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Future of low back pain: unravelling IVD components and MSCs' potential

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Abstract

Low back pain (LBP) mainly emerges from intervertebral disc (IVD) degeneration. However, the failing mechanism of IVD's components, like the annulus fibrosus (AF) and nucleus pulposus (NP), leading to IVD degeneration/herniation is still poorly understood. Moreover, the specific role of cellular populations and molecular pathways involved in the inflammatory process associated with IVD herniation remains to be highlighted. The limited knowledge of inflammation associated with the initial steps of herniation and the lack of suitable models to mimic human IVD's complexity are some of the reasons for that. It has become essential to enhance the knowledge of cellular and molecular key players for AF and NP cells during inflammatory-driven degeneration. Due to unique properties of immunomodulation and pluripotency, mesenchymal stem cells (MSCs) have attained diverse recognition in this field of bone and cartilage regeneration. MSCs therapy has been particularly valuable in facilitating repair of damaged tissues and may benefit in mitigating inflammation' degenerative events. Therefore, this review article conducts comprehensive research to further understand the intertwine between the mechanisms of action of IVD components and therapeutic potential of MSCs, exploring their characteristics, how to optimize their use and establish them safely in distinct settings for LPB treatment.

Keypoints

- LBP Burden: Poorly understood factors contribute to significant low back pain impact on health and well-being.
- IVD and LBP: Disc degeneration links to low back pain, disrupting the intervertebral matrix and causing pain.
- Regenerative Focus: Improving IVD components crucial for targeted regenerative therapies addressing inflammation.
- Research Advances: IVD complexity, inflammatory markers, and MSC potential guide research despite replication challenges.
- MSC Therapies: MSCs offer the potential for anti-inflammation, regeneration, and reduced costs, with ongoing research needed.

Keywords Low back pain, Intervertebral disc, Degeneration, Annulus fibrosus, Nucleus pulposus, MSCs, Regenerative medicine

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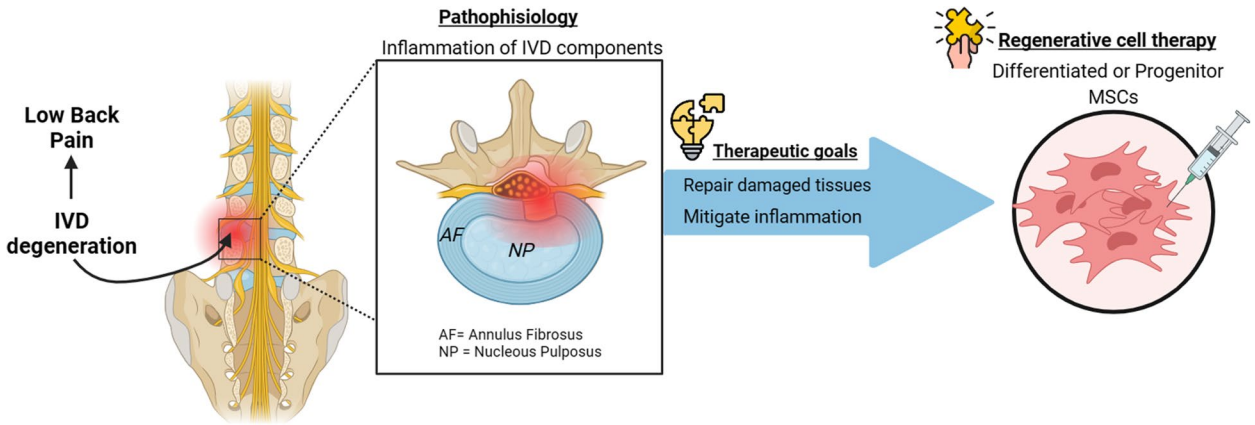
Graphical Abstract

This review article focuses on low back pain (LBP) caused by intervertebral disc (IVD) degeneration and the need to better understand the mechanisms involved. The specific roles of cellular populations and molecular pathways in the inflammatory process associated with IVD herniation are not well understood, and suitable models to mimic human IVD complexity are insufficient. However, due to their unique immunomodulatory and pluripotency abilities, mesenchymal stem cells (MSCs) have gained recognition in cellular therapy for bone and cartilage regeneration. MSCs have shown the potential in facilitating tissue repair and mitigating inflammation-related degenerative events. Therefore, this review article explores the intertwine between the mechanisms of action of IVD components and therapeutic potential of MSCs, exploring their characteristics, how to optimize their use and establish them safely in distinct settings for LPB treatment.



Background

According to the Global Burden of Disease Study 2019, LBP belongs among the 10 most important burden causes of higher DALYs (Disability-adjusted life years) in several age groups, making it fourth place in the 25–49 year age group with increasing age-standardized DALY rates for adolescents as well (Vos et al. 2020). Its disability effects frequently arise from teenage years into old age, which converts it into a high magnitude burden of social health coverage. Exhibits high epidemic proportions in Western societies with risk factors that are still poorly understood, like bending, repetitive work, lifting heavy weights, or twisting and it is also a main cause for most workers' absenteeism (Serranheira et al. 2020). Due to this high prevalence and work loss, LBP leads to enormous costs in informal care to enhance occupational physical demands. As an example, in the United Kingdom these costs could reach £10,668 million annually (Maniadakis et al. 2000), but this economic analysis may be broadened up to other countries as well (Alonso-García and Sarría-Santamera 1976; David et al. 2017; Shmagel et al. 2016).

Outlining it all, LBP embodies leading roles in global disability. It can result from acute, chronic, or progressive injuries within the intervertebral disc (IVD) (Kreiner et al. 2020). In most cases it is classified as an idiopathic pathology, but can also be specifically diagnosed, being this latter case due to hernias, osteoporosis fractures, rheumatic diseases and others (Mattiuzzi et al. 2020). Despite distinct diagnoses, concurrent IVD injuries comprise progressive degenerative damage in a group of disorders known as degenerative disc diseases (DDD) (Kos et al. 2019).

As for current clinical solutions in disc repair and LBP control, most patients are prescribed with rest, exercise, physio, or pain medication as conservative therapies (Ng et al. 2021). When shown unsuccessful, invasive surgical procedures are needed, being the most frequent a discectomy, excision of affected IVD degenerated region, followed by an arthrodesis, also known as spinal fusion, where two adjacent vertebral bodies are fused together to aid in spinal stability and patient comfort (Gupta et al. 2012). Since IVD tissue regeneration does not occur in any of these procedures, disc degeneration likely reappears in the future and further contributes to the recurrence of LBP (Oshina et al. 2018).

With this, investigations surrounding the pathophysiology of IVD degeneration have become pivotal and, upon that, developing innovative regenerative therapies that target the IVD and thus impact LBP management.

IVD physiology

An IVD is a complex vertebral spine structure composed by 3 major components: a gel-like nucleus pulposus (NP) encapsulated by a lamellar fibrocartilaginous tissue, the annulus fibrosus (AF), and a hyaline cartilaginous surface, the endplate (EP), that inextricably intertwines vertebral bodies (Fig. 1; Daly et al. 2016; Raj. 2008).

All these distinct IVD components arise from the mesoderm but end up diverging into different embryonic progenitors during its development. The NP derives from the notochord while AF and vertebral bodies along with EP derive from the sclerotome compartment of the somites, respectively, leading to several biochemical and phenotypical differences in composition for the ultimately adult IVD (Chan et al. 2014; Harfe 2022). As a result, each of these tissues impacts IVD function differently, and their maintenance depends on balanced matrix and cell population turnover events (Pattappa et al. 2012).

Besides that, the IVD is an avascular tissue that depends on a marginal blood supply coming from EP capillaries for nutrients, oxygen, and removal of metabolites, culminating in precarious nutritional pathways for IVD cells, mainly, through diffusion (Raj pp. 2008; Whatley and Wen 2012; Zhu et al. 2012). Also, few nerves have been demonstrated to follow up these vessels and may derive from the ventral rami, gray rami communicants or branch from the sinuvertebral nerve (Viseux et al. 2021). Therefore, the understanding of these singular morphological attributes in the degenerating IVD becomes not only significant to IVD development but also to tissue remodelling and degenerative processes that may occur.

NP

Through the scope of an adult IVD, NP contains predominantly collagen type II fibers organized randomly and elastin fibers arranged radially (Raj pp. 2008; Shankar et al. 2009). Together, they hold an highly hydrated proteoglycan-containing gel, mostly aggrecan whose negative side chains allow water retention (Pattappa et al. 2012; Roughley et al. 2006), with hydrophilic chondroitin and keratin sulphate attached as well (Shankar et al. 2009). Other proteoglycans include versican, decorin, byglycan and fibromodulin (Shankar et al. 2009; Chan et al. 2011), summing up to an overall content of about 18% proteoglycans,77% water and 5% collagen fibrils (Raj 2008; Pattappa et al. 2012; Whatley and Wen 2012). Due to this, the NP maintains disc height and a hydrostatic pressure that confers resistance to disc deformation (Tomaszewski et al. 2015). Besides that, its viscoelastic features allow it to sustain different magnitudes of loading and to withstand shock from activities requiring multi-axial movements (Newell et al. 2017).

Concerning NP cells, these derive from the notochord, as previously described. During early childhood, they feature a large vacuolated size (30–40 μm) (Pattappa et al. 2012) but, up to adulthood, notochordal cells (NCs) start to be replaced by smaller spherical chondrocyte-like cells (~ 10 μm) (Colombier et al. 2014; Ruffilli et al. 2003) reaching an estimated density of 4×10^6 cells/mm^3 in the developed IVD (Pattappa et al. 2012; Roughley 2004). These mature NP cells start to express classic chondrogenic markers like SOX9, type II collagen (COL2A1) or aggrecan (Wu et al. 2018) but present a

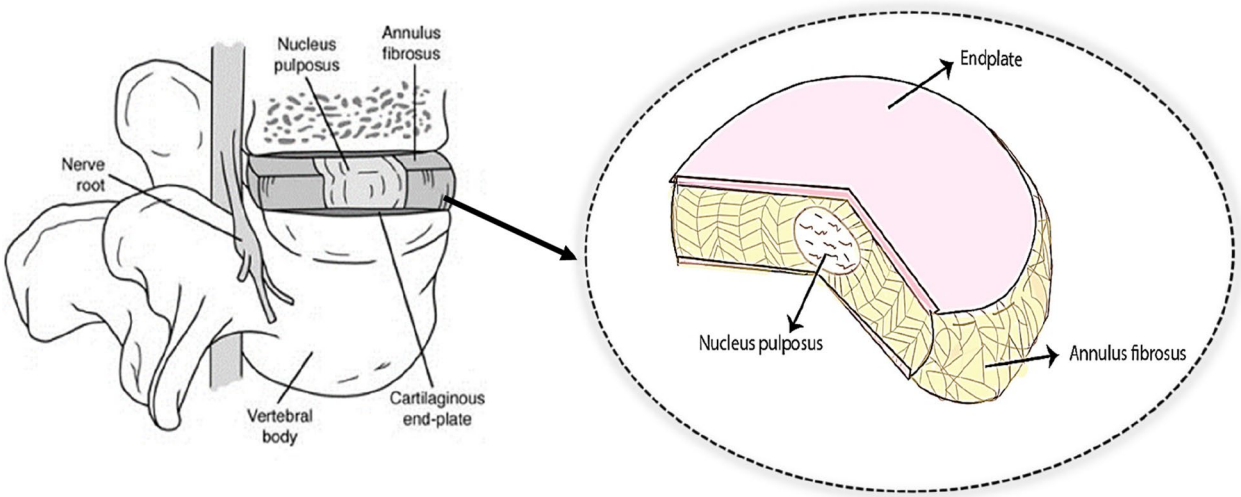


Fig. 1 Line drawing of a spinal segment with an IVD between two vertebral bodies (left) and a cutout portion representing a normal IVD (right). Observe the vertebral EP sandwiched between discs, the centered NP and the AF surrounding it. The colors altered on the right IVD were only for differentiation purposes, inspired and approved by (Raj 2008)

higher proteoglycan to collagen ratio (27:1) than hyaline cartilage chondrocytes (2:1) (Mwale et al. 2004).

To avoid controversy among the different laboratories, a group of top researchers in the field proposed a panel of markers to define a healthy NP cell phenotype, including: HIF-1α (hypoxia inducible factors), GLUT-1 (glucose transporter), aggrecan/collagen II ratio > 20, Shh (sonic hedgehog), Brachyury, KRT18/19 and carbonic anhydrase XII (Risbud et al. 2015; Thorpe et al. 2016). Then, also some cell surface markers like Tie2+ (angiopoietin-1 receptor), GD2+ (disialoganglioside 2) (Sakai et al. 2012) and CD24 (Thorpe et al. 2016; Guan et al. 2014) were reported to be found within reminiscent NP progenitor cells, but decreased considerably with age and IVD degeneration as they lost differentiative and proliferative capacity. Although hard to isolate and identify, Tie2+ progenitor cells have already been found in human, bovine, canine, and mouse specimens. Due to this remarkable multilineage differentiation and direct link with IVD degeneration these cells also become an intriguing target for regenerative techniques (Sakai et al. 2018). Additionally, markers associated with mesenchymal stem cells (MSCs) like CD44, CD49f, CD56, CD73, CD90, CD105 and CD166, have also been identified throughout NP cells on distinct differentiation stages (Risbud et al. 2015; Sakai et al. 2018; Choi et al. 2015). Besides, endogenously, NP phagocytic cells and macrophage-like cells, have also been reported on human surgical non-herniated NP samples that had a high number of resident CD68 + cells (Minogue et al. 2010) and human cadaveric IVDs with distinct degenerative stadiums displaying high expression of CCR7 and CD163 (Feng et al. 2023).

Overall, the phenotypical expression profile varies a lot through development, aging and degeneration, which diverges a specific cellular characterization of NP cells amidst those stages.

AF

Regarding the AF, it consists of an IVD tough circular exterior surrounding the soft inner core, the NP, providing both mechanical force and resilience so the IVD can recover from countless movements. It is organized in concentric lamellar fibers rich in collagen type I or II and elastin, with an angle-ply orientation that determines its ability to absorb shock from bending and torsional rotation motion (Daly et al. 2016; Raj 2008). Moreover, the elastin fibers intertwined with the collagen fibers create an intermediate zone in the AF, termed translamellar bridging network (TLBN) that enables AF to contain NP bulging under high magnitude loads (Raj 2008; Whatley and Wen 2012). Overall, AF extracellular matrix (ECM) content comprises water levels lower than NP (60–70%) and, within dry weight, 10–20% proteoglycans, 50–70% collagen and 2% elastin (Pattappa et al. 2012; Whatley and Wen 2012).

As for AF cell populations, whose reported density range stands at approximately 3000–9000 cells/mm^3 in an adult IVD (Daly et al. 2016) they can be subdivided into two major regions as represented in Fig. 2: the inner AF, with chondrocyte-like cells, round cells that produce collagen type II, and outer AF, comprising fibroblast-like cells, elongated, fusiform cells responsible for synthesizing collagen type I (Daly et al. 2016; Torre et al. 2019). Plus, average cellular density

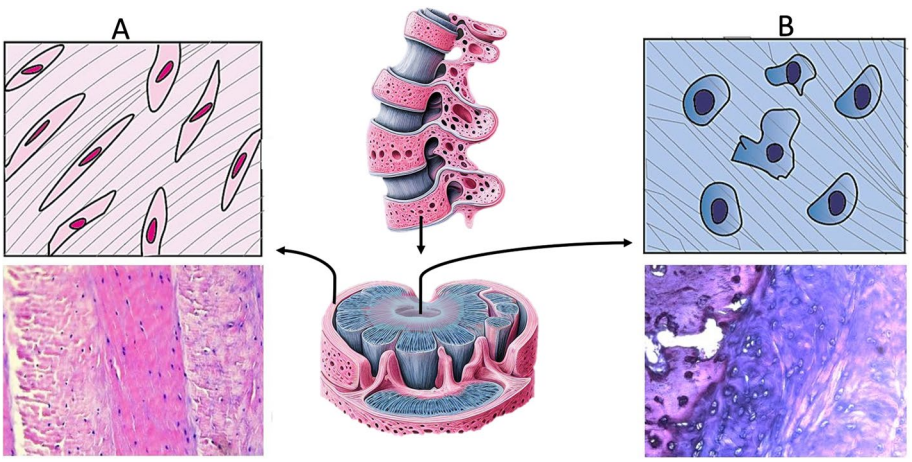


Fig. 2 Scheme illustrating main cell phenotypes already identified in inner and outer healthy AF, surrounding the NP (represented in blue), with respective hematoxylin-eosin images below obtained during immunohistochemistry assays. The vertebral body scheme is to represent the complex changeover between these AF regions, whose cell populations are hard to distinguish since there are scarcely any definitive or exclusive markers. (**A**) Outer AF with fibroblast like-cells and rich in collagen type I. (**B**) Inner AF with chondrocyte-like cells, also called fibrochondrocytes, rich in collagen type II

increases towards outer AF and, while the outer AF contains an aligned lamellar organization, the inner AF shows a more disordered array of fibrils (Molladavoodi et al. 2020). These cellular regions are responsible for both anabolic and catabolic reactions in ECM homeostasis, guaranteeing AF functionality and remodelling abilities up to a point (Daly et al. 2016; Molladavoodi et al. 2020).

Besides, the changeover between the two regions is very heterogenous, and both their behaviour in IVD regenerative healing is yet unknow. Other cell populations have also been described more recently in the AF, such as: innate progenitor cells identified by immunolocalization of CD24, CD44, CD29 or CD105 (Daly et al. 2016; Chan et al. 2014; Choi et al. 2015) with additional stem cell markers like platelet-derived growth factors or CD90 (Daly et al. 2016; Stein et al. 2021) and (MSC)-like cells, also seen in NP verified through osteogenesis, chondrogenesis, and adipogenesis assays (Tang et al. 2012).

Under the exposal of a reshaping degenerative microenvironment, the AF may be evaluated by upregulation of specific cytokines or pain-related molecules expressed by stem/mesenchymal progenitor cell receptors or macrophages, such as CD44 and CD14, respectively (Tang et al. 2012). Up to an extent, such cells imply that the IVD may contain a quiescent progenitor-like niche that enables IVD repairment (Gruber et al. 2016). Consequently, studying these cell profiles and respective markers holds futuristic expertise in therapeutic applications to manage IVD inflammatory-driven degeneration.

Regarding CD44, it regulates several cellular mechanisms, including cell adhesion and differentiation. During IVD formation, CD44 is particularly important by anchoring hyaluronan (HA) to the cells and regulating its metabolism (Lyu et al. 2019). Moreover, it contributes to the formation and expansion of ECM from the developing IVD (Whatley and Wen 2012). In most vertebrate cells, either hematopoietic, endothelial, or epithelial, CD44 is expressed on its surface, and it is responsible for mobilizing leukocytes to sites of inflammation and mediating rolling interactions with activated endothelial cells (Thorne et al. 2004). Additionally, its neighbouring markers may consist of collagen, fibromodulin, and laminin, all together found in the AF structure as well. As for its expression, it has not only been recently described in the AF (Baaten et al. 2012) but also in NP cells (Wu et al. 2018; Guo et al. 2018), which turns it into an enticing cell marker to assess during IVD´s immunomodulatory processes. As for CD14, already exhibited in harvested IVD-derived mononuclear cells from patients with lumbar disc herniation (Stevens et al. 2000), it stands as a macrophage marker responsible for expressing some of the inflammatory cytokines, calcitonin gene-related peptide (CGRP) (Miyagi et al. 2020) and nerve growth factor (NGF) (Miyagi et al. 2020; Nakawaki et al. 2019), through paracrine or autocrine systems, leading ultimately to discogenic LBP. Therefore, both markers are alluring to discern inflammatory mechanisms involved in either degenerative or injured IVDs.

IVD degeneration

With growth and natural aging, all IVD elements endure some modifications, in terms of their ECM composition, cell density and population as well as nutritional mechanisms or functionality range. However, discerning the difference between normal ageing and pathological IVD changes is hard (Lee et al. 2020). For once, they have similar attributes and may be extended through equivalent pathways, like abnormal mechanical loads or nutritional failure showing low pH, low glucose, and oxygen levels (Daly et al. 2016; Tomaszewski et al. 2015; Lee et al. 2020). Thence, defining these degenerative ambiances is pivotal to target novel regenerative therapies to the appropriate circumstance.

Either way, in degenerated discs the limits between the AF and NP become more blurred, NP loses its gel-features becoming more fibrotic and ECM content becomes more disorganized and degraded enzymatically, affecting mechanical load range possible to sustain effectively (Galbusera et al. 2014). The proteoglycan´s content decreases, diminishing the capacity of water retention, which affects most IVD tissue´s biomechanical properties. On the other hand, collagens remain present, but its types and ratios seem to interchange in all IVD elements although, particularly, affecting the TLBN crosslinking properties (Desmoulin et al. 1976; Duance et al. 1976). As shown, angiogenesis in the outer region associated to scar distension and nerve ramification also appear within degeneration (Roberts et al. 2006), along with cluster formations, especially in NP (Saggese et al. 2019). Cell death increases which, as reported, can cover up to 50% of adult disc cells by showing necrotic or apoptosis characteristics. Plus, cellular microstructure may change from differentiated NP chondrocyte phenotypes gaining a more fibrotic format (Tomaszewski et al. 2015; Saggese et al. 2019).

Continuous IVD degenerative damage may further lead to AF tearing circumferentially without complete disruption or it may rupture sufficiently to prolapse NP, leading to intense discogenic pain and to the emergence of a hernia (Johnson et al. 2001).

The stretched fibers of the weakened AF allow an extramurally extravasation of substances, like glycosaminoglycans or proteoglycans, ensuing a decrease in osmotic pressure (Schmidt et al. 2007) and resulting in a bulky

AF that compresses the nerves, subjects NP to higher mechanical load pressures, severe hypoxia, limited nutrition, all aggravating LPB (Daly et al. 2016; Tomaszewski et al. 2015; Mwale. 2004).

Thus, degenerated discs undergo other transformations such as becoming stiffer than unaffected discs and changing their overall metabolism. For instance, a decrease of ECM proteins, such as collagen type II and aggrecan (Roberts et al. 2006; Yao et al. 2002), is exhibited due to high enzymatic activity and loss of IVD cell's ability in reproducing native ECM (Teixeira et al. 2015).

IVD degeneration's impact on MSCs and their therapeutic potential

Since IVD´s degenerative microenvironment results in gradual residents' cells depletion, various studies have tried to reinstate NP/AF with replenishing cells. Therefore, several attempts have been made by infusing viable stem cells such as MSCs into the degenerating IVD, employing various cell sources, animal models, injection techniques, and bioengineered scaffolds (Nguyen et al. 2017). Due to their known tri-potency to differentiate into osteoblasts, chondrocytes, and adipocytes, MSCs are the ancestors of mesenchymal lineages and are responsible for growth, immunomodulatory properties, exerting stimulatory effects on other cell types and ongoing turnover of tissues as inherent regenerative promoters (Clouet et al. 2019). However, more specifically, their chondrogenic and immunomodulation abilities can be applied to IVD therapy (Nguyen et al. 2017; Clouet et al. 2019).

MSCs can either be obtained from a variety of tissues and organs (Liu et al. 2022) to be grafted into IVD matrix (Lv et al. 2014) or, as previously described (Daly et al. 2016; Chan et al. 2014; Choi et al. 2015; Tang et al. 2012), MSCs with minor differences in potency and surface marker expression can be found endogenously in both AF and NP as a progenitor-like niche that is dormant with potential to support IVD repairment after stimulation. Although these endogenous cells can significantly uphold tissue balance, gradually replenishing the tissue during normal physiological conditions, the pathologic milieu of the host tissue is related to variations in their capacity for differentiation, cytokine secretion, or gene expression profile (Liu et al. 2022; Chu et al. 2022). Regarding exogenous MSCs, their source of origin also affects their profile. As an example, bone marrow-derived MSCs have a lot of increased genes linked to antimicrobial activity and osteogenesis, when compared to umbilical cord-derived MSCs, which have more transcripts linked to matrix remodelling and angiogenesis (Lyu 2022).

The chronic progressive character of DDD associated with hypoxia, low glucose levels, mechanical loading, acidic pH, hyperosmolarity, and inflammation not only greatly impacts cell survival, but also makes all types of MSCs susceptible to phenotype divergence (Xu et al. 2019). To address this problem, the Mesenchymal and Tissue Stem Cell Committee of the ISCT (International Society for Cell Therapy) have previously proposed a set of standards to define multipotent human MSC with regenerative potential for both scientific (Table 1) purposes and pre-clinical studies (Vadalà et al. 2019):

Nonetheless, these promising findings do not fully validate the viability of employing MSCS to supplement or replenish IVD cells, plus enhancing the synthesis of a more effective ECM. Their stemness and differentiation stability also depends on the timing of treatment from the onset of discomfort, the stage of degeneration to treat, and the dosage of implanted cells (Dominici et al. 2006). Therefore, a regenerative strategy is ideal in the early stages of DDD, before structural degenerative changes appear, and the local stem cell reserve is completely depleted.

Alternatively, it is also important to understand that not all microenvironment shifts in a degenerating IVD are harmful for the survival and action´ mechanisms of stem cells. For once, MSCs are known to not be as sensible to apoptotic induction effects as resident IVD cells. Moreover, it has been proved that the lack of oxygen encourages them to maintain their unique properties, while promoting the conversion of MSCs into NP-like cells, being the latter already used to natural hypoxia levels. With this, hypoxia may be evaluated as a favourable factor (Chu et al. 2022; Zhou et al. 2021). Besides that, the healthy IVD typically exhibits high osmolarity due to proteoglycans and collagen concentrations, which tends

Table 1 Standards to identify multipotent human MSCs (Vadalà et al. 2019)

1. Adherence to plastic in standard culture conditions		
2. Phenotype	*Positive (≥ 95% +)*	*Negative (≤ 2% +)*
	CD105	CD45
	CD73	CD34
	CD90	CD14 or CD11b
		CD19 or CD79α
		HLA-DR
3. In vitro multipotent differentiation: osteoblasts, adipocytes, chondroblasts (shown by staining of in vitro culture)		

to decrease during the degenerative process. This change could uplift both MSCs and progenitor cells as well, since high osmolarity tends to be hostile for ECM production and cell growth.

2D aspects to enhance MSCs' interventions

As seen, the complex cascade of events in IVD degeneration makes it hard to assess effective cellular recruitment strategies, either endogenous or transplanted MSCs. Yet, their potential can be enhanced using the appropriate strategies to each cellular pool.

Within their microenvironment, MSCs are known to regulate the immune system by specifically detecting abnormal ambiance factors through their own toll-like receptors and are known to be hypoimmunogenic (Clouet et al. 2019), which makes them relevant for allogeneic transplant. However, when pro-inflammatory factors become overbearing due to progressive degeneration, MSCs develop an anti-inflammatory phenotype to prevent chronic inflammation and promote tissue repair (Zhou et al. 2021; Gupta et al. 2022). Therefore, their high sensitivity to the inflammatory milieu requires approaches prior to cells´ administration, also known as *cell priming* (Noronha et al. 2019).

Among the distinct procedures of *cell priming* (Noronha et al. 2019), cells may be enriched with pro-inflammatory mediators, undergo morphological, immunophenotypic, or genetic/epigenetic changes. Upon that, and mostly due to the avascular nature of IVD, systemically appliance is less appropriate and other means such as intradiscal injections of cells, transplant adjacent to hydrogels, exosomes, viral vectors, or combinations of these are needed for both exogenous and endogenous interventions. Plus, it also becomes important to consider tissue tension, range motion, and injection needle size used, since the degree of IVD disruption may fluctuate the risk of leakage and, therefore, its clinical success (Noronha et al. 2019; Binch et al. 2021).

Pre-conditioning MSCs under hypoxic culture conditions has also proven to be a crucial factor for increased proliferation, superior plasticity, and extended survival upon IVD transplantation since its hypoxic structures are physiologically prepared for these circumstances (Samanta et al. 2023). Other culture nutrients, like serum or glucose, and frequent medium changes are also considered for growth, but may not accurately reflect a natural IVD environment, arising uncertainty when evaluating *in-vitro* experiments data (Samanta et al. 2023; Schubert et al. 2018). To further validate results, more advanced organ culture models and *in-vivo* models are required, along with 3D biomimetic strategies to enable better cellular interactions and provide structural cell support.

3D aspects to enhance MSCs' interventions

The inherent complexity of the human IVD makes it hard to find an appropriate animal model that can fully mimic disc degeneration/inflammation. Therefore, assessing a suitable model implies some requisites. Some common models include rat, rabbits, canine and goat models but, although of quadrupedal nature, a bovine model is currently more fitting than the others for its analogous qualities to humans. It has equivalent weight, absence of NCsand similar biomechanical features (Harfe 2022). In in vitro cultures the intrinsic variability makes it hard to assemble each mediator´s role in a singular mechanism. Additionally, their manipulation may increase the changes of modifying receptors expression and introduce impurities (Samanta et al. 2023). As for in vivo models, their distinct NP/AF dimensions, and spine biomechanics from human IVDs, aside with bioethical constraints, discard them from being a convenient model. Contrarily, *ex-vivo* organ culture models using disc implants have already been successfully established for studying degeneration-associated inflammation (Yao et al. 2002) with distinct pro-inflammatory agents and verify the benefits of MSCs based-treatments (Saparov et al. 2016).

On the other hand, by integrating precision medicine techniques with biomaterial-based tissue engineering, more tailored approaches to patients of distinct stages of degeneration have also been establishing an extensive repertoire. These biomaterials can mimic and preserve the ECM of the IVD for cells after injection through minimally invasive procedures or surgical implantation, target the pathophysiology involved by adding therapeutic small molecules/drugs or work as a cell delivery system for stem cell transplantation. Mohd Isa et al. shows an up-to-date review on biomaterials already developed to target different severities of disease and bioengineering perspectives for the materials used (Chen et al. 2009). Besides, 3D-printing manufacturing techniques are being explored to customize adequate scaffolds, spheroids, or hydrogel characteristics to sustain specific anatomic features and improve patient´s disc balance. Current 3D experimental models show ability to maintain NP/AF phenotype, regulate cellular functions, reduce pain and inflammation in animal studies (Mohd Isa et al. 2022; Du et al. 2019; Pirvu et al. 2015). Even so, their efficacy in human trials is still divergent and narrow.

Conclusions and perspectives

Low back pain continues to exhibit high magnitude burden of social health coverage and elevated morbidity proportions with risk factors (genetics, loading pressure, age …) that are still poorly understood, but it is mostly associated to IVD degeneration leading to DDD. In result,

the metabolic balance of the ECM is disrupted, encouraging catabolism and cellular pool depletion. Therefore, improving the molecular and cellular profile of IVD components becomes alluring to discern inflammatory mechanisms involved in these events and essential to target novel cellular regenerative therapies to the appropriate circumstance.

Ongoing research with several models has been successful in understanding the complexity of IVD structures and degenerative ambiances, although precisely replicating *in-vivo* models across several degenerative stages is hard to obtain due to tissue inherent divergence. Even so, as described, several markers have been found to have crucial biomechanical and guiding roles for the inflammatory events implied across all structures and there are potential stem cellular niches for tissue regeneration, such as MSCs.

The mechanisms by which MSCs exert their therapeutic effects are believed to involve multiple mechanisms, including immunomodulation, anti-inflammatory effects, and the secretion of various growth factors and cytokines. Therefore, cellular therapies using either endogenous or exogeneous MSCs are intriguing to be able to adapt therapies aim and scope to each IVD degenerative ambiance, accordingly. Not only that, but cellular therapies can contribute to replace invasive surgeries like discectomies, be combined with distinct pharmaceuticals or biomaterials and, if offering a single (or temporary) treatment, may drastically reduce healthcare and social costs. Regardless, while MSCs show promise in cellular therapies, more research is needed to fully understand their therapeutic potential, optimize their use, and establish their safety and efficacy for future clinical trials and ongoing research actively exploring this area. Their number is expected to increase overtime since these cells are yet used only as a palliative treatment of DDD to reduce discomfort or surgical replacement and, up to date, there is still the need to find more diverse mechanistic models for preclinical testing and establish guidelines regarding patient stratification for clinical trials. Besides, since IVDs continue to exist in a hostile environment, most strategies are still in the experimental stage, and even if symptoms are relieved, degeneration may still be occurring.

With this, unravelling IVD structures and their immunomodulatory mechanisms associated with degeneration are a starting point for posterior regenerative therapies with stem cells pools such as MSCs, leading to inflammatory management in patients with DD, while reducing LBP.

Abbreviations

LBP	Low back pain
IVD	Intervertebral disc
AF	Annulus fibrosus
NP	Nucleus pulposus
MSCs	Mesenchymal Stem cells
DALYs	Disability-adjusted life years
EP	Endplate
DDD	Degenerative disc diseases
ECM	Extracellular matrix
TLBN	Translamellar bridging network
NC´s	Notochordal cells

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Authors' contributions
R.L.M was the primary contributor to both the writing and figures in the manuscript. The author has thoroughly reviewed and endorsed the final manuscript. R.L.M. has ownership rights over the figures designed on Adobe Illustrator.

Authors' informations
BSCs in Biochemistry and currently a second year MSCs student in molecular pathology at ESS, with parallel interests in diagnostic platforms, tissue bioengineering and regenerative medicine. Previous experience in studying immunomodulatory targets in disc degeneration/herniation.

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Availability of data and material
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. The references used to support the findings of this study are included within the article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The author declares no competing interests.

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