Ferroptosis Piezo1 and Cartilage Degeneration in Osteoarthritis: A Survey

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Abstract

This survey explores the interconnected roles of ferroptosis, Piezo1, and mechanotransduction in osteoarthritis (OA), focusing on their impact on chondrocyte behavior and cartilage integrity. Ferroptosis, characterized by iron-dependent lipid peroxidation, significantly contributes to cartilage degradation and chondrocyte apoptosis. Piezo1, a mechanosensitive ion channel, mediates mechanotransduction, converting mechanical stimuli into biochemical responses essential for cartilage health. The survey highlights the influence of inflammation and mechanical stress on OA progression, emphasizing the need for integrated therapeutic approaches. Pharmacological interventions, such as RCGD 423 and Loganin, target inflammatory pathways and cellular signaling mechanisms, while lifestyle modifications, including weight management and physical activity, are crucial for effective OA management. The potential of advanced imaging techniques and biomaterials, such as hydrogels, is also discussed, underscoring their role in enhancing diagnostic accuracy and treatment efficacy. The survey concludes by advocating for a comprehensive approach that combines diagnostic advancements, pharmacological therapies, and lifestyle interventions to improve patient outcomes and quality of life in OA.

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1 Introduction

1.1 Significance of Osteoarthritis

Osteoarthritis (OA) is the most prevalent degenerative joint disease, affecting millions globally and imposing significant economic burdens through healthcare costs and lost productivity. It primarily impacts the knee, rendering knee OA a leading cause of disability among the elderly [1]. The disease is characterized by the progressive degeneration of articular cartilage, osteophyte formation, and alterations in subchondral bone, which collectively compromise joint integrity.

The incidence of OA is particularly high in aging populations, with projections indicating a rise as the global demographic ages [2]. This trend emphasizes the urgent necessity for innovative therapeutic strategies that not only alleviate symptoms but also address the underlying mechanisms of OA. The limited self-repair capacity of adult articular cartilage complicates management efforts, underscoring the need for a deeper understanding of the disease's pathophysiology and the development of more effective treatment modalities [3].

Beyond physical health, OA significantly diminishes quality of life due to chronic pain and reduced mobility [4]. This situation highlights the importance of early detection and intervention strategies to mitigate joint damage and enhance patient outcomes. Current challenges in OA management include the difficulty of delivering therapeutic agents through the dense extracellular matrix of cartilage, which limits the efficacy of treatments aimed at halting disease progression [5]. Thus, advancements in diagnostic techniques and therapeutic approaches that effectively target OA's pathophysiological processes are critically needed.

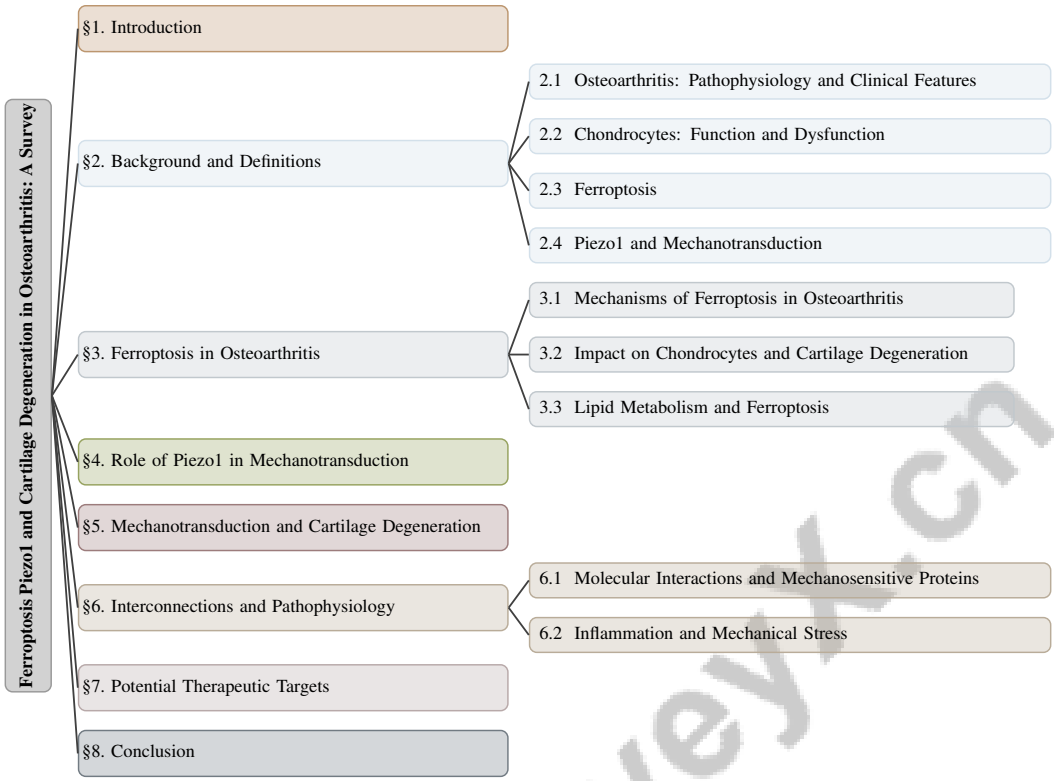

Figure 1: chapter structure

1.2 Interconnectedness of Key Elements

Understanding the pathogenesis of osteoarthritis (OA) requires examining the intricate interplay between ferroptosis, Piezo1, and cartilage degeneration. Ferroptosis, a newly identified form of regulated cell death, is characterized by the iron-dependent accumulation of lipid peroxides and reactive oxygen species (ROS), significantly affecting chondrocyte viability and contributing to cartilage tissue degradation. This process, distinct from traditional apoptotic pathways, is triggered by factors such as glutathione peroxidase 4 (GPX4) inhibition and cysteine starvation, leading to increased lipid peroxidation. Elucidating ferroptosis mechanisms is essential for developing therapeutic strategies against cartilage degeneration [6].

Piezo1, a mechanosensitive ion channel, plays a critical role in mechanotransduction, converting mechanical stimuli into biochemical signals that regulate cellular function and maintain cartilage integrity. Mechanical loading and cellular responses are interconnected processes that influence lesion formation in articular cartilage, a key aspect of OA progression [7]. Additionally, lubrication mechanisms, including boundary and hydration lubrication, are vital for cartilage health, which is compromised in OA [8]. The inability of current treatments to effectively prevent cartilage degradation underscores the necessity for a deeper understanding of these interconnected pathways [9].

Advanced imaging techniques are crucial for assessing knee cartilage defects, which are key manifestations of OA [1]. Electromagnetic stimulation has also been proposed to induce mechanical forces within cells, potentially modulating their functions and influencing mechanotransduction processes involved in OA [2]. Thus, comprehending the complex interactions between ferroptosis, Piezo1, and cartilage degeneration is vital for developing innovative diagnostic and therapeutic strategies to improve OA management and patient outcomes [3].

1.3 Structure of the Survey

This survey is systematically organized to explore the multifaceted interplay between ferroptosis, Piezo1, and cartilage degeneration within the context of osteoarthritis (OA). The introduction estab-

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lishes the significance of OA, emphasizing its prevalence and public health impact, and elucidates the interconnectedness of ferroptosis, Piezo1, and cartilage degeneration. The background section provides foundational definitions and explanations of key concepts, including OA pathophysiology, the role of chondrocytes, and the mechanisms of ferroptosis and mechanotransduction.

Subsequent sections delve into the specific roles and mechanisms of ferroptosis in OA, examining its biochemical pathways and impact on chondrocytes and cartilage integrity. The survey transitions to the role of Piezo1 in mechanotransduction, detailing its function as a mechanosensitive ion channel and its influence on chondrocyte behavior. The implications of mechanotransduction for cartilage degeneration are also explored, focusing on integrin-mediated pathways and chondrocyte morphology.

The interconnections and pathophysiology section analyzes the molecular interactions between ferroptosis, Piezo1, and mechanotransduction, along with the contributions of inflammation and mechanical stress to OA progression. The survey concludes by identifying potential therapeutic targets within these pathways, reviewing current strategies, and exploring pharmacological and lifestyle interventions.

Throughout the paper, advanced imaging techniques and innovative methodologies are discussed, including the Swin Transformer architecture for classifying knee OA severity [10], the Diffusion-based Morphing Model for representing KOA progression [11], and the Cartilage-on-Chip platform for testing disease-modifying osteoarthritis drug candidates [12]. Additionally, the investigation of biomarkers related to synovitis and pain [13], as well as the roles of lncRNAs in cartilage processes [4], provides a comprehensive overview of current research and emerging directions in OA management.The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Osteoarthritis: Pathophysiology and Clinical Features

Osteoarthritis (OA) is a degenerative joint disorder marked by the gradual degradation of articular cartilage, leading to joint pain and functional limitations [4]. Its pathophysiology is driven by mechanical, biological, and inflammatory factors, with mechanoflammation playing a pivotal role. This process involves mechanical stress-induced inflammation that exacerbates cartilage damage, though the precise upstream activators remain unclear [14]. Chondrocytes, the cartilage's primary cells, undergo phenotypic changes and senescence in OA, impairing their reparative capabilities and accelerating disease progression [9]. The breakdown of collagen and aggrecan compromises cartilage's structural integrity, increasing susceptibility to mechanical stress [8]. Inflammatory cytokines, such as interleukin-1 and tumor necrosis factor-alpha, further influence chondrocyte activity and perpetuate tissue degradation [4].

Clinically, OA presents with joint pain, stiffness, and reduced mobility, varying widely among patients and complicating diagnosis and management. Traditional radiographic techniques often fail to detect early cartilage changes, necessitating advanced imaging modalities like MRI for accurate evaluation [1]. However, challenges such as artifacts from bone marrow lesions and cysts complicate automated segmentation of knee structures. The subjective Kellgren-Lawrence grading system for OA severity underscores the need for objective, automated evaluation systems [15]. Moreover, the limitations of conventional biomechanical data in predicting disease progression highlight the importance of incorporating comprehensive movement analyses and advanced modeling techniques to enhance prognostic accuracy [3]. Addressing these challenges through improved diagnostic and therapeutic strategies is critical for optimizing patient outcomes and enhancing the quality of life for individuals with OA.

2.2 Chondrocytes: Function and Dysfunction

Chondrocytes, the sole cellular constituents of articular cartilage, synthesize and maintain the extracellular matrix (ECM), which includes collagen and proteoglycans essential for cartilage's mechanical resilience and structural integrity. Their unique morphology, characterized by a rounded shape and condensed nucleus, reflects their specialized function within the cartilage matrix [16]. Chondrocytes are highly responsive to mechanical stimuli, with cyclic loading influencing their metabolic activity and contributing to cartilage lesion development [7]. In OA, chondrocytes undergo de-differentiation and apoptosis, impairing ECM maintenance and increasing cartilage vulnerability

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to degradation [17]. This dysfunction is exacerbated by mechanical and oxidative stress, along with inflammatory cytokines like TNF-, disrupting the balance between ECM synthesis and degradation [17]. Consequently, the breakdown of collagen and aggrecan networks accelerates OA progression [4].

The complexity of chondrocyte dysfunction in OA is further compounded by interactions of long non-coding RNAs (lncRNAs) with signaling pathways regulating chondrocyte activity and cartilage health [4]. Despite advancements in imaging techniques, challenges persist in accurately assessing cartilage health due to difficulties in delineating bone and cartilage structures amidst artifacts such as bone marrow lesions [18]. While automated segmentation methods show promise, they continue to encounter obstacles in evaluating chondrocyte function and dysfunction [1]. Developing effective in vitro models to study chondrocyte behavior and dysfunction is crucial for advancing our understanding of OA pathogenesis and for developing targeted therapies [16]. Enhancing the identification of motion-based biomarkers through advanced imaging and motion capture systems aims to improve evaluations of chondrocyte function and its impact on joint health [1]. Addressing these challenges is essential for developing therapeutic strategies that preserve cartilage integrity and mitigate OA progression, ultimately improving patient outcomes and quality of life.

2.3 Ferroptosis

Ferroptosis is a regulated form of cell death characterized by iron dependency and lipid peroxide accumulation, leading to oxidative damage and plasma membrane disruption. Unlike apoptosis and necrosis, ferroptosis is primarily driven by iron-catalyzed lipid peroxidation, a critical pathway in the pathophysiology of various diseases, including OA [19]. In OA, ferroptosis contributes to articular cartilage deterioration, where oxidative stress plays a pivotal role in exacerbating cartilage damage [8]. The interplay between cyclic mechanical loading and ferroptosis is significant, as repetitive compressive forces can enhance therapeutic agent penetration, potentially influencing the oxidative environment within cartilage tissue [5]. Understanding cartilage biomechanics, such as lubrication mechanisms, is crucial for maintaining joint health and mitigating ferroptosis effects. Lubrication mechanisms, categorized into boundary and hydration lubrication, are essential for sustaining low friction in articular cartilage, thus preserving its structural integrity [8].

Recent methodologies, such as Elastic Shape Analysis, provide insights into biomechanical variations in cartilage, capturing amplitude and phase variations critical for understanding OA progression [20]. Studying ferroptosis in cellular biology not only elucidates cartilage degeneration mechanisms but also offers potential therapeutic targets for intervention in joint diseases. By exploring the intricate relationship between iron metabolism, lipid peroxidation, and cellular oxidative stress, researchers can develop novel strategies to manage and treat OA effectively.

2.4 Piezo1 and Mechanotransduction

Piezo1, a critical mechanosensitive ion channel, mediates cellular responses to various mechanical stimuli, such as hydrostatic pressure and tensile force, playing an essential role in mechanotransduction [21]. Mechanotransduction refers to the conversion of mechanical signals into biochemical responses, fundamental to various physiological processes, including maintaining cartilage health and function [22]. In chondrocytes, Piezo1, along with its homolog Piezo2, acts as a key sensor of mechanical stimuli, influencing cellular behavior and maintaining cartilage integrity [23]. The mechanotransduction process involves intricate interactions between the cytoskeleton, focal adhesions, and specific proteins responsible for mechanosensing and signal transduction [24]. These interactions are vital for sustaining cellular homeostasis and adapting to mechanical changes within the environment. The CDM model, integrating the tensegrity concept with divided medium mechanics, captures dynamic changes in connectivity and mechanical interactions that characterize real cellular behavior, further highlighting the complexity of mechanotransduction pathways [25].

The biophysical properties of the cellular environment, including the extracellular matrix and anionic lipids, modulate the activity of mechanosensitive proteins like Piezo1 [26]. This modulation underscores the multifaceted nature of mechanotransduction, where mechanical signals integrate across different cellular structures, such as the cytoskeleton and organelles [27]. Advanced biophysical tools and methodologies, such as traction force microscopy, magnetic twisting cytometry, and shear flow microfluidic devices, are instrumental in elucidating mechanotransduction mechanisms by

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providing experimental validation of theoretical models [28]. Piezo1's role in mechanotransduction extends to linking mechanical stimuli with inflammatory signaling pathways, which has significant implications for tissue injury and fibrosis [29]. Understanding the mechanobiology of Piezo1 and its contribution to cellular mechanotransduction is crucial for elucidating OA pathophysiology and identifying potential therapeutic targets for intervention.

In recent years, the study of ferroptosis has gained significant attention, particularly in the context of osteoarthritis. Understanding the intricate mechanisms underlying this form of regulated cell death is crucial for developing effective therapeutic strategies. As illustrated in Figure 2, the hierarchical structure of ferroptosis mechanisms and their impacts in osteoarthritis is depicted, categorizing the biochemical pathways, mechanical influences, and therapeutic strategies that are essential for maintaining chondrocyte viability, preventing cartilage degeneration, and regulating lipid metabolism. This comprehensive overview not only highlights the complexity of ferroptosis but also emphasizes the interconnectedness of various factors that contribute to the pathophysiology of osteoarthritis.

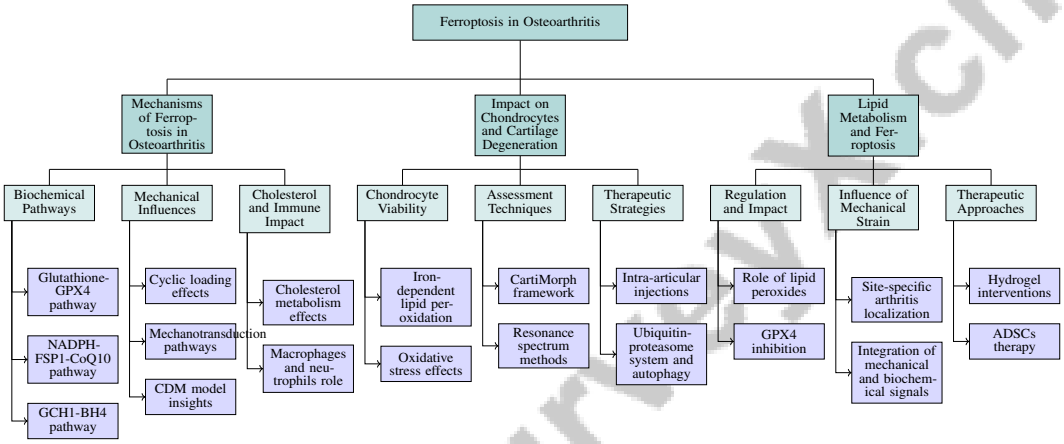

Figure 2: This figure illustrates the hierarchical structure of ferroptosis mechanisms and impacts in osteoarthritis, categorizing the biochemical pathways, mechanical influences, and therapeutic strategies involved in chondrocyte viability, cartilage degeneration, and lipid metabolism regulation.

3 Ferroptosis in Osteoarthritis

3.1 Mechanisms of Ferroptosis in Osteoarthritis

Ferroptosis, characterized by iron-dependent lipid peroxidation, plays a crucial role in cartilage degradation and chondrocyte apoptosis in osteoarthritis (OA) [19]. This process is regulated by biochemical pathways such as glutathione-GPX4, NADPH-FSP1-CoQ10, and GCH1-BH4, which manage oxidative stress and lipid peroxidation, highlighting the oxidative mechanisms' complexity in OA pathophysiology [30]. The mechanical environment of cartilage influences ferroptosis, with cyclic loading intensifying local inflammation and oxidative stress, promoting conditions favorable to ferroptosis [31]. Mechanotransduction pathways, involving mechanosensitive ion channels like Piezo1 and integrin-mediated signaling, are essential for understanding mechanical stimuli's effects on chondrocyte fate and ferroptosis susceptibility. The CDM model provides insights into mechanical interactions and cytoskeletal reorganization affecting ferroptotic pathways and chondrocyte behavior [25].

Cholesterol metabolism significantly impacts OA, with elevated cholesterol levels disrupting chondrocyte function and hastening disease progression through lipoprotein receptors and syndecan signaling [32]. Immune cells, such as macrophages and neutrophils, contribute to the inflammatory milieu driving ferroptosis by modulating oxidative stress and lipid peroxidation [33]. Innovative methodologies like Principal Component Analysis (PCA) in motion data analysis offer clinically relevant insights into cartilage degeneration mechanisms, enhancing the understanding of ferroptosis in OA [34]. The Reaction-Diffusion-Delay Model (RDDM) elucidates interactions between factors like erythropoietin (EPO) and tumor necrosis factor-alpha (TNF-), which are crucial for understanding cartilage lesion abatement and ferroptosis's role in these processes [17].

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Pharmacological strategies, including intra-articular injection of poly(phosphocholinated) liposomes, aim to mitigate shear stress and suppress inflammatory gene regulation in chondrocytes, potentially reducing ferroptosis in OA [35]. Additionally, electromagnetic fields may influence cellular functions through induced mechanical forces, offering alternative biochemical pathways for intervention in OA [2]. These insights into ferroptosis mechanisms are vital for developing targeted therapies to combat cartilage degeneration in OA.

3.2 Impact on Chondrocytes and Cartilage Degeneration

Ferroptosis significantly contributes to osteoarthritis (OA) pathogenesis by affecting chondrocyte viability and cartilage integrity through iron-dependent lipid peroxidation and oxidative stress. These mechanisms lead to chondrocyte apoptosis and extracellular matrix degradation, exacerbated by inflammatory cytokines [36]. The interaction between reactive oxygen species and pro-inflammatory cytokines accelerates cartilage degradation, impacting chondrocyte behavior and expanding lesions during cartilage injury [17].

To elucidate these processes, Figure 3 illustrates the impact of ferroptosis on chondrocytes and cartilage degeneration, highlighting key mechanisms, assessment techniques, and therapeutic strategies. Advanced imaging techniques have improved cartilage health assessment. The CartiMorph framework provides precise measurements of full-thickness cartilage loss, essential for evaluating chondrocyte viability [1]. Despite high segmentation accuracy by various networks, challenges persist in accurately determining cartilage thickness, underscoring the complexity of assessing cartilage integrity [37]. Resonance spectrum methods further assist in evaluating the structural and functional properties of articular cartilage affected by ferroptosis [3].

Mechanical stress, especially cyclic loading, is crucial in modulating chondrocyte viability and cartilage integrity. The cyclic loading model simulates cellular population dynamics under mechanical stress, providing insights into how mechanical forces influence chondrocyte behavior and cartilage health [7]. Additionally, marker-less motion analysis systems can accurately identify biomarkers for knee disorders, potentially linking them to chondrocyte viability and cartilage integrity [34].

Therapeutic strategies targeting ferroptosis hold promise in preserving cartilage integrity. Intra-articular injections of epigallocatechin gallate (EGCG) significantly enhance articular cartilage's mechanical properties, suggesting a preventative approach to cartilage damage in arthritis [9]. The roles of the ubiquitin-proteasome system (UPS) and autophagy in ferroptosis also present potential therapeutic targets for diseases associated with this form of cell death [30]. Understanding chondrocyte differentiation and behavior through advanced culture systems is crucial for developing targeted therapies aimed at mitigating ferroptosis's impact on cartilage degeneration [16].

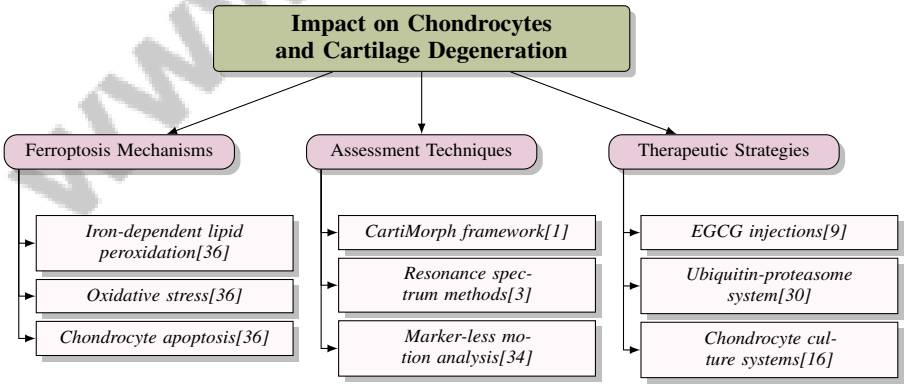

Figure 3: This figure illustrates the impact of ferroptosis on chondrocytes and cartilage degeneration, highlighting key mechanisms, assessment techniques, and therapeutic strategies.

3.3 Lipid Metabolism and Ferroptosis

Lipid metabolism is central to regulating ferroptosis, marked by iron-dependent lipid peroxidation. The accumulation of lipid peroxides is a critical mediator in ferroptosis induction, primarily through

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the inhibition of glutathione peroxidase 4 (GPX4), an enzyme crucial for mitigating lipid peroxidation [6]. The interplay between lipid metabolism and ferroptosis has significant implications for osteoarthritis (OA), as oxidative stress and lipid peroxidation contribute to chondrocyte apoptosis and cartilage degradation [19].

In osteoarthritic cartilage, dysregulated lipid metabolism exacerbates pathological processes leading to degeneration. Time of Flight Secondary Ion Mass Spectrometry (TOF-SIMS) facilitates detailed molecular distribution studies in cartilage, distinguishing healthy from OA tissues by analyzing lipid profiles and oxidative damage [38]. This approach underscores lipidomic profiling's potential in elucidating metabolic alterations associated with ferroptosis in OA.

Mechanical strain significantly influences lipid metabolism and ferroptosis in OA. It can localize arthritis site-specifically, linking mechanical stress to inflammation and oxidative damage in cartilage [31]. Integrating mechanical and biochemical signals is essential for understanding how lipid peroxidation contributes to OA progression.

Recent therapeutic strategies, such as hydrogels, show promise in modulating the mechanical properties and biochemical environment of cartilage under inflammatory conditions [39]. These interventions aim to restore lipid metabolism balance and mitigate ferroptosis effects, preserving cartilage integrity and function. Additionally, MHC-unmatched allogenic adipose-derived stem cells (ADSCs) present a novel approach for OA treatment, potentially providing an off-the-shelf solution to address lipid dysregulation and oxidative stress [40].

The development of confidence-driven deep learning frameworks for assessing OA severity highlights the importance of integrating lipid metabolic profiles with advanced imaging and analytical techniques [41]. These methodologies enhance the understanding of lipid metabolism's role in ferroptosis and its implications for OA, paving the way for innovative diagnostic and therapeutic approaches to manage this degenerative joint disease.

4 Role of Piezo1 in Mechanotransduction

4.1 Mechanosensitive Ion Channels and Piezo1

Piezo1, a critical mechanosensitive ion channel, facilitates mechanotransduction by converting mechanical stimuli into biochemical signals [26]. Its structure is adept at detecting joint-specific mechanical forces like shear stress and tensile strain, leading to conformational changes that allow ion influx, particularly calcium, which triggers diverse cellular responses [42]. The lipid bilayer's mechanical properties significantly influence Piezo1's mechanosensitivity, underscoring its crucial role in cellular responses to mechanical stimuli [26].

Beyond ion transport, Piezo1 profoundly affects chondrocyte mechanobiology by modulating responses to mechanical loading, thereby impacting cartilage health [43]. Activation of Piezo1 channels initiates downstream signaling pathways that regulate gene expression and maintain cellular homeostasis across the entire cell, integrating signals from multiple compartments rather than being confined to focal adhesions [42, 44].

Piezo1's interaction with the cytoskeleton and integrins is pivotal in mechanotransduction, facilitating mechanical signal transmission across the cell membrane [25]. The Cytoskeletal Dynamics Model (CDM) simulates cellular mechanical behavior during adhesion, providing insights into the dynamic interactions mediated by Piezo1 [25].

Advanced methodologies, such as Quantum-Enhanced Diamond Molecular Tension Microscopy (QDMTM), offer high-sensitivity measurements of cellular forces, addressing traditional fluorescence technique limitations [45]. Moreover, mathematical models analyzing mesenchymal stem cell differentiation under mechanical conditions enhance understanding of Piezo1's mechanotransduction role [46]. This knowledge is crucial for developing therapeutic interventions for conditions like osteoarthritis, where mechanotransduction pathways are disrupted.

4.2 Piezo1 and Chondrocyte Behavior

Piezo1 is essential for modulating chondrocyte activity and maintaining cartilage health by converting mechanical stimuli into biochemical signals. Chondrocytes, the primary cartilage cells, distinguish

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various mechanical stimuli intensities through mechanosensitive ion channels, including Piezo1 [23]. This capability is vital for their function and survival, enabling appropriate responses to mechanical forces crucial for cartilage homeostasis.

Molecular dynamics simulations reveal Piezo1's influence on chondrocyte behavior, illustrating conformational changes and interactions at the atomic level [42]. These simulations elucidate mechanotransduction pathways that convert mechanical signals into cellular responses, regulating gene expression and behavior.

Extensive experimental studies have explored chondrocyte mechanical behavior under diverse conditions, highlighting Piezo1's role in shaping these responses [47]. The integration of mechanical signals through Piezo1 affects not only chondrocyte activity but also overall cartilage health. Novel culture systems designed to induce paralyzed chondrocytes provide insights into modulating mechanotransduction processes, impacting chondrocyte behavior and cartilage health [16].

Understanding Piezo1's role in chondrocyte mechanotransduction is vital for developing therapeutic strategies aimed at preserving cartilage integrity and preventing degeneration in joint diseases like osteoarthritis. Targeting mechanosensitive pathways mediated by Piezo1 and Piezo2 channels may effectively modulate chondrocyte activity, enhancing cartilage resilience against mechanical stress and injury. The critical roles these ion channels play in chondrocyte mechanotransduction allow responses to varying mechanical stimuli intensities. Manipulating these pathways could offer therapeutic potential for conditions like osteoarthritis, exacerbated by repetitive mechanical loading and inflammation [42, 5, 36, 23, 48].

5 Mechanotransduction and Cartilage Degeneration

5.1 Integrin-Mediated Mechanotransduction

Integrins are pivotal in mechanotransduction, converting mechanical stimuli into biochemical signals crucial for chondrocyte behavior and cartilage integrity [26]. These transmembrane receptors connect the extracellular matrix (ECM) to the cytoskeleton, facilitating cellular adhesion and enabling the sensing of mechanical forces. This dynamic interaction is vital for regulating chondrocyte morphology, influencing proliferation, differentiation, and survival [49].

Research highlights integrin-associated mechanotransduction pathways, emphasizing their role in cell morphology and implications for regenerative medicine [49]. Integrating mechanical strain analysis with cellular responses has advanced models of articular cartilage lesion formation, enhancing our understanding of integrin roles in cartilage responses to mechanical stress [50]. These models simulate the interplay between mechanical forces and cellular responses, contributing to insights into osteoarthritis (OA) pathophysiology and therapeutic development.

Innovative methodologies, such as Quantum-Enhanced Diamond Molecular Tension Microscopy (QDMTM), have advanced studies on integrin-mediated mechanotransduction by detecting minute changes in spin relaxation time due to mechanical forces, translating these into measurable cellular adhesion forces [45]. Research on lipid bilayer properties and their impact on mechanosensitive channel function underscores the significance of integrins in cartilage responses, highlighting the role of the cellular microenvironment in modulating mechanotransduction pathways [26].

Exploring integrin-mediated pathways is crucial for understanding cartilage degeneration mechanisms and joint disease progression, such as OA. Investigating molecular interactions and signaling pathways associated with integrins may reveal novel therapeutic targets to enhance cartilage health and mitigate degeneration. This includes examining proteins like glycoprotein 130 (gp130) and LRP3 that influence chondrocyte behavior and ECM metabolism, alongside innovative strategies like cartilage-penetrating hyaluronic acid hydrogels to preserve tissue integrity and reduce catabolic activity in degenerative environments [36, 32, 39, 9]. Such insights are essential for devising strategies to alleviate mechanical stress impacts on cartilage and improve outcomes for OA patients.

5.2 Chondrocyte Morphology and Mechanical Signals

Chondrocyte morphology significantly affects mechanotransduction processes, influencing how mechanical signals are converted into biochemical responses. The physical characteristics of chondrocytes, including shape and volume, are critical determinants of their functional behavior and

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phenotype stability [51]. Their rounded shape and dense ECM enable efficient sensing of mechanical stimuli and regulation of cartilage homeostasis.

Hall et al. categorize chondrocyte behavior based on morphology and volume, emphasizing their role in phenotype stability regulation [51]. This framework is essential for understanding how variations in chondrocyte structure can affect mechanotransduction pathways and cartilage health. Changes in morphology, often induced by mechanical stress or pathological conditions, can alter mechanosensitive signaling pathways, impacting proliferation, differentiation, and matrix synthesis.

Mechanical signals are transduced through pathways such as integrin-mediated adhesion and the activation of mechanosensitive ion channels like TRPV4 and Piezo2. These pathways are influenced by chondrocyte shape and structural organization, modulating responses to mechanical stimuli and maintaining cartilage homeostasis. TRPV4 senses physiological levels of repetitive mechanical stress, while Piezo2 responds to extreme loading conditions, underscoring the importance of chondrocyte morphology in controlling phenotype and mechanical cue responses [28, 52, 51, 23, 53]. The interaction between chondrocytes and the ECM, mediated by integrins and cytoskeletal components, is crucial for translating mechanical forces into intracellular signals that regulate gene expression and maintain cartilage integrity.

Advanced imaging techniques and molecular dynamics simulations have elucidated mechanotransduction processes in chondrocytes, emphasizing the role of cellular morphology in these pathways. Investigating the relationship between chondrocyte morphology, volume, and mechanotransduction can inform targeted therapies aimed at preserving cartilage health and addressing cartilage degeneration mechanisms in joint diseases like OA. Understanding how mechanical stimuli and structural changes influence chondrocyte phenotype stability is vital for developing effective cartilage repair strategies and engineering resilient tissues, ultimately preventing OA progression and improving patient outcomes [51, 47, 39].

6 Interconnections and Pathophysiology

6.1 Molecular Interactions and Mechanosensitive Proteins

The intricate interplay of ferroptosis, Piezo1, and mechanotransduction is crucial for comprehending osteoarthritis (OA) pathophysiology. These pathways form a network of mechanosensitive proteins that regulate chondrocyte function and cartilage integrity. Ferroptosis, characterized by iron-dependent lipid peroxidation, is linked to oxidative stress and cellular metabolism, significantly impacting chondrocyte viability and cartilage health [30]. Modulation of ferroptosis through various degradation pathways can either promote or inhibit this process, contingent upon the targeted substrates [30].

Mechanotransduction, converting mechanical signals into biochemical responses, is mediated by mechanosensitive ion channels like Piezo1, vital for regulating chondrocyte behavior and maintaining cartilage health [22]. The categorization of mechanotransduction mechanisms, emphasizing cytoskeletal force transmission and integrin-mediated adhesion, underscores the mechanical signals' role in cellular responses [22]. Anionic lipids further modulate mechanosensitive protein functions, highlighting complex molecular interactions [26].

Electromagnetic fields and induced mechanical forces elucidate the interaction between ferroptosis and mechanotransduction in OA [2]. Insights into the acoustic propagator's spectral problem and its resonances enhance understanding of OA molecular interactions [3]. Research identifies key mechanosensitive receptors and pathways, emphasizing these molecular interactions' significance in OA pathophysiology [28].

Investigating these pathways is crucial for identifying therapeutic targets to mitigate mechanical stress impacts on cartilage health. Future research should explore clinical applications, focusing on therapeutic agents targeting mitochondrial dysfunction and other molecular pathways in OA. Integrating machine learning with traditional models shows promise in enhancing patient selection for OA drug trials and informing personalized treatment plans [2].

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6.2 Inflammation and Mechanical Stress

Inflammation and mechanical stress are pivotal in osteoarthritis (OA) pathogenesis, significantly influencing chondrocyte function and cartilage integrity. Chondrocytes, the primary cartilage cells, are sensitive to their mechanical environment, with osmolarity and mechanical stress being vital for their functionality and survival [51]. Mechanical forces, such as shear stress and compressive loading, can exacerbate inflammatory responses within chondrocytes, accelerating OA-associated degenerative changes [35].

Cellular mechanotransduction dynamics reveal how mechanical stimuli modulate inflammatory pathways, linking mechanical stress to OA cellular responses [54]. These interactions involve a complex network of molecular pathways regulating cellular adaptation to mechanical changes, underscoring the need for comprehensive models representing in vivo conditions [24]. Current methodologies often rely on simplified systems that may not fully capture the cellular microenvironment's complexity, indicating a gap in understanding [52].

Obesity is a significant knee OA risk factor, with modern populations exhibiting higher prevalence rates than historical cohorts [55]. Increased body weight exacerbates joint mechanical load, intensifying inflammatory processes and contributing to cartilage degradation. Erythropoietin (EPO)'s role in modulating inflammation and maintaining cell health in response to mechanical stress further illustrates the connection between mechanical forces and inflammatory pathways [7].

Despite advances in imaging techniques and automated segmentation methods crucial for OA clinical research, substantial gaps remain in understanding mechanical stress and inflammation's impact on disease progression [56]. Future research should aim to develop real-time imaging techniques to study mechanotransduction and its implications for inflammatory processes in OA and other disease contexts [22]. Investigating molecular mechanisms underlying paralyzed chondrocyte differentiation and their role in cartilage growth may provide further insights into inflammation and mechanical stress interplay [16]. Addressing these challenges is essential for advancing OA pathophysiology understanding and developing targeted interventions to mitigate mechanical stress and inflammation effects on joint health. Current studies often lack a comprehensive understanding of mechanotransduction's dynamic nature and the interplay between different signaling pathways, vital for devising effective therapeutic strategies [28].

7 Potential Therapeutic Targets

7.1 Therapeutic Implications and Potential Targets

Addressing the multifaceted nature of osteoarthritis (OA) requires an integrated therapeutic approach that combines traditional treatments with emerging insights into disease mechanisms. Pharmacological interventions remain pivotal, with agents like RCGD 423 effectively inhibiting IL-6 family cytokines and promoting chondrocyte proliferation [36], while Loganin targets NFB signaling and pyroptosis [57]. These treatments underscore the significance of inflammatory pathways in OA management. Advances in molecular understanding of cartilage lubrication have identified new therapeutic targets [8], and modulating ferroptosis presents novel opportunities for treating degenerative diseases, including OA. The potential of long non-coding RNAs (lncRNAs) as biomarkers or therapeutic targets further supports precision medicine in cartilage disorders [4].

Innovative techniques such as Quantum-Enhanced Diamond Molecular Tension Microscopy (QDMTM) enhance understanding of cellular mechanics and mechanotransduction, offering new therapeutic strategies by revealing cellular membrane tension [45]. Electromagnetic stimulation also suggests novel intervention pathways in OA [2]. Biomaterials, like injectable self-healing hydrogels that inhibit matrix metalloproteinases (MMPs), show promise in reinforcing cartilage mechanically and preserving it biochemically. Future research should focus on optimizing these hydrogels for improved cell compatibility and evaluating their long-term efficacy in vivo.

Recent imaging advancements, including automated systems like SS-FewSOME utilizing self-supervised learning for continuous knee OA severity grading, enhance cartilage health assessment accuracy. These innovations address the limitations of the traditional Kellgren-Lawrence grading system, facilitating more effective OA monitoring and management strategies. Multi-modal machine learning models integrating radiographic and clinical data have shown promise in predicting OA pro-

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gression, offering potential therapeutic targets and improving OA drug development and personalized treatment plans [15, 58].

Dynamic indentation tests as non-destructive tools for cartilage health assessment provide potential for monitoring OA progression and evaluating treatment efficacy [7]. The use of 3D patches for cartilage representation suggests improvements in therapeutic strategies and assessment techniques, with ongoing research aimed at refining these methods to handle atypical curves and explore additional applications of full movement data [20].

7.2 Pharmacological and Lifestyle Interventions

Pharmacological and lifestyle interventions are vital in managing OA, focusing on symptom alleviation, disease progression deceleration, and quality of life enhancement. Allogenic adipose-derived stem cells (ADSCs), sourced from healthy donors, offer a promising therapeutic avenue without the need for patient-specific cell preparation [40]. This approach leverages the regenerative potential of ADSCs for broader clinical application.

In addition to stem cell therapy, targeting inflammatory pathways through pharmacological interventions, such as regulating gp130 signaling and manipulating mechanotransduction processes, is crucial for addressing cartilage degeneration and promoting tissue repair in OA [36, 53, 59, 60]. Agents inhibiting key inflammatory cytokines and signaling pathways can mitigate the catabolic processes driving cartilage degradation. Developing novel pharmacological agents specifically inhibiting pathways involved in cartilage degeneration, including those regulating ferroptosis, holds potential for modifying disease progression and enhancing cartilage preservation.

Lifestyle modifications are equally critical in OA management, with weight management and physical activity playing significant roles. Obesity is a well-documented risk factor for OA, particularly affecting weight-bearing joints like knees and hips. Excess body weight increases joint stress and inflammation, exacerbating degenerative processes. Weight reduction can alleviate these pressures, improve joint function, and potentially slow disease progression, emphasizing the need to address obesity in OA management and prevention strategies [55, 61, 62, 63, 64]. Regular physical activity, tailored to individual capabilities, helps maintain joint mobility and muscle strength, essential for joint stability and function. Low-impact exercise programs, such as swimming and cycling, can enhance cardiovascular health and reduce OA symptoms without exacerbating joint damage.

Nutritional interventions, including dietary supplements and anti-inflammatory diets, may support OA management. Integrating omega-3 fatty acids, antioxidants, and other anti-inflammatory nutrients can complement pharmacological treatments, potentially enhancing overall joint health by mitigating oxidative stress and promoting cartilage integrity, especially in aging populations and those experiencing mechanical stress on joints [9, 61, 65, 35, 64]. Patient education and self-management strategies empower individuals to actively participate in their treatment, promoting adherence to therapeutic regimens and lifestyle changes.

8 Conclusion

This survey provides a comprehensive examination of the complex interactions among ferroptosis, Piezo1, and mechanotransduction in osteoarthritis (OA), emphasizing their pivotal roles in influencing chondrocyte function and maintaining cartilage health. The recognition of inflammation as a central factor in OA progression highlights the necessity for innovative treatment models. Emerging research into cholesterol metabolism's impact on cartilage degradation, including potential therapies such as LRP3 gene therapy, offers promising avenues for future exploration. The therapeutic efficacy of RCGD 423 in mitigating cartilage deterioration and promoting repair in OA models further underscores its potential clinical applications.

The integration of deep learning into biomedical imaging presents significant opportunities for enhancing diagnostic precision and facilitating early OA detection. The CartiMorph framework, noted for its proficiency in automating cartilage morphometrics, merits further investigation for its potential clinical utility. Additionally, optimizing differential privacy mechanisms to reduce computational demands while assessing their broader applicability could refine research methodologies.

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The use of hydrogels to support damaged cartilage and prevent tissue loss suggests their potential in delaying OA onset. Future research should prioritize longitudinal studies on biomarkers like C1M and IL-6 as therapeutic targets in OA management. Investigating the interactions of loganin with other components in Corni Fructus and its clinical benefits, alongside the mechanisms governing pyroptosis in OA, presents valuable research directions.

This survey underscores the importance of integrating advancements in diagnostics, pharmacology, and lifestyle interventions to improve OA management. Future research should concentrate on promoting effective lifestyle modifications to reduce OA risk and exploring emerging trends in diet and physical activity. By adopting a holistic approach, future studies can enhance patient care and quality of life for those affected by OA.

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