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Insights of stem cell-based endogenous repair of intervertebral disc degeneration

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Abstract

Low back pain has become more prevalent in recent years, causing enormous economic burden for society and government. Common therapies used in clinics including conservative treatment and surgery can only relieve pain. Subsequent cell-based treatment such as mesenchymal stem cell transplantation poses problems such as short duration of therapeutic effect and tumorigenesis. Recently, the discovery and identification of stem cell niche and stem/progenitor cells in intervertebral disc bring increased attention to endogenous repair strategy. Therefore, we review the studies involving endogenous repair strategy and present the characteristics and current status of this treatment. Meanwhile, we also discuss the strategy and perspective of endogenous repair strategy in future.

Key words: Low back pain; Intervertebral disc degeneration; Stem cell niche; Stem/progenitor cell; Endogenous repair strategy; Stem cell treatment

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Core tip: Low back pain has become more prevalent and brought enormous economic burden in recent years. However, therapies including conservative treatment, surgery, and cell-based treatment still have several defects. Endogenous repair is a novel therapeutic strategy for intervertebral disc degenerative disease that draws increased attention. We review the research regarding endogenous repair strategy using

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stem/progenitor cells as main cell resource, concluding and analyzing the status at present and perspective of endogenous repair strategy in future.

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INTRODUCTION

Low back pain (LBP) has become one of the most frequent causes for hospital visits and the leading reason of disability with population aging in the worldwide today^[1]. In addition, about 80% of adults will suffer from LBP at some point in their lives, which brings frequent sick leave and enormous economic burden for society and government^[2]. Especially in the United States, the estimated total expenses including direct and indirect costs of LBP exceed \$100 billion per year^[3]. Despite the complex and dim pathogeny and pathology of LBP, it is widely reported that 40% of LBP cases are associated with intervertebral disc (IVD) degeneration^[4-6].

The IVD is fibrocartilaginous tissue located between the vertebral bodies and composed of outer annulus fibrosus (AF), inner nucleus pulposus (NP), and cartilaginous endplates (CEP)^[7]. The structure of AF is formed by types I and II collagen fibers and elastin fibers arranged in concentric circles, which can withstand the tension produced by vertebral motion to maintain the position of NP^[8]. Meanwhile, the NP tissue is constituted by the extracellular matrix (ECM) including collagen type II and aggrecan synthesized and secreted by NP cells^[9]. Therefore, NP cells are so vitally important in IVD degeneration that we should pay more attention to them.

However, clinical therapies such as pharmacological treatments and surgeries are mainly focused on removing NP tissue and thus can only deal with relief of symptoms rather than restoration^[10]. Although many studies based on mesenchymal stem cell (MSC) transplantation have obtained positive results in attenuating or even reversing IVD degeneration in pre-clinical and clinical studies^[11-13], there are still some obstacles such as survival and differentiation of transplanted MSC caused by a specifically harsh environment in the degenerated IVD^[14,15]. Moreover, various complications including oncogenicity, ectopic ossification, and immune reactions indicated that more therapies should be explored^[16,17]. Thus, searching a new candidate for degenerative IVD treatment is especially important.

Niche, first proposed by Schofield^[18], is a specific anatomic localization composed of ECM and other noncellular components^[18,19]. Since this concept was introduced, many niches were found in a variety of tissues and organs including the skin, bone marrow, and the neural and digestive systems. The niche in the IVD defined as the perichondrium region adjacent to the epiphyseal plate (EP) and outer zone of the AF (AFo), raises a growing interest in boosting endogenous repair strategy (ERS) in degenerative IVD^[20-24]. And the novel ERS focuses on improving proliferation and promoting differentiation of stem cells derived from the IVD niche.

Thus, this review concentrates on the retrospect and assessment of research regarding the conception of endogenous repair through activating and mobilizing reparative MSCs located in specific anatomical niches of the IVD. Besides that, the review will also analyse the obstacles and difficulties needed to be conquered, which may help to accelerate the process of endogenous repair.

ENDOGENOUS REPAIR STRATEGY

Cell resource of ERS

It has been well accepted that NP cells consist of notochordal cells (NTC) and nucleopulocytes (NPCy; another known name is chondrocyte-like cells). Among them, NTC are responsible for maintaining tissue homeostasis and promoting growth while NPCy play a vital role in ECM synthesis^[25]. However, the NTC usually coexist with NPCy in the young and health IVD and decline with aging, thus other endogenous stem/progenitor cells may help to boost the progress of endogenous

repair in IVD degeneration by differentiating into various damaged IVD cells or excreting intercellular signaling molecules such as exosomes.

The cells first isolated from degenerative human NP and AF cells were characteristic of marrow MSCs and showed capacity of osteogenic, adipogenic, and chondrogenic differentiation^[26]. The following research studies illustrated that MSCs derived from NP can better withstand the terrible environment in degenerative IVD with improved proliferation and vitality compared with other MSCs^[27-29]. And the results of our previous study showed that the vitality and characteristics of such cells would be affected with aggravative degeneration^[30]. Besides that, previous studies have not only proved the presence of stem/progenitor cells in the NP, but also isolated stem/progenitor cells from the AF and CEP^[31-33]. Above all, these results show that stem/progenitor cells may migrate from the IVD niche to NP, AF, and CEP tissues. Thus, the key point of endogenous repair strategy is to increase the vitality of stem/progenitor cells in NP tissue or motivate their migration from the niche (**Figure 1**).

Characteristics of stem/progenitor cells in the NP, AF, and CEP

Stem/progenitor cell immunophenotypes: Those kinds of cells, also called MSCs derived from the NP, AF, and CEP, grow adherently in spindle shape after passage^[30] and mostly express MSC-like marker including CD73, CD90, and CD105 but not CD11b, CD14, CD19, CD34, CD45, or HLA-DR according to criteria of International Society for Cellular Therapy (ISCT) (**Table 1**)^[35]. Various research studies also found that NP-MSCs can be isolated from human^[40], rat^[39,56,58], rabbit^[54], and dog samples, which were positive (> 95%) for marker proteins CD29 and CD44 except in dogs. Furthermore, CD13 expressed frequently in granulocyte and CD24 related to proliferation and differentiation of B cells are membrane glycoprotein and detected in NP-MSCs from degenerative and normal IVD, respectively^[50,57]. Interestingly, a study by Jia *et al.*^[54] indicated that NP-MSCs derived from rabbits are negative not only for CD14 but also for CD4 and CD8, which has not been proposed before.

Stem/progenitor genes: Besides cellular markers, stem genes are considered as another criterion for identification of MSCs derived from the IVD, especially in NP tissue. Among them, Nanog (homeobox-containing), Oct4 (the POU domain-containing), and Sox2 (the HMG domain-containing) are transcription factors that play an essential role in the development and maintenance of normal pluripotent cells and are often used to assess the stemness of NP-MSCs (**Table 1**)^[28,30,59]. In addition, Notches and their ligand named Jagged show a crucial effect on the function and differentiation of human bone marrow MSCs (hBMMSC) and NP-MSCs^[35,60,61]. Moreover, our previous study provided further evidence that PCNA, CD166, and C-KIT can be chosen as stem/progenitor markers for NP-MSCs and decline with aging^[30,62]. Notably, a recent study by Tekari *et al.*^[63] demonstrated that Tie2⁺ NP-derived progenitor cells could be maintained in subsequent monolayer culture for up to 7 d by addition of fibroblast growth factor 2 or hypoxic conditions. Thus, it may be better to isolate NP-MSCs by Tie sorting method rather than just by plastic-adherent method^[36,63].

Multi-differentiation: Many studies confirmed that MSCs derived from the NP, AF, and CEP have the ability to differentiate into osteogenic, adipogenic, and chondrogenic lineages^[35-44]. Liu *et al.*^[49] compared the characteristics of three types of MSCs derived from human IVD including NP-MSCs, AF-MSCs, and CEP-MSCs and found that they showed similar multilineage differentiation capacities, whereas CEP-MSCs showed the best migration and invasion potency. Moreover, a stronger capacity of osteogenic and chondrogenic differentiation was confirmed by Wang *et al.*^[41] in CEP-MSCs. Above all, CEP-MSCs may be a new useful candidate for cell-based therapy and ERS.

NP-MSCs, another essential cell resource, show different advantages and drawbacks in differentiated capacity compared with other MSCs. Several reports have shown that NP-MSCs have the regeneration ability similar to BM-MSCs and adipose tissue-derived MSCs with same or superior capacity of chondrogenesis^[27,36,45,69]. But in the studies by Blanco *et al.*^[27] and Wang *et al.*^[41], NP-MSCs displayed weaker multilineage differentiation potentials and were even not able to differentiate into adipocytes. Besides the multilineage differentiation potential, such stem/progenitor cells are also capable of differentiation along neurogenic lineages both *in vitro* and *in vivo*, which needs to be further compared with other MSCs^[47,50]. Furthermore, Wu *et al.*^[40] discovered that MSCs derived from degenerative NP tissue show lower differentiation potentials compared with umbilical cord derived MSCs (UC-MSCs). These results demonstrated the differentiation potentials of NP-MSCs may be affected and impaired by the degeneration status of the IVD.

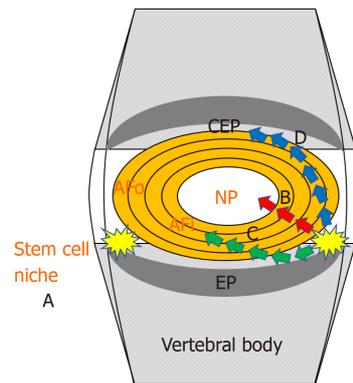


Figure 1 Cell resources of endogenous repair strategy. A: Stem cell niche, defined as the perichondrium region adjacent to the epiphyseal plate and outer zone of the annulus fibrosus (AF); B-D: Stem/progenitor cells could be isolated from the nucleus pulposus, AF, and cartilaginous endplates or migrate from the stem cell niche toward the nucleus pulposus (B), AF (C), and cartilaginous endplates (D). NP: Nucleus pulposus; EP: Epiphyseal plate; AF: Annulus fibrosus; AFo: Outer zone of the AF; AFi: Inner zone of the AF; CEP: Cartilaginous endplates.

Obstacles of endogenous repair

Since the existence of stem cell niche and stem/progenitor cells in the IVD has been proved, there may be three reasons for the degeneration of the IVD and failure of restoration still occurring. First, with increasing age and degeneration of the IVD, the stem/progenitor cells in the IVD or stem cell niche are possible to exhaust with aging, which cannot support the requirement of endogenous repair. Second, the degeneration of the IVD is prone to destroy the potential cellular migration pathways from the specific location of stem cell niche defined as the perichondrium region adjacent to the EP and AFo^[24]. Lastly, the harsh environment such as low pH condition^[35], inflammation^[37,56], compression loading^[42], high glucose^[57,68], oxidative stress^[64], hypoxia^[45], and hyperosmolarity^[55] may impair the biological function and arrest the proliferation of stem/progenitor cells in the IVD. Thus, searching solutions to resolve these questions may be our first priority to overcome the obstacles of endogenous repair.

Strategies and outcomes of endogenous repair

One simply effective strategy is to reduce the apoptosis and senescence of stem/progenitor cells in the IVD during IVD degeneration induced by various factors or increase the vitality and differentiation of stem/progenitor cells directly. It is well accepted that a normal pH is necessary to maintain normal cell function, whereas an excessively acidic environment induces increased cell apoptosis, reduced cell proliferation, and disordered matrix metabolism in the degenerated IVD^[67]. Amiloride, an acid-sensing ion channel, may meliorate IVD degeneration by improving the biological characteristics of NP-MSCs^[35]. Besides acid condition, inflammation is also a vitally important factor to induce IVD degeneration *via* some cytokines such as tumor necrosis factor (TNF)- α ^[37]. Cheng *et al.*^[56] found that TNF- α at low concentrations (0.1-10 ng/mL) promote the proliferation and migration ability of NP-MSCs, but inhibit their differentiation toward NP cells, indicating that the function of inflammatory cytokines may be a double-edged sword. In addition, pure/leukocyte-containing platelet-rich plasma (P/L-PRP) and modified notochordal cell-rich NP explants were confirmed to attenuate cell apoptosis and dysfunction of NP-MSCs induced by inflammation in the IVD^[37,54]. Moreover, oxidative stress caused by mitochondrial dysfunction plays a vitally important role in IVD degeneration^[68]. Our pervious research and other studies illustrated that some medicines such as cyclosporine and naringin are capable of alleviating mitochondrial dysfunction and oxidative stress^[64,52]. Tao *et al.*^[53] found that synergy between transforming growth factor beta 3 and insulin-like growth factor 1 could enhance NP-MSC viability, ECM biosynthesis, and differentiation towards NPCs by the MAPK/ERK signaling pathway.

The other strategy of endogenous repair is to replenish the stem/progenitor cells straightly. Various pre-clinical and clinical studies claimed that injection of MSC or MSC-like cells with or without biomaterial could significantly relieve degeneration of the IVD^[25,65]. The results of our recent study demonstrated that injectable hydrogel loaded NP-MSCs transplantation could delay the degeneration of the IVD and promote IVD regeneration in a rat model^[46]. This kind of strategy involved the expansion and reservation of NP-MSCs *in vitro*, which is the foundation of

Table 1 Expression of stem/progenitor immunophenotypes and genes of the intervertebral disc

Ref.	Type of stem cells	Expression of stem cell/progenitor immunophenotypes and genes
Human		
Liu <i>et al</i> ^[35] , 2016	NP-MSCs	CD73+, CD90+, CD105+, Oct4+, Nanog+, Jagged+ and Notch1+, CD34-, CD45-, HLA-DR-
Li <i>et al</i> ^[36] , 2017	NP-SCs	GD2+, Tie2+
Li <i>et al</i> ^[37] , 2018	NP-MSCs	CD73+, CD90+, CD105+, CD34-, CD45-, HLA-DR-
Jia <i>et al</i> ^[38] , 2017	D-NP-MSCs/ND-NP-MSCs	CD73+, CD90+, CD105+, Oct4+ and Nanog+, CD34-, CD45-, HLA-DR-
Wu <i>et al</i> ^[40] , 2017	NP-SCs/NPPCs	CD29+, CD44+, CD 73+, CD90+, CD105+, Oct4+ and Nanog+, CD11b-, CD14-, CD34-, CD45-, HLA-DR-
Wang <i>et al</i> ^[41] , 2016	NP-SCs/AF-SCs/CEP-SCs	CD73+, CD90+, CD105+, CD19-, CD34-, CD45-, HLA-DR-
Liang <i>et al</i> ^[42] , 2018	NP-MSCs	CD73+, CD90+, CD105+, Sox2+ and Oct4+, CD14-, CD19-, CD34-, HLA-DR-
Daisuke <i>et al</i> ^[43] , 2012	NPPCs	Tie2+, GD2+
Chen <i>et al</i> ^[44] , 2018	NP-MSCs	CD73+, CD90+, CD105+, CD34-, HLA-DR-
Quan <i>et al</i> ^[48] , 2015	NP-MSCs	CD29+, CD44+, CD105+, CD14-, CD34-, CD45-, HLA-DR-
Liu <i>et al</i> ^[49] , 2017	AF-MSCs, NP-MSCs, CEP-MSCs	CD73+, CD90+, CD105+, CD34-, CD45-, HLA-DR-
Blanco <i>et al</i> ^[27] , 2010	NP-MSCs	CD73+, CD90+, CD105+, CD106+, CD166+, CD19-, CD34-, CD45-, HLA-DR-
Lazzarini <i>et al</i> ^[50] , 2018	NP-MSCs	CD13+, CD73+, CD90+, CD105+, CD11b-, CD14-, CD19-, CD45-, HLA-DR-
Pereira <i>et al</i> ^[51] , 2016	CEP-MSCs	Not shown
Qi <i>et al</i> ^[57] , 2018	NP-MSCs	CD24+, CD73+, CD90+, CD105+, CD29-, CD45-
Rat		
Zhao <i>et al</i> ^[34] , 2017	NP-MSCs	CD73+, CD90+, CD105+, CD34-, CD45-
Li <i>et al</i> ^[39] , 2019	NP-MSCs	CD44+, CD73+, CD90+, CD105+, Oct4+, Nanog+ and Sox2+, CD34-, HLA-DR-
Li <i>et al</i> ^[45] , 2013	NP-MSCs	CD73+, CD90+, CD105+, CD34-, CD45-
Wang <i>et al</i> ^[46] , 2019	NP-MSCs	CD73+, CD90+, CD105, Tie2+, CD34-, CD45-
Nan <i>et al</i> ^[52] , 2019	NP-MSCs	CD73+, CD90+, CD105+, CD34-, CD45-
Han <i>et al</i> ^[29] , 2014	NP-MSCs	CD73+, CD90+, CD105+, CD34-, CD45-
Tao <i>et al</i> ^[28] , 2013	NP-MSCs	CD73+, CD90+, CD105+, Nanog+, Sox2+, Rex1+ and Oct4+, CD34-, CD45-
Tao <i>et al</i> ^[53] , 2015	NP-MSCs	CD73+, CD90+, CD105+, CD34-, CD45-
Liu <i>et al</i> ^[50] , 2019	N-NP-MSCs/D-NP-MSCs	CD73+, CD90+, CD105+, CD166+, Sox2+, Nanog+, Oct4+, LIF+, PCNA+ and C-KIT+, CD34-, CD45-
Li <i>et al</i> ^[55] , 2018	NP-MSCs	CD73+, CD90+, CD105+, CD34-, CD45-
Cheng <i>et al</i> ^[56] , 2019	NP-MSCs	CD29+, CD44+, CD90+, CD34-, CD45-
Lin <i>et al</i> ^[58] , 2017	NP-MSCs/NPPCs	CD29+, CD44+, CD90+, Nanog+, Oct4+ and Sox2+, CD34-, CD45-
Liu <i>et al</i> ^[68] , 2019	NP-MSCs	CD73+, CD90+, CD105+, Sox2+, Nanog+ and Oct4+, CD34-, CD45-
Zhang <i>et al</i> ^[69] , 2015	NP-MSCs	CD44+, CD73+, CD90+, CD105+, Sox2+, Nanog+ and Oct4+, CD14-, CD34-, CD45-, HLA-DR-
Dog		
Erwin <i>et al</i> ^[47] , 2013	NPPCs	Oct3/4+, Sox2+, CD133+, Nanog+ and Nestin+
Bovine		
Tekari <i>et al</i> ^[63] , 2016	NPPCs	Tie2+
Rabbit		
Jia <i>et al</i> ^[54] , 2018	NP-MSCs	CD29+, CD44+, CD166+, CD4-, CD8-, CD14-

MSC: Mesenchymal stem cell; NP: Nucleus pulposus; AF: Annulus fibrosus; CEP: Cartilaginous endplates; NPPC: NP-derived progenitor cell.

endogenous repair. Therefore, searching techniques that can facilitate culturing and

preservation seems to be especially crucial. A study by Lin *et al.*^[58] indicated that NP-MSCs at a low plated density (L-PD) (5 cells/cm²) show better biological characteristics, stronger multilineage differentiation, and higher expression of stem cell biomarkers compared with those at an M-PD (100 cells/cm²) and H-PD (10000 cells/cm²), suggesting that the limiting dilution method is a better method to isolate NP-MSCs^[58]. Moreover, the importance of cryopreservation cannot be ignored as it could prolong the application of NP-MSCs. The conventional cryopreservation methods were classified into slow freezing and vitrification (rapid freezing). The most often used dimethyl sulfoxide is regarded as the standard cryoprotectant which may cause cytotoxicity to MSCs^[69,70]. A recent study by Chen *et al.*^[44] showed that the addition of Icaritin known as antioxidant to the conventional freezing medium could improve the viability and function of cryopreserved human NP-MSCs, which may be a new method of preserving stem/progenitor cells in the IVD for ERS (Table 2).

CONCLUSION

Although IVD cell-based therapies have achieved some accomplishment in pre-clinical and clinical studies, there are still some defects such as short duration and tumorigenicity. The discovery of stem cell niche and stem/progenitor cells in the IVD inspired a novel treatment for degenerative IVD. These stem/progenitor cells, isolated from the NP, AF, and CEP, express MSC markers proposed by the ISCT. In addition, stemness related genes including *Nanog*, *Oct4*, and *Sox2* are proved to be expressed in these stem/progenitor cells. Moreover, such cells are similar to other MSCs as not only be capable of osteogenic, chondrogenic, and adipogenic differentiation, but also differentiate into the neurogenic lineages.

However, the ERS still faces some challenges such as exhaustion of stem/progenitor cells, broken migration pathway, and harsh microenvironment such as acid condition, hypoxia, compression loading, hyperosmolarity, high glucose, inflammation, and oxidative stress in degenerative IVD. Therefore, it is essential to look for methods which are able to overcome these obstacles and boost the process of ERS. These methods including reduced apoptosis and senescence caused by degenerative microenvironment or supplying stem/progenitor cells directly have been confirmed to be beneficial to treat degenerative IVD. Nevertheless, the ERS is still in pre-clinical studies and needs to be further investigated in future. In addition, seeking factors or medicines that are able to promote mobilization and migration of stem/progenitor cells in stem cell niche may become another novel direction of ERS.

Table 2 Highlights and strategy of endogenous repair

Ref.	Cells, biomaterial, and medicine	Highlights and strategy
Human		
Liu <i>et al</i> ^[35] , 2016	Amiloride	The biological behavior of NP-MSCs could be inhibited by acidic conditions, and amiloride may meliorate IVD degeneration by improving the activities of NP-MSCs.
Li <i>et al</i> ^[36] , 2017	NP-SCs	NP-SCs keep the regeneration ability similar to BMSCs with superior capacity in chondrogenesis.
Li <i>et al</i> ^[37] , 2018	Modified notochordal cell-rich NP explants	Modified notochordal cell-rich NP explants can attenuate degeneration and senescence of NP-MSC induced by TNF- α .
Jia <i>et al</i> ^[38] , 2017	D-NP-MSCs/ND-NP-MSCs	D-NP-MSCs displayed decreased biological characteristics compared with NP-MSCs.
Wu <i>et al</i> ^[40] , 2017	D-NP-MSCs/UCMSCs	D-NP-MSCs had lower expression of phenotype markers and exhibited reduced proliferation capability and differentiation potentials compared with UCMSCs.
Wang <i>et al</i> ^[41] , 2016	NPSCs/AFSCs/CESCs	A comparison of the osteogenic capacities: CESC > AFSC > BM-MSC > NPSC; for adipogenesis: BM-MSC > NPSC > CESC > AFSC; in chondrogenesis: CESC > AFSC > BMSC > NPSC.
Liang <i>et al</i> ^[42] , 2018	NP-MSCs	The biological behavior of NP-MSCs could be inhibited by compression loading.
Daisuke <i>et al</i> ^[43] , 2012	NPPCs	The frequency of Tie2+ cells decreases markedly in tissue with age and degeneration of the IVD, suggesting exhaustion of their capacity for regeneration.
Chen <i>et al</i> ^[44] , 2018	ICA	The addition of ICA to the conventional freezing medium could improve the viability and function of cryopreserved human NP-MSCs.
Quan <i>et al</i> ^[48] , 2015	MSC-like cells from NP	NP tissue contains MSC-like cells which could be isolated and proliferate <i>in vitro</i> .
Liu <i>et al</i> ^[49] , 2017	AF-MSCs, NP-MSCs, CEP-MSCs	AF-MSCs, NP-MSCs, and CEP-MSCs showed similar multilineage differentiation abilities; CEP-MSCs have the most powerful properties of migration and invasion when compared with AF-MSCs and NP-MSCs.
Blanco <i>et al</i> ^[27] , 2010	NP-MSCs	NP-MSCs were quite similar to BM-MSCs, with the exception that NP-MSCs are not able to differentiate into adipocytes.
Lazzarini <i>et al</i> ^[50] , 2018	NP-MSCs	NP-MSCs have the capacity of neuronal differentiation and could express neural markers without any electric functional properties.
Pereira <i>et al</i> ^[51] , 2016	CEP-MSCs	MSCs from CEP promote IVD regeneration by remodeling ECM.
Qi <i>et al</i> ^[57] , 2018	MSC-CM	MSC-CM has potential to alleviate HG induced cell cycle arrest and ECM degradation of NP-MSCs <i>via</i> p38 MAPK pathway.
Li <i>et al</i> ^[64] , 2018	CsA	CsA efficiently inhibited compression-induced NP-MSCs apoptosis by alleviating mitochondrial dysfunction and oxidative stress.
Rat		
Zhao <i>et al</i> ^[34] , 2017	NP-MSCs	The efficacy of NP-MSCs is compromised by age, and old NP-MSCs displayed senescent features.
Li <i>et al</i> ^[39] , 2019	NP-MSCs	The MSC-CM + CC method (MSC complete medium culture + cloning cylinder) is a more reliable and efficient way for isolating and purifying NP-MSCs.
Li <i>et al</i> ^[45] , 2013	NP-MSCs	Compared to AD-MSCs, NP-MSCs showed greater viability, proliferation, and chondrocytic differentiation under hypoxia.
Wang <i>et al</i> ^[46] , 2019	Injectable hydrogel-loaded NP-MSCs	Injectable hydrogel-loaded NP-MSCs transplantation can delay the level of IVD degeneration and promote the regeneration of the degenerative IVD in a rat model.

Nan <i>et al</i> ^[52] , 2019	Nar	Nar efficiently attenuated H ₂ O ₂ -induced NP-MSCs apoptosis and mitochondrial dysfunction through PI3/AKT pathway.
Han <i>et al</i> ^[29] , 2014	NP-MSCs	An acidic environment is a major obstacle for IVD regeneration by AD-MSCs or NP-MSCs; NP-MSCs appeared less sensitive to inhibition by acidic PH.
Tao <i>et al</i> ^[28] , 2013	NPCs-NP-MSCs co-culture	NP-MSCs could tolerate IVD-like high osmolarity and NPCs-NP-MSCs co-culture increased cell proliferation and the expression of SOX-9, aggrecan, and collagen-II.
Tao <i>et al</i> ^[53] , 2015	TGF-β3/IGF-1	The synergy between TGF-β3 and IGF-1 enhanced NP-MSCs viability, ECM biosynthesis, and differentiation towards NPCs by activating the MAPK/ERK signaling pathway.
Liu <i>et al</i> ^[30] , 2019	N-NP-MSCs/D-NP-MSCs	N-NP-MSCs showed a significantly higher proliferation rate, better stemness maintenance ability, but reduced cell apoptosis rate compared with D-NP-MSCs.
Li <i>et al</i> ^[55] , 2018	NP-MSCs	Hyperosmolarity of the IVD significantly inhibited the proliferation and chondrogenic differentiation of NP-MSCs by activating the ERK pathway.
Cheng <i>et al</i> ^[56] , 2019	TNF-α	Treatment with a high concentration of TNF-α (50-200 ng/mL) could induce apoptosis of NP-MSCs, whereas a relatively low TNF-α concentration (0.1-10 ng/mL) promoted the proliferation and migration of NP-MSCs, but inhibited their differentiation toward NP cells.
Lin <i>et al</i> ^[58] , 2017	L-PD of NP-MSCs	NP-MSCs at a L-PD (5 cells/cm ²) have better biological characteristic, stronger multilineage differentiation, and higher expression of stem cell biomarkers compared with those at an M-PD (100 cells/cm ²) and H-PD (10000 cells/cm ²).
Yang <i>et al</i> ^[65] , 2009	BMSCs	BMSCs could arrest the degeneration of the murine notochordal NP and contribute to the augmentation of the ECM in the NP by both autonomous differentiation and stimulatory action on endogenous cells.
Liu <i>et al</i> ^[68] , 2019	NP-MSCs	High glucose concentration significantly decrease vitality, migration, and stemness of NP-MSCs.
Zhang <i>et al</i> ^[69] , 2015	NP-MSCs	The chondrogenic ability of NP-MSCs and BM-MSCs was similar under induction <i>in vitro</i> .
Dog		
Erwin <i>et al</i> ^[47] , 2013	NPPCs	NPPCs have higher expression of the <i>Nanog</i> gene compared to MSCs and are capable of differentiation along chondrogenic, adipogenic, and neurogenic lineages <i>in vitro</i> and into oligodendrocyte, neuron, and astroglial specific precursor cells <i>in vivo</i> in the myelin-deficient shiverer mouse.
Bovine		
Tekari <i>et al</i> ^[63] , 2016	NPPCs	The Tie2+ cells (NPPC) were spheroid in shape with capacity of multi-differentiation and may decline fast, which was partially reversed by FGF2 and hypoxic conditions.
Rabbit		
Jia <i>et al</i> ^[54] , 2018	P-PRP/L-PRP	Both P-PRP and L-PRP could induce the proliferation and NP-differentiation of NP-MSCs; P-PRP could reduce the inflammatory and catabolic responses by avoiding the activation of the NF-κB pathway.
Rhesus macaque		
Huang <i>et al</i> ^[66] , 2013	DPCs, SLRP	SLRP could reduce the susceptibility of DPCs to hypoxia-induced apoptosis <i>via</i> promoting the activation/stabilization of HIF-1α and HIF-2α.

MSC: Mesenchymal stem cell; IVD: Intervertebral disc; NP: Nucleus pulposus; AF: Annulus fibrosus; CEP: Cartilaginous endplates; UCMSCs: Umbilical cord MSCs; AD: Adipose tissue; ECM: Extracellular matrix; ICA: Icaritin; CM: Conditioned medium; HG: High glucose; CsA: Cyclosporine; Nar: Naringin; TGF-β3: Transforming growth factor beta 3; IGF: Insulin-like growth factor; TNF: Tumor necrosis factor; L-PD: Low plating density; NPPC: NP-derived progenitor cell; BM-MSC: Bone marrow mesenchymal stem cell; P-PRP: Pure platelet-rich plasma; L-PRP: Leukocyte-containing platelet-rich plasma; DPCs: Intervertebral disc progenitor cells; SLRP: Leucine-rich proteoglycans.

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