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REVIEW

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pH: A major player in degenerative intervertebral disks

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Abstract

Chronic lower back pain is the leading cause of disability worldwide, generating a socioeconomic cost of over $100 billion annually in the United States. Among the prominent causes of low back pain (LBP) is degeneration of the intervertebral disk (IVD), a condition known as degenerative disk disease (DDD). Despite the prevalence of DDD and multiple studies demonstrating its relationship with LBP, the mechanisms by which it contributes to pain remain unknown. Previous studies have identified potential causes for this pain, such as extracellular matrix (ECM) breakdown, changes in biomechanics, and pro-inflammatory signals. Possible pain treatments targeting these factors have been developed but with limited effects. However, low pH in DDD is a potential pain generator whose role has largely been unexplored and underappreciated. This review highlights hyperacidity's effects on the IVD, such as catabolism of disk cells and ECM, neoinnervation, altered mechanical signaling, and expression of pro-inflammatory cytokines and ion channels. This review aims to discuss what is known about the contributions of acidity to DDD pain, identify the knowledge gaps on this topic, and propose what research can be conducted to fill these gaps. We must better understand the underlying mechanisms of DDD and the interaction between hyperacidity and nociception to develop better therapeutics for this disease.

KEYWORDS
acidic, degenerative disk disease, low pH, pain

1 | INTRODUCTION

Low back pain (LBP) is the leading cause of disability globally,[1] ranks sixth in terms of overall disease burden according to disability-adjusted life years,[1] and has an annual socioeconomic cost estimated at more than $100 billion in the United States.[2] In addition, back pain ranks among the most prevalent chronic musculoskeletal pain conditions in the United States, with an estimated 9.4% of people reporting LBP at one time.[1] Degenerative disk disease (DDD) has been reported to account for approximately 40% of LBP cases.[3,4] Despite the prevalence of DDD, treatment strategies capable of providing effective relief from chronic back pain mechanisms remain elusive.

DDD is a malady of multifactorial origins, with genetic predisposition,[5] abnormal biomechanics,[6] excessive manual labor,[7] smoking,[8] infection,[9] decreased nutrient flow to the intervertebral disk (IVD),[10] and age[11] identified as risk factors. While the relative importance of each risk factor and their exact contributions to DDD initiation remain unknown, DDD can be characterized by a complex

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cascade of interrelated processes that lead to a breakdown of the IVD.[7] These pathological changes include disk height loss,[12] changes in innervation,[13] extracellular matrix (ECM) breakdown,[12] endplate changes,[14] inflammation,[15] and acidification[16] in the IVD. While these pathological changes to the IVD have been well documented and several hypotheses linking these changes to pain have been posited,[17] the exact mechanisms by which each change contributes to LBP remain poorly understood. A better understanding of these underlying pain mechanisms, including those caused by low pH, will lead to better treatments. Interestingly, acidic pH has not been studied in depth as a driver of degenerative changes and pain.

Increasing hyperacidity of the IVD is among the pathological changes that accompany DDD,[18] coinciding with the progression of disk degeneration.[18] While the acidic pH of the degenerative IVD has been shown to contribute to altered cell metabolism,[19] breakdown of the ECM of the IVD,[20] and changes in neuronal function,[21–25] the mechanisms by which these pathological changes contribute to LBP remain unknown.[26] There is a need to elucidate further these contributions from low pH and the mechanisms by which they act.

A literature search was performed for the terms "degenerative AND ivd AND acidic" and "degenerative AND ivd AND inflammation" in Embase from 2014 to June 2024, and there were 20 results compared to 305 results for the latter. Despite the prevalence and importance of both intradiscal acidity and inflammation associated with DDD, the former has seen relatively little attention, and the field would benefit from more focus on this critical aspect of DDD.

2 | CLINICAL FINDINGS OF DEGENERATIVE IVD ACIDIFICATION

From early on, it was established that an unhealthy IVD could become degenerative and lead to low pH in the disk. In 1968, clinical researchers found a correlation between acidic pH in patient IVDs with lumbar nerve root pathologies.[27] In 1969, Nachemson continued this work and showed statistically significant correlations between the following: (1) acidic pH and severity of IVD degeneration, (2) pH and preoperative pain, and (3) the pH and degeneration of connective tissue around the dorsal root ganglion (DRG).[18] Since these early clinical correlations were established, few clinical studies have focused on the role of pH in degenerative IVD pain; the reason for this gap in focus is somewhat unknown. While the pH of most bodily fluids is 7.4, the pH of a healthy IVD is 7.1 due to diffusion effects but drops to 6.8–6.2 in mild to severely degenerated IVDs and sometimes even as low as 5.7[18,27,28] in the worst cases of degeneration. This acidic environment leads to degenerative changes and indirect and direct mechanisms of nociception, which are discussed in this review.

More recently, there has been renewed interest in studying the acidic microenvironment of DDD and its contribution to pain, as some studies have shown that it contributes to altered nociception.[29] Clinical researchers have demonstrated that specialized magnetic resonance imaging (MRI) is a promising, non-invasive technique to detect pH-dependent IVD pain that could be used in a clinical setting.[30] Clinical researchers have also shown that lactate could serve as a metabolic marker for discogenic pain,[29] which could be expanded to clinical applications. Together with basic science research, these clinical studies underscore the need for further understanding of the role of low pH in discogenic pain and the specific mechanisms by which this pain occurs, such as changes in metabolism and nutrient supply, degradation of the ECM, cell death, neoinnervation, and gene expression changes.

3 | STRUCTURE AND FUNCTION OF THE HEALTHY IVD

The IVD is an organ that, together with the facet joints, forms a three-part joint between adjacent vertebrae of the spine (Figure 1). IVDs compress under normal movement,[31] provide weight dispersion,[31] act as shock absorbers,[31] provide proper spacing between vertebrae,[32] facilitate the passage of nutrients and fluid to the vertebral bodies and the spinal cord,[32] and allow for rotation, extension, and flexion of the spine.[32]

Each disk consists of three main parts (Figure 1): the nucleus pulposus (NP), the annulus fibrosus (AF), and the endplates (EPs). When the IVD is loaded, the healthy NP generates an intradiscal pressure, putting the AF fibers in tension and distributing the load evenly over the surrounding EPs[33] (Figure 2). The EPs consist of the vertebral body's cortical bone and a hyaline cartilage region. In healthy IVD, they are of uniform thickness and form semi-permeable layers, which allow for the regulation and transport of nutrients into and waste out

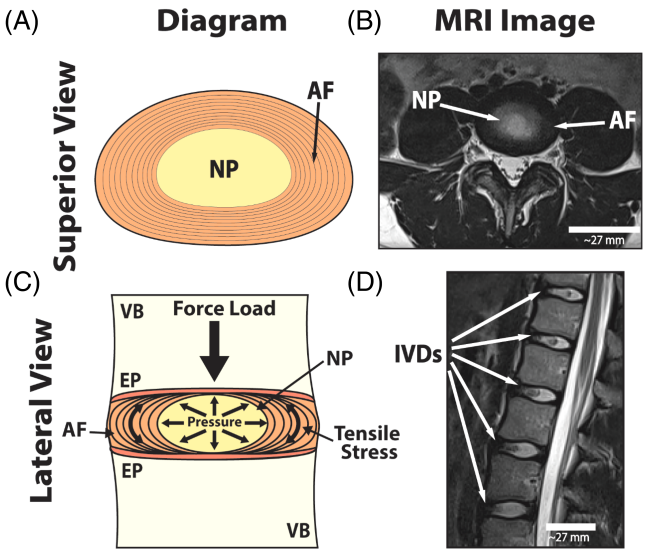

FIGURE 1 Schematics and MRI images of healthy intervertebral disk (IVDs). (A) Superior view of a healthy intervertebral disk showing the nucleus pulposus (NP) and annulus fibrosus (AF). (B) Superior view MRI image of a healthy disk. (C) Lateral view of a healthy intervertebral disk showing the vertebral body (VB), NP, AF, and endplates (EP). Forces at play in the IVD are also shown. (D) Lateral view MRI image of healthy disks.

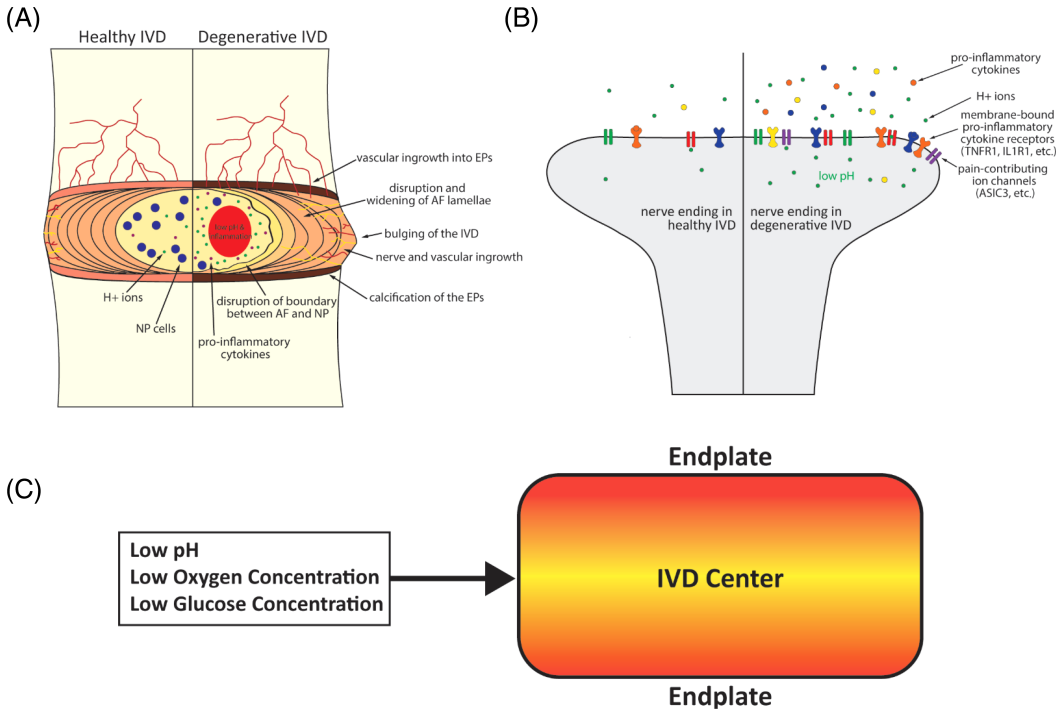

FIGURE 2 Healthy versus degenerative intervertebral disk (IVD) and nerve ending. (A) Schematic showing a side-by-side comparison of a healthy versus degenerative IVD. (B) Schematic showing a side-by-side of a nerve ending innervating a healthy IVD versus a degenerative IVD, including mechanisms of low pH nociception. (C) Concentrations across the healthy IVD. Schematic showing pH and concentrations of oxygen and glucose across the disk from endplate to endplate in a healthy IVD. AF, annulus fibrosus; EPs, endplates; NP, nucleus pulposus.

of the disk by diffusion.[34] This transport directly helps maintain a healthy pH in the tissue.[35,36] Specific DDD-related changes that affect pH within the IVD can directly lead to altered nociceptive signaling, while others lead to further changes that cause nociception; we will discuss both in this review.

4 | METABOLISM OF THE HEALTHY IVD

The IVD is one of the most avascular organs in the human body. Upon skeletal maturity, blood and lymph vessels are only present in the outer regions of the AF and EPs[37,38] of healthy IVDs. These vessels provide blood and nutrients to the EPs and outer AF via the lumbar arteries but rely on diffusion for transport deeper into the IVD.[39] In healthy IVDs, there are steep oxygen and glucose concentration gradients, with the partial pressure of O_2 falling as low as 1% at the center[40,41] (Figure 3). The IVDs produce ATP for metabolism mainly through anaerobic glycolysis, even in the presence of oxygen. Lactic acid is produced in this process, which is removed via diffusion, along with other waste products. This lactic acid contributes to low pH toward the center of the healthy IVD.[10,17,42] Ishihara and Urban report that in addition to anaerobic glycolysis, a significant amount of a disk's energy is supplied by oxidative phosphorylation, which requires oxygen and produces H^+ ions as a product, contributing to the low pH in the IVD.[40] Removing excess acid in the IVD is crucial to maintaining a healthy metabolism.

5 | DIRECT MECHANISMS OF ACIDIC NOCICEPTION IN THE DEGENERATIVE IVD

In addition to several degenerative changes caused by acidity in the IVD that lead to changes in nociception, there are also several ways that acidity directly leads to nociceptive signaling, such as neoinnervation, increased expression of ion channels and pro-inflammatory cytokines, and direct activation of neurons via altered signaling thresholds (Figures 2 and 3).

5.1 | Neoinnervation

The healthy IVD is a poorly innervated organ containing three main types of nerve fibers: (1) sensory nerve fibers, (2) perivascular nerve fibers, and (3) mechanoreceptors.[43–45] Of primary interest in this review are the sensory nerve fibers from the nociceptive neurons that innervate the IVDs. The nociceptive neuron cell bodies that innervate the IVDs reside within the dorsal root ganglia (DRG), which are found bilaterally at every vertebral level within the foramina of the vertebrae. Evidence is mixed about whether human IVDs are innervated segmentally or have segmental overlap.[43,46–48]

Two main types of DRG neurons are responsible for pain signaling in the IVD: non-peptidergic, small-sized glial cell-line derived neurotrophic factor-dependent neurons and peptidergic nerve growth factor (NGF)-dependent small-sized neurons.[48] The small peptidergic

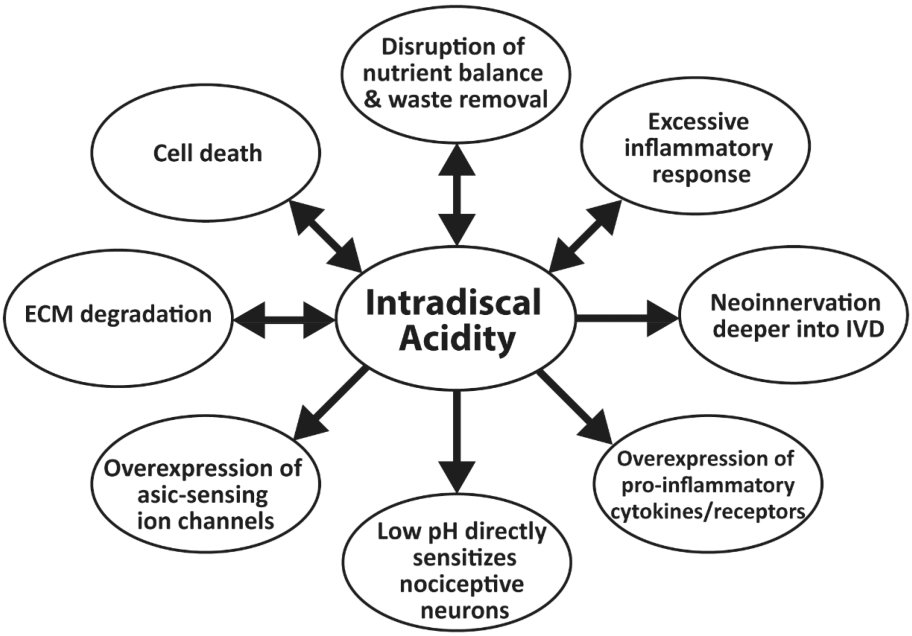

FIGURE 3 Changes caused by low pH in the degenerative disk. Uncertain causes lead to low pH in the disk, contributing to further degenerative changes and directly or indirectly leading to nociception.[17] ECM, extracellular matrix; IVD, intervertebral disk.

fibers provide the majority of the innervation to the IVDs. They express *TrkA/TrkB* (the receptor for NGF/brain-derived neurotrophic factor), *glial cell-line-derived neurotrophic receptor subtype α3* (*GFRα3*), the neuropeptide substance P, *transient receptor potential vanilloid receptor subtype 1* (*TRPV1*), and *calcitonin gene-related peptide* (*CGRP*).[48] The fibers from these two neuron types are either myelinated Aδ or unmyelinated C fibers.[48,49] The peptidergic neurons are necessary for hyperalgesia responses induced by inflammation. In contrast, the non-peptidergic neurons are critical in neuropathic pain signaling.[48]

A nociceptive signal travels from the nerve fiber endings in the IVD, down the axon to the DRG, and into the dorsal horn of the spine. The signal then travels up the spinal cord and through the spinothalamic tract to the thalamus. There, it may be registered as pain and relayed to various brain regions.[50]

At birth, there are many nerve fibers in the IVD, but these nerves retreat to the peripheral one-third of the AF upon skeletal maturity and are absent from the NP in healthy adults.[43,44] In cases of DDD, however, nerve growth has been shown to occur deeper into the AF and, occasionally, the NP. Immunochemical methods have shown that nerve fibers in patients reporting back pain penetrate deeper into AF tissue.[51] Growth of nerves occurs deep into the AF and the NP of degenerative disks, mainly along the AF tears in the posterior part of the painful IVD.[52] Nerves were usually found alongside blood vessels, suggesting neovascularization occurs as well, but some were found independent of vasculature.[7,13,48]

Increases in lactic acid and the subsequent drop in pH are associated with increased NGF, which likely contributes to neoinnervation.[20] Neoinnervation is one of the direct mechanisms of discogenic back pain because of the increased number of nerve fibers in the IVD that can respond to noxious stimuli. The nerve fibers are also exposed to stimuli generally not present in the outer AF, such as the high pressure and low pH of the inner IVD, causing them to fire more frequently than in healthy IVDs.[43,53] In addition, Freemont et al. showed that NGF and its receptor, TrkA, are typically expressed at increased levels in degenerative IVDs.[54] The increase in innervation results in increased pain signaling, mainly to stimuli that would not otherwise result in pain in a healthy IVD. This is especially prevalent when the innervation extends into the NP, which has a high hydrostatic pressure when loaded.[43]

5.2 | Increased expression of acid-sensing ion channels in neurons

Acid-sensing ion channels (ASICs) are voltage-independent, proton-gated cation channels that are susceptible to low extracellular pH.[55] They activate between pH 5.0 and 8.0, depending on the channel. The expression of ASICs has been shown to increase in degenerative IVDs.[56] *ASIC3* is of particular interest because it is also expressed on DRG neurons and could have an increase in expression as shown in IVD cells, which is described later.[57] *ASIC3* forms trimeric ion channels that, when activated, cause a transient inward current inducing cellular excitability.[57] Additionally, *ASIC3* does not fully inactivate after activation, leading to a prolonged nociceptive signal.[57] Although understudied in the IVD microenvironment, overexpression of the *ASIC3* ion channel likely occurs in DRG neurons that innervate the disk.[58] This overexpression has been shown in cancer-colonized bone, where an acidic environment leads to overexpression of *ASIC3* and direct sensitization of DRG neurons innervating the bone.[58] Chen et al. reported that *ASIC3* plays a role in modulating high-intensity pain stimuli.[59] In addition to its role in pain signaling, *ASIC3* has been shown to play a role in sensory mechanotransduction in proprioceptors.[60] Further studies are needed to determine this in the context of the DRG neurons innervating the DDD environment.

A similar response occurs in transient receptor potential families, such as *transient receptor potential ankyrin 1* (*TRPA1*) and (*TRPV1*), which are expressed in nociceptive neurons in the DRG. Similar to ASICs, when nerve endings are stimulated, these ion channels allow sodium and calcium ions to inflow into nociceptive neurons and thus generate action potentials.[61] Along with capsaicin and pro-inflammatory cytokines, TRP channels are activated by protons. Their activation also leads to a pro-inflammatory response and an increased nociceptive neuron sensitization in degenerative IVDs.[58]

5.3 | Increased expression of pro-inflammatory cytokines and receptors

Little is known about the interaction of low pH and inflammatory cytokines. However, it is known that with degeneration, sensitization of the nociceptive nerve fibers occurs via changes in pro-inflammatory cytokine levels and protein expression, leading to hyperalgesia and allodynia.[25] tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) directly sensitize nociceptive neurons to noxious stimuli, such as heating and mechanical loading, in models of radiculopathy.[49] These pro-inflammatory cytokines bind to their corresponding receptors, increasing inflammatory response, neuronal sensitization, and pain. Additionally, this signaling perpetuates degeneration by promoting chronic inflammation, which furthers the breakdown of the IVD and can lead to chronic neuron sensitization and pain. Stover et al. demonstrated that degenerative IVDs trigger IL-6-induced increases in neuronal activity, which are further elevated in acidic pH.[25] In general, it is thought that the increased cytokine levels are a response by cells to decreased nutrient availability, the presence of invading immune cells, and a drop in pH.[49] These pro-inflammatory cytokines and hydrogen ions increase inflammation and pain by acting on specific pathways and ion channels, such as signaling through TNF-α/TNFR1, IL1/IL1R1, and others.[62] In a study by Baumann et al., human DRG neurons were patch-clamped to measure action potentials, and sensitivity to proton concentration was tested by rapidly changing the extracellular fluid from pH 7.35 to 6.0. They report that low pH evoked a reversible transient depolarization followed by a sustained reversible depolarization, resulting in neuron firing, which could be sensed as painful stimuli.[63] Borrelli and Buckley also showed that acidic pH works synergistically with the pro-inflammatory signaling of IL-1β and TNF-α, leading to enhanced signaling and potentially driving additional cyclical pathologies.[64] Although many studies show increased levels of cytokines and neurotrophins in degenerative IVDs, the link between this and low pH remains somewhat unclear, and further studies are needed.

5.4 | Summary of direct mechanisms

There are many degenerative changes associated with intradiscal hyperacidity. Despite many of the details and specific mechanisms needing to be better understood, there are some mechanisms we do understand. In summary, low pH in the disk leads to neoinnervation, an increased expression of ASICs in neurons, and an increased expression of pro-inflammatory cytokines and their receptors. As discussed, these changes lead to pain mainly by increasing the presence of neurons in the disk, driving inflammation, and increasing the sensitivity of neurons, causing them to signal pain to otherwise non-painful stimuli. Despite these direct effects being known, additional studies are needed, especially in vivo studies, so that these mechanisms can be better understood.

6 | INDIRECT MECHANISMS OF ACIDIC NOCICEPTION IN THE DEGENERATIVE IVD

The acidic environment of DDD creates some degenerative changes that do not directly cause nociception but can lead to changes that cause an increase in stimuli that cause pain. This section will discuss some of these known indirect pain mechanisms.

6.1 | Changes in nutrient supply and IVD metabolism

Upon degeneration and the associated drop in intradiscal pH, rates of IVD metabolism drop. Bibby et al. showed in vitro in bovine NP cells that oxygen consumption rates at pH 6.2 are 32% of those at pH 7.4.[19] Additionally, they showed that similar relationships were seen for markers of glycolysis rates: lactic acid production and glucose consumption rates, which fell at low pH.[19] Advanced modeling has also shown that cellular metabolism depends strongly on pH in the IVD, which is consistent with experimental data.[65]

In some cases of DDD, the cartilaginous EPs calcify, and nutrient supply decreases.[14,66] This calcification lowers the amount of viable vasculature leading to the IVD, resulting in ischemia due to reduced diffusion of oxygen and nutrients.[14] Modeling has shown that in addition to the diffusion coefficient and the EP diffusion area, solute distribution in the IVD depends greatly on EP porosity, which is greatly affected by calcification.[65,67] From this calcification, anaerobic respiration occurs more than usual, producing lactic acid at an increased rate.[20,29] Because of the lack of viable vasculature that can remove it, lactic acid accumulates, thus perpetuating the drop in pH and this vicious cycle[29] (Figure 3). This acidity increases the most toward the center of the IVD because of diffusion effects.[68,69] There are steep concentration gradients of oxygen, glucose, and lactic acid across the disk, and they are in a delicate balance of nutrient supply and waste removal. Concentrations of glucose and oxygen drop with increasing distance from the EP's while acidity increases.[41] With increasing calcification, acidity accumulation increases even more; this change is somewhat compensated by a decrease in disk height, which is often associated with DDD.[70] Disruption of this delicate balance leads to hyperacidity and other degenerative pathologies, including pain and a decline in cell and ECM health.[10]

6.2 | ECM degradation

The most abundant non-water components of the ECM of the IVD are collagens (mainly type II), proteoglycans (mainly aggrecan), and glycosaminoglycans.[71–73] Aggrecan largely contributes to the hydration of the tissue by binding many water molecules, smaller proteoglycans contribute to the regulation of matrix assembly,[73,74] collagen mainly contributes to the structure and function of the IVD,[20] and glycosaminoglycans largely contribute to cell signaling.[72]

Low pH promotes the depletion of proteoglycans,[75] which play crucial roles in facilitating the load-bearing capability of the IVD,[76] maintaining tissue hydration and osmotic pressure,[76] slowing fluid loss,[77] and maintaining disk height.[77] The resulting increased IVD density causes lower diffusion of nutrients and removal of lactic acid and other waste products, thus perpetuating further drops in pH, cell death, and additional structural changes.[20] Shi et al. showed increased lactic acid content is associated with ECM depletion caused by an annular puncture in a porcine DDD model.[20] Breakdown of the ECM may also cause fissures or other structural damage, exposing nociceptive neurons to acidic tissue and fluids of the NP and leading to nociception.[78] These structural changes due to ECM breakdown and loss of tissue hydration can also lead to changes in biomechanics. The IVD is an organ that receives consistent mechanical loading; this can lead to nociception in the degenerative disk since it cannot cushion and distribute loads as effectively, contributing to further breakdown and increased pressure on mechanoreceptors and nociceptors in the IVD.[79] We have demonstrated that rat DRG nociceptive neurons seeded on bovine AF tissue exhibited increased activity at increasing physiological cyclical strain, which was exacerbated in acidic pH, denoting an effect of low pH on mechanical signaling and a synergistic effect between low pH and inflammatory signaling.[22]

IVD acidity leads to ECM degradation and negatively affects matrix synthesis rates and the ability to repair the degraded ECM.[80,81] A significant decrease in aggrecan production occurred in NP cells cultured at low pH and an increase in some metalloproteinases, enzymes that break down ECM. In this study, tissue inhibitors of metalloproteinases (TIMPs) decreased at acidic pH, leading to an overall catabolic response of the NP cells.[75] An increased lactic acid concentration is also correlated with AF structural damage and depletion of ECM by reducing the expression of types I and II collagen and aggrecan in mature and progenitor NP cells in an in vitro model.[20,74] Shi et al. reported that increasing lactic acid content and ECM breakdown co-occur during IVD degeneration[20] in a porcine model, and clinical studies suggest that removing the excessive accumulation of lactic acid could reduce degeneration and pain.[82]

6.3 | Cell death

Intradiscal acidity leads to degenerative changes and contributes to indirect and direct pain mechanisms. One early pathological change that drives disease progression is IVD cell senescence and death.[83] Low pH inhibits cell proliferation, reduces viability, and induces a catabolic, apoptotic response in NP, AF, EP, and stem cells.[74,75,84] IVD cell apoptosis is mainly induced by the death receptor, mitochondrial, and endoplasmic reticulum stress pathways.[61] This cell death can lead directly to nociception by causing nerve root pain. Additionally, it can lead to pain by causing inflammation, invasion of inflammatory immune cells, and breakdown of the ECM,[61] leading to inflammatory nociception and changes in biomechanics, as we discussed in the previous section. Bibby and Urban showed that low glucose concentrations decrease disk cell viability, especially when combined with an acidic environment.[10] Long-term exposure to low pH upregulates endoplasmic reticulum stress markers involved in the NP's natural degradation and acid-induced apoptosis.[61] Cell senescence and death caused by low pH lead to many adverse changes in the IVD, including changes discussed previously, such as lack of ability to repair ECM,[80] inflammation,[61] and changes in biomechanics,[85] which can lead to pain.

6.4 | Increased pro-inflammatory signaling and acid-sensing ion channel expression in IVD cells

Gilbert et al. demonstrated that low pH drives the expression of inflammatory cytokines and neurotrophins in human NP cells in vitro. They showed a significant increase in protein and gene expression of IL-1β, IL-6, NGF, and *brain-derived neurotrophic factor* when cultured at low pH compared to control.[75] This increase is influenced by *ASIC3*,[75] which is overexpressed at low pH. Acidic pH has been shown to synergize with pro-inflammatory cytokines IL-1β and TNF-α, thus increasing the breakdown of the IVD, altering mechanical signaling, increasing pain signaling, and causing other degenerative changes.[86]

In general, a low pH condition has been shown to activate and increase the expression of *ASIC1*, *ASIC2*, *ASIC3*, and *ASIC4* in the degenerative IVD and may be involved in IVD degeneration,[56] although this has not been well established. In general, ASICs help regulate the health and viability of the IVD cells and ECM.[74] Gilbert et al. reported that *ASIC3* expression significantly increased in NP cells when exposed to a pH similar to that in severely degenerative disks and could be a potential target for therapeutics.[75] In addition to their increased expression, these channels are also activated by low pH, resulting in a catabolic response in IVD cells.[75]

6.5 | Summary of indirect mechanisms

Many degenerative changes are associated with low pH in the IVD, although the details of these mechanisms are not fully understood. In summary, low pH perpetuates degeneration by causing changes in nutrient supply and cell metabolism, EP calcification, disrupted nutrient and waste removal balances, breakdown of ECM, depletion of proteoglycans, cell death, and increased pro-inflammatory signaling and *ASIC3* expression (Figures 2 and 3). As discussed, these changes may cause pain by exposing nociceptive nerve endings to low pH

from the NP, also causing chronic inflammation, changes in biomechanics, and altered load cushioning.

7 | ANIMAL MODELS OF DDD AND LOW pH

DDD is challenging to study because of the relative difficulty of studying it in humans. As a result, most studies and initial tests of therapeutics are performed in rodents, human cadavers, and ex vivo disks,[48] and a few studies using other in vivo animals models such as pigs, dogs, rabbits, goats, sheep, and non-human primates.[87,88] These models induce degeneration in various ways, including mechanical methods (such as annular puncture, mechanical force, or endplate injury), chemical induction,[87,88] or genetic predisposition, such as with secreted protein acidic and rich in cysteine-null mice or sand rats.[14] These models have replicated many aspects of the human degenerative IVD condition, such as a change in tissue morphology and loss of healthy structure, inflammation, loss of healthy cellularity, and endplate calcification.[14] However, they have been unable to create all conditions known to be present with DDD.

Despite the existence of many animal models of degenerative IVDs, few studies have focused on recreating and studying the acidic environment of the IVD present with degeneration in humans. Additionally, therapeutic agents that have shown promise in animal degeneration and pain models have had mixed results in treating pain in humans.[89] One potential reason for this is that pH effects that may contribute to degeneration and pain in humans are generally absent in animal models, either from lack of focus or because of the relative difficulty of studying it in small animal models. Mechanically induced, chemically induced, and genetic models likely do not yield hyperacidity as in natural degeneration.[87,88] Additionally, different disk sizes in animal models lead to different rates of nutrient diffusion and likely to different accumulations of acidity because of differences in waste removal diffusivity,[87,90] although this has not been tested directly. A minipig annular puncture model used in two publications has been used to study changes in pH in the microenvironment of the IVD. One study measured pH with ex vivo measurements of lactic acid and saw

TABLE 1 Summary of what is known and what needs additional studying about general research areas and about the direct and indirect mechanism of acidic nociception in the intervertebral disk (IVD).

Condition	What we know	Needs additional studying
Clinical findings	There is a clinical correlation between acidity and degeneration and between acidity and pain. MRI could be used to non-invasively detect pH-dependent pain.	Methods for early detection of hyperacidity are needed, and methods to mitigate or reverse this pathology.
Animal models	Low pH is correlated with degeneration in a limited number of animal models.	Animal models that directly study hyperacidity and its effects in animal models are needed.
Effects on treatment strategies	Most restorative therapies have varying levels of success, especially biologic-based therapies.	Additional studies are needed to aid the survival and delivery of introduced cells and other biologics.
Direct mechanisms of acidic nociception		
Neoinnervation	Acidity drives neoinnervation and the expression of NGF and *TrkA*, which is hypothesized to drive pain.	More studies are needed to establish how neoinnervation leads to pain and what types of stimuli lead to hypersensitization.
ASICs in neurons	Acidity drives increased expression of ASICs in neurons. *ASIC3* plays a prominent role in pain signaling.	Further studies are needed to determine the effects of increased ASIC expression in a DDD model.
Cytokines and receptors	It is believed that acidity drives pro-inflammatory cytokines and receptors. Acidity synergizes with this signaling, leading to neuron sensitization.	Animal models that study this interaction are needed.
Indirect mechanisms of acidic nociception		
Nutrient supply and metabolism	Low pH decreases rates of metabolism. It can also lead to EP calcification, which causes changes in mechanics, nutrient availability, and further acidity.	In vivo studies are needed to study how lower pH alters metabolism rates.
ECM degradation	Acidity promotes the depletion of proteoglycans and lowers matrix synthesis rates.	More in vivo and biomechanics studies are needed to study the contribution of low pH-induced ECM breakdown to pain.
Cell death	Low pH leads to cell death in in vitro IVD cells.	In vivo studies are needed to study the contribution of intradiscal acidity to IVD cell death.
Cytokine signaling and ASICs in IVD cells	Low pH increases expression of ASICs 1–4. ASIC3 leads to increased expression of pro-inflammatory cytokines.	More studies are needed to further establish the contribution of each ASIC to IVD degeneration and pain.

Abbreviations: ASICs, acid-sensing ion channels; DDD, degenerative disk disease; ECM, extracellular matrix; EP, endplates.

that the content of lactic acid gradually increased after an annular lesion.[20] The other non-invasively quantified changes in pH via measurement of chemical exchange saturation transfer via MRI and found that there was a significant drop in pH after degeneration, which also correlates with metabolic markers for DDD pain.[30] Acidic pH plays a prominent role in pain from degenerating disks, but it has been challenging to understand the specific mechanisms because in vivo studies rarely include it.

8 | EFFECTS OF ACIDIC pH ON TREATMENT STRATEGIES

Current treatments for DDD are primarily palliative and focus on pain reduction and improving patient mobility. LBP treatments can be broadly grouped into three categories: (1) conservative pain treatments, (2) surgical interventions, and (3) biologic-based therapies.

Of these treatment strategies, biologic-based therapies for DDD pain have also been developed,[91] which are highly prone to interactions with the acidic environment of the degenerative IVD.[92] Despite their focus on IVD restoration, these therapies have shown varying levels of success in early-stage clinical trials.[93–95] These failures likely result from differences between clinical and animal model conditions, including low pH. Just as it leads to the breakdown of native IVD, the acidic environment in degenerative IVD can lead to the breakdown of introduced cells, biomaterials, antibodies, molecular inhibitors, and other biologics.[64] For these therapies to remain effective after introduction, modifications to the cells and materials or the acidic environment of the IVD are needed. Some work has been done to modify introduced cells with CRISPR gene editing to promote cell survival.[25,96] Levis et al. performed a CRISPRa screen and identified 20 genes that aided adipose-derived stem cells in survival in low pH, pointing to the potential of upregulation of targeted genes to aid in cell survival in the acidic diseased disk.[24] Work from the Buckley Lab has proposed cell priming[97,98] and antacid biomaterials[99] to mitigate pH effects. Other modifications have been made to aid the survival and delivery of other biologics.[92,100,101] Understanding and controlling the low pH microenvironment of DDD is crucial to improving the current treatment strategies.

9 | FUTURE WORK

The acidic pH in the degenerative disk plays a significant role in pain and perpetuating degenerative changes, such as cell apoptosis, ECM degradation, inflammation, endplate calcification, disruption of nutrient supply, and altered mechanical signaling. It has also been established that pH directly leads to nociception via overexpression of ASICs, overexpression of pro-inflammatory cytokines and receptors, and neoinnervation. Despite this critical microenvironmental factor being established, there is still a need for more studies on how low pH contributes to a painful disk and what therapies can help lessen this pain (Table 1).

10 | CONCLUSION

Lower back pain is a significant burden on the societal and individual levels. One of the major causes of back pain is degeneration of the IVD. Many changes occur with DDD, but the pain mechanisms are still largely unknown, leading to treatments with varying levels of success. Acidification of the IVD tissue is one crucial change related to DDD. Although this pathology is understudied, there are some established mechanisms by which we know that low pH contributes to degeneration and pain in the IVD. There is a need for additional cell-based and animal models that include the condition of acidic pH present with human IVD degeneration in order to better understand its contributions to DDD pathology and pain and improve treatment strategies.

AUTHOR CONTRIBUTIONS

The authors confirm contributions to the paper as follows: manuscript design: **M. Trone**, **J. D. Stover**; literature review: **M. Trone**; draft manuscript submission: **M. Trone**, **J. D. Stover**, **A. Almarza**, **R. Bowles**. All authors reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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