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REVIEW

Bromodomain and Extraterminal Protein Inhibition: A Novel Therapeutic Strategy in Arthritis

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Abstract: Arthritis is an inflammatory condition that affects the joints and surrounding tissues, triggered by factors such as inflammation, infection, degeneration, and trauma. The major forms of arthritis include osteoarthritis (OA), rheumatoid arthritis (RA), and gouty arthritis (GA). Its pathogenesis primarily involves synovial inflammation, cartilage degradation, and subchondral bone remodeling, with pro-inflammatory cytokines, collagenases, and other mediators playing central roles in disease onset and progression. The bromodomain and extraterminal (BET) protein family-a subclass of the larger bromodomain protein superfamily-comprises BRD2, BRD3, BRD4, and BRDT. The regulatory functions of BET proteins in inflammation highlight their considerable potential for mitigating arthritis-related pathology. This review provides a comprehensive overview of recent research on the role of BET proteins in OA, RA, and GA, aiming to deepen our understanding of the protective mechanisms of BET inhibitors, underscore their potential as therapeutic targets, and emphasize their relevance in the development of novel treatment strategies.

Keywords: arthritis, osteoarthritis, rheumatoid arthritis, gouty arthritis, bromodomain and extraterminal protein

Introduction

Arthritis is an inflammatory disease affecting the joints and surrounding tissues, triggered by factors such as inflammation, infection, degeneration, and trauma.[1–3] Based on its etiology, pathogenesis, and clinical presentation, arthritis can be classified into osteoarthritis (OA), rheumatoid arthritis (RA), gouty arthritis (GA), and other subtypes.[1–3] OA is a chronic degenerative joint disease that primarily affects the cartilage and surrounding tissues, commonly seen in the elderly.[1] Current treatments for OA are largely limited to symptom management, including the use of nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroid injections, and, in advanced cases, joint replacement surgery. These approaches do not effectively halt disease progression or reverse cartilage damage, highlighting the need for disease-modifying therapies. RA is a chronic, systemic autoimmune disease characterized by inflammation in multiple joints.[2] Current treatments, including disease-modifying antirheumatic drugs (DMARDs), biologics, and corticosteroids, primarily aim to control inflammation and slow disease progression; however, they often fail to achieve complete remission, can cause significant side effects, and may be insufficient to prevent long-term joint damage in all patients. GA is an inflammatory joint disease caused by the deposition of urate crystals within the joints.[3,4] Current clinical treatments, including urate-lowering therapies, nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids, primarily aim to control acute flares and reduce uric acid levels. However, these approaches often fail to fully prevent recurrent attacks or halt long-term joint damage, highlighting the need for more effective and disease-modifying strategies. Although the etiology and pathogenesis of these conditions differ, all three types of arthritis involve

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inflammation and damage to the joints and surrounding tissues, with inflammatory mediators playing a crucial role in disease progression.[1–3] Additionally, interactions among chondrocytes, synovial fibroblasts, macrophages, and other cells are central to the progression of arthritis.

Chondrocytes, subjected to mechanical stress and inflammatory stimuli, secrete matrix metalloproteinases (MMPs) and pro-inflammatory cytokines, including Interleukin-1 (IL-1) and Tumor Necrosis Factor-alpha (TNF-α), which contribute to the degradation of the cartilage matrix in OA.[5] Meanwhile, synovial fibroblasts and macrophages within the synovium proliferate and become activated, producing significant amounts of inflammatory mediators such as prostaglandin E2 (PGE2) and nitric oxide (NO).[6,7] These mediators exacerbate joint inflammation and tissue destruction. Additionally, the dorsal root ganglion is involved in pain perception and transmission in OA.[8] In rheumatoid arthritis (RA), synovial fibroblasts undergo abnormal proliferation and activation, exhibiting aggressive invasiveness. These cells secrete large quantities of MMPs and inflammatory cytokines, such as Interleukin 6 (IL-6), Interleukin 8 (IL-8), and TNF-α, leading to the degradation of joint cartilage and bone.[9] Immune cells, including macrophages, monocytes, T cells, and B cells, drive the inflammatory response within the synovium, further contributing to tissue destruction.[10,11] In gouty arthritis (GA), macrophages are key effector cells.[12] They recognize and engulf monosodium urate (MSU) crystals deposited in the joints. The MSU crystals trigger excessive activation of the NLRP3 inflammasome within macrophages, leading to caspase-1 activation and the subsequent secretion of large amounts of pro-inflammatory cytokines, particularly IL-1β.[13] This cascade significantly exacerbates joint inflammation. The etiology and pathogenesis of arthritis are complex and multifactorial, with increasing evidence pointing to a significant role of epigenetic regulation in its development.[14,15]

The bromodomain (BRD) is a highly conserved protein domain that specifically recognizes and binds to acetylated lysine residues on histones. It is composed of approximately 110 amino acids, arranged into four antiparallel α-helices and two hydrophobic loops.[16] BRD proteins are categorized into eight families, with the bromodomain and extra-terminal domain (BET) protein family being the most extensively studied.[17] This family includes BRD2, BRD3, BRD4, and BRDT, which regulate gene transcription by recognizing acetylated lysine residues. Members of the BET family play crucial roles in the regulation of inflammatory gene expression, cell cycle progression, and DNA damage repair.[18] Given that inflammation is a key pathological feature of arthritis, BET proteins are likely critical in its progression.

BET inhibitors, particularly those targeting BRD4, have shown promise in suppressing inflammatory responses in chondrocytes by inhibiting the Nuclear Factor kappa B (NF-κB) signaling pathway.[19] Additionally, these inhibitors can activate the Nuclear Factor Erythroid 2-Related Factor 2 (NRF2) signaling pathway, reducing oxidative stress and apoptosis in chondrocytes.[20] BET inhibitors also downregulate the expression of pro-inflammatory cytokines in inflammatory macrophages and alleviate joint pain by modulating dorsal root ganglion function.[21] In RA, BET inhibitors suppress disease progression by inhibiting inflammatory responses in RA synovial fibroblasts (RASFs) and reducing their proliferation, migration, and invasion.[22,23] They also modulate receptor expression on the surface of monocytes, further inhibiting RA progression. In gouty arthritis (GA), BET inhibitors reduce joint inflammation by preventing macrophage pyroptosis.[13]

This review highlights recent advancements in BET inhibitor research within the contexts of OA, RA, and GA, offering new perspectives for the development of novel therapeutics to mitigate these diseases.

Structure and Function of BET Proteins

The BET protein family is a subclass of the larger bromodomain protein superfamily. The human genome encodes over 40 different proteins containing more than 60 types of bromodomains.[24] Based on sequence homology, the bromodomain protein family is divided into eight subfamilies, with the BET family representing a distinct group. As shown in Figure 1, the BET family includes BRD2, BRD3, BRD4 (which has subtypes A, B, and C), and BRDT. BET proteins are characterized by two conserved bromodomains (BD1 and BD2) at the N-terminus and an extraterminal (ET) domain at the C-terminus.

The primary functions of the BET proteins are centered on gene transcription regulation, chromatin structure modulation, and the maintenance of cellular functions.[24] BET proteins activate gene transcription by binding to acetylated histones and recruiting the transcription initiation complex to promoter regions, thereby facilitating the initiation of RNA polymerase II.[16] These proteins play critical roles in regulating inflammation and immune

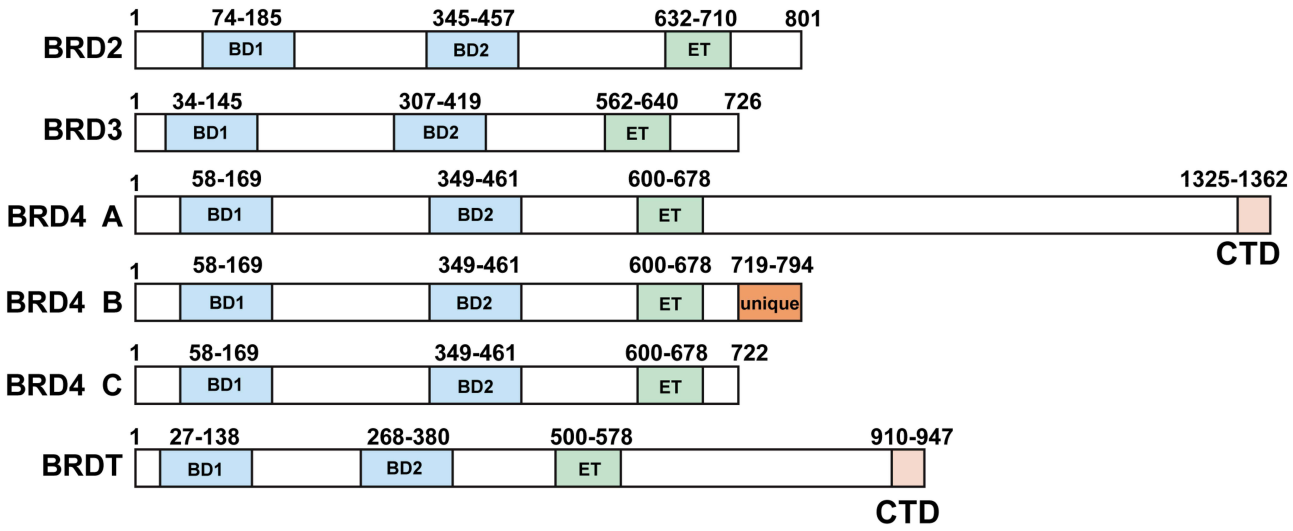

Figure 1 Domain Architecture of BET proteins. Three isoforms of BRD4 are indicated. Isoform B of BRD4 has a unique C terminus, which interacts with condensing II complexes.[25] The CTD of BRD4 and BRDT is referred to as a C-terminal motif (CTM).
Abbreviations: ET, extraterminal domain; CTD, C-terminal domain.

responses.[26–28] For instance, BRD4 enhances the expression of inflammation-related genes such as TNF-α and IL-6 by binding to acetylated histones, a process that is crucial in various inflammatory diseases, including OA and RA.[28–30]

Moreover, BET proteins influence immune cell functions, including the proliferation, differentiation, and cytokine secretion of T cells, B cells, and macrophages.[31–33] By binding to acetylated histones, BET proteins also contribute to chromatin relaxation and remodeling, thereby modulating gene accessibility. Additionally, BET proteins, particularly BRD4, are involved in cell cycle regulation, especially during the G1/S phase transition.[34] BRD4 ensures proper cell cycle progression by regulating the expression of key cyclins. These diverse functions position BET proteins as crucial regulatory factors in many diseases, providing a strong scientific foundation for their targeting in therapeutic strategies.

The Role of BET Inhibitors in Osteoarthritis

Osteoarthritis (OA) is the most common joint disease, primarily characterized by cartilage damage and affecting the entire joint structure.[1,35,36] Pathological changes in OA include cartilage destruction, subchondral bone sclerosis, and synovial inflammation, among others.[37] Current treatments for OA are mainly conservative, focusing on pain relief through medication.[38,39] However, no drugs are currently available that can slow the progression of the disease, highlighting the need for further research. In recent years, there has been growing interest in the role of BET proteins in OA. BET inhibitors, especially BRD4 inhibitors, have demonstrated potential in protecting OA chondrocytes, reducing the expression of inflammatory cytokines in activated macrophages, and alleviating joint pain by modulating the function of the dorsal root ganglia (DRG). These findings suggest that BET inhibitors, particularly BRD4 inhibitors, could represent a promising therapeutic option for OA. The regulatory functions of BRD4 inhibitors in OA are summarized in Figure 2 and Table 1.

Protecting Chondrocytes

Inhibiting Inflammatory Responses in Chondrocytes

Chondrocytes, the only cell type found in articular cartilage, are responsible for maintaining the balance of the cartilage matrix.[43] In OA, this balance between matrix synthesis and degradation is disrupted, leading chondrocytes to adopt an inflammatory phenotype.[44–47] Under inflammatory stimuli, chondrocytes secrete significant amounts of pro-inflammatory factors, such as TNF-α, IL-1β, and IL-6. These factors not only directly damage cartilage but also further activate chondrocytes and synovial cells through autocrine and paracrine mechanisms, creating a positive feedback loop of

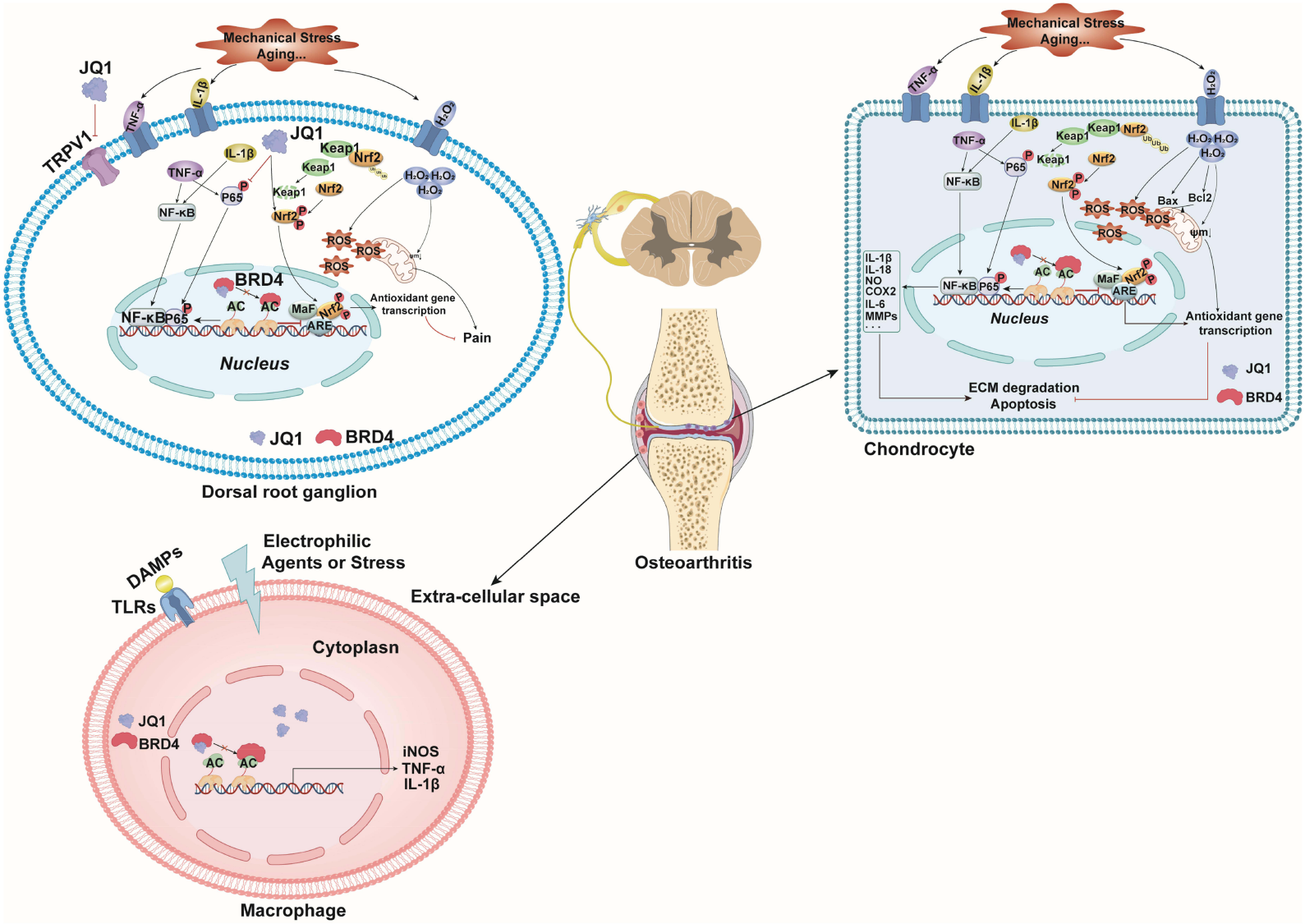

Figure 2 The regulatory mechanism of the BRD4 inhibitor JQ1 on chondrocytes, macrophages, and dorsal root ganglia (DRG) in osteoarthritis.

Abbreviations: TNF-α, Tumor Necrosis Factor-alpha; IL-1β, Interleukin-1 beta; H_2O_2, Hydrogen Peroxide; P-P65, Phosphorylated Nuclear Factor Kappa B P65 Subunit; NRF2, Nuclear Factor Erythroid 2–Related Factor 2; Keap1, Kelch-like ECH-Associated Protein 1; AC, acetylated chromatin; MaF, Musculoaponeurotic Fibrosarcoma Oncogene Homolog; ARE, Antioxidant Response Element; NF-κB, Nuclear Factor Kappa B; IL-18, Interleukin-18; NO, Nitric Oxide; COX2, Cyclooxygenase-2; IL-6, Interleukin-6; MMPs, Matrix Metalloproteinases; ECM, Extracellular Matrix; TRPV1, Transient Receptor Potential Vanilloid 1; DAMPs, Damage-Associated Molecular Patterns; TLRs, Toll-Like Receptors; iNOS, Inducible Nitric Oxide Synthase.

Table 1 Advances in Targeting BET Proteins for the Treatment of Osteoarthritis

BET Protein Type	Inhibitor	Cell or Animal Type	Effect	Mechanism	Reference
BRD4	JQ1 (200, 400 nM)	SW1353 chondrocytes treated with 10 ng/mL IL-1β	Reduces pro-inflammatory cytokine release	Inhibition of the HMGB1 and NF-κB signaling pathways	Jiang et al, 2017[19]
BRD2	BBC0403 (20 μM)	Mouse primary chondrocytes treated with 1 ng/mL IL-1β	Reduces pro-inflammatory cytokine release	Inhibition of the NF-κB signaling pathway	Lee et al, 2024[40]
BRD4	JQ1	H_2O_2–treated rat chondrocytes	ROS↓, MDA↓; SOD↑, CAT↑, and GPx↑	Activation of NRF2-HO-1 signaling	An et al, 2018[20]
BRD4	JQ1	H_2O_2–treated rat chondrocytes	Reduce chondrocyte apoptosis	Bcl-2↑, Bax↓, Caspase-3↓	An et al, 2018[20]
BRD4	JQ1	H_2O_2–treated chondrocytes	Mitigate cartilage matrix damage	Col2A1↑, aggrecan↑, MMP13↓, ADAMTS5↓	Fukui et al, 2021[41]
BRD2	BBC0403	IL-1β–treated mouse cartilage explants	Reduced IL-1β-induced cartilage matrix damage	MMP3↓, MMP13↓, p38 signaling pathway↓	Lee et al, 2024[40]
BRD4	BRD4 flox/flox mice	ACLT mouse model	M1 macrophage↓, synovial inflammation↓		Xu et al, 2024[42]
BRD4	JQ1	DRG tissues from the ACLT mouse model	Reduces pain perception	Inhibiting TRPV1 in the DRG	Xu et al, 2024[42]
BRD4	JQ1 or MS417	MIA-induced OA	Reduces inflammatory cytokines in both the spinal cord and DRG	NF-κB↓; NRF2↑	Sun et al, 2023[21]

Abbreviations: BET, Bromodomain and Extra-Terminal domain; BRD, Bromodomain-containing protein; JQ1, Thieno-triazolo-1,4-diazepine small-molecule BET inhibitor; IL-1β, Interleukin-1 beta; HMGB1, High mobility group box 1; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; H_2O_2, Hydrogen peroxide; ROS, Reactive oxygen species; MDA, Malondialdehyde; SOD, Superoxide dismutase; CAT, Catalase; GPx, Glutathione peroxidase; NRF2, Nuclear factor erythroid 2–related factor 2; HO-1, Heme oxygenase-1; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; Col2A1, Collagen type II alpha 1 chain; MMP13, Matrix metalloproteinase-13; ADAMTS5, A disintegrin and metalloproteinase with thrombospondin motifs 5; MMP3, Matrix metalloproteinase-3; p38, p38 mitogen-activated protein kinase; flox/flox mice, Mice carrying loxP-flanked (floxed) alleles; ACLT, Anterior cruciate ligament transection; DRG, Dorsal root ganglion; TRPV1, Transient receptor potential vanilloid 1.

inflammation.[48] Therefore, inhibiting the expression of these inflammatory factors is crucial for mitigating inflammatory responses and protecting chondrocytes.

The BRD4 inhibitor JQ1 (200 nM, 400 nM) effectively suppresses the expression of inflammatory factors IL-6 and TNF-α in SW1353 chondrocytes treated with 10 ng/mL IL-1β.[19] JQ1 also inhibits the mRNA expression of inflammatory mediators, such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX2), in chondrocytes treated with IL-1β, IL-6, or TNFα.[41,49] Additionally, JQ1 reduces the mRNA expression of pro-inflammatory factors (IL-1β, IL-6) following joint damage. Mechanistically, BRD4 inhibitors modulate the expression of high mobility group box protein 1 (HMGB1) and NF-κB, thereby alleviating inflammatory responses. HMGB1, a ubiquitous chromatin component widely expressed in immune and other cells, activates the NF-κB signaling pathway, which is involved in the inflammatory responses of various diseases. The NF-κB signaling pathway is notably upregulated in OA. Thus, JQ1 effectively inhibits inflammation and slows OA progression by targeting HMGB1 and the NF-κB pathway.

The BRD2-specific inhibitor BBC0403 (20 μM) significantly suppresses the expression of inflammation-related factors, including COX2, prostaglandin E2 (PGE2), and IL-6, in mouse primary chondrocytes treated with 1 ng/mL IL-1β.[40] The anti-inflammatory effects of the BRD2 inhibitor are also mediated through the inhibition of the NF-κB signaling pathway.

Inhibiting Oxidative Stress in Chondrocytes

Oxidative stress plays a critical role in the pathogenesis of OA.[50] It is defined as an imbalance between reactive oxygen species (ROS) and the antioxidant defense system, leading to excessive ROS accumulation, which in turn causes cellular damage and tissue destruction.[51–53] In OA, oxidative stress not only disrupts chondrocyte function and degrades the cartilage matrix but also affects other joint tissues, such as the synovium and bone, thereby accelerating disease progression.[54] Consequently, therapeutic strategies targeting oxidative stress hold promise for developing new treatment options for OA patients, potentially alleviating symptoms and slowing disease progression.

The BRD4 inhibitor JQ1 and BRD4 silencing (si-BRD4) have been shown to significantly reduce ROS and malondialdehyde (MDA) levels in rat chondrocytes treated with hydrogen peroxide (H_2O_2).[20] Additionally, JQ1 and si-BRD4 may enhance the expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and

glutathione peroxidase (GPx), indicating that BRD4 inhibitors can effectively lower oxidative stress in chondrocytes exposed to H_2O_2. Similarly, the BRD2 inhibitor BBC0403 has been found to reduce oxidative stress in a Destabilization of Medial Meniscus (DMM) mouse model. Treatment with 10 μg/kg BBC0403 for 10 weeks in DMM mice decreases the levels of oxidative stress markers, such as 8-hydroxy-2′-deoxyguanosine (8-OHdG), in the joints.[40,55] These findings suggest that BRD2 and BRD4 inhibitors may help mitigate OA progression by targeting and reducing oxidative stress in chondrocytes.

Reducing Chondrocyte Apoptosis

In OA, factors such as mechanical stress, inflammatory cytokines, and oxidative stress can induce chondrocyte apoptosis, which accelerates cartilage degradation.[56,57] As the number of chondrocytes decreases, the synthesis of the cartilage matrix diminishes, impairing the tissue's repair capacity and leading to progressive thinning and degeneration. Additionally, apoptotic chondrocytes release degradative enzymes and inflammatory mediators, such as MMPs and A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), which degrade type II collagen and proteoglycans in the cartilage matrix, further damaging the cartilage.[58,59] Moreover, apoptotic chondrocytes can activate synovial and immune cells by releasing fragmented organelles and DNA, triggering local inflammatory responses. This inflammation not only increases the release of inflammatory cytokines but also induces further chondrocyte apoptosis, creating a vicious cycle that accelerates OA progression.[56] Therefore, reducing chondrocyte apoptosis is crucial for mitigating OA progression.

BRD4 inhibitors have been shown to significantly reduce chondrocyte apoptosis induced by H_2O_2, thereby protecting chondrocytes.[20] At the molecular level, BRD4 inhibitors increase the expression of the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) in H_2O_2-treated chondrocytes while inhibiting the expression of pro-apoptotic proteins Bcl-2-associated X protein (Bax) and cysteine-aspartic protease 3 (Caspase-3).[20]

Protecting the Cartilage Matrix

The cartilage matrix is the primary component of articular cartilage, consisting of collagen, proteoglycans, glycoproteins, and water. It provides structural support and functional elasticity to the cartilage.[60] In OA, an imbalance between the degradation and remodeling of the cartilage matrix leads to cartilage degeneration and subsequent loss of joint function.[61]

BRD4 inhibitors have been shown to effectively mitigate cartilage matrix damage induced by oxidative stress, such as that caused by H_2O_2. These inhibitors enhance the expression of matrix synthesis-related factors, including Collagen Type II Alpha 1 Chain (Col2A1) and aggrecan, while reducing the expression of matrix degradation-related factors, such as MMP13 and ADAMTS5. Additionally, the BRD4 inhibitor JQ1 can decrease cartilage degradation in explant cultures and reduce the expression of MMPs in damaged joints in vivo.[41] These findings suggest that BRD4 inhibitors may protect against cartilage matrix damage associated with oxidative stress, inflammation, or joint injury.

Similarly, the BRD2 inhibitor BBC0403 has demonstrated protective effects against cartilage matrix degradation induced by IL-1β. When mouse cartilage explants were treated with BBC0403 (5, 10, or 20 μM) and IL-1β (1 ng/mL) for 72 hours, followed by Alcian blue staining, BBC0403 significantly reduced IL-1β-induced cartilage matrix damage, with the most pronounced effect observed at 20 μM. BBC0403 also decreased the expression of MMP3 and MMP13 in IL-1β-treated chondrocytes, thereby protecting the cartilage matrix.

The protective effects of BBC0403 have been further validated in vivo. In a DMM mouse model, intra-articular injection of 10 μg/kg BBC0403 for 10 weeks significantly reduced the expression of MMP3 and MMP13 in chondrocytes and effectively protected joint cartilage.[40] Mechanistically, BBC0403 inhibits the upregulation of MMPs and the activation of the p38 signaling pathway, which is involved in type II collagen degradation. A deeper understanding of the protective mechanisms of BRD inhibitors on the cartilage matrix will provide valuable insights into how these inhibitors alleviate OA.

Inhibiting M1 Macrophages

M1 macrophages, also known as classically activated macrophages, are typically considered pro-inflammatory cells that play a significant role in the pathology of OA.[6,62,63] These macrophages contribute to cartilage matrix degradation by

secreting pro-inflammatory cytokines and degradative enzymes. In OA, M1 macrophages exacerbate synovial inflammation through various mechanisms, further deteriorating the joint environment. They can induce chondrocyte apoptosis by releasing nitric oxide (NO), ROS, and other pro-inflammatory factors.[64] Additionally, M1 macrophages contribute to joint damage by influencing bone remodeling processes.[65] Therefore, targeting M1 macrophages presents a potential therapeutic strategy to alleviate OA symptoms and slow disease progression.

BRD4 is highly expressed in iNOS-positive M1 macrophages within the synovium of both human and mouse OA models.[42] A research team led by Huan Tian Zhang at Jinan University employed Lyz2-cre conditional knockout to delete BRD4 specifically in the myeloid lineage. In BRD4 flox/flox mice, this deletion resulted in a significant reduction in M1 macrophage accumulation and synovial inflammation in an anterior cruciate ligament transection (ACLT) mouse model.[42]

Relieving Joint Pain

Pain is a central symptom of OA, arising from various factors such as cartilage damage, synovial inflammation, osseous lesions, and soft tissue abnormalities.[66,67] Among these factors, the DRG plays a pivotal role in OA-related pain.[68] Located outside the spinal cord, the DRG houses the cell bodies of sensory neurons responsible for transmitting peripheral pain signals to the central nervous system.[69] In OA, DRG neurons are not only involved in pain signal transmission but also in the perception and maintenance of pain.[70] Given the critical role of the DRG in OA pain, it has emerged as a promising therapeutic target.

BRD4 inhibitors have demonstrated the ability to alleviate joint pain through multiple mechanisms. The BRD4 inhibitor JQ1, for instance, reduces pain perception in OA mice by inhibiting Transient Receptor Potential Ankyrin 1 (TRPV1) in the DRG.[42] TRPV1, an ion channel discovered by David Julius in 2021, is known to play a significant role in pain perception, particularly in response to stimuli such as ACLT surgery.[71,72] Furthermore, BRD4 inhibition suppresses NF-κB and NF-κB-mediated inflammatory cytokines in both the spinal cord and DRG in rats with monosodium iodoacetate (MIA)-induced OA pain.[21]

Oxidative stress, marked by increased ROS accumulation and impaired antioxidant activity, is also critical in the development of OA pain.[73,74] BRD4 inhibition mitigates oxidative stress and promotes NRF2-dependent antioxidant gene expression in both the spinal cord and DRG in models of MIA-induced OA pain, thereby alleviating joint pain associated with OA.[21]

The Role of BET Inhibitors in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by symmetrical inflammation of multiple joints.[75,76] Its hallmark features include inflammation and hyperplasia of the synovial membrane, which result in joint pain, swelling, stiffness, and functional impairment.[75] Recent research has highlighted the significance of BET proteins in RA.[29,77,78] The BET protein family is increasingly recognized for its crucial roles in regulating gene expression and inflammatory responses.[28] BET inhibitors, especially BRD4 inhibitors, have shown potential in modulating RA through several mechanisms. They inhibit the expression of inflammatory factors and matrix-degrading enzymes,[23] suppress Fcγ receptor expression in monocytes,[77] and impede the proliferation, migration, and invasion of RA synovial fibroblasts (RASFs).[22,23] Figure 3 and Table 2 summarize the regulatory effects of BRD4 inhibitors on RASFs and monocytes.

Regulating the Function of Rheumatoid Arthritis Synovial Fibroblasts

Inhibition of the Expression of Inflammatory Factors and Matrix Degrading Enzymes

Inflammatory factors and matrix-degrading enzymes play crucial roles in the pathogenesis of RA.[80] These factors collaboratively drive disease progression, leading to chronic joint inflammation and damage.

Inflammatory factors are small proteins secreted by immune cells, synovial fibroblasts, and other cells that regulate immune responses and inflammation.[11,81,82] Key inflammatory factors in RA include TNF-α, IL-1, IL-6, interleukin-17 (IL-17), and so on.[83] TNF-α is a critical factor in RA, promoting synovial fibroblast proliferation, stimulating the production of additional inflammatory factors such as IL-1β and IL-6, and increasing MMPs secretion. This cascade ultimately leads to cartilage and bone destruction.[84] IL-1 contributes to RA by promoting synovial cell proliferation and inflammatory responses, enhancing the expression of matrix-degrading enzymes, and further stimulating the release of

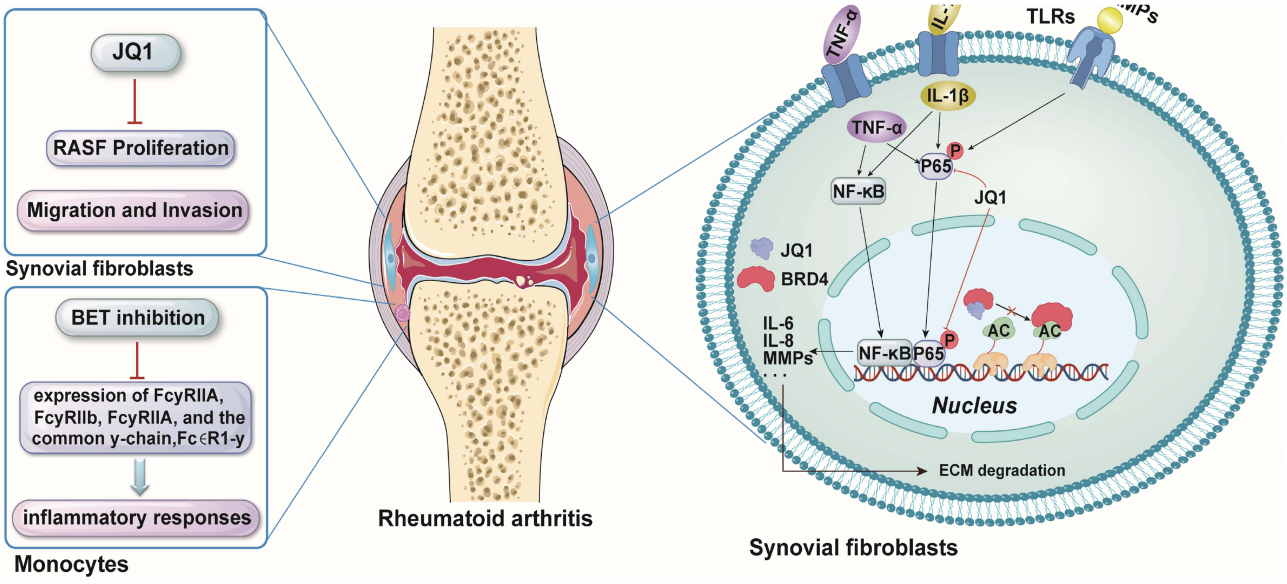

Figure 3 The regulatory mechanism of the BRD4 inhibitor JQ1 on synovial fibroblasts and monocytes in rheumatoid arthritis.
Abbreviations: DAMPs, Damage-Associated Molecular Patterns; TLRs, Toll-Like Receptors; IL-1β, Interleukin-1 Beta; TNF-α, Tumor Necrosis Factor Alpha; P-P65, Phosphorylated Nuclear Factor Kappa B P65 Subunit; AC, acetylated chromatin; IL-6, Interleukin-6; IL-8, Interleukin-8; MMPs, Matrix Metalloproteinases; ECM, Extracellular Matrix; RASF, Rheumatoid Arthritis Synovial Fibroblasts; BET, Bromodomain and Extra-Terminal Domain; FcγR, Fc Gamma Receptor.

inflammatory factors.[85] IL-6 is a multifunctional cytokine that promotes inflammation, synovial cell proliferation, and bone resorption.[86] IL-17 amplifies the effects of other inflammatory factors like TNF-α and IL-1, exacerbating inflammation and tissue destruction.[87]

Matrix-degrading enzymes, which are secreted by synovial fibroblasts, chondrocytes, and immune cells, disrupt the structural integrity of joint tissues.[88,89] Matrix metalloproteinases (MMPs), zinc-dependent enzymes, degrade extracellular matrix (ECM) components such as collagen and elastin.[90] In RA, elevated levels of MMP1, MMP3, and MMP13 lead to cartilage matrix degradation and joint damage.[91] Additionally, the ADAMTS family, particularly ADAMTS4 and ADAMTS5, degrades proteoglycans in the cartilage matrix, causing structural damage.[92] Therefore, targeting both inflammatory factors and matrix-degrading enzymes is essential for mitigating RA progression.

BRD4, a BET bromodomain coactivator protein, modulates inflammation via the NF-κB signaling pathway.[93] The small-molecule inhibitor JQ1, which targets BRD4, has demonstrated anti-inflammatory effects.[94] BRD4 siRNA significantly reduces the expression of pro-inflammatory factors, including IL-1β, IL-6, IL-17, and IL-18, in TNF-α-

Table 2 Advances in Targeting BET Proteins for the Treatment of Rheumatoid Arthritis

BET Protein Type	Inhibitor	Cell type	Effect	Mechanism	Reference
BRD	BET pan-inhibitors	TNF-α-treated SFs	Inhibit the expression of pro-inflammatory factors; Reduce the expression of matrix-degrading enzymes	Inhibiting IκB kinase-dependent NF-κB activation	Xiao et al, 2016[22]
BRD	BET pan-inhibitors	TNF-α-treated SFs	Suppress the proliferation of RASFs		Xiao et al, 2016[22]
BRD4	BRD4 siRNA	TNF-α-treated human SFs	Inhibit the migration and invasion of RASFs		Zhang et al, 2015[23]
BRD4	PLX51107	Monocytes from both healthy donors and RA patients	Downregulate the expression of FcγRIIA, FcγRIIB, FcγRIIIA, and tFcεR1-γ		Shankar et al, 2023[77]
BRD4	JQ1	RAW264.7 macrophages	Inhibited osteoclast differentiation and function		Wang et al, 2025[79]

Abbreviations: BET, Bromodomain and Extra-Terminal domain; TNF-α, Tumor necrosis factor-alpha; SFs, Synovial fibroblasts; IκB kinase, Inhibitor of nuclear factor kappa-B kinase; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; RASFs, Rheumatoid arthritis synovial fibroblasts; FcγR, Fc gamma receptor; tFcεR1-γ, truncated Fc epsilon receptor I gamma chain.

stimulated synovial fibroblasts (SFs).[23] In vitro RA models, created by stimulating SFs with TNF-α, IL-1β, and toll-like receptor (TLR) ligands (Pam3, pIC, and lipopolysaccharide (LPS)), and then treating with BET inhibitors such as I-BET151 or siRNA targeting BRD2, BRD3, and BRD4, show that BET inhibition significantly reduces inflammatory mediator expression in RA synovial fibroblasts (RASFs).[29] Another study confirms that BET pan-inhibitors, including JQ1, shBRD2, or shBRD4, significantly inhibit the expression of pro-inflammatory factors like IL-1β, IL-6, and IL-8 in TNF-α-treated SFs.[22] Furthermore, BET pan-inhibitors, such as JQ1, shBRD2, or shBRD4, significantly reduce the expression of matrix-degrading enzymes like MMP1, MMP3, and MMP13 in RASFs.[22]

Mechanistically, BET inhibitors suppress inflammation in the synovium by inhibiting IκB kinase-dependent NF-κB activation {Xiao, 2016 #179}.

Inhibition of RASFs' Proliferation

In RA, SFs undergo abnormal proliferation and activation, a condition referred to as "synovial hyperplasia". Proliferated SFs release elevated levels of inflammatory factors, chemokines, and MMPs. These substances collectively exacerbate the destruction of articular cartilage and bone tissue.[9,95] Thus, inhibiting the abnormal proliferation of RASFs is essential for managing RA.[96,97] BET pan-inhibitors, such as JQ1, shBRD2, and shBRD4, effectively suppress the proliferation of RASFs, thereby slowing RA progression.[22] However, the mechanism by which it inhibits the proliferation of RASFs needs further investigation.

Inhibition of RASFs' Migration and Invasion

The migration and invasion of SFs are critical processes in the pathology of RA.[98] In RA, SFs exhibit abnormal migratory behavior, allowing them to extend from the synovium into the surrounding articular cartilage and bone tissues.[98] Furthermore, RASFs demonstrate significant invasive capabilities, enabling them to penetrate the cartilage and bone matrices.[98] They release MMPs, cathepsins, and other degradative enzymes, which contribute to the breakdown of joint cartilage and bone matrix.[99] In addition to causing direct tissue destruction, the migration and invasion of SFs sustain local inflammatory responses, thereby exacerbating disease progression.[95,99] Targeting these migratory and invasive capabilities may offer a novel therapeutic approach to prevent joint damage. BRD4 siRNA can inhibit the migration and invasion of RASFs, positioning it as a potential therapeutic target for RA. However, the specific mechanisms underlying this effect require further investigation.[23]

Inhibition of Monocytes' Fcγ Receptors

Fcγ receptors (FcγRs) are critical in the pathogenesis of RA.[100] These receptors are present on various immune cells and bind to the Fc region of IgG antibodies within immune complexes. This binding mediates several immune responses, including phagocytosis, antibody-dependent cellular cytotoxicity, and amplification of inflammatory reactions.[100] In RA, FcγRs significantly contribute to inflammatory responses and tissue damage. Activation of FcγRs, such as FcγRI (CD64), FcγRIIA (CD32a), FcγRIIC (CD32c), and FcγRIIIA (CD16a), involves binding to IgG and triggering downstream signaling pathways that lead to immune cell activation, phagocytosis, oxidative bursts, and the secretion of inflammatory cytokines.[101–103] Thus, inhibiting activating FcγRs can reduce immune complex-mediated inflammation and alleviate RA symptoms.

FcγRs on myeloid cells bind immunoglobulin G (IgG) immune complexes, which induces an inflammatory phenotype, resulting in tissue damage and exacerbation of the inflammatory response.[104] The BRD4 inhibitor PLX51107 has been shown to significantly downregulate the expression of FcγRIIA, FcγRIIB, FcγRIIIA, and the common γ-chain (FcεR1-γ) in monocytes from both healthy donors and RA patients.[77] Treatment with PLX51107 also attenuates signaling events downstream of FcγR activation. In a collagen-induced arthritis (CIA) mouse model, PLX51107 treatment reduced FcγR expression and significantly decreased footpad swelling.[77]

Regulate the Architectural Integrity of Bone

JQ1 markedly inhibited osteoclast differentiation and function, underscoring the pivotal role of BRD4 in osteoclastogenesis and its potential as a target for therapeutic intervention in RA-induced bone destruction.[79]

Suppressing the Progression of Arthritis in Mice

In RA research, mouse models are critical for studying the disease's pathogenesis, pathophysiology, and for evaluating new therapeutic agents. Among these models, CIA is extensively used due to its close similarity to human RA. This model replicates key pathological features of RA, including joint inflammation, synovial hyperplasia, and cartilage and bone erosion.[105] The therapeutic effects of the BRD inhibitor JQ1 have been demonstrated in the CIA mouse model. JQ1 significantly reduces arthritis scores and paw swelling in CIA mice.[22,23] Additionally, it lowers serum levels of anti-CII IgG, anti-IgG1, anti-IgG2a, IL-6, and TNFα,[22] and effectively mitigates cartilage and bone destruction.[23]

The Role of BET Inhibitors in Gouty Arthritis

Gouty arthritis (GA) is an inflammatory disease characterized by the deposition of urate crystals in the joints, leading to severe pain and inflammation.[106] Anti-inflammatory strategies may serve as preventive approaches to limit long-term joint destruction. BRD4 inhibitors influence the progression of GA by modulating inflammatory responses and immune cell activation.[107] The mechanisms by which BRD4 inhibitors affect monosodium urate (MSU) crystal-induced macrophages are illustrated in Figure 4 and Table 3.

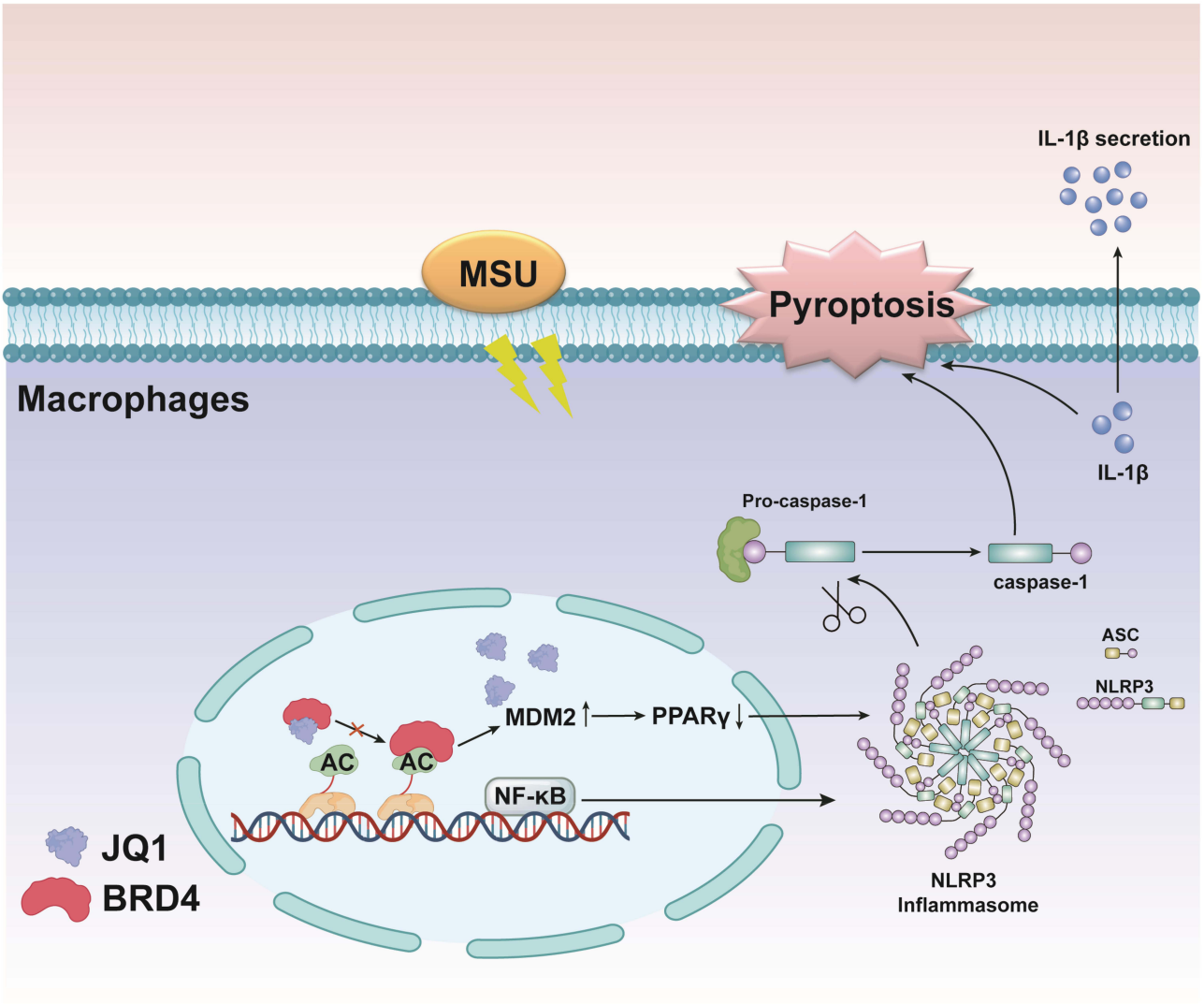

Figure 4 The regulatory mechanism of the BRD4 inhibitor JQ1 on macrophages in gouty arthritis.
Abbreviations: MSU, Monosodium Urate; AC, acetylated chromatin; MDM2, Mouse Double Minute 2; PPARγ, Peroxisome Proliferator-Activated Receptor Gamma; NF-κB, Nuclear Factor-Kappa B; NLRP3, Nod-Like Receptor Protein 3; ASC, Apoptosis-Associated Speck-Like Protein Containing a CARD; Caspase-1, Cysteine-Dependent Aspartate-Directed Protease 1; IL-1β, Interleukin-1 Beta.

Table 3 Advances in Targeting BET Proteins for the Treatment of Gouty Arthritis

BET Protein Type	Inhibitor	Cell type	Effect	Mechanism	Reference
BRD4	Compound 68	MSU-treated THP-1 cells	Inhibit MSU-induced pyroptosis	Inhibiting the NF-κB/ NLRP3 signaling pathway	Jiang et al, 2019[108]
BRD4	JQ1 or BRD4 siRNA	MSU-treated THP-1 cells	Inhibit MSU-induced pyroptosis	Inhibited activation of p65 NF-κB signaling	Hao et al, 2020[13]
BRD4	BRD4 siRNA	LPS and MSU-treated J774 cells	Suppressed NLRP3 inflammasome activation and pyroptosis	Inhibited MDM2-mediated PPARγ degradation	Xu et al, 2024[107]

Abbreviations: BET, Bromodomain and Extra-Terminal domain; BRD4, Bromodomain-containing protein 4; JQ1, Thieno-triazolo-1,4-diazepine small-molecule BET inhibitor; MSU, Monosodium urate; THP-1, Human acute monocytic leukemia cell line; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family pyrin domain-containing 3; LPS, Lipopolysaccharide; MDM2, Mouse double minute 2 homolog; PPARγ, Peroxisome proliferator-activated receptor gamma.

Inhibition of MSU-Induced Macrophage Pyroptosis

MSU crystals can trigger excessive activation of the NLRP3 inflammasome.[109] The assembly of the NLRP3 inflammasome involves the interaction between Nod-Like Receptor Protein 3 (NLRP3) and apoptosis-associated speck-like protein (ASC), as well as the cleavage of pro-caspase-1, a pattern recognition receptor.[110] This activation leads to the secretion of the inflammatory cytokine IL-1β by activating Caspase-1, which promotes the maturation of pro-IL-1β.[111,112]

In acute GA induced by MSU crystals, elevated articular BRD4 expression is associated with joint lesions and pyroptosis.[108] Compound 68 was shown to inhibit MSU-induced pyroptosis in THP-1 cells via the BRD4/NF-κB/NLRP3 signaling pathway.[108] Similarly, the protective effects of BRD4 inhibition—achieved either through JQ-1 treatment or siRNA-mediated knockdown—in MSU-induced models appear to be mediated by the BRD4/NF-κB/NLRP3/Gasdermin D (GSDMD) axis.[13] Research led by Hongbin Qiu at Jiamusi University has further elucidated that BRD4 enhances inflammation and pyroptosis in GA through Murine Double Minute 2 (MDM2)-mediated degradation of Peroxisome Proliferator-Activated Receptor Gamma (PPARγ).[107] The regulatory effects of BET inhibitors on macrophages in GA models require further investigation. Additionally, research should also be expanded to explore the effects of BET inhibitors on other cell types involved in GA, including synovial fibroblasts, chondrocytes, osteocytes, and T cells.

Conclusion and Prospects

The BET protein family regulates the transcription of inflammation-related genes by recognizing acetylated lysine residues. Inhibitors targeting BET proteins, such as BRD4 and BRD2, have demonstrated substantial therapeutic potential across various forms of arthritis, including OA, RA, and GA. In OA, BET inhibitors suppress inflammatory responses and oxidative stress in chondrocytes, thereby reducing apoptosis and preserving the cartilage matrix. They also decrease inflammatory macrophage infiltration, mitigate synovial inflammation, and alleviate arthritis-associated pain by activating the NRF2 signaling pathway in the DRG while inhibiting TRPV1 and NF-κB signaling. In RA, these inhibitors primarily suppress the expression of inflammatory cytokines and matrix-degrading enzymes in synovial fibroblasts, inhibit the proliferation, migration, and invasion of RASFs, and reduce Fcγ receptor expression on monocytes. Moreover, they attenuate RANKL-induced osteoclast activation, thereby preventing bone erosion. In GA, BET inhibitors inhibit MSU-induced macrophage pyroptosis, limiting inflammation and joint damage. This cell-type-specific variability underscores the need for personalized strategies in clinical applications. Approaches such as targeted drug delivery systems or patient stratification based on cellular or molecular profiles could help mitigate heterogeneous treatment responses, enhance therapeutic efficacy, and minimize potential adverse effects. Incorporating these strategies into future research will strengthen the translational potential of BET inhibitors across diverse patient populations and arthritis subtypes.

While the manuscript primarily discusses BET inhibitors as standalone therapies, investigating their potential in combination with conventional treatments is highly valuable. For instance, combining BET inhibitors with DMARDs in RA, urate-lowering agents in GA, or viscosupplements in OA could enhance therapeutic efficacy, lower the required doses, and potentially reduce adverse effects. Such combination strategies represent a promising direction for future research and may facilitate the development of more effective, personalized treatment approaches for arthritis patients.

While BET inhibitors have demonstrated promising results in clinical research for cancer and immune-related diseases, clinical trials have also highlighted safety concerns and adverse effects. Common toxicities include hematological effects, such as thrombocytopenia, anemia, and neutropenia, as well as non-hematological effects, including nausea and diarrhea. In addition, BET inhibitors may trigger off-target consequences, such as activation of resistance mechanisms, reactivation of latent viral genomes, and potential cardiovascular complications.

Therefore, translating preclinical findings into effective clinical therapies for chronic arthritic conditions remains highly challenging due to the complexity of drug design, the need for optimization of clinical trial protocols, and the requirement for comprehensive evaluation of long-term safety and efficacy. Future research should focus on delineating cell-type-specific mechanisms, determining optimal dosing regimens, developing more selective BET inhibitors, identifying reliable and validated biomarkers, and advancing precision medicine strategies to improve patient stratification and therapeutic outcomes. Addressing these aspects will not only facilitate the clinical translation of BET inhibitors but also contribute to the development of safer and more effective therapeutic approaches for arthritis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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