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Nrf2-Keap1 Signaling in Arthritis: Therapeutic Potential of Nanoparticle-Based Approaches with Special Reference to Silver Nanoparticles

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Abstract | Arthritis represents a heterogeneous group of inflammatory and degenerative joint disorders characterized by persistent inflammation, oxidative stress, cartilage degradation, synovial dysfunction and progressive impairment of joint integrity. Rheumatoid Arthritis (RA) and Osteoarthritis (OA), although distinct in etiology, share several pathological mechanisms involving excessive production of Reactive Oxygen Species (ROS), mitochondrial dysfunction, inflammatory cytokine activation and dysregulation of redox-sensitive signaling pathways [1-4]. The nuclear factor erythroid 2-related factor 2 (Nrf2)-Kelch-like ECH-associated protein 1 (Keap1) pathway is a major endogenous defense mechanism responsible for maintaining cellular redox homeostasis. Under basal conditions, Keap1 promotes Nrf2 degradation; however, oxidative or electrophilic stress disrupts this interaction, allowing Nrf2 to accumulate and translocate into the nucleus, where it activates antioxidant response element (ARE)-dependent genes, including heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1) and glutathione-related enzymes [5,6]. Increasing evidence indicates that impaired or insufficient Nrf2 activity contributes to persistent oxidative stress and inflammation in arthritic joints [1,7]. Nrf2 also interacts with major inflammatory pathways, particularly nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK) and NLRP3 inflammasome signaling [8]. Nanotechnology offers an opportunity to improve the delivery, stability, bioavailability and tissue targeting of therapeutic agents capable of modulating redox and inflammatory pathways. Among different nanomaterials, silver nanoparticles (AgNPs) have attracted considerable interest because of their antimicrobial, anti-inflammatory, antioxidant and immunomodulatory properties [9-11]. Experimental studies have demonstrated that AgNPs can reduce inflammatory cytokines, regulate NF-κB and MAPK signaling, influence macrophage polarization and alleviate inflammatory tissue injury [9,10]. In experimental RA, targeted folic-acid-modified AgNPs have demonstrated the ability to interact with inflammatory macrophages, promote macrophage apoptosis and repolarization and reduce disease severity [12]. Nevertheless, the relationship between AgNP exposure, oxidative signaling and Nrf2-Keap1 activation is complex and excessive nanoparticle-induced oxidative stress may also produce adverse biological effects. This review examines the role of the Nrf2-Keap1 pathway in arthritis, evaluates nanoparticle-based strategies for modulating redox and inflammatory mechanisms and critically discusses the therapeutic potential and safety considerations of AgNPs. Particular emphasis is placed on the potential intersection between AgNP-mediated redox regulation, Nrf2-Keap1 signaling, NF-κB inhibition, macrophage polarization and joint protection.

Key Words Arthritis, Rheumatoid Arthritis, Osteoarthritis, Nrf2, Keap1, Oxidative Stress, Reactive Oxygen Species, Nanoparticles, Silver Nanoparticles, NF-κB, Macrophage Polarization, Nanomedicine

INTRODUCTION

Arthritis encompasses a broad spectrum of musculoskeletal disorders characterized by joint inflammation, structural deterioration, pain, stiffness and functional disability. Rheumatoid Arthritis (RA) is primarily an autoimmune inflammatory disease in which persistent synovial inflammation leads to cartilage destruction and bone erosion, whereas osteoarthritis

(OA) is a multifactorial joint disorder involving cartilage degradation, subchondral bone remodeling, synovial inflammation and progressive loss of joint function [1,2].

Although RA and OA differ in their initiating mechanisms, oxidative stress is increasingly recognized as an important contributor to joint pathology. Reactive oxygen species (ROS), including superoxide anion, hydrogen peroxide and hydroxyl radicals, are generated by mitochondrial respiration, NADPH oxidases, activated immune cells and other cellular processes. Under physiological conditions, ROS participate in cellular signaling and host defense. However, excessive ROS production or inadequate antioxidant defense results in oxidative stress, which can cause lipid peroxidation, protein oxidation, DNA damage, mitochondrial dysfunction and disruption of cellular homeostasis [1,3].

In RA, oxidative stress is closely associated with chronic synovial inflammation. Activated macrophages, neutrophils, fibroblast-like synoviocytes and lymphocytes generate ROS while simultaneously releasing inflammatory cytokines and tissue-degrading mediators. This interaction creates a self-amplifying relationship between oxidative stress and inflammation [1]. Kaur et al. emphasized that oxidative stress represents an important pathogenic component of RA and highlighted the Nrf2-Keap1 pathway as an important endogenous mechanism for maintaining redox and inflammatory homeostasis [1].

The Nrf2-Keap1 signaling pathway is one of the major cellular defense systems against oxidative and electrophilic stress. Under basal conditions, Keap1 binds Nrf2 and facilitates its ubiquitination and proteasomal degradation. During oxidative stress, modification of critical cysteine residues in Keap1 disrupts its ability to promote Nrf2 degradation. Stabilized Nrf2 subsequently accumulates in the nucleus and binds ARE sequences, promoting transcription of antioxidant and cytoprotective genes [5,6].

Nrf2 is therefore not simply an antioxidant transcription factor; it is increasingly considered an important regulator of inflammatory signaling. Its interaction with NF-κB and other redox-sensitive pathways provides a mechanistic link between oxidative stress and chronic inflammation [8]. Recent literature has further described Nrf2 as a redox checkpoint capable of influencing macrophage behavior, fibroblast-like synoviocytes, inflammasome activity, ferroptosis and other cellular processes relevant to inflammatory arthritis.

Despite this biological potential, conventional pharmacological modulation of Nrf2 can be limited by problems involving solubility, stability, bioavailability and tissue-specific delivery. Nanotechnology may overcome some of these limitations by improving drug delivery, cellular uptake, controlled release and targeting of inflamed tissues [13].

Silver nanoparticles have emerged as an interesting candidate because of their multifunctional biological properties. Experimental studies indicate that AgNPs can influence inflammatory cytokines, oxidative stress, NF-κB signaling, macrophage polarization and other pathways involved in inflammatory disease [9-11]. Importantly, targeted AgNPs have shown therapeutic effects in experimental RA through macrophage apoptosis and repolarization [12].

Therefore, this review evaluates the role of the Nrf2-Keap1 pathway in arthritis and explores the potential application of nanoparticle-based strategies, with particular emphasis on AgNPs and their possible interaction with redox and inflammatory signaling.

Arthritis and Oxidative Stress

Oxidative Stress in Rheumatoid Arthritis: RA is characterized by autoimmune activation, persistent synovitis, pannus formation, cartilage destruction and bone erosion. Macrophages, fibroblast-like synoviocytes, neutrophils, T cells and B cells contribute to the inflammatory microenvironment through the release of cytokines, chemokines, proteolytic enzymes and ROS [1,2].

TNF-α, IL-1β and IL-6 are among the principal inflammatory mediators involved in RA. These cytokines activate intracellular signaling pathways that increase inflammatory gene expression and stimulate production of matrix-degrading enzymes. At the same time, ROS can activate redox-sensitive pathways such as NF-κB and MAPK, thereby amplifying inflammatory responses [1,8].

The relationship between oxidative stress and inflammation is consequently bidirectional. ROS stimulate inflammatory pathways, whereas inflammatory mediators can increase ROS production through mitochondrial dysfunction and activation of ROS-generating enzymes. This creates a persistent “oxidative stress-inflammation” cycle that contributes to progressive joint injury [1].

Oxidative Stress in Osteoarthritis

OA was traditionally viewed primarily as a mechanical degenerative disorder; however, it is now recognized as a complex disease involving inflammation, metabolic dysfunction, oxidative stress, cellular senescence and altered joint homeostasis [2,4].

Excessive ROS can impair chondrocyte function and promote mitochondrial dysfunction, apoptosis, inflammatory signaling and extracellular matrix degradation. ROS-mediated activation of NF-κB and MAPK pathways can increase expression of matrix metalloproteinases and other cartilage-degrading enzymes [4].

Nrf2 has consequently attracted considerable interest as a potential protective pathway in OA. Enhancement of Nrf2-mediated antioxidant responses may reduce oxidative injury and inflammatory signaling while supporting chondrocyte survival and cartilage homeostasis [4].

Nrf2-Keap1 Signaling Pathway

Nrf2 belongs to the Cap’n’Collar family of basic leucine zipper transcription factors and regulates numerous

genes involved in antioxidant defense, detoxification, metabolism and cellular protection [5,6].

Under normal conditions, Keap1 functions as a negative regulator of Nrf2 by facilitating its ubiquitination and subsequent proteasomal degradation. This mechanism maintains relatively low basal Nrf2 activity. Oxidative or electrophilic stress modifies reactive cysteine residues in Keap1, resulting in impaired Nrf2 ubiquitination and stabilization of Nrf2 [5,6].

Nrf2 then translocates to the nucleus, where it heterodimerizes with small Maf proteins and binds antioxidant response elements. This results in transcription of numerous cytoprotective genes, including HO-1, NQO1, glutamate-cysteine ligase, glutathione-related enzymes and other antioxidant proteins [5,6].

The Nrf2 pathway is therefore essential for restoring cellular redox balance following oxidative injury.

Nrf2-Keap1 Signaling in Rheumatoid Arthritis

Evidence increasingly supports a protective role for Nrf2 in Kaur *et al*. [1] identified oxidative stress as an important component of RA pathogenesis and described the Nrf2-Keap1 pathway as a major endogenous defense mechanism against redox imbalance and inflammation [1].

Experimental evidence has also demonstrated that activation of Nrf2 can protect rheumatoid arthritis-associated fibroblast-like synoviocytes against oxidative injury. For example, miR-30a-3p was shown to activate Nrf2-ARE signaling through regulation of the Keap1/CUL3 system, thereby reducing oxidative stress in RA synovial fibroblasts [7].

A recent review further emphasized that Nrf2 signaling interacts with several redox-sensitive inflammatory pathways in RA, including NF-κB and suggested that pharmacological Nrf2 activation may represent a potential therapeutic strategy. Nrf2 may influence several disease-relevant cell populations.

Fibroblast-Like Synoviocytes

Fibroblast-like synoviocytes contribute to synovial hyperplasia, inflammatory mediator production and cartilage degradation. Activation of Nrf2 may protect these cells against oxidative injury and reduce pathological inflammatory activity [7].

Macrophages

Macrophages are central regulators of RA inflammation. Pro-inflammatory M1 macrophages produce TNF-α, IL-1β, IL-6, ROS and other mediators. Nrf2 activation can enhance antioxidant defense and influence macrophage inflammatory phenotype.

Chondrocytes

Nrf2-mediated antioxidant responses may protect chondrocytes against ROS-induced mitochondrial dysfunction, apoptosis and matrix degradation [4].

Osteoclasts

Because oxidative stress participates in osteoclast differentiation and inflammatory bone destruction, Nrf2 may also contribute to regulation of pathological bone remodeling.

Nrf2 and NF-κB Crosstalk

NF-κB is one of the principal transcriptional regulators of inflammatory responses in arthritis. Persistent NF-κB activation promotes transcription of TNF-α, IL-1β, IL-6, COX-2, adhesion molecules, chemokines and matrix-degrading enzymes.

Nrf2 and NF-κB are closely interconnected. Enhancement of Nrf2-mediated antioxidant responses can reduce oxidative conditions that support inflammatory signaling, while persistent inflammatory signaling may disrupt redox homeostasis.

This crosstalk is particularly important because it provides a mechanistic explanation for how antioxidant pathways can indirectly suppress inflammation. Therefore, therapeutic activation of Nrf2 may provide effects beyond simple ROS scavenging.

Nanotechnology in Arthritis Management

Nanotechnology provides opportunities to improve the delivery and pharmacological performance of therapeutic compounds. Nanoparticles can enhance drug solubility, stability, cellular uptake, pharmacokinetics, controlled release and tissue targeting [13].

In inflammatory arthritis, nanoparticle systems may exploit changes in vascular permeability and inflammatory-cell recruitment to increase delivery to diseased joints. Surface modification can further improve targeting of macrophages, synovial fibroblasts or other disease-associated cells [13].

Nrf2-modulating compounds may particularly benefit from nanoparticle-based delivery because many natural and synthetic Nrf2 activators have limitations related to bioavailability and pharmacokinetics.

Silver Nanoparticles and Anti-Inflammatory Activity

AgNPs possess antimicrobial, antioxidant, anti-inflammatory and immunomodulatory properties. Their biological effects are influenced by particle size, morphology, surface charge, coating, synthesis method, silver-ion release, concentration and exposure duration [9-11].

A systematic review and meta-analysis of *in vivo* studies found evidence that AgNPs can reduce pro-inflammatory mediators and increase anti-inflammatory responses. The authors also reported effects involving COX-2 and NF-κB-related inflammatory mechanisms [9].

A 2026 updated systematic review similarly concluded that AgNPs can influence NF-κB and MAPK signaling, suppress pro-inflammatory cytokines, regulate oxidative stress and modify macrophage polarization [10].

These findings support the concept that AgNPs may act through multiple interconnected mechanisms rather than through a single inflammatory target.

Silver Nanoparticles in Experimental Rheumatoid Arthritis

One of the most important studies directly relevant to this review was conducted by Yang et al., who developed folic-acid-modified AgNPs for targeted RA therapy [12].

The nanoparticles were designed to target M1 macrophages through folate receptors. Following cellular uptake, intracellular glutathione promoted AgNP dissolution and silver-ion release. The system induced M1 macrophage apoptosis and reduced ROS while promoting M1-to-M2 macrophage repolarization [12].

Importantly, the nanoparticles accumulated in inflamed joints and demonstrated therapeutic efficacy in mouse models of RA. The investigators also reported favorable biosafety findings and progressive clearance of the nanoparticles without appreciable long-term tissue accumulation [12].

These observations are highly relevant to the Nrf2-centered framework because macrophage redox status and polarization are closely associated with Nrf2 signaling.

However, the study did not establish that the observed therapeutic effects were specifically dependent on Nrf2-Keap1 activation. Consequently, it would be inappropriate to state that AgNPs definitively treat RA by activating Nrf2. Instead, the evidence supports a plausible mechanistic intersection requiring further validation.

Potential Interaction Between AgNPs and Nrf2-Keap1

The potential relationship between AgNPs and Nrf2-Keap1 signaling represents an important research opportunity.

AgNPs can interact with intracellular redox systems through silver-ion release, mitochondrial effects, ROS modulation and interactions with antioxidant systems [10,11]. Controlled modulation of redox status may activate endogenous antioxidant pathways, including Nrf2.

A proposed mechanism is:

- AgNP exposure → modulation of intracellular redox status → Keap1 modification → Nrf2 stabilization → nuclear Nrf2 accumulation → ARE activation → increased HO-1/NQO1/glutathione-related defenses → reduced oxidative stress → attenuation of inflammatory signaling

This proposed mechanism should, however, be distinguished from established evidence. Current literature provides strong evidence for Nrf2 involvement in arthritis and strong evidence for anti-inflammatory effects of AgNPs but direct demonstration that AgNP-mediated antiarthritic effects are Nrf2-dependent remains limited [1,10,12].

This distinction represents one of the major scientific gaps and potential novelty areas for future research.

AgNPs, Macrophage Polarization and Redox Regulation

Macrophage polarization is an important therapeutic target in RA. M1-like macrophages contribute to inflammatory amplification through production of TNF-α, IL-1β, IL-6, ROS and other mediators, whereas M2-like macrophages are generally associated with resolution of inflammation and tissue repair [12].

Nrf2 can regulate macrophage metabolic and redox responses and may promote a less inflammatory cellular phenotype.

The study by Yang et al. demonstrated that targeted AgNPs could reduce M1 macrophages and promote M2 repolarization in experimental RA [12]. The authors also reported ROS-scavenging activity, suggesting that redox regulation may contribute to the observed immunomodulatory effects.

Future experiments should therefore determine whether pharmacological inhibition or genetic deletion of Nrf2 can abolish AgNP-mediated macrophage repolarization. Such studies would provide direct evidence for or against an Nrf2-dependent mechanism.

Nrf2, NF-κB and NLRP3 Signaling

Nrf2 is interconnected with several inflammatory pathways, including NF-κB and the NLRP3 inflammasome.

Excessive ROS can promote inflammatory signaling and contribute to NLRP3 inflammasome activation. NLRP3 subsequently promotes maturation of IL-1β and IL-18, thereby amplifying inflammatory responses.

The proposed interaction can therefore be represented as:

- Oxidative stress → NF-κB activation → pro-inflammatory cytokines → NLRP3 activation → IL-1β/IL-18 release → joint inflammation.

Conversely, enhanced Nrf2-mediated antioxidant defense may decrease oxidative conditions that support these inflammatory processes.

Because AgNPs have been reported to influence NF-κB, MAPK, cytokines, oxidative stress and macrophage polarization, investigation of the AgNP-Nrf2-NF-κB-NLRP3 axis may provide an important mechanistic direction for future arthritis research [9,10].

Green-Synthesized Silver Nanoparticles

The synthesis method is a major determinant of nanoparticle physicochemical characteristics and biological activity. Green synthesis uses biological materials such as plant extracts, microorganisms or naturally derived compounds as reducing and stabilizing agents.

Green-synthesized AgNPs may provide additional biological activity because phytochemicals can remain associated with the nanoparticle surface. This may contribute to antioxidant and anti-inflammatory effects [10].

Experimental studies using plant-mediated AgNPs have reported antiarthritic effects, including reductions in paw edema, inflammatory infiltration, oxidative stress and tissue destruction. These findings support further investigation of green-synthesized formulations as multifunctional therapeutic platforms.

Nevertheless, the biological activity of green-synthesized AgNPs can vary substantially according to plant species, extract composition, synthesis conditions, nanoparticle size and surface chemistry. Standardization is therefore essential before meaningful comparisons can be made between studies.

Safety and Toxicological Considerations

Despite promising therapeutic effects, AgNPs must be evaluated carefully for potential toxicity.

Depending on concentration and physicochemical properties, AgNPs can induce oxidative stress, mitochondrial dysfunction, membrane injury, DNA damage and inflammatory responses [10,11].

This creates an important therapeutic challenge. Moderate redox modulation may stimulate protective cellular responses, whereas excessive ROS production may result in toxicity.

Therefore, future studies should systematically assess:

- Acute toxicity
- Chronic toxicity
- Hepatic and renal effects
- Biodistribution
- Silver-ion release
- Immunotoxicity
- Genotoxicity
- Reproductive toxicity
- Tissue accumulation
- Long-term clearance
- Environmental effects

The 2024 systematic review also emphasized substantial heterogeneity between AgNP studies and the need for improved standardization and higher-quality evidence [9].

Current Knowledge Gaps

Several important gaps remain in the current literature:

- First, most evidence concerning AgNP-mediated arthritis treatment comes from experimental animal models rather than human clinical studies [9,10,12]
- Second, direct evidence demonstrating that AgNP-mediated antiarthritic effects depend on Nrf2-Keap1 signaling is limited
- Third, considerable heterogeneity exists in AgNP size, shape, surface chemistry, synthesis method, concentration and route of administration [9,10]
- Fourth, long-term toxicity and repeated-dose safety require additional investigation
- Fifth, the optimal level of Nrf2 activation remains uncertain because both insufficient and excessive redox modulation may have undesirable consequences
- Finally, future studies should use mechanistic experiments involving Nrf2 knockdown, knockout models or pharmacological inhibitors to establish causality rather than relying solely on changes in Nrf2-related biomarkers

Future Perspectives

Future research should focus on developing Nrf2-informed, joint-targeted nanoparticle systems.

A rigorous experimental design could compare:

- Untreated arthritic animals
- AgNP-treated arthritic animals
- Nrf2 inhibitor+AgNP treatment
- Nrf2-deficient+AgNP treatment
- Conventional antiarthritic therapy
- AgNP plus conventional therapy

Such experiments would determine whether Nrf2 is required for the therapeutic activity of AgNPs.

Future nanoparticles could incorporate:

- Folate targeting
- Peptide targeting
- Antibody-based targeting
- ROS-responsive release
- pH-responsive release
- Macrophage-specific targeting
- Synovial fibroblast targeting

Combining AgNPs with Nrf2-modulating phytochemicals or conventional anti-inflammatory agents may also provide synergistic effects.

Advanced transcriptomic, proteomic, metabolomic and single-cell approaches should be incorporated to characterize changes within the arthritic joint microenvironment.

CONCLUSIONS

The Nrf2-Keap1 pathway represents an important endogenous defense mechanism against oxidative stress and inflammation and has substantial therapeutic relevance in arthritis. Nrf2 activation enhances antioxidant and cytoprotective responses while interacting with inflammatory pathways such as NF-κB and NLRP3 [1].

Nanotechnology offers a promising strategy for improving the delivery and targeting of therapeutics that modulate these pathways. AgNPs have demonstrated anti-inflammatory and antiarthritic effects in experimental studies through modulation of inflammatory cytokines, oxidative stress, NF-κB signaling and macrophage polarization [9-12].

Targeted AgNP formulations are particularly promising because they may selectively affect pathogenic inflammatory macrophages while limiting systemic exposure [12]. However, direct evidence linking AgNP-mediated arthritis treatment specifically to Nrf2-Keap1 activation remains insufficient.

Therefore, AgNPs should currently be considered a promising experimental nanotherapeutic platform rather than an established clinical treatment for arthritis. Future studies should establish Nrf2 dependence using appropriate genetic and pharmacological approaches, standardize nanoparticle formulations, determine optimal dosing, evaluate long-term toxicity and ultimately investigate clinical translation.

The integration of Nrf2-Keap1 biology, redox regulation, macrophage targeting and nanoparticle engineering may provide a novel approach for simultaneously controlling oxidative stress and inflammation in arthritis.

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