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REVIEW
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The role of nucleus pulposus progenitor cells in intervertebral disc degeneration and regeneration

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Abstract

Intervertebral disc degeneration (IDD) is a significant public health issue, commonly associated with symptoms such as low back pain (LBP), and poses a substantial burden on both society and affected families. The pathogenesis of IDD primarily involves the depletion and impaired function of nucleus pulposus (NP) cells, as well as alterations in the extracellular matrix (ECM) composition. Current clinical management strategies, including conservative and surgical treatments, aim primarily to alleviate symptoms rather than reverse the pathological process or promote structural regeneration of the intervertebral disc (IVD). In recent years, studies have identified the presence of nucleus pulposus progenitor cells (NPPCs) within the NP region and characterized specific surface markers associated with these cells. Due to their ability to adapt to the harsh, nutrient-poor IVD microenvironr potential to effectively differentiate into NP-like cells, NPPCs have emerged as a promising candidate for cell-based regenerative therapies aimed at IVD repair. A deeper understanding of the biological properties and regulatory mechanisms of NPPCs is crucial for advancing their therapeutic application. This review summarizes current knowledge on NPPCs, including their characteristics, pathological alterations and associated signaling pathways during disc degeneration, and recent advances in NPPC-based therapies for IDD. Finally, the ongoing challenges for the clinical translation of NPPC-based therapies are discussed, along with potential directions for future research.

Keywords Intervertebral disc degeneration, Nucleus pulposus progenitor cells, Trilineage differentiation, MEK/ERK, Stem cell therapy, Intervertebral disc regeneration

Introduction

Intervertebral disc degeneration (IDD) is recognized as a major cause of lower back pain (LBP), which is a significant public health problem associated with substantial global disability [1–4]. Epidemiological studies suggest that approximately 50–80% of adults will experience LBP caused by IDD during their lifetime, significantly impairing quality of life and imposing a considerable socioeconomic burden [4–6]. The characteristics of IDD include decreased expression of proteoglycans and type II collagen, increased infiltration of inflammatory cells, and disruption of the extracellular matrix (ECM) structure [7]. Currently, the clinical treatment strategies for IDD,

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encompassing both conservative and surgical interventions, are primarily palliative, aimed at symptom relief rather than restoring the structure or biological function of degenerated discs [8]. Therefore, there is a pressing need for therapies capable of addressing the underlying structural pathology of IDD.

The intervertebral disc (IVD) is a fibrocartilaginous tissue connecting adjacent vertebral bodies, facilitating spinal mobility while providing mechanical stability [9]. It comprises three distinct anatomical regions: the nucleus pulposus (NP), a hydrated proteoglycan-rich gelatinous core; the annulus fibrosus (AF), consisting of concentric lamellae of collagen fibers; and the cartilaginous endplates (CEP), which interface with the vertebral bodies [10, 11]. The avascular NP tissue contains an ECM rich in highly hydrated proteoglycans and collagen, which functions to evenly distribute external forces to the AF, thereby preventing localized injuries from overloading [12, 13]. The highly organized, multi-lamellar AF offers strength and stability to the disc, enabling it to resist compressive forces [14, 15], while the CEP mediates nutrient diffusion between the vertebral marrow and the disc [16]. IDD progression is driven by an imbalance between repair and damage, which is characterized by increased catabolism and decreased anabolism, leading to altered matrix composition and a progressive loss of resident nucleus pulposus cells (NPCs) [17–19]. However, the precise molecular pathogenesis of IDD remains incompletely elucidated.

The depletion of NPCs is a central event in IDD, resulting in reduced synthesis of glycosaminoglycans and type II collagen, and ultimately impairing the IVD biomechanical function [20]. Regenerative strategies aimed at replenishing the NPC population have shown promise in reversing degenerative changes and promoting tissue restoration, highlighting the potential of cell-based therapies for IDD [21, 22]. Notably, nucleus pulposus progenitor cells (NPPCs) exhibit superior adaptability to the harsh microenvironment of the IVD, characterized by hypoxia, hyperosmolarity, and acidic conditions compared to other cell types such as adipose-derived mesenchymal stem cells (AD-MSCs) [23, 24]. Moreover, NPPCs demonstrate capacities for self-renewal and differentiation into NP-like cells, contributing to ECM synthesis and providing structural and biochemical support to neighboring IVD cells [25, 26]. These properties position NPPCs as promising candidates for cellular therapy in disc regeneration. Interestingly, evidence also suggests that NPPCs may possess the ability to differentiate into Schwann-like cells, indicating a potential role in neural repair applications [27].

Given their ability to mitigate the core pathological processes of IDD and stimulate tissue regeneration, NPPCs represent a compelling therapeutic avenue with potential advantages over conventional treatments [28]. Therefore, enhancing the understanding of NPPC biology is essential for advancing IDD treatment paradigms. This review seeks to synthesize current knowledge on NPPCs by outlining their origin, characteristic markers, and differentiation potential; examining their pathological alterations and signaling pathways during degeneration; and summarizing recent advances in NPPC-based therapies. Furthermore, it discusses the challenges in clinical translation and outlines future research directions. The overall goal is to contribute to the development of regenerative treatments that improve outcomes for IDD patients.

Characteristics of NPPCs

Source of NPPCs

In immature and young human IVDs, the initial cells within the NP are notochordal cells (NCs) [28]. NCs are present during early NP development and persist in the adult NP tissue [27, 29, 30]. These cells exhibit a distinct morphology, characterized by their large size and vacuolated appearance. During maturation and aging, NCs undergo terminal differentiation and transform into chondrocyte-like NPCs, which are smaller and lack vacuoles [31–33]. Consequently, NCs serve as the embryonic precursors for the predominant cell type found in the mature NP [29, 30].

Evidence indicates the presence of cells with stem/progenitor characteristics derived from the NP tissue, termed NPPCs [28, 34]. NPPCs are considered to represent an intermediate state in the gradual replacement of NCs by NPCs [35]. These progenitor cells have been identified in multiple species, including humans, rats, and pigs [36]. Morphologically, NPPCs exhibit a long spindle shape, uniform appearance, and a whirlpool arrangement (Fig. 1) [37]. Furthermore, potential stem cell niches have been identified in the outer AF regions and adjacent to the epiphyseal plate across mammalian species [38]. Within these niches, stem/progenitor cells may either remain in a quiescent state or undergo epithelial-mesenchymal transition (EMT) to migrate for tissue regeneration, serving as a local reservoir that may contribute to the maintenance and repair of the adult mammalian IVD [39, 40].

Cell markers of NPPCs

NPPC identity is commonly characterized by specific surface and molecular markers. Co-expression of Tie2 (CD202) and GD2 was initially proposed as a defining feature of progenitor cells across several species and has been used to identify NPPCs [36, 41–43]. However, more recent lineage tracing studies in mice suggest that Tie2 is not expressed in certain NP cell populations and does not mark NPPCs or their progeny [44]. Consistent with this,

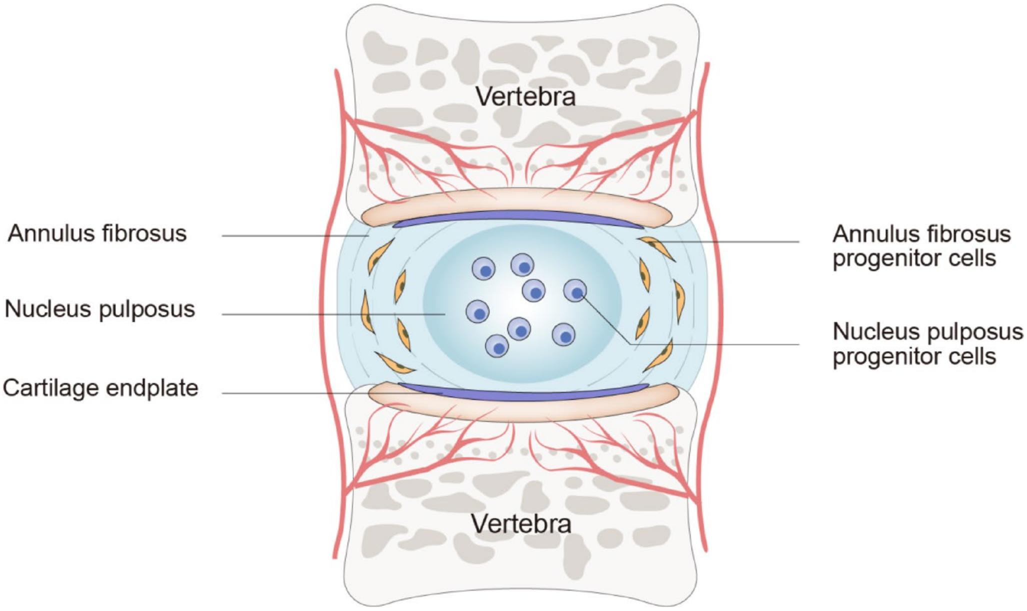

Fig. 1 Nucleus pulposus progenitor cells (NPPCs) in intervertebral discs (IVDs). NPPCs are situated within the nucleus pulposus (NP) of the IVDs, displaying a elongated spindle shape and a whirlpool-like arrangement [37]

analyses of human NP tissue indicate that GD2$^+$ cells are abundant, whereas TIE2$^+$ cells are rarely detected [45]. Interestingly, Tie2 expression has instead been associated with disc senescence and degeneration, pointing to its potential role as a biomarker of pathological states [36]. This is supported by the finding of a reduced percentage of Tie2$^+$ cells in elderly NP cells compared to young cells, while GD2 expression is maintained with age. [46].

CD24 expression identifies NP cells with progenitor characteristics. CD24$^+$ cells demonstrate multipotent differentiation and self-renewal potential in vitro, along with elevated expression of stem/progenitor-associated genes [47, 48]. Gene expression profiling reveals that CD24$^+$ subpopulations (both CD24$^+$/GD2$^+$ and CD24$^+$/GD2$^-$) express significantly higher levels of notochordal cell (NC) markers than CD24$^-$ subpopulations or unsorted NP cells, suggesting retention of a healthier, NC-like phenotype primarily associated with CD24 expression [45]. A small but persistent CD24$^+$/GD2$^+$ subpopulation maintains stable marker expression during human NP culture [45].

Several other genes have been proposed as potential markers for postnatal NPPCs in both mouse and human, including CD24 [48–51], CD221 [50], CD90 (Thy1) [44, 52], Fgfr3 [53], Lepr [54], Pdgfra (CD140a) [44], Uts2r [55], and Sox9 (Table 1) [44, 56]. Among these, CD24, Sox9, Pdgfra, Fgfr3, and Lepr, along with the canonical notochord marker Krt19, are expressed at both embryonic and postnatal stages [57]. In contrast, Thy1 (CD90) and UTS2R expression is detected only until E13.5 after IVD formation [44]. Progenitor-associated genes GREM1, KRT18, and TAGLN are expressed in young/non-degenerated NP, with TAGLN expression declining during aging [58]. More recently, Ctsk and MKI67$^+$ have been reported as novel postnatal NPPC markers [44, 51]. Ctsk, also labeling periosteal stem cells and tendon progenitors, shows predominant localization in the peripheral region of NP tissue, aligning with the observed peripheral residency of most NPPCs [44]. Compared to CD24$^+$ progenitors, the MKI67$^+$ progenitor subcluster exhibits enhanced activity in cell division, EMT, and inflammatory responses, and has been proposed to contribute to NP tissue self-repair during inflammation [51].

Multilineage differentiation potential of NPPCs

In vitro studies demonstrate that NPPCs possess broad multilineage differentiation potential. Beyond mesenchymal lineages, NPPCs can differentiate not only into neuronal cells but also into Schwann-like cells [27]. Additionally, they are capable of differentiating into osteoblasts, adipocytes, and chondrocytes under specific conditions (Table 2) [36, 42, 55, 60, 61]. Heterogeneity exists within the NPPC population, with Tie2$^+$ NPPCs exhibiting robust trilineage differentiation potential (osteogenic, adipogenic, chondrogenic) in vitro, whereas Tie2$^-$ cells lack this multipotency [43]. This functional difference is further reflected in clonogenicity assays, where Tie2$^+$ NPPCs form spheroid colonies in 3D culture, while Tie2$^-$ cells generate spread, fibroblastic colonies [42, 43].

Similarly, nucleus pulposus stem cells (NPSCs) exhibit similar tri-lineage differentiation potential comparable to bone marrow-derived stem cells (BMSCs) [62]. However, nucleus pulposus mesenchymal stem cells (NP-MSCs)

Table 1 Cell markers of NPPC

Study	Cells studied	Species	Key findings	References
Fujita et al. (2005)	NP cells	Rat	CD24 is a specific marker for NP	[49]
Scott et al. (2010)	Neural stem cells	Mouse and chick	Sox9 is expressed in radial glia, astrocytes, and oligodendrocyte precursor cells throughout development in the CNS, as well as in other types of stem cells	[56]
Sakai et al. (2012)	NP cells	Human and mouse	Tie2^{+} and GD2^{+} are populations of progenitor cells in the NP Tie2^{+} cells in patient tissues significantly decline with age and IVD degeneration CD24 is identified as a marker of progenitor cells in NP	[36]
Jin et al. (2013)	ADMSCs	Rat	CD90-positive ADMSCs led to the expression of IVD cell differentiation markers, such as aggrecan, collagen II, and Sox9	[52]
Chen et al. (2013)	Embryonic fibroblasts	Mouse	CD24 has been reported as an NP-specific marker	[49]
Tang et al. (2016)	NP cells	Human	CD24 and CD221 may be served as the notochordal NP cell markers	[50]
Tekari et al. (2016)	NP cells	Bovine	The bovine NP contains NPPCs that are Tie2^{+}	[43]
Sakai et al. (2018)	IVD tissue	Human, canine, bovine and murine	Tie2^{+} NPPCs have been detected across species	[41]
Frauchiger et al. (2019)	NP cells	Bovine	NPPCs expressed the angiopoietin-1 receptor Tie2 and exhibited self-renewal capacity and in vitro multipotency	[42]
Gao et al. (2020)	NP cells	Mouse	Lepr is one of the novel markers for notochord-derived cells	[54]
Sako et al. (2021)	NP cells	Human	WTC combined with FGF2 and cFGF supplementation to support and enhance NPPC and Tie2 expression	[59]
Xu et al. (2022)	NP cells	Mouse	Fgfr3^{+} NP cells were found to proliferate from outer region to inner region of NP during postnatal growth	[53]
Gao et al. (2022)	NP cells	Human and mouse	Uts2r^{+} NP cells are postnatal resident stem/progenitor cells	[55]
Wang et al. (2023)	IVD tissue	Human	CD24^{+} and MKI67^{+} progenitor were found in NP by scRNA-seq	[51]
Soma et al. (2023)	NP cells	Human	The expression of cell surface markers in NP includes Tie2, GD2, and CD24	[48]
Molinos et al. (2023)	NP cells	Bovine	Compared to young NP cells, elderly NP cells showed a reduced percentage of Tie2^{+} cells but maintained GD2 expression with age	[46]
Chen et al. (2024)	NP cells	Mouse	Numerous marker genes of postnatal NPPCs includes CD24a, CD90 (Thy1), Fgfr3, Lepr, Pdgfra (CD140a), Uts2r, Sox9 Ctsk serves as a novel postnatal NPPC marker, with predominant localization in the peripheral region of NP tissue Tie2^{+} is neither expressed in NP subsets nor labels NPPCs and their descendants in mouse models in cell lineage tracing	[44]
Tan et al. (2024)	NP cells	Human and mouse	Progenitor-associated genes GREM1, KRT18, and TAGLN were expressed in young/non-degenerated NP, with TAGLN expression declining during aging	[58]
Ionescu et al. (2024)	NP cells	Human	CD24^{+} and GD2^{+} cells were found in all NP samples regardless of age or degeneration grade, whereas Tie2^{+} cells were consistently very rare CD24^{+}/GD2^{+} co-expressing cells was identified and maintained its marker expression over time in culture	[45]

NP, nucleus pulposus; Tie2^{+}, Tie2-positive; GD2^{+}, disialoganglioside 2-positive; IVD, intervertebral disc; NPPCs, nucleus pulposus progenitor cells; CNS, central nervous system; ADMSCs, Adipose-Derived Mesenchymal Stem Cells; WTC, Whole tissue culture; FGF2, fibroblast growth factor 2; cFGF, chimeric FGF; Fgfr3^{+}, Fgfr3-positive; Uts2r, urotensin II receptor–expressing; Ctsk, cathepsin K; GREM, gremlin 1; KRT18, keratin 18; TAGLN, transgelin

exhibit a distinct differentiation profile: they can differentiate into osteocytes and chondrocytes in vitro but lack adipogenic potential, despite meeting other International Society for Cell Therapy (ISCT) criteria [63]. Notably, quiescence induction in NPSCs helps maintain key stem cell properties, including clonogenic self-renewal and differentiation capacity [64].

NPPCs can promote chondrogenic differentiation and support cartilage-like matrix formation in vitro [47]. Under hypoxic conditions, rat NPPCs show higher viability, proliferation, and chondrogenic differentiation capacity compared to adipose tissue-derived mesenchymal stem cells (AT-MSCs), suggesting potential utility for endogenous IVD repair [24]. Furthermore, ECM properties significantly influence NPPC differentiation

Table 2 Multilineage differentiation potential of NPPCs

Study	Cells studied	Method	Key findings	References
Bovine				
Tekari et al. (2016)	NP cells	Tri-lineage differentiation	Tie2$^+$ NP cells possess trilineage differentiation potential, whereas Tie2$^-$ NP cells lack this capacity	[43]
Frauchiger et al. (2019)	NP cells	Tri-lineage differentiation	Tie2$^+$ NPPCs are able to differentiate into osteogenic, adipogenic, and chondrogenic lineages in vitro	[42]
Mouse				
Sakai et al. (2012)	NP cells	Multipotent differentiation	NPPCs identified in Tie2$^+$ and GD2$^+$ populations demonstrated high proliferative capacity and multipotent differentiation potential into mesenchymal and NP lineages	[36]
Ishii et al. (2017)	NPPCs	Multipotent differentiation	NPPCs can differentiate not only into neuronal cells but also into Schwann-like cells	[27]
Rat				
Li et al. (2019)	NPSCs	Tri-lineage differentiation	The induction of quiescence in NPSCs maintains clonogenic self-renewal, osteogenic differentiation, and chondrogenic differentiation	[64]
Gao et al. (2022)	NP cells	Tri-lineage differentiation	Rat UTS2R$^+$ ProNPs formed CFU-F and displayed chondrogenic, osteogenic, and adipogenic differentiation abilities in vitro	[55]
Ma et al. (2024)	NPSCs	Tri-lineage differentiation	NPSCs had similar tri-lineage-induced differentiation characteristics to BMSCs	[62]
Human				
Gan et al. (2021)	NP cells	Tri-lineage differentiation	In the NP, a PROCR$^+$ resident progenitor population showed enriched CFU-F activity and trilineage differentiation capacity	[60]
Guerrero et al. (2021)	NP cells	Tri-lineage differentiation	3D expansion of NP cells were able to better differentiate into osteogenic, chondrogenic, and to a lesser extent adipogenic lineage even after in vitro expansion than 2D monolayer expanded NPCs	[61]

NP, nucleus pulposus; NPCs, nucleus pulposus cells; NPPCs, nucleus pulposus progenitor cells; NPSCs, nucleus pulposus stem cells; BMSCs, bone marrow-derived stem cells; CFU-F, colony-forming unit-fibroblast

pathways. Increased matrix stiffness promotes osteogenic differentiation, whereas softer hydrogel environments enhance chondrogenesis [65–67]. Consistent with the importance of the cellular microenvironment, 3D expansion better preserves NP cell differentiation capacity compared to 2D monolayer culture [61]. Collectively, these findings support the progenitor-like characteristics of NPPCs. Current evidence indicates a low risk of malignant transformation for potential regenerative applications [27].

NPPCs in IDD

Pathological alterations of NPPCs during IVD degeneration

The acidic and hypoxic microenvironment within the degenerating IVD inhibits NPPC proliferation and impedes endogenous stem cell recruitment [26]. While pathological hypoxia contributes to these inhibitory effects, physiological hypoxia ($\leq 5\%$ O$_2$) is essential for normal NP cell function; human NP cells, including progenitor populations, exhibit significantly higher metabolic activity under physiological hypoxia compared to normoxia (21% O$_2$) [68]. Studies in both rodents and humans demonstrate a progressive decline in NPPC number with advancing age and increasing severity of disc degeneration [36]. Disc degeneration and cellular senescence reduce stem cell marker expression (CD90$^+$, CD73$^+$, TIE2$^+$, CD24$^+$) and impair spheroid colony-forming unit (CFU-S) capacity in NPPCs, accelerating cellular depletion [69]. Concomitantly, aging induces characteristic morphological changes in notochordal NP cells, including increased cell area, diameter, and vesicle content [46], and diminishes NPPC pluripotency, characterized by decreased expression of core pluripotency markers like POU5F1 (also known as OCT4) and NANOG (Fig. 2) [70].

At the pathological level, excessive oxidative stress induces NPPC apoptosis and senescence [71], while abnormal mechanical loading compromises differentiation capacity and viability [72–74]. Parallel depletion occurs in perinuclear progenitor cells (periNP cells), which normally maintain NP homeostasis; these cells diminish in aged mice and are absent in degenerated discs, directly linking their loss to degeneration [58]. Furthermore, certain NPPCs may additionally contribute to pathological disc innervation through neurogenic potential [75]. Collectively, these alterations impair NPPC proliferative and differentiation capacities, limiting their regenerative potential for IVD repair.

Molecular mechanisms regulating NPPCs in IDD

Under conditions of elevated oxidative stress, excessive reactive oxygen species (ROS) accumulation and mitochondrial damage activate senescence pathways like P53/P21, contributing to accelerated ECM catabolism and

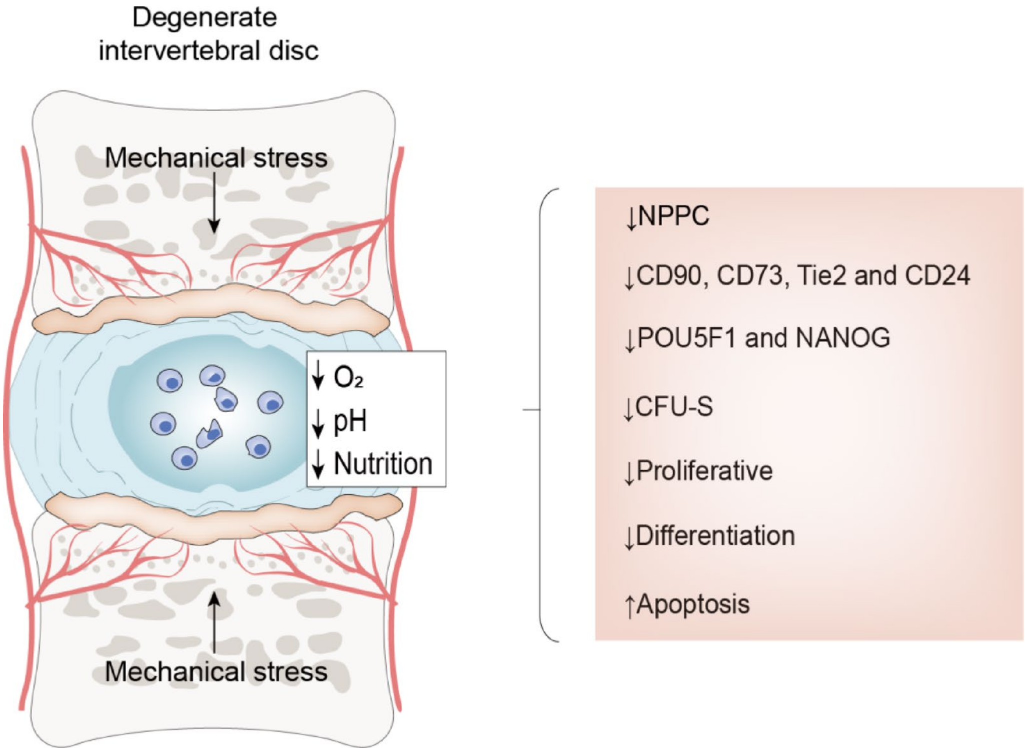

Fig. 2 Pathological alterations of NPPCs during IVD degeneration. IVD degeneration leads to several key alterations in NPPCs, including: reduced expression of stem cell markers (CD90, CD73, Tie2, CD24) and pluripotency markers (POU5F1, NANOG); diminished spheroid colony-forming unit (CFU-S) capacity; reduced proliferation and differentiation potential; and increased apoptosis

NPPC senescence [76]. Concurrently, inflammatory cytokines (TNF-α, IL-1β) promote ECM degradation correlating with degeneration severity [77, 78]. Conversely, some pathways collectively contribute to the survival and proliferation of NP cells, supporting the regeneration of NPPCs. The researchers found that platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and insulin-like growth factor-I (IGF-I) promote proliferation IVD cell proliferation and stimulate DNA synthesis via the MEK/ERK and PI3K/Akt signaling pathways [79]. The Ang1/Tie2 signaling axis enhances basal Notch signaling—partly through Akt-mediated β-catenin activation and subsequent increased Dll4 expression—reinforcing basement membrane formation and regulating vascular quiescence [80]. Furthermore, the MCE protein fibronectin (FN) preserves NPC function and viability during degeneration by activating PI3K/Akt signaling [81].

Stromal cell-derived factor-1α (SDF-1α) promotes chondrogenic differentiation and migration of $CXCR4^+$ NPPCs while enhancing aggrecan and collagen II synthesis [82]. Maintaining NPPC quiescence is essential for progenitor properties [37], with autophagy modulating elevated P27 levels in quiescent cells [64, 83]. In hypoxic disc environments, hypoxia-inducible factor 1 alpha (HIF-1α) activates autophagy pathways, helping to mitigate ROS generation while promoting chondrogenic differentiation and cartilage matrix synthesis [84]. Moreover, HIF-1α protects against NP cell death and ECM loss, largely through VEGF upregulation [85]. Heat shock protein 70 (HSP70) further protects NPPCs from stress and injury by regulating apoptotic pathways and suppressing JNK activation [86]. Collectively, modulating the IVD microenvironment, growth factor signaling, and specific intracellular pathways represents a potential strategy to enhance NPPC function and promote endogenous repair in degenerative disc disease (Fig. 3).

NPPCs-based therapy for IDD

Given the therapeutic potential for IVD regeneration, cell-based therapies for IDD encompass both in vitro stem cell transplantation and in vivo endogenous regeneration strategies aimed at restoring disc function and alleviating pain [87, 88]. NPPCs represent a promising cellular source due to their inherent adaptability to the harsh IVD microenvironment. Significant research therefore focuses on optimizing ex vivo NPPC culture to preserve critical progenitor traits.

The Whole Tissue Culture (WTC) method supplemented with FGF2 enhances in vitro maintenance of $Tie2^+$ NPPCs compared to standard primary culture [59]. For scalable expansion, optimized EZSPHERE spheroid culture enables large-scale production of phenotypically stable NPPCs, with CryoStor10 cryopreservation

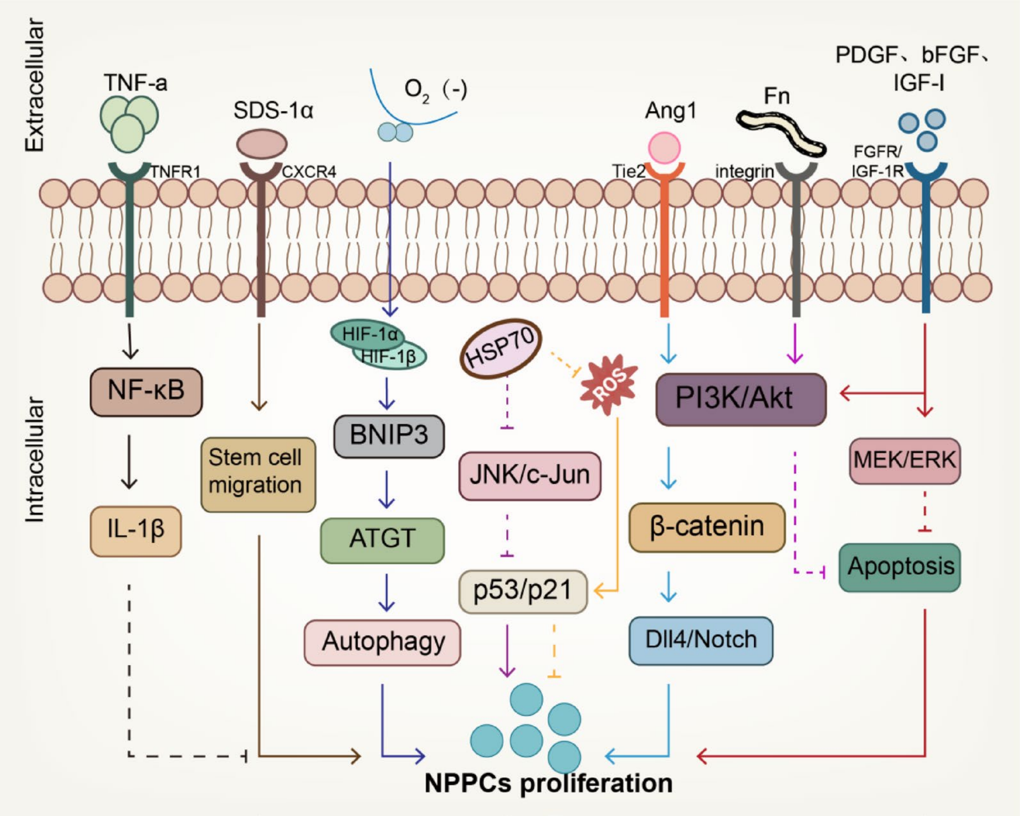

Fig. 3 Molecular mechanisms regulating NPPCs in IDD. The survival and apoptosis of NPPCs are regulated by various signaling pathways, including β-catenin, PI3K/Akt, MEK/ERK, NF-κB and JNK/c-Jun, in the context of IDD. Activation pathways are represented by '→' symbols, while inhibition pathways are represented by '⊥' symbols

maintaining post-thaw viability and Tie2 expression [89]. This spheroid system selectively enriches Tie2$^+$ NPPCs by inhibiting Tie2-negative cell proliferation [90]. To address low Tie2$^+$ yields during expansion—a key limitation in transplantation approaches—the PPARδ agonist GW501516 increases Tie2$^+$ NPPC proportions from approximately 7% to 50% across passages [91].

Preconditioning strategies help overcome transplantation barriers. Pretreatment with PEG-PIB inhibits pyroptosis induced by the acidic degenerative microenvironment [35]. Maintaining cellular quiescence supports homeostasis and reduces apoptosis compared to proliferating cells [37]. Engineered self-assembling peptides such as RADA-RKPS enhance NPPC survival, proliferation, and differentiation in apoptotic conditions, suggesting utility as delivery scaffolds [92].

While in vitro transplantation faces challenges including limited cell sources, restricted proliferative capacity, and low NP-specific differentiation potential, endogenous regeneration approaches offer advantages by potentially avoiding immune rejection and improving safety profiles [87]. However, effectively recruiting stem cells to injury sites remains challenging [35, 93]. Paracrine signaling provides alternative mechanisms: Conditioned media from umbilical cord mesenchymal stem cells (UCMSC-CM) restores stemness in degenerated NP cells and enhances NPPC differentiation [94], while exosomes from normal nucleus pulposus progenitor cells (N-NPSC-exo) transfer microRNAs that support AF cell growth and disc repair (Fig. 4) [95]. Collectively, these complementary NPPC-focused strategies demonstrate significant potential for advancing IDD treatment beyond conventional paradigms.

Challenges and limitations

Significant challenges impede the therapeutic application of NPPCs for IDD. A major challenge is obtaining sufficient quantities of NPPCs, such as the scarce Tie2$^+$ subpopulation [90]. To overcome this limitation, NCs have been investigated as a promising alternative due to their regenerative properties [22]. However, they are difficult to isolate from human tissue and their therapeutic efficacy remains unevaluated in clinical studies [22]. Furthermore, expanding NPPCs in vitro presents challenges in reliably maintaining their progenitor phenotype during culture. The acquisition of viable autologous IVD cells is also problematic: harvesting cells from healthy discs risks iatrogenic damage, while cells derived from degenerated

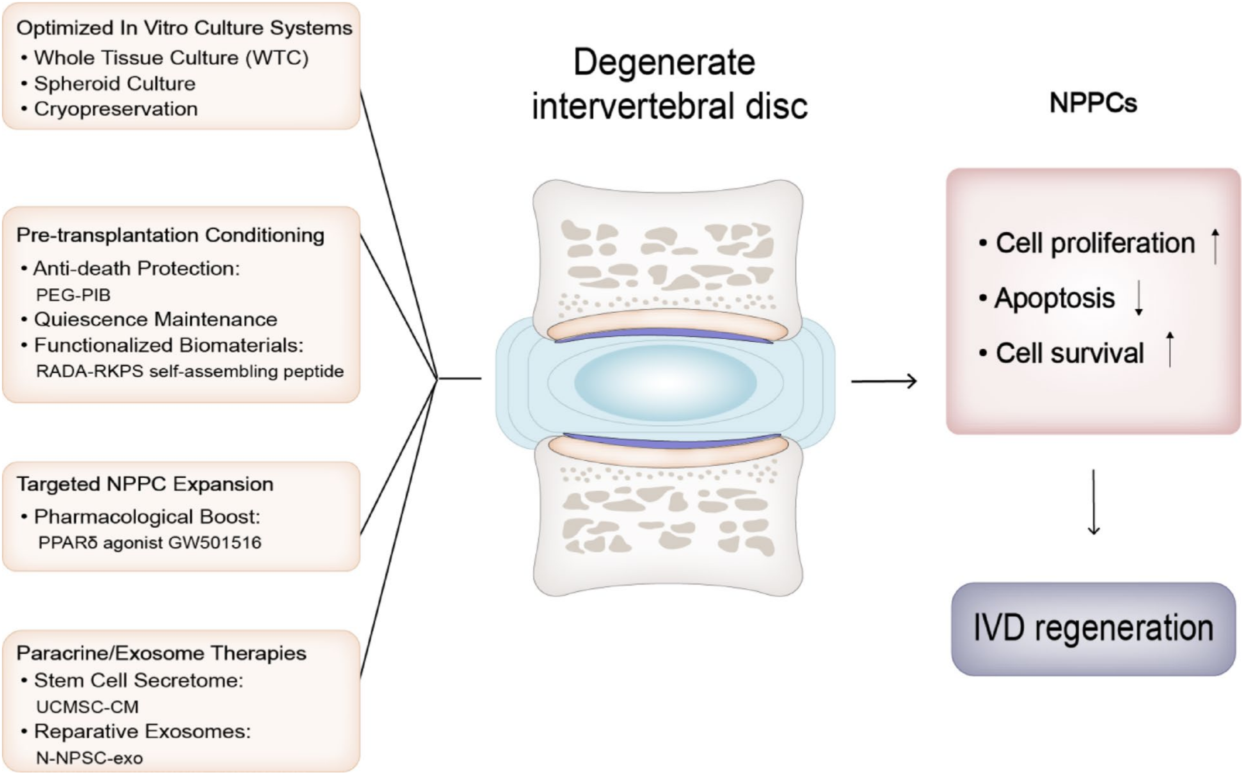

Fig. 4 NPPCs-based therapy for IDD. The treatment of IDD with NPPC involves multiple options, including Whole Tissue Culture (WTC), targeted NPPC expansion, pre-transplantation preconditioning, and paracrine/exosome therapies, which enhance therapeutic outcomes by modulating NPPC differentiation potential, promoting proliferation, and inhibiting apoptosis

discs often exhibit reduced viability and functionality. Although allogeneic or xenogeneic cell sources have been explored in animal models [96, 97], their clinical translation is constrained by potential immune rejection, ethical concerns, and a lack of supporting human data.

Even after successful isolation and expansion, NPPCs exhibit restricted proliferative capacity and a limited potential for specific differentiation into functional NP-like cells. Following transplantation, these cells must survive a hostile degenerative microenvironment characterized by nutrient deficiency, acidity, and inflammatory cytokines, which may induce cell death (e.g., pyroptosis) and further compromise their viability and function [36]. Additional concerns include the potential for immune rejection, as well as uncertainties around their long-term survival, integration, and functional persistence within the degenerate disc.

Strategies aimed at activating endogenous NPPCs or promoting their migration to sites of injury are also fraught with difficulties. Efficiently recruiting progenitor cells from niches such as the outer AF or the endplate to the NP remains a major hurdle [39]. The degenerative process itself may deplete these resident progenitor pools, impair essential EMT processes required for cell migration, or hinder the ability of migrated cells to reach their target locations [39]. Other intrinsic biological constraints include the limited differentiation capacity of NP-derived cells, such as the inability of NP-MSCs to undergo adipogenic differentiation, unlike BMSCs [63].

Beyond these biological and technical barriers, appropriate patient selection adds another layer of complexity. IDD is a multifactorial condition influenced by genetics, aging, mechanical stress, smoking, and obesity [98–100]. As disc degeneration can be a natural, asymptomatic part of aging, the specific pathological and symptomatic profiles that would most benefit from cell therapy are not well defined [101]. Current clinical trials often target patients with chronic low back pain; this symptom may not directly originate from IVD degeneration. Nevertheless, cell therapy could potentially benefit patients with progressive disc degeneration before the onset of secondary degenerative conditions (e.g., spinal canal stenosis or degenerative spondylolisthesis), provided that treatment safety and efficacy are conclusively demonstrated [22]. Collectively, major barriers to the clinical translation of NPPC-based therapies include difficulties in cell sourcing and characterization, in vitro expansion, post-transplantation survival and integration, the efficient recruitment of endogenous cells, and the identification of suitable patient populations. Addressing these challenges is essential for advancing this promising therapeutic strategy.

Discussion and conclusion

The identification of NPPCs within the IVD represents a pivotal advancement in disc biology, revealing an endogenous cell population with significant regenerative potential. This discovery positions NPPCs as a highly promising candidate for cell-based strategies aimed at counteracting IDD [36, 87]. Phenotypically, NPPCs are reported to express a combination of characteristic mesenchymal stem cell (MSC) markers and core pluripotency factors such as OCT3/4 and NANOG, which are thought to underpin their self-renewal and multilineage differentiation capabilities (e.g., chondrogenic, osteogenic) [60, 102]. The number of NPPCs declines precipitously with aging and degeneration [36, 60], and those that remain must contend with a hostile microenvironment defined by acidity, profound hypoxia, inflammatory mediators, and aberrant mechanical loading. This milieu actively suppresses NPPC function, leading to diminished proliferative and differentiation capacities, loss of stemness markers, and a fate skewed towards cell death or senescence [36, 60]. Therefore, preserving NPPC viability and function within this harsh environment is paramount for developing effective IDD interventions.

The behavior of NPPCs is governed by a complex interplay of molecular signaling pathways that act as central regulators of their fate. Key among these are β-catenin, PI3K/Akt, MEK/ERK, NF-κB, and JNK/c-Jun, which intricately balance NPPC proliferation, survival, apoptosis, and differentiation. Alterations in these pathways are a significant factor in NPPC dysfunction and impaired disc repair during degeneration. Therapeutically, this molecular landscape offers promising targets for intervention. For instance, growth factors like PDGF, bFGF, and IGF-I have been shown to promote disc cell proliferation by activating pro-survival ERK and Akt signaling [103]. Similarly, the Ang1/Tie2 axis and interactions with MCE components like fibronectin enhance NP cell survival and proliferation through PI3K/Akt activation [81]. This suggests that targeted pharmacologic or biologic modulation of these pathways could mitigate NPPC depletion and bolster their innate regenerative capacity, effectively transforming the diseased microenvironment from an inhibitory into a supportive one.

Given the central role of NP cell loss in IDD, cell-based therapies represent a rational strategy aimed at restoring disc structure rather than solely alleviating symptoms. Among these, NPPCs, which derive from the embryonic notochord, possess several advantageous properties such as their native identity within the IVD, inherent adaptation to its hypoxic environment, and a higher propensity to differentiate into NP-like cells [104]. However, NPPC-based therapies have not yet advanced to clinical trials, and translating them into practice remains challenging. Key obstacles include limited cell availability, difficulties in maintaining the progenitor phenotype during in vitro expansion, potential immune reactions, and uncertainties regarding their long-term survival, integration, and functional persistence within degenerative disc tissue.

These challenges have prompted the development of more advanced combinatorial approaches. One major direction involves engineered delivery systems—for example, incorporating NPPCs into biomaterial scaffolds such as RADA-RKPS hydrogels—to improve cell retention, offer mechanical support, and enhance survival and differentiation by mitigating the harsh local microenvironment [92]. Another strategy focuses on paracrine-based interventions, including the use of conditioned medium from umbilical cord MSCs or exosomes from NP cells, which may modulate inflammation, help maintain NPPC stemness, and stimulate matrix production without requiring live cells [94, 95]. Additionally, there is growing interest in activating endogenous NPPCs in situ. Approaches such as maintaining NPPCs in a protective quiescent state or preconditioning them to enhance resilience (e.g., via PEG-PIB to inhibit pyroptosis) could potentially promote intrinsic repair mechanisms while avoiding complex cell transplantation procedures [35]. The most successful future therapies will likely not rely on a single modality but will instead be multimodal, potentially combining a supportive biomaterial loaded with preconditioned NPPCs and controlled-release factors that simultaneously modulate the microenvironment and promote endogenous cell activation.

In conclusion, NPPCs contribute significantly to both the maintenance of disc health and the pathogenesis of IDD. Their depletion and functional impairment, driven by a hostile degenerative microenvironment and dysregulated signaling pathways, are critical factors in disease progression. Consequently, leveraging the inherent biological properties of NPPCs represents a promising therapeutic opportunity. Advancing this field depends on a deeper understanding of how the dynamic disc environment influences NPPC fate and function, and the mechanisms governing their interactions with other disc cell types. While NPPC-centered therapy holds substantial potential for mitigating IDD, translating this promise into effective clinical treatments requires overcoming major translational challenges. Future research must therefore prioritize: (1) optimizing methods for NPPC sourcing, expansion, and phenotype maintenance; (2) developing advanced biomaterial delivery systems and microenvironment-modulating strategies; (3) addressing potential immune compatibility issues; (4) conducting rigorous preclinical validation in biologically relevant models; and (5) exploring safe and efficient methods for endogenous NPPC activation. Addressing these key areas will be essential for developing robust NPPC-based regenerative therapies aimed at achieving structural and functional restoration of the degenerated disc.

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Author contributions
Ping Wang: Writing—review & editing, Writing—original draft, methodology, investigation, formal analysis, data curation, conceptualization. Dandan Wang: Writing—review & editing, Project administration, supervision, methodology, conceptualization. Huiying Li: Writing—review & editing, supervision, methodology, conceptualization. Xiangyuan Chen: Supervision, methodology, conceptualization. Wen Luo: Supervision, methodology, data curation. Yanli Yao: Supervision, methodology, conceptualization.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
As this manuscript is a review article, so conventional requirements of ethical approval and participant consent are not applicable.

Consent for publication
Not applicable.

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The authors declare no competing interests.

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