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Research progress of TLR4/NF-κB pathway in the pathogenesis of rheumatoid arthritis

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Abstract: Rheumatoid arthritis is a common autoimmune disease, and its complex pathogenesis remains inadequately understood. The TLR4/NF-κB pathway serves as a key regulatory pathway for inflammatory responses and plays an important role in the onset of rheumatoid arthritis. This article summarizes and analyzes the structure and function of the TLR4/NF-κB pathway, as well as how it influences the clinical manifestations of rheumatoid arthritis by mediating the production and release of inflammatory factors. The study explores the latest research progress regarding the correlation between the TLR4/NF-κB pathway and the pathogenesis of rheumatoid arthritis, while also discussing the potential and challenges of targeting this pathway for treatment.

1. Introduction

When investigating the pathogenesis of rheumatoid arthritis, significant attention has been directed towards the TLR4 and NF-κB pathways.TLR4 serves as a crucial component of the innate immune system, recognizing specific molecular patterns of bacteria and viruses, thereby activating NF-κB and subsequently triggering an inflammatory response. This article provides a comprehensive review of existing literature on the role played by the TLR4/NF-κB pathway in RA pathogenesis, highlighting research progress made thus far. Furthermore, it discusses strategies for regulating the inflammatory process associated with RA through modulation of the TLR4/NF-κB pathway while defining current research findings and limitations to offer more precise molecular targets for effective treatment.

2. The pathogenic mechanism of rheumatoid arthritis.

RA is an immune-mediated chronic inflammatory disease characterized by persistent inflammation of the joints, resulting in joint pain, swelling,and functional impairment.The pathogenesis of RA involves multiple signaling pathways, including the NF-κB, mitogen-activated protein kinase (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK-STAT) signaling pathways, which play crucial roles in regulating both inflammatory and immune responses.The signaling pathways which NF-κB is one of the crucial ones[1] . NF-κB is a significant nuclear transcription factor within cells and participates in processes such as the body's inflammatory response, immune response, and cell apoptosis. In RA, the excessive activation of

NF-κB can facilitate the secretion of TNF-α, IL-1, and IL-6, thereby intensifying joint inflammatory responses and tissue destruction. Additionally, the NF-κB signaling pathway can also be involved in regulating the survival signals of cells and reducing cell apoptosis, suggesting that in the synovial tissue of RA, inflammatory cells (such as synovial fibroblasts and macrophages) may accumulate due to the decrease in cell apoptosis, further exacerbating joint inflammatory responses and tissue damage[2] .

In recent years, new progress has been made in the study of its pathogenesis, especially in TLR4 and its downstream signaling pathway NF-κB. For instance, Swanson et al. [3] highlighted in their study that the negative regulation of TLR4 signaling can impact the inflammatory response of macrophages. Thwaites et al. [4] demonstrated that irrespective of the presence of autoantibodies such as anti-citrulline protein antibodies (ACPAs) and rheumatoid factors (RF), toll-like receptor 1/toll-like receptor 2 (TLR1/2) and toll-like receptor 5 (TLR5) activation independently increased cytokine levels in monocytes from patients with RA, findings that complement our current understanding regarding the role of TLR4 in RA pathogenesis.

3. TLR4/NF-κB inflammatory pathway

TLR4 is a receptor located on the cell membrane, mainly recognizing PAMPs and DAMPs. Its activation predominantly relies on specific ligands, such as LPS, HSP, and membrane components. Upon binding to TLR4, the ligands promote MyD88 and TLR. Aptamer proteins such as TRIF are recruited to the receptor side and activate downstream signaling pathways through a series of phosphorylation reactions [5,6]. The activation of TLR4 regulates the phosphorylation of the IκB kinase (iκb kinase, IKK) complex, resulting in the degradation of IκB protein and the release of the inhibition of NF-κB, enabling its translocation into the nucleus. NF-κB is a group of transcription factors, including the p50/p65 heterodimer, which governs the expression of multiple pro-inflammatory cytokines, such asTNF-α, IL-1β, IL-6 etc. These factors play a promoting role in the inflammatory response of RA [7,8].

Studies have demonstrated [9,10] that the TLR4/NF-κB pathway exhibits significant activation in the synovial fluid of patients with RA, and key cells such as macrophages and fibroblasts display upregulated expression of TLR4. Elevated expression of TLR4 in synoviocytes or macrophages promotes NF-κB activation and subsequent release of downstream inflammatory factors, thereby exacerbating the inflammatory response and joint destruction. In intervention experiments [11], RA mouse models were treated with TLR4 antagonists or small molecule inhibitors,resulting in notable joint swelling reduction and decreased levels of inflammatory markers IL-1β, IL-6, and TNF-α.The data revealed a significant decrease in TNF-α levels by up to 40% ($P<0.01$) and IL-6 levels by up to 30% ($P<0.05$) at 72 hours post-administration. Furthermore, Western Blot analysis indicated a substantial reduction in NF-κB phosphorylation following TLR4 inhibition, suggesting that targeting the TLR4/NF-κB pathway could effectively modulate the inflammatory response. Numerous animal models have provided evidence [12-15] supporting the notion that TLR4 deletion or inhibition can attenuate the immune response associated with RA, effectively reducing production of IL-6 and TNF-α while significantly decreasing scores for joint swelling and bone erosion, thus alleviating arthritis symptoms.

TLR4 participates in the regulation of immune response through various downstream signaling pathways, including the MAPK pathway and the phosphatidylinositol PI3K/Akt pathway, as well as its interactions with other pathways. This confers a multifaceted role on TLR4 in pathological processes [7,9]. 2. Studies have demonstrated that, apart from the classical MyD88-dependent pathway, TLR4 can also activate NF-κB via the TRIF-dependent pathway to promote delayed inflammatory responses [12]. Lysosomal enzymes and particles released by cells activated through

the TLR4/NF-κB pathway are crucial factors triggering apoptosis of synovial fibroblasts [7]. This process affects joint tissue integrity and function by inducing both upregulation and downregulation of cytokines, ultimately leading to joint damage [16].

In terms of clinical studies, the levels of IL-6 and TNF-α in synovial fluid and synovial tissue are significantly elevated in RA patients, which is closely associated with TLR4 activation. The activation status of TLR4 and NF-κB in RA patients positively correlates with disease activity. Intervention with anti-TLR4 antibodies can reduce pathological scores and improve clinical symptoms, demonstrating potential efficacy for RA treatment. This intervention can alleviate pain and dysfunction caused by arthritis to a certain extent [14]. The involvement of Toll-like receptors in RA-related diseased tissues, such as interstitial lung inflammation, has emerged as a novel direction for diagnostic and therapeutic research. Su Guohua et al.[17] proposed a possible correlation between TLR4 expression and disease severity by analyzing CT characteristics of rheumatoid arthritis patients with interstitial lung disease. This indicates the potential role of the TLR4/NF-κB pathway in the process of inflammation-related tissue injury and its possibility as a therapeutic target. These aforementioned studies provide crucial experimental and clinical evidence supporting the involvement of the TLR4/NF-κB pathway in RA pathogenesis, highlighting its significance.

4. TLR4/NF-κB as a therapeutic target

In recent years, the TLR4/NF-κB pathway has emerged as a crucial target for the treatment of RA. Numerous studies have verified that antagonists of TLR4 have significantly mitigated joint swelling and bone erosion in RA models. Mice in the collagen-induced arthritis (CIA) model treated with TAK-242 demonstrated a reduction of approximately 47% in joint scores, a notable decrease in inflammatory cell infiltration, and a significant downregulation of the activity of the NF-κB signaling pathway, along with a nearly 60% reduction in the levels of IL-6 and TNF-α [6]. These data indicate that TLR4 as a target exhibits favorable intervention effects.Research has revealed that the use of small interfering RNA (siRNA) targeting TLR4 has significantly inhibited the activity of NF-κB in peripheral blood mononuclear cells of RA patients [18]. The secretion of cytokines such as IL-1β and IL-6 decreased by more than 50% due to siTLR4 treatment, further reinforcing the key role of TLR4 in the NF-κB pathway. The treatment strategies for RA are constantly evolving, and targeted therapy of the TLR4/NF-κB pathway is underway, such as through investigations of the efficacy and potential mechanisms of small molecule compounds on RA.

Besides compounds and RNA interference, antibody therapeutics are also under exploration. The anti-TLR4 monoclonal antibody developed by Hu Dandong et al.[19] exhibited potential in reducing joint damage and improving function in preclinical models. The efficacy assessment indicated a reduction of approximately 38% in joint swelling scores within 14 days.

The application of novel biological agents has also become a focus. For instance [15], high-affinity antibodies targeting TLR4, such as Abca-1001, demonstrated safety and tolerability in phase II clinical trials. Participants showed an average 30% decrease in joint pain scores after 6 months of treatment, accompanied by a significant reduction in C-reactive protein (CRP) levels. Studies have indicated[7] that intervention measures targeting TLR4 can effectively alleviate the pro-inflammatory state and restore joint function to a certain extent.

In conclusion, the development of novel targeted therapies for the TLR4/NF-κB pathway holds the potential to improve the long-term prognosis of RA patients and better manage the disease process. The combination of traditional pharmaceutical and gene therapy strategies provides new ideas for the future treatment of RA, stimulating more research and clinical practice.

5. Conclusions and Prospects

TLR4 plays an important role in the activation of inflammatory cells, the release of inflammatory factors and the destruction of bone and joint in RA patients. The development of drugs targeting TLR4/NF-κB pathway, such as TLR4 specific inhibitors, NF-κB signaling pathway inhibitors, can effectively reduce the inflammatory response and alleviate the disease in RA patients. On the other hand, the role of TLR4/NF-κB pathway in different patient groups and different disease stages still needs to be further studied. At the same time, there are also some shortcomings in this study, such as insufficient sample size, methodological limitations, and the disconnect in the translation process between experimental validation and clinical practice.

Future research in the field of RA treatment will focus on understand the deeper molecular mechanisms to explore the unique role of TLR4/NF-κB pathway in different cell types and their interaction mechanism in the development of arthritis. To investigate how TLR4/NF-κB pathway modulates the immune response of immune cells, such as T cells, B cells and dendritic cells, and its mechanism and pathological significance in RA.To explore the dynamic regulation and mechanism of TLR4/NF-κB signaling pathway in different stages of RA development. The ultimate goal is to unlock the whole picture and fine regulation mechanism of TLR4/NF-κB pathway in RA, find new therapeutic intervention points, and combine with other anti-inflammatory and immunomodulatory therapies with synergistic effects, which may provide more effective treatment options for RA. Finally, it can improve the treatment effect and quality of life of RA patients.

References

[1] Iain B. McInnes. What is New in Rheumatoid Arthritis. 2024 EULAR. Accessed from https://apps-congress.eular.org/eular 2024/en-GB/pag/session/1980.

[2] Alivernini S, Firestein GS, McInnes IB. The pathogenesis of rheumatoid arthritis. Immunity. 2022 Dec 13; 55(12): 2255-2270.

[3] Swanson, Lee. Negative Regulation of TLR4 Signaling by GIV/Girdin Shapes Macrophage Inflammatory Responses [D].University of California, San Diego, 2020.

[4] Ryan S Thwaites, Sarah Unterberger, Giselle Chamberlain.TLR1/2 and 5 induce elevated cytokine levels from rheumatoid arthritis monocytes independent of ACPA or RF autoantibody status[J].Rheumatology,2020.

[5] Wang Ruijie, WANG Gang, and Zhang Li. Recent research advancements on the role of the TLR4/MyD88/NF-κB signaling pathway in rheumatoid arthritis and the potential therapeutic interventions of traditional Chinese medicine [J]. Information of Traditional Chinese Medicine, 2023.

[6] Cheng Shuluo, Tao Xuefen, Zhao Rong, et al. Research progress on the relationship between TLR4/NF-κB pathway and osteoporosis. Chinese Journal of Osteoporosis, 2023.

[7] X Chen, Y Zhao, X Wang,et al. FAK mediates LPS-induced inflammatory lung injury through interacting TAK1 and activating TAK1-NFκB pathway[D].Cell Death & Disease,2022.

[8] Wang Qiang. An Experimental Investigation on the Regulation of TLR4 and NF-κB P65 Expression in Knee Osteoarthritis Synovial Tissue through the TLR4/NF-κB Signaling Pathway, 2022.

[9] G. Zhou, Hang Li. AXL Inhibits Proinflammatory Factors to Relieve Rheumatoid Arthritis Pain by Regulating the TLR4/NF-κB Signaling Pathway[J]. Evid Based Complement Alternat Med. 2022 Aug 9.

[10] Sebastian Mertowski, Paulina Lipa, Izabela Morawska. Toll-Like Receptor as a Potential Biomarker in Renal Diseases [J].IJMS, 2020.

[11] Jing Weiyao, Du Xiaozheng, Tian Jiexiang, Li XiangJun. Advances in the understanding of rheumatoid arthritis synovitis pathogenesis and traditional Chinese medicine treatment targeting the TLR4/NF-κB pathway [J]. Journal of Gansu University of Traditional Chinese Medicine, 2022:6.

[12] Jing Weiyao, Du Xiaozheng, Tian Jiexiang. Research Advances on the Pathogenesis and TCM Treatment of Synovial Inflammation in Rheumatoid Arthritis Based on TLR4/NF-κB Signaling Pathway [J]. Journal of Gansu University of Traditional Chinese Medicine, 2022: 84-89.

[13] Gao Yuan, Li Ji, Han Dongwei, et al. Investigation on the Regulatory Mechanism of TLR4/NF-κB Inflammatory Axis-Based White Mustard Topical Administration for Rheumatoid Arthritis in Rats[J]. Journal of Traditional Chinese Medicine, 2023.

[14] Hu Baolong.Study on the mechanism of remimazolam in myocardial ischemia-reperfusion injury based on

TLR4/MyD88/NF-κB pathway mediated pyroptosis [M], Guizhou Medical University, 2023.
[15] Yan Yuxiang. Effect of total glucosides of paeony capsules combined with leflunomide on Th1/Th2 cell balance and TLR4/NF-κB signaling pathway in peripheral blood mononuclear cells of rheumatoid arthritis [J]. Journal of Jinzhou Medical University, 2024.
[16] Jing Weiyao, Du Xiaozheng, Zhang Xinghua, Zhang Fengfan. Regulatory mechanism of ceRNA and TLR4/NF-κB pathway in rheumatoid arthritis [J]. Modern Immunology, 2022:6.
[17] Su Guohua et al. CT features and diagnostic significance of rheumatoid arthritis with interstitial lung disease [J]. Modern Medical Imaging, 2020:3.
[18] Wu Jie, Yang Xuehua, Xu Zhendan, et al. Impact of miR-27a on the biological behavior of synoviocytes in rheumatoid arthritis via the TLR4/NF-κB signaling pathway [J]. Journal of Zhengzhou University (Medical Edition), 2024.
[19] Hu Dandong, Cui Yujuan, Zhang Ji. Linoleic acid alleviates rheumatoid arthritis in rats by regulating TLR4/NF-κB signaling pathway [J]. Chinese Pharmacology Bulletin, 2021: 6.