Acta Scientific Microbiology (ISSN: 2581-3226)

Volume 7 Issue 8 August 2024

Research Article

Ror β proteins - Novel Target Discovered for Potentially Treating and Preventing Osteoarthritis of Tmj - A Systematic Review

Namitha MV[1]*, Merina Antony[1], Gaurav[2] and Karthik A[3]

[1]House Surgeon, Coorg Institute of Dental Sciences, Virajpet, Karnataka, India

[2]Associate Professor, Department of Oral Medicine and Radiology, Coorg Institute of Dental Sciences, Virajpet, Karnataka, India

[3]Assistant Professor, Department of Oral Medicine and Radiology, Coorg Institute of Dental Sciences, Virajpet, Karnataka, India

***Corresponding Author:** Namitha MV, House Surgeon, Coorg Institute of Dental Sciences, Virajpet, Karnataka, India.

DOI: 10.31080/ASMI.2024.07.1417

Received: July 15, 2024

Published: July 29, 2024

Abstract

ROR β (Retinoic acid-related Orphan Receptor beta) proteins are members of the nuclear receptor superfamily of transcription factors. They play important roles in various biological processes such as cell differentiation, immune function, metabolism, and circadian rhythm regulation. Recently several preclinical studies have demonstrated the potential of ROR beta agonists as a therapeutic approach for osteoarthritis. A recent study showed that a ROR beta agonist reduced the expression of inflammatory cytokines and enzymes in chondrocytes from osteoarthritic cartilage and also the inhibition of ROR beta signaling reduced cartilage destruction in a mouse model of osteoarthritis. Furthermore, it also demonstrated the potential of a ROR beta agonist in promoting cartilage repair and reducing joint inflammation in osteoarthritis. This systematic review aims to highlight the significance of ROR β proteins as a promising therapeutic approach for Osteoarthritis of Temporomandibular Joint (TMJ).

Keywords: Osteoarthritis; ROR Beta Protein; Targeted Therapy; ROR Beta Agonist; Joint Inflammation

Introduction

Osteoarthritis (OA) of TMJis the most common chronic degenerative joint disease, with its risk increasing due to age and obesity. OA tends to develop later in life after years of mechanical wear and tear on cartilage, which cushions and lines the joints. Current treatments primarily focus on alleviating pain, and there are no effective methods to slow the disease's progression. Over time, OA leads to irreversible cartilage loss, and when the articular cartilage is severely damaged or completely lost, joint replacement surgery becomes necessary. Although the exact link between aging and OA development remains unclear, it is evident that age-related changes in the musculoskeletal system, along with mechanical injuries and genetic factors, contribute to the disease's pathogenesis [1].

ROR beta (Retinoic acid-related Orphan Receptor beta) proteins belong to the nuclear receptor superfamily of transcription factors. They are crucial in numerous biological processes, including cell differentiation, immune function, metabolism, and the regulation of circadian rhythms. ROR beta proteins are associated with several diseases, including cancer, autoimmune disorders, and metabolic conditions. ROR beta has demonstrated tumor-suppressive properties in certain cancers, and ROR beta agonists are being investigated as potential treatments for autoimmune diseases like multiple sclerosis. Numerous studies have demonstrated that ROR beta expression is elevated in the cartilage and synovial tissue of osteoarthritic joints. Additionally, ROR beta is involved in regulating the production of inflammatory cytokines and enzymes that lead to cartilage degradation [2,3].

Aim of the Study

To determine the significance of targeting ROR β protein in potentially preventing and treating osteoarthritis.

Research question

Will targeting ROR beta proteins be an ultimate solution for TMJ Osteoarthritis in completely curing it?

- **Null hypothesis:** Targeting ROR beta proteins will treat TMJ Osteoarthritis.
- **Alternate hypothesis:** Targeting ROR beta proteins will not treat TMJ Osteoarthritis.

Materials and Methodology

Numerous research endeavours and studies have been conducted on this topic to date. Referencing the Cochrane Collaboration and other scientific databases like Medline and Medknow, 36 research articles were initially selected, each having undergone a definitive Randomized Controlled Trial (RCT). Out of these, 22 articles passed the screening process and were ultimately chosen for inclusion in our study, following the predetermined inclusion and exclusion criteria outlined below.

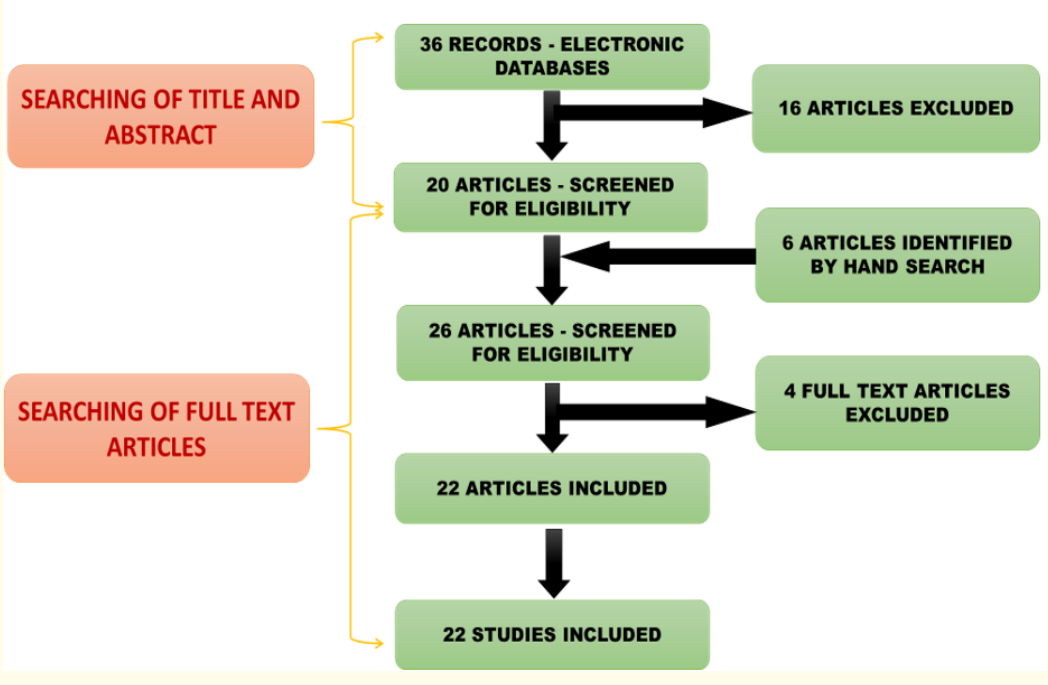

Figure 1

Result

The result, obtained after statistical analysis, has shown significant alignment with the null hypothesis, indicating that targeting the ROR beta protein is definitely effective in preventing and treating TMJ Osteoarthritis.

Discussion

Osteoarthritis is a degenerative joint disease that primarily targets the articular cartilage, the smooth, cushioning tissue that covers the ends of bones in a joint. Over time, this cartilage can become damaged and worn down, resulting in pain, stiffness, and reduced mobility in the affected joint. Osteoarthritis can develop in any joint, but it most commonly affects the TMJ, hands, knees, hips, and spine. Clinical manifestations include joint pain, stiffness, decreased range of motion, swelling, cracking or popping sounds, bone spurs etc [1].

The molecular pathophysiology of osteoarthritis is explained by nf-kaeppab signalling pathway.

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that plays a crucial role in regulating the immune response and inflammation [4].

NF-κB is activated in response to pro-inflammatory cytokines such as IL-1β and TNF-α, which are elevated in osteoarthritic joints. Once activated, NF-κB translocates to the nucleus and induces the

expression of various inflammatory mediators, including cytokines, chemokines, and adhesion molecules, contributing to chronic inflammation in the joint [5].

NF-κB then upregulates the expression of matrix metalloproteinases (MMPs) and aggrecanases (such as ADAMTS-13 and ADAMTS-5). These enzymes degrade extracellular matrix components like collagen and aggrecan in the cartilage, leading to cartilage breakdown and joint damage [6].

NF-κB activation can promote apoptosis (programmed cell death) of chondrocytes, the cells responsible for maintaining cartilage. The loss of chondrocytes exacerbates the degeneration of cartilage in OA [7].

NF-κB is also involved in the formation of osteophytes (bone spurs) by influencing the activity of osteoblasts and osteoclasts, the cells responsible for bone formation and resorption. Osteophyte formation contributes to joint stiffness and pain in OA [7].

NF-κB activation in synovial cells leads to synovial inflammation, which further contributes to joint pain and swelling. The inflamed synovium produces more pro-inflammatory cytokines and catabolic enzymes, creating a vicious cycle of inflammation and tissue degradation [3].

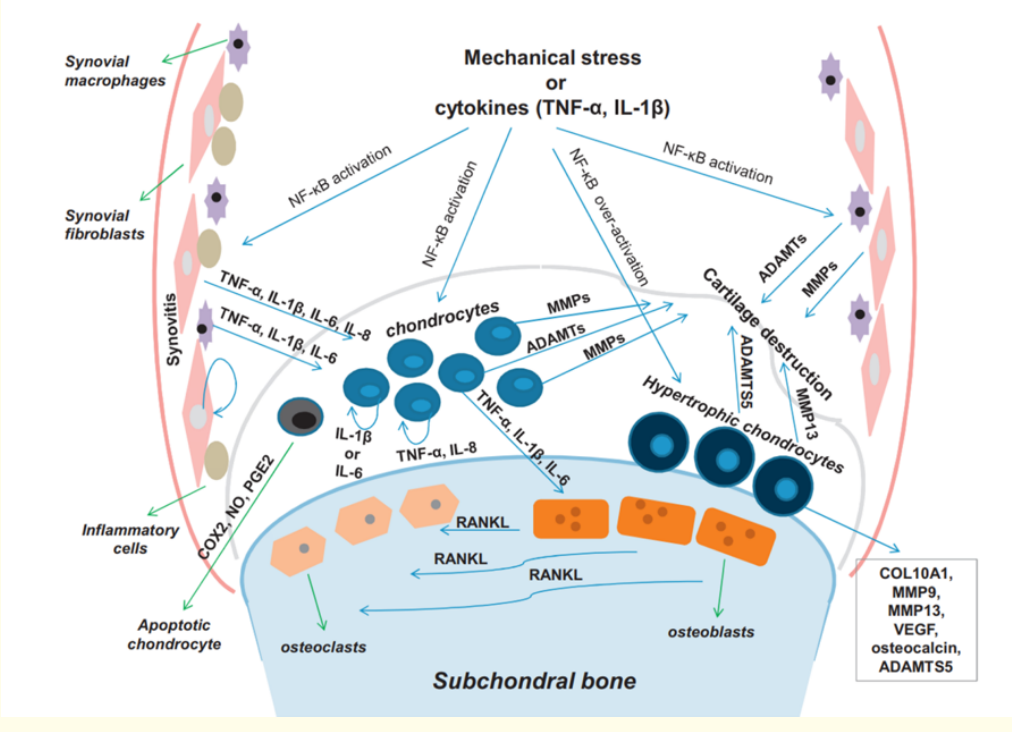

Figure 2: Molecular Pathophysiology of Osteoarthritis [5].

Molecular mechanism of osteoarthritis is clinically manifested as [8]:

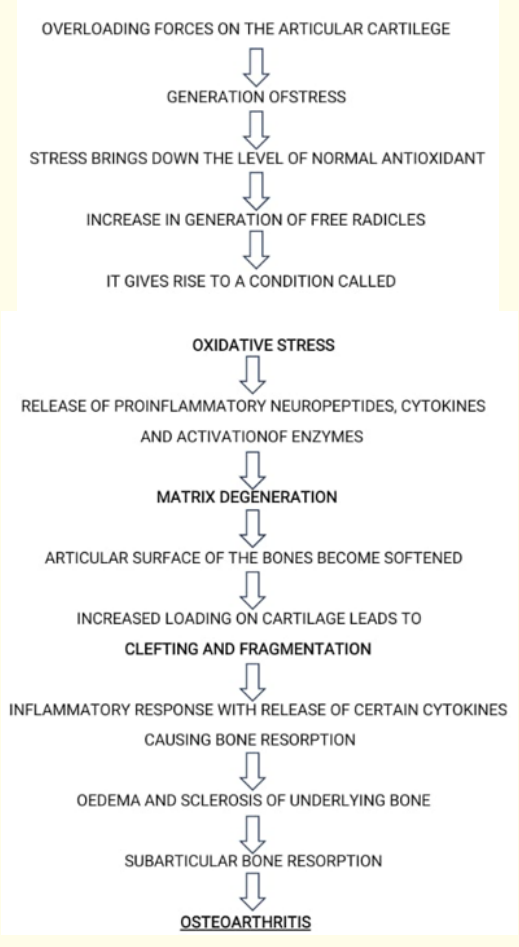

Figure 3

Function of ror-β

ROR-β (Retinoic acid-related Orphan Receptor beta) is a member of the nuclear receptor superfamily of intracellular transcription factors. These receptors are involved in the regulation of various physiological processes, including development, metabolism, and the immune response. ROR-β has been identified to have anti-inflammatory properties [2].

ROR-β plays a role in the regulation of various physiological processes, including the immune response. Its presence can inhibit the activation of NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) by interfering with its binding to DNA. NF-κB is a transcription factor that controls the expression of various proinflammatory cytokines and enzymes. By inhibiting NF-κB, ROR-β helps reduce inflammation and protect joints from damage [2].

Inhibition mechanism

Interference with NF-κB Activation

- **Binding Interference:** RORβ can interfere with NF-κB's ability to bind to DNA. NF-κB activates the transcription of proinflammatory genes by binding to specific sequences in their promoters. When RORβ is present, it can inhibit this binding process, thereby reducing the transcription of these genes [5].
- **Reduction of Proinflammatory Molecules:** By preventing NF-κB from binding to DNA, RORβ reduces the expression of proinflammatory cytokines (like TNF-α, IL-1β, IL-6) and enzymes (like COX-2 and iNOS). These molecules are key players in the inflammatory response, and their reduction leads to decreased inflammation [3].

Protective effect on joints

In diseases like osteoarthritis and rheumatoid arthritis, chronic inflammation leads to joint damage and destruction. By inhibiting NF-κB, ROR-β helps to reduce inflammation and the resulting damage to the joint tissues. This protective effect is beneficial in managing and potentially preventing the progression of inflammatory joint diseases [2].

Conclusion

In conclusion, the emerging evidence from recent preclinical studies underscores the significant potential of ROR β proteins as a therapeutic target for osteoarthritis. The findings highlight that ROR β agonists can effectively reduce the expression of inflammatory cytokines and enzymes in chondrocytes derived from osteoarthritic cartilage, suggesting an anti-inflammatory role. Additionally, the inhibition of ROR β signalling has been shown to mitigate cartilage destruction in a mouse model of osteoarthritis, further emphasizing its protective effects on cartilage. Moreover, the potential of ROR β agonists in promoting cartilage repair and reducing joint inflammation provides a promising avenue for developing novel osteoarthritis treatments. Collectively, these insights advocate for further research and development of ROR β-targeted therapies, which could revolutionize the management of osteoarthritis and improve patient outcomes.

Bibliography

1. JP Pelletier., *et al*. "Etiopathogenesis of osteoarthritis". W.J. Koopman (Ed.), Arthritis and Allied Conditions. A textbook of Rheumatology (13 edn.), Williams & Wilkins, Baltimore (1997): 1969-1984.

2. Anton M Jetten., *et al*. "The ROR nuclear orphan receptor subfamily: Critical regulators of multiple biological processes". *Progress in Nucleic Acid Research and Molecular Biology* 69 (2001): 205-247.

3. Matthew M Roforth., *et al*. "Identification of Rorβ targets in cultured osteoblasts and in human bone". *Biochemical and Biophysical Research Communications* 440.4 (2013): 768-773.

4. Mi Ra Chang., *et al*. "RORβ modulates a gene program that is protective against articular cartilage damage". *Plos One* 17.10 (2022).

5. Stella Rigoglou., *et al*. "The NF-B signalling pathway in osteoarthritis". *The International Journal of Biochemistry and Cell Biology* 45 (2013) 2580-2584.

6. LX Chen., *et al*. "Suppression of early experimental osteoarthritis by in vivo delivery of the adenoviral vector-mediated NF-κBp65-specific siRNA". *Osteoarthritis and Cartilage* 16 (2008)174-184.

7. Ruben Aquino-Martinez., *et al*. "miR-219a-5p Regulates Rorβ During Osteoblast Differentiation and in Age-related Bone Loss". *Journal of Bone and Mineral Research* 34.1 (2019): 135-144.

8. Qing Yao., *et al*. "Osteoarthritis: pathogenic signaling pathways and therapeutic targets". *Signal Transduction and Targeted Therapy* 8.56 (2023).