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REVIEW

Pathogenesis of Osteoarthritis: Mechanisms of Action of Disulfidptosis and Targeted Therapeutic Strategies

Yicheng Liang*, Kang Wang*, Chaoquan Yang*, Jinke Huang*, Zhiling Huang, Yan Chen

Department of Bone and Joint Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yan Chen, Department of Bone and Joint Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, People's Republic of China, Email cy003@connect.hku.hk

Abstract: The onset of osteoarthritis (OA) involves the interplay of mechanical stress, inflammatory responses, and metabolic disorders. Pro-inflammatory cytokines, including IL-1β, TNF-α, and IL-6, drive cartilage degradation, synovitis, and subchondral bone remodeling through activation of NF-κB and MAPK signaling pathways. Recent studies have identified disulfidptosis, a novel form of programmed cell death, and suggest its potential involvement in OA pathogenesis. This death modality is triggered by abnormal intracellular accumulation of disulfide bonds, dependent on high SLC7A11 expression and NADPH depletion, leading to cytoskeletal protein cross-linking and cellular collapse. In the OA microenvironment, chondrocytes and synovial cells are hypothesized to exhibit increased susceptibility to disulfidptosis owing to metabolic imbalance, impaired glucose uptake, and oxidative stress. This process may not only cause direct loss of cellular function but also potentially amplify inflammatory responses through the release of damage-associated molecular patterns (DAMPs) and senescence-associated secretory phenotype (SASP) factors, thereby theoretically contributing to a vicious cycle of inflammation and M1 macrophage polarization that exacerbates cartilage destruction. Potential therapeutic strategies targeting this pathway include: phytochemicals (eg, curcumin, resveratrol) that modulate redox balance; traditional Chinese medicines (eg, Duhuo Jisheng Decoction) with multi-target anti-inflammatory properties; specific inhibitors such as SLC7A11 antagonists or G6PD activators; hydrogel-based drug delivery systems for localized sustained release; and bone transport technology that activates Piezo1 mechanoreceptors to enhance antioxidant defense. While these approaches represent promising investigational directions, direct evidence validating their efficacy against disulfidptosis in OA remains limited. Future studies must clarify the functional significance of disulfidptosis in OA and rigorously evaluate targeted therapies in preclinical models before clinical translation can be considered.

Keywords: osteoarthritis, disulfidptosis, chondrocytes, synovial cells, targeted therapy

Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis and a leading cause of chronic disability worldwide. Global estimates indicate that approximately 528 million people were living with OA in 2019, with the knee and hip being the most commonly affected joints.[1] OA is a chronic degenerative joint disease and a leading cause of disability worldwide, characterized by articular cartilage degeneration, synovial inflammation, subchondral bone sclerosis, and osteophyte formation. Its pathogenesis is multifactorial, involving aging, mechanical overload, metabolic dysregulation, and genetic susceptibility. Central to OA progression is a low-grade, persistent inflammatory response driven by pro-inflammatory cytokines and chemokines, which disrupt cartilage homeostasis and promote joint tissue destruction.[2] Although therapeutic strategies targeting these inflammatory pathways have been extensively explored, current treatments offer limited disease-modifying efficacy, underscoring the need to identify novel pathophysiological mechanisms and innovative therapeutic targets.[3]

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In recent years, the diversity of cell death modes and their roles in diseases have attracted attention. In addition to the classic apoptosis, necroptosis and ferroptosis, a novel form of programmed cell death, disulfidptosis, has emerged. Its characteristic is that under specific metabolic stress (such as glucose deprivation), excessive uptake of cystine within the cell (dependent on the high expression of SLC7A11) and depletion of the reduced cofactor NADPH lead to abnormal accumulation of disulfide bonds in cytoskeletal proteins and other sites, causing damage to the cytoskeletal network and subsequently cell death.[4] This mode of death is independent of the classic Caspase pathway and lipid peroxidation, providing a new perspective for understanding cell damage caused by metabolic and redox imbalances. The microenvironment of the OA joint often features metabolic disorders (such as abnormal glucose metabolism), elevated levels of oxidative stress, and continuous stimulation by pro-inflammatory factors. These conditions are highly consistent with the key prerequisites for inducing disulfide death.[5] This has prompted us to propose a scientific hypothesis: In the OA joint microenvironment, chronic inflammation and mechanical overload converge to induce metabolic stress and elevated reactive oxygen species (ROS), leading to altered glucose metabolism. This metabolic shift results in NADPH depletion and SLC7A11 upregulation—two established prerequisites for disulfidptosis—thereby creating a cellular milieu that is theoretically permissive to this novel form of cell death.

This study aims to systematically elucidate the potential role of disulfidptosis in the pathogenesis of OA and the corresponding targeted therapeutic strategies. We will begin by reviewing the classic inflammatory and metabolic pathogenesis mechanisms of OA. Secondly, the discussion focuses on elucidating the definition, molecular mechanisms, and general biological implications of disulfidptosis. This study delves into the pathogenesis of OA by investigating the specific triggers of disulfidptosis in chondrocytes and synovial cells within the OA pathological milieu. It further explores how this process exacerbates joint inflammation and tissue degradation through mechanisms such as the release of DAMPs, promotion of the SASP, and modulation of immune cell polarization—particularly the shift of macrophages toward the M1 phenotype. Collectively, these interactions contribute to a vicious cycle that accelerates OA progression. In conclusion, building upon the aforementioned mechanisms, this review explores potential therapeutic strategies for targeted inhibition of disulfidoptosis, encompassing phytochemicals, proprietary Chinese medicines, specific small-molecule inhibitors, intelligent hydrogel delivery systems, and physical interventions (eg, bone transport). These approaches offer novel theoretical foundations and therapeutic insights for the prevention and management of OA. This comprehensive review will contribute to a deeper understanding of the complex pathogenesis of OA and facilitate translational medical research targeting this novel form of cell death.

It is important to emphasize that direct experimental evidence confirming the occurrence of disulfidptosis in human OA joint tissues is currently lacking. The hypothesis presented in this review is based on extrapolation from the known metabolic and oxidative stress profiles of OA chondrocytes and synovial cells, which align conceptually with the established prerequisites for disulfidptosis. This article therefore serves as a hypothesis-generating synthesis aimed at stimulating targeted investigation rather than a statement of established fact.

Pathogenesis of OA

The pathogenesis of OA is complex, involving the interplay of mechanical stress, inflammatory responses, and metabolic dysregulation. At the molecular level, cytokines and chemokines mediate local inflammatory processes that drive articular cartilage degradation, synovial inflammation, and subchondral bone remodeling.[6] Pro-inflammatory cytokines —including IL-1β, TNF-α, and IL-6—are significantly upregulated in the OA joint. IL-1β binds to IL-1R and activates NF-κB, MAPK, and PI3K/Akt signaling pathways, stimulating chondrocytes and synovial cells to release matrix-degrading enzymes (MMPs/ADAMTS) and further inflammatory mediators.[7,8] TNF-α similarly activates NF-κB and MAPK via TNFR1/TNFR2, inducing chondrocyte apoptosis while suppressing collagen and proteoglycan synthesis.[9] IL-6 activates the JAK/STAT pathway, promoting synovial cell proliferation and osteoclast differentiation via RANKL, thereby accelerating subchondral bone remodeling.[10] Chemokines such as CCL2 and CXCL8 recruit immune cells into the joint cavity by activating PI3K/Akt and JAK/STAT signaling, facilitating infiltration of monocytes, macrophages, and neutrophils. This immune cell influx further amplifies the local inflammatory milieu, promoting synovial angiogenesis, nerve ingrowth, and synovial thickening.[11] Collectively, these cytokine and chemokine networks interconnect chondrocytes, synovial cells, and infiltrating immune cells to disrupt cartilage homeostasis, drive matrix degradation, and

accelerate OA progression.[12] Notably, the inflammatory and metabolic alterations described above—particularly oxidative stress and altered glucose metabolism—establish conditions that align with the known prerequisites for disulfidptosis, a novel cell death modality discussed in detail in the following sections. Figure 1

Despite decades of research, several fundamental questions regarding OA pathogenesis remain contentious. First, the "cytokine paradox" highlights a major translational gap: while preclinical studies consistently demonstrate that IL-1β and TNF-α drive cartilage degradation, multiple randomized controlled trials of IL-1 receptor antagonists and TNF-α inhibitors have failed to demonstrate significant disease-modifying effects in human OA.[13] This discrepancy has prompted debate regarding whether these cytokines are essential drivers of early disease or secondary amplifiers of established pathology, and whether redundant signaling pathways or compensatory mechanisms limit the efficacy of single-cytokine blockade. Second, the relative contribution of cartilage-intrinsic versus synovium-driven mechanisms to OA initiation is unresolved. Some evidence supports a "cartilage-first" model wherein biomechanical injury initiates chondrocyte stress responses and matrix degradation prior to synovial involvement, whereas other studies suggest that low-grade synovitis precedes and potentiates cartilage damage. Third, the functional significance of regulated cell death in OA remains poorly defined. While apoptosis of chondrocytes is well-documented, the contributions of ferroptosis, necroptosis, and disulfidptosis—and their potential interactions—have only recently begun to be explored. These controversies underscore the need for a critical re-evaluation of OA pathogenesis that integrates emerging concepts such as metabolic dysregulation and novel cell death pathways.

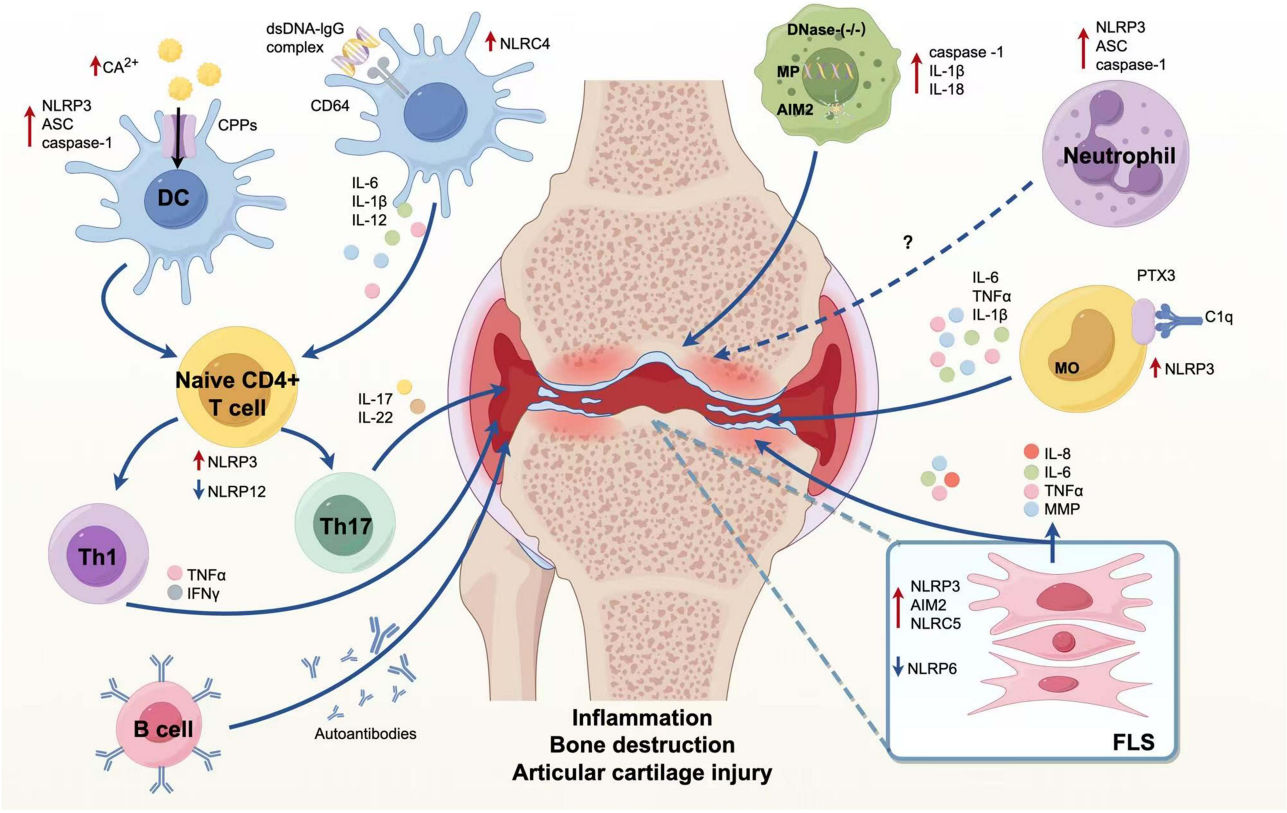

Figure 1 This figure systematically illustrates the immune regulatory network centered on inflammasomes such as NLRP3, AIM2, and NLRC4: Dendritic cells (DCs) activate NLRP3 or NLRC4 upon stimulation with CPP crystals or dsDNA-IgG complexes, secrete cytokines including IL-6 and IL-1β, and drive the differentiation of naive $CD4^+$ T cells into Th1 (secreting TNFα/IFNγ) and Th17 (secreting IL-17/IL-22) subsets. Macrophages (MOs) activate NLRP3 via the PTX3-C1q axis; neutrophils activate caspase-1 through the AIM2 inflammasome under DNase-deficient conditions and release IL-1β/IL-18; while fibroblast-like synoviocytes (FLS) act as key effector cells for local inflammation amplification by upregulating NLRP3/AIM2/NLRC5 and downregulating NLRP6. Meanwhile, autoantibodies produced by B cells further exacerbate tissue damage, ultimately synergistically driving inflammatory infiltration, bone destruction, and articular cartilage injury in joint tissues such as the knee joint, thus providing important mechanistic insights for targeted therapy of inflammatory joint diseases.

Notes: Legend symbols: Red ↑: Upregulation/increased expression or activity of the listed molecules; Blue ↓: Downregulation/decreased expression or activity of the listed molecules; Solid blue arrows: Confirmed biological interactions and processes (eg, cell activation, cytokine release, inflammatory effects on the joint); Dashed blue arrows (?): Unconfirmed or proposed mechanisms requiring further validation; Black solid arrows: Uptake of molecules into cells.

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Mechanism of Disulfidptosis

Definition and Characteristics of Disulfidptosis

Disulfidptosis represents a recently identified modality of cell death characterized by excessive accumulation of intracellular disulfide bonds, resulting in redox imbalance and cytoskeletal collapse. This process is fundamentally a form of programmed cell death triggered by intracellular disulfide stress.[14] A disulfide bond is a covalent linkage formed through the oxidation of sulfhydryl groups (-SH) derived from two cysteine residues, which contributes significantly to the stabilization of protein folding. However, under conditions of intracellular reductive stress deficiency, the excessive accumulation of disulfides within the cell can induce the formation of ectopic disulfide bonds among certain intracellular proteins—such as actin and tubulin—thereby leading to cytoskeletal disintegration and ultimately cell death.[15]

The morphological characteristics of disulfidptotic cells differ markedly from other forms of cell death, with cytoskeletal disruption and pronounced alterations in cellular morphology representing the most prominent hallmarks. Distinct from other forms of cell death such as apoptosis, necroptosis, and ferroptosis, disulfidptosis does not rely on lipid peroxide accumulation or caspase activation. Instead, it is directly triggered by aberrant disulfide bond cross-linking, leading to cytoskeletal disintegration and subsequent cell death.[16] Figure 2

Molecular Mechanism of Disulfidptosis

Two prerequisites are mandatory for disulfidptosis to occur: elevated expression of SLC7A11 and depletion of NADPH. These two factors collectively contribute to the abnormal accumulation of intracellular disulfide bonds, consequently triggering cell death. Table 1

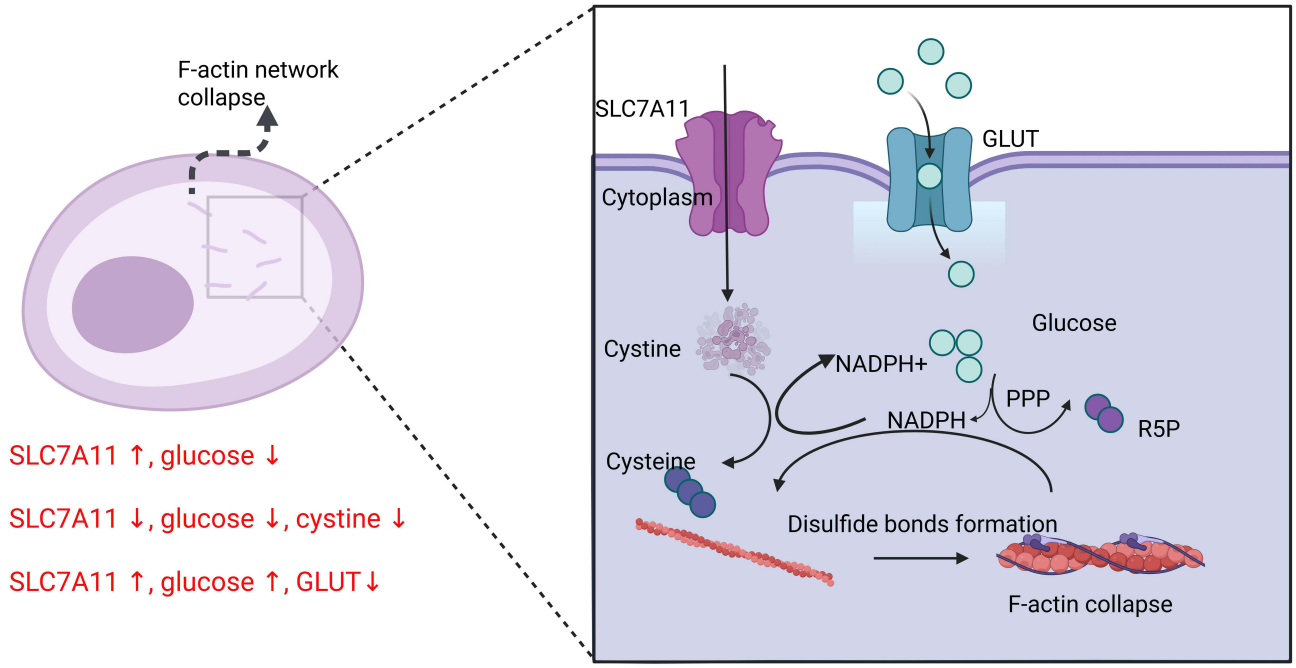

Figure 2 This figure systematically illustrates the molecular mechanism of a novel form of cell death — disulfidptosis (disulfide death), whose core lies in the synergistic imbalance between SLC7A11-mediated cystine metabolism and glucose metabolism. When cells encounter any of the three metabolic imbalance states: upregulated SLC7A11 expression accompanied by decreased glucose levels, downregulated SLC7A11 expression accompanied by simultaneous decreases in both glucose and cystine levels, or upregulated SLC7A11 expression accompanied by increased glucose levels but decreased GLUT expression/function, this leads to insufficient intracellular NADPH production, promotes the abnormal formation of disulfide bonds from cysteine, thereby disrupting the structural stability of the F-actin network, and ultimately triggering the collapse of the F-actin network and the induction of disulfidptosis, thus providing new mechanistic insights for the targeted regulation of cell fate and the treatment of related diseases.
Notes: Symbol definitions: Red ↑/↓ arrows indicate upregulation/downregulation of molecules. Solid black arrows represent biological processes including molecular transport, metabolic reactions, and functional consequences. Dashed black arrows denote magnified inset views or causal relationships leading to cellular outcomes.

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Table 1 Sequential Stages of Disulfidptosis

Stage	Core Event	Upstream Drivers	Key Molecules/ Mechanisms
NADPH Depletion	Intracellular NADPH is massively consumed, leading to the collapse of the reductive environment.	High SLC7A11 expression → Increased cystine import → Surge in NADPH demand. Low glucose supply / GLUT inhibitors → Reduced glucose uptake → Insufficient NADPH production (impaired Pentose Phosphate Pathway)	GLUT family, Pentose Phosphate Pathway (PPP)
Disulfide Stress	Intracellular redox balance is disrupted, leading to abnormal accumulation of disulfide bonds.	NADPH depletion resulting from Stage 1. Persistently high intracellular cystine levels (the core substrate for disulfide bond formation)	Cystine, Redox Imbalance
F-actin Network Collapse	Loss of structural integrity of the actin cytoskeleton.	Disulfide stress triggers aberrant intermolecular disulfide bonding in cytoskeletal proteins (eg, Actin), causing F-actin filaments to contract and detach from the plasma membrane.	F-actin, Abnormal Disulfide Cross-linking
Disulfidptosis	The cell executes programmed cell death.	High cystine levels activate the Rac-WRC pathway → Aberrant lamellipodia formation, amplifying cytoskeletal damage. Execution of the death program via molecules such as SLC7A11, SLC3A2, RPN1, and NCKAP1.	Rac-WRC signaling complex, Lamellipodia, NCKAP1 and other executioner molecules

Note: Arrows: right arrows (→) represent a sequential or causal effect in the signaling pathway.

The Role of SLC7A11

SLC7A11 functions as a pivotal transporter protein responsible for mediating the cellular uptake of extracellular cystine while facilitating the efflux of intracellular glutamate. During the biosynthesis of glutathione (GSH) from cystine via cysteine, GSH functions as an antioxidant to counteract oxidative stress. However, intracellular glucose deprivation can lead to depletion of NADPH. Insufficient NADPH hinders the reduction of cystine to cysteine, which may result in intracellular cystine accumulation, aberrant disulfide bond formation, cytoskeletal impairment, and ultimately, disulfidptosis.[17]

Under this condition, SLC7A11 exhibits a dual-edged function: on one hand, its elevated expression sustains the cellular antioxidative capacity; on the other hand, glucose deprivation impedes NADPH production, thereby preventing the conversion of cystine to cysteine. This leads to disulfide accumulation, resulting in disulfide stress and ultimately inducing cell death.[18]

Generation of NADPH Under Glucose Starvation Conditions

NADPH functions as the primary intracellular reducing cofactor, predominantly synthesized through the pentose phosphate pathway (PPP). Under conditions of glucose deprivation, cellular uptake of glucose is insufficient to sustain the hexokinase (HK)-mediated conversion of glucose into glucose-6-phosphate (G6P), thereby impeding its entry into the PPP for NADPH synthesis. The resultant decline in intracellular NADPH levels compromises the oxidation of cysteine to cystine, leading to impaired disulfide bond resolution. Consequently, excessive accumulation of disulfide bonds induces oxidative stress and ultimately triggers apoptosis.[19]

Activation of the RAC1-WRC Pathway

When a substantial quantity of disulfides accumulates within the cell, the Rac1-WRC signaling pathway becomes activated. In this process, Rac1 activates the NCKAP1 protein and promotes the assembly of the WAVE regulatory complex (WRC), which comprises subunits such as WAVE-2, CYFIP1, Abi2, and HSPC300. The WRC is capable of regulating actin polymerization and lamellipodia formation.[20] Upon exposure to disulfidptosis, activation of the Rac1-WRC signaling pathway triggers extensive rearrangement of the actin cytoskeletal network, resulting in disruption of cytoskeletal architecture and alterations in cellular morphology, ultimately culminating in cell death.

Clinical and Biological Significance of Disulfidptosis

Disulfidptosis represents a novel modality of regulated cell death. While its precise role in human disease is only beginning to be explored, the underlying mechanisms—abnormal disulfide accumulation and cytoskeletal disruption—may theoretically contribute to pathologies characterized by oxidative stress and metabolic dysregulation, including neurodegenerative disorders, malignancies, and cardiovascular diseases. Direct evidence linking disulfidptosis to these conditions is currently limited, and further investigation is required to determine its pathophysiological significance.[21]

Mechanisms of Disulfidptosis in Chondrocytes

In osteoarthritic conditions, chondrocytes persistently reside in a state of metabolic stress, thereby predisposing them to disulfidptosis. The mode of cell death may provide novel perspectives for investigating degenerative processes in osteoarthritic cells. Furthermore, it elucidates how metabolic dysregulation activates the inflammatory response via the NF-κB signaling pathway and subsequently exacerbates OA progression.[22]

Inducers of Disulfidptosis in Chondrocytes

Osteoarthritic chondrocytes exhibit distinctive metabolic profiles and microenvironmental alterations that render them particularly susceptible to disulfidptosis induction. It is crucial to emphasize that direct experimental evidence confirming the occurrence of disulfidptosis in primary human osteoarthritic chondrocytes or synovial cells remains limited. The following discussion extrapolates from the documented metabolic characteristics of OA joint tissues—specifically, confirmed upregulation of SLC7A11 in response to IL-1β,[23] impaired glucose uptake and glycolytic flux,[24] and elevated oxidative stress—to construct a hypothetical framework wherein these established conditions create a permissive cellular environment conducive to disulfidptosis.[25] This mechanistic extrapolation serves as a rationale for future targeted investigation rather than a statement of established fact.

Metabolic Imbalance and Susceptibility to Disulfidptosis

OA chondrocytes exhibit SLC7A11 upregulation in response to inflammatory cytokines such as IL-1β and TNF-α, leading to increased cystine uptake for glutathione biosynthesis.[26] However, under conditions of NADPH depletion, cystine cannot be efficiently reduced to cysteine, resulting in intracellular cystine accumulation and disulfide stress.[27]

Concurrently, OA chondrocytes experience impaired glucose uptake due to chronic inflammation and oxidative stress, limiting glycolytic flux and reducing NADPH production via the pentose phosphate pathway.[28] This NADPH deficiency compromises the cellular reductive capacity, thereby creating a permissive environment for disulfidptosis.[29]

Research indicates that the SASP upregulates the expression of oxidative stress response genes in chondrocytes via transcription factors such as TCF7L2, thereby increasing the susceptibility of chondrocytes to disulfidptosis.[30] The SASP constitutes a specific secretory profile characteristic of senescent cells. It encompasses a group of secretory factors, including numerous pro-inflammatory cytokines and immunomodulatory mediators, which play a critical role in OA progression. Furthermore, senescent chondrocytes can release the aforementioned factors into the local microenvironment, thereby exacerbating the inflammatory response locally. This process may lead to elevated oxidative stress levels within chondrocytes by activating signaling pathways such as NF-κB, subsequently inducing the onset of disulfidptosis.[31,32] The aforementioned metabolic dysregulation observed in OA chondrocytes, the overexpression of SLC7A11, excessive cystine uptake, and the deficiency of NADPH collectively contribute to the induction of oxidative stress and abnormal accumulation of disulfide bonds. Under the cumulative effects of these four phenomena, the likelihood of osteoarthritic chondrocytes undergoing disulfidptosis is significantly enhanced. Furthermore, it leads to metabolic imbalances in cells and promotes the secretion of inflammatory factors, thereby initiating a vicious cycle that exacerbates chondrocyte apoptosis.[33,34]

Impact of Disulfidptosis on Chondrocytes

Disulfidptosis not only induces cell death in OA chondrocytes, but also exerts broader impacts on the inflammatory microenvironment of the joint.

Loss of Chondrocyte Function

Disulfidptosis induces direct chondrocyte death and impairs their extracellular matrix synthesis capacity. Chondrocytes serve as the pivotal cellular entities responsible for maintaining the synthesis and reparative functions of the cartilage matrix. During disulfidptosis of chondrocytes, their ability to synthesize extracellular matrix components such as collagen and proteoglycans is compromised, consequently impairing both repair and regenerative functions of the cartilage matrix.[35] Once articular cartilage matrix is compromised, the load-bearing capacity of the joint diminishes, articular surfaces become irregular, and increased friction within the joint cavity accelerates the progression of OA.[36]

Release of Damage-Associated Molecular Patterns and Senescence-Associated Secretory Phenotype Factors

Disulfidptosis not only induces chondrocyte death but also triggers the secretion of DAMPs and SASP factors by chondrocytes. DAMPs refer to a class of molecules released upon cellular death that activate immune responses in the organism. These immunostimulatory molecules initiate local immune reactions and facilitate the development of local inflammatory responses.[37] In the OA microenvironment, fibroblast-like chondrocytes, synovial cells, and immune cells can all be activated by reactive oxygen species (ROS) and subsequently produce DAMPs. These DAMPs can induce both localized and systemic pro-inflammatory responses, further exacerbating tissue necrosis in the affected area. SASP factors facilitate the establishment of both local and systemic inflammatory microenvironments, induce pyroptosis in adjacent cells, and modulate cytokine networks to exert persistent pro-inflammatory effects on synovial and immune cells.[38]

Form a Self-Perpetuating Vicious Circle

Following chondrocyte disulfidptosis, the released DAMPs and SASP factors activate local immune cells, which subsequently secrete additional proinflammatory cytokines such as IL-1β, TNF-α, and IL-6. Disulfidptosis promotes cartilage matrix degradation by mediating the release of death-associated DAMPs and SASP factors.[39] On the other hand, it accelerates chondrocyte death, thereby continuously stimulating immune cells to produce additional pro-inflammatory cytokines, ultimately establishing a positive-feedback inflammatory cycle. With the propagation of this inflammatory response and the progressive degradation of cartilage matrix, OA progressively advances in severity.[40,41]

The Impact of Disulfidptosis on OA Progression

Following disulfidptosis in chondrocytes, cellular demise, inflammatory amplification, extracellular matrix degradation, and aberrant bone remodeling can be triggered, thereby further exacerbating the onset and progression of OA. Due to the unique metabolic characteristics of chondrocytes, disulfide-dependent cell death plays a pivotal role in the degeneration of OA. Modulating SLC7A11 expression, improving glucose metabolism, or enhancing NADPH production can mitigate the progression of OA.[42–44]

Mechanism of Disulfidptosis in Synovial Cells

In the OA joint, synovial cells—including synovial fibroblasts and macrophages—exist in a hypermetabolic and inflamed state. Based on the known metabolic prerequisites for disulfidptosis, it is plausible to hypothesize that these cells may be susceptible to this form of cell death, although direct evidence in OA synovial tissue is not yet available.[45,46]

Triggers of Disulfidptosis in Synovial Cells

Synovial cells, particularly synovial fibroblasts and macrophages, are situated within the inflammatory milieu of OA and frequently exhibit a state of heightened metabolic activity. This elevated metabolic state renders them susceptible to disruptions in metabolic equilibrium and oxidative stress.[47] The primary inducers of disulfidptosis in synovial cells are as follows.

Insufficient Glucose Supply and NADPH Depletion

Synovial cells exhibit impaired glucose uptake under pathological conditions of OA. Under OA conditions, articular joints are subjected to persistent mechanical loading and inflammatory stimulation, leading to reduced glucose transport in synovial cells. This results in restricted energy acquisition via glycolysis. Consequently, insufficient glucose availability attenuates the activity of the PPP and diminishes NADPH production. NADPH is a crucial cofactor that maintains the intracellular reduced state, counteracts oxidative stress, and participates in the synthesis of glutathione (GSH).[48,49]

Therefore, due to the deficiency of NADPH, the intracellular antioxidative capacity is compromised, rendering the cells susceptible to oxidative stress and ultimately leading to disulfidptosis.[50]

Elevated Fatty Acids and Increased Metabolic Stress

In addition to OA related to gout, in obesity-related OA, the increase in FAF levels is also another important cause of disulfidptosis of synovial cells. Under conditions of a high-fat diet or obesity, elevated FAF levels impair the efficient utilization of glucose by synovial cells, thereby inducing greater metabolic stress.[51,52] When the FAF level increases further, the intracellular glucose supply becomes insufficient, leading to a gradual decline in NADPH content. This results in an excessive accumulation of disulfides, ultimately inducing disulfidptosis in synovial cells.[53]

Senescence and the SASP Response

In OA, the SASP promotes synovial cell disulfidptosis by inducing alterations in the expression of oxidative stress-related genes. Specific SASP factors (eg, IL-1β, IL-6, TNF-α) can enhance the susceptibility of synovial cells to disulfidptosis, which in turn amplifies local inflammation, exacerbates the metabolic burden on synovial cells, and establishes a vicious cycle.[54,55]

Polarization Orientation of Synovial Cells

Disulfidptosis in synovial cells not only directly impacts cellular viability but also exacerbates OA progression by modulating the polarization state of immune cells. In particular, the polarization state changes of synovial macrophages are directly related to the inflammatory response and cartilage destruction in OA. Studies in non-OA systems have reported that cells undergoing disulfidptosis release DAMPs that can promote M1 macrophage polarization.[56] Given that OA synovium is characterized by M1 macrophage predominance and elevated DAMP levels, it is plausible to hypothesize that disulfidptotic synovial cells might contribute to this polarization shift. However, whether disulfidptosis-derived DAMPs specifically drive M1 polarization in the unique microenvironment of the OA joint has not been empirically demonstrated. Future studies using co-culture systems of disulfidptotic synovial fibroblasts with naïve macrophages are needed to test this proposed link.

M1 Polarization of Macrophages

Studies have reported that synovial macrophages undergoing disulfidptosis exhibit a propensity to polarize toward the M1 phenotype.M1 macrophages express elevated levels of proinflammatory cytokines, such as TNF-α, IL-1β, and IL-6, thereby promoting synovial inflammation and stimulating chondrocytes to secrete matrix-degrading enzymes (eg, MMPs), which exacerbate the degradation of the cartilage matrix. Simultaneously, the accumulation of M1-type macrophages represents one of the key contributors to pathological bone resorption and joint swelling in inflammatory manifestations.[57,58]

Disulfidptosis induces cytoskeletal remodeling, which subsequently disrupts intracellular signaling pathways. The accumulation of disulfides and aberrant cross-linking of scaffold proteins can compromise signal transduction pathways. Moreover, injuries to the skeletal system can alter receptor signaling, thereby activating several pro-inflammatory signaling pathways and promoting M1 macrophage polarization.[59,60]

A deficiency of NADPH compromises antioxidant capacity across various organs and tissues and alters numerous signaling pathways implicated in metabolic and immune responses. Furthermore, research indicates that NADPH depletion under the influence of disulfidptosis inhibitors can affect the activity of PPARγ (peroxisome proliferator-activated receptor gamma), thereby promoting a shift toward M1 polarization in macrophages. PPARγ, as a key transcription factor, plays a regulatory role in lipid metabolism and inflammatory responses. Reduced PPARγ activity may enhance the pro-inflammatory phenotype of M1 macrophages.[61] Additionally, disulfidptosis activates the NF-κB signaling pathway to promote macrophage polarization, which plays a critical role in facilitating the secretion of pro-inflammatory cytokines.[62–64]

Disulfidptosis induces the release of DAMPs from cells, which activates immune receptors such as TLR and subsequently triggers localized immune responses. The accumulation of DAMPs not only activates synovial macrophages but also promotes their polarization toward the M1 phenotype. The subsequent excessive secretion of inflammatory cytokines further disrupts the synovial tissue barrier.[65–68]

Impact of Disulfidptosis in Synovial Cells on OA Progression

Synovial cell disulfidptosis contributes to the onset and progression of OA by modulating immune cell polarization and altering localized inflammatory responses. Following disulfidptosis, synovial cells release DAMPs and SASP factors into the surrounding microenvironment. These released mediators activate local synovial fibroblasts, macrophages, and other immune cells, thereby inducing the secretion of additional proinflammatory cytokines such as IL-1β, TNF-α, and IL-6, thereby exacerbating joint inflammation and cartilage matrix degradation, forming a vicious cycle.[69,70] Simultaneously, the polarization of M1 macrophages promotes increased secretion of matrix-degrading enzymes, such as MMPs and ADAMTS, thereby accelerating the degradation of the cartilage matrix.[71,72] Concurrently, the secretion of inflammatory factors adversely affects chondrocytes and interferes with subchondral bone remodeling, leading to osteoporosis and skeletal degeneration.[73,74] The phenomenon of disulfidoptosis, along with alterations in the polarization state of synovial cells, may also inflict damage on non-chondrocytic cells and immune cells within the joint, thereby compromising articular structure and function. Modulating the metabolic and immune polarization status of synovial cells can, to a certain extent, decelerate or mitigate the progression of OA.[74,75]

Synovial cell disulfidptosis not only induces cellular apoptosis but also promotes the progression of pan-articular OA pathologies by modulating immune cell polarization, particularly through the transition of synovial macrophages toward the M1 phenotype. Furthermore, disulfidptosis can exacerbate local inflammatory responses and cartilage matrix degradation in OA through mechanisms such as cytoskeletal rearrangement, NADPH depletion-induced metabolic alterations, as well as the secretion of DAMPs and activation of TLR signaling pathways.[60,76–79] Therefore, disulfidptosis in synovial cells may constitute a critical component in the pathogenesis of OA and could serve as a potential therapeutic target for this condition. Table 2

Targeted Inhibition of Disulfidptosis Mitigates OA

Given the pivotal role of disulfidptosis in OA, various targeted therapeutic strategies are being explored, offering new avenues for OA treatment. Given the hypothesized role of disulfidptosis in OA, several approaches that modulate redox balance and metabolic stress warrant investigation as potential interventional strategies. It is important to note that none of the following agents or techniques have been clinically validated for the specific purpose of inhibiting disulfidptosis in OA patients. Their mention is based on mechanistic plausibility and their known effects on the molecular prerequisites of disulfidptosis (eg, SLC7A11 expression, NADPH levels).

Phytochemicals

Several phytochemicals, including curcumin, resveratrol, and quercetin, possess well-documented antioxidant properties and can modulate NADPH homeostasis and reduce oxidative stress.[80–82] While none of these compounds have been directly evaluated for their ability to inhibit disulfidptosis in OA chondrocytes or synovial cells, their capacity to mitigate the redox imbalance that predisposes cells to disulfidptosis provides a mechanistic rationale for their consideration as potential investigational agents.

Chinese Patent Medicine

Duhuo Jisheng Decoction represents a quintessential formulation in the realm of traditional Chinese medicine. Through dual inhibition of COX-2/5-LOX, it effectively suppresses inflammation and reduces the production of prostaglandins, leukotrienes, and related mediators. Both Biqi Capsules and Guizhi Fuling Pills are multi-target traditional Chinese medicinal preparations characterized by their multi-component composition and multi-target mechanism of action. They synergistically regulate various pathological processes, including inflammation, cell death, and extracellular matrix metabolism.[83–86]

Disulfidoptosis Inhibitor

Specific inhibitors for targeted induction of disulfidptosis include SLC7A11 inhibitors (which reduce cystine uptake in the cytoplasm), G6PD activators (which enhance the PPP and NADPH production), AMPK agonists (such as metformin, which

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Table 2 Summary of Established and Hypothesized Pathways Linking OA Pathogenesis to Disulfidptosis

Category	Component/Pathway	Description	Evidence Status in OA	Potential Interventional Node
OA Risk Factors	Mechanical overload	Excessive joint loading initiates chondrocyte stress responses.	Established	Weight management; Activity modification
	Aging	Age-related accumulation of senescent cells and oxidative damage.	Established	Senolytics (experimental)
	Obesity	Adipose tissue-derived inflammatory mediators contribute to systemic inflammation.	Established	Weight loss interventions
Established OA Pathways	IL-1β, TNF-α, IL-6 → NF-κB/MAPK activation	Cytokine-driven signaling directly promotes MMP/ADAMTS expression, cartilage degradation, and synovitis.	Established	Anti-cytokine therapies; NF-κB inhibitors
	MMPs/ADAMTS upregulation	Enzymatic degradation of type II collagen and aggrecan in articular cartilage.	Established	MMP inhibitors (clinical trials)
	Synovial inflammation and subchondral bone remodeling	Hallmark pathological features of OA progression.	Established	Anti-inflammatory agents
Metabolic Alterations in OA Joint	Glucose deprivation	Impaired glucose uptake and glycolytic flux documented in OA chondrocytes.	Established	Metabolic modulators
	Oxidative stress	Elevated ROS levels and compromised antioxidant capacity.	Established	Antioxidants
	NADPH depletion	Reduced PPP activity leads to diminished reducing equivalents.	Established	NADPH precursors; G6PD activators
	SLC7A11 upregulation	Documented increase in response to IL-1β and oxidative stress in OA joint tissues.	Established	SLC7A11 inhibitors (experimental)
Hypothesized Disulfidptosis Pathway	SLC7A11 ↑ + NADPH ↓ → Cystine accumulation → Disulfide stress	Metabolic conditions in OA create a permissive environment for abnormal disulfide bond accumulation.	Hypothesized	G6PD activators; Cystine uptake inhibitors
	Actin cross-linking → RAC1-WRC activation → Cytoskeletal collapse	Aberrant disulfide bonding triggers cytoskeletal disintegration and cell death.	Hypothesized	RAC1 inhibitors (experimental)
Proposed Downstream Consequences	Release of DAMPs and SASP factors	Disulfidptotic cells may release immunostimulatory molecules that amplify local inflammation.	Hypothesized	DAMP antagonists; Senolytics
	M1 Macrophage Polarization	DAMPs and inflammatory milieu potentially shift synovial macrophages toward a pro-inflammatory M1 phenotype.	Hypothesized	PPARγ agonists; NF-κB inhibitors
	Exacerbation of cartilage degradation	The proposed vicious cycle theoretically accelerates OA progression.	Hypothesized	Combination therapies
Potential Therapeutic Strategies	Phytochemicals (Curcumin, Resveratrol)	Modulate redox balance and exert anti-inflammatory effects.	Indirect support; Not validated for disulfidptosis in OA	Oral/local supplementation
	Traditional Chinese medicines (Duhuo Jisheng Decoction)	Multi-target anti-inflammatory and metabolic regulatory properties.	Indirect support	Oral administration
	SLC7A11 inhibitors; G6PD activators	Direct targeting of molecular prerequisites for disulfidptosis.	Experimental; Not tested in OA models	Small molecules
	Hydrogel drug delivery systems	Enable localized, sustained release of therapeutic agents to the joint.	Established drug delivery platform	Intra-articular injection
	Bone transport technology (Piezo1 activation)	Mechanical stimulation may enhance Nrf2-mediated antioxidant defense.	Indirect mechanistic link	Physical rehabilitation

Notes: Arrows: Upward (↑) and downward (↓) arrows indicate upregulation and downregulation, while right arrows (→) represent a sequential or causal effect in the signaling pathway.

maintain cytoplasmic NADPH levels), and YBX1 modulators (which affect intracellular AMPK protein content). Intervening in the disulfidptosis signaling pathway from multiple perspectives represents a highly promising class of novel therapeutics.[87–90]

Combination Therapy Utilizing Hydrogel-Loaded Anti-Inflammatory Factors and Phytochemicals

Hydrogels represent a promising platform for the localized, sustained delivery of therapeutic agents to the OA joint. In the context of disulfidptosis, hydrogels could be engineered to encapsulate and release redox-modulating phytochemicals, SLC7A11 inhibitors, or NADPH precursors directly into the synovial space, thereby maximizing local efficacy while minimizing systemic exposure.[91–94]

Role of Piezo1 Receptor in Bone Transport on the Impact of Disulfidptosis

Bone transport techniques can suppress disulfidptosis via mechanical microstress, which is potentially mediated through the Piezo1 receptor pathway. As a mechanosensitive cation channel, Piezo1 enhances cellular antioxidant defense mechanisms via the Nrf2 signaling pathway, improves cellular metabolism through AMPK activation, and attenuates inflammatory signaling by suppressing NF-κB activity following its activation. These coordinated actions mitigate disulfidptosis and promote cartilage repair. However, the magnitude and frequency of mechanical stress are of paramount importance, as excessive load may induce opposite effects through channels such as TRPV4 and TRPA1.[95–98]

3D Printing and Bioink Synergistic Therapy

3D bioprinting technology offers a versatile platform for fabricating patient-specific scaffolds that can be functionalized with bioinks containing disulfidptosis-modulating agents. This approach may enable precise, localized delivery of therapeutics alongside structural cartilage repair, representing a potential future direction for combinatorial OA therapy.[99,100]

Conclusion and Foresight

Disulfidptosis represents a novel and intriguing mode of regulated cell death that may hold relevance for the complex pathophysiology of osteoarthritis. The metabolic hallmarks of OA—chronic inflammation, oxidative stress, and glucose dysmetabolism—align conceptually with the known triggers of disulfidptosis, namely SLC7A11 overexpression and NADPH depletion. This review has synthesized these parallel lines of evidence to propose a hypothetical framework wherein disulfidptosis could serve as an amplifying mechanism of joint degeneration.

However, it is essential to acknowledge the current limitations of this field. Direct, causal evidence linking disulfidptosis to OA progression in animal models or human clinical samples is still lacking. The therapeutic strategies discussed herein—phytochemicals, traditional medicines, specific inhibitors, hydrogel delivery systems, and mechanical stimulation—should be viewed as experimental concepts grounded in mechanistic plausibility, not as established or clinically applicable treatments for OA targeting this specific death pathway.

Moving forward, priority must be given to validating the occurrence and functional significance of disulfidptosis in OA-specific contexts. This will require the development of sensitive biomarkers to detect disulfidptosis in situ, the use of genetically modified mouse models (eg, inducible chondrocyte-specific Slc7a11 knockout), and rigorous pharmacological studies to dissect the contribution of disulfidptosis relative to other forms of cell death (apoptosis, ferroptosis) in joint tissues. Only through such dedicated investigation can the true translational potential of targeting disulfidptosis for OA therapy be rigorously evaluated.

Data Sharing Statement

This is a review article, and all relevant information is provided in the article.

Ethical Approval and Consent to Participate

This is a review paper and does not involve direct research on humans or animals.

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Disclosure

The authors report no conflicts of interest in this work.

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