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Research Progress of Abnormal Glycosylation in Osteoarthritis

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Abstract: ***Osteoarthritis is a common degenerative joint disease mainly caused by degenerative damage to articular cartilage and reactive hyperplasia of the marginal and subchondral bone of the joint, which seriously affects the quality of life of patients. In recent years, the role of glycosylation as a key post-translational modification of proteins in the occurrence and development of OA has received increasing attention. Abnormal glycosylation involves not only the accumulation of advanced glycation end products (AGEs), but also dysregulation of enzymatic glycosylation processes, both of which are involved in the pathological changes of joint multitissue, but the specific mechanisms have not been fully elucidated. This article aims to systematically explore the association between abnormal glycosylation and OA, with a focus on its mechanism of action in articular cartilage, synovial membrane and subchondral bone, and to review the research progress in recent years, with the aim of providing a new perspective for the mechanism study and treatment strategy of OA.***

Keywords: Glycosylation, Osteoarthritis, Chondrocytes, Synovial fibroblasts, Molecular mechanisms, Signaling pathways**.**

1. Introduction

Osteoarthritis (OA) is a common degenerative and progressive joint disease characterized by abnormal subchondral bone perfusion, loss and hardening of extracellular matrix (ECM) proteins, and the formation of new blood vessels invading the synovial membrane and articular cartilage. Synovial inflammation, subchondral bone remodeling, osteophyte formation, degenerative changes in articular cartilage, and progressive degeneration of the entire synovial joint structure are chronic reactive diseases caused by the combined effects of multiple pathogenic factors. It is more common in middle-aged and elderly people and often affects the knee, hip, spine and finger joints, with the knee being the most common [1]. Worldwide, the economic loss and prevalence of OA are steadily increasing, making it a representative public health problem for the future [2]. Pain is a key feature of osteoarthritis and the main complaint of osteoarthritis patients, which seriously affects the quality of life of patients [3]. Osteoarthritis is a multifactorial disease, and at present, due to the incomplete understanding of its pathogenesis, treatment mainly focuses on alleviating symptoms, with surgical treatment in a few cases. In general, there is still a lack of effective treatment methods [4]. In recent years, the role of glycosylation in the occurrence and development of OA has gradually attracted attention. It involves structural and functional changes in articular tissues such as articular cartilage, synovial membrane, and subchondral bone. This article aims to explore the complex association between glycosylation and OA, and comprehensively describe the current research status of glycosylation in the pathogenesis, pathological progression, and potential therapeutic targets of OA. To provide new therapeutic ideas for osteoarthritis.

2. Overview of Glycosylation

2.1 Types of Glycosylation

Glycosylation is a common post-translational modification of proteins and lipids, which is divided into enzymatic glycosylation and non-enzymatic glycosylation [5]. Glycosylation is the process by which sugar molecules are covalently bonded to biological macromolecules such as proteins and lipids. Under physiological conditions, enzymatic glycosylation is involved in the regulation of many cellular functions; In pathological conditions, advanced glycation end products (AGEs) produced by non-enzymatic glycation accumulate, triggering a series of harmful reactions [6]. There are different types of glycosylation, amino acid and chitosan based on their key is divided into four categories: O-glycosylation, N-glycosylation, C-glycosylation and sugar-based phosphatidyl inositol (GPI) glycosylphosphatidylinositol, anchor connection [7,8]. Among them, N-glycosylation and O-glycosylation are the most common types, and they contain most of the glycosylation mechanisms associated with disease pathogenesis and progression. Among them, N-glycosylation refers to the connection of sugar chains to the asparagine residue of a protein, a process that begins in the endoplasmic reticulum and is further modified in the Golgi apparatus. O-glycosylation, on the other hand, involves attaching sugar chains to serine or threonine residues of proteins, mainly in the Golgi apparatus [9]. For example, N-acetylgalactosamine (GalNAc) O-glycosylation occurs in the Golgi apparatus, while n-glycosylation takes place in the endoplasmic reticulum, further processed, and terminates in the Golgi apparatus.

2.2 Glycosylation Function

In living organisms, glycosylation plays many important roles. It can affect the folding, stability and solubility of proteins. For example, the glycosylation of immunoglobulin G (IgG) is crucial for its structural stability and normal functioning. At the same time, glycosylation plays a crucial role in processes such as cell recognition, intercellular communication, and signal transduction. Physiological enzymatic glycosylation, a highly precise biological process catalyzed by specific enzymes and strictly regulated, is of great significance. In the

endoplasmic reticulum, the newly synthesized protein is labeled by n-glycosylation, and the correct sugar chain structure enables the protein to fold properly and obtain a stable three-dimensional structure. If the glycosylation is abnormal or the protein folding fails, the protein will be degraded to maintain the stability of the intracellular environment. The cell surface is covered with a variety of proteins and lipids with unique sugar chains, which together form the cell's "calyx". This sugar coating is involved in specific recognition and adhesion between cells and between cells and the matrix. For example, during inflammation, Selectin on the surface of white blood cells enables the rolling and adhesion of white blood cells by recognizing specific glycoligands on vascular endothelial cells, which is a key first step in the recruitment of inflammatory cells [10]. In addition, the activity of many hormones, such as erythropoietin (EPO) and receptors, also strictly depends on their correct glycosylation patterns. In contrast to fine enzymatic glycosylation, non-enzymatic glycosylation is a passive, enzyme-free, randomly occurring chemical reaction process. When the concentration of reducing sugars such as glucose in the blood is too high, they attack free amino groups on proteins, lipids and even DNA through a series of complex condensation, rearrangement and oxidation reactions, eventually forming irreversible cross-linked compounds - advanced glycation end products (AGEs) [11].

3. The Association Between Glycosylation and Osteoarthritis

Osteoarthritis was long regarded as a simple wear and tear disease. However, recent studies have shown that it is actually an active disease involving the entire articular organ, including cartilage, synovial membrane, subchondral bone, ligaments and muscles, with a complex metabolic and inflammatory background [12]. In this pathological process, abnormal glycosylation plays a dual role, closely linking metabolic disorders to structural damage to joint tissues.

3.1 Effects on Articular Cartilage

Avascular cartilage is an essential part of maintaining joint health and remains in a state of continuous hypoxia throughout life [13]. Cartilage damage associated with osteoarthritis can lead to deeper synovial fluid permeation, resulting in increased oxygen supply. Chondrocytes, the resident cell type in articular cartilage, play a unique role in the development, maintenance, and repair of ECM and are highly specialized and metabolally active. Many studies have shown that bone dysplasia is associated with impaired normal life processes of chondrocytes and degradation of extracellular matrix of chondrocytes [14]. Cartilage degradation is characterized by the early hydrolytic loss of aggregated proteins, and aggregated proteoglycans form large aggregates with hyaluronic acid in ECM [15]. In recent years, the molecular pathogenesis of orthopedic diseases such as osteoarthritis and chondrodysplasia has been studied in greater depth, clarifying the molecular mechanisms of some growth factors and transcription factors that regulate chondrocyte proliferation and differentiation, for example, SRY-box transcription factor 9 Sox9, Runx2, Runt-related Transcription Factor 2, bone morphogenetic protein BMP plays a significant role in the regulation of extracellular glycosaminoglycan biosynthesis, chondrocyte differentiation, and osteoblast differentiation in chondrocytes. Transforming growth factor beta (β) TGF-β Signaling Pathway, Wnt signaling pathway, FGF (Fibroblast Growth Factors FGF) The signaling pathway, the Ihh signaling pathway, and the glycosylation process have significant effects on chondrocyte proliferation, differentiation, and osteogenesis by cooperating with and regulating the active expression of these key factors [16]. Glycosaminoglycans, one of the key components of the extracellular matrix, together with type II collagen, form a highly hydrated and gel-like matrix outside the chondrocytes, giving the cartilage tissue compressive and elastic properties [17]. The sulfation patterns of glycosaminoglycans, including hypersulfation, sulfation of side-chain disaccharide units, deacetylation, and differential isomerization, regulate chondrocyte differentiation and endochondral osteogenesis by influencing the activity of other proteoglycan molecules or extracellular cytokines, thereby activating the expression of downstream signaling molecules or transcription factors. Glycosaminoglycan biosynthesis regulates cartilage differentiation and endochondral osteogenesis. Some of these signaling molecules and pathways do not act alone but are cross-linked and interact to influence the process of chondrocyte differentiation. As one of the key extracellular substrates of bone cells, glycosaminoglycans indirectly or directly affect several of these signaling pathways. For example, during stem cell differentiation, the Wnt/β-catenin pathway not only regulates the direction of stem cell differentiation through its cascade amplification reaction, but also combines other signaling molecules and pathways to influence the direction of stem cell differentiation, including the FGF pathway, the TGF-β pathway, and the Ihh pathway [18]. Exostosin glycosyltransferase1 (EXT1) is a glycosyltransferase that acts on the elongation of glycosaminoglycans. A recent study found that EXT1 and glycosaminoglycans can influence the differentiation potential of endochondral osteogenesis, and EXT1 controls the activity of the Wnt signaling pathway by modulating glycosaminoglycan levels. The absence of EXT1 in mouse bone marrow derived mesenchymal stem cells (BMSCs) inhibited the Wnt pathway, downregulated extracellular matrix glycosylglycan residues, and increased matrix proteoglycans and osteogenic markers. Likewise, it has been shown that the Wnt pathway can regulate the activity of EXT1 enzymes [19]. Osterholm et al. found that the FGF signaling pathway affects ext1-mediated glycosaminoglycan biosynthesis [20]. In addition, Chikazu et al. demonstrated that the FGF-2 molecule could affect nuclear factor kappa-B NF-κB ligand Receptor activator ofnuclear factor kappa-B ligand (RANKL) expression induces osteoblasts to differentiate into osteoclasts. FGF-2 binds to FGFR-1 with the help of the glycosaminoglycan receptor, enabling RANKL to bind to intercellular cell adhesion molecule-1 ICAM-1 works together to activate the extracellular regulated protein kinases (ERK) pathway and promote osteoclast production [21,22]. This suggests that the biosynthesis of glycosaminoglycans is closely associated with the expression of chondrocyte differentiation and osteogenesis-related signaling pathways, which interact and crosslink together to affect osteogenic differentiation. Meanwhile, the osteogenic differentiation effects of the signaling pathways are not separate but mutually promote the formation of osteogenic differentiation signaling transduction networks that jointly influence osteogenic

differentiation.

3.1.1 Direct effects of AGEs on cartilage matrix

There is also an accumulation of AGEs and the expression of RAGE in synovial tissue. AGEs bind to RAGE on FLS and activate classic pro-inflammatory signaling pathways such as MAPK (like p38, JNK) and NF-κB, driving FLS to produce large amounts of cytokines such as IL-1β, IL-6, IL-8, TNF-α. These factors are released into the synovial fluid of the joint, causing damage to the tissue from the originally lubricating and nourishing synovial fluid [23]. The most direct harm of AGEs' accumulation in the cartilage matrix lies in their strong cross-linking ability. They form random, non-physiological covalent cross-links within and between collagen fibers and on the core proteins of proteoglycans [24]. This kind of cross-linking has serious consequences. The normal type II collagen network is a dynamic, resilient framework. When cross-linked by AGEs, this framework becomes stiff, fragile and has reduced tensile strength. The changes in the mechanical properties of this matrix make it more prone to micro-damage and accumulation when subjected to the stress of daily joint movement. AGEs bind to proteoglycans such as aggregated proteoglycans and mask their negatively charged glycosaminoglycan chains, affecting their hydrophilicity and fixed charge density, thereby weakening their water retention capacity [25]. The compressive strength of cartilage largely depends on the high degree of hydration of the matrix. A decrease in water retention directly leads to a significant reduction in the buffering function of cartilage.

3.1.2 AGEs-RAGE axis

The harm of AGEs goes far beyond physical damage. When they bind to specific receptors (RAGE) on the surface of chondrocytes, they trigger a powerful intracellular signaling cascade [26]. When AGEs bind to RAGE, they activate the transcription factor NF-κB and transfer it from the cytoplasm to the nucleus, which is the core pro-inflammatory pathway. NF-κB activates the transcription of a series of pro-inflammatory genes, leading chondrocytes to synthesize and secrete large amounts of interleukin-1 β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor -α (TNF-α). These factors not only further activate the chondrocyte in an autocrine manner, but also affect the surrounding chondrocytes in a paracrine manner, creating a persistent inflammatory microenvironment locally [27]. Driven by inflammatory factors, the phenotype of chondrocytes shifts from anabolic dominance to catabolic dominance. They highly express matrix metalloproteinases (MMPs such as MMP-1, MMP-3, MMP-13) and aggregator proteanase (ADAMTS-4, ADAMTS-5). MMP-13, known as collagenase-3, is the leading enzyme for degrading type II collagen, while ADAMTS-4/5 is specifically responsible for cutting the core protein of aggregator. These enzymes cause further damage to the already damaged extracellular matrix. The AGEs-RAGE interaction also promotes the production of reactive oxygen species (ROS) within cells, exacerbating oxidative stress. Oxidative stress not only directly damages cell macromolecules, but also forms a positive feedback loop with inflammatory signals, amplifying each other. In addition, persistent inflammation and oxidative stress accelerate the senescence of chondrocytes, which secrete more inflammatory factors and matrix-degrading enzymes (known as senesior-associated secretory phenotypes, SASP), creating a vicious cycle in which the destruction process continues even when the initial stimulus disappears [28].

3.2 Effects on Synovial Tissue

Synovitis is usually the initial pathological change of OA and may occur before visible changes in cartilage [29]. Fibroblast-like synoviocytes (FLS), the main population of synoviocytes, are believed to be involved in OA progression by secreting inflammatory factors, including interleukin (interleukin) And tumor necrosis factor (TNF), as well as matrix metalloproteinase (MMP) and ADAM metallopeptidase (ADAMTS) with platelet reactive protein motifs These proteases regulate the composition of the extracellular matrix (ECM) of chondrocytes [30]. In addition, collagen I accumulation was observed in synovial tissue of Streptozotocin (STZ) -induced diabetic (DM) rats, and catabolism and inflammatory responses were observed in primary mouse chondrocytes treated with high glucose [31,32,33]. Because the synovial membrane has a better blood supply than the cartilage and is more sensitive to serum regulators, we believe that the synovial membrane, rather than the cartilage, may be the main target tissue for hyperglycemia in the pathogenesis of DM-related OA [34].

Synovitis is a typical feature of OA progression and one of the important regulatory factors. Inflammatory factors and MMP and ADAMTS proteases are released from the synovium, which further accelerates the progression of OA [35,36]. Synovial tissue is rich in blood vessels, while articular cartilage lacks blood supply, making the synovial membrane more susceptible to hyperglycemic stimulation. Previous studies have shown that FLS are much more sensitive to hyperglycemia than chondrocytes. FLS not only secrete inflammatory factors including TNF and IL into the joint cavity [37], but also release more MMP and ADAMTSX after being stimulated by joint inflammation [38], thereby further inducing inflammation and degeneration of articular cartilage [39,40,41]. Clinical data from Luo et al. showed that the concentration of MMPs in the synovial fluid of patients in the DM-OA group was significantly higher than that in the OA group without DM or the healthy control group [42]. Other studies have shown that the concentrations of IL-6 and IL-1β in the synovial fluid of DM patients were significantly higher than those of non-DM patients [43,44]. These data suggest that DM leads to elevated levels of ECM degenerative enzymes and inflammatory factors in the synovial fluid. In our current study, enhanced inflammatory responses were observed in the synovium of both humans and rats in the OA with DM group.

Glucose was reported to be one of the highly differentiated metabolites in synovial fluid between DM and non-DM patients [45]. To date, most studies have focused on the direct adverse effects of hyperglycemia on cartilage. However, the synovium is a joint tissue that is well-supplied with blood. Therefore, it is directly exposed to high blood sugar, and the blood sugar component in the synovial fluid is also filtered through the synovial membrane, suggesting that the indirect effect of the synovial membrane on cartilage in a high blood sugar environment caused by DM cannot be ignored. In vitro

results confirmed that excessive glucose could induce a degenerative phenotype of chondrocytes through FLS. Therefore, we believe that hyperglycemia induces or exacerbates articular cartilage degeneration by stimulating an inflammatory response in the synovium.

3.2.1 Synovia-cartilage axis

Synovia-derived inflammatory factors and degrading enzymes cause damage to articular cartilage through the "synovia-cartilage axis", an indirect pathway. Factors such as IL-1β and TNF-α secreted by the synovial fluid spread to the cartilage area and act directly on chondrocytes, activating pathways such as NF-κB within chondrocytes through their own receptors, thereby affecting chondrocytes and putting them in an inflammatory and catabolic state. This means that even if the chondrocytes themselves are not directly severely impacted by hyperglycemia, they will be affected by inflammatory signals from the synovium [46]. Although synovium-derived MMPs (such as MMP-3) do not directly degrade type II collagen, they can activate other latent MMPs (such as precursors of MMP-13) and broadly degrade other protein components in the matrix, disrupting the integrity of the matrix. They work in synergy with the degrading enzymes produced by chondrocytes themselves, significantly accelerating the disintegration of the matrix. Therefore, in diabetes-associated osteoarthritis, there is a clear pathological chain of "hyperglycemia → synovial activation/inflammation → deterioration of synovial fluid composition → cartilage destruction." This explains why controlling blood sugar levels throughout the body has a clear protective effect in delaying the progression of osteoarthritis, as it reduces the stimulation to the synovial membrane from the source.

3.3 Effects on Subchondral Bone

Subchondral bone is the main structure that regulates the pathogenic mechanism of OA [47]. In early OA, abnormal mechanical stress and other factors induce microdamage to subchondral bone and increase subchondral bone remodeling, osteoclasts promote bone resorption, thinning of the subchondral bone plate and trabecular dissociation. In the late stage of OA, bone remodeling is weakened, osteoblaster-mediated bone formation is strengthened, subchondral plates and trabeculae are thickened, angiogenesis is increased, manifested as subchondral bone hardening, affecting the degeneration of the overburden cartilage [48]. Subchondral sclerosis is the most direct manifestation of bone transformation in OA. However, the exact mechanism by which abnormal subchondral bone formation leads to bone hardening remains unknown. It is widely believed that subchondral bone structures adapt to abnormal mechanical stress through bone remodeling. Local bone hardening and non-hardening areas can lead to an unbalanced distribution of shear stress, generating heterogeneity in the subchondral osteochondral complex, tearing attached cartilage, and triggering fibrosis. An OA meniscus instability model in mice based on the Sclerostin (SOST) gene suggests that increased subchondral bone density and hardness is a prerequisite for OA progression [49]. In addition, the subchondral bone-bone interface showed significant chondrocyte hypertrophy and intrachondral ossification, induced remodeling, enhanced subchondral bone hardening, and more severe cartilage degeneration in the weight-bearing area compared with the non-weight-bearing area [50].

The occurrence and development of OA are closely associated with cellular senescence [51], and N-glycosylation contributes to a variety of molecular mechanisms of cellular senescence [52].

Gu et al [53]. analyzed 50 subchondral bone specimens from 40 OA patients and 10 non-OA patients and found differential expression of collagen type II alpha 1 chain (COL2A1), COL5A2, COL3A1, MMP2, and COL6A1. In addition, the study showed that N-glycosylation of the COL6A1 protein was highly expressed in patients with type II diabetes and OA [54]. Chou et al [55]. also confirmed that modifications to COL5A1, COL6A3 and COL16A1 can simultaneously improve the pathological changes and disease progression of articular cartilage and subchondral bone. Abnormal glycosylation of subchondral collagen can lead to trabecular bone injury, resulting in subchondral bone collapse, which is highly correlated with the occurrence and development of OA.

3.3.1 Abnormal glycosylation disrupts the metabolic balance of subchondral bone

The homeostasis of subchondral bone depends on a precise balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption. Abnormal glycosylation disrupts this balance in multiple ways:

Affecting the RANKL/OPG system: Osteoprotegerin (OPG) competitively binds to RANKL, thereby inhibiting osteoclast differentiation and activation. Studies have shown that N-glycosylation modification is crucial for the secretion, stability, and function of OPG. Abnormal N-glycosylation may affect the biological activity of OPG, or alter the glycosylation state of RANKL and affect its interaction with OPG/RANK, ultimately leading to a balance tilting towards RANKL, enhanced osteoclast activity, and excessive bone resorption. This may be more pronounced in the early stages of osteoarthritis [56].

Promoting osteoblast/osteocyte aging: Similar to chondrocytes, osteoblasts and osteocytes in subchondral bone are also affected by factors such as AGEs to accelerate aging. Senescent bone line cells express SASP and secrete inflammatory factors including IL-6, which not only disrupt osteocyte activity but also affect chondrocytes by penetrating the subchondral bone plate [57].

3.3.2 Abnormal glycosylation impairs the quality of bone matrix

The mechanical properties of bones are not only determined by bone mass but also by bone quality, and the network structure of bone collagen is a key determinant of bone quality. AGEs form non-enzymatic cross-links on bone collagen, which are essentially different from normal enzymatic cross-links such as pyridinoline. Normal cross-linking enhances the toughness and strength of bone, while AGEs cross-linking makes the bone matrix stiff and fragile. This change in the properties of the bone material makes

subchondral bones more prone to microfractures when subjected to loads. The accumulation of these micro-injuries, in turn, abnormally activates bone remodeling, which, due to signal disruption during the repair process, eventually leads to structurally disordered braided bone formation and bone hardening [58]. Abnormal N-glycosylation of collagen such as COL6A1 may interfere with the normal assembly and mineralization of collagen fibers and affect the interaction between collagen and other matrix components, thereby damaging the microstructural integrity of trabeculae. Poor-quality trabeculae have difficulty effectively distributing stress, causing microdamage and further intensifying the hardening process of subchondral bone, creating a vicious cycle. Therefore, abnormal glycosylation shakes the subchondral bone of the joint at both biological (affecting cell function and balance) and mechanical (altering the properties of the matrix material) levels. Hardened, mechanically poor subchondral bone loses its effective buffering capacity and transmits greater stress directly to the already fragile articular cartilage above, thereby accelerating cartilage degeneration.

4. Conclusions and Prospects

Osteoarthritis (OA) is a common degenerative orthopedic disease that poses a serious threat to human joint health. Its pathogenesis is complex and involves multiple tissue levels, and glycosylation is an important biological process that plays a key role in the occurrence and development of OA. Although numerous studies have shown that glycosylation is closely related to OA, the specific molecular signaling pathways have not been fully clarified, and there are still many unknown links that need to be further explored. Details of the interactions between AGEs and a variety of intracellular signaling molecules, as well as the mechanisms by which these interactions work together to promote the development of OA, remain to be further clarified. And most of the current research on the application of glycosylation in the treatment of OA is still in the laboratory stage, and there are many challenges in clinical translation. On the one hand, verifying the safety and efficacy of drugs in a clinical setting requires a large number of clinical trials and long-term follow-up observations; On the other hand, issues such as drug administration routes, dose optimization, and combination strategies with existing OA treatments have not been properly addressed. Future research should focus on clarifying the detailed molecular mechanisms by which glycosylation affects OA, developing specific inhibitors or interventions targeting the glycosylation process, and strengthening the transition from preclinical research to clinical application, which is expected to provide new ideas and strategies for the prevention and treatment of osteoarthritis and improve the prognosis and quality of life of patients.

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