

# Regenerative Treatments for Spinal Conditions



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## KEYWORDS

- Spine • Regenerative • Intradiscal • Platelet rich plasma • Mesenchymal stem cells
- Fibrin • Annular fissure • Low back pain

## KEY POINTS

- Low back pain is a common and expensive cause of disability.
- Nonhealing annular fissures are the most common cause for low back pain.
- Early treatment of painful annular fissures may also help prevent progression to spinal deformity, stenosis, and disability.
- Intradiscal platelet rich plasma, mesenchymal stem cells, and fibrin are promising therapeutic options for intervertebral disc degeneration.
- Regenerative treatments may offer a more cost-effective solution for refractory discogenic pain and perhaps avoid expensive surgery altogether.

## INTRODUCTION

Although there are many causes of low back pain, most experts agree that the beginning of the end of the spine starts with an injury to the intervertebral disc (IVD). When the disc begins to fail, the “degenerative cascade” begins and the subsequent sequelae of facet loading, spinal deformity, stenosis, and nerve root compression ensue.<sup>1</sup> Adult spinal deformity is increasingly common in the aging population, with prevalence as high as 68% in adults older than 60 years.<sup>2</sup> Adult spinal deformity is also a debilitating disease that greatly affects quality of life. Studies have shown that adults with scoliosis score significantly lower in self-reported outcome measures, such as the 36-item Short Form Health Survey (SF-36) questionnaire, compared with the general US population, including physical functioning, vitality, social functioning, emotional role, physical role, and mental health.<sup>3</sup> Adult spinal deformity has a similar

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global burden as well. In fact, a prospective multicenter international database including 8 industrialized countries found that patients with adult spinal deformity actually have lower health-related quality of life scores when compared with patients with common chronic conditions, such as self-reported arthritis, chronic lung disease, congestive heart failure, and diabetes.<sup>4</sup>

The rising health care costs, the physical impact, and functional decline related to adult spinal deformity engender a need for more preventive measures and cost-effective treatments, such as preventive and regenerative interventions. Despite spending billions of dollars in various treatments, both surgical and nonsurgical current treatments have failed to meet patient expectations and curb the ever-escalating health care costs related to managing this condition. The concepts of cutting out discs, fusing the spine, burning disc nerve endings, and injecting steroids around inflamed structures all fail to address the underlying pathophysiology and do little to change the natural history of disc degeneration. It is our opinion that we need to be less aggressive with our surgical treatment of the spine, and more aggressive with intervening earlier in the disease process with regenerative treatments. Hopefully this approach will not only lead to better patient outcomes, but also to a more sustainable, cost-efficient way to manage this significant societal burden. In this article, we focus our review on the current literature that exists regarding the clinical and translational studies on regenerative treatments for healing the IVD.

## DISCOGENIC PAIN

The IVD is composed of a central nucleus pulposus, consisting of hydrophilic proteoglycan and type II collagen, and the outer annulus fibrosus, made of a fibrous ring of mostly type I collagen.<sup>5,6</sup> Due its intrinsic hydrostatic pressure, the nucleus pulposus can bear heavy compressive loads, whereas the annulus fibrosus resists heavy tensile stresses.<sup>7</sup> Biomechanical studies have shown that torsion and flexion contribute to degenerative changes in the lumbar discs.<sup>8</sup> Disc herniations can be due to progressive degenerative changes from repetitive stress, or acute in nature due to trauma.<sup>8</sup> With repetitive stress, the annulus fibrosus fibers swell and disrupt as the annulus fibrosus undergoes myxomatous degeneration and cyst formation.<sup>8</sup> At the same time, the nucleus pulposus dehydrates, turns fibrotic, and eventually undergoes necrosis and herniation. The nucleus pulposus can herniate through annular fissures or endplate disruptions. The adult IVD is the largest avascular structure in the human body and relies on passive diffusion from adjacent endplate vessels for nutrition,<sup>9</sup> resulting in poor inherent healing potential. In fact, only 3% of disc bulges and 38% of focal protrusions resolve spontaneously.<sup>10</sup> Broad-based disc protrusions, extrusions, and sequestrations have a better prognosis, with approximately 75% to 100% resolving spontaneously.<sup>10</sup>

Nonhealing annular fissures of the IVD have been implicated as one of the major causes for chronic low back pain. A concomitant upregulation of proinflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis (TNF) alpha, leads to chemical sensitization of the rich network of nerve fibers that supply the outer annulus fibrosus, resulting in pain with normal activities of daily living.<sup>11-13</sup> As the degenerated disc cells upregulate IL-1 expression, the native disc cells also increase matrix degrading enzyme production expression.<sup>5</sup> TNF-alpha expression from the degenerated tissue also upregulates matrix degrading enzymes and stimulates nerve ingrowth. Furthermore, annular fissures may also contribute to a chemical radiculitis due to the release of inflammatory mediators into the epidural space.<sup>14</sup> As the IVDs degenerate, there is

loss of disc space height, and subsequent loading onto the posterior elements.<sup>15</sup> When the disc degenerates asymmetrically, spinal deformity and stenosis ensue.

Considering the pathophysiology of disc degeneration, regenerative treatments need to focus on either stimulating production of extracellular matrix, or inhibiting the cytokines that upregulate matrix degrading enzymes. In turn, as the regenerative treatments slow down or reverse disc degeneration, the subsequent loss of disc space height, increased loading on posterior elements, and spinal stenosis also may be prevented.

## PLATELET RICH PLASMA

The solution for IVD regeneration and inhibition of matrix degrading enzymes may be found in platelet rich plasma (PRP). PRP is acquired from an autologous sample of blood that is centrifuged to increase the platelet concentration up to 3 to 8 times the normal concentration in whole blood.<sup>16</sup> At the same time, PRP also contains amplified levels of growth factors and cytokines, which stimulate tissue healing. The alpha granules in platelets also secrete growth factors that are essential for tissue repair, such as basic fibroblast growth factor (b-FGF), epithelial growth factor, insulinlike growth factor (IGF-1), platelet-derived growth factor, and vascular endothelial growth factor.<sup>17</sup> The growth factors also increase collagen content, promote endothelial regeneration, and stimulate angiogenesis.<sup>17,18</sup>

## INTRADISCAL PLATELET RICH PLASMA

### *Intradiscal Platelet Rich Plasma: In Vitro and In Vivo Studies*

Clinicians have hypothesized that placing a high concentration of growth factors, such as in PRP, directly at the site of collagen injury can allow the growth factors to act as humoral mediators to induce the natural healing cascade<sup>19</sup> (**Box 1**). An in vitro study of PRP-infused human IVD cultures supports this hypothesis and exhibited nucleus pulposus proliferation and differentiation as well as upregulated proteoglycan synthesis.<sup>20</sup> Animal models of experimentally injured IVD treated with intradiscal PRP have also demonstrated restoration of normal cellular architecture and disc height.<sup>21,22</sup> Furthermore, PRP may also have an anti-inflammatory effect. An in vitro study found that cytokine (TNF-alpha and IL-1) induced proinflammatory degrading enzymes and mediators were suppressed with the addition of PRP into the collagen matrix of human nucleus pulposus cells.<sup>23</sup> A rabbit model with degenerated IVDs injected intradiscally

#### Box 1

#### Benefits of platelet rich plasma (PRP)

- Increased platelet concentrations 3 to 10 times over whole blood
- Platelets secrete growth factors (basic fibroblast growth factor, epithelial growth factor, insulinlike growth factor-1, platelet-derived growth factor, vascular endothelial growth factor)
  - Increase collagen content
  - Endothelial regeneration
  - Stimulate angiogenesis
- Suppress proinflammatory cytokines (tumor necrosis factor-alpha and interleukin-1)
- Reduce apoptosis
- Concentrated fibrinogen content

with PRP-impregnated gelatin hydrogel microspheres resulted in significantly higher water content determined by MRI, which corresponded with increased intradiscal proteoglycan content, upregulated mRNA precursors for type II collagen, and significantly reduced apoptotic nucleus pulposus cells.<sup>24</sup> Similarly, in a percutaneous annulus puncture-induced degenerated disc rat model, discs treated with PRP had fewer inflammatory cells, higher preservation of normal morphology, and higher fluid content in T2 MRI compared with sham at 4 weeks postinjection.<sup>21</sup>

### ***Intradiscal Platelet Rich Plasma: Clinical Studies***

A recent double-blind randomized control trial (RCT) involving intradiscal PRP injections of patients with chronic moderate to severe lumbar discogenic pain, has demonstrated improvement in functional and pain scores.<sup>25</sup> This study involved 47 participants randomized to receive a single injection of autologous PRP (29 in the treatment group) or contrast agent alone (18 in the control group) into symptomatic degenerative IVDs. The patients included were those with low back pain persisting for at least 6 months and refractory to conservative treatment, including oral medications, rehabilitation therapy, and/or injection therapy (**Box 2**). Before the intradiscal PRP procedure, a caudal epidural injection was trialed to determine if the patient with presumed discogenic low back pain would receive therapeutic benefit from the caudal injection. A prospective cohort study has shown that patients with at least 3 months of axial low back pain associated with central disc protrusions at L4–5 and/or L5–S1 do experience improvements in pain, function, and satisfaction after receiving caudal epidural steroid injections (Lee J, Nguyen E, Harrison J, et al. Fluoroscopically guided caudal epidural steroid injections for axial low back pain as a result of central disc protrusions: a prospective outcome study. *Pain Med*. Submitted for publication). The subjects who had relief of low back pain after the caudal injection then were considered for inclusion in the intradiscal PRP randomized control study.

Furthermore, there was strict selection criteria for included IVDs. Only the IVD heights of at least 50% of normal and with disc protrusion less than 5 mm on MRI or computerized tomography were included in the study. Disc extrusions, sequestered discs, and spinal stenosis at the levels investigated were excluded. The symptomatic discs were found via provocative discography performed on the day of the intradiscal PRP injection. Only grade 3 or 4 annular fissures as determined by discography were included. At 8 weeks, the intradiscal control (contrast only) group was allowed to cross over to receive intradiscal PRP if they failed to show improvement.

At 8 weeks, there were statistically significant improvements in pain (Numeric Rating Scale [NRS] for best pain), function (Functional Rating Index [FRI]), and patient satisfaction (North American Spine Society Outcome Questionnaire) in the intradiscal PRP group as compared with the control groups. In addition to the RCT, a longitudinal

#### **Box 2**

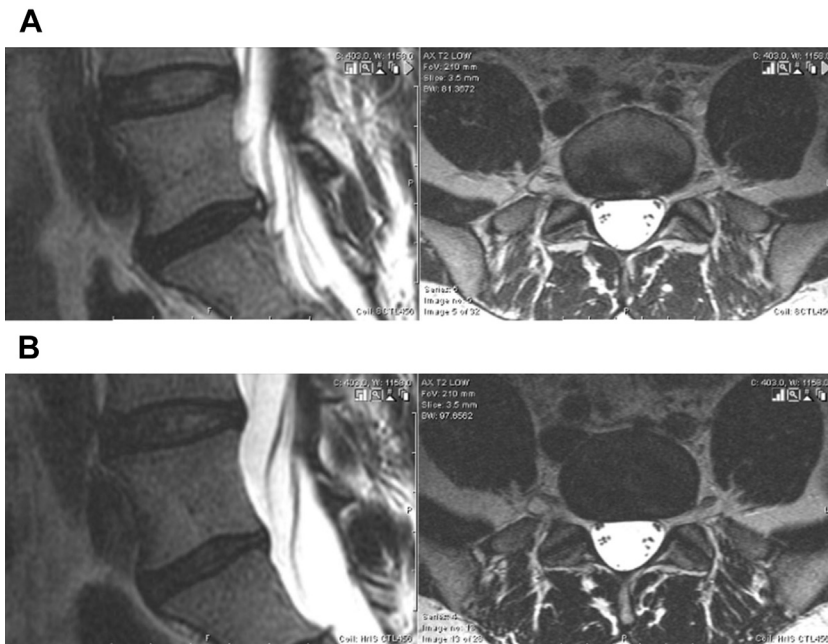
##### **Selection for intradiscal PRP injection**

- Low back pain greater than 6 months
- *Failed conservative treatment*: oral medications, physical therapy, injections
- *Transient relief following caudal epidural steroid injection*
- *MRI*: disc heights of at least 50% of normal, disc protrusion <5 mm
- *Provocative discography*: grade 3 or 4 annular fissures and <2 mL filling of contrast into annular fissure

analysis of the intradiscal PRP treatment group at 6 months, 1 year, and 2 years was conducted. This revealed continued improvement in the NRS best pain, FRI function, and SF-36, and clinically significant improvement sustained at 2 years postinjection for NRS worst pain, FRI function, SF-36 pain and function (reference both of our articles here). No adverse events of neurologic injury, progressive disc herniation, or disc space infection occurred throughout the course of the study.

The investigators concluded that PRP is a safe and sustainable treatment option for lumbar discogenic pain. This study demonstrated improved functional outcomes after intradiscal PRP, but the regenerative properties of PRP in the IVD is still inferred. The next step in our research will be a prospective cohort study of intradiscal PRP that will include sequential MRI of the spine to ascertain improvements in disc space height, healing of high-intensity zones (HIZs), resorption of focal protrusions, and possible improvement in Pfirrmann scores.<sup>26</sup> A case report with the same investigators demonstrated positive increased T2 nuclear signal intensity on MRI of IVD 1 year after intradiscal PRP injections, which correlated with improvement in the patient's low back pain and ability to return to running (Fig. 1) (JR Harrison, RJ Herzog, GE Lutz. Increased nuclear T2 signal intensity following intradiscal platelet rich plasma: a case report, Submitted to PM&R).

The investigators in this randomized control study described their technique for intradiscal PRP injection with 1 to 2 mL of autologous PRP and a double-needle extrapedicular technique, immediately after contrast administration for discography (Box 3). The patient is positioned prone on the fluoroscopy table after receiving 1 g cephazolin at 30 minutes before the procedure. After sterile preparation and local anesthesia, a 25-gauge needle is advanced through a 20-gauge needle introducer into the midportion of the suspected disc levels using anteroposterior and lateral



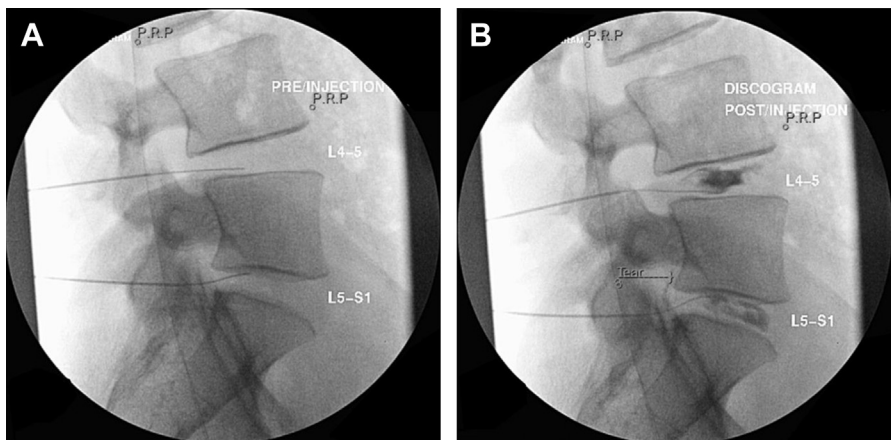
**Fig. 1.** Axial and sagittal MRIs depicting L4–5 and L5–S1 IVDs before (A) and 1 year after (B) intradiscal PRP injection at L5–S1.

**Box 3**  
**Intradiscal PRP injection technique**

1. 1 g intravenous cephazolin 30 minutes before injection
2. Local anesthesia with consideration of intravenous sedation
3. Double-needle technique (20-gauge needle introducer and 25-gauge needle) via extrapedicular technique (Fig. 2)
4. 1 to 2 mL contrast injected intradiscally to confirm concordant low back pain; and contrast filling of annular fissure (<2 mL)
5. PRP 1 to 2 mL injected intradiscally slowly over 2 to 3 minutes

fluoroscopic imaging to confirm proper needle positioning. Thereafter, 1 to 2 mL of contrast agent is injected into the disc and the participant endorses concordant or discordant pain reproduction of low back pain. Only the discs that produce concordant pain and exhibit the contrast filling an annular fissure with incomplete annular disruption (<2 mL) are injected with PRP. No extension tubing is used during the injection. If more than one disc reproduces concordant pain, then the 3 to 4 mL of PRP obtained is divided into each of the affected discs.

Another recent prospective study<sup>27</sup> also found improvement in pain on the visual analog scale (VAS) and function based on the Oswestry Disability Index (ODI) after a single intradiscal PRP injection at one or multiple lumbar spinal discs. The investigators defined a successful outcome as 30% improvement in ODI and 50% improvement in VAS, which was achieved in 47% of patients in their preliminary 6-month results. This study involved 22 patients with discogenic back pain and a pain intensity of at least 40 mm of 100 mm on the VAS. The injected discs were determined either by discography or MRI findings for discogenic low back pain, such as disc HIZ, decreased disc signal on T2 sequence, disc protrusion, or type 1 or 2 endplate Modic changes. The investigators also ruled out other sources of low back pain with facet and sacroiliac joint blocks.



**Fig. 2.** Sagittal fluoroscopic images of a patient undergoing L4–5 and L5–S1 provocative discography before (A) and after injection of contrast at both levels and subsequent injection of PRP at L5–S1 (B).

The investigators of this study used a single-needle technique via a posterolateral extrapedicular approach into the disc nucleus. These investigators also used 1 mL of contrast to ensure intranuclear placement. The main differences in technique in this study compared with the RCT, is that 0.5 mL of 4% lidocaine for anesthesia and gentamicin for discitis prophylaxis were also injected intradisally. Prior studies have indicated that anesthetics and antibiotics can decrease IVD cell synthesis *in vitro*.<sup>28–30</sup> Another limitation of this study is that the subjects paid out of pocket for the procedures, unlike in the RCT, which was completely funded. The study institution's research and education fund paid for the procedure and related fees, whereas the PRP kits were donated by the PRP centrifuge company.<sup>25</sup> Paying out of pocket for the treatment may be a source of bias, because the subjects may have a perceived investment in the treatment.

## STEM CELL TREATMENTS IN THE SPINE

Stem cell treatments offer another promising solution for regenerative treatments in the spine. Autologous sources for stem cell treatments that have been studied in the spine thus far include native disc cells, adipose-derived and bone marrow-derived mesenchymal stem cells.<sup>31</sup> However, it has proven difficult to isolate pure nucleus pulposus cells without fibroblasts and macrophages.<sup>32</sup> Furthermore, the centrifugation process of autologous stem cells derived from bone marrow do not contain a high concentration of pure homogeneous mesenchymal stem cells, as there is also adherence to plastic during the process.<sup>31</sup> Mesenchymal stem cells may serve as the ideal cell source for IVD degeneration, as they can differentiate into nucleus pulposus-like cells and promote extracellular matrix synthesis. Mesenchymal stem cells may also influence nucleus pulposus cell function to secrete anabolic growth factors via paracrine signaling between the native and injected cells.<sup>5</sup>

There is currently ongoing research focusing on the optimum mixture of growth factors needed to stimulate differentiation into nucleus pulposus-like phenotype. Mesenchymal stem cells have been shown to differentiate into IVD-like phenotypes with induction by ascorbate, dexamethasone and transforming growth factor-beta.<sup>33</sup> Bone marrow-derived and adipose-derived mesenchymal stem cells stimulated with growth differentiation factor 6 (GDF6) have demonstrated increased nucleus pulposus marker genes and secrete an extracellular matrix that is more proteoglycan rich with a micromechanical composition most similar to the nucleus pulposus in 3-dimensional culture.<sup>34</sup> Animal models have established that autologous bone marrow mesenchymal cells survive and replicate within 8 to 48 weeks after transplantation.<sup>35</sup> Because mesenchymal cells have a relatively short survival time, a biomaterial scaffold may enhance the differentiation and viability of mesenchymal cells in the desired location (**Box 4**).

### Box 4

#### Beneficial properties of mesenchymal stem cells

- Easy to harvest and culture
- Biocompatible
- Self-renewing
- Can differentiate into nucleus pulposus-like cells
- Enhanced extracellular matrix production
- Secrete anabolic factors

### ***Intradiscal Stem Cell Treatments: In Vivo Studies***

In vivo studies of implanted mesenchymal stem cells have shown enhanced matrix production, predominantly with glycosaminoglycan synthesis, as well as increased disc hydration and disc height. An in vivo model was used to study the differentiation status of mesenchymal stem cells transplanted to the nucleus pulposus of degenerative discs in rabbits.<sup>36</sup> At 48 weeks posttransplantation, significant augmentation of proteoglycan content and cell-associated matrix molecules, like type II collagen, chondroitin sulfate, and nucleus pulposus phenotypic markers, were seen in biochemical and gene expression analyses.

Similarly, an in vivo sheep model showed increased nucleus pulposus proteoglycan synthesis in IVDs injected with mesenchymal progenitor cells combined with pentosane polysulfate and embedded in a gelatin/fibrin scaffold.<sup>37</sup> The sheep in this study underwent standardized microdiscectomy and then the spines underwent MRI, biochemical, and histologic analysis at 6 months postoperatively. Interestingly, the discs with scaffolding and mesenchymal cells had better MRI imaging Pfirrmann scores compared with the discs injected with scaffolding alone.

An in vivo model of mice with severely degenerated discs implanted with adipose-derived stromal cells intradiscally also found positive radiographic findings.<sup>38</sup> At 7 weeks posttreatment, MRI spine imaging displayed increased disc signal intensity in the treated mice compared with the nontreated controls.

### ***Intradiscal Stem Cell Treatments: Clinical Studies***

A prospective, controlled, randomized, multicenter study titled Euro Disc Randomized Trial comparing autologous disc chondrocyte transplantation plus discectomy with discectomy alone has found promising results for autologous intradiscal stem cell treatment.<sup>32,39</sup> This study had a high sample size of 112 patients. Autologous disc chondrocytes were sequestered intraoperatively during the open discectomy. Thereafter, the sequestered disc material was expanded in culture and reinserted into the disc in a fluoroscopically guided procedure after 12 weeks. This study found a clinically significant reduction in low back pain scores, with regard to the Oswestry Low Back Pain Disability Questionnaire, Quebec Back Pain Disability Scale, and VAS at 2 years in the patients who received autologous disc cell transplantation after discectomy compared with those who had discectomy alone. Furthermore, the MRI for the treatment group revealed retained disc hydration when compared with the adjacent levels that had undergone discectomy without autologous disc chondrocyte transplantation. Specifically, the treatment group had 41% normal fluid content, whereas the discectomy alone group had only 25% normal fluid content. However, MRI found no significant differences in the mean IVD heights between the 2 groups.

Allogeneic mesenchymal stem cells, cultured from other patients, also have been studied. Intradiscal allogeneic mesenchymal stem cells are currently being explored in a phase 2, randomized controlled study.<sup>40</sup> Single-level mildly degenerated lumbar IVDs were selected. Preliminary data show that a greater number of patients treated with intradiscal mesenchymal stem cells reported greater than or equal to 50% reduction in low back pain compared with controls at 12 months after injection. Specifically, of the patients treated with intradiscal mesenchymal stem cells, 69% reported this successful outcome, compared with only 33% of control patients.

## **INTRADISCAL FIBRIN INJECTIONS**

Intradiscal fibrin injections have the potential to ameliorate several concerns hindering successful treatment of degenerated and injured IVDs. Intradiscal fibrin injection



targeted at injured annulus fibrosis benefits in treating IVD-related symptoms assuming 1 or all of the following 3 premises are true: (1) tears within the annulus fibrosis initiate the inflammatory and autoimmune cascade, (2) autologous nucleus pulposus instigates radiculopathy and radiculitis through its contact with adjacent descending spinal nerves, and (3) intradiscal injections of mesenchymal stem cells and PRP may possess the ability to improve disc pathology, yet their efficacy may be hindered by their leakage from targeted IVDs through annulus fibrosis tears. If these premises are true, sealing IVD tears may alleviate symptoms of internal disc disruption, and radiculopathy.

Injected fibrin sealant serves to occupy rents within tears of the lamella of the torn annulus fibrosis, thus functioning as a physical barrier between inflammatory constituents and the disc's nociceptors. Furthermore, fibrin sealant functions as a barrier, potentially limiting outflow of nucleus pulposus and associated inflammatory constituents onto dura, meninges, and descending spinal nerves. Logic dictates benefit would be derived from sealing fissures within the annulus fibrosis, thus stopping the outflow of IVD contents. More specifically, inflammatory components form when centrally located nucleus pulposus flows through tears of the annulus fibrosis. This instigates the expression of interleukins, cytokines, and other inflammatory and autoimmune cascade constituents.<sup>41,42</sup> Additionally, flow or extravasation of nucleus pulposus outside the torn annulus fibrosis causes injury to the adjacent descending spinal nerves,<sup>6,43–47</sup> and these inflammatory components on the spinal nerve affect structures as distant as the thalamus.<sup>48</sup> In addition to IVD disruption causing axial and extremity symptoms, through both inflammatory and autoimmune constituents stimulating annular nociceptors within the disc, and through leakage outside the disc (“leaky disc syndrome”), respectively, another potentially problematic issue results with treatment using intradiscal biologics such as mesenchymal stem cells and PRP. There exists potential for diminished efficacy and iatrogenic tissue growth caused by leakage of the injected biologics meant to repair the damaged disc. One investigation injected radiolabeled bone marrow mesenchymal stem cells into rabbit degenerated IVDs with the objectives of determining their effect and fate. Outcomes at 9 weeks following injection of radiolabeled mesenchymal stem cells into the disc's nucleus pulposus revealed no radiolabeled mesenchymal stem cells within the disc. More disconcerting, however, was visual and radiographic observation of new, large anterolateral osteophytes, and these osteophytes contained the radiolabeled mesenchymal stem cells.<sup>49</sup>

Fibrin may be the ideal biomaterial scaffold to enhance the differentiation and viability of mesenchymal cells in IVDs. Fibrin has been studied as a scaffold for repair of degenerated IVDs. Fibrin can act as a space filler of disc defects, retaining cells and facilitating cell growth and formation of new tissue.<sup>50</sup> Fibrin is a biocompatible composite hydrogel of fibrinogen and thrombin that acts as a hemostatic agent, sealant, and cell carrier.<sup>51</sup> Fibrin facilitates cell attachment because of its numerous binding sites for integrins.<sup>51</sup>

### ***Intradiscal Fibrin: Translational Studies***

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In vitro and in vivo studies on intradiscal fibrin have displayed the many valuable characteristics of fibrin. Fibrin is easily modifiable to take on the ideal characteristics of disc cells and act as a potential adhesive for annulus repair. An in vitro study has found that fibrin gels composed of 250 mg/mL of fibrin and 0.25:1 or 0.5:1 genipin:fibrin showed a shear behavior similar to native annulus fibrosus.<sup>52</sup> Fibrin also may play an anti-inflammatory and anticatabolic role. An vitro study of fibrin embedded with human and porcine annulus fibrosus cells cultured in type I collagen beads and

stimulated with IL-1 alpha demonstrated increased synthesis of anti-inflammatory cytokine IL-455. Meanwhile, fibrin embedded with human and porcine nucleus pulposus cells resulted in reduced secretion of proinflammatory cytokines.<sup>53</sup> Similarly, intradiscal fibrin prevented disc degeneration and stimulated proteoglycan content recovery in denucleated IVDs in a minipig model.<sup>54</sup> In a randomized, controlled investigation, approximately 120 porcine discs were treated with either normal saline or concentrated fibrin with aprotinin. In one investigation, statistical significance was demonstrated in all categories comparing fibrin treatment with normal saline. Intradiscal fibrin versus normal saline was demonstrated superior in all categories, including morphologic and histologic growth, proteoglycan composition, cytokine content, and mechanical properties with pressure and volume testing (**Box 5**).<sup>54</sup>

### ***Intradiscal Fibrin Injections: Clinical Studies***

Intradiscal fibrin has been effectively used as a sealant in a prospective study on patients with chronic lumbar pain.<sup>55</sup> Fibrin is a drug approved by the Food and Drug Administration (FDA), and at the time of this writing, its intradiscal injection is an off-label use of an FDA-approved drug.

Prior human cadaveric studies confirmed that the intradiscal flow patterns of fibrin sealant into annular fissures closely approximate the distribution of intradiscal contrast. Fifteen adults with chronic discogenic pain at a single or contiguous 2 lumbar disc levels were included and confirmed via provocation discography. The volume and pressure-controlled Biostat Delivery Device system (BIOSTAT BIOLOGIX, Spinal Restoration Inc., Austin, Texas) was used to percutaneously deliver 1.0 to 4.0 mL of Biostat Biologix fibrin sealant into the selected IVDs. The injector stopped injecting when the sustained delivery pressure reached or exceeded 100 psi, the minimum pressure found to cause annular rupture based on biomechanical studies.<sup>56</sup>

There was clinically significant pain relief and function in a high percentage of patients at 26 weeks. Clinically significant pain relief, defined as at least 30% reduction in low back pain VAS, was achieved in 87% of subjects at 26 weeks postinjection. Clinically significant improvements in function, defined as at least 30% reduction in Roland-Morris Disability Questionnaire score, was achieved in 73% of subjects at 26 weeks postinjection. This improvement was sustained at 52 weeks in 73% of subjects and slightly decreased to 60% of subjects at 104 weeks. With regard to global improvement in low back pain, 85% of subjects responded that their pain was better or much better compared with baseline at 52 weeks, and 54.5% of subjects at 104 weeks. However, long-term conclusions were confounded by the loss of subjects at extended follow-up (2 at 52 weeks and 4 subjects at 104 weeks). Furthermore, there

#### **Box 5**

#### **Beneficial properties of fibrin**

- Biocompatible
- Hemostatic
- Space filler and sealant
- Cell carrier
- Numerous binding sites for integrins
- Anticatabolic: reduced secretion of proinflammatory cytokines
- Anti-inflammatory: increased synthesis of interleukin-4

were 3 adverse events during the study, including a case of discitis and 2 cases of lumbar muscle spasms within 1 week after treatment.

Fibrin has been safely used as a scaffold for allogeneic cells in an intradiscal clinical trial. A prospective study on allogeneic juvenile chondrocyte cells injected intradiscally with commercial fibrin under fluoroscopic guidance has demonstrated improved functional outcome scores as well as improvements on MRI.<sup>57</sup> Fifteen patients received a single percutaneous intradiscal injection of 1 to 2 mL of juvenile chondrocytes with approximately  $10^7$  chondrocyte cells/mL with fibrin carrier. Single-level L3–S1 degenerated discs with Pfirrmann Grades III–IV were selected for injection. At 12 months postinjection, patients had significant improvement in ODI, NRS, and SF-36. At the 6-month follow-up, 10 of 13 patients who had an MRI showed improvements, with 3 showing improved disc contour or height, and 89% had improved or resolved HIZs. No adverse events like discitis or neurologic deterioration occurred during the study.

### FUTURE CONSIDERATIONS

Further research is needed to better determine which patients are the ideal candidates for regenerative treatments, the ideal number of treatments, single-level versus multiple-level intradiscal injections, and to elucidate the ideal injectate (PRP or mesenchymal stem cells) with or without scaffolding like fibrin to provide the best environment for cell growth. Perhaps there are certain biomarkers or MRI variations that could serve as prognostic indicators for ideal candidates for these treatments. The exact number and frequency of intradiscal injections have yet to be confirmed in literature. Furthermore, single-level versus multilevel intradiscal injections have not yet been compared in clinical studies. Upcoming clinical trials should focus on verifying the optimal PRP concentration and composition that promotes IVD regeneration. Both intradiscal PRP studies presented in this article used a centrifuge that concentrates platelets to 5 times the concentration in whole blood. Yet there are many other centrifuge systems that can concentrate the platelets to 8 to 10 times that of whole blood, and thus result in higher levels of growth factors, and perhaps also improved regenerative ability. Based on the studies presented previously, perhaps a combination of PRP and mesenchymal stem cells and the use of fibrin:genipin gels as a scaffold will result in the most favorable injectate.

Current intradiscal therapies have focused on targeting the nucleus pulposus. Perhaps injecting the annulus fibrosus in addition to the nucleus pulposus may also reveal additional benefits. There may also be a role for injectable regenerative therapies to augment surgical treatments at the time of intervention and serve as a protective tool against post-procedural IVD degeneration. In fact, the Euro Disc Randomized Trial described previously supports that autologous disc cell transplantation resulted in greater pain reduction and improved disc fluid content on MRI after discectomy.<sup>39</sup>

### SUMMARY

Low back pain is a universal and disabling chronic condition that has significantly contributed to rising health care costs. IVD degeneration is the leading cause of back pain and is also often the precursor to the degenerative cascade of facet arthropathy, spinal deformity, and stenosis. Treatments targeting the painful annular fissures early on may also help prevent progression of spinal deformity and disability. Interventions that hinder ongoing cell degradation or that supplement anabolic cell production are necessary cost-effective treatments for low back pain, as the current epidural injection options offer only transient relief and current surgical options cost exorbitantly

more. Surgeries themselves may contribute to adjacent-level degeneration, as seen in spinal fusions.<sup>58</sup> Regenerative treatments may also offer a great solution for those refractory to pain management and injections and those who prefer to avoid surgery. The existing translational and clinical studies presented in this article provide supportive evidence for regenerative treatments for discogenic pain, including intradiscal PRP, mesenchymal stem cell, and fibrin treatments. These studies are paving the way to the future of spine medicine, which is shifting toward regenerative biologic treatments and away from spinal fusion surgeries for discogenic low back pain.

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