Review

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Aggrecan remodeling in degenerate discs

Patterns, determinants, measurement, and emerging therapies

Haoyu Liu[a], Tianqi Fan[a], Lin Shi[a], Yong Yang[a,*], Bin Zhu[a,*]

Abstract: Aggrecan is the principal determinant of water retention in the nucleus pulposus and a core regulator of intervertebral disc mechanics. This review synthesizes evidence on aggrecan alterations during intervertebral disc degeneration (IVDD), associated upstream drivers, and current approaches for assessment and therapy. Based on published literature, we present the first comprehensive, 4-part classification of aggrecan modifications observed across degeneration: (1) a reduced chondroitin sulfate–to–keratan sulfate ratio; (2) increased enzymatic cleavage of the core protein; (3) decreased core protein expression; and (4) exacerbated hyaluronic acid degradation. These shifts converge on loss of fixed charge density and osmotic pressure, reduced water content, and altered tissue mechanics in the degenerating disc. We further provide the first integrative synthesis of upstream drivers linked to these aggrecan alterations, systematizing them into a convergent set that includes hypoxia, metabolic dysregulation with lactate accumulation and acidosis, inflammatory cytokine signaling, and osmotic imbalance. For assessment, we outline conventional biochemical/chemical assays for proteoglycans and glycosaminoglycans and summarize emerging readouts that infer aggrecan or glycosaminoglycan content and may aid early evaluation. From a therapeutic standpoint, current strategies fall into 2 broad categories. Restorative approaches attempt to mitigate 1 or more modification domains—most commonly via anti-inflammatory signaling control or modulation of matrix-degrading enzymes—but typically focus on single targets and may not address the multifactorial nature of degeneration. Substitution approaches seek to supplement water-retaining function with aggrecan-mimicking materials; although several candidates reproduce key biophysical features *in vitro*, *in vivo* validation in disc models remains limited. Collectively, these findings position aggrecan as a molecular and biophysical anchor for understanding IVDD and designing interventions. Future work should prioritize multitarget repair strategies that address the convergent drivers identified here and support *in vivo* evaluation of aggrecan substitutes to restore osmotic function and matrix homeostasis in nucleus pulposus (NP).

Abbreviations: IVDD, intervertebral disc degeneration; NP, nucleus pulposus; AF, annulus fibrosus; ECM, extracellular matrix; GAG, glycosaminoglycan; CS, chondroitin sulfate; KS, keratan sulfate; HA, hyaluronic acid; MMP, matrix metalloproteinase; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; SDC4, syndecan-4; HYAL, hyaluronidase; gagCEST, glycosaminoglycan chemical exchange saturation transfer; HR-MAS NMR, high-resolution magic-angle spinning nuclear magnetic resonance; BPG, biomimetic proteoglycan.

Keywords: aggrecan, chondroitin sulfate, glycosaminoglycans, hyaluronic acid, intervertebral disc degeneration, keratan sulfate, matrix metalloproteinases, nucleus pulposus

1. Introduction

Intervertebral disc degeneration (IVDD) is multifactorial, yet its defining change is water loss in nucleus pulposus (NP). Accordingly, this review concentrates on the NP microenvironment rather than the annulus fibrosus. Although disc cell biology,[1] surgical interventions,[2] and imaging diagnostics[3] have been thoroughly investigated, the extracellular matrix (ECM) remains underexplored despite its crucial influence on disc mechanics. This omission is significant because ECM—particularly the components responsible for retaining water—directly influences both structural integrity and functional capacity of intervertebral disc.

The NP contains various proteoglycans and collagens, each playing distinct roles—some contribute to tissue repair, while others are involved in signaling. Among these components, aggrecan stands out as the most critical for

YY and BZ contributed to this article equally and are co-corresponding authors.

HL and TF contributed to this article equally and are co-first authors.

[a] Department of Orthopaedics, Beijing Friendship Hospital, Capital Medical University, Beijing, China.

* Correspondence: Yong Yang, Department of Orthopaedics, Beijing Friendship Hospital, Capital Medical University, No. 95, Yong'an Road, Xicheng District, Beijing 100050, China (e-mail: spineyang@126.com); Bin Zhu, Department of Orthopaedics, Beijing Friendship Hospital, Capital Medical University, No. 95, Yong'an Road, Xicheng District, Beijing 100050, China (e-mail: zhubin@bjmu.edu.cn).

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water retention, as it provides essential hydrophilic properties that enable NP to maintain its osmotic pressure and load-bearing function.[4] Despite its fundamental importance, aggrecan has not received the same level of scientific scrutiny as cellular or surgical approaches, which hinders our understanding of the underlying pathophysiological mechanisms of IVDD. By highlighting the centrality of aggrecan within the ECM, this review aims to underscore its critical role in the development and progression of IVDD, ultimately calling attention to the need for more targeted investigations and potential therapeutic strategies based on preserving or enhancing aggrecan function.

Search strategy

We conducted a structured literature search in PubMed and Web of Science (January 1970–August 2025; English only). Core queries combined controlled terms and keywords: ("aggrecan" OR "ACAN") AND ("intervertebral disc" OR "nucleus pulposus") AND ("chondroitin sulfate" OR "keratan sulfate" OR "hyaluronic acid" OR "ADAMT" OR "MMP" OR "MRI" OR "CEST" OR "HR-MAS" OR "measurement" OR "regeneration" OR "replacement"). We prioritized primary research and reviews that reported aggrecan composition/turnover, enzymatic mechanisms, imaging of IVDD, and repair/substitution strategies. Reference lists of relevant articles were hand-screened to identify additional studies.

2. Components of aggrecan in the intervertebral disc

Proteoglycans are complex macromolecules composed of a central core protein covalently linked to glycosaminoglycan (GAG) chains. GAGs are linear, heterogeneous, and sulfated polysaccharides, structurally characterized by repeating disaccharide units consisting of alternating uronic acid and hexosamine residues.[5] In addition, aggrecan molecules interact with hyaluronan via their globular domain 1, leading to the formation of aggregated aggrecan complexes that are essential for their biological function *in vivo*. As the structural organization of aggrecan has already been comprehensively elucidated in previous studies,[6,7] we will only underscore the structure again with a single illustrative figure (Fig. 1).

3. Key function of aggrecan: water retention

Aggrecan's critical role in intervertebral disc by its key function: attracting water. Studies have shown the NP contains a remarkably high water content, reaching up to 80.06%.[8] As illustrated in Figure 2, water in intervertebral disc exists in 2 forms: free water and bound water. Bound water is associated with the electrostatic charges of proteoglycans and collagen within the tissue, while the amount of free water is governed by the osmotic and hydrostatic pressures in the disc environment.

3.1. Bound water attracted by aggrecan

It is well-established that GAGs play a key role in retaining bound water within skeletal[9] and joint tissues[10] by electrostatically attracting water molecules. However, in terms of intervertebral disc, compared with the free water regulated by osmotic pressure, the proportion of bound water is relatively small.[11,12]

3.2. Free water attracted by aggrecan

The negative charges, which are driven by chondroitin sulfate (CS) and keratan sulfate (KS), present in aggrecan not

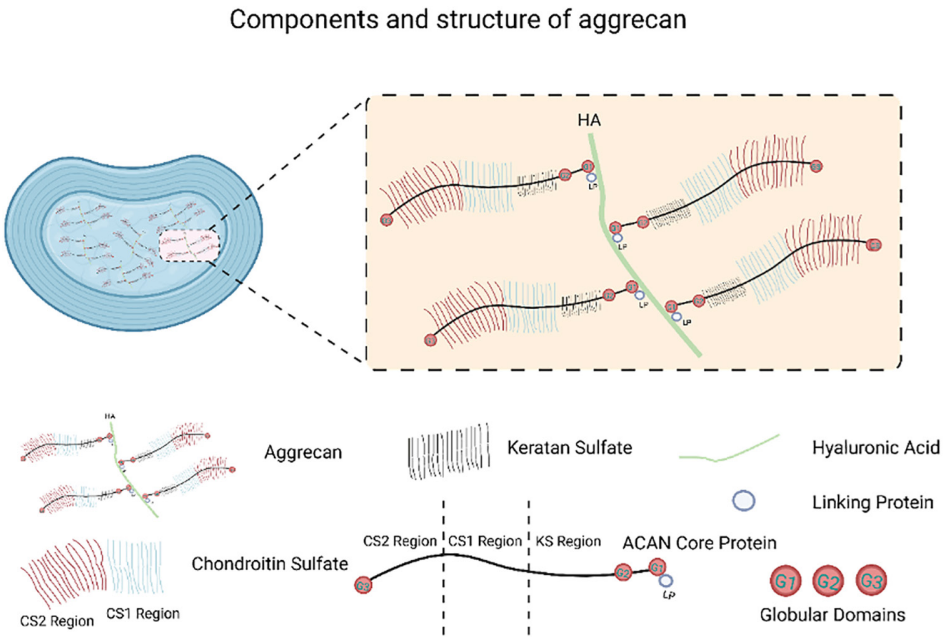

Figure 1. Components and structure of aggrecan.

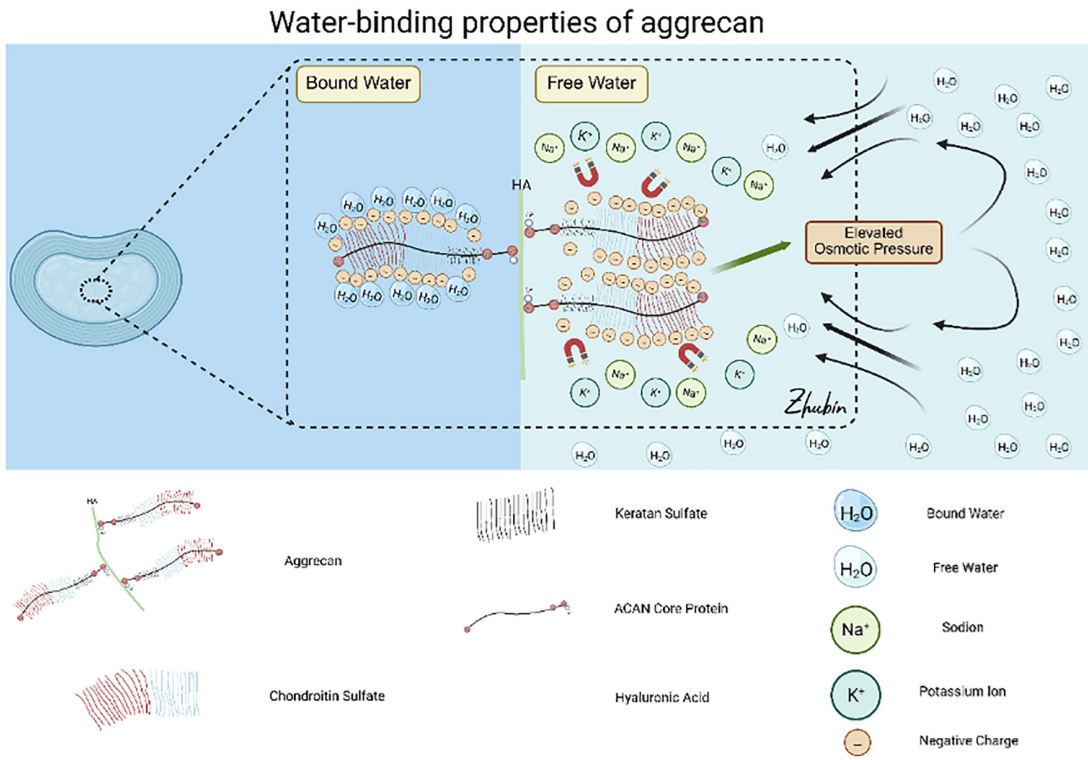

Figure 2. Mechanisms by which aggrecan attracts water.

only attract bound water but also draw in cations, such as sodium and potassium ions. This attraction increases osmotic pressure, which contributes to the presence of free water.[11] Another critical aspect is that the hydration state fluctuates in response to varying mechanical stresses, deriving from body weight and muscular activity. During nighttime rest, stress is relatively low, and during daytime activities, stress can rise significantly.[13] Under high-stress conditions, water is expelled from NP, leading to temporary dehydration. However, when stress levels decrease at night, NP can rehydrate as water molecules are re-attracted with proteoglycans, restoring hydration and disc height. This dynamic interplay underscores the role of osmotic pressure in facilitating the movement of water in and out of the NP, which is essential for nutrient transport and waste removal.[7,14]

4. Aggrecan modifications in degenerative NP

While previous studies have addressed various changes in aggrecan during IVDD, to the best of our knowledge, no existing review has systematically summarized these alterations. As a result, our current understanding of aggrecan degeneration remains fragmented and incomplete. This gap is particularly important because, as our synthesis reveals, despite the diverse forms of aggrecan degradation observed, the underlying mechanisms converge on a limited number of core pathological changes. Recognizing these key alterations is essential for developing targeted therapeutic strategies aimed at restoring aggrecan function and improving NP integrity.[15] As shown in Figure 3, four aspects of aggrecan modifications during disc degeneration are presented.

4.1. Decline of the CS/KS ratio

Intervertebral discs rely on negatively charged CS and KS to maintain water content. Chemical analyses reveal a GAG concentration gradient that increases from the outer annulus fibrosus to the central NP.[16] However, this GAG content decreases with age, particularly in individuals over 30, and shows significant correlation with the severity of IVDD.[17] The study by Seyithanoğlu et al.[18] revealed KS levels and CS/KS ratio were significantly higher in patients classified with grade IV degeneration compared with those with grade III based on the Pfirrmann grading system, indicating a correlation between increased radiological degeneration and elevated KS levels.

In fact, the CS/KS ratio indicates differing biological characteristics; for instance, while aggrecan in the NP and articular cartilage shares a similar structure, they differ in their CS/KS ratios, which affects their mechanical properties.[19] At birth, aggrecan is predominantly composed of CS and lacks KS, but as growth occurs, the proportion of KS increases.[20] As people age, the quantity of KS rises, while the CS/KS ratio declines, and the chain length of CS decreases.[21] These changes are likely linked to a diminishing oxygen supply as the disc grows larger and moves further from vascular sources, exacerbated by the loss of vascularization over time.[22] Evidence suggests that the increase in KS serves as a reluctant compensatory mechanism to offset the decline in negative charge associated

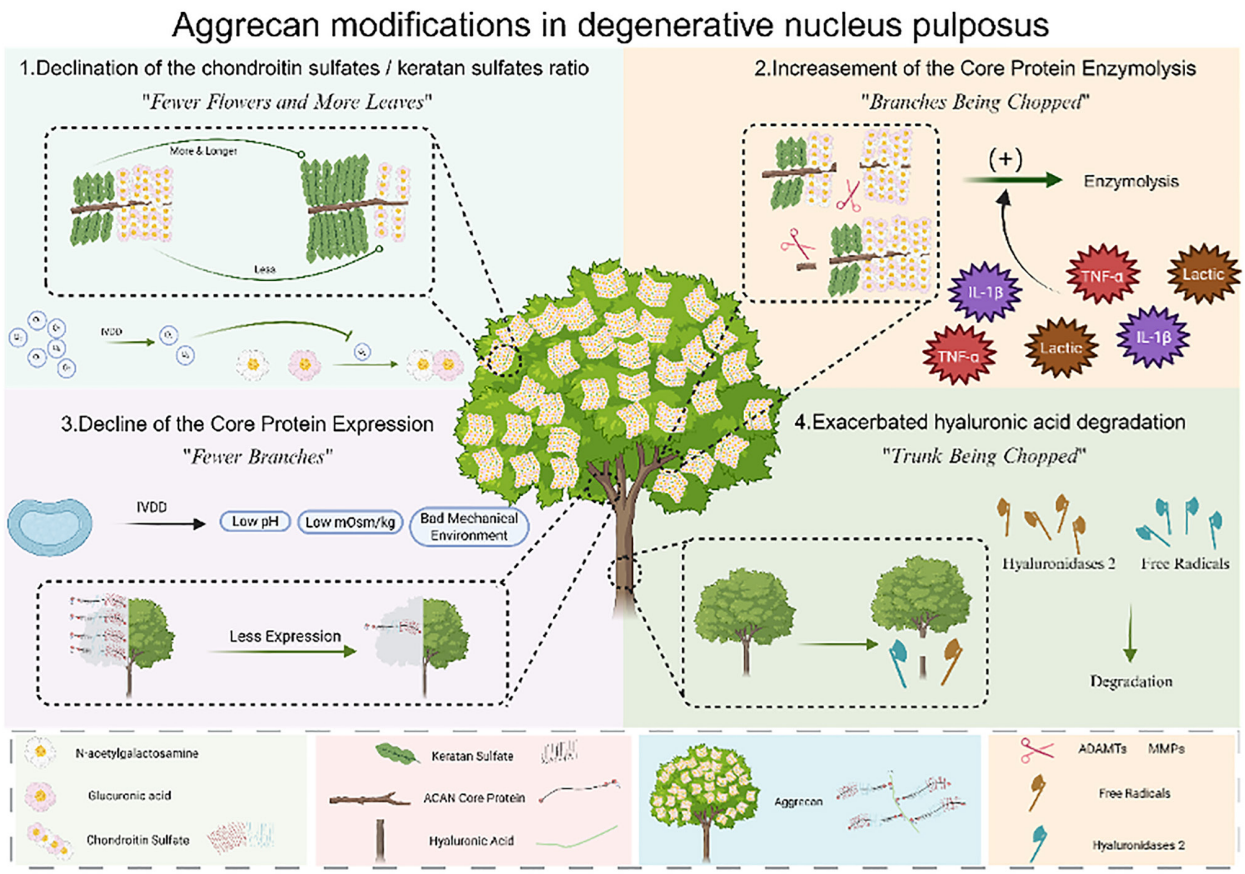

Figure 3. Four aggrecan alterations during nucleus pulposus degeneration.

with reduced CS levels. However, this substitution is insufficient[23]; while the amount of KS increases, it cannot fully restore the hydration capacity provided by CSs. As a result, the disc faces a significant decrease in hydration ability, leading to IVDD.[24] Moreover, researches support that KS increment induced by low oxygen is linked to inferior intervertebral disc (IVD) function. For instance, a decline in the CS/KS ratio, particularly notable by the age of 10, corresponds with a deterioration in disc nutrition and oxygenation due to the loss of vascular supply from the vertebrae.[23] And extremely thin intervertebral discs, such as those found in mice, lack KS entirely, supporting the hypothesis that KS may serve as a compensatory mechanism in response to reduced CS levels under low-oxygen conditions.[25] Additionally, thicker tissues, like the cornea, exhibit a higher KS/CS ratio than thinner tissues, suggesting a critical role of oxygen availability in influencing GAG ratios.[26]

4.2. Increment of the core protein enzymolysis

4.2.1. Key enzymes and sites involved in aggrecan degradation within the disc. Aggrecan, a proteoglycan, exhibits minimal intrinsic resistance to proteolytic degradation, as most proteases that interact with it tend to target 1 or more of its domains, particularly interglobular domain and the GAG attachment region, as illustrated in Figure 3.[27] While many proteases can degrade aggrecan *in vitro*, only a limited number play a significant role. Among these, matrix metalloproteinases (MMPs) and aggrecanases are the most important.[28] Evidence for MMPs-1, -2, -3, -8, -9, and -13 in intervertebral discs has been found.[29] The degradation of aggrecan may also be mediated by members of the second family of metalloproteinases known as a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), specifically ADAMTS4 and ADAMTS5.[30]

4.2.2. MMPs and ADAMTS differ in core protein cleavage timing and efficiency. While all MMPs appear to be capable of cleaving aggrecan, the rates of cleavage *in vitro* vary significantly among them.[31] Specifically, MMP-3, MMP-7, and MMP-12 show the highest levels of activity. However, the efficiency of MMPs remains relatively low compared with aggrecanases. For instance, when comparing MMP-3 to ADAMTS5, the cleavage efficiency of MMP-3 in interglobular domain and the CS2 region of aggrecan is approximately 100-fold and 10-fold lower.[31] This highlights significant differences in effectiveness between MMPs and aggrecanases in the degradation of aggrecan.

Within the ADAMTS family, ADAMTS4 and ADAMTS5 are the most active aggrecanases.[32] *In vitro* studies indicate ADAMTS5 possesses greater enzymatic activity

than ADAMTS4, contributing significantly to aggrecan degradation.[33] Notably, the age-related increase in the abundance of degradation products generated by MMPs occurs earlier than that of aggrecanase-derived products,[28] while the levels of aggrecanase-derived products are higher during late-stage degeneration.[34] Moreover, aggrecanase knockout mouse models do not protect animals from spontaneous age-related IVDD, which aligns with the concept that MMPs are involved in IVDD.[27]

4.2.3. Contributing factors that enhance enzymatic degradation of aggrecan in intervertebral disc. The accelerated degradation of aggrecan in NP is driven by a combination of inflammatory cytokines, mechanical stress, hypoxia, and low osmotic pressure. Elevated levels of proinflammatory cytokines, namely tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), are commonly observed in degenerative discs.[35] During IVDD and disc herniation, in addition to the infiltration of immune cells, resident NP and annulus fibrosus cells produce high levels of cytokines such as TNF-α and IL-1.[36] Importantly, both TNF-α and IL-1 upregulate MMPs and aggrecanases in NP cells.[37,38] Moreover, TNF-α/IL-1β upregulate syndecan-4 (SDC4) in NP cells via nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). SDC4 then promotes ADAMTS5-mediated aggrecan cleavage, as evidenced by reduced cytokine-induced aggrecan neoepitopes after SDC4 knockdown and by parallel increases of SDC4, ADAMTS5, and aggrecan fragments in degenerate discs.[39] In parallel, TNF-α–dependent MMP-3 induction in NP cells requires cooperative signaling through SDC4 and the tumor necrosis factor receptor 1–mitogen-activated protein kinase–NF-κB axis, while pharmacologic inhibition of p38/ERK or NF-κB, or stable SDC4 silencing, blunts this response.[40] Together, SDC4 acts as a cytokine-inducible organizer that localizes aggrecanases and amplifies matrix-degrading cascades, thereby promoting aggrecanolysis under inflammatory stress in NP tissue.

Excessive mechanical loading on the IVD can induce early degenerative changes, resulting in the accumulation of aggrecan degradation products. This degradation is closely linked to MMP activity, especially in the early stages of degeneration. Notably, MMP-3 can activate other MMPs, creating a cascading effect that accelerates disc degeneration.[40] Although both MMPs and aggrecanases are related to degeneration, a study showed that unfavorable mechanical forces are more associated with MMP activity than with aggrecanase activity.[27] The hypoxic microenvironment within NP prompts cells to undergo anaerobic metabolism, leading to lactate accumulation. This accumulation creates an acidic environment that favors protease activity, promoting further degradation of the ECM. While disc cells might adapt to such conditions, the presence of these factors enhances the action of proteases.[21] Low osmotic pressure also plays a role in disc degeneration. For instance, studies have shown that increasing the osmotic pressure from 300 to 500 mOsm/kg enhances proteoglycan expression while simultaneously decreasing MMP-3 mRNA levels.[41] This indicates that relatively high osmotic pressures can promote ECM synthesis, whereas reduced osmotic pressure may contribute to accelerated disc degeneration through increased levels of degrading enzymes.

4.3. Decline of the core protein expression

Aggrecan downregulation, both at the transcriptional and translational levels, is associated with several degenerative stressors, including lactate-induced acidosis, inappropriate mechanical stress, and decreased osmotic pressure. Researchers examined the relationship between mRNA and protein levels of aggrecan in the annulus fibrosus and NP of human lumbar intervertebral discs at various stages of degeneration, showing that in NP, both aggrecan protein content and mRNA expression levels gradually decreased with increasing degeneration.[42]

First, in relation to the lactic acid-induced acidic environment, Ohshima and Urban explored the relationship between lactate levels and proteoglycan synthesis in the intervertebral disc.[43] They noted that the anaerobic metabolism of the disc leads to significantly elevated lactate concentrations in the disc center, reaching levels 8 to 10 times higher than those found in plasma, which results in an acidic environment. Besides, they conducted experiments measuring the incorporation rates of ^{35}S-sulfate and ^{3}H-proline in the nucleus of bovine coccygeal discs and human discs obtained during percutaneous nucleotomy. Their findings revealed that increased lactate levels may lead to a decline in proteoglycan synthesis rates, which could ultimately contribute to reduced proteoglycan content and accelerate disc degeneration. Further, the expression of *ACAN* gene is influenced by mechanical environment.[44] Studies have proved that both static compressive load and absence of load have been shown to reduce proteoglycan content in the intervertebral disc. In a study by Hutton et al.,[45] high compressive forces were applied to lumbar intervertebral discs of dogs using coil springs, showing increased compressive force correlated with decreased aggrecan. Researchers also investigated the effects of tensile force, simulating weightlessness, on the proteoglycan and collagen content in the lumbar intervertebral discs of Sprague–Dawley rats.[46] The experiment involved tail-suspending for 2 or 4 weeks, showing a 35% decrease in proteoglycan content in the 4-week tail-suspended group, establishing a clear link between decreased proteoglycan content and tensile stress, highlighting the potential impact of low hydrostatic pressure on IVDD. Moreover, researchers conducted experiments on human and bovine NP cells in culture media with osmotic pressures of 300, 400, and 500 mOsm/kg, observing that as osmotic pressure increased, expression of proteoglycans also elevated.[41] While there is no consensus among research groups regarding the optimal osmotic pressure for NP cell culture, it is evident that elevated osmotic pressure within a certain range promotes the synthesis of ECM components and supports the function of NP cells.

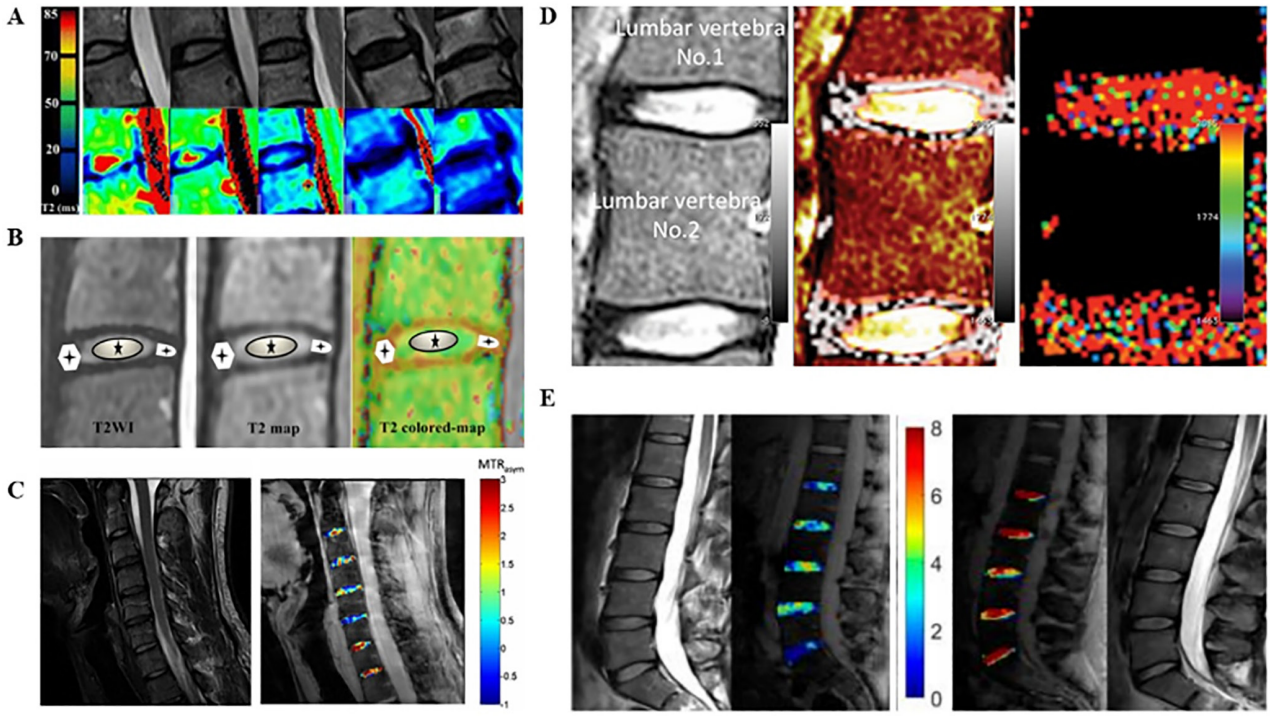

Figure 4. Imaging readouts for quantifying aggrecan/GAG in the nucleus pulposus. (A) T2 mapping MRI from Xie et al. showing a negative correlation between T2 relaxation time and Pfirrmann grade in lumbar IVDs, indicating decreased hydration with increasing degeneration. (B) Quantitative T2 MRI from Chen et al. demonstrating an inverse relationship between T2 values and Pfirrmann grades in cervical intervertebral discs of asymptomatic young adults. (C) gagCEST imaging from Schleich et al. illustrating significant differences in GAG content between non-degenerate and degenerated cervical IVDs in healthy volunteers. (D) gagCEST findings from Haneder et al. in patients with low back pain, showing clear differentiation between degenerative and non-degenerate IVDs. (E) gagCEST imaging from Wollschl äger et al., revealing lower GAG levels in IVDs of patients with adolescent idiopathic scoliosis compared with healthy controls. GAG = glycosaminoglycan, IVD = intervertebral disc, MRI = magnetic resonance imaging. All images have been authorized and permitted.

4.4. Exacerbated hyaluronic acid degradation

Researches indicate that as individuals age and IVDD progresses, the proportion of aggregated aggrecan in NP gradually decreases, while monomeric aggrecan increases.[47,48] In the human adult intervertebral disc, a significant amount of monomeric aggrecan is present; approximately 30% aggrecan in the NP exists in aggregate form in 6-month-old infants, but this proportion drops to as low as 10% in adults.[16,49] These monomeric or fragmentary forms of aggrecan are believed to result from the hydrolytic degradation of aggregated aggrecan and are retained within the disc due to their size and structure.[21] Research by Roughley et al. has demonstrated that the loss of hyaluronic acid (HA) is associated with disc tissue dysfunction, characterized by notochord remnants, increased chondrocytes, decreased ECM, and vertebral malformations—highlighting HA's essential role in maintaining normal intervertebral disc function.[50] However, the relationships between the quantity and ratio of aggregated aggrecan, negative charge, and osmotic pressure warrant further quantitative investigation.

The degradation of HA in the intervertebral disc occurs primarily due to 2 factors: enzymatic degradation and radical-induced degradation. Enzymatic degradation is facilitated by hyaluronidases (HYAL), with HYAL2 being the most likely candidate responsible for HA depolymerization within the ECM.[51] While such degradation can be seen as a means of facilitating normal turnover, excessive degradation is detrimental. Additionally, HA is susceptible to degradation by free radicals, particularly hydroxyl radicals generated from hydrogen peroxide and superoxide.[52] Link protein (LP) present in the intervertebral disc serves to protect HA. In the study by Rodriguez and Roughley, the role of LP in stabilizing proteoglycan aggregates and influencing HA degradation was examined. The findings revealed that high concentrations of hyaluronidase significantly cleaved PG aggregates, whereas lower concentrations had a much lesser impact on LP-stabilized aggregates.[53]

5. Current approaches to detect aggrecan

5.1. Conventional methods for detecting aggrecan content

Proteoglycans are central to IVDD, and their importance has spurred a spectrum of analytical techniques ranging from classical chemical assays to advanced solid-state nuclear magnetic resonance (NMR) and Raman spectroscopy. Because conventional approaches—such as gel chromatography, Alcian blue staining, and transmission

electron microscopy—have already been extensively documented, they are not discussed further in this review.[4,54,55]

5.2. Using aggrecan metabolites as surrogate markers for aggrecan content

Studies have employed solid-state NMR spectroscopy, particularly high-resolution magic-angle spinning NMR, to investigate the biochemical composition of lumbar intervertebral discs. In 2005, Keshari et al.[56] reported that reduced glycine levels and diminished GAGs were closely associated with IVDD. Moreover, by using ^{1}H high-resolution magic-angle spinning NMR, Radek et al.[57] found that discs with Pfirrmann grades IV and V showed markedly higher concentrations of metabolites (including creatine, glycine, and hydroxyproline) and a reduced N-acetyl peak of CS—compared with those classified as grade III.

5.3. Inferring total aggrecan content through detection of its specific regions

In addition to detecting aggrecan metabolic products or cleavage fragments, some researchers have studied specific portions of the aggrecan molecule to estimate aggrecan content in the NP. First, as shown in Figure 4A, the study by Xie et al.[58] explored the use of magnetic resonance imaging to indirectly assess aggrecan content in IVDs by measuring T2 relaxation time, finding a negative correlation between T2 values and Pfirrmann grades. Similarly, Chen et al.[59] showed that quantitative T2 magnetic resonance imaging effectively detects early cervical IVDD in asymptomatic young adults, demonstrating a strong inverse correlation between Pfirrmann grade and T2 values of the NP, as shown in Figure 4B.

Glycosaminoglycan chemical exchange saturation transfer (gagCEST) has emerged as a novel method for assessing GAG content. For instance, research by Schleich et al. demonstrated a significant negative correlation between gagCEST values and the Pfirrmann degeneration grades in lumbar IVDs, indicating that reduced GAG content corresponds to increasing degeneration severity. Schleich et al. found that healthy volunteers exhibited higher gagCEST values compared with patients with conditions like spondyloarthritis, where significantly lower GAG levels were observed in degenerate NP.[60] Additionally, as shown in Figure 4C, research contribution by Schleich et al.[61] highlighted the feasibility of gagCEST imaging in assessing cervical IVDs in healthy volunteers, demonstrating significant differences in gagCEST values between nondegenerate and degenerated discs. In another study by Haneder et al.,[62] as shown in Figure 4D, conducted with patients suffering from low back pain, it was shown that gagCEST could effectively differentiate between degenerative and nondegenerate IVDs based on GAG content, emphasizing its utility in evaluating disc health. Similarly, as shown in Figure 4E, the study by Wollschläger et al.[63] involving patients with adolescent idiopathic scoliosis revealed that the IVDs of these individuals had lower gagCEST values compared with healthy controls, underscoring the technique's sensitivity to early degenerative changes.

5.4. Application-driven method recommendations

For mechanism-focused *ex vivo* validation, established assays remain reliable and widely used. The 1,9-dimethylmethylene blue assay enables rapid quantification of sulfated GAGs; aggrecan and type II collagen can be quantified by enzyme-linked immunosorbent assay or detected by immunoblot; and gene/protein expression is routinely profiled by quantitative polymerase chain reaction and quantitative Western blotting. However, when the objective is to interrogate mechanisms of NP degeneration, conventional assays alone may be insufficient; complementary high-resolution biophysical modalities, ranging from label-free Raman spectroscopy, high-resolution magic-angle spinning/solid-state NMR, small-angle scattering, to cryo-electron microscopy, can provide microstructural and compositional readouts of the NP ECM and may help reveal microscale ECM alterations across degeneration stages.

For clinical application and translational studies, *in vivo* evaluation provides clinical observability, noninvasiveness, and repeatable longitudinal follow-up. Quantitative T2 mapping is among the most widely used and accessible techniques; it is sensitive to NP hydration and collagen/matrix status, reduces the subjectivity of qualitative grading, and shows robust correlations with degeneration severity and patient-reported outcomes—supporting its use for preoperative diagnosis and standardized postoperative/post-treatment follow-up.[64] Beyond hydration-weighted metrics, gagCEST yields a GAG-weighted signal; human studies have demonstrated feasibility and strong associations with disc health indices, and emerging evidence suggests gagCEST may detect NP compositional change earlier than gross hydration changes. Nonetheless, broader standardization and multicenter validation are still required. Consequently, we recommend T2 mapping as the default *in vivo* tool for preoperative quantification and routine follow-up, with gagCEST incorporated at equipped centers to enhance sensitivity to early biochemical change and enable earlier diagnosis and intervention.

6. Current strategies and limitations in aggrecan regeneration and supplementation

Based on our analysis, current therapeutic strategies can be broadly categorized into 2 approaches. The first aims to interrupt 1 or more of the 4 modifications in aggrecan, thereby promoting its regeneration. The second approach focuses on supplementing specific components of aggrecan, with the goal of partially restoring its functional properties.

6.1. Aggrecan regeneration

As discussed earlier, successful regeneration of aggrecan requires addressing the 4 modifications during NP

degeneration. At the core of this strategy lies the need to improve the microenvironment of the NP. Although these 4 modifications in aggrecan have been categorized individually, the underlying causes are often interrelated. For example, hypoxia can increase anaerobic glycolysis, leading to lactate accumulation and the formation of an acidic microenvironment; inflammatory conditions can trigger the release of various cytokines that activate degradative enzymes; reduced osmotic pressure may suppress core protein translation. Therefore, the optimal regeneration strategy should aim for a comprehensive and sustained improvement of the adverse microenvironment, rather than relying on transient or single-target interventions. However, current research has yet to identify such an integrative solution. As shown in Table 1, most existing strategies still focus on anti-inflammatory effects, which, while limited in scope, provide a valuable foundation for future work.

6.2. Anti-inflammation and adjust acid environment

Bu et al.[65] developed a reductive hydrogel that utilizes the reactive oxygen species-scavenging properties of copper to mitigate inflammation. Similarly, Zhou et al.[66] designed a novel hydrogel incorporating TGF-β-loaded nanoparticles and microspheres (GM@T-NNPs) capable of sustained release, which can alleviate the inflammatory milieu by reducing proinflammatory cytokines and MMP expression. Moreover, researchers have also explored the use of extracellular vesicles. For example, the introduction of bone marrow–derived mesenchymal stem cells-derived exosomes into the NP significantly reduced the expression of MMP-13, IL-1β, and IL-6.[67] Likewise, Qian et al.[68] demonstrated that urine-derived stem cell exosomes could reverse IL-1β-induced NP cell degeneration and restore aggrecan expression.

Another promising approach addresses the acidic microenvironment caused by disrupted oxygen metabolism. Li et al. constructed nanoparticle–microsphere composites capable of restoring redox balance within NP cells. Their system effectively reduced extracellular acidity, lowered H_2O_2 levels, and blocked inflammatory cascades and MMP expression—thus promoting aggrecan regeneration from the perspective of oxygen metabolism regulation.[69]

While these studies lay a solid foundation for NP repair, clinical application still requires high-quality evidence to overcome several hurdles. First, in the avascular, hyperosmotic, acidic, and mechanically loaded NP microenvironment, achieving durable intradiscal retention and survival of delivered cells or extracellular vesicles remains challenging if they are to exert sustained therapeutic effects. Second, clinical deployment must address biomaterial immunogenicity, material availability, and scalable manufacturing. Looking ahead, given the multifactorial nature of disc degeneration, single-modality approaches are unlikely to suffice; repair strategies should be designed to be multifunctional—enabling simultaneous, multitarget modulation (e.g., buffering acidity and restoring osmotic balance while attenuating proinflammatory cytokines).

6.3. Potential materials for osmotic pressure regulation

Studies have developed chemical substitutes with aggrecan-mimetic structures designed to replicate its water-attracting properties and thereby regulate osmotic

Table 1

Current therapeutic strategies in aggrecan regeneration.

Aim	Approach	Results	Research level	Experimental model	Reference
Alleviate inflammation environment	Cleavage ROS and offer mild photothermal therapy	Promote aggrecan expression	*In vivo*	SD rats with 21-G needle puncture-induced IVDD model	[65]
Alleviate inflammation environment	Release TGF-β	Reduced inflammatory cytokines and MMP expression and upregulated aggrecan expression	*In vivo*	Male SD rats with 21-G needle puncture-induced IVDD model	[66]
Alleviate inflammation environment	Introduce BMSC-derived exosomes	Reduced expression of MMP-13 and inflammatory cytokines	*In vitro*	—	[67]
Upregulate aggrecan expression	Introduce urine-derived stem cell exosomes	Restored aggrecan expression	*In vitro*	—	[68]
Restore redox balance	Introduce GelMA with strong reductive black phosphorus quantum dots (BPQDs)	Reduced extracellular acidity, blocked inflammatory cascades and MMP expression	*In vivo*	Male SD rats with puncture-induced IVDD model	[69]

BMSC = bone marrow–derived mesenchymal stem cells, GelMA = gelatin methacryloyl, IVDD = intervertebral disc degeneration, MMP = matrix metalloproteinase, ROS = reactive oxygen species, SD = Sprague–Dawley.

pressure. Although these materials have not yet been explicitly applied in intervertebral disc repair or replacement, they hold significant potential for future applications in NP regeneration and substitution. In the study by Prudnikova et al.,[70] biomimetic proteoglycans were created by grafting native CS bristles onto a synthetic poly(acrylic acid) core, resulting in a bottlebrush structure that mimics aggrecan's 3D architecture. This design achieves a molecular weight of roughly 1.6 MDa and demonstrates water uptake exceeding that of native aggrecan. Besides, in the study by Prudnikova et al.,[71] biomimetic proteoglycans were synthesized by end-on grafting of natural CS bristles onto a synthetic poly(acryloyl chloride) backbone, preserving the GAG's native structure. Atomic force microscopy confirmed a 3D core-bristle architecture, while dynamic light scattering indicated particles of about 60 nm in size and a ~50% increase in water uptake compared to native aggrecan.

7. Conclusions and prospects

Aggrecan is a critical structural and functional component of NP, playing an essential role in maintaining its physiological integrity. Its early degeneration represents a key event in the onset and progression of IVDD. Increasing evidence supports aggrecan as a promising biomarker for early disc degeneration, and recent advances in imaging techniques now enable noninvasive assessment of GAG content, providing opportunities for early clinical diagnosis. Through our original classification of aggrecan modifications during degeneration, we have clarified the major factors driving aggrecan deterioration in IVDD, thereby establishing a foundation for the identification of more precise therapeutic targets. Current treatment strategies predominantly focus on specific aspects of the 4 major aggrecan modifications observed in NP degeneration. However, no existing approach comprehensively addresses all 4 alterations. Most studies have primarily targeted the inflammatory microenvironment, while key contributors such as lactic acid accumulation, osmotic imbalance, and enzymatic degradation of HA remain insufficiently explored. Furthermore, recent efforts have introduced chemical analogs with strong water-retaining capacity that mimic aggrecan's functional role. Although these materials have not yet been evaluated in intervertebral disc models, they represent a promising direction for restoring aggrecan-mediated osmotic regulation and improving disc hydration.

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Figures 1, 2, and 3 were created using BioRender.

Ethical statement

Not applicable.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

BZ and YY conceived and supervised the study. HL and TF conducted the literature review and drafted the manuscript. HL and LS contributed to figure preparation and table organization. All authors discussed the content, revised the manuscript critically for important intellectual content, and approved the final version for publication.

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