis: Mechanisms and Clinical Applications

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Abstract: In recent years, long non-coding RNA (LncRNA) has garnered widespread attention in the study of osteoarthritis (OA). LncRNA not only plays an important role in the pathogenesis of OA, but also may serve as a potential biomarker and therapeutic target. A large number of studies have shown that LncRNA regulates inflammatory responses and cartilage degeneration, playing a critical role in the pathogenesis of OA. Meanwhile, the expression and function of LncRNA in chondrocytes, macrophages, and fibroblasts have been extensively studied, revealing its importance in cell-cell interactions. The potential of LncRNA as a biomarker has also been preliminarily validated, especially in early diagnosis and assessment of disease severity. Furthermore, the prospects of gene silencing technology and other intervention approaches in targeted LncRNA therapy are promising. However, LncRNA research still faces technical challenges and obstacles in clinical translation. This review summarizes the latest research progress of LncRNA in osteoarthritis, discusses its role mechanisms, relationship with inflammatory responses, effects on chondrocyte metabolism, and potential as a biomarker and therapeutic target, providing a new perspective for future research and clinical applications.

Keywords: LncRNA; Osteoarthritis; Pathogenesis; Biomarker; Therapeutic Target.

1. Introduction

Osteoarthritis (OA) is one of the most common joint diseases worldwide, mainly affecting the elderly population, resulting in joint pain, stiffness and dysfunction[1]. With the intensification of population aging, the incidence of OA increases significantly, seriously affecting patients' quality of life and social and economic burden [2]. Despite the variety of current treatments for OA, there is still a lack of effective means of disease repair and reversal, so there is an urgent need to explore new therapeutic targets and biomarkers.

Long non-coding RNA (LncRNA) is a class of non-coding RNA with a length of more than 200 nucleotides, which has attracted extensive attention in gene regulation research in recent years [3]. Lncrnas regulate gene expression at transcriptional, post-transcriptional and epigenetic levels through various mechanisms, and participate in various biological processes such as cell proliferation, differentiation and apoptosis[4]. Studies have shown that LncRNA plays an important role in the occurrence and development of a variety of diseases, including cancer, neurodegenerative diseases and metabolic syndrome [5]-[6][7]. In recent years, the role of LncRNA in osteoarthritis research has been paid more and more attention. Studies have found that LncRNA has multiple functions in the pathological process of OA, including regulation of chondrocyte metabolism, inflammatory response and matrix degradation [8]-[9]. In addition, LncRNA is also considered as a potential biomarker and therapeutic target for OA, which has important clinical application prospects[10]-[11][12].

This review summarizes the latest research progress of LncRNA in osteoarthritis (OA) and explores its role in OA, its relationship with inflammatory responses, its impact on chondrocyte metabolism, and its potential as a biomarker and therapeutic target. By systematically summarizing existing studies, we aim to provide new perspectives and directions for future research and clinical applications.

In conclusion, the investigation into LncRNA in Osteoarthritis (OA) has elucidated its pivotal role in the pathophysiology of the condition, and has also demonstrated its considerable promise as a diagnostic and therapeutic target. Subsequent chapters will delve into the nuanced mechanisms of action of LncRNA in OA and explore its clinical utility.

1.1. The Role of LncRNA in the Pathogenesis of Osteoarthritis

1.1.1. Regulation of LncRNA on Inflammatory Response

Long non-coding Rnas (lncrnas) play a key role in the regulation of inflammatory responses in osteoarthritis (OA). Studies have shown that lncrnas affect inflammatory responses through multiple mechanisms. For example, the expression of LncRNA HOTAIR was significantly increased in OA chondrocytes, and inhibition of HOTAIR could reduce the expression of OA-related genes [13]. HOTAIR inhibits the expression of Wnt 1 by increasing the trimethylation of histone-H3K27 in the promoter region of Wnt Inhibitor 1 (WIF-1), thereby activating the Wnt/β-catenin signaling pathway and promoting cartilage degradation [1]. In addition, LncRNA GAS5 has been shown to play a regulatory role in a variety of inflammation-related diseases, and its role in OA has been gradually revealed. GAS5 interacts with various mirnas to participate in signal transduction and regulate inflammatory response [14]. These studies suggest that the regulatory roles of lncrnas in OA inflammation are complex and diverse, and a deeper understanding of these mechanisms could help develop new therapeutic strategies.

1.1.2. Relationship between LncRNA and Articular Cartilage Degeneration

LncRNA also plays an important role in the process of articular cartilage degeneration. Studies have found that the

abnormal expression of LncRNA is closely related to the degeneration of OA cartilage. For example, LncRNA XIST is up-regulated in OA chondrocytes, and inhibition of XIST can alleviate cartilage degradation [15]. In addition, LncRNA HOTAIR activated the Wnt/β-catenin signaling pathway by inhibiting the expression of WIF-1, and promoted the degradation of cartilage matrix [16]. Another study showed that LncRNA LOC100130207 and LINC02035 promoted hypertrophic differentiation of chondrocytes by stabilizing RUNX2 protein, thus exacerbating cartilage degradation [17]. These findings suggest that lncrnas play a complex and diverse role in OA cartilage degeneration, and in-depth study of these mechanisms will help reveal the pathological process of OA and provide a theoretical basis for developing new therapeutic targets.

1.2. Interaction of LncRNA with Arthritis-related Cell Types

1.2.1. Expression and Function of LncRNA in Chondrocytes

In osteoarthritis (OA), dysfunction of cartilage cells is a key factor in disease progression. Long non-coding Rnas (LNcrnas) play an important role in regulating various biological processes of chondrocytes, such as proliferation, apoptosis, inflammatory response and extracellular matrix (ECM) degradation. For example, LncRNA H19 promotes the proliferation and migration of chondrocytes and inhibits matrix degradation by regulating the miR-106b-5p/TIMP2 axis[18]. In addition, LncRNA AP001505.9 is significantly down-regulated during chondrocyte dedifferentiation, and its overexpression can inhibit the dedifferentiation of chondrocytes, indicating its important role in maintaining the chondrocyte phenotype[19]. LncRNA DLEU1 regulates the activity, apoptosis and ECM degradation of chondrocytes through the miR-492/TLR8 axis, further revealing the complex mechanism of LncRNA in the regulation of chondrocyte function [20]. These studies suggest that the expression and function of LncRNA in chondrocytes have an important impact on the occurrence and development of OA, and may become a new target for OA treatment.

1.2.2. The Role of LncRNA in Macrophages and Fibroblasts

Macrophages and fibroblasts play key roles in the inflammatory response and tissue remodeling of OA. The expression and function of LncRNA in these cell types have also received widespread attention. For example, LncRNA H19 regulates the interaction between macrophages and chondrocytes through the exosomal miR-106b-5p/TIMP2 axis, promoting cartilage repair [18]. In addition, LncRNA LINC00265 is highly expressed in OA fibroblasts, and it promotes the proliferation, apoptosis, and inflammatory response of fibroblasts by sponging miR-101-3p [21]. These studies show that the mechanisms of action of LncRNA in macrophages and fibroblasts are complex and diverse, possibly affecting the progression of OA by regulating inflammatory responses and intercellular communication. Further research on the mechanisms of action of these LncRNAs will help reveal the pathophysiological processes of OA and provide a theoretical basis for developing new treatment strategies.

1.3. The Potential of LncRNA as Biomarkers in Osteoarthritis

1.3.1. Research Progress of LncRNA as Early Diagnostic Biomarkers

In recent years, the potential of LncRNA as early diagnostic biomarkers in osteoarthritis (OA) has received widespread attention. Studies have shown that LncRNA exhibits specific expression patterns in the blood, synovial fluid, and cartilage tissues of OA patients. For example, the expression level of LncRNA HOTAIR is significantly upregulated in the cartilage tissue of OA patients, and its expression level is closely related to the early pathological changes of the disease [22]. In addition, the expression of LncRNA MEG3 in the synovial fluid of OA patients also shows significant changes, suggesting that it may serve as a non-invasive early diagnostic biomarker [23]. These research results indicate that changes in the expression of LncRNA can reflect the early pathological processes of OA, thereby providing new avenues for early diagnosis.

1.3.2. Correlation between LncRNA and the Severity of Osteoarthritis (OA)

LncRNA not only has potential in the early diagnosis of OA, but is also closely related to the severity of the disease. Studies have found that the expression level of LncRNA GAS5 is significantly downregulated in the cartilage tissue of OA patients, and its expression level is negatively correlated with the severity of cartilage degradation[24]. In addition, the expression level of LncRNA PVT1 is closely related to the joint pain score and imaging score of OA patients, suggesting its potential application value in assessing disease severity [25]. These research results indicate that the expression level of LncRNA can be used as a biomarker for assessing the severity of OA, thereby providing a basis for individualized treatment.

1.4. The Prospects of LncRNA as Therapeutic Targets

1.4.1. Application of Gene Silencing Technology in LncRNA-Targeted Therapy

The application of gene silencing technology in LncRNA-targeted therapy offers new hope for the treatment of osteoarthritis (OA). LncRNA plays an important role in the pathogenesis of OA by regulating gene expression and cellular functions, thus targeting LncRNA with gene silencing technology has become a potential therapeutic strategy. RNA interference (RNAi) is a common gene silencing technique that specifically degrades target LncRNA using small interfering RNA (siRNA) or short hairpin RNA (shRNA), thereby inhibiting its function. For example, studies have shown that siRNA targeting LncRNA HOTAIR can significantly reduce the expression of inflammatory factors in OA chondrocytes and slow cartilage degradation[22]. In addition, the CRISPR/Cas9 system has also been used for gene editing of LncRNA, blocking its expression by specifically cleaving LncRNA genes, thereby achieving therapeutic effects[23]. The application of these gene silencing technologies not only reveals the key role of LncRNA in OA but also provides a theoretical basis for developing new treatment methods.

1.4.2. The Impact of LncRNA Intervention on OA Models

The application of LncRNA intervention in OA models further validates its potential as a therapeutic target. Animal

model studies have shown that specifically inhibiting the expression of certain LncRNAs can significantly improve the pathological features of OA. For example, in a mouse OA model, inhibiting the expression of LncRNA PVT1 can reduce cartilage damage and joint inflammation, improving joint function [24]. Similarly, intervention targeting LncRNA MALAT1 also showed an effect of alleviating OA symptoms, indicating its important role in regulating chondrocyte apoptosis and inflammatory responses[25]. In addition, LncRNA intervention can also promote cartilage repair and regeneration by regulating the intra-articular environment[26]. These research results not only support the feasibility of LncRNA as a therapeutic target for OA, but also provide experimental evidence for future clinical applications.

1.5. Future Research Directions and Challenges

1.5.1. Technical Challenges in LncRNA Research

Despite the immense potential of LncRNA in osteoarthritis (OA) research, its study still faces numerous technical challenges. Firstly, the expression levels of LncRNA are typically low and are highly specific across different tissues and cell types, making their detection and quantification difficult[27]. Additionally, the functional mechanisms of LncRNA are complex and diverse, involving regulation at the transcriptional, post-transcriptional, and translational levels, which increases the difficulty of studying their specific roles[28]. Currently, the main methods for studying LncRNA function include RNA interference (RNAi), CRISPR/Cas9 gene editing technology, and antisense oligonucleotides (ASO), but these methods still have deficiencies in specificity and efficiency[29]. Furthermore, the secondary structure of LncRNA is complex and less stable, posing higher requirements for its functional study and clinical application in vivo[30]. Therefore, more efficient and highly specific technological methods need to be developed in the future to study the mechanisms of LncRNA in OA more accurately.

1.5.2. Potential Barriers to Clinical Translation

LncRNA holds broad prospects for clinical applications in osteoarthritis, but its translation into clinical therapeutics still faces many obstacles. Firstly, the biological functions and mechanisms of LncRNA have not been fully elucidated, especially its specific roles under different pathological conditions[31]. Secondly, the stability and delivery issues of LncRNA also pose significant challenges to its clinical application. LncRNA molecules are large and structurally complex, making them susceptible to degradation by nucleases in the body, and effectively delivering LncRNA to target tissues and cells is an urgent problem to be addressed [32]. Currently, delivery systems such as nanoparticles, viral vectors, and chemical modifications have improved the stability and delivery efficiency of LncRNA to some extent, but their safety and immunogenicity still need further verification [33]. In addition, the specificity and targeting of LncRNA are also key issues for its clinical application. How to avoid non-specific effects and potential side effects of LncRNA in non-target tissues requires further research and optimization [34]. In summary, the clinical application of LncRNA in osteoarthritis still needs to overcome multiple technical and biological barriers. Future research should focus on improving the stability, delivery efficiency, and specificity of LncRNA to promote its clinical translation process.

2. Conclusion

Current research indicates that the importance of LncRNA in osteoarthritis (OA) cannot be overlooked. As an emerging biomolecule, LncRNA not only plays a key role in the pathogenesis of OA but also demonstrates its immense potential as a biomarker and therapeutic target. By regulating inflammatory responses and chondrocyte metabolism, LncRNA plays multiple roles in joint cartilage degradation and pathological changes, providing us with a new perspective to deeply understand the complex pathological mechanisms of OA.

In terms of inflammatory response regulation, LncRNA affects the progression of OA through interactions with various cell types such as chondrocytes, macrophages, and fibroblasts. This discovery not only deepens our understanding of disease mechanisms but also provides a theoretical basis for the future development of LncRNA-based diagnostic and treatment methods.

The potential of LncRNA as a biomarker is also remarkable. Studies have shown that specific LncRNAs exhibit differential expression at different stages and severity levels of OA, providing new tools for early diagnosis and disease monitoring. However, further research and validation are needed to translate these findings into clinical applications.

In terms of therapeutic targets, intervention strategies for LncRNA, such as gene silencing technology, have shown significant efficacy in animal models. This provides strong support for the future development of LncRNA-targeted therapies. However, LncRNA research still faces many challenges, such as technical difficulties and obstacles to clinical translation. Precise identification and regulation of specific LncRNA expression, as well as ensuring its safety and effectiveness in the human body, are important directions for future research.

Overall, research on LncRNA in osteoarthritis is still in its early stages, but its potential cannot be overlooked. Future research should focus on addressing the challenges in existing technologies and clinical translation to promote the application of LncRNA in OA diagnosis and treatment. Through multidisciplinary cooperation and technological innovation, we hope to achieve new LncRNA-based treatment plans for OA in the near future, thereby improving patient quality of life.

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