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REVIEW

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Biomolecular therapies for chronic discogenic low back pain: A narrative review

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Abstract

Chronic low back pain caused by intervertebral disc (IVD) degeneration, also termed chronic discogenic low back pain (CD-LBP), is one of the most prevalent musculoskeletal diseases. Degenerative processes in the IVD, such as inflammation and extracellular matrix breakdown, result in neurotrophin release. Local elevated neurotrophin levels will stimulate sprouting and innervation of sensory neurons. Furthermore, sprouted sensory nerves that are directly connected to adjacent dorsal root ganglia have shown to increase microglia activation, contributing to the maintenance and chronification of pain. Current pain treatments have shown to be insufficient or inadequate for long-term usage. Furthermore, most therapeutic approaches aimed to target the underlying pathogenesis of disc degeneration focus on repair and regeneration and neglect chronic pain. How biomolecular therapies influence the degenerative IVD environment, pain signaling cascades, and innervation and excitability of the sensory neurons often remains unclear. This review addresses the relatively underexplored area of chronic pain treatment for CD-LBP and summarizes effects of therapies aimed for CD-LBP with special emphasis on chronic pain. Approaches based on blocking pro-inflammatory mediators or neurotrophin activity have been shown to hamper neuronal ingrowth into the disc. Furthermore, the tissue regenerative and neuro inhibitory properties of extracellular matrix components or transplanted mesenchymal stem cells are potentially interesting biomolecular approaches to not only block IVD degeneration but also impede pain sensitization. At present, most biomolecular therapies are based on acute IVD degeneration models and thus do not reflect the real clinical chronic pain situation in CD-LBP patients. Future studies should aim at investigating the effects of therapeutic interventions applied in chronic degenerated discs containing established sensory nerve ingrowth. The in-depth understanding of the ramifications from biomolecular therapies on pain (chronification) pathways and pain relief in CD-LBP could help narrow the gap between the

pre-clinical bench and clinical bedside for novel CD-LBP therapeutics and optimize pain treatment.

KEYWORDS
biologic therapies, degeneration, pain, pre-clinical models

1 | INTRODUCTION

Low back pain is defined as chronic when it persists for longer than 3 months.[1] Chronic low back pain (CLBP) is a common clinical indication and globally the number one cause of disability burden.[2] In approximately 26%–39% of the CLBP cases, degeneration of the intervertebral disc (IVD) without herniation, also referred to as chronic discogenic low back pain (CD-LBP), has been established to be the underlying cause.[3] The peripheral nociceptive sensory neurons in degenerated IVDs[1] suggest a predominant role of nerve innervation in the development and maintenance of discogenic pain. Various classical (conventional) treatment options for CD-LBP are available, but are limited to conservative management or invasive procedures such as spinal fusion or arthroplasty.[4] Also non-surgical treatments primarily intend to alleviate pain symptoms by exerting anti-inflammatory agents, or analgesics can be used. Regenerative therapies aimed to restore IVD homeostasis or reverse the degenerative state are abundantly being developed as proxy treatment options for CD-LBP. However, pre-clinical studies assessing novel biomolecular therapies aiming to relieve pain by repairing the IVD rarely report on pain relief. Over the past years, biomolecular therapies including monoclonal antibodies,[5–10] platelet-rich plasma (PRP)[11–13] or multipotent mesenchymal stromal cells (MSCs)[14] have been investigated to improve current pain treatment. Systematic reviews and meta-analyses evaluating clinical studies using monoclonal antibodies, PRP or MSCs to treat patients with CLBP demonstrated low quality of the trials and high heterogeneity in study designs. Therefore, randomized (placebo)-controlled trials could not provide robust evidence for long-term safety and efficacy on pain relief in CD-LBP of any of these therapeutic agents. In-depth understanding of the exact mechanisms driving IVD degeneration and concomitant sensory nerve innervation is required for successful development of regenerative and analgesic therapies. Furthermore, improving drug efficacy by exploiting targeted drugs or controlled release platforms might offer new opportunities for CD-LBP therapy.

This narrative review therefore provides a short overview of the pathophysiological aspects of CD-LBP as related to cellular processes involved in pain and pain chronification. This review deals with current preclinical research aimed toward the development of regenerative and anti-inflammatory therapies in the treatment of CD-LBP, with special emphasis on their effects on chronic pain. This review ends with a critical evaluation and discussion of potential future developments with respect to possible regenerative therapies in CD-LBP.

2 | PATHOPHYSIOLOGY OF IVD AND CD-LBP

2.1 | Anatomy of the painful IVD

The IVD is a fibro-cartilaginous joint located between vertebral bodies that keeps the spine flexible, absorbs shocks and facilitates movement and load transmission through the spinal column.[15] Each IVD is characterized by three distinct components; a central gelatinous-like nucleus pulposus (NP) surrounded by a more rigid annulus fibrosus (AF) needed to retain the NP and resist tensile forces.[16] The two components are enclosed by the cartilaginous endplates (CEP) anchoring the IVD to the vertebral bodies and ensuring IVD nutrient-waste exchange.[17] The IVD is predominantly a-vascular and a-neuronal as only the outer layer of the AF is innervated by the sinuvertebral nerve (SVN) in healthy IVDs.[15] The exact mechanism of action by which a degenerated IVD is innervated by nociceptive neurons resulting in a painful disc progressing into CD-LBP has not yet been fully understood. The pro-inflammatory cascade activated upon degenerative IVD alterations have been indicated to play a key role in the acceleration of the degenerative processes.[18] The accompanying production and release of local neurotrophic factors during inflammation can stimulate the ingrowth of peripheral nociceptive sensory neurons into the IVD, finally resulting in pain sensitization and chronification[19,20] (Figure 1A). Nerve fiber ingrowth into the inner AF and central NP was shown to occur more frequently in painful or degenerated IVDs, leading to the current hypothesis that nerve ingrowth and innervation of the IVDs are the main source of CD-LBP.[21] There are two main pain pathways involved in lumbar discogenic pain.[22] (1) segmentally signaling from the somatic SVN root to the corresponding lumbar dorsal root ganglion (DRG) neurons and/or (2) non-segmentally signaling from the autonomic SVN root with nociceptive fibers ascending through the gray rami communicantes (GRC) and sympathetic trunk to L1-L2 DRG neurons (Figure 1B).

2.2 | Biomolecular processes in the painful IVD

The degenerative IVD contains a hostile environment containing proteolytic enzymes, pro-inflammatory mediators, neurotrophins and neuropeptides that have shown to contribute to the development and maintenance of CD-LBP.

Aging or injury are two main contributors to the gradual degenerative changes occurring during IVD degeneration[23] leading to a loss and remodeling of extracellular matrix (ECM) proteins from the

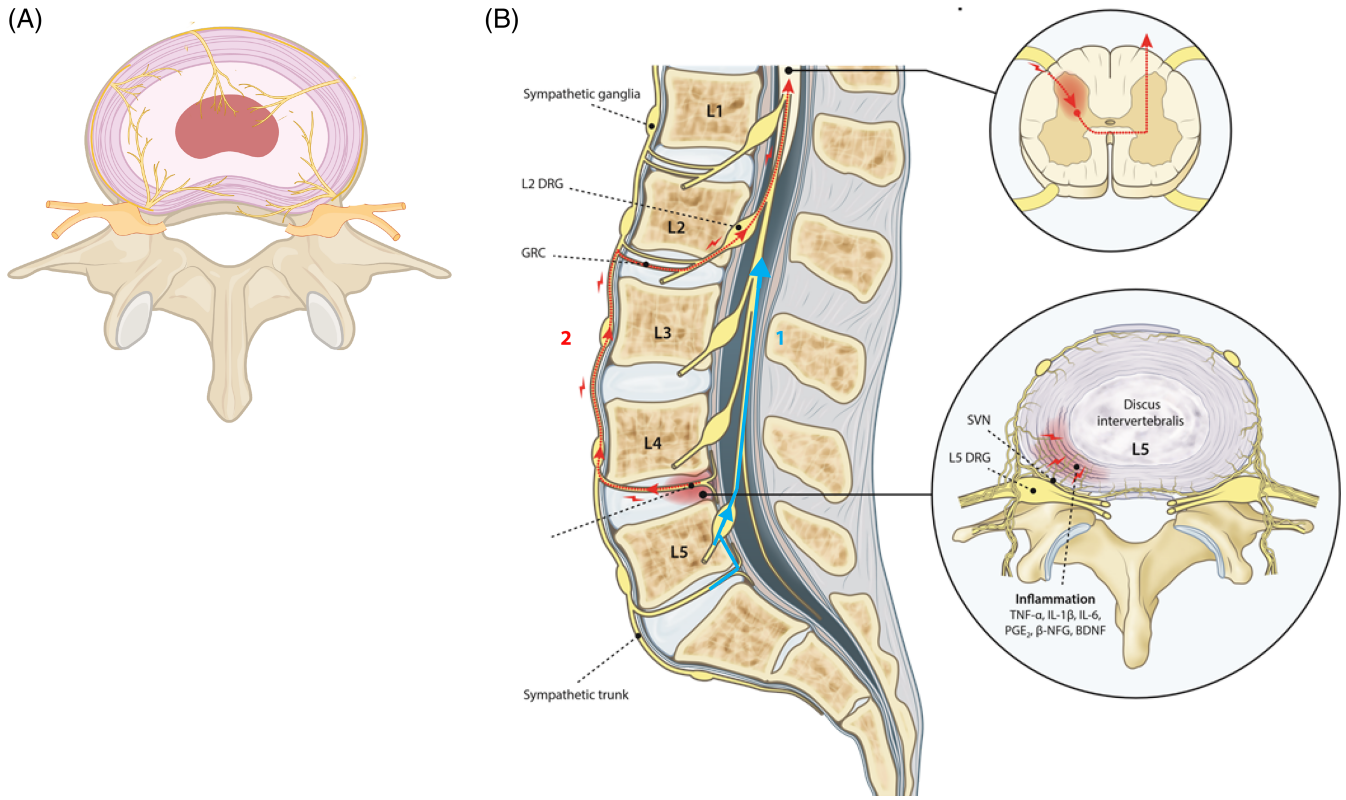

FIGURE 1 (A) Peripheral nociceptive sensory neuron innervation in the intervertebral disc, resulting from local pro-inflammatory factors. (B) Two described pain pathways; 1 (blue lines) segmentally signaling from the somatic sinuvertebral nerve (SVN) root to the corresponding level dorsal root ganglion (DRG) neurons, 2 (red lines) non-segmentally signaling from the autonomic SVN root with nociceptive fibers ascending through the gray rami communicantes (GRC) and sympathetic trunk to L1-L2 DRG neurons (adapted with permission from Rogier Trompert Medical Art).

macromolecular framework of collagens and proteoglycans.[24,25] Growth factors, such as transforming growth factor-β (TGF-β) and growth and differentiation factors (GDFs), positively affect ECM metabolism and thus loss of growth factors can further promote degenerative processes.[26,27] As a result, the disorganized and dehydrated IVD will fail to provide the compressive strength needed to absorb shocks and to allow movements of the spine.[28] Low-grade inflammation promotes a catabolic environment, whereas thickening of the subchondral plates restricts exchange of nutrients and waste products within the IVD[29] eventually leading to NP cell senescence.[30] The altered NP cell phenotype can maintain the catabolic environment during disc degeneration[31] and has shown to be responsible for the drop in local pH mediated by, among others, acid-sensing ion channels (ASICs)[32] that in turn causes IVD cell loss and ECM breakdown.[33] Importantly, the downward spiral of induced pro-inflammatory mediators, IVD cell loss and ECM breakdown will also diminish the neuro-inhibitory properties of the IVD. In a healthy situation, the ECM proteoglycans such as aggrecan, inherently inhibit neurite growth.[20,34] The loss of the nerve (in-)growth suppressive factors from the ECM and the concomitant presence of pathologically high levels of inflammatory cytokines stimulating release of neurotrophins enhances nociceptive sensory neuron ingrowth into the disc.[35] The nerve fibers innervating the painful degenerated IVDs are primarily small unmyelinated neurons expressing the neural growth associated protein (GAP)-43 and co-express the neuropeptide substance P (SP) that confirm their nociceptive identity.[36] The expression of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) as well as other neuropeptides such as calcitonin gene-related peptide (CGRP) are well known mediators in the nociceptive neurotransmission and are most likely responsible for the discogenic pain. Furthermore, retrograde transport of NGF from innervating nociceptive fibers present in the IVD to the cell bodies in the DRG can lead to the upregulation of various ion channels, including members of the transient receptor potential vanilloid (TRPV) family. TRPV ion channels have been shown to play a role in sensitization and pain hypersensitivity in CD-LBP.[37] Repressing the various related biomolecular processes involved in inflammation, neurotrophin release and remodeling of ECM components in the IVD might desensitize the intradiscal nociceptive fibers and minimize the acute and/or chronic pain.[38]

3 | INSTIGATORS OF IVD DEGENERATION INDUCED PAIN IN CD-LBP

Many different in vitro models for IVD degeneration are established to study neurite outgrowth and pain-related biomarkers. However, the various biomolecular processes related to degeneration of the IVD, which then may result in the development and maintenance of

(chronic) pain can only be studied using in vivo animal models. Various animal models developed to mimic human CD-LBP have been described in detail.[39,40] Predominantly mouse[41] or rat[42] IVD degeneration models have been utilized in the assessment of effective therapeutics in treating CD-LBP and the most common practice mimicking lumbar IVD degeneration is to injure the discus (NP, AF or both) via needle puncture. Alternatively, rat tail IVDs have been punctured or nucleotomized to mimic CD-LBP. The majority of these studies focus on the degenerative processes to restore IVD homeostasis, but often lack pain-related readouts such as neurite outgrowth or pain sensitization.

3.1 | Nerve sprouting and sensitization in the IVD and spinal dorsal horn

Excessive pro-inflammatory cytokines present in a degenerating IVD are considered to mediate the pain signaling cascade.[43] TNF-stimulated gene-6 (TSG-6), a protein secreted during inflammation, has been implicated to have anti-inflammatory and tissue-protective properties.[44] The role of TSG-6 during IVD degeneration was investigated by transiently over-expressing human NP cells from patients with degenerative IVDs and healthy controls with TSG-6.[45] In an IL-1β-induced inflammatory environment, TSG-6 mRNA and protein expression was upregulated, proposedly as a response to excessive inflammation to elicit anti-inflammatory effects. TSG-6-transfected NP cells, however, attenuated IL-1β-induced ECM degradation and nociception-related molecule expression of CGRP, NGF and SP.[45] Hence, TSG-6 might serve as a potential target to inhibit the pro-inflammatory processes in the NP which ultimately reduce pain.[46]

Neurotrophins such as NGF and BDNF have been reported to be associated with neuronal development, function and nociception.[47] In an in vitro co-culture using primary NP cells isolated from degenerated IVDs and human neuroblastoma cells, NGF and BDNF were pinpointed as responsible mediators to enhance neurite outgrowth from the neuroblastoma cells.[48] It has been suggested that CD14+ macrophages at the inflammatory site in the IVD contribute to the release of NGF, thereby stimulating sprouting and innervation of NGF-dependent neurons co-expressing CGRP.[49] Retrograde tracing of CGRP-positive neurons from degenerated IVDs in rats confirmed increased sensory nerve innervation, originating from L1-L6 DRGs.[50] In addition, DRG neuron remodeling has been observed following IVD puncture in rats. For example, TRPV1, an ion-channel involved in heat nociception and present on the innervated nerves has been shown to be responsible for NGF-receptor (trkA)-mediated remodeling in DRG neurons ex vivo. This TRPV1 ion-channel, among others, may thus be responsible for the adaptive nociceptive changes of innervating sensory neurons during CD-LBP.[51]

Overall, in rodent IVD degeneration models, nerve sprouting into a damaged IVD increased which are directly connected to the corresponding DRGs.[50] In these DRGs, sensitized nociceptive neurons have been associated with microglia and astrocyte activation.[52] Microglia activation can also be evoked by the pro-inflammatory environment of the degenerative IVD,[53] as shown by the effect of conditioned medium from degenerated mechanically overloaded bovine IVDs on a murine microglial cell line. After 48 hours, increased activation and proliferation was observed as well as mRNA upregulation of pro-inflammatory markers expressed by microglia exposed to degenerated IVDs, compared to microglia exposed to unloaded controls.[53] Furthermore, the activation of satellite cells in the DRGs associated with the degenerating IVDs was shown to also contribute to the maintenance of the neuronal network activation during chronification of discogenic LBP.[54] Other work confirmed the role of microglia and astrocytes in the spinal dorsal horn for the initiation and maintenance of pain sensitization during IVD degeneration.[50]

The activation of astrocytes and/or microglia cells in brain areas involved in nociceptive processing may result in the release of neuronal signaling molecules preceding the pro-inflammatory responses.[55,56] In CLBP patients, integrated positron emission tomography/magnetic resonance imaging (PET/MRI) was used to demonstrate an increase in activated glia cells, compared to healthy controls,[57] suggesting a role of glial activation in thalamic regions during pain chronification in CD-LBP. The potential link between microglia activation and CD-LBP and nociceptive neurite ingrowth was further investigated in a modified disc puncture-induced degeneration-related back pain mouse model, using transgenic $CX3CR1^{GFP/+}$ mice to fluorescently label microglia in the lumbar spinal cord.[58] After disc puncture surgery, upregulated levels of CSF1 in CGRP-positive sensory neurons and in the dorsal horn were found, whereas the number of microglia remained elevated over the 4 week study period. It was proposed that IVD degeneration leads to elevation of CSF1 in the DRG, activating microglia in the spinal cord.

In conclusion, glial cell activation is closely related to the inflammatory response as documented in spinal cord dorsal horn and this interferes with central sensitization processes known to be pivotal in chronification of CD-LBP. Further research is needed to understand the exact neural mechanisms involved in CD-LBP and in particular the effects and responses at supraspinal (cortical) levels.

3.2 | Pain-related behaviors in CD-LBP

The biomolecular and cellular processes occurring in the painful IVD have been associated to pain-related behaviors in animal models with injury and degeneration of the IVD. Intradiscal injection of TNF-α or NGF in combination with vascular endothelial growth factor (VEGF) immediately after IVD injury induction has shown to accelerate pain behavior in rats.[59] This study underlines the role of pro-inflammatory and/or neurotrophins in the development of painful degenerated IVDs.

In the rat model of induced IVD degeneration via artificial annular tears,[60] subsequent nerve sprouting following disc degeneration highly correlated to grip strength impairment was observed, most likely mediated by axial hypersensitivity. Shi et al. described the earliest IVD degeneration-associated LBP in a needle puncture mouse model, examining the link between disc tissue alterations and

symptomatic LBP.[52] Animals with degenerated IVDs showed pain-associated behaviors such as mechanical hypersensitivity, thermal hypersensitivity, reduced burrowing behaviors and reduced rearing activities. Moreover, degenerated IVDs contained more nerve fibers and the DRG neurons expressed pain-related neuropeptides that proposedly resulted in plasticity changes in the central nervous system, represented by the progressive astrocyte activation.[52] Another disc needle puncture study in mice has shown that 1 year after IVD degeneration induction, cold hypersensitivity (as indicator for radiating pain) persisted and was shown to be correlated with disc height, in a subset of the animals, whereas axial pain-behaviors such as tail suspension and grip strength did not.[61] Axial discomfort during a short-term follow-up (3–9 months after IVD degeneration surgery) was noted in the rat model of induced IVD degeneration[60] but did not persist at the long-term follow-up of 12 months.[61] AF innervation was increased in injured mice, but no nerve fibers were observed deep into any of the degenerative discs of these mice. The stratification of cold hypersensitivity responders or non-responders was performed to delineate whether this could be associated to IVD degeneration and innervation. Interestingly, all animals with degenerated IVDs, verified by x-ray, T2–magnetic resonance imaging and histology, showed axial discomfort that did not persist during the 1 year follow-up and half of these animals demonstrated signs of radiating pain that was associated with IVD narrowing and dorsal nerve innervation. It was therefore concluded that the pathological changes of the IVD (narrowing and innervation) are associated with radiating pain behaviors, since behavioral signs of axial discomfort did not persist for up to 1 year.[61]

Aberrant firing activity and signaling of peripheral sensory neurons to the CNS will generate persistent pain signals, induce a process of central sensitization in the spinal dorsal horn and then results in chronic pain if it will last for more than 3 months.[62] Central sensitization, the perception of pain and therapeutic efficacy of pain relieving drug and/or treatments are commonly tested and evaluated in pain-related animal behavior. For example, the minimally invasive needle IVD puncture procedure in rats aimed to model CD-LBP, demonstrated that these animals developed pain based on a reduction of distance covered in the open field testing, inhibited rearing positions and twitching as compared to control sham animals.[63] Another disc needle puncture rat model from Muralidharan et al. was designed to retain an intact NP to exclude adjacent sensory nerve root injuries that might result in lumbar radicular pain as opposed to discogenic lumbar pain.[64] The sensitivity of L1 and L4/L5 lumbar axial deep tissues, evaluated by pain-related vocalization upon spinal compression using an algometer, was elevated in IVD degeneration animals compared to sham and age-matched controls. In a rat needle puncture model investigating pain-related phenotypic changes at chronic time points (>16 weeks post-surgery), decreased hind limb stride frequency compared to the forelimbs and decreased activity was observed.[51]

The changes in the local neuronal network (IVD innervation and projecting to DRGs, leading to microglia activation in spinal cord) (see Section 3.1) are correlated to various pain-associated behaviors. The pain-related behavioral outcomes, however, seem to differ between CD-LBP-animal models and/or pain tests used, which complicates the interpretation of therapeutic strategies for CD-LBP and makes translation of findings to the clinic very complex. Notably, the majority of pain-related behaviors resulting from the induced IVD degeneration in animal models include radiating lumbosacral radiculopathy into the lower extremities (measured by von Frey paw withdrawal test), whereas CD-LBP patients often do not suffer from pain radiating into the extremities.

Numerous neuroimaging studies have demonstrated that plasticity changes in supraspinal brain areas is associated with CLBP.[65] CLBP patient populations are heterogeneous and often include CD-LBP. Various regions have been described to play a role in the chronification of LBP. Thalamocortical dysfunction and dysrhythmia in chronic pain demonstrated that CLBP pathophysiology and clinical pain intensity are associated with distinct thalamo-cortical network dynamics.[66,67] Resting-state functional MRI data acquired from nonspecific CLBP patients at baseline and after a manipulation for back pain intensification implicated a role of the mesocortical and mesolimbic pathways, potentially mediating the contribution of pain sensitization to pain chronification in CLBP.[68] A reduced connectivity between the posterior cingulate cortex and angular gyrus has also been observed in non-specific CLBP patients.[69] The involvement of the amygdala in the neuropathology of non-specific CLBP patients has been described to exhibit greater resting state function connectivity between the left amygdala and left dorsal medial prefrontal cortex, and was negatively correlated with pain intensity ratings.[70] The reproducibility of functional MRI data has shown to be limited and this may be related to variables that systematically alter pain perception and concomitant brain activity in each individual pain patient such as mood, painful experiences, social support/distraction and expectations of pain intensity.[71] Also, the CLBP patients studied in these neuroimaging experiments have not been explicitly selected for discogenic CLBP. Whether these findings might be analogue to CD-LBP patients warrants future studies that delineate the cause of CLBP.

4 | BIOMOLECULAR THERAPIES IN TREATMENT OF CD-LBP AND PAIN RELIEF

4.1 | Modulators of inflammation

Pro-inflammatory cytokines are widely used to mimic the inflammatory processes during IVD degeneration[72] and have been considered as targets for CD-LBP therapy. For example, the natural phenol hydroxytyrosol (HT) contains anti-inflammatory effects. TNF-α induced inflammation of human NP cells was inhibited in the presence of 20 or 100 μM HT, thereby mitigating ECM degradation.[73] Also in a culture of rat microglia cells, LPS-induced inflammation was hampered if 20 or 100 μM HT was added to the culture and thus reduce microglial inflammatory responses.

In another work, the anti-inflammatory effects of a TNF-α inhibitor (etanercept) was evaluated in a bovine IVD organ culture model.[74] Etanercept (3.5 mg/70 μL) was injected into the center of the NP after the first loading cycle followed by TNFα injection 5 min later and

was able to reduce NGF expression in the AF during the 4-day culture. In other work, the mechanism of action was investigated in a rat needle puncture model immediately injecting etanercept or saline into the disc after inducing injury. Also the neurotracer Fluoro-gold was added to the surfaces of L4/L5 discs to label the innervating DRG neurons. Fourteen days after surgery, the direct intradiscal application of etanercept was shown to suppress CGRP-expressing neurons in DRGs that innervate degenerating IVDs.[75]

To delineate why some degenerated IVDs are painful, while others are not, CSF from patients with CD-LBP, IVD degeneration patients without pain and healthy controls was compared and tested for presence of inflammatory markers.[76] CSF IL-8 levels were shown to be elevated in CD-LBP patients, thereby suggesting this cytokine to play an important role in generating CLBP. Therefore, the potential therapeutic value of inhibition of IL-8 was further evaluated preclinically in SPARC-null mice using the molecular IL-8 inhibitor reparixin (20 mg/kg, 3x i.p/week). Chronic inhibition of the IL-8 signaling pathway resulted in decreased mechanical allodynia, decreased cold sensitivity and improved grip strength. Furthermore, the astrocyte marker GFAP was significantly decreased in reparixin-treated SPARC-null mice indicating reparixin could attenuate neurogenic inflammation.[76]

First line pain medication used in the clinic for managing LBP are often nonsteroidal or steroidal anti-inflammatory drugs. The effects of a nonsteroidal drug (NS-398, selective COX-2 inhibitor) and a steroid (dexamethasone) on human IVD cells were investigated in vitro. The result of this study suggest that dexamethasone strongly inhibit IL-1mediated induction of NGF, whereas the selective COX-2 inhibitor enhances it.[77] On the other hand, in two similar studies using a preclinical canine IVD degeneration model, the intradiscal delivery of either nonsteroidal (celecoxib, selective COX-2 inhibitor) or steroidal anti-inflammatory (triamcinolone acetonide) drug release by a microsphere platform was able to reduce NGF expression in the IVD.[78,79] In different work, a prospective clinical trial including canine CD-LBP patients evaluated the safety and efficacy of intradiscal injected PCLA-PEG-PCLA hydrogel loaded with the selective COX-2 inhibitor celecoxib.[80] The evaluation of a dog owner's questionnaire indicated an improved quality of life in the 10 canine patients treated, although fine-tuning of the delivery platform is warranted for future implications.[80]

An acidic pH in the degenerating IVD and acid-sensing ion channel-3 (ASIC-3) has also been linked to low back pain.[81] The work of Gilbert et al. demonstrated an increase of acid-sensing ion channel 3 (ASIC-3) and catabolic responses in cultured NP cells as a result of acidic pH culture conditions (pH 6.5).[82] Pro-inflammatory markers IL-1β, IL-6 as well as neurotrophins NGF, and BDNF expression has been shown to mediate these catabolic responses in the cultured NP cells as a result of the increased ASIC-3 expression. In turn, these in vitro experiments showed that the APETx2 induced blocking of ASIC-3 was able to prevent the pro-inflammatory and neurogenic responses in NP cells during the 7-day culture period, even in an acidic culture environment.[82] These findings suggest ASIC-3 to be a useful target molecule for treatment of CD-LBP.

Overall, pre-clinical data has shown that inhibiting the pro-inflammatory mediators could be exploited to reduce CD-LBP by reducing neuronal inflammation. Thus far, etanercept has been evaluated for the safety and efficacy in CLBP patients,[83] but could only provide a short-term reduction of pain.

4.2 | Extracellular matrix components

Transforming growth factor-β (TGF-β) is a growth factor that may play a protective role during IVD degeneration, whereas excessive TGF-β signaling has been shown to evoke progression of IVD degeneration.[26] Recent work of Luo et al. improved the delivery of growth factor TGF-β therapy by using a bio-orthogonal hydrogel as delivery platform.[84] An injectable gelatin hydrogel was designed in which the two chemical moieties tetrazine and norbornene were used to selectively crosslink gelatin without external triggers or toxic byproducts. This gelatin hydrogel showed comparable biomechanical (e.g., viscoelasticity) properties to the native IVD and was further supplemented with TGF-β to provide cell-signaling cues facilitating tissue regeneration and remodeling by the scaffold. Rats received intradiscal injections of either TGF-β, gelatin hydrogel or TGFβ-loaded gelatin hydrogel (10 μL) directly following nucleotomy surgery in tail IVDs. Animals treated with TGFβ-loaded gelatin hydrogel showed a significant reduction in CGRP nerve fiber staining in the NP region and increased mechanical allodynia tolerance over the 42-day follow-up period, as compared to only TGF-β or hydrogel-treated animals.[84] Notably, the increased mechanical allodynia that was observed indicates that the CD-LBP animal model used includes radiating pain. In other work by Matta et al., the molecular therapeutic NTG-101, a drug containing Connective Tissue Growth Factor (CTGF) and TGF-β1, was able to suppress the expression levels of neurotrophins within AF regions after single injection into canine IVDs injured by needle puncture.[85] Here, needle puncture injury at levels L1/2, L3/4 and L5/6 was induced in 3 year old Beagle dogs and 4 weeks later intradiscally injected with a single injection (350 μL) of either PBS or NTG-101. The discs were harvested 14 weeks after treatment and evaluated for trkA, BDNF, TrkB and Calcitonin Receptor-Like Receptor (CALCRL) expression using immunohistochemistry. Significantly lower expression in the posterior/central AF of all studied pain-related biomarkers was detected in NTG-101-injected discs.

Another growth factor candidate for CD-LBP treatment is growth differentiation factor-6 (GDF-6).[86] In a series of pharmacological in vivo experiments, the effectivity of intradiscally injected GDF-6 was tested based on the use of an applied posterior IVD puncture model in which the left facet joint between the fourth and fifth lumbar vertebrae was removed as well as the left small joints of L2/3, L3/4, and L4/5. Then, a 21-gauge needle was inserted into one segment or three IVD segments and kept there for 30 seconds. One or 2 weeks after IVD injury, GDF-6 (10, 50 or 100 μg) was intradiscally injected and pain-related behavior, assessed as mechanical and thermal hypersensitivity, was evaluated 35 days later. Low dose of GDF-6 (10 and 50 μg) did not alleviate pain-related behaviors, whereas 100 μg of

GDF-6 alleviated pain-related behaviors in both the single- and three-IVD segment models.

The prominent role of disc-derived proteoglycans on preventing nerve innervation suggest the potential of ECM components as regenerative factors exploiting the inherent IVD properties. The work of Piening et al. has demonstrated the neuro-inhibitory properties of intact IVD tissue and ECM components that can be exploited to prevent nerve ingrowth to degenerating painful discs.[87] Here, decellularized porcine NP tissue was enzymatically modified into a hydrogel and co-cultured with rat DRGs in a 3D system for 15 days. Neurite sprouting into this porcine NP hydrogel was significantly inhibited compared to collagen controls and thus might be of use to replace degenerated NP tissue and minimize neurite ingrowth into degenerated discs. To what extent this approach can show feasibility in clinical practice remains to be seen, as immune responses may need to be overcome.

A hyaluronic acid (HA)-based hydrogel has also shown to contain neuro-inhibitory properties by binding to the receptor of CD44 (a cell-surface glycoprotein involved in cell–cell interactions) located on the NP cells. This blocks pro-inflammatory cytokines from binding to their receptors and consequently inhibits transcription of neurotrophins.[88] The neuro-inhibitory therapeutic properties of a cross-linked HA-hydrogel was further investigated in a model of painful IVD degeneration in the rat tail, described by Isa et al.[89] Sensory (nociceptive) fibers co-expressing GAP-43, CGRP and TRPV1 were observed to be present in both the injured AF and the NP of painful degenerated IVDs. In animals in which the HA-hydrogel (0.03 mg/mL) was intradiscally implanted immediately after needle puncture, less sensory fiber ingrowth into the disc was noted after 29 days. At the same time, neuronal expression of cell activity markers c-Fos and Tac1 was found to be significantly decreased in dorsal horn neurons of HA-hydrogel-treated animals, compared to untreated controls. From this, it was speculated that the cross-linked HA-based hydrogel does suppress nociceptive fiber ingrowth and neurotransmission and should result in pain relief. Indeed, HA-based hydrogel implanted animals displayed increased heat sensitivity and mechanical allodynia responses compared to untreated controls.[89] The effectivity of the HA-based hydrogel could be further enhanced and used as a carrier to locally administer other novel drugs for CD-LBP treatment.

In conclusion, in vitro and in vivo ECM components such as decellularized IVD tissue or HA were shown to have inherent neuro-inhibitory properties. Especially in the form of hydrogels they may also function as drug delivery platform suitable for local administration of small molecule drugs such as TGF-β, in particular with a short half-life. The decellularization process enables the removal of many xenogeneic cellular antigens, which minimizes the immunogenicity risk of tissue-derived ECM. Still, the immunological features of decellularized xenogeneic IVD tissue should be investigated in greater detail before implanting in CD-LBP patients. Another important consideration before its clinical use is the fact that in most IVD degeneration animal models, drugs are administered acutely after injury of the IVD. This might not be translated in view of the clinical reality where degenerative IVD processes are chronic and established over a time-period of years before the treatment will be applied.

4.3 | Inhibition of neurotrophic factors

Pro-inflammatory mediators such as IL-1 β and TNFα are well known for their role within IVD degeneration and are related to the upregulation of neurotrophic factors, including NGF and BDNF[35] (see Section 3.1).

Healthy NP cells can inhibit the neurite growth of human neuroblastoma cells in proximity, whereas degenerated NP cells lose this capacity, leading to an increase of neuroblastoma neurite outgrowth and length.[48] Richardson et al. identified NGF and BDNF as potential mediators released by the degenerated NP cells that could be potentially exploited to block neurite ingrowth or modulate sensitization from a painful IVD.

Orita et al. explored the direct intradiscal injection of antibodies against NGF or NGF receptors (trkA and $p75^{NTR}$) to suppress downstream CGRP neurotransmitter expression in projecting DRGs.[90] Here, L5–L6 IVDs were punctured multiple times to cause disc degeneration, injected with the retrograde neurotracer Fluoro-gold and different antibodies; anti-NGF or anti-trkA, or anti-$p75^{NTR}$ or saline vehicle control. The proportion of retrograde labeled DRG neurons co-expressing CGRP was highest in the vehicle group and decreased in the antibody-treated groups in particular in the anti-$p75^{NTR}$ group. From this study, it is concluded that injection of anti-NGF or anti-NGF receptor antibodies into the disc results in decreased nociceptive fiber ingrowth into the disc and this might be an effective therapeutic approach for CD-LBP treatment. Blocking NGF activity in vivo has also been postulated to be effective in cervical punctured IVD that reported less CGRP-expressing cervical DRGs in animals treated with an anti-NGF antibody.[91]

In conclusion, modulation of intradiscal NGF activity has shown to be highly effective in reducing neurite ingrowth of nociceptive fibers into the disc. Future in vivo studies need to determine the analgesic effect of intradiscal NGF antibody treatment on pain behavior in CD-LBP animal models. The impact of anti-NGF antibodies in CLBP patients has remained unsatisfactory and either provide only short-term relief or come with serious adverse effects.[6]

4.4 | Cell transplantation

Mesenchymal stem cells (MSCs) can differentiate into various musculoskeletal cell types and, therefore, are emerging as frontiers in regenerative medicine for musculoskeletal disorders including CD-LBP, due to their anti-inflammatory, immunosuppressive properties.[92] MSCs are transplanted into CD-LBP patients to replenish or replace the damaged native IVD cells and/or alter the pathological behavior of the native IVD cells.[14] A recent study by Suzuki et al. reported the effect of human MSC-loaded alginate gel injected immediately after NP needle puncture, in rat tail IVDs.[93] Injection of the human MSC-loaded alginate gel was shown to suppress elevated trkA expression in both NP and AF cells and resulted in increased heat sensitivity and mechanical allodynia responses as compared to untreated controls. Tail-flick latencies indicating axial low back pain remained

present in sham, MSC only or alginate gel only animals, while a single injection of MSC-loaded alginate gel increased latencies over the study period of 28 days and thus was able to relieve pain.[93] It seems that gel encapsulation does not represent a mechanism of IVD regeneration by itself, but rather functions as a technique to prevent cell leakage and assist in cell activation. In different work, an injectable gel made from human fetal cartilage cells was injected immediately after nucleotomy surgery into rat tail IVDs.[94] Injured rat tail discs treated with this cartilage gel showed enhanced matrix turnover, downregulation of inflammation, decreased CGRP expression in the NP and at the same time alleviated mechanical allodynia compared to cells only and ECM only controls.[94]

In conclusion, the regenerative and neuro-inhibitory properties of MSCs that are implanted using various carriers like alginate immediately after IVD injury might suggest good therapeutic potential for clinical use and pain relief in CD-LBP animal models. From a translational perspective, the question remains if and how the intradiscal implantation of MSCs (whether or not delivered using a carrier) in chronic degenerated discs will result in the inhibition of neurite ingrowth into the disc and pain relief.

5 | DISCUSSION AND FUTURE PERSPECTIVES

The multifactorial etiology of IVD degeneration which may result in CD-LBP remains a complex process that is not yet fully understood. Upregulation of pro-inflammatory cytokines triggers intradiscal ECM breakdown and neurotrophin release that ultimately result in peripheral neuron innervation with concomitant aberrant excitability. The innervation of nociceptive sensory neurons into the IVD has been widely recognized as a source of low back pain, while the increased sensitization of these neurons plays a prominent role in pain chronification. Biomolecular therapies to minimize CD-LBP are designed to intervene at different levels within the pain-signaling cascade.[95,96] For now, the clinical outcomes on pain relief of these biomolecular therapies is limited and remains unsatisfactory.[95]

The biomolecular therapies describing their effects on chronic pain in CD-LBP (see Section 4) suggest that blocking pro-inflammatory mediators or NGF activity might hamper neuronal ingrowth into the disc. Furthermore, the tissue regenerative and neuro-inhibitory properties of ECM components or MSCs could be exploited. However, there are still significant challenges to overcome, such as stem cell engraftment or immune reactions that may occur due to repeated injections of MSCs.

ECM-based hydrogels containing decellularized IVD tissue or HA have been utilized for sustained drug delivery approaches to improve drug administration route and half-life. Sustained delivery platforms based on ECM- hydrogels may potentiate long-acting biomolecular therapeutics in treatment of CD-LBP. Indeed, a number of studies have been performed investigating effect of biomaterials (such as HA) and cell-based regenerative therapies on pain relief in herniated disc animal models (review Yamada et al.[97] provides a good overview). The activated pain-signaling cascade leading to CD-LBP is comparable to the pain pathways involved in herniated discs and might be applicable in both clinical settings. This is exemplified with the biomolecular therapy using the monoclonal antibodies against TNF-α, such as etanercept. The effects of this drug on pain relief was initially evaluated pre-clinically in herniated NP animal models and could attenuate NP-induced structural changes of the DRG.[98–100] Therefore, the investigation of etanercept for the management of low back pain with or without sciatica was continued in clinical trials, but failed to provide robust evidence for its effect on pain relief.[5,6]

It appears that acute treatment strategies (shortly after the induction of disc injury) as used and studied in most pre-clinical IVD degeneration models do not reflect the real life clinical chronic pain situation. The "acute study design" represent a prophylactic approach, opposed to the common chronic pain situation in clinical CD-LBP in which IVD innervation has already been established. Importantly, to the best of our knowledge, effects of therapeutic interventions applied in chronic degenerated discs have not been investigated and thus effects on well-established nociceptive nerve fiber innervation, among other processes, is not yet known.

Overall, it seems that the effect of biomolecular interventions in pain (chronification) pathways and on pain relief in CD-LBP is an important but yet underexplored aspect of this indication. Thereby, the high variety between studies, in for example the IVD degeneration model, follow-up period or pain-behavioral assays, renders it problematic to present a systematic literature review of pre-clinical work describing the effects of CD-LBP therapy on neuronal growth, effects on nociception and/or pain. Future pre-clinical studies for biomolecular therapies in CD-LBP should include read-outs focused on aspects in the pain signaling cascade such as nerve innervation and/or sensitization as this occurs in the IVD. Notably, a golden standard to assess pre-clinical CLBP is still missing but is urgently needed to substantiate therapeutic efficacy of novel biomolecular therapies for CD-LBP.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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