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Potential Mechanisms and Research Progress in SIRT3 and NF-κB Signaling during Macrophage Polarization in Osteoarthritis

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Abstract

Osteoarthritis (OA) affects the entire joint, not cartilage alone. Synovial macrophages respond to local change and may influence inflammation, repair, and pain. SIRT3 is linked with mitochondrial balance, redox control, and energy metabolism. NF-κB regulates inflammatory transcription and macrophage behavior. We reviewed whether published work connects these factors in OA. We searched PubMed, Google Scholar, China National Knowledge Infrastructure, Wanfang Data, and SinoMed. The final set contained 50 reviews published from 2017 to 2026. Forty-three were in English, and seven were in Chinese. The papers covered OA, macrophages, SIRT3 or sirtuins, NF-κB, mitochondrial homeostasis, redox regulation, and immunometabolism. We separated OA findings from evidence obtained in other diseases or cell systems. We also marked steps that depended on inference. The literature links SIRT3 with mitochondrial dysfunction and reactive oxygen species. Separate studies link NF-κB with inflammation and macrophage function. No included review demonstrated the complete sequence in OA synovial macrophages. Future studies should assess SIRT3, mitochondrial status, NF-κB activity, macrophage function, and joint outcomes within one model.

Keywords

SIRT3, NF-κB, Macrophage Polarization, Osteoarthritis, Mitochondrial Homeostasis, Immunometabolism

1. Introduction

OA research now looks beyond cartilage. It also covers synovium, bone, immune cells, and their shared environment [1]-[3]. This whole-joint view makes synovitis

clinically relevant. Macrophages can amplify inflammation, but they can also support resolution and repair [2] [4] [5]. Many papers still use M1/M2 labels. The labels are convenient, yet OA macrophages occupy a wider functional range. Cell origin, local conditions, and disease stage all shape their behavior [3] [6]-[8].

NF-κB appears often in work on OA inflammation, cartilage injury, and macrophage function [9]-[12]. SIRT3 appears mainly in studies of mitochondria, oxidative stress, and cartilage cells [13]-[15]. The cell types do not match across much of this literature. That mismatch matters. Evidence for each factor in OA does not prove that SIRT3 controls macrophages through NF-κB. We examine this sequence as a testable idea, not an established pathway.

2. Review Scope and Literature Search

OA combines cartilage degeneration, synovial inflammation, and loss of joint homeostasis. Recent reviews no longer treat the disease as simple mechanical wear. They also describe roles for innate immunity, metabolic change, and chronic low-grade inflammation [1] [16]. Synovial macrophages sit at this intersection. They respond to the local environment and are linked with inflammation, cartilage injury, repair, and pain [17] [18].

SIRT3 research has followed a different path. Most studies examine mitochondria, redox control, metabolism, and cellular stress [13] [19]. NF-κB studies focus on danger signals, inflammatory transcription, and macrophage function [9] [10]. Each field overlaps with OA, but that overlap does not prove one continuous pathway. For this reason, we kept direct OA evidence separate from cross-disease evidence. We describe any untested connection as an inference.

We performed a narrative review. We searched PubMed, Google Scholar, China National Knowledge Infrastructure, Wanfang Data, and SinoMed. We checked bibliographic details against journal websites. The search and record check ended on 11 October 2026. The main English query was: ("osteoarthritis" OR "OA") AND ("SIRT3" OR sirtuin*) AND ("NF-κB" OR "nuclear factor kappa B") AND (macrophage* OR "synovial macrophage*" OR polarization). We also paired shorter terms because few records contained every concept. Chinese queries used matching terms for OA, macrophages, polarization, SIRT3, sirtuins, NF-κB, and mitochondrial homeostasis.

We considered narrative and systematic reviews published from January 2017 through October 2026. Eligible papers covered at least one topic in the review framework. We excluded duplicates, primary studies, conference abstracts, non-review publications, and unrelated records. Screening began with titles and abstracts. Accessible full texts informed the synthesis. Abstract-only or publisher-page records helped map the topic. They never supported a molecular claim by themselves. We removed duplicates using titles, authors, years, journals, and DOI or URL details.

The final corpus contained 50 reviews: 43 in English and seven in Chinese. We sorted the evidence into direct OA findings, cross-disease mechanisms, and cross-field inferences. This was not a systematic review or meta-analysis. We did not

reconstruct stage-specific screening counts that were never recorded. Three primary reports clarified the SIRT3-SOD2 mechanism and the honokiol example [20]-[22]. They were not part of the 50-review corpus.

3. Macrophage States in Osteoarthritis

The focus of OA macrophage reviews has changed since 2019. Early papers emphasized innate inflammation and the broad role of synovial cells [3] [7] [12] [17] [23]-[25]. Later work gives more attention to cell origin, subset diversity, metabolism, and treatment. A 2019 review already questioned whether M1/M2 labels covered every joint macrophage state [7]. Later reviews placed inflammatory and repair functions within the same joint [3]. They also warned against merging monocyte-derived and tissue-resident cells [2].

One systematic review gives useful scale to this discussion. It searched PubMed, Web of Science, ScienceDirect, and Medline. Two investigators assessed 28 studies independently [6]. Twelve studies used human tissue or cells, and 16 used animal models. Most reported more inflammatory-like macrophages during OA development. Repair-associated cells tended to decrease. Models, markers, and outcomes varied, so the pattern was common rather than universal [6].

Later reviews continued to stress phenotypic diversity [8]. Chinese-language papers discussed polarization, synovial macrophage features, and regulatory mechanisms in knee OA [26]-[29]. Across both language groups, one point remained stable. Macrophage states changed with OA. Their function, however, depended on local context and disease stage.

The reviews did not all examine the same outcomes. Some linked macrophage polarization with synovitis, cartilage loss, tissue repair, and treatment [23]. Zhang and Ji also discussed osteophytes and pain [24]. Another review mapped macrophage contact with synovial cells, chondrocytes, osteoclasts, and adipocytes [30]. That view treats joint inflammation as a cell network, not a single mediator. Pain-focused work makes a similar point. Cartilage structure alone may miss clinically important changes [18]. Metabolic OA research adds obesity and immunometabolism to the picture [31].

Recent papers discuss several pathways around macrophage polarization [12] [25] [32] [33]. They include NF-κB, MAPK, JAK/STAT, PI3K/Akt/mTOR, NLRP3, oxidative stress, and mitochondrial function. The field has moved from labels toward interacting mechanisms. Study models, markers, and outcomes still differ. We use "inflammatory-like" and "repair-associated" as broad descriptions, not fixed identities. Cell origin, timing, and disease stage remain part of every interpretation.

4. NF-κB in OA Inflammation and Macrophage Function

NF-κB evidence comes from two levels of research. OA tissue reviews describe cartilage damage, inflammatory mediators, and canonical or noncanonical signaling [9] [34]. Immune-cell reviews examine monocytes and macrophages [10]. Both levels matter, but they answer different questions. Cartilage findings do not prove

a macrophage polarization state. General macrophage findings are not automatically specific to OA synovium.

A newer OA review connects mechanical stress, innate immunity, macrophage polarization, and cartilage degeneration [11]. Other reviews place NF-κB beside MAPK, STAT, PI3K/Akt, mTOR, and NLRP3 [12] [25] [32] [33]. This pattern points to a network, not a single switch. NF-κB has clear links with OA inflammation and macrophage regulation. Its exact role in OA synovial macrophages still requires cell-specific testing.

Redox biology offers one possible bridge between SIRT3 and NF-κB. Wang and He reviewed OA macrophages, Nrf2, reactive oxygen species, and NF-κB [35]. Their framework separates disease evidence from cell mechanisms. It cannot be relabeled as a SIRT3 study because Nrf2 is the central molecule.

Macrophage reviews link reactive oxygen species with cell state, NF-κB, and inflammasomes [36]-[38]. Mitochondrial reviews add mitochondrial DNA and metabolic reprogramming [39] [40]. OA synovial research also links altered metabolites and mitochondrial dysfunction with macrophage activation [1]. K. Zhang *et al.* brought these themes together for OA macrophages [25]. During our review, this was the clearest area of overlap. It still did not provide the missing SIRT3-to-NF-κB experiment. We treated that step as a hypothesis.

5. SIRT3 and Mitochondrial Homeostasis in OA

SIRT3 reviews repeatedly return to four themes: redox balance, metabolism, inflammation, and autophagy [41]. J. Zhang *et al.* discussed reactive oxygen species and inflammation across several diseases [19]. Trinh *et al.* added the electron transport chain, tricarboxylic acid cycle, SOD2, and mitochondrial dynamics [42]. Yang *et al.* focused on the mitochondrial permeability transition pore and oxidative stress [43]. These reviews explain the biological range of SIRT3. They do not show a macrophage effect in OA.

The OA literature is narrower. Y. He *et al.* reviewed SIRT3, reactive oxygen species, mitophagy, and mitochondrial homeostasis [13]. Most direct findings came from cartilage and chondrocytes. Reviews by Y. Liu *et al.* and Sun *et al.* reached a similar focus [14] [15]. Another review placed AMPK-SIRT regulation beside metabolism, reactive oxygen species, and mitophagy [44]. Chinese reviews also centered on chondrocytes and mitochondrial quality control [45] [46].

One pattern stayed consistent across the corpus. OA evidence for SIRT3 came mainly from cartilage cells and mitochondrial processes. Macrophage-specific evidence was sparse. The literature supports an association between SIRT3 and disturbed mitochondrial homeostasis. It does not show NF-κB-mediated macrophage polarization in OA.

6. Where SIRT3 NF-κB and Macrophage State May Intersect

6.1. Redox Balance and the Proposed SIRT3 NF-κB Link

Could redox balance connect SIRT3 with NF-κB? Existing papers make this idea

possible, but not proven. Wang and He built their macrophage model around Nrf2 [35]. K. Zhang *et al.* placed reactive oxygen species, mitochondrial dysfunction, NF-κB, and metabolism within OA macrophages [25]. Neither review tested the complete SIRT3 sequence.

The strongest direct biochemical evidence concerns SOD2. Experimental studies showed that SIRT3 deacetylates SOD2 at the conserved Lys122 site [20] [21]. This change increased SOD2 activity and supported mitochondrial superoxide removal. Those experiments used non-OA cells and mouse models. They did not examine OA synovial macrophages. Broader SIRT3 reviews also identify SOD2 as an important functional node [19] [42].

General macrophage reviews connect mitochondrial reactive oxygen species with NF-κB and inflammatory reprogramming [36]-[38]. This supports a limited model. Low SIRT3 activity may weaken antioxidant defense and allow ROS-related signals to persist. A direct NF-κB effect has not been shown in OA macrophages. A useful study should measure SIRT3, SOD2 acetylation, reactive oxygen species, NF-κB activity, and macrophage function together.

6.2. Mitochondrial Homeostasis and Macrophage Responses

Mitochondrial homeostasis includes more than reactive oxygen species. SIRT3 reviews discuss energy metabolism, electron transport, mitochondrial dynamics, oxidative stress, and membrane permeability [19] [42] [43]. Much of this evidence comes from several diseases or basic models. OA reviews discuss similar processes, but their direct findings mainly involve chondrocytes [13] [44] [46]. General macrophage reviews connect mitochondrial metabolism, mitochondrial DNA, and inflammatory signaling [39] [40].

K. Zhang *et al.* place mitochondrial dysfunction and NF-κB/MAPK signaling within an OA macrophage framework [25]. The combined evidence permits a cautious model. Lower SIRT3 activity may allow damaged-mitochondrial signals to persist. Restored mitochondrial balance may reduce inflammatory input. Neither effect has been demonstrated in OA synovial macrophages. A direct test must measure mitochondrial change, NF-κB activity, and macrophage function in one model.

6.3. Mitophagy NLRP3 and NF-κB

Mitophagy and NLRP3 add a separate question. OA reviews place SIRT3 and mitophagy within mitochondrial quality control [13] [44] [46]. Their direct evidence mainly concerns chondrocytes and overall joint pathology. Cross-disease reviews link SIRT3 with autophagy, mitochondrial inflammation, NLRP3, and cell death [47] [48]. Tran and Mills provide wider macrophage context for NF-κB and NLRP3 [38].

NF-κB-dependent transcription can raise NLRP3 and pro-IL-1β expression. That step primes the system. NLRP3 activation needs another signal and assembly of the inflammasome. Mitochondrial stress may supply part of that signal. Prim-

ing and activation are related, but they are not the same event. OA macrophage reviews discuss mitophagy, ROS, metabolism, and NF-κB/MAPK together [25]. No included review showed that SIRT3 changes NLRP3 activation in OA macrophages. Separate experiments must test each step.

6.4. Immunometabolism and Macrophage State

Immunometabolism offers another route into the question. C. Q. Xu *et al.* reviewed sirtuins and macrophage metabolism in cardiovascular disease [49]. You, Li, and Chong discussed related patterns in sepsis [50]. General macrophage reviews connect mitochondrial metabolism, reactive oxygen species, mitochondrial DNA, and inflammatory signaling [39] [40]. Pérez and Rius-Pérez examined redox control during acute inflammation [36]. These papers offer mechanism, but not direct OA evidence.

OA-specific context comes from K. Zhang *et al.* [25]. Their review links metabolic reprogramming, mitochondrial dysfunction, reactive oxygen species, and NF-κB with synovial macrophage state. Read together, the papers support only a provisional interpretation. SIRT3-related metabolic change may alter inflammatory programs and NF-κB-associated activity. No OA study tested every step. One M1 or M2 marker cannot settle the question. Metabolism, signaling, and cell function should be measured in the same experiment.

6.5. Macrophage and Chondrocyte Communication

A macrophage-chondrocyte link requires cell-specific evidence. NF-κB reviews connect this pathway with OA inflammation and cartilage matrix loss [9] [11]. Sirtuin reviews link SIRT3 with mitochondrial and survival processes in chondrocytes [13]-[15] [45]. A different review links mitochondrial dysfunction and NF-κB with synovial macrophage state [25]. These findings come from different cell populations.

The papers support an association between macrophage state and cartilage homeostasis. They do not show a direct SIRT3/NF-κB signal between macrophages and chondrocytes. One working model places macrophage change before altered chondrocyte homeostasis. The direction, timing, and mediator remain unknown. Chondrocyte protection cannot be described as macrophage regulation without direct testing. Co-culture studies, cell-specific interventions, and OA models could clarify the direction of communication. **Table 1** summarizes the evidence and its limits.

7. Therapeutic Implications and Testing Strategies

Current OA reviews treat synovial macrophages as a possible intervention target. They do not present SIRT3/NF-κB as a ready therapeutic pathway. Polarization reviews suggest measuring inflammatory and repair functions together [12] [23] [24]. Studies should also follow synovitis, cartilage damage, and pain. Reviews of intra-articular treatment support local approaches within the joint [18] [51] [52].

Table 1. Evidence supporting each step of the proposed SIRT3-NF-κB-macrophage pathway in OA.

Proposed link	Main supporting literature	Nature of the evidence	Current conclusion
Macrophage state and OA	Reviews and systematic reviews of synovial macrophages in OA [2] [3] [6] [25]	Direct evidence in the OA context	OA studies directly link macrophage state with inflammation, repair, and pain. Two labels cannot cover the observed range.
NF-κB, OA, and macrophage function	Reviews of cartilage destruction and signaling in OA, together with focused reviews of monocytes and macrophages [9]-[11]	Disease evidence and general cellular mechanistic evidence	NF-κB is involved in OA inflammation and macrophage function. No reviewed study tested SIRT3 control of this pathway in OA synovial macrophages.
SIRT3 and OA	Reviews of SIRT3, the sirtuin family, and mitochondrial quality control [13]-[15] [46]	OA-related evidence, mainly from chondrocyte studies	OA studies link SIRT3 with mitochondrial and redox imbalance, mainly in chondrocytes. These findings cannot stand in for macrophage data.
SIRT3 and macrophage immunometabolism	Reviews of sirtuins in immunometabolism and inflammation and of SIRT3 function [19] [47] [49] [50]	Cross-disease mechanistic evidence	SIRT3 may influence macrophage metabolism and inflammatory activity. Most evidence comes from non-OA or general cell models.
Complete SIRT3 - NF-κB - polarization - OA chain	Integrated interpretation of evidence from different levels [25] [35]	Mechanistic model requiring validation	The full chain remains a working model. It lacks OA macrophage-specific evidence, causal ordering, and pathway-dependence tests.

They support macrophage targeting, but not SIRT3-mediated treatment.

SIRT3 reviews discuss mitochondrial metabolism, reactive oxygen species, inflammation, and small-molecule activators [13] [19] [53]. Much of that work comes from basic research or non-OA disease. Wang and He discuss Nrf2, not SIRT3, as the redox regulator [35]. At present, SIRT3, oxidative stress, NF-κB, and macrophage state remain separate therapeutic entry points. Direct pathway tests are needed before these points can form one treatment axis.

A lower inflammatory marker does not prove pathway mediation. The same model must document SIRT3, mitochondrial function, reactive oxygen species, and NF-κB activity [25] [38]. It must also measure macrophage function and joint outcomes. Better cartilage without macrophage data cannot establish macrophage mediation. Lower NF-κB activity also cannot place SIRT3 upstream without a dependence test.

Honokiol shows why this distinction matters. Liu *et al.* list it as a natural SIRT3-modulating compound [53]. A 2023 study tested honokiol in IL-1β-stimulated chondrocytes and a mouse OA model [22]. The authors measured the SIRT3-COX4I2 axis and reported improved cartilage outcomes. These results support SIRT3 engagement in chondrocytes and the mouse joint. They do not show that honokiol acts only through SIRT3. They also do not demonstrate a SIRT3-NF-κB-macrophage pathway.

Local delivery can raise drug exposure within the joint, but it does not establish cell specificity [18] [51]. A stronger study would manipulate SIRT3 or NF-κB before repeating treatment. Loss of the original effect would support pathway de-

pendence. The same experiment should assess synovitis, cartilage degeneration, and pain. Until such data exist, these interventions remain research strategies rather than established therapies.

8. Evidence Gaps and Future Studies

No included review showed the four proposed events within one OA system. Those events are SIRT3 change, an NF-κB response, altered macrophage function, and a joint outcome. OA SIRT3 reviews mainly concern chondrocytes, mitochondria, oxidative stress, autophagy, and cell fate [13]-[15] [45] [46]. Macrophage immunometabolism studies often come from cardiovascular disease, sepsis, or general inflammation [47] [49] [50]. NF-κB evidence is also spread across cartilage, immune cells, and OA tissues [9]-[11] [34].

This distribution limits the claims that can be made. Accessible full texts supported the mechanistic synthesis. Abstract-only and bibliographic records were used only to map the topic. The review cannot determine whether SIRT3 directly changes NF-κB in OA macrophages. It also cannot establish timing or effects on joint structure and pain. Cross-field evidence helps frame a testable question. It cannot replace a direct experiment.

Macrophage classification creates another limit. M1/M2 labels offer simple shorthand for inflammatory and repair tendencies. A systematic review found inconsistent models, markers, and outcomes [6]. Other reviews stress cell origin, continuous states, and the joint environment [2]-[4] [8]. Tissue-resident and monocyte-derived macrophages are not one population. A change in one marker does not prove a complete functional shift.

Disease stage can also change the observed signal. Reviews describe macrophage contact with chondrocytes, synovial cells, and other joint cells [1] [5] [30]. They do not define SIRT3/NF-κB activity in every cell type. Whole-synovium or whole-joint measurements cannot reveal the cellular source. Future reports should pair cell identity with functional state and disease stage. Molecular markers should also be linked with measured cell functions.

Future work should test causal order, not add isolated correlations. One design could use patient synovium, animal models, and macrophage cultures. The same outcomes should be measured in each setting. Patient samples can show whether SIRT3, NF-κB, and macrophage state change together. They cannot establish causality alone.

Cell and animal studies can test macrophage-specific gain or loss of SIRT3. They should measure mitochondria, reactive oxygen species, NF-κB, and cell function in parallel. Inhibition studies can ask whether NF-κB blockade reduces changes caused by SIRT3 loss. Rescue studies can test whether restored SIRT3 still works when NF-κB remains active.

Mitophagy, metabolic reprogramming, and NLRP3 require separate tests [25] [38] [39] [48]. Their appearance in the same review does not prove mediation. Studies should distinguish tissue-resident from monocyte-derived macrophages

and compare disease stages [2] [4] [52]. Treatment studies should measure macrophage function, synovitis, cartilage damage, and pain. A pathway claim also needs blockade of a critical step that weakens the treatment effect.

9. Conclusions

The literature provides three connected lines of evidence, but they remain incomplete. OA macrophage states are linked with inflammation, cartilage damage, repair, and pain [2] [3] [6] [18]. NF-κB is linked with OA inflammation and macrophage regulation [9]-[11]. SIRT3 is linked with mitochondrial homeostasis, metabolism, and redox control. Most direct OA evidence for SIRT3 still comes from chondrocytes [13] [44] [46].

General immunology and cross-disease studies connect SIRT3 with macrophage metabolism and inflammatory responses [19] [36] [49]. These findings support a testable model, not a completed causal chain. SIRT3 may influence NF-κB-associated macrophage responses through mitochondrial change. No included review established the order of every step in OA synovial macrophages. Chondrocyte findings cannot stand in for macrophage findings. Evidence from other diseases also needs OA-specific testing.

The field now looks beyond simple M1/M2 labels. Current work considers macrophage origin, heterogeneity, immunometabolism, mitochondrial quality control, and communication among joint cells [6] [8] [25] [52]. This shift raises practical questions. Which macrophage populations show altered SIRT3? Does NF-κB drive the response, or change beside it? Do these cell changes affect cartilage and pain?

We separated direct OA findings from cross-disease support and author inference. That distinction is essential when treatment claims are made. Changing SIRT3, reactive oxygen species, NF-κB, or macrophage state does not prove a complete pathway. Patient samples, cell-specific animal models, and rescue experiments can answer different parts of the question. The proposed mechanism is reasonable and testable. It has not yet been demonstrated as one continuous OA pathway.

Author Contributions

Conceptualization, T.X.W. and D.G.L.; methodology, T.X.W.; investigation, T.X.W., F.D. and R.X.M.; data curation, T.X.W. and F.D.; formal analysis, F.D. and R.X.M.; writing—original draft preparation, T.X.W.; writing—review and editing, D.G.L., F.D. and R.X.M.; visualization, R.X.M.; supervision, D.G.L.; project administration, D.G.L. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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