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Therapeutic implications of 14-3-3 zeta protein in rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease characterized by joint destruction accompanied by inflammatory, systemic complications. Its chronic and progressive course severely affects the quality of life of patients. Recent animal studies have shown that the application of 14-3-3 zeta (14-3-3ζ) during the pre-symptomatic phase through active immunological function suppresses pro-inflammatory cytokines such as interleukin-1beta, while increasing the anti-inflammatory interleukin-1 receptor antagonist levels and collagen synthesis, thus preserving joint and bone quality. However, when anti-14-3-3ζ antibodies were applied through passive immunization, the same effect was not observed. These findings suggest that the 14-3-3 protein family may be used in the diagnosis and treatment of RA and has significant potential. This review examines the pathophysiology of RA, the multifunctionality of the 14-3-3 protein family, and the therapeutic potential of 14-3-3ζ.

Keywords: 14-3-3 zeta, bone loss, interleukin-1beta, rheumatoid arthritis, vaccine.

Rheumatoid arthritis (RA) is a chronic, systemic, progressive autoimmune disease characterized by synovial inflammation, leading to joint destruction and deformity, as well as severe functional loss and multi-organ involvement.[1] Rheumatoid arthritis affects women 2-3 times more than men.[2] The peak age of the disease is between 50 and 60 years, and it occurs in approximately 0.5-1% of the population worldwide.[3] Rheumatoid arthritis, in which immune system dysfunctions and chronic inflammation play a role in its pathogenesis, poses a significant public health burden due to its insidious onset, progressive course, and complex treatment processes.[4] According to the World Health Organization, within 10 years of the onset of the disease, 50% of patients are unable to continue their full-time jobs due to the disabilities that develop.[1] Rheumatoid arthritis is a heterogeneous disease characterized by variable clinical presentations and different pathogenic processes, which can occur in individuals with the same diagnosis or at different stages of the disease. Its primary features include symmetrical pain and swelling, often affecting the hands, wrists, feet, and knees (polyarthritis), although other joints may also be involved. While it is a non-fatal disease in its early stages, if left untreated, symptoms related to the involvement of additional organs, such as interstitial lung disease, pericarditis, pleural effusion, or bronchiectasis, may develop over time. Considering the long-term disease complications, RA is associated with a shortened life expectancy.[5] Early diagnosis and treatment are crucial to prevent the polyarthritis and systemic complications caused by the disease.[6]

The 14-3-3 protein family first discovered in 1967 in bovine brain homogenate, consists of a group of regulatory proteins that are found in all eukaryotic cells and are highly conserved.[7] Although they share a common core structure, this family consists of seven different isoforms-beta, gamma, epsilon, eta, sigma, tau/theta, zeta (β, γ, ε, η, σ, τ/θ, and ζ)-each encoded by different genes.[8] Each protomer, with a molecular weight of approximately 30 kDa, consists structurally of nine antiparallel alpha-helices. These helices form ligand-binding grooves that interact with

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target proteins containing phosphoserine/phosphothreonine through phosphorylation-dependent binding mechanisms.[9] The 14-3-3 proteins, which exist in a dimeric structure, are stabilized by hydrophobic and electrostatic interactions. Their dimeric form serves as a molecular scaffold, stabilizing multiple binding sites on target proteins and thereby regulating signal transduction.[10] Due to all these characteristics, 14-3-3 proteins play a critical role in the regulation of various signaling pathways and cellular functions, such as the cell cycle, apoptosis, metabolic regulation, autophagy, and stress response.[10,11]

The specific biological roles of each isoform of the 14-3-3 protein family in different tissues enhance the functional diversity of the family. For example, the 14-3-3 zeta (14-3-3ζ) isoform plays a critical role in the regulation of inflammatory processes and immune responses, while other isoforms target different signaling pathways to support cellular homeostasis. These versatile regulatory functions in cellular signaling pathways have made the 14-3-3 protein family particularly significant in the study of various pathophysiological conditions, especially autoimmune and inflammatory diseases.[7]

THE PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

In the pathogenesis of RA, an autoimmune disorder, the cellular components of the immune system, particularly B and T lymphocytes, macrophages, and the cytokines they secrete, play a critical role. These cells can be present in the synovium or circulate in peripheral blood. This section provides an overview of the roles of various immune cells and cytokines involved in RA pathogenesis.

B Lymphocytes

B cells are an important component of the human adaptive immune system. However, they are also one of the underlying factors in cases of RA. Autoreactive B cells are those that recognize the host's antigen and are responsible for the destruction of such cells and tissues.[12] In a healthy individual, autoreactive B cells are eliminated through repair mechanisms during the maturation process in the bone marrow. These repair mechanisms are divided into two categories: central and peripheral B cell checkpoints. In patients with RA, dysfunction of these checkpoints leads to the production of autoreactive B cells.[13] Genetic mutations, such as those in the PTN22 gene, have been shown to play a role in the disruption of central tolerance, while an increase in the levels of B cell activating factor in the serum contributes to the breakdown of peripheral tolerance. These conditions prolong the survival of autoreactive B cells and exacerbate autoimmune conditions.[14,15]

Although the underlying mechanisms by which autoreactive B cells target host cells remain to be fully clarified, autoantibodies associated with RA have been identified, and the list continues to expand over time.[12] The two most studied antibodies, rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), contribute to the intensification of the inflammatory process by facilitating their production through autoreactive B cells.[16] Rheumatoid factor activates the complement system by binding to the Fc region of immunoglobulin G, while ACPA reacts against citrullinated proteins such as filaggrin, fibrinogen, vimentin, collagen II, enolase, and histones, playing a role in the progression of the disease.[16,17] These autoantibodies not only increase inflammation but also play a role in the activation of T cells and the damage to synovial tissues.[12]

T Lymphocytes

Although studies have been conducted in recent years to understand the effects and activation of T cells in RA, their roles have not yet been fully defined. However, it is known that CD4+ T cells play a significant role in the chronic autoimmune effects of RA. After being activated by antigen-presenting cells, such as macrophages and dendritic cells, CD4+ T cells undergo maturation via the phosphoinositide 3-kinase signaling pathway, thereby participating in pro-inflammatory processes.[18,19]

It is known that T helper (Th) cells contribute to the pathogenesis of RA through the secretion of various cytokines and chemokines.

Cytokines such as interferon-gamma (IFN-γ) and anti-tumor necrosis factor alpha (TNF-α), secreted by Th1 cells, support macrophage activity and increase inflammation.[18,20] Th17 cells, by producing interleukin (IL)-17, contribute to osteoclastogenesis and pannus formation.[21] Additionally, T cells contribute to the pathogenesis of RA by activating B cells, which increases the production of autoantibodies.[22]

Macrophages

Macrophages play a crucial role in synovial inflammation and joint destruction by secreting pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, and enzymes like matrix metalloproteinases. These secreted cytokines exacerbate inflammation by damaging articular cartilage and bone tissue.[23,24] In the treatment of RA, promoting the transformation of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype is considered a promising target for new therapeutic approaches.[25]

Cytokines

Pro-inflammatory cytokines, which play important roles in the pathogenesis of RA, are proteins that function as mediators in cell signaling.[26,27] Pro-inflammatory cytokines such as TNF-α, IL-6, and IL-17 increase inflammation, leading to damage in joint cartilage and bones. The TNF-α, which activates B and T lymphocytes, exacerbates synovial inflammation.[28] Interleukin-17 induces immune cell infiltration in the synovium, triggering neoangiogenesis and osteoclastogenesis present in the pathogenesis of RA. Interleukin-6 regulates acute phase responses and increases autoantibody production.[29] These pro-inflammatory cytokines typically cause cytokine-mediated inflammation by suppressing the protective effects of anti-inflammatory cytokines such as IL-4 and IL-10.[28]

Cellular and immune regulatory roles of 14-3-3 proteins

14-3-3 proteins regulate the activities of the proteins they bind to, influencing a wide range of cellular processes. By stabilizing the active conformations of the proteins they bind to, they enhance their functions or prevent unwanted interactions. An example of this is 14-3-3ζ, which stabilizes the enzyme arylalkylamine N-acetyltransferase, thereby increasing melatonin production.[30] Additionally, 14-3-3 proteins regulate the intracellular distribution of target proteins by masking their nuclear localization signals. This is particularly important in the regulation of forkhead box-O transcription factors. Moreover, due to their dimeric structure, 14-3-3 proteins contribute to the formation of signaling complexes by bringing together different target proteins. An example of this mechanism is the regulation of v-Raf murine sarcoma viral oncogene homolog B kinase.[31] The 14-3-3 protein family influences the immune system through processes such as apoptosis, regulation of inflammation, and T-cell signaling. While contributing to the maintenance of homeostatic balance in the immune system, they prevent cell death in apoptosis regulation by sequestering pro-apoptotic proteins within the cell.[32] In addition to these functions, it is also known that 14-3-3 proteins activate *Pseudomonas aeruginosa* exotoxins, thereby increasing the virulence of the pathogen.[33]

The 14-3-3ζ is a particularly noteworthy protein, being widely expressed in various tissues, especially the human brain. Its roles in neuronal plasticity and synaptic signaling increase its therapeutic significance in central nervous system disorders. Additionally, the overexpression of 14-3-3ζ in certain cancer types makes it of oncological importance as well.[34] In the absence of 14-3-3ζ, the transformation of macrophages into osteoclasts increases, accelerating bone degradation.[35]

All these characteristics suggest that the 14-3-3 protein family could play a crucial role not only in the treatment of RA but also in the treatment of various other diseases.

As important adaptor proteins regulating immune responses, the effects of the 14-3-3 protein family on the immune system are of critical importance in understanding inflammatory and autoimmune diseases. 14-3-3 proteins regulate signaling pathways through phosphoserine/phosphothreonine binding regions, influencing the activation,

polarization, and function of immune cells.[34] It plays a role in the modulation of various immune signaling pathways, such as Janus kinase/signal transducer and activator of transcription, nuclear factor kappa-light-chain-enhancer of activated B cells, and mitogen-activated protein kinase pathways. For example, it can control the severity of inflammation by regulating the balance between macrophages' M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes. Additionally, it modifies immune processes, such as the production of pro-inflammatory cytokines and the induction of anti-inflammatory mediators.[7]

The biomarker potential of 14-3-3 proteins in the diagnosis and monitoring of rheumatoid arthritis

Currently, two groups of biomarkers are used for RA classification criteria. The first group includes antibodies such as RF and ACPA, while the second group consists of inflammation markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).[36] However, the serological biomarkers used do not appear in about one-third of patients.[37] However, ESR and CRP can appear at normal levels in 35 to 45% of patients, especially in the early stages. These findings highlight the need to discover potential new biomarkers for RA, which are crucial for the diagnosis and treatment of the disease.[38] In addition to being important for potential therapy in RA, 14-3-3 proteins are also significant for the diagnosis of RA. Studies have shown that the levels of 14-3-3ζ are noticeably elevated in RA patients compared to healthy control groups.[39,40] In another study, when the levels of 14-3-3ζ were examined between patients with ankylosing spondylitis and healthy individuals, no significant difference was found. These findings suggest that 14-3-3ζ has diagnostic value in distinguishing RA from other arthropathies, connective tissue disorders, and autoimmune diseases, indicating that it is a highly specific biomarker for RA.[41] Additionally, in RA patients treated with methotrexate, adalimumab, tocilizumab, and tofacitinib, a significant decrease in 14-3-3ζ levels was observed after one year of treatment. These findings suggest that 14-3-3ζ is not only an effective biomarker for diagnosis but also for monitoring disease progression.[42]

The Effects of 14-3-3ζ Protein on Immunity and Bone Health in Rheumatoid Arthritis

The 14-3-3ζ protein is an adaptor protein that plays a critical role in cellular signaling pathways and is involved in various processes, including immune regulation and bone remodeling.[43,44] It plays a significant role in the mechanisms of autoimmune diseases such as RA. A study by Kim et al.[45] revealed that the 14-3-3ζ protein has an immune-regulatory and suppressive effect on RA.

In addition to its regulatory function, the 14-3-3ζ protein also acts as an antigen in RA. It modulates immune responses by supporting human T cell polarization, particularly favoring Th1 and Th17 cells.[46,47] In experiments conducted by Kim et al.,[45] the absence of 14-3-3ζ (in knockout models) was shown to disrupt immune balance and exacerbate arthritis symptoms. In the absence of this protein, an increase in the production of proinflammatory cytokines, particularly IL-17A and IFN-γ, was observed.

Another important role of the 14-3-3ζ protein is its ability to suppress inflammatory pathways. Interleukin-1 beta, a key inflammatory factor in the pathogenesis of RA, plays a significant role in the progression of arthritis.[48] In animal studies, the absence of 14-3-3ζ was observed to lead to an increase in the production of IL-1β, which caused osteoclast activation, bone erosion, and synovial inflammation. Furthermore, vaccination with recombinant 14-3-3ζ protein suppressed IL-1β levels and enhanced the expression of interleukin-1 receptor antagonist (IL-1RA). This immunosuppressive effect reduces inflammation while preserving bone structure.[45] The decrease in IL-1β, IFN-γ, and TNF-α levels following 14-3-3ζ immunization may explain the preserved bone health and lower arthritis scores.[49-51]

In addition to affecting the immune system, RA severely disrupts bone integrity, leading to trabecular and cortical bone loss. In a study by Kim et al.,[45] it was shown that 14-3-3ζ plays a significant role in bone remodeling, supports collagen synthesis, and preserves bone mineral density. In its absence, significant trabecular

loss, expansion of the bone marrow area, and trabecular disintegration were observed. Immunization with 14-3-3ζ protein increased collagen accumulation, stabilized bone microarchitecture, and prevented bone erosion.

14-3-3ζ Immunization: Potential in Rheumatoid Arthritis Treatment

One of the notable aspects of 14-3-3ζ is its function as an autoantigen in RA.[46,47] A study has shown that under normal physiological conditions, anti-14-3-3ζ antibodies are naturally present, but their levels decrease as arthritis progresses, indicating an inverse correlation with the disease's progression. Interestingly, passive immunization with these antibodies was insufficient in suppressing inflammation, suggesting that the active immunogenic function of 14-3-3ζ is necessary for the suppression of arthritis. Before arthritis induction with pristane or type-II collagen, rats were given two doses of vaccine (the first dose on day 1, and the second dose on day 8). This vaccination with recombinant 14-3-3ζ protein was shown to be effective in both pristane-induced and collagen-induced arthritis animal models. The vaccination resulted in the following:

- Prevention of severe inflammation in the joints and suppression of arthritis symptoms.
- Reduction in the production of pro-inflammatory cytokines, including IL-1β, IFN-γ, and TNF-α, while increasing anti-inflammatory IL-1RA levels.
- Bone health can be preserved by improving trabecular bone volume, cortical thickness, and collagen production.[45]

In conclusion, RA is a significant public health issue due to its complex pathogenesis, progressive nature, and various systemic complications. Currently, treatment approaches focus on alleviating symptoms and improving the patient's quality of life. However, a definitive and continuous cure has not yet been found. Additionally, the low-sensitivity biomarkers used in RA diagnosis make it challenging to detect the disease at its early stages. In recent years, studies on 14-3-3 proteins have increased, with findings, especially vaccine studies, generating excitement. The 14-3-3ζ protein vaccine has been shown to suppress pro-inflammatory cytokines like IL-1β, increase anti-inflammatory IL-1RA levels, and contribute to the preservation of bone integrity by preventing bone erosion. Moreover, 14-3-3ζ has shown high specificity in diagnosing RA, and its use alongside other biomarkers has significant importance in early disease detection. Furthermore, it has proven valuable in monitoring disease progression during treatment. This family of proteins, which can be used as biomarkers in RA diagnosis and monitoring, holds promise for new therapeutic approaches. However, further studies are required before transitioning to clinical applications.

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