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Intervertebral disc degeneration and regeneration: a motion segment perspective

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Abstract

Back and neck pain have become a primary cause of disability and healthcare spending globally. While the causes of back pain are multifactorial, intervertebral disc degeneration is frequently cited as a primary source of pain, and the annulus fibrosus (AF) and nucleus pulposus (NP) subcomponents of the disc are common targets for regenerative therapeutics. However, disc degeneration is also associated with degenerative changes to adjacent spinal tissues, and successful regenerative therapies will likely need to consider and address the pathology of adjacent spinal structures beyond solely the disc subcomponents. This review summarizes the current state of knowledge in the field regarding associations between back pain, disc degeneration, and degeneration of the cartilaginous and boney endplates, the AF-vertebral body interface, the facet joints and spinal muscles, in addition to a discussion of regenerative strategies for treating pain and degeneration from a whole motion segment perspective.

Keywords

nucleus pulposus; annulus fibrosus; cartilage endplate; interface; facet; spinal muscle; tissue engineering; physical therapy

Introduction

Low back pain is the most common cause of disability globally, and in the United States is the number one condition contributing to healthcare spending, totaling $134.5 billion in 2016 alone.(Dieleman et al., 2020) While the causes of back pain are complex and often include psychosocial factors, the anatomic structures within the spine are likely direct contributors to pain. The basic unit of the spine is the motion segment (Figure 1), which

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consists of the intervertebral disc and adjacent cartilaginous endplates and boney vertebral bodies anteriorly, the neural structures including the spinal cord, cauda equina and nerve roots posteriorly, surrounded by the paraspinal muscles and boney elements including the facet joints.(Raj, 2008) The intervertebral disc is composed of a central water- and proteoglycan-rich nucleus pulposus (NP), encompassed circumferentially by the annulus fibrosus (AF), which consists of primarily collagen type I fibers oriented at approximately ±30° to the long axis of the spine in alternating lamellae.(Humzah and Soames, 1988) Degeneration of the intervertebral disc is commonly associated with back pain, and is characterized by a cascade of cellular, structural, compositional and mechanical alterations to the AF and NP tissues.(American Academy of Orthopaedic Surgeons, 2008; Haefeli et al., 2006) However, degeneration of the disc is associated with, and potentially precipitated by, degenerative changes across the whole motion segment, and not solely the result of changes in the disc itself. This “whole motion segment” view of disc degeneration is less frequently studied compared to changes to the NP and AF alone. Understanding the cross-talk between spinal tissues during degeneration will not only advance our knowledge of disease pathogenesis, but may also aid in developing new and more efficacious treatments for disc degeneration and back pain. This review will detail what is known regarding structure-function alterations across the whole motion segment with degeneration, with a focus on the intervertebral disc interfaces with the vertebral body. We will also summarize known associations between degeneration of non-disc structures (facet joints, muscle, vertebral bone) and disc degeneration and back pain, in addition to reviewing potential therapeutic strategies that treat degeneration from a whole motion segment perspective.

Vertebral Bodies and Boney Endplate

The vertebral bodies of the spine consist of highly porous trabecular bone surrounded by a thin cortical shell. Adjacent to the disc, this cortical shell is referred to as the boney endplate, which ranges in thickness for 0.4 to 0.9 mm.(Thomas Edwards et al.,2001) The thickness of the boney endplate is greatest in the lumbar vertebra, with the anterior shell thickness greater than the posterior shell thickness in both endplates cranial and caudal to the disc. (Thomas Edwards et al.,2001) The boney endplate is thinnest and most porous in the central region of the vertebra adjacent to the NP.(Thomas Edwards et al.,2001; Zehra et al., 2015) The caudal boney endplate has significantly more marrow contact pores than the cranial endplate.(Martins et al., 2018)

The intervertebral discs are the largest avascular structures in the body, and thus cells within the disc rely on the vessels and marrow channels within the vertebral body as their primary source of nutrients. The blood supply to the vertebral body arises from pairs of segmental arteries, which branch from the aorta (Figure 2A).(Crock and Yoshizawa, 1976) Ten to twenty periosteal arteries branch off of the segmental arteries and traverse the surface of each vertebral body. The periosteal arteries give rise to several intra-osseous arteries, which form anastomoses and supply the center of the vertebral body. The intra-osseous arteries extend additional anastomoses and form continuous capillary networks at both the inferior and superior ends of the subchondral bone of the vertebral body. At the boney endplate-disc junction, the capillaries form microvascular loops termed vascular buds (Figure 2B–C).(Oki et al., 1996) The density of the vascular buds is greatest at the central region of the vertebral

body, adjacent to the NP. In order to reach the cells at the center of the disc, nutrients diffuse from the vascular buds, across the cartilage endplate, and then into the disc itself. Smaller solutes, including glucose, lactate, sulfate and oxygen, were classically thought to rely on diffusion, whereas larger solutes rely on convection for transport.(Katz et al., 1986; Maroudas et al., 1975a; Urban et al., 1982) However, recent work has demonstrated that convective fluid flow can also impact the transport of small molecules into the disc. (Gullbrand et al., 2015a; Sampson et al., 2019) The vessels within the vertebral body are frequently accompanied by nerves adjacent to the vessel wall, with the highest density of nerves in the central vertebral body and a decreasing frequency towards the boney endplate. (Bailey et al., 2011)

So-called “double endplate” structures are observed in the lower thoracic and lumbar spines.(Fields et al., 2012; Thomas Edwards et al.,2001) These structures have a thinner superficial layer without compromising the biomechanical function of the endplate region, and so this feature may be an adaptation to increase nutrient availability to the avascular disc and protect against disc degeneration. Discs with double endplates have higher glycosaminoglycan (GAG) content than discs with single layer endplates, after adjusting for age.(Fields et al., 2012) Furthermore, the structural and mechanical properties of the boney endplate may be dictated by mechanical loading from the hydrostatic pressure of the adjacent NP. Studies have demonstrated a positive linear correlation between disc fixed charge density and the stiffness of the adjacent vertebral bone, and an inverse relationship between intradiscal pressure and endplate porosity.(Keller et al., 1993; Zehra et al., 2015)

Many studies have examined associations between disc degeneration and remodeling of the boney endplate and vertebral bone, however, much of this evidence is conflicting – with some studies suggesting sclerotic thickening and others suggesting thinning. For example, the boney endplate is noted to be thinner and more porous with increasing age and degeneration, in studies of human cadaveric tissues.(Rodriguez et al., 2012; Wang et al., 2011) In a cross-sectional study of human patients, a loss of bone in the central region of the boney endplate adjacent to the disc was associated with increased odds for disc height loss, however, severe disc height loss was significantly associated with increases in the bone mineral density of the superior and anterior regions.(Kaiser et al., 2018) This study also found that bone mineral density declines in the L3 vertebral body more quickly in women than men, pointing to a confounding factor of sex in studying the association of boney changes with disc degeneration. The findings from this work parallel the results from large cohort studies, which reported that disc degeneration is positively correlated with bone mineral density of the lumbar spine in female patients (Livshits et al., 2010), and inversely associated with osteoporosis (Pye, 2006). However, the relationship between vertebral bone changes and disc degeneration is likely complex and multifactorial, as mouse ovariectomy models provide evidence that osteoporosis may be associated with *increased* disc degeneration.(Xiao et al., 2018)

In contrast, boney endplate remodeling has been reported in human cadaveric samples with mild degeneration (Thompson Grade II). In this scenario, increases in bone volume and trabecular thickness were reported in the endplate with increasing degeneration, after adjusting for age, with these changes occurring primarily in the anterior regions.(Rutges

et al., 2011; Simpson et al., 2001) In a cohort of samples from only male donors, disc degeneration (as measured by discography) was associated with greater endplate thickness but not higher bone mineral density.(Wang et al., 2011) Occlusion of the boney endplate marrow and vascular channels also significantly correlated with disc degeneration assessed morphologically and biochemically.(Benneker et al., 2005) Furthermore, the maximum percentage of gadolinium enhancement on MRI in the vertebral bone marrow is reduced with increasing age, suggesting that the vascular network within the vertebral body is compromised during aging.(Montazel et al., 2003) Since the endplate route is considered the predominant route for nutrient and waste product transport into the vertebral body, a compromise of this nutritional pathway has long been hypothesized as a causative factor in disc degeneration.(Maroudas et al., 1975b; Nachemson et al., 1970; Urban et al., 1977)

Several animal models of disc degeneration also support the role of endplate remodeling and reduced disc nutrition in the degenerative cascade. The sand rat develops spontaneous disc degeneration, which is significantly associated with increases in endplate bone mineral denisty.(Gruber et al., 2007; Gruber et al., 2008) In a rabbit annular puncture model, significant increases in bone volume fraction occur in the 12 weeks following needle puncture, and these changes were associated with reductions in endplate vascularity and small molecule transport into the degenerative disc.(Ashinsky et al., 2020) Similar increases in endplate trabecular bone volume were observed in a sheep annular injury model, though this occurred at much longer time points (2 years).(Moore et al., 1996) Studies in aging mice also demonstrated that endplate porosity is reduced with increasing age, and coincided with disc height loss.(Cao et al., 2017) Notably, studies across multiple species demonstrated that the surgical or chemical disruption of the vessels of the vertebral endplate could instigate degenerative changes to the disc assessed histologically,(Feng et al., 2018; Imanishi et al., 2019; Kang et al., 2014; Yin et al., 2019) providing some mechanistic support for this hypothesis.

While alterations to the thickness and density of the boney endplate with degeneration remain unclear, changes within the vertebral body bone marrow and endplate defects have been consistently reported to associate with both disc degeneration and back pain. In particular, the size of endplate defects correlates with the severity of disc degeneration and with worsening disability due to back pain as measured by the Oswestry Disability Index (ODI). In a longitudinal study of human patients, endplates with defects or erosions spanning at least 25% of the endplate area were associated with a greater risk of progression of degeneration, and levels with progression of bone marrow changes were significantly associated with advanced grades of disc degeneration.(Farshad-Amacker et al., 2017) These bone marrow changes, termed Modic changes, are bone marrow and endplate lesions visible via signal intensity changes in these regions on T2 and T1 weighted MRIs.(Zhang et al., 2008) The presence of Modic changes is frequently associated with the presence of back pain.(Herlin et al., 2018) Studies of biopsy samples taken during fusion procedures suggest a fibrogenic and pro-inflammatory cross-talk between the disc and bone at levels showing Modic changes, with significant correlations between gene expression in the marrow and the adjacent discs.(Dudli et al., 2017) Increased expression of pro-inflammatory cytokines has also been observed in discs adjacent to endplates with Modic changes.(Schroeder et al., 2017) Additionally, the MRI T2 relaxation time of the vertebral bodies has been found to

be significantly higher in back pain patients compared to asymptomatic controls, adjusted for the presence of Modic changes and Pfirrmann grade, which may further point to early inflammatory processes.(Lagerstrand et al., 2019)

Nucleus Pulposus-Cartilage Endplate-Boney Endplate Interface

Adjacent to the vascular buds in the vertebral endplate and immediately bordering the NP, is the cartilaginous endplate (CEP). The CEP is a thin layer (0.6-1.2mm thick) of hyaline-like cartilage whose collagen fibers run horizontally with respect to the spine axis, extending across the width to the inner AF.(Roberts et al., 1989) The CEP is thinnest and most porous at the center region immediately adjacent to the NP.(Wu et al., 2016) Fibers within the NP orient themselves perpendicular and attach to the CEP via so-called ‘nodal insertions’. (Brown et al., 2017; Wade et al., 2011)

The CEP also functions as a mechanical interface between the disc and the vertebral body, transmitting multiaxial forces between the two tissues. The CEP uniformly distributes the high intradiscal pressures generated from the NP over the surface of the vertebrae, preventing the highly pressurized NP from locally bulging into the underlying trabeculae. (Brinckmann et al., 1983; Rolander and Blair, 1975) Therefore, the inherent structure and composition of the endplate play important roles in biomechanical function, where thick and dense endplates are stronger than thin and porous endplates.(Langrana et al., 2006; Zhao et al., 2009) The CEP is composed primarily of type II collagen, proteoglycans and water. (Berg-Johansen et al., 2018; Fields et al., 2014b; Fields et al., 2015; Roberts et al., 1989; Roberts et al., 1991) There is a gradient in composition through the depth of the endplate, where proteoglycan and water content decrease and collagen content increases towards the vertebral bone. There is also compositional variation in the lateral plane, where the CEP adjacent to the inner AF has higher collagen and lower proteoglycan and water content than the region adjacent to the NP.(Roberts et al., 1989)

With aging and degeneration, the CEP undergoes several compositional changes that could reduce permeability and limit nutrient transport (Figure 3). Specifically, Grant et al. measured higher calcium content in CEPs adjacent to more severely degenerated human discs, and increasing levels of calcium diminished collagen and proteoglycan synthesis in cultured human CEP cells, via the activation of the extracellular calcium-sensing receptor.(Grant et al., 2016) Calcium also enhances the cleavage of aggrecan by ADAMTS5, suggesting that higher calcium levels may promote CEP degeneration by increasing the activity of this aggrecanase. These findings are important since increased calcification and decreased proteoglycan content adversely impact tissue hydration and may therefore impede solute diffusion. Furthermore, recent advances in MRI, such as T2* relaxation time mapping, have facilitated the non-invasive visualization of CEP hydration and collagen/GAG ratios.(Fields et al., 2015) A recent study using live human patients and cadaveric spines suggested that CEP T2* values were associated with more severe disc degeneration, but only in younger individuals (<50 years old), further suggesting a link between CEP composition and disc degeneration.(Wang et al.,2020)

The permeability of the CEP is at least an order of magnitude lower than the bony endplate permeability(DeLucca et al., 2016; Rodriguez et al., 2011), which may suggest that solutes' ability to diffuse through the CEP is the primary factor that dictates the amount of nutrients and metabolites entering and exiting the disc. Calcification and dehydration of the CEP matrix, associated with degeneration, also can influence transport properties. Recently, Wong et al. showed that CEPs with poor diffusion have compositional deficits that block solute passage, such as increased amounts of collagen, aggrecan, and mineral, and lower cross-link maturity.(Wong et al., 2019) Further, these deficits to CEP transport had a negative effect on NP cell viability.

As with other cartilaginous tissues, the biochemical composition of the CEP dictates its mechanical properties. Endplate collagen content and collagen/GAG ratios significantly influence tensile properties of the CEP.(Fields et al., 2014b) As noted above, CEP fibers are organized parallel to the vertebral body and NP, and finite element modeling indicated high shear deformation of the CEP, which was attributed to significant lateral expansion of the NP.(DeLucca et al., 2016) As such, Since the CEP is poorly integrated with the vertebral body(Brown et al., 2017), the CEP can become stripped off or avulse from the underlying trabecular bone at relatively low tensile loads.(Berg-Johansen et al., 2017; Berg-johansen et al., 2018) Additionally, the CEP and boney endplate interface lacks structural integrity, and the degree of detachment between the two structures has been shown to positively correlate with disc degeneration.(Brown et al., 2017) This may suggest that detachment of the CEP from the boney endplate not only destabilizes the motion segment at this local interface, but also may alter the mechanobiology within the disc, potentially further contributing to the degenerative cascade.

Annulus Fibrosus-Endplate Interface

The collagen fibers of the inner AF are continuous with the collagen fibers of the cartilaginous endplate.(Berg-Johansen et al., 2017) Fibers of the inner AF insert directly into the CEP and then into the bone for anchorage.(Nosikova et al., 2012; Rodrigues et al., 2015) The strength and the loading rate of the interface between the inner AF and cartilaginous endplate influences the failure strength and location. Under slow loading rates, there is localized stretching of the AF (Veres et al., 2010), but when the disc is loaded rapidly, the AF fibers have little time to recruit and realign. This results in annular displacements across the entire disc, particularly at the AF-CEP junction. At the outer AF, the vertebral interface is formed by an enthesis, where the AF collagen fibers pass through a hyaline-like cartilage and then embed into a zone of calcified cartilage that is anchored to the subchondral bone.(Nosikova et al., 2012) This complex interdigitation serves to minimize the stress concentrations during complex loading in tension, compression and shear.(Berg-Johansen et al., 2017) At the outermost AF, some of the collagen fibers from the lamella curve laterally to the outer aspect of the bone and merge directly with the periosteum of the vertebral body.(Nosikova et al., 2012)

With injury, age, or degeneration, the interface between the outer AF and the calcified cartilage layer of the endplate can separate, a condition termed a "tidemark avulsion".(Berg-johansen et al., 2018) This interface is significant, as there are marrow changes and increases

in innervation of the vertebral bone adjacent to the avulsion (Fields et al., 2014a), which may contribute to the clinical symptoms of painful disc degeneration. The mechanism of tidemark avulsions is unclear, however. One biomechanical study of ex vivo bovine tissues reported that motion segments were more likely to exhibit tidemark avulsions in axial tension than in torsion(Rodrigues et al., 2015), suggesting that this failure may occur during bending when the AF is under tension. Another recent study evaluating endplate remodeling during degeneration in a rabbit model found that the endplate-AF interface undergoes progressive microscale stiffening, over time following AF puncture, as measured by atomic force microscopy (Ashinsky et al., 2020). This stiffening was accompanied by a substantial increase in organized collagen deposition along the interface over time following injury. Our preliminary studies suggest similar remodeling also occurs with human disc degeneration (Figure 3). While the results from these animal studies shed important light on the structural and functional alterations to the endplate-AF interface following a laboratory-controlled injury, there is sparse literature evaluating this region during human idiopathic degeneration.

Facet Joints and Spinal Muscles

The diarthrodial zygapophysial joints, or the facet joints, are located posterior to the vertebral bodies, intervertebral disc and spinal nerves, and play a critical role in constraining spinal range of motion while aiding in the transmission of loads.(O'Leary et al., 2018) In 1982, Kirkaldy-Willis described the concept of spinal degeneration in the context of instability, postulating a relationship between intervertebral disc and facet joint degeneration.(Kirkaldy-Willis and Farfan, 1982) Facet OA is typically characterized by joint space narrowing, cartilage thinning and fissuring, subchondral sclerosis and osteophyte formation.(Li et al., 2011; O'Leary et al., 2018) Correlations have been established between disc degeneration and facet osteoarthritis (OA), in addition to facet OA and endplate Modic changes.(Li et al., 2011; Netzer et al., 2018; Paholpak et al., 2018; Suri et al., 2011) Facet and disc degeneration have also been positively correlated with instability of the spine during flexion extension movements, usually via increased anterior translation.(Fujiwara et al., 2000; Kitanaka et al., 2018; Paholpak et al., 2018) As the facet joint synovial membrane is highly innervated, this instability has been postulated to contribute to spinal pain, however, the relationship between facet degeneration and back pain remains unclear. Although facet OA increases with increasing age and occurs at an high prevalence (60% in men, 67% in women), no differences were found in the prevalence of facet OA in individuals with and without back pain.(Kalichman et al., 2008) However, analysis of facet tissues from patients undergoing spinal fusion for back pain demonstrated significant increases in neovascularization, neurogenesis and pro-inflammatory cytokine expression, compared to facets from healthy donor tissue.(Kim et al., 2015) Significant increases in mRNA and protein levels for inflammatory pain mediators (iNOS and COX-2) and neuromodulators (CGRP, NGF, TrkA) were also observed, and this may prompt DRG neurons to increase pain sensitization.(Kim et al., 2015)

While disc degeneration and facet degeneration are correlated, the chronological relationship between two remains unclear. In a study of human skeletal remains, a higher prevalence of facet osteophytes was noted compared to vertebral rim osteophytes at certain levels of the lumbar spine in individuals under the age of 40, suggesting that facet degeneration may

precede disc degeneration.(Eubanks et al., 2007) Studies of cadaveric tissue supported this hypothesis, with relatively healthy discs frequently exhibiting signs of facet degeneration involving fissuring of the cartilage surface.(Li et al., 2011) However, a cross-section study of human patients concluded that, for the majority of individuals, degeneration begins anteriorly (in the disc), though a small subset of the study population (10-20%) do exhibit significant facet OA without disc degeneration.(Suri et al., 2011) Indeed, in our own studies in human cadaveric specimens, we observed facets adjacent to a Pfirrmann grade 5 disc with minimal obvious boney remodeling, and facets adjacent to a Pfirrmann grade 3 disc demonstrating substantial osteophyte formation (Figure 4). Many of the studies on facet OA and disc degeneration summarized here are cross sectional in nature, making it difficult to draw cause and effect conclusions. While many studies are performed in vivo in human patients, this limits analysis to semi-quantitative scoring of degeneration based on MRI or CT images. Future longitudinal in vivo studies are clearly needed, in addition to more comprehensive structure-function analyses of human cadaveric tissues.

Associations between facet OA, disc degeneration and the structure and function of the trunk musculature have also been explored. In a cohort of patients with low back pain, patients with facet OA had a higher paraspinal muscle fat index compared to patients without facet OA, independent of age, body mass index and sex.(Yu et al., 2017) Increasing disc degeneration is also associated with a larger fat signal fraction within the paraspinal muscles.(Faur et al., 2019; Teichtahl et al., 2016; Urrutia et al., 2018) Recent work has also found an increase in the number of fibro-adipogenic progenitors (FAPs), accompanied by increased expression of adipogenic genes and α smooth muscle actin in multifidus muscle samples from patients undergoing surgery for disc herniation, compared to control hamstring muscle from patients undergoing anterior cruciate ligament reconstruction.(Agha et al., 2020) Back pain is consistently correlated with reduced paraspinal muscle and psoas muscle cross sectional areas, and reduced isometric strength of the trunk muscles compared to asymptomatic individuals.(Danneels et al., 2000; Hides et al., 2008; Parkkola et al., 1993; Ploumis et al., 2011) On histology, marked degeneration of the multifidus muscle has been observed in biopsies from patients undergoing surgical treatment for back pain, with multifidus tissue from patients with acute back pain having an increased number of PDFGRβ-positive cells and leukocytes compared to tissue from patients with chronic back pain.(Shahidi et al., 2020) These findings are paralleled in disc injury models of degeneration across several species, where atrophy of the paraspinal muscles has been observed concomitant with the progression of disc degeneration, in addition to increased stiffness of the multifidus muscle.(Brown et al., 2011; Hodges et al., 2006; Maas et al., 2018) Furthermore, damage to the cartilage endplate at the L4-L5 level is predictive of chronic low back pain when adjacent to paraspinal muscles with high fat fractions, further highlighting the interrelationships across spinal structures.(Bailey et al., 2019)

Strategies for Regeneration from a Whole Motion Segment Perspective

To date, the majority of efforts to address disc degeneration have focused on regenerative strategies for the NP and AF in isolation. Strategies for NP repair have focused largely on cell, growth factor, and hydrogel delivery, as reviewed recently by Tang et al (Tang et al., 2020) and Tandulkar et al (Tendulkar et al., 2019). Strategies for AF repair encompass

scaffolds or adhesives designed for herniation repair. (Peredo et al., 2020; Sloan et al., 2017) However, as summarized above, intervertebral disc degeneration comprises a wide variety of pathologic changes to the adjacent disc interfaces, vertebral bone, facet joints and muscles, any number of which may contribute to back pain, and all of which impact one another. In the sections below, we will focus on first reviewing cell-free regenerative approaches which may have the potential to impact all spinal tissues (i.e. physical therapy/anabolic mechanical loading). We then discuss cell-mediated regenerative approaches that harness vertebral bone-disc cross talk (i.e. cell homing), and those which aim to tissue engineer whole motion segment replacements (AF, NP and interface/VB components). Ultimately, regenerative approaches that consider and address these concomitant changes may prove to be more efficacious than strategies that only seek to address a deficit and promote regeneration in only a single tissue within the spine.

Cell-Free Approaches: Physical Therapy & Anabolic Loading

Conservative therapy, including exercise and physical therapy regimens, is the first line of treatment for patients presenting to physicians with low back pain. Physical therapy regimens can be clinically effective in managing back pain in some patients, particularly patient-specific programs delivered in a supervised manner.(Hayden et al., 2005) Despite this, the biologic effects of exercise and physical therapy on the spinal substructures remains understudied, particularly in human subjects.

Physical therapy and exercise subject the spine to cyclic mechanical loading. The effects of mechanical loading on the disc (AF and NP tissues) has been well characterized in vitro, ex vivo, and in vivo in live animal models. In vitro studies have shown that moderate cyclic loading has an anabolic effect on disc cells, whereas static super-physiological loading exhibits catabolic effects. High tensile strain applied to human disc cells in vitro has been shown to drive the cytokine and inflammatory responses associated with disc degeneration, as well as the neurotrophic factors associated with neoinnervation in low back pain. (Gawri et al., 2014b) The effects of mechanical load on cell viability and extracellular matrix synthesis has been evaluated in several organ culture models; Illien-Junger et al (Illien-Jünger et al., 2010) reported that high-frequency loading and limited glucose availability results in upregulation of MMP13 gene expression and reduced cell viability in ex vivo ovine discs, without compensatory changes to GAG synthesis. However, organ culture models have also shown that *physiologic* dynamic loading can promote type II collagen and aggrecan synthesis in chemically degraded bovine discs(Gawri et al., 2014a), and preserve cell viability and mechanical properties in healthy goat discs (Paul et al., 2012). This effect translates to the in vivo setting, where dynamic loading at physiologic rates and magnitudes enhances anabolic remodeling of the disc, primarily via increased proteoglycan production. (Korecki et al., 2008; MacLean et al., 2003; Walsh and Lotz, 2004; Wuertz et al., 2009) Distraction of the disc can mitigate degenerative changes induced by static compression in mice and rabbits(Kroeber et al., 2005; Lotz et al., 2008), indicating that tension may protect collagen from enzymatic degradation(Nabeshima et al., 1996). Running exercise in both healthy and degenerative rat discs increases cell proliferation in the stem cell niche consisting of the perichondrium of the vertebral body adjacent to the disc, and attenuates disc degeneration-associated mechanical allodynia.(Luan et al., 2015; Sasaki et al., 2012)

However, as disc degeneration is usually induced via artificial means (i.e. needle puncture or chronic static compression) in animal models, further study of the effects of anabolic loading in human subjects will be necessary. In a cross-sectional study in middle aged men, long-term runners had greater disc height and lower disc Pfirrmann grade compared to age-matched non-physically active controls, although no differences in T2 relaxation times in the disc were found between groups, indicating similar levels of disc hydration.(Mitchell et al., 2020)

In the disc, physical therapy regimens may also elicit a regenerative effect via the enhancement of convective fluid flow. In an in vivo rabbit model, low-rate dynamic loading increased the uptake and clearance of a small molecule MRI contrast agent in both healthy and degenerative discs. This suggests that cyclic compression and distraction of the disc may benefit disc cell viability via increasing nutrient transport.(Gullbrand et al., 2015b) In a different study, Guehring et al. showed that daily distraction of rabbit discs can rehydrate the NP and upregulate gene expression of collagens and proteoglycans.(Guehring et al., 2006) Additionally, Holm and Nachemson found that nutrient transport was increased during long term exercise and decreased following motion segment fusion in canines.(Holm and Nachemson, 1982) In humans, a single session of lumbar joint mobilization increased the diffusion of water into degenerative discs,(Beattie et al., 2009) however the relationship between enhanced disc nutrition and relief of symptoms warrants future investigation. Since nutrient and waste product exchange to and from the disc relies primarily on the integrity of the endplate, recapitulating healthy structure and function of the CEP could potentially promote disc health. Recently, Dolor et al. sought to increase solute transport across degenerative CEPs by treating human cadaveric CEPs with matrix mettaloproteinase-8 (MMP-8), which reduced the matrix constituents that impede solute uptake.(Dolor et al., 2019) Increasing solute transport across the CEP also improved adjacent NP cell viability, suggesting that enhancing the transport properties of the CEP can improve disc health and nutrition. While these ex vivo studies are promising, how this treatment approach would be practically applied in vivo has yet to be determined.

Despite the breadth of knowledge on the effects of mechanical loading on disc tissues, the effects of anabolic loading induced via exercise or physical therapy on the facet joints and spinal muscles in the context of disc degeneration is severly understudied. From the study of other synovial joints, it is known that physiologic loading can have anabolic effects on articular cartilage characterized by increased cell proliferation and extracellular matrix production – an effect which should translate to facet cartilage. (Jaumard et al., 2011) However, an organ culture model utilizing whole rabbit functional spinal units demonstrated that cyclic flexion-extension loading elicited a pro-inflammatory response in facet joint cartilage characterized by increased gene expression of COX-2 and MMP-1, with no significant changes in aggrecan gene expression. (Hartman et al., 2015) Further work is needed in facet joints investigating alternate loading modalities, magnitudes and frequencies, as well as assaying additional anabolic outputs. In skeletal muscle, exercise is known to increase collagen synthesis rates and have broad anti-inflammatory effects.(Miller et al., 2005; Petersen and Pedersen, 2005) Work in the SPARC null mouse model, which exhibits spontaneous disc degeneration, demonstrated that fibrotic remodeling and inflammation of the multifidus muscle could be successfully attenuated with physical activity.(James et al.,

2018; James et al., 2019) In human patients, exercise programs generally lead to an increase in trunk muscle size, particularly those programs using machine-based resistance exercises or programs utilizing motor control exercises combined with non-machine based resistance exercises.(Shahtahmassebi et al., 2014) However, the effects on muscle quality are less clear, with evidence in small cohorts of low back pain patients that fatty infiltration of the paraspinal muscles is either slightly decreased or unchanged with exercise therapy.(Berry et al., 2019; Welch et al., 2015)

Cell and Tissue Engineering Strategies: Cell Homing and Motion Segment Tissue Engineering

Although exercise and physical therapy may provide some inherent regenerative effect, in patients with more advanced degeneration, the resident population of AF and NP cells may be incapable of mounting a sufficient regenerative response. Increased cell senescence (Le Maitre et al., 2007; Patil et al., 2018) combined with the inflammatory milieu present in the degenerative disc (Maidhof et al., 2014; Molinos et al., 2015; Shamji et al., 2010) may further limit the capacity of resident cells to mount a regenerative response. To mitigate this, recruiting, or homing of, mesenchymal stem/stromal cells (MSCs) has been explored as a mechanism to maintain tissue homeostasis and promote endogenous repair in several musculoskeletal tissues. This approach aims to exploit the inherent regenerative capacity of MSCs, whereby MSCs are mobilized from their niche outside of the disc in response to injurious signals and chemical mediators.(Sakai et al., 2012) Indeed, potential stem cell niches have been identified in the perichondrium of the vertebral body adjacent to the disc and at the insertion of the outer AF into the vertebral body.(Henriksson et al., 2009) In the disc, exogenously delivered bone marrow derived MSC migration through the endplate has been described as a potential therapeutic for stimulating endogenous disc cell repair in organ culture models.(Illien-Jünger et al., 2012; Pereira et al., 2014; Pereira et al., 2016; Vadalà et al., 2013; Wangler et al., 2019) These studies demonstrate that MSCs can migrate through degenerative disc tissues.(Illien-Jünger et al., 2012) These ‘homed’ MSCs promoted matrix remodeling, with longer lasting and sustained effects than exogenous delivery of MSCs directly to the disc.(Clouet et al., 2019; Pereira et al., 2016; Wangler et al., 2019) Such MSC mobilization and homing techniques could be combined with exercise or physical therapy to further encourage regeneration, although future in vivo investigations in this area are warranted.

The aforementioned strategies based on physical therapy, enhancing disc nutrition, and cell homing are likely only to be effective in cases of mild to moderate degeneration. In cases of severe degeneration, more invasive strategies will likely be required to functionally regenerate or replace the disc and surrounding tissues. Over the past decade, there has been an emerging interest in the field to tissue engineer complete discs by combining cells and biomaterials to recapitulate the form and function of the native tissue. Several groups have produced composite engineered discs with only AF and NP components, (Bowles et al., 2011; Moriguchi et al., 2017) however, far fewer constructs have been developed that incorporate cartilage or boney endplate analogs to comprise a whole motion segment (Figure 5).(Gullbrand et al., 2018c)

Our group has developed tissue engineered disc-like angle-ply structures (DAPS) composed of an alternating, orientated electrospun polycaprolactone (PCL) AF analog and a hydrogel NP region, and extensively evaluated this design in both in vitro and in vivo settings. (Martin et al., 2014; Martin et al., 2017a; Martin et al., 2017b; Nerurkar et al., 2010) When implanted into the rat caudal disc space, cell-seeded DAPS motion segments achieved mechanical properties equivalent to native values, though the NP region showed a progressive loss of proteoglycan content and there was little evidence of DAPS integration with the adjacent vertebral bodies. To address these limitations, acellular PCL foams were apposed to the DAPS, serving as endplate analogs, which substantially improved their short-term in vivo performance. This advance underscored the importance of addressing the bone-disc interface in a tissue engineered construct. Improved outcomes included maintenance of T2 MRI signal and proteoglycan content, as well as evidence of integration with the native vertebral body, observed via μCT and histology.(Martin et al., 2017a) These endplate-modified DAPS (eDAPS), were further evaluated for in vivo integration and mechanical function in the rat caudal spine, and demonstrated near-native tensile and compressive mechanical properties by 20 weeks.(Gullbrand et al., 2018a) Improvements in tensile mechanics over time in vivo were accompanied by an increase in maturation of the interface between the adjacent vertebral body and the endplate, where host cells deposited collagen and began to mineralize and vascularize in the endplate region. This work was later translated to a large animal model, where the eDAPS were evaluated in the goat cervical spine, which has a length scale similar to the human cervical spine.(Gullbrand et al., 2018a) Results from that study illustrated that, after 4 weeks of implantation, the eDAPS maintained or improved in terms of matrix distribution, and at 8 weeks, the eDAPS compressive mechanical properties either matched or exceeded that of the native disc.

Others in the field have designed whole, tissue engineered motion segments utilizing aligned polycarbonate urethane scaffolds for the AF region, combined with an NP hydrogel and calcium phosphate endplate composite.(Iu et al., 2017b; Iu et al., 2017a) In vitro, these constructs demonstrated component integration and mechanical stability, as determined by a pushout test. However, peel tests indicated that the engineered AF lamellae were an order of magnitude weaker than native AF after 2 weeks of culture.(Iu et al., 2017a) Although the interfacial strength between the AF and NP matured between 1 and 2 weeks of culture, they did not continue to functionally mature beyond 2 weeks. When these composites were implanted into a localized bone-disc defect in the bovine tail, all of implants subsided into bone and there was no identifiable NP tissue present after 1 month. Notably, however, the engineered AF layers were still adherent to one another and to the bone substitute material. More recently, Chong et al. attempted to recapitulate the AF-cartilage endplate interface in vitro.(Chong et al., 2020) Bovine outer AF cells seeded on a multilamellar polycarbonate urethane scaffold were cocultured with articular chondrocytes to recapitulate the cartilage endplate. After 2 weeks in vitro, collagen I and II and aggrecan immunohistochemical staining distributions were similar to the native interface, and tensile strength increased over time in culture.

Chik et al. developed a multiphasic construct consisting of two osteochondral subunits, an NP-like core and a multi-lamellae AF-like component and evaluated its performance following in vitro culture with a compressional-torsional bioreactor(Chik et al., 2015).

Although this study only evaluated construct in vitro performance, it importantly assessed the diffusivity of the endplate analog, which is a critical feature for recapitulating nutritional function. They reported that the osteochondral subunits enabled passive nutrient diffusion, which in turn, supported the viability of NP cells. While promising, these constructs will need to be evaluated in vitro and in vivo at larger size scales which may pose a more substantial nutritional challenge. Overall, there has been continued progress toward whole-disc regenerative replacement techniques for advanced stage degeneration, but more work is needed to understand how these constructs will fare at large size scales and in a degenerative environment.

As mentioned previously, facet joint changes have also been reported to occur concomitant with disc degeneration and as such, facet joint repair will be an important consideration when addressing whole motion segment replacement. Arthroplasty prostheses have been described(McAfee et al., 2007; Phillips et al., 2009; Sjovold et al., 2012; Wilke et al., 2006; Zhu et al., 2007), as has a facet joint resurfacing system(Anekstein et al., 2015; de Kelft, 2016). however, only limited preliminary data exist that support that these devices result in improved pain and functionality. Additionally, both systems are susceptible to device related failure or implant dislocation that commonly require reoperation with posterior lumbar interbody fusion. Despite similar joint pathology to osteoarthritis, facet tissue engineering remains almost completely unexplored.(O'Leary et al., 2018) The future application of anatomical osteochondral tissue-engineering approaches to the facet may provide a much-needed, long-term, motion-preserving solution.(Daly et al., 2019; Grayson et al., 2008; Hung et al., 2003)

Conclusions

It is evident that disc degeneration is associated with pathologic alterations to the disc interfaces, and the adjacent vertebral bone, facet joints and paraspinal muscles, all of which may contribute to pain in patients. However, these tissues are frequently studied in isolation, and there remain significant gaps in knowledge regarding the mechanism by which degenerative changes occur concomitantly across these substructures. Further study of the crosstalk between spinal tissues during degeneration and regeneration is warranted, particularly using in vivo animal models and human subjects where possible. Treatment of degeneration from a whole motion segment perspective also has the potential to improve the efficacy of new therapeutics and lead to improved quality of life for patients suffering from back pain. Finally, while this review is focused on the musculoskeletal tissues of the spine, further study on the contributions of systemic factors at the whole patient level (such as environmental and psychosocial factors) to degeneration and pain is also warranted.

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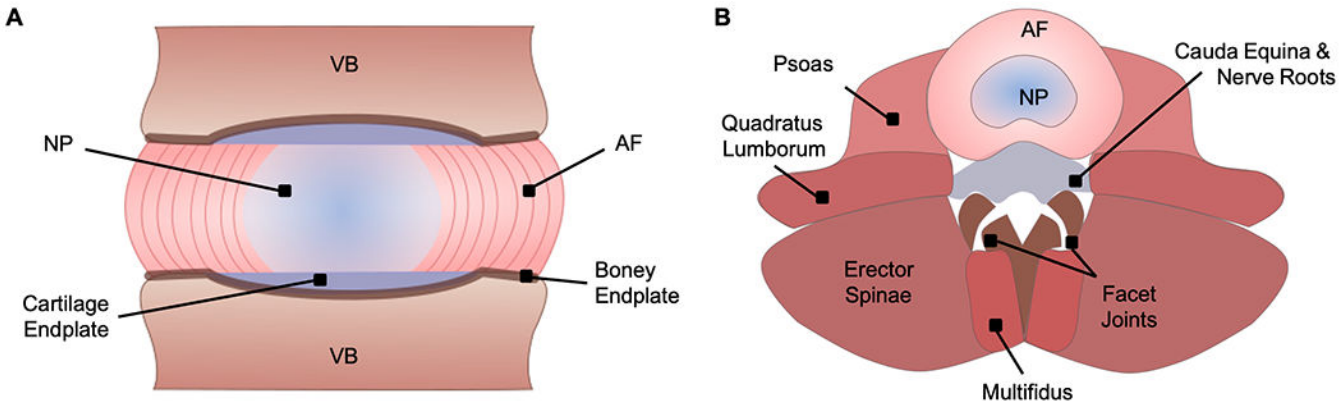

Figure 1.

Schematic of (A) coronal and (B) axial crossections of the spinal motion segment, demonstrating relevant anatomical regions. VB = vertebral body, NP = nucleus pulposus, AF = annulus fibrosus.

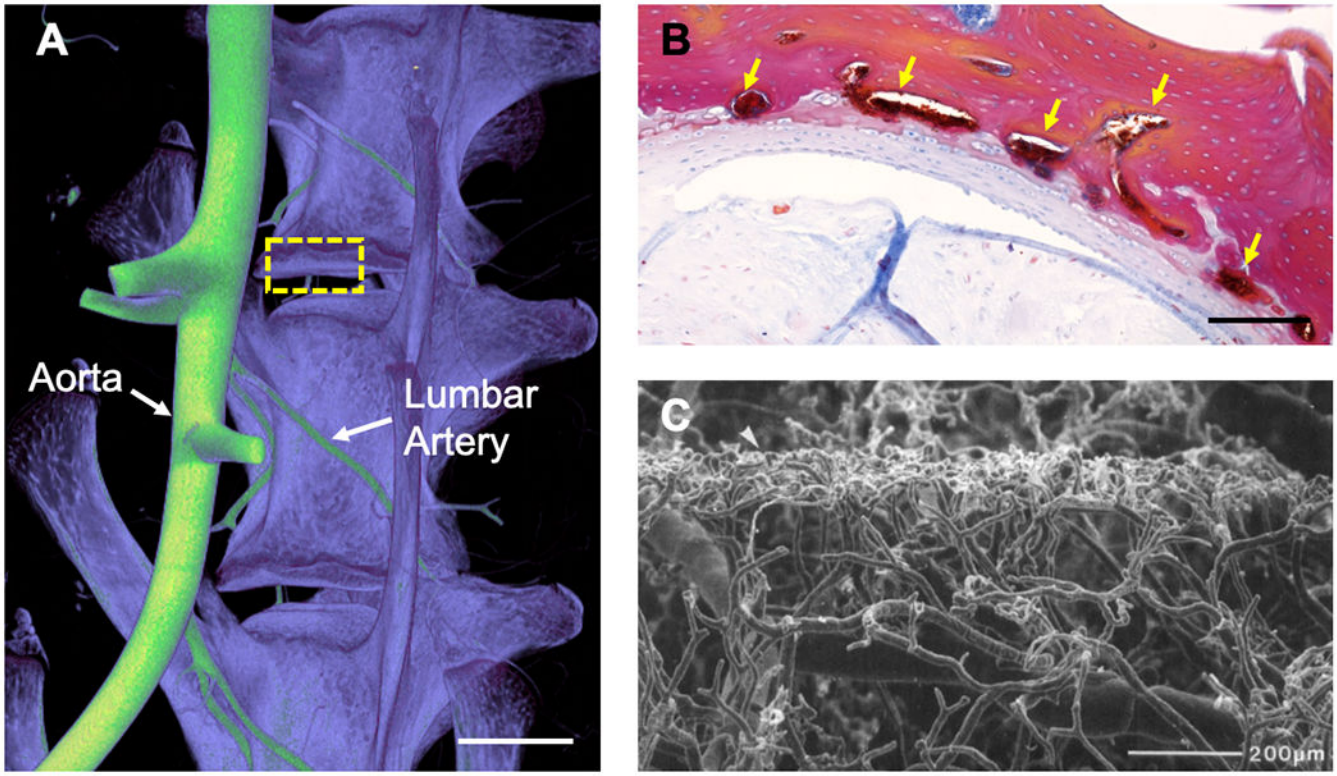

Figure 2.

(A) μCT scan of the rabbit lumbar spine perfused with microFil (scale = 5 mm). Dashed box highlights the boney endplate region shown in B and C.(Ashinsky et al.,2020) (B) Mallory-Heidenhain trichrome stain of a sagittal section of the rabbit endplate-NP interface. Yellow arrows denote vessels (scale = 100 μm).(Ashinsky et al., 2020) (C) Scanning electron micrograph of a cast of the rabbit endplate vasculature.(Oki et al., 1996) Images reproduced with permissions.

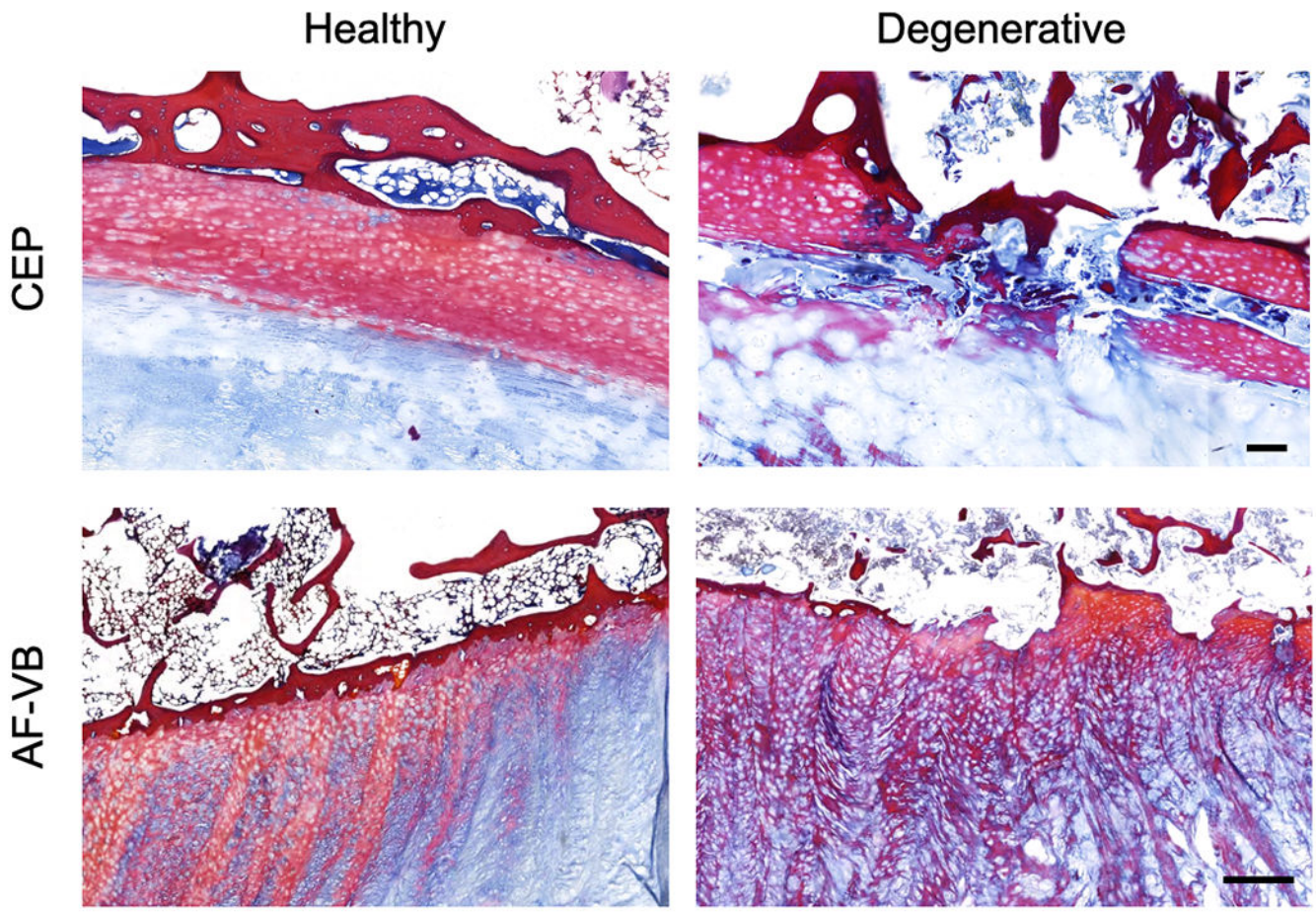

Figure 3.

Histology sections stained with the Mallory-Heidenhain trichrome stain of healthy and degenerative human intervertebral disc interfaces. CEP = cartilage endplate, AF = annulus fibrosus, VB = vertebral body. CEP scale = 200μm, AF-VB scale = 800μm.

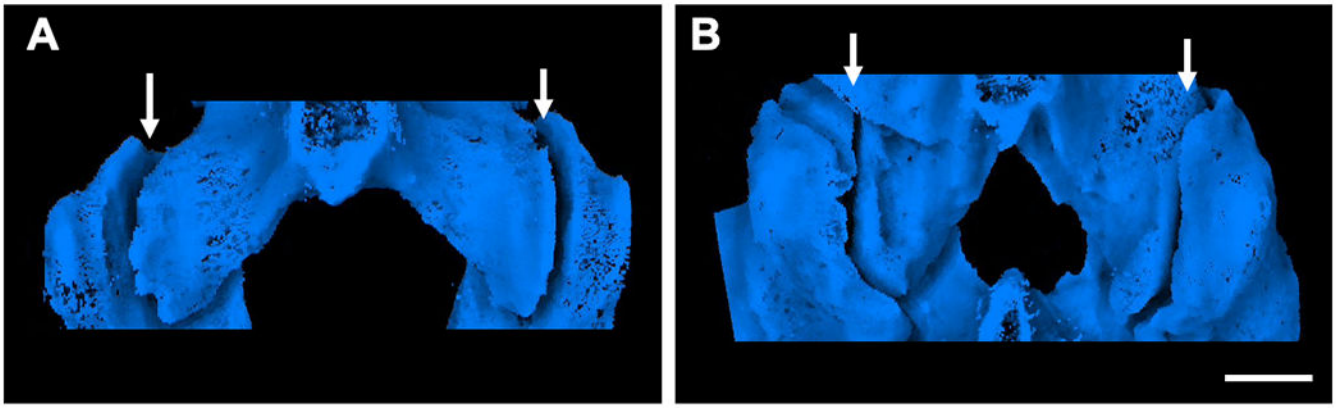

Figure 4.

μCT scans of human facet joints (arrows) adjacent to the (A) L1-L2 disc, Pfirmman grade 5, from a 66 year old female, and (B) the L1-L2 disc, Pfirrmann grade 3, from a 65 year old male. Scale = 5mm.

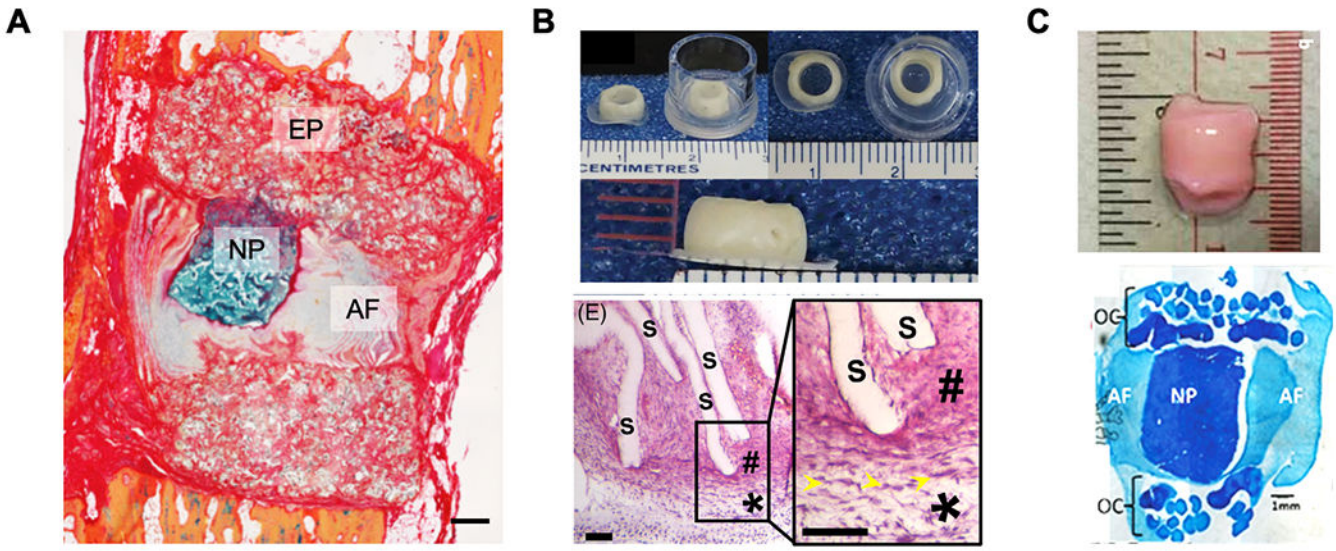

Figure 5.

Examples of tissue engineered disc implants with endplate interfaces from the literature. (A) Endplate-modified disc-like angle ply structures after 20 weeks implantation in the rat tail.(Gullbrand et al., 2018b) (B) A tissue engineered CEP-AF interface. S = scaffold, # = outer AF, * = cartilage, yellow arrow heads = directional orientation of outer AF cells. (Chong et al., 2020) (C) A tissue engineered whole disc replacement with an osteochondral endplate component.(Chik et al., 2015) Images reproduced with permission.