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Roles of Galactose and Its Glycosylation Modifications in Inflammatory Arthritis

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Abstract

Disorders of galactose metabolism and the aberrant glycosylation it mediates play a central role in the pathological mechanisms of rheumatoid arthritis (RA) and osteoarthritis (OA). In RA, hypo-galactosylation (G0 glycoform) of the IgG Fc region drives synovial inflammation and bone destruction by enhancing FcγRI binding, hyperactivating the complement system, and promoting immune complex deposition. In OA, galactose-dependent glycosylation modifications (e.g., terminal modifications of aggrecan) maintain cartilage extracellular matrix (ECM) homeostasis. Abnormal galactose metabolism (dysfunction of the Leloir pathway, activation of the galactitol pathway) exacerbates inflammation and cellular senescence by regulating the PI3K/Akt/NF-κB signaling axis. Herein, we aim to review roles of galactose and its glycosylation modifications in inflammatory arthritis, including RA and OA, thereby providing strategies and basis for the diagnosis and treatment for inflammatory arthritis by targeting galactose-metabolizing enzymes such as B4GALT1/GALK1 or glycosylation nodes such as Galectin-4.

Keywords

Galactose Metabolism, Glycosylation Modification, Rheumatoid Arthritis, Osteoarthritis, Keratan Sulfate, Leloir Pathway

1. Introduction

Inflammatory arthritis encompasses a group of diseases characterized by joint inflammation, typically accompanied by pain, swelling, and functional impairment. It is a major global cause of pain, disability, and socioeconomic burden. Rheumatoid arthritis (RA) and osteoarthritis (OA), as the most common types, exhibit

distinct pathological mechanisms and clinical manifestations [1]. RA is a chronic autoimmune disease primarily manifested by joint swelling, pain, and dysfunction, often with systemic symptoms like fatigue and weight loss. Its pathology involves autoimmune reactions, featuring persistent synovial inflammation leading to destruction of articular cartilage and bone, potentially resulting in disability. Early diagnosis and timely treatment are crucial to prevent joint damage [2]. OA is mainly characterized by degeneration and damage of articular cartilage, commonly affecting weight-bearing joints like knees and hips, leading to pain, stiffness, and restricted movement. Its pathological mechanisms involve cartilage matrix degradation and bone remodeling, causing structural changes in the joint. OA incidence increases with age, making it one of the most common joint diseases in the elderly [3]. Both are chronic conditions requiring long-term management.

Galactose is an important natural monosaccharide [4]. As a component of lactose, it is widely found in dairy products. Lactose is hydrolyzed into galactose and glucose during digestion. Galactose is metabolized to glucose via enzymatic reactions, primarily in the liver. Once converted, glucose can supply cellular energy and participate in various carbohydrate metabolic pathways [5]. Abnormalities in its metabolism can lead to metabolic diseases like galactosemia, impacting health. Beyond being an energy source, galactose is also a precursor for glycan synthesis involved in glycosylation, enabling it to regulate cellular functions and participate in various biological signaling pathways [6].

Gal metabolism disorders and the abnormal glycosylation they mediate play a core role in the pathological mechanisms of RA and OA [7] [8]. Furthermore, Systemic factors like dietary galactose and liver metabolism influence UDP-galactose availability in joints, modulating synovial and cartilage glycosylation. The gut-joint axis further implicates microbiota-derived galactose metabolites in regulating joint inflammation and glycosylation patterns [5]. Targeting galactose-metabolase or glycosylation nodes will open up new avenues for individualized treatment for inflammatory arthritis.

2. Biological Properties and Metabolism of Galactose

2.1. Basic Properties of Galactose

Galactose ($C_6H_{12}O_6$) is a six-carbon reducing monosaccharide. Its molecular structure resembles glucose but differs in spatial configuration, leading to differences in metabolism and biological functions within organisms [9]. Like all other aldohexoses, galactose has two enantiomers: D-galactose and L-galactose. The latter is not naturally occurring in higher organisms as it cannot be further metabolized intracellularly [6]; therefore, "galactose" typically refers to D-galactose. Galactose can exist in linear or cyclic forms. The six-membered cyclic form, pyranogalactose, is the sole cyclic form found in mammals, while the five-membered furanogalactose is common in lower organisms [10]. Galactose is highly soluble in water and can interact with various biomacromolecules like proteins and nucleotides. It is less sweet than glucose but sweeter than many other mono- and

disaccharides, finding some application as a sugar substitute in the food industry. Galactose can polymerize with other monosaccharides to form polysaccharides (e.g., galactans) with diverse biological functions [11].

2.2. Metabolic Pathways of Galactose

Galactose is typically ingested as lactose, which is hydrolyzed to galactose and glucose by lactase in the small intestine. Galactose is then absorbed into the portal venous blood via transporters in intestinal epithelial cells [12]. Most ingested galactose is retained in the liver, while small amounts reach other organs (e.g., brain for amino acid synthesis, mammary glands for lactose production) [9]. In the liver, skeletal muscle, and other target tissues, galactose is primarily metabolized via three main pathways: **Leloir Pathway** (Highly Conserved): β-D-Galactose (β-D-Gal) entering the cell is converted to its stereoisomer α-D-Galactose (α-D-Gal) by galactose mutarotase (GALM). α-D-Gal is then phosphorylated to Galactose-1-phosphate (Gal-1-P) by galactokinase (GALK). Gal-1-P reacts with UDP-Glucose (UDP-Glc) via galactose-1-phosphate uridylyltransferase (GALT) to yield Glucose-1-phosphate (Glc-1-P) and UDP-Gal. UDP-Gal can also be formed from UDP-Glc by UDP-galactose 4'-epimerase (GALE) [13] [14]. Ultimately, galactose enters glycolysis/glycogenesis or glycosylation pathways. **Galactonate Pathway:** During galactose excess, galactose can be oxidized to galactonic acid, which is excreted in urine or further metabolized to D-xylulose-5-phosphate, entering the non-oxidative part of the pentose phosphate pathway [15] [16]. **Galactitol Pathway:** Excess galactose can be reduced to galactitol by aldose reductase. Galactitol has poor lipid solubility and is poorly metabolized. Its accumulation increases intracellular osmotic pressure, potentially causing cell membrane rupture. It also consumes NADPH and inhibits GALM, exacerbating galactose accumulation, and is associated with cellular senescence [16] [17]. The three galactose metabolic pathways are summarized in **Figure 1**, with UDP-Gal produced via the Leloir pathway entering the glycosylation process.

2.3. Glycosylation Roles of Galactose

2.3.1. Protein Glycosylation

Glycosylation is the most significant step in protein modification. It is estimated that over 50% of human proteins are glycosylated, explaining its crucial role in numerous biological events [18]. Galactose is a key precursor for glycan biosynthesis. Transported into the endoplasmic reticulum (ER) and Golgi via specific transporters, it is covalently attached to glycans on proteins or lipids by glycosyltransferases. Protein glycosylation includes N-glycosylation and O-glycosylation, essential for protein structure and functional maturation. In RA: Kissel *et al.* [7] showed that the abundance of variable domain glycosylation (VDG) on serum anti-citrullinated protein antibody (ACPA)-IgG increases at RA onset and correlates with ACPA response maturation. Lower VDG levels at onset are associated with poor prognosis. In OA: α-1,3-Fucosylation, an important regulatory mechanism for protein N/O-glycosylation, delays ECM degradation by upregulating and

inhibiting Tumor Necrosis Factor Receptor 1 (TNFR1) binding to Tumor Necrosis Factor-α (TNF-α), thereby blocking the NF-κB/p38/JNK-MAPK pathway. Thus, upregulation of α-1,3-fucosylation has potential as a therapeutic target [19]. Senescent chondrocytes promote ECM degradation by secreting SASP factors like Interleukin-6 (IL-6) and matrix metalloproteinase-13 (MMP13), while aberrant glycosylation exacerbates subchondral bone remodeling by regulating integrin signaling. This dual mechanism drives OA joint degeneration [20], providing a molecular basis for novel therapeutic strategies targeting senolysis and glycosylation homeostasis.

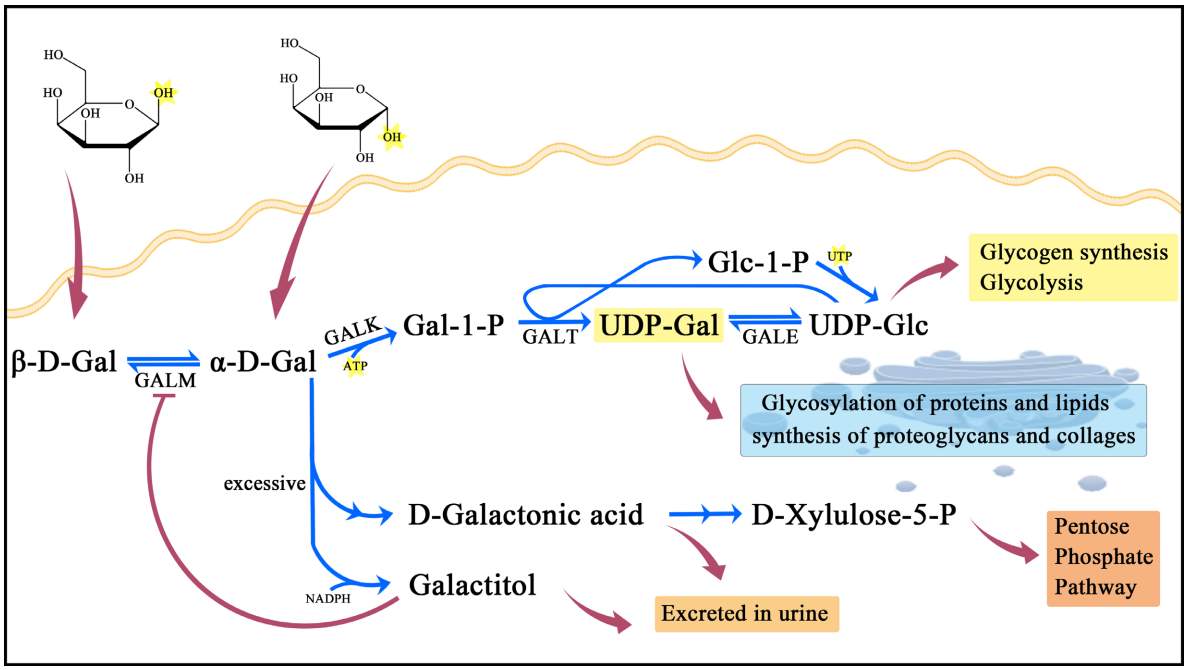

Figure 1. Galactose undergoes metabolism through three primary pathways. In the Leloir pathway, β-D-Gal is converted to UDP-glc, which serves as a substrate for glycogen synthesis and glycolysis, and to UDP-Gal. UDP-Gal acts as a central node in the glycosylation network, directly participating in the glycosylation of proteins and lipids, as well as the synthesis of proteoglycans and collagen. Alternatively, via the galactonate pathway, galactose yields D-galactonic acid, which can either be excreted in urine or further metabolized to D-xylulose-5-phosphate for entry into the non-oxidative phase of the pentose phosphate pathway. Finally, metabolism through the galactitol pathway produces galactitol, which is primarily excreted in urine.

2.3.2. Roles of Proteoglycans and Keratan Sulfate

Glycosaminoglycans (GAGs), also known as mucopolysaccharides, are polysaccharides composed of repeating disaccharide units carrying a negative charge. Found in virtually every mammalian tissue, their diverse functions are determined by their unique molecular structures [21]. Sundar *et al.* [22] showed that polystyrene sulfonate, as a polyanionic polyelectrolyte, is a potential functional candidate molecule for reconstructing the mechanical microenvironment by restoring charge density in GAG-deficient cartilage. Keratan sulfate is the only GAG containing galactose, composed of repeating disaccharide units of galactose and N-acetylglucosamine. Synthesized by specific glycosyltransferases and bound to core

proteins to form proteoglycans, it plays vital roles in ECM formation and tissue support [23]. Despite its importance in cartilage metabolism, its specific mechanism in OA pathology remains incompletely elucidated and requires further exploration.

2.3.3. Collagen Glycosylation

Collagen undergoes glycosylation in the ER, where specific hydroxylysine residues carry galactose or glucosyl-galactose disaccharides, aiding in correct folding and structural stability [24]. This process, particularly the addition of galactose to hydroxylysine mediated by specific beta(1-O) galactosyltransferases, is critical for the proper folding and stabilization of the collagen triple-helix structure and enhances fibril stability and resistance to enzymatic degradation [25]. These glycosylated collagen fibers subsequently cross-link within the extracellular matrix, forming a robust structural scaffold that provides cartilage with essential tensile strength, elasticity, and mechanical stability. However, impaired galactosylation—often resulting from dysregulated expression of glycosyltransferases such as COLGALT1—is frequently observed in arthritic joints. Defects in these enzymes, including those associated with pathogenic COLGALT1 variants, compromise collagen integrity, reduce mechanical strength, and increase susceptibility to degradation by matrix metalloproteinases [26]. Together, these findings underscore the fundamental role of galactose-mediated glycosylation in maintaining collagen stability and cartilage homeostasis, suggesting its potential as a therapeutic target in arthritis.

2.3.4. Lipid Glycosylation

Galactose can bind to lipids to form glycolipids, crucial for cell membrane structure and function. For example, galactocerebroside is a major component of myelin, and its sulfated derivative, sulfatide, has important functions in the nervous system and other tissues [27]. Galectin-4 (Gal-4), a member of the galectin family, utilizes its unique two tandem carbohydrate recognition domains (CRDs) to specifically bind galactose and mediate intermolecular crosslinking of glycoproteins. It acts as a key bridge, particularly in the directional transport of glycoproteins dependent on sulfation modifications [28]. Pichler *et al.* [29] demonstrated that in primary human OA chondrocytes *in vitro*, blocking Gal-4's galactose-binding capacity with carbohydrate inhibitors significantly upregulated pro-degradative and pro-inflammatory factors like IL-1β and MMP-13 expression. This suggests Gal-4 may physiologically inhibit inflammatory signaling and matrix degradation via glycan recognition, maintaining cartilage homeostasis. Conversely, impaired Gal-4 function might exacerbate cartilage degeneration and OA pathology by disrupting glycoprotein transport networks or activating inflammation-related pathways like NF-κB. This finding offers new perspectives on Gal-4's biological function and suggests targeting Gal-4-galactose interactions as a potential OA intervention strategy, though its specific molecular mechanisms and cross-tissue functional heterogeneity require further elucidation.

2.4. Roles of Galactose in Cell Signaling

Activation of PI3K/Akt Pathway: Galactose influences the PI3K/Akt signaling pathway, promoting cell survival and proliferation. This pathway plays a vital role in inflammation and tissue repair, enhancing immune cell function and reducing apoptosis rates [30]. Dysregulation of galactose metabolism plays significant roles in various diseases. In hepatocellular carcinoma, GALK1 and GALT are upregulated, and their knockdown inhibits cell growth and reduces PI3K/AKT signaling at the protein but not mRNA level, suggesting post-transcriptional regulation via glycosylation [14]. Similarly, in arthritis, GALK1 dysregulation disrupts galactose metabolism, leading to galactose-1-phosphate accumulation (activating p38 MAPK) and UDP-galactose deficiency (impairing glycosylation). Targeting GALK1 may therefore restore metabolic homeostasis and ameliorate disease progression in both cancer and arthritis. Regulation of NF-κB Signaling Pathway: The NF-κB pathway plays a central role in inflammatory responses. Galactose can inhibit NF-κB activation, thereby reducing pro-inflammatory cytokine expression and dampening inflammation intensity [31]. Influence on MAPK Pathway: Galactose regulation of the MAPK signaling pathway is also significant. By modulating the activity of subfamilies like ERK, JNK, and p38, galactose can influence the synthesis of inflammatory mediators and the activity of immune cells [32].

3. Pathological Roles of Galactose in Inflammatory Arthritis

3.1. Roles of Galactose in RA

3.1.1. Molecular Mechanisms of IgG Galactosylation and Inflammation Regulation

Altered Fc Receptor Binding Affinity: Aberrant glycosylation of the IgG Fc region in RA patients is primarily characterized by terminal galactose deficiency (G0 glycoform). Core residue exposure significantly alters its biological function [33]. Studies found that the sialylation and galactosylation levels of purified ACPA-IgG in RA serum inversely correlate with inflammatory markers like CRP, ESR, and RF. Dimerized ACPA-IgG significantly promoted TNF-α release from monocytes via FcγRI binding, and TNF-α release intensity inversely correlated with the abundance of the G0 glycoform lacking galactose and sialic acid. This suggests abnormal ACPA-IgG glycosylation enhances its pro-inflammatory activity by modulating Fc receptor interactions [34]. Seeling *et al.* [35] found that while IgG antibodies typically promote inflammation, pooled serum IgG (IVIg) has anti-inflammatory effects; in RA models, IVIg inhibited joint inflammation via sialylation, enhancing IgG binding and reprogramming monocytes.

Differential Complement Activation: In RA pathology, G0 agalactosylated IgG immune complexes exhibit unique complement-activating properties. They enhance classical pathway activation efficiency twofold by increasing C1q binding. Concurrently, affinity of mannose-binding lectin (MBL) for glycosylation-deficient IgG is significantly increased, lowering the activation threshold for the lectin pathway. This dual-pathway synergistic activation mechanism elevates synovial

fluid chemokine C5a levels to 5 - 8 times those of healthy controls, sustaining an inflammation-tissue destruction vicious cycle by recruiting neutrophils and promoting synovial pannus proliferation [36]. Furthermore, terminal complement complex (TCC) levels are significantly elevated in active RA patients, directly reflecting complement system hyperactivation. Clinical intervention data showed that while TCC levels decreased with reduced disease activity after 6 weeks of conventional anti-inflammatory therapy, only patients receiving TNF inhibitors (TNFI) with/without methotrexate (MTX) maintained sustained TCC suppression over 6 months. Notably, RA patients with endothelial dysfunction had baseline TCC levels ~30% higher than those without vascular complications ($p < 0.01$), suggesting complement may mediate vascular endothelial cell damage and inflammatory signal amplification, contributing to accelerated atherosclerosis in RA. These findings elucidate the core mechanism of aberrantly glycosylated IgG driving the inflammatory network via the complement cascade at molecular-cellular-tissue levels and provide a mechanistic explanation for the advantage of TNFI therapy in regulating complement activation and improving vascular complications [37]. Additionally, hypo-galactosylated ACPA-IgG exhibits ~30% enhanced binding to citrullinated fibrinogen. The resulting immune complexes deposit more readily in sub-synovial tissues, activating dendritic cells and persistently driving autoimmune responses, increasing IL-10 secretion and reducing osteoclastogenesis [38].

Glycosylation and Autoantibody Function: Hypo-galactosylation of ACPA-IgG not only increases its affinity for FcγRI but may also enhance binding to citrullinated antigens by exposing cryptic epitopes, forming more stable immune complexes that persistently drive autoimmune reactions [38] [39]. Blöchl *et al.* [33] analysis of plasma-synovial fluid paired samples revealed significant heterogeneity in glycosylation profiles between ACPA-IgG and total IgG. This heterogeneity stems from IgG subclass-specific post-translational modification (PTM) features: including IgG3 heavy chain CH3 domain-specific galactose deficiency, allotype proportion imbalance, and enrichment of non-glycosylated IgG. IgG3 CH3 glycosylation abnormalities may enhance interaction with mannose-binding lectin (MBL) by exposing core residues, while accumulation of non-glycosylated IgG in synovial fluid may relate to altered Fcγ receptor binding. Specific glycoforms (e.g., hypo-galactosylated ACPA-IgG) strongly correlate with synovial fluid inflammatory markers like IL-6 and MMP-3, suggesting glycosylation-driven immune complex conformational changes may exacerbate local inflammation by activating the complement-phagocyte axis.

3.1.2. Clinical Potential of Galactosylation as a Dynamic Biomarker

Disease Activity Monitoring: Longitudinal studies show that the IgG Galactosylation Index (GI) inversely correlates with DAS28 scores in RA patients. When GI falls below 0.35, the risk of joint erosion increases 4.2-fold. After 6 months of methotrexate treatment, 82% of patients whose GI rebounded above 0.45 achieved ACR50 remission, significantly higher than the group with no GI improvement

(34%), indicating its potential as a treatment response predictor [40].

Subtype-Specific Differences: The degree of galactosylation abnormality varies among different IgG subclasses (e.g., IgG1 vs IgG4). IgG1 shows the most significant GI decrease, possibly related to its dominant role in immune complexes. Sarilumab, a human monoclonal IgG1 antibody against the IL-6 receptor, is used to treat RA and other autoinflammatory diseases [41]. Saint-Gerons *et al.* [42] found RA is sometimes accompanied by abundant IgG4 plasma cells, meeting histological diagnostic criteria for IgG4-related disease.

Metabolomics Association: Elevated serum free galactose levels in RA patients may relate to decreased glycosyltransferase activity (e.g., β-1,4-galactosyltransferase) or disordered sugar metabolism pathways [43]. Schwedler *et al.* [44] revealed increased hypo-galactosylation of IgG in RA, suggesting a preconditioned humoral immune response; reduced B4GALT3 expression in B cells further supports its association with early B cell activation. Abnormal galactose metabolism may exacerbate autoimmune responses by affecting glycoprotein synthesis.

3.1.3. Therapeutic Interventions Modulating Galactosylation

Anti-TNF-α Therapy: Infliximab, by inhibiting TNF-α signaling, upregulates β-1,4-galactosyltransferase expression, significantly reducing the proportion of G0 IgG while increasing mono-galactosylated (G1) and di-galactosylated (G2) glycoforms, improving clinical symptoms. Ozoralizumab, a novel TNFI, shows promise as a practical option for RA patients, with early symptom improvement despite subcutaneous administration [41].

Natural Remission During Pregnancy: Elevated estrogen and progesterone levels during pregnancy may enhance IgG galactosylation levels by regulating B cell glycosylation enzyme activity (e.g., increasing galactosyltransferase function), thereby reducing pro-inflammatory immune complex formation. However, other pregnancy-related factors (e.g., HLA-G) may act synergistically [45].

Potential Therapeutic Targets: Small molecule agonists targeting glycosylation enzymes (e.g., ST6Gal1 or B4GALT1) or gene editing techniques (e.g., CRISPR-Cas9) may restore normal IgG glycosylation, currently in preclinical stages [46].

3.1.4. Technological Advances and Multi-Omics Integration

High-Resolution Mass Spectrometry: Combined MALDI-TOF-MS^n and capillary electrophoresis (CE) can distinguish positional isomers of galactosylation, revealing glycan branch heterogeneity associated with disease subtypes [47]. Ma *et al.* [48] found via MALDI-TOF-MS that CCL24 may be an important auxiliary diagnostic indicator for RA.

3.2. Roles of Galactose in OA

3.2.1. Cartilage Matrix Metabolism and Galactose-Dependent Glycosylation

Progressive degradation of the chondrocyte extracellular matrix (ECM) is a core pathological feature of OA, where galactose-involved glycosylation modifications play a key role in maintaining ECM homeostasis [49]. Aggrecan (ACAN), a core

cartilage ECM component, relies on terminal galactosylation modifications of its GAG chains to maintain proteoglycan compressive resistance and ECM mechanical function by enhancing molecular hydrophilicity and charge stability [50]. Yuan *et al.* [51], using an *in vitro* model of ATDC5 cell line and chondrocytes with galactose intervention, showed significantly upregulated gene expression of type II collagen (COL2) and ACAN, alongside enhanced synthesis and deposition of ECM core proteins (COL2, ACAN). This indicates galactose positively regulates chondrogenic differentiation and ECM homeostasis reconstruction by promoting expression and accumulation of cartilage-specific matrix components. Furthermore, galactose forces chondrocytes to shift from glycolysis to mitochondrial respiration, repairing mitochondrial dysfunction and thereby blocking IL-1β-induced OA-characteristic destruction including MMP13 expression and matrix degradation [8], providing a novel rationale for metabolism-targeted OA therapies. Kim *et al.* [52] revealed that 5-aminosalicylic acid (5-ASA) inhibits COX-2-related inflammation by reversing OSCAR-mediated PPARγ transcriptional suppression in articular chondrocytes. It also significantly improves chondrogenic function by strongly downregulating ECM catabolism (e.g., inhibiting matrix metalloproteinase activity) and promoting ECM anabolism (e.g., upregulating type II collagen and aggrecan expression), synergistically maintaining cartilage homeostasis and repair. Li *et al.* [53] histological analysis showed 5-ASA effectively preserved proteoglycan content in cartilage tissue and maintained matrix structural integrity by inhibiting degradation of ECM core proteins. In inflammatory joint explant models, 5-ASA further significantly alleviated OA pathology by reducing pro-inflammatory factor release and blocking GAG loss, while regulating ECM metabolic balance by inhibiting catabolic pathways (e.g., MMP activity) and promoting anabolic marker expression, synergistically protecting cartilage homeostasis and function.

3.2.2. Abnormal Galactose Metabolism and Cellular Senescence

During OA pathology, chondrocyte metabolic reprogramming is often accompanied by galactose metabolism disorders, manifested as decreased activity of key Leloir pathway enzymes. This leads to galactose-1-phosphate accumulation and impaired UDP-galactose synthesis, exacerbating cartilage degeneration via a dual mechanism. Cao *et al.* [54] *in vitro* experiments confirmed that infrapatellar fat pad-derived small extracellular vesicles (IPFP-sEVs) accelerate cartilage degeneration by activating ECM catabolism and inducing chondrocyte senescence. They significantly promoted ECM degradation and exacerbated experimental OA progression in mouse and human cartilage explant models. Intra-articular injection of let-7b/c-5p antagonists effectively restored lamin B receptor (LBR) expression, inhibited senescence, and alleviated pathology in a mouse OA model, suggesting targeting the miRNA-LBR axis may offer a new OA treatment strategy. Galactose-1-phosphate activates the p38 MAPK signaling axis, inducing the senescence-associated secretory phenotype (SASP) and promoting the release of inflammatory mediators like IL-6 and MMP-13 [55]. Geng *et al.* [56] found that 10-hydroxy-2-

decenoic acid inhibits the function of aspartyl β-hydroxylase domain-containing protein (ASPHD) by targeting its glycosylation sites and regulates cartilage metabolism: Molecularly, it alleviates chondrocyte senescence by inhibiting ERK/p53/p21 and GSK3β/p16 signaling pathways. Functionally, it blocks abnormal activation of galactose metabolism disorders and inflammatory pathways (e.g., p38 MAPK, NLRP3), while improving UDP-galactose supply by maintaining Leloir pathway enzyme activity, thereby repairing proteoglycan glycosylation defects and enhancing ECM stability. This provides a new strategy for treating OA by targeting the metabolism-senescence interaction network. These processes are mechanistically linked to the PI3K/Akt/NF-κB axis: galactose-1-phosphate accumulation activates p38 MAPK and NF-κB, driving SASP and matrix degradation, while impaired Leloir pathway function reduces UDP-galactose supply, compromising glycosylation-dependent ECM stability [30] [31] [55] [56]. Concurrently, abnormal activation of the galactitol metabolic pathway occurs. Aldose reductase (AKR1B1) catalyzes excess galactose into galactitol, triggering chondrocyte pyroptosis via osmotic stress and activating the NLRP3 inflammasome [57]. In the mouse destabilization of the medial meniscus (DMM) model, intra-articular injection of compound HL significantly reduced cartilage degeneration and inflammation, evidenced by lower OARSI histopathology scores, downregulated expression of catabolic factors and senescence markers (p16, p21), alongside restored COL2 and ACAN content, reduced pro-inflammatory cytokine (IL-6, CXCL-1) release, and improved chondrocyte number and matrix synthesis function. This suggests HL exerts chondroprotective effects by inhibiting galactitol metabolic dysregulation and its downstream inflammation-senescence cascade [58]. Notably, O-GlcNAc glycosylation levels are significantly elevated in the superficial zone of OA cartilage. O-GlcNAcylation at the S406 site of GATA4 protein enhances its stability, inhibiting p62-mediated selective autophagic degradation, thereby promoting SASP-related pathological phenotypes [59].

3.2.3. Regulatory Network of Galactose-Binding Proteins

The galectin family exhibits dual regulatory properties in OA. Galectin-3 (Gal-3): Binding galactose residues in cartilage ECM can inhibit MMP-3 activity and promote TIMP-1 expression, exerting a protective effect [60]. Udomsinprasert *et al.* [61] found significantly upregulated Gal-3 mRNA and protein expression in inflamed synovium of knee OA patients (immunohistochemistry showed enrichment in the synovial lining and sublining). *In vitro* studies confirmed its aberrant expression is regulated by TNF-α in synovial cells. Gal-3 promotes nitric oxide and IL-6 generation by activating the Akt phosphorylation pathway, upregulates mRNA expression of IL-6, NF-κB, and MMP-13, while inhibiting transcription of ACAN and the key chondrogenic factor SOX-9. This indicates Gal-3 exacerbates synovial inflammation and cartilage degeneration through pro-inflammatory and catabolic effects. Its dual role may be context-dependent: in early OA, it may exert protective effects by stabilizing the ECM, whereas in chronic inflammation, sustained overexpression promotes catabolic and inflammatory responses, driven by

factors such as cytokine milieu, cellular stress, and glycosylation status of its ligands [60] [61]. Gal-4: Functional inhibition of Gal-4 upregulates IL-1β and COX-2 via the NF-κB pathway, exacerbating inflammation [62]. Pichler *et al.* further found that the affinity of Gal-4's CRD for sulfated GAGs is reduced in OA, preventing it from effectively blocking Toll-like receptor 4 oligomerization, thereby enhancing inflammatory signaling [29]. This loss of glycan-binding capacity may relate to competitive inhibition by elevated free galactose levels in OA synovial fluid. The role of galactose and its glycosylation in OA and RA is summarized in **Figure 2**.

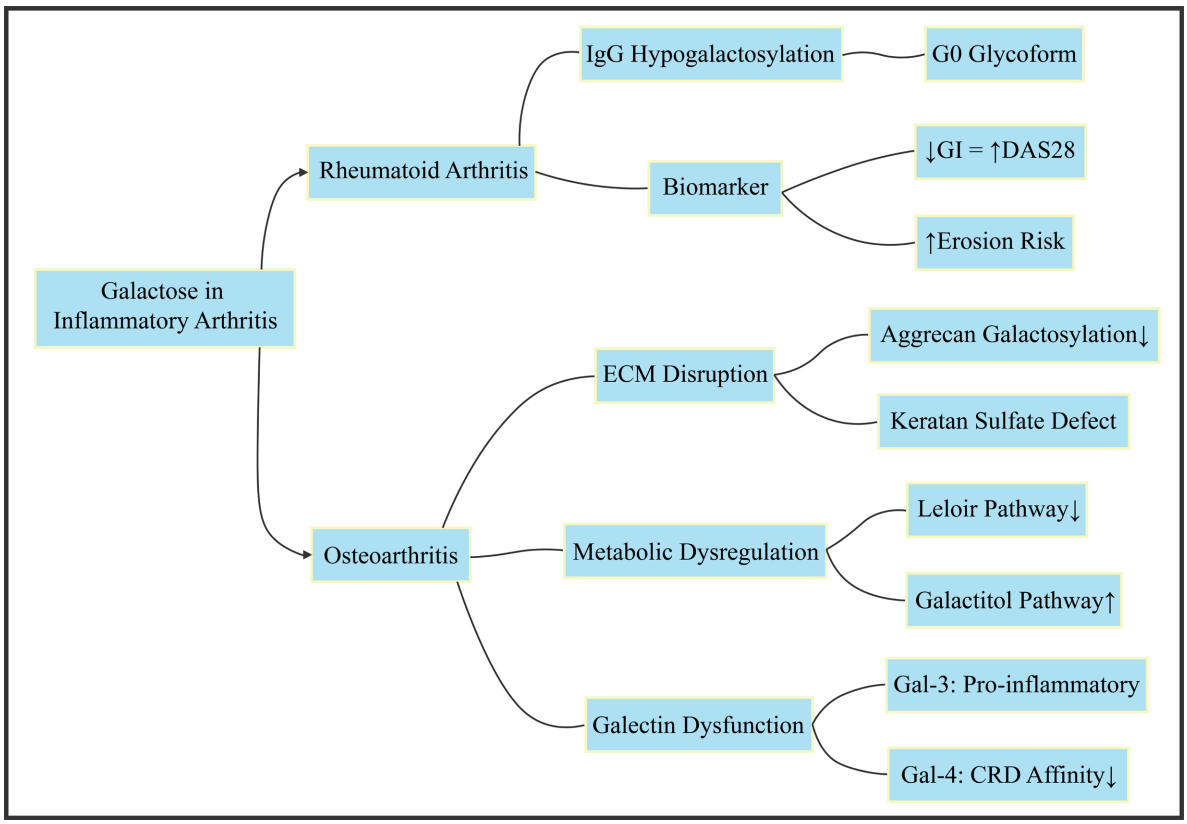

Figure 2. Brief concept map summarizing roles of galactose and its glycosylation modifications in Rheumatoid Arthritis (RA) and Osteoarthritis (OA).

4. Conclusions

Galactose, as a key metabolic substrate and glycosylation modifier, plays a dual role in the pathology of inflammatory arthritis. In RA, hypo-galactosylation (G0 glycoform) of the IgG Fc region amplifies the inflammatory cascade by enhancing Fcγ receptor binding, complement hyperactivation, and immune complex deposition, leading to joint destruction. In OA, galactose-involved key glycosylation modifications (e.g., keratan sulfate on proteoglycans) maintain ECM stability; galactose metabolism disorders causing GAG synthesis defects and galectin dysfunction collectively accelerate cartilage degeneration. Although RA and OA have distinct pathological mechanisms, both involve disturbances in galactose-dependent

glycosylation networks, suggesting targeting sugar metabolic reprogramming and restoring glycosylation homeostasis could become novel cross-disease therapeutic strategies.

Biomarkers: The IgG Galactosylation Index (GI) in RA patients significantly inversely correlates with disease activity (DAS28 score) and joint erosion risk, serving as a treatment response predictor (e.g., methotrexate, anti-TNF therapy). Therapeutic Targets: RA: Restore IgG galactosylation (e.g., upregulate β-1,4-galactosyltransferase); Block complement activation (e.g., anti-C5 antibody). OA: Inhibit galactitol production (target aldose reductase AKR1B1); Regulate galectin function (e.g., Gal-4 CRD agonist); Repair Leloir pathway enzyme activity.

Future research should focus on: Elucidating the functional differences of tissue-specific galactose-metabolizing enzymes (e.g., GALK1 isoforms). Developing high spatiotemporal resolution glycosylation dynamic imaging technologies to reveal the spatiotemporal regulation patterns of glycan modifications. Exploring the impact of microbe-host galactose metabolism interactions (e.g., gut microbiota lactose breakdown) on arthritis. The integration of multi-omics and precision intervention strategies, including those targeting the gut-joint axis through dietary or microbial modulation of galactose availability, will pave new paths for personalized treatment of inflammatory arthritis.

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Conflicts of Interest

The authors declare that there are no potential competing interests, either financial or non-financial, related to this paper.

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