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REVIEW

The Role of TFEB-Regulated Autophagy in Intervertebral Disc Degeneration and Its Therapeutic Potential

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Abstract: Intervertebral disc degeneration (IVDD) is a major cause of chronic low back pain, driven by nucleus pulposus cell (NPC) senescence, extracellular matrix imbalance, and chronic inflammation. Transcription Factor EB (TFEB), a master regulator of autophagy and lysosomal biogenesis, has emerged as a pivotal player in degenerative diseases. By modulating autophagy-related genes, TFEB promotes the clearance of damaged components and maintains metabolic homeostasis in NPCs. Its dysfunction impairs autophagic flux, exacerbating cellular apoptosis, oxidative stress, and ECM degradation, thereby accelerating IVDD progression. Critically, this review is the first to systematically synthesize evidence positioning TFEB at the nexus of these pathological processes, establishing it as an integrative therapeutic target. We detail the molecular regulation of TFEB and its dysfunction in IVDD. Furthermore, we evaluate emerging TFEB-targeted strategies and discuss the key translational challenges. This work provides not only a mechanistic synthesis but also a forward-looking perspective on overcoming bottlenecks in TFEB-based therapy for IVDD.

Keywords: TFEB, intervertebral disc degeneration, autophagy flux, nucleus pulposus cells

Introduction

Low back pain (LBP) affects up to 80% of individuals during their lifetime, imposing substantial economic burdens on individuals, families, and society.[1] A comprehensive study spanning 204 countries identified LBP as the leading cause of disability-adjusted life years lost globally, with 619 million cases reported in 2020 and projected to increase to 843 million by 2050.[2] Intervertebral disc (IVD) degeneration (IVDD) constitutes the primary etiology of LBP.[3] The pathogenesis of IVDD involves complex mechanisms that frequently encompass cellular senescence, apoptosis, inflammatory responses, oxidative stress, and nutrient deprivation.[4–6] With advancing age, metabolic dysfunction in senescent nucleus pulposus cells (NPCs) and progressive extracellular matrix (ECM) degradation collectively drive the structural and functional deterioration of the IVD, thereby initiating and exacerbating IVDD.[7,8] Current clinical management of IVDD-related disorders primarily involves pharmacological and surgical interventions. However, conservative approaches (e.g., oral medications and physical therapy) and surgical procedures fail to address the underlying pathology.[9,10] Consequently, elucidating the molecular regulatory mechanisms of IVDD and developing targeted therapeutic strategies are urgently needed.

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Autophagy has emerged as a focal point of recent scientific inquiry into IVDD pathology, serving as a fundamental cellular mechanism for maintaining homeostasis.[11,12] It plays a context-dependent dual role in IVDD: while moderate autophagy protects cells, its dysregulation (either excessive or insufficient) can contribute to disease progression.[13–16] This duality underscores the importance of identifying its precise upstream regulators. Studies have indicated that autophagy activation can suppress cellular senescence and apoptosis, inhibit ECM degradation and inflammation, thereby delaying IVDD.[17,18] For example, Yurube et al[19,20] demonstrated that targeting the mammalian target of rapamycin complex 1 (mTORC1) effectively repairs IVDD both in vivo and in vitro through autophagy induction. Nevertheless, the precise modulation of autophagic activity presents significant challenges, highlighting the need to understand its master regulators.

Within the regulatory network of autophagy, Transcription Factor EB (TFEB) emerges as a pivotal master regulator.[21] TFEB is a core member of the microphthalmia-associated transcription factor (MiT/TFE) family and enhances autophagic and lysosomal function by regulating related genes.[22–24] Its therapeutic potential has been demonstrated in multiple pathologies, primarily through modulating the autophagy-lysosomal pathway.[25–28] However, systematic research on TFEB within the IVDD field remains limited and fragmented. Previous studies have revealed that TFEB expression and activity decline during aging, potentially accelerating IVDD.[12,29] This evidence suggests TFEB may play a key role, yet a comprehensive synthesis is lacking. Specifically, the integrative role of TFEB at the nexus of autophagy dysfunction, oxidative stress, and chronic inflammation in IVDD has not been critically reviewed, and its potential as a therapeutic target remains underexplored.

Therefore, elucidating the mechanistic role of TFEB-regulated autophagy in IVDD is crucial. This review systematically summarizes the central role of TFEB in regulating autophagy in NPCs, examines its pathological implications in IVDD, and critically analyzes the current advances in TFEB-targeted therapeutic strategies to provide novel insights and therapeutic targets for IVDD management.

Literature Search Methodology

To identify relevant literature for this narrative review, a systematic search was conducted in the PubMed and Web of Science electronic databases up to February 2026. The search strategy employed a combination of the following keywords and their variants: “Transcription Factor EB” OR “TFEB” AND “autophagy” AND (“intervertebral disc degeneration” OR “IVDD” OR “nucleus pulposus”). The reference lists of key articles were also manually screened to identify additional pertinent studies. Articles were included if they primarily investigated the role of TFEB and/or its regulated autophagy in the context of intervertebral disc biology or degeneration. Studies focusing solely on autophagy in IVDD without reference to TFEB, or on TFEB in other organ systems without disc relevance, were excluded. This approach aimed to ensure a comprehensive and focused synthesis of the current evidence linking TFEB to IVDD pathology.

Dual Regulatory Role of Autophagy in Intervertebral Disc Degeneration

Autophagy Overview

Autophagy is a highly conserved cellular process that is dependent on the lysosomal system to degrade damaged or redundant intracellular macromolecular structures, such as proteins and organelles. It serves as a critical mechanism for maintaining cellular homeostasis and responding to stress.[30,31] Based on substrate delivery mechanisms and membrane origin, autophagy is primarily classified into three categories, macroautophagy, which involves the formation of double-membraned autophagosomes that engulf cytoplasmic components, ultimately fusing with lysosomes for degradation. This is the most extensively studied form and plays a central role in IVDD.[32,33] Moreover, microautophagy and chaperone-mediated autophagy (CMA) represent two supplementary autophagic modalities.[34,35] Mitophagy, a specialized form of macroautophagy, selectively removes damaged or depolarized mitochondria to maintain cellular metabolic balance and function.[36,37] However, excessive mitophagy activation can lead to mitochondrial dysfunction and cell death.[38,39] The autophagic continuum encompasses stress-induced initiation, followed by autophagosome biogenesis, subsequent lysosomal fusion, and terminating in substrate degradation with material recycling.[40,41]

Pathobiological Progression of Intervertebral Disc Degeneration

The IVD is a fibrocartilaginous cushion situated between adjacent vertebrae, comprising three distinct structural components: the central gelatinous NP, the inner and outer layers of the annulus fibrosus (AF), and the superior and inferior cartilaginous endplates (CEP).[42] IVDD arises from the synergistic action of multiple pathological mechanisms, among which NPC senescence and apoptosis, imbalance between ECM catabolism and anabolism, activation of inflammatory responses, fibrosis of the AF, and calcification of the CEP all play pivotal roles.[6,43] As degeneration progresses, NPC senescence and inflammation lead to decreased ECM synthesis and increased activity of degradative enzymes (such as matrix metalloproteinases and a disintegrin and metalloproteinase with thrombospondin motifs), exacerbating matrix degradation. This process severely compromises the structural integrity and functional capacity of the IVD. Chronic inflammation triggered by cellular senescence further exacerbates ECM degradation and AF disruption via proinflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α).[44,45]

Fibrosis within the AF and the loss of proteoglycans diminish their mechanical strength, resulting in compromised disc stability. These pathological alterations interact synergistically, collectively impairing the biomechanical function of the IVD and driving pathological progression of IVDD.

Dual Regulatory Mechanisms of Autophagy in Intervertebral Disc Degeneration

With NPC senescence, ECM metabolic imbalance, and exacerbated inflammatory responses within the IVD, autophagy functions as a critical cellular self-protection mechanism, exerting complex regulatory roles in this process. Moderate autophagy degrades intracellular proteins and organelles, thereby maintaining normal cellular metabolism and homeostasis. However, both the overactivation and inhibition of autophagy may exacerbate IVDD. Particularly in hypoxic and nutrient-deficient microenvironments, dysregulation of autophagic function in NPCs further aggravates IVDD (Figure 1) and (Table 1). Therefore, a comprehensive analysis of the role of autophagy in IVDD not only facilitates the elucidation of its pathophysiological mechanisms but also provides novel insights for developing related therapeutic strategies.

Autophagy Inhibits Nucleus Pulposus Cell Senescence

Cellular senescence constitutes a core pathological hallmark of IVDD, characterized by irreversible cell cycle arrest and induction of the senescence-associated secretory phenotype (SASP).[63] Activation of the autophagic pathway has been shown to effectively mitigate NPC senescence. For instance, *Tbxt* expression is reduced in degenerative NPCs. Its overexpression significantly enhances autophagy by driving the transcriptional upregulation of *ATG7*, thereby mitigating H_2O_2-induced cellular senescence and death. This protective effect is abrogated by the autophagy inhibitor 3-methyladenine (3-MA).[46] Concurrently, Wang et al[47] elucidated that isorhapontigenin mitigates NPC senescence and suppresses ECM degradation by augmenting PI3K/AKT/mTOR-mediated autophagy. Furthermore, Chen et al[48] observed decreased *SIRT6* expression in senescent cells. Overexpression of SIRT6 activates autophagy and reduces stress-induced senescence in NPCs, an effect that is partially reversed by autophagy inhibitors. Collectively, these findings confirm that targeted modulation of the autophagic pathway provides a novel therapeutic strategy for IVDD intervention by delaying NPC senescence.

Autophagy Inhibits Nucleus Pulposus Cell Apoptosis

Apoptosis, a classical form of programmed cell death, plays a pivotal role in metabolic processes in living organisms. Autophagy is closely associated with apoptosis of NPCs. Zhou et al[49] observed that irisin inhibits NPC senescence and apoptosis by activating autophagy, thereby delaying IVDD. Further investigations by Lin et al[50] confirmed that urolithin A (UA) significantly suppressed NPC apoptosis through the selective activation of the mitophagy pathway, consequently maintaining cell viability and secretory-metabolic function under stress conditions. Animal experiments revealed that UA intervention effectively ameliorated pathological damage in the IVD and surrounding tissues in a puncture-induced IVDD rat model, while decelerating IVDD progression. Additionally, Bai et al[51] discovered that cyanidin modulated the expression levels of LC3-II/I conversion (0.83-fold upregulation), cleaved Caspase-3, and pro-apoptotic protein BAX through the activation of autophagic

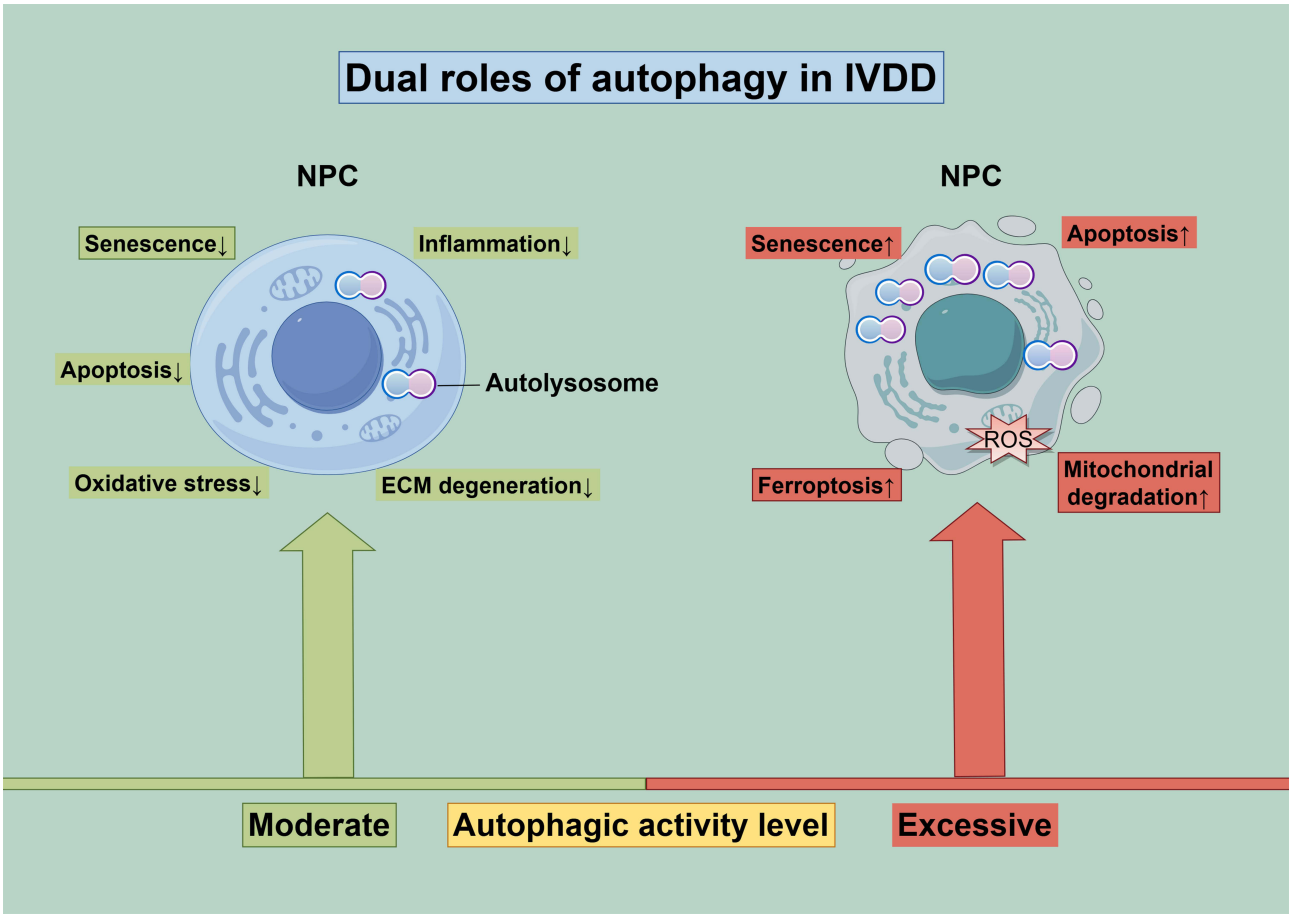

Figure 1 The dual roles of autophagy in IVDD. Autophagy serves as a critical cellular survival mechanism. Within the IVDD, autophagy delays or prevents the progression of IVDD by facilitating the clearance of damaged organelles and misfolded proteins; conversely, excessive autophagy accelerates degeneration by inducing apoptosis and senescence of NPCs.When the non-protective effects of autophagy become progressively amplified, they may potentiate IVDD progression.

activity in rat NPCs. This upregulated the autophagic flux, thereby delaying NPC degeneration and inhibiting apoptosis. This study showed that cyanidin ameliorated NPC functionality in IVDD by modulating the JAK2/STAT3 signaling pathway, providing experimental evidence for its potential as a therapeutic target.

Autophagy Activation Maintains Extracellular Matrix Homeostasis

The ECM constitutes an essential external environment for cell survival, and ECM metabolic imbalance is a major pathological hallmark of IVDD. Zhang et al[52] found that quercetin significantly enhanced the protein expression levels of the autophagy markers LC3-II and Beclin-1 in NPCs, while simultaneously reducing MMP-13 expression. This maintains a balance between ECM synthesis and degradation, thereby preserving normal compositional proportions. Further mechanistic investigations confirmed that quercetin enhanced autophagic flux through the activation of the SIRT1 signaling pathway, significantly inhibiting ECM degradation. Animal model studies demonstrated that quercetin exerts protective effects on degenerated IVDs by suppressing ECM degradation.[53] Another study identified miR-210 as a critical regulatory target that modulates IVDD by regulating NPC autophagy activity and ECM metabolic homeostasis.[54] Taken together, these results indicate that autophagy effectively regulates the synthesis-degradation equilibrium of the ECM, suggesting that targeted modulation of autophagy may serve as an efficient strategy for preventing and treating IVDD.

Autophagy Suppresses Inflammation

The pathological progression of IVDD is closely associated with an inflammatory microenvironment. Degenerated disc tissues exhibit abnormal accumulation of proinflammatory mediators such as TNF-α, IL-1β, and interleukin-17 (IL-17). These inflammatory cytokines play crucial roles in IVDD pathogenesis by driving matrix metabolic imbalance and

Table 1 Dual Role of Autophagy in IVDD: Key Evidence Summary

Effect Type	Primary Function/Effect	Key Regulators/ Interventions	Core Molecular Mechanisms/Pathways
Protective Role	Inhibition of NPC senescence	*Tbxt*,[46] isorhapontigenin,[47] *SIRT6*[48]	*ATG7* gene transcription ↑; PI3K/AKT/mTOR pathway ↑; autophagic activity ↑
	Inhibition of NPC apoptosis	Irisin,[49] urolithin A,[50] cyanidin[51]	Autophagic activity ↑; mitophagy activity ↑; JAK2/STAT3 pathway ↑
	Maintenance of ECM homeostasis	Quercetin,[52,53] miR-210[54]	LC3-II ↑; Beclin-1 ↑; MMP-13 ↓; SIRT1 signaling pathway ↑; regulate ECM metabolism
	Suppression of inflammation	Rapamycin,[55] *p65*[56]	mTORC1 ↓; IL-1β ↓; NF-κB signaling pathway ↓
	Attenuation of oxidative stress	Delphinidin,[57] Isoginkgetin,[58] Lycopene[59]	SIRT1/AMPK/mTOR pathway ↑; NRF2 signaling pathway ↑
Detrimental Role	Induction of NPC apoptosis/senescence	Excessive mechanical load (>1.0 MPa stress)[60]	ROS ↑
	Enhancement of mitochondrial degradation	Chronic mechanical stress[61]	Mitophagy activity ↑
	Promotion of NPSC ferroptosis	*RBX1*[62]	Ferritinophagy ↑

cellular senescence.[64] A recent study revealed that rapamycin effectively ameliorates IL-1β-induced inflammatory injury in NPCs through mTORC1 inhibition and subsequent activation of autophagic flux.[55] Yi et al[56] reported that specific inhibition of the nuclear factor-kappa B (NF-κB) signaling pathway in NPCs substantially alleviates lipopolysaccharide (LPS)-induced inflammatory cascades via autophagy activation. In vitro experiments confirmed that *p65* gene silencing not only significantly elevated LC3-II levels and promoted p62 protein degradation but also concomitantly reduced the expression of proinflammatory mediators, including TNF-α and IL-1β. Notably, these anti-inflammatory effects were markedly reversed following intervention with the autophagy inhibitor, chloroquine, indicating that autophagy activation plays an essential role in suppressing inflammatory responses.

Autophagy Attenuates Oxidative Stress

Oxidative stress refers to a pathological process characterized by excessive accumulation of reactive oxygen species (ROS) generated during cellular metabolism, leading to structural and functional damage to cells.[65] Oxidative stress can mediate cellular senescence and death through activation of multiple signaling pathways.[45] Current evidence indicates that delphinidin protects NPCs from oxidative stress-induced damage by activating the SIRT1/AMPK/mTOR pathway to promote autophagy.[57] Yu et al[58] reported that targeted delivery of isoginkgetin via a ROS-responsive delivery system significantly suppresses H_2O_2-induced ROS accumulation in NPCs, upregulates ECM synthesis proteins, and counteracts mitochondrial damage through autophagy activation. Notably, this protective effect was markedly attenuated by treatment with inhibitors of autophagy. Additionally, Yang et al[59] revealed that lycopene potentially mitigates oxidative stress-induced IVDD by activating the nuclear factor erythroid 2-related factor 2 (NRF2) signaling pathway.

Excessive Autophagy Accelerates Intervertebral Disc Degeneration

Autophagy manifests as a paradoxical double-edged sword effect in IVDD. Although moderate autophagy activation exerts cytoprotective effects, excessive or sustained autophagic activity exacerbates IVDD.

In an early study, researchers discovered that excessive autophagy activation promotes NPC apoptosis and senescence. When murine NPCs were treated with the autophagy inhibitor 3-MA under 1.0 MPa pressure, cell mortality

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increased significantly within 48 hours compared to pressure-only control groups.[60] However, this pro-death effect of 3-MA markedly diminished beyond the 48-hour timeframe. This suggests that moderate autophagy activation during initial stress exposure protects NPCs; however, when the stimulus intensity or duration exceeds critical thresholds, enhanced autophagic flux may paradoxically accelerate NPC apoptosis. Jin et al[66] revealed that estradiol alleviates menopause-induced IVDD in rat models by suppressing autophagy. Subsequent investigations have substantiated that this temporally dependent shift in autophagic function manifests more pronouncedly within distinct autophagic pathways. Huang et al[61] demonstrated that prolonged mechanical stress accelerates NPC senescence by activating the *PINK1/Parkin*-mediated mitophagy pathway, which triggers excessive mitochondrial degradation. Notably, Zhou et al[62] identified that within the acidic microenvironment of IVDD, *NCOA4*-mediated ferritinophagy becomes aberrantly enhanced, driving intracellular iron overload and inducing ferroptosis in nucleus pulposus stem cells (NPSCs). *Ring-box 1* (*RBX1*) functions as a critical negative regulator and its functional inhibition exacerbates this pathological cascade. Experimental overexpression of *RBX1* effectively protected NPSCs and retarded degeneration progression, thereby providing novel evidence of the detrimental consequences of excessive autophagy activation.

Autophagy plays a dual role in IVDD. Moderate activation facilitates the clearance of damaged organelles, maintains ECM homeostasis, delays cellular senescence and apoptosis, and suppresses inflammatory responses, thereby conferring protective effects. Conversely, the excessive activation of autophagy may induce cellular dysfunction, senescence, and programmed cell death, ultimately exacerbating IVDD. Consequently, precise modulation of autophagic activity to prevent both hyperactivation and oversuppression represents a pivotal challenge for future IVDD prevention and treatment research. However, the precise threshold or molecular switch that defines the transition of autophagy from a protective to a detrimental process in IVDD remains unclear. Future studies are needed to elucidate how TFEB activity precisely regulates this equilibrium across different disease stages or under varying microenvironmental stresses.

Fundamental Functions and Regulatory Mechanisms of TFEB

Given the central role of autophagy in the pathological progression of IVDD and its dual regulatory nature, precise targeting of autophagic activity has emerged as a highly promising therapeutic strategy. However, achieving such a precise modulation presents significant challenges. TFEB, which functions as the master transcriptional regulator of the autophagy-lysosome pathway, orchestrates key processes including autophagosome formation, lysosomal biogenesis, and autophagic substrate degradation. Therefore, it plays a pivotal role in maintaining autophagic homeostasis. A comprehensive understanding of the biological characteristics of TFEB and its intricate regulatory network is fundamental for elucidating its mechanistic role in IVDD and developing targeted intervention strategies.

Biological Characteristics of TFEB

TFEB is a member of the microphthalmia-associated transcription factor E (MiT/TFE) family. As a central regulator of lysosomal biogenesis and autophagy, TFEB plays an indispensable role in maintaining cellular homeostasis and in clearing damaged organelles and proteins.[67] Under nutrient-replete conditions, TFEB is predominantly localized within the cytoplasm. However, under stress conditions, including starvation, lysosomal stress, infection, inflammation, and mitochondrial damage, TFEB translocates to the nucleus and activates the transcription of genes encoding autophagy regulators and lysosomal functional components.[68,69] Furthermore, TFEB participates in the regulation of multiple biological processes, including cellular senescence, DNA repair, carbohydrate metabolism, lipid metabolism, and the WNT signaling pathway.[70–72]

Regulatory Mechanisms of TFEB

The activity of TFEB primarily depends on its subcellular localization and is stringently regulated through post-translational modifications (Figure 2).[68] The phosphorylation status of specific serine residues within the TFEB protein directly determines its cellular localization. Phosphorylated TFEB predominantly resides in the cytoplasm, whereas dephosphorylated TFEB translocates to the nucleus.[30] Kinases involved in TFEB phosphorylation include mTORC1, extracellular signal-regulated kinase 2 (ERK2, also known as MAPK1), calcineurin (e.g., protein phosphatase 2A), protein kinase B (AKT), and glycogen synthase kinase 3 beta (GSK3β).[69,73,74]

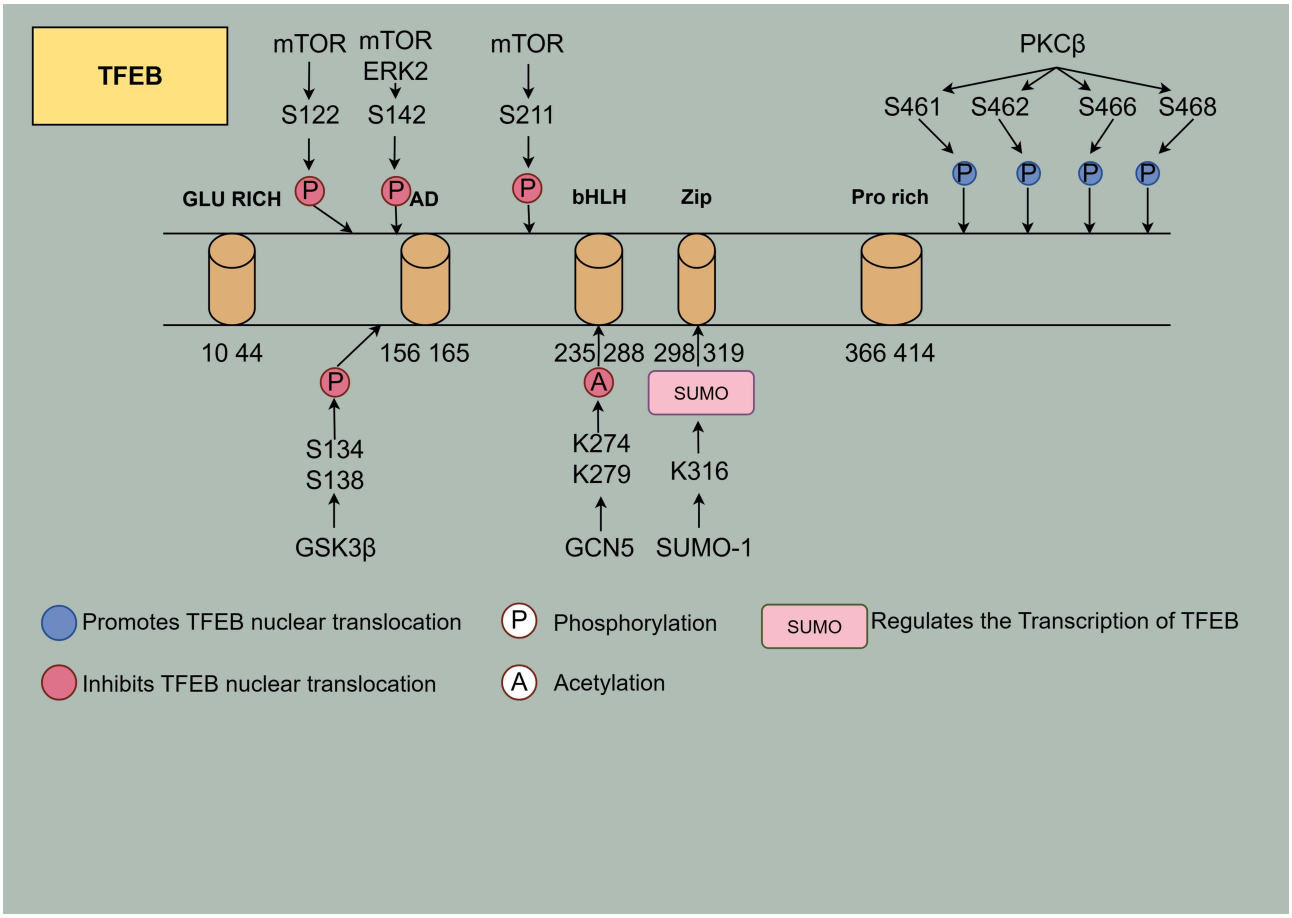

Figure 2 Post-translational modifications of TFEB and their modification sites within TFEB structural domains. The activity of TFEB is tightly regulated by post-translational modifications, including phosphorylation, acetylation, and sumoylation. This figure illustrates the various post-translational modifications of TFEB and their corresponding modification sites.

As a central metabolic regulatory hub, mTORC1 dynamically coordinates cellular responses to environmental signals by mediating the phosphorylation of multiple substrates.[75] Under nutrient-sufficient conditions, activated mTORC1 phosphorylates TFEB, retaining it in the cytoplasm and consequently suppressing the transcription of autophagy and lysosomal biogenesis genes. Conversely, during amino acid deprivation, mTORC1 inactivation leads to TFEB dephosphorylation and dissociation from RAG GTPases, enabling its nuclear translocation and activation of autophagy-related gene expression.[29] The S122, S142, and S211 residues of TFEB serve as phosphorylation targets for mTORC1.[76] Notably, phosphorylation at S142 is mediated not only by mTORC1 but also by ERK2. Under nutrient-replete conditions, ERK2 phosphorylates TFEB, thereby inhibiting its nuclear entry.[77] GSK3β phosphorylates TFEB at S134 and S138 residues, promoting cytoplasmic retention. Conversely, GSK3β inhibition facilitated TFEB nuclear translocation. Protein kinase C isoforms PKCα and PKCδ induce TFEB nuclear translocation by inhibiting GSK3β-mediated phosphorylation of TFEB.[78]

In addition to phosphorylation, TFEB activity is regulated through other post-translational modifications, including acetylation and SUMOylation.[67] These are critical post-translational modifications that finely regulate protein stability, solubility, enzymatic activity, and intracellular localization. Acetyltransferase GCN5 inhibits the nuclear translocation of TFEB at lysine residues K274 and K279.[74] Lysine acetyltransferase p300 (KAT3B, encoded by *EP300*) is one of the core enzymes involved in this modification. It primarily localizes within the nucleus but undergoes dynamic shuttling. p300 acetylates multiple autophagy-regulatory proteins (ATG proteins) and its expression is inversely correlated with autophagic activity. Activated mTORC1 complex phosphorylates and activates p300, thereby suppressing starvation-induced autophagy and promoting lipid synthesis. Crucially, p300 acetylates TFEB, suggesting that mTOR signaling may

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constitute a key regulatory axis through p300-mediated acetylation, profoundly affecting TFEB subcellular localization, transcriptional activity, and its mediation of autophagy-lysosomal function.[77] Sumoylation is a process that modulates protein function through the attachment of small ubiquitin-like modifiers (SUMO). Sumoylation modulates the transcriptional activity of TFEB, playing a regulatory role, particularly within the promoter regions of MITF target genes.[79]

TFEB in Intervertebral Disc Degeneration

TFEB functions as the master transcriptional regulator of the autophagy-lysosome pathway, orchestrating cellular homeostasis through sophisticated regulatory mechanisms such as phosphorylation-dependent modulation and nucleocytoplasmic shuttling dynamics. During the pathological progression of IVDD, a convergence of endogenous factors (e.g., cellular senescence and mitochondrial dysfunction) and exogenous stressors (e.g., oxidative damage, inflammatory microenvironments, and aberrant mechanical loading) culminates in diminished TFEB expression, impaired nuclear localization, and significantly reduced transcriptional activity. TFEB dysfunction plays a pivotal role in the pathogenesis of IVDD. It not only directly compromises autophagic flux homeostasis, but also weakens cellular antioxidant defenses, amplifies inflammatory responses, and disrupts mitochondrial quality control along with extracellular matrix metabolic equilibrium. It is critical to distinguish between general autophagy modulation and TFEB-specific effects. This section focuses on the latter, synthesizing how the loss of TFEB function—a specific defect in the autophagy-lysosomal transcriptional program—uniquely contributes to IVDD pathogenesis beyond a simple reduction in autophagic activity. Consequently, elucidating the precise mechanisms by which TFEB dysregulation drives these pathological processes is crucial for deciphering the essence of IVDD and for developing targeted therapeutic strategies.

Role of TFEB in Regulating Autophagic Flux

Autophagic flux serves as a critical indicator of cellular capacity to clear damaged proteins and organelles, and is essential for maintaining cellular homeostasis. During IVDD progression, insufficient autophagic flux leads to intracellular waste accumulation, cellular damage, and ECM degradation. As a master regulator of autophagic flux, TFEB maintains a dynamic equilibrium by modulating the expression of autophagy-related genes. Studies have shown that diminished TFEB activity induces lysosomal dysfunction and reduces autophagosome clearance efficiency, thereby exacerbating NPC senescence and apoptosis.[80,81]

20-Deoxyingenol (20-DOI) activates TFEB to significantly enhance autophagic flux while suppressing the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) signaling pathway, thereby inhibiting cellular senescence phenotypes associated with IVDD.[82] Notably, Liang et al[81] found that lysine methylation of protein phosphatase 1 catalytic subunit alpha (*PPP1CA*) inhibits TFEB dephosphorylation, thereby impeding its nuclear translocation and further disrupting autophagic flux. Targeted inhibition of the methyltransferase *SUV39H2* restores TFEB activity, delays NPC senescence, and effectively mitigates IVDD. Furthermore, mechanical overload impairs the NPC autophagic flux and induces cell death by causing lysosomal dysfunction. During this process, the expression of TFEB, the master regulator governing lysosomal quality control, is significantly downregulated. TFEB overexpression restores lysosomal function, mitigates autophagic flux impairment, and effectively prevents mechanical overload-induced IVDD. Human IVDD specimens exhibit lysosomal quality control defects and compromised autophagic function, confirming TFEB's central role in maintaining autophagic flux through lysosomal regulation and its therapeutic targeting potential.[83] These observations collectively establish that enhancing TFEB activity plays a pivotal role in preserving autophagic flux during IVDD.

Protective Role of TFEB Against Oxidative Stress

Oxidative stress is a major contributor to IVDD, damaging mitochondria through ROS accumulation and disrupting ECM metabolic equilibrium. TFEB mitigates oxidative stress-induced cellular damage by promoting the autophagy-lysosomal pathway, thereby protecting NPCs from apoptosis and senescence.[84,85] Xie et al[84] elucidated that apigenin activates TFEB through modulation of the AMPK/mTOR signaling pathway, restoring autophagic flux levels and significantly inhibiting ROS-mediated damage to mitochondria and the ECM. Further studies revealed that the natural alkaloid palmatine enhances autophagic flux by promoting TFEB nuclear translocation, effectively

suppressing tert-butyl hydroperoxide (TBHP)-induced ROS accumulation and oxidative injury while alleviating NPC degeneration. Animal experiments have further validated its efficacy in delaying IVDD progression.[86] Moreover, Apelin enhances collagen type II and aggrecan synthesis in NPCs under oxidative stress by promoting TFEB nuclear translocation, thereby proposing a novel therapeutic strategy for IVDD.[85]

The antioxidant effect of TFEB is mediated by modulation of inflammatory signaling pathways. Under oxidative stress conditions, NF-κB signaling is activated, whereas enhanced TFEB expression reduces proinflammatory cytokine release by suppressing NF-κB activity.[87] In oxidative stress models, TFEB not only restores autophagic flux but also significantly reduces levels of NF-κB-dependent inflammatory factors. This dual regulatory mechanism indicates that TFEB not only effectively alleviates oxidative stress damage, but also exerts critical protective effects through the suppression of inflammation, consequently facilitating IVDD repair.

Role of TFEB in Regulating Inflammation

Inflammation represents a key initiating factor in IVDD, manifesting as elevated proinflammatory cytokine levels in NPCs, dysregulation of ECM anabolism/catabolism, and deterioration of the tissue microenvironment.[88] In recent years, the role of autophagy in modulating chronic inflammation has garnered substantial attention. As a master regulator of the autophagy-lysosomal system, TFEB demonstrates a significant potential for alleviating IVDD-associated inflammation.

TFEB exerts critical anti-inflammatory effects through dual regulation of autophagy and inflammatory signaling pathways. Research has established that TFEB alleviates chronic inflammation-induced tissue damage by enhancing autophagy-lysosomal function to clear damaged intracellular organelles and inflammatory mediators.[89] Notably, in sepsis models, Erbin has been shown to restore autophagy-lysosomal function and mitigate inflammatory responses by promoting TFEB nuclear localization.[90] Given that TFEB exerts anti-inflammatory effects by enhancing autophagic-lysosomal clearance capacity and suppressing key inflammatory signaling pathways (e.g., NF-κB), this mechanism has been established as critical within the chronic inflammatory milieu of IVDD.[87] Consequently, targeting the Erbin-TFEB axis or analogous upstream regulators to activate TFEB represents a highly promising therapeutic approach for mitigating chronic inflammation associated with IVDD.

Furthermore, TFEB functions as a pleiotropic mediator of anti-inflammatory responses through multi-pathway regulation. For instance, in non-alcoholic steatohepatitis (NASH) models, the AMPK agonist buddleoside suppresses inflammation and fibrosis through TFEB activation.[27] In atherosclerosis, Wang et al[91] observed that TFEB mitigates inflammatory damage by regulating the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway. These results suggest that the TFEB-mediated integration of multiple signaling pathways is a conserved mechanism underlying its pleiotropic anti-inflammatory functions. Building upon TFEB regulatory paradigms in diseases such as sepsis, NASH, and atherosclerosis, developing disc-targeted TFEB activation strategies constitutes a potential breakthrough point for alleviating IVDD-associated inflammation.

In summary, TFEB plays a pivotal regulatory role in suppressing IVDD-related inflammation by enhancing autophagic function and intervening in the key inflammatory pathways. Developing targeted TFEB activation strategies provides novel therapeutic avenues for anti-inflammatory treatment of IVDD.

TFEB in Mitochondrial Quality Control and Matrix Metabolism Regulation

Mitochondrial dysfunction is the core mechanism of IVDD. ROS accumulation and loss of mitochondrial membrane potential trigger cellular apoptosis and ECM degradation, whereas mitochondrial quality control is essential for maintaining cellular homeostasis. TFEB mitigates oxidative stress and inflammation-induced damage in NPCs by regulating mitophagy, thereby promoting mitochondrial quality control.

Jin et al[92] reported that exosomes derived from hypoxia-preconditioned bone marrow mesenchymal stem cells (BMSCs) activated the BNIP3-ANAX2-TFEB axis, enhancing mitophagy and significantly improving mitochondrial function and matrix synthesis capacity in degenerated NPCs. Additionally, trigonochinene E enhances lysosomal biogenesis and mitochondrial quality control through the TFEB/TFE3 pathway, restoring ECM component synthesis while alleviating oxidative stress-induced cellular damage.[93] These findings demonstrate that TFEB plays a pivotal

role in regulating mitochondrial function and ECM metabolism and has significant implications for IVDD regeneration.

The preceding sections delineate TFEB's multifaceted protective roles. Importantly, these functions are not isolated but are integrated through TFEB's position as a central node. For instance, TFEB-mediated restoration of autophagic flux directly mitigates oxidative stress by clearing damaged mitochondria, which in turn reduces a major trigger for inflammation. This interconnectedness underscores that TFEB is not merely involved in discrete pathways but coordinates a holistic cellular response to degeneration. A critical gap remains in understanding how this integrated network dynamically adapts—or fails—across the spectrum from early to end-stage IVDD.

In summary, the central regulatory role of TFEB in IVDD is well-established. It participates in IVDD pathogenesis by orchestrating four critical homeostatic mechanisms: autophagy-lysosomal clearance, antioxidant defense, anti-inflammatory regulation, and mitochondrial quality control (Figure 3). Mechanistically, TFEB dysfunction triggers impairment of autophagic flux, leading to accumulation of damaged substrates and induction of oxidative stress; the synergistic crosstalk between autophagic disruption and oxidative damage further amplifies inflammatory responses. In concert, this triad of perturbations disrupts mitochondrial bioenergetics and ECM homeostasis, ultimately mediating progressive structural and functional deterioration of the disc. This self-reinforcing pathological cycle elucidates the molecular basis of irreversible IVDD progression, and provides a fundamental theoretical framework for the development of targeted interventions.

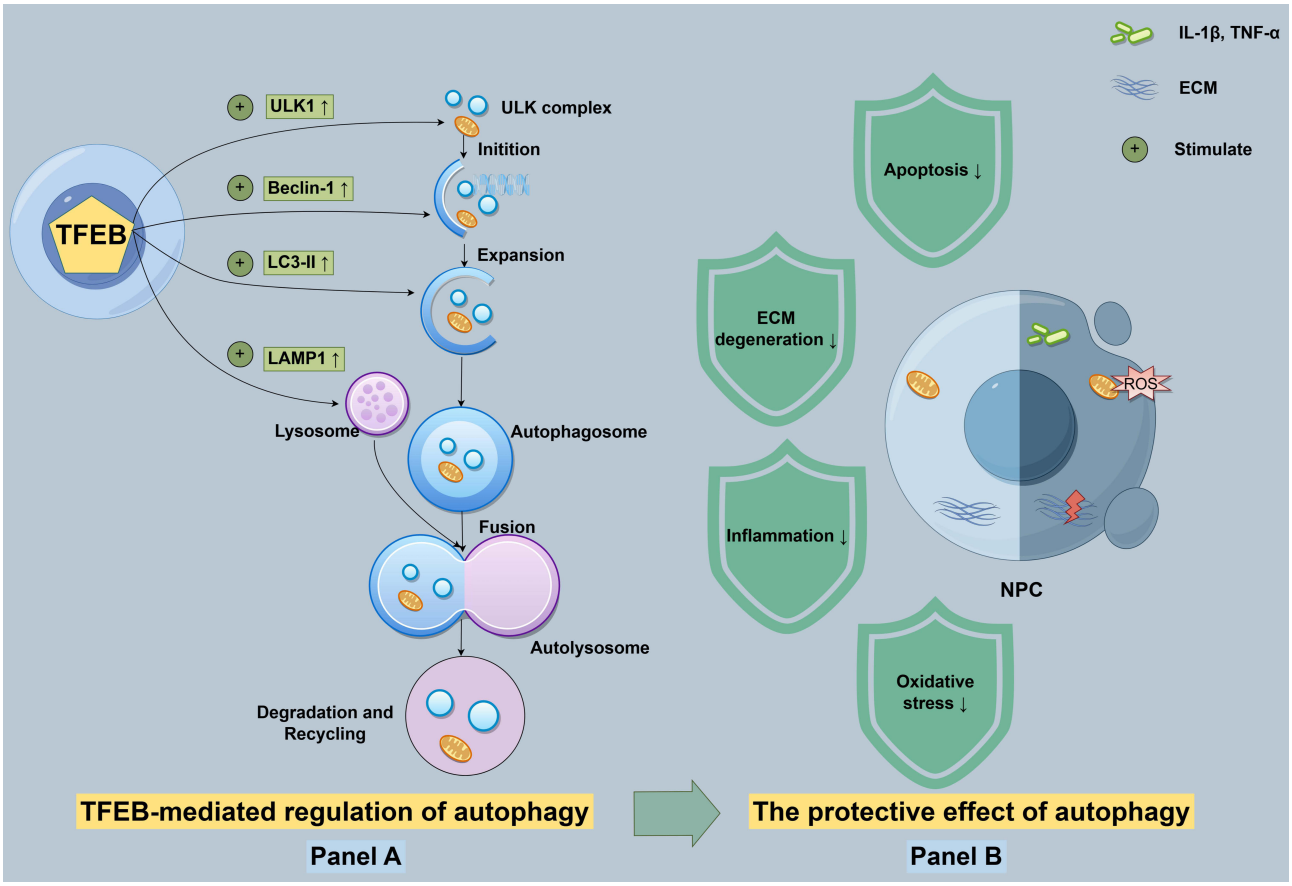

Figure 3 TFEB mitigates IVDD through modulation of autophagic flux. TFEB enhances autophagy through transcriptional upregulation of core autophagy-related genes (e.g., *ATG* family members, *lamp1*, *beclin-1*, *ulk1*), driving lysosomal biogenesis and autophagosome formation. This coordinated response protects NPCs via suppression of ECM degradation, attenuation of inflammatory cascades, mitigation of oxidative damage and inhibition of apoptosis, collectively preserving NPC homeostasis and retarding IVDD progression.

TFEB Repairs Intervertebral Disc Degeneration Through Promoting Autophagy

TFEB Activator

The activation of TFEB represents an effective strategy for enhancing autophagy and lysosomal function, facilitating the clearance of damaged organelles, degradation of abnormal proteins, and maintenance of cellular homeostasis. This approach provides a potential therapeutic avenue for effective prevention and treatment of IVDD. In recent years, numerous small-molecule compounds, natural products, and pharmaceutical agents have been shown to activate TFEB, thereby exhibiting promising therapeutic potential (Table 2). Multiple pharmacological agents promote TFEB nuclear translocation and transcriptional activity by inhibiting the mTOR signaling pathway, including rapamycin, celastrol, bimiralisib, omipalisib, PP242, torin1, torin2, and PP30.[94–98] These agents inhibit mTORC1 activity, thereby preventing TFEB phosphorylation and facilitating its nuclear translocation, which subsequently enhances autophagic and lysosomal functions. Curcumin analog C1 serves as a direct TFEB activator that functions without relying on mTOR inhibition.[99,100] Additionally, curcumin and SB216763 indirectly promote TFEB nuclear translocation by inhibiting GSK3β activity.[22,101] Narirutin induces TFEB dephosphorylation and nuclear entry through enhanced calcineurin activity.[102] Trehalose promotes TFEB nuclear localization by mediating intracellular calcium ion release and further activating the autophagic pathway.[103] These compounds enhance TFEB activity by modulating intracellular calcium ion concentration and calcium signaling, providing novel insights for IVDD treatment.

Bottlenecks in Therapeutic Applications of TFEB Activators for Intervertebral Disc Degeneration

Current TFEB activators act on multiple signaling pathways, potentially causing aberrant regulation of non-target cellular functions. Consequently, achieving cell type-specific TFEB activation within disc cells while avoiding adverse effects in other tissues or organs remains a critical challenge. Additionally, sustained TFEB activation may exert negative effects on cellular homeostasis, such as induction of metabolic dysregulation or drug resistance. Future studies should evaluate the safety profiles and potential side effects associated with prolonged administration of TFEB activators. Furthermore, targeted drug delivery to disc cells remains a bottleneck. Integrating nanotechnology or targeted delivery platforms could

Table 2 TFEB Activators

Activator	Primary target/ Mechanism	Related Models	Efficacy in Related Models	Reference
Rapamycin	mTORC1 inhibitor	Alzheimer's disease models	Reverses Aβ deposition, tauopathy, and cognitive deficits	[95]
Torin1	mTORC1 inhibitor	Human IVDD models	Reverse autophagic impairment and extracellular matrix degradation	[94]
Curcumin	GSK3β inhibitor	Neurodegenerative models	Synergize with NRF2/HO-1 to combat oxidative stress	[101]
SB216763	GSK3β inhibitor	Presenilin-1-deficient neural stem cells	Significantly elevate transcription of autophagy-related genes in *PS1*−/− NSCs (qRT-PCR validated)	[22]
Trehalose	Calcium signaling, mTORC1 inhibitor	Peritoneal macrophage	Promote autophagy-related gene expression and clearance of misfolded proteins via PPP3/TFEB axis	[103]
Narirutin	Calcium signaling	Hepatic injury models	Target PPP3/calcineurin to activate TFEB and promote autophagy	[102]
Curcumin analog C1	Direct TFEB activator	Alzheimer's disease models	Facilitating robust clearance of Aβ and Tau aggregates, thereby ameliorating synaptic and cognitive functions	[99,100]

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enhance local drug concentration while reducing systemic side effects, thereby enabling more precise therapeutic strategies for IVDD.[104,105] Future directions for TFEB-targeted therapeutic strategies may be realized through interdisciplinary technological breakthroughs, including the development of more potent and specific small-molecule activators and enhanced precision in TFEB activation via gene-editing technologies (e.g., CRISPR/Cas9),[106] and the implementation of biomaterials and nanotechnology for disc cell-targeted delivery (Figure 4). In summary, TFEB activation is a promising strategy for delaying or reversing IVDD progression. By addressing current challenges and integrating emerging technologies, TFEB-targeted therapies hold significant potential for achieving breakthrough advances in the efficient prevention and management of IVDD.

Beyond these translational hurdles, deeper mechanistic contradictions must be reconciled. A fundamental paradox exists: while TFEB activation is generally proposed as therapeutic, its activity is inherently suppressed by the nutrient-sensing mTORC1 pathway, which itself may be aberrantly regulated in IVDD. Furthermore, the potential for dual outcomes based on context is not fully resolved. Could forceful TFEB activation in the severely degenerative, acidic disc core—where lysosomal efficiency is already compromised—overwhelm the system and exacerbate pathology? Most evidence comes from models of induced or early-stage degeneration; its efficacy and safety in advanced disease remain speculative. Finally, the field largely focuses on TFEB, neglecting its family members (e.g., TFE3). Their potential compensatory roles or distinct functions in IVDD constitute a significant knowledge gap.

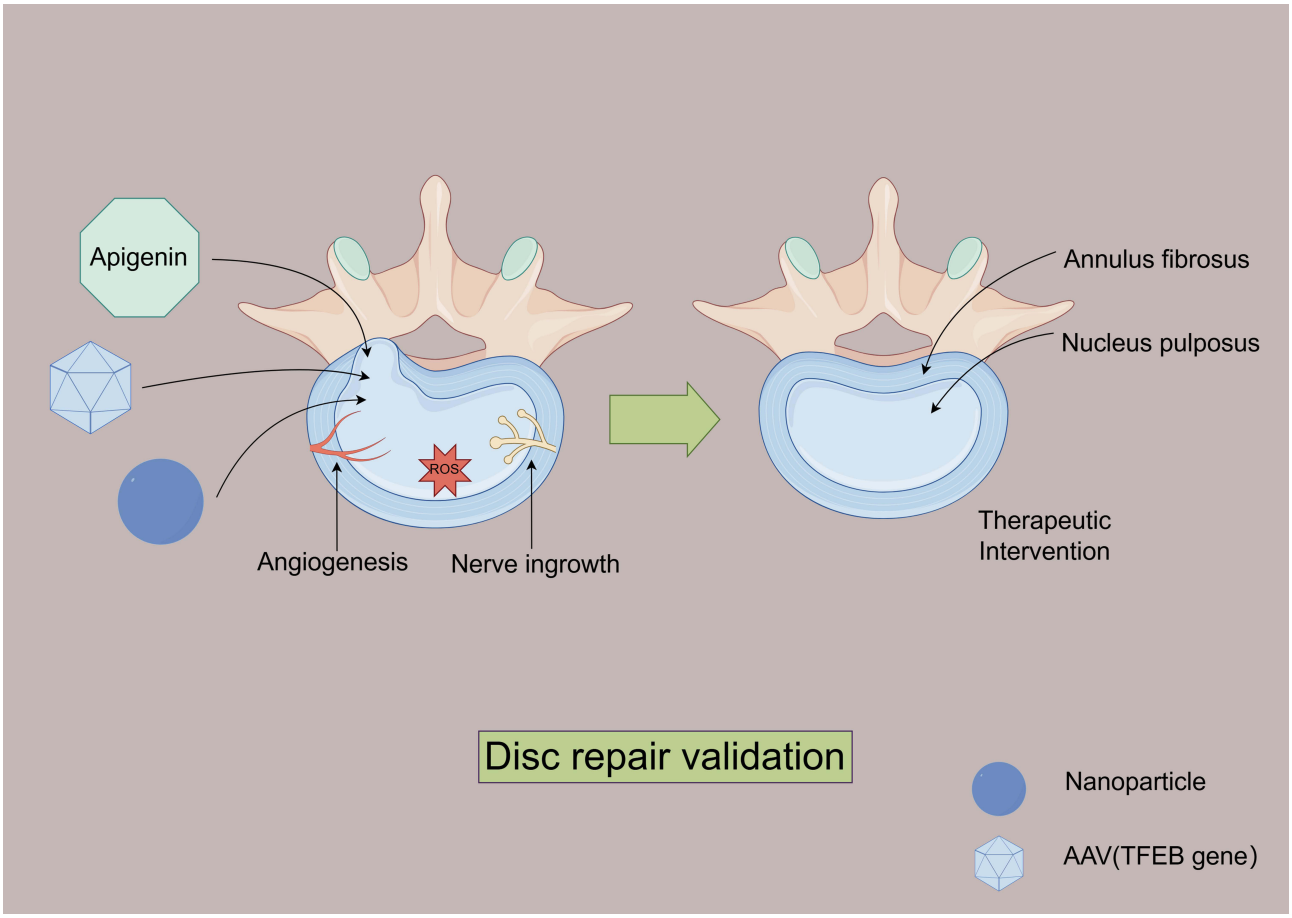

Figure 4 Exploring novel strategies for intervening in degeneration. Targeted delivery of apigenin and AAV-TFEB via nanoparticles activates the TFEB-autophagy axis to remodel NPC homeostasis.

Conclusion and Perspectives

As a master regulator of the autophagy-lysosomal system, TFEB plays a pivotal role in IVDD initiation and progression. By coordinately enhancing autophagic flux, maintaining mitochondrial homeostasis, and suppressing inflammatory and oxidative stress responses, TFEB activation effectively mitigates NPC dysfunction and decelerates degenerative processes in preclinical models. These findings establish TFEB as a compelling novel therapeutic target for IVDD.

The therapeutic rationale for targeting TFEB follows a defined mechanistic cascade: Strategies aim to enhance TFEB activity within NPCs via pharmacological or genetic means. This boosts autophagic flux and lysosomal function through transcriptional programming, thereby restoring a core homeostatic axis. The anticipated cellular outcomes include attenuated oxidative stress, mitigated inflammation, improved mitochondrial quality, and balanced ECM metabolism. Collectively, these changes are expected to preserve disc structure and function, ultimately translating into the clinical goals of pain reduction and disability prevention.

Despite this compelling mechanistic rationale, translating TFEB-targeted strategies into clinical therapies faces formidable, interconnected barriers. Currently, no TFEB modulator has entered clinical trials for IVDD, primarily due to four core limitations. First, the specificity and safety challenge: achieving NPC-restricted activation is crucial to avoid systemic effects, given TFEB's role in broad cellular processes. Second, the disc-specific delivery bottleneck: the avascular, high-pressure disc microenvironment severely limits drug penetration, necessitating advanced delivery systems (e.g., biomaterial carriers, nanoparticles). Third, the unclear therapeutic window: the "dual role" of autophagy implies a narrow optimal range. The required dosage, timing, and stage-specificity of TFEB activation remain poorly defined, with sustained activation risking lysosomal or metabolic stress. Fourth, the human evidence gap: robust validation in clinically relevant human disc tissue models across degeneration grades is critically needed.

Future research must therefore address these translational bottlenecks. Key directions include: (i) developing disc-homing or conditional TFEB agonists; (ii) integrating these agents with advanced intra-disc delivery platforms; and (iii) establishing human disc organoid/explant models for efficacy and safety testing. Addressing these challenges will determine whether TFEB transitions from a promising molecular target to a viable therapeutic.

In summary, through interdisciplinary integration, TFEB-targeted strategies hold significant potential to overcome current limitations in IVDD management. The path forward requires a balanced focus on mechanistic depth and practical solutions to delivery and specificity challenges. This dual approach aims to provide new strategies to delay IVDD progression and improve patient quality of life.

Data Sharing Statement

Data sharing is not applicable to this review as no new data were generated or analyzed in this study.

Author Contributions

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References

1. Hu J, Jiang L, Cao Y, Qu J, Lu H. Effectiveness and safety of inelastic versus elastic lumbosacral orthoses on low back pain prevention in healthy nurses: a randomized controlled trial. *Spine*. 2022;47:656–665. doi:10.1097/BRS.0000000000004258
2. Ferreira ML, De Luca K, Haile LM, et al. Global, regional, and national burden of low back pain, 1990–2020, its attributable risk factors, and projections to 2050: a systematic analysis of the global burden of disease study 2021. *Lancet Rheumatol*. 2023;5:e316–e329. doi:10.1016/S2665-9913(23)00098-X
3. Zhang L, Li Z, Zhang L, Qin Y, Yu D. Dissecting the multifaced function of transcription factor EB (TFEB) in human diseases: from molecular mechanism to pharmacological modulation. *Biochem Pharmacol*. 2023;215:115698. doi:10.1016/j.bcp.2023.115698
4. Guo Z, Wang X, Sun J, et al. Injectable nanocomposite hydrogels for intervertebral disc degeneration: combating oxidative stress, mitochondrial dysfunction, and ferroptosis. *Adv Healthc Mater*. 2025;14. doi:10.1002/adhm.202403892
5. Wu S, Wang J, Wang M, et al. Glucose deprivation-induced disulfidptosis in human nucleus pulposus cells: a novel pathological mechanism of intervertebral disc degeneration. *Biol Direct*. 2024;19:81. doi:10.1186/s13062-024-00528-4
6. Kuzu Ş, Jawad SR, Canli M, Özüdoğru A. Investigation of efficacy of high and low intensity laser therapy in patients with lumbar disc herniation: a randomized controlled trial. *J Med Biol Eng*. 2025;1–7.
7. Xia Q, Zhao Y, Dong H, et al. Progress in the study of molecular mechanisms of intervertebral disc degeneration. *Biomed Pharmacother*. 2024;174:116593. doi:10.1016/j.biopha.2024.116593
8. Ma W, Wang W, Zhao L, et al. Reprogramming to restore youthful epigenetics of senescent nucleus pulposus cells for mitigating intervertebral disc degeneration and alleviating low back pain. *Bone Res*. 2025;13. doi:10.1038/s41413-025-00416-1
9. Samanta A, Lufkin T, Kraus P. Intervertebral disc degeneration—current therapeutic options and challenges. *Front Public Health*. 2023;11:1156749. doi:10.3389/fpubh.2023.1156749
10. Dou Y, Sun X, Ma X, Zhao X, Yang Q. Intervertebral disk degeneration: the microenvironment and tissue engineering strategies, Front. *Bioeng Biotechnol*. 2021;9:592118. doi:10.3389/fbioe.2021.592118
11. Wang J, Zhang Y, Cao J, et al. The role of autophagy in bone metabolism and clinical significance. *Autophagy*. 2023;19:2409–2427. doi:10.1080/15548627.2023.2186112
12. Gong C, Zhang H. Autophagy as a potential therapeutic target in intervertebral disc degeneration. *Life Sci*. 2021;273:119266. doi:10.1016/j.lfs.2021.119266
13. Cabrera-Serrano AJ, Sánchez-Maldonado JM, González-Olmedo C, et al. Crosstalk between autophagy and oxidative stress in hematological malignancies: mechanisms, implications, and therapeutic potential. *Antioxidants*. 2025;14:264. doi:10.3390/antiox14030264
14. Michalak KP, Michalak AZ. Understanding chronic inflammation: couplings between cytokines, ROS, NO, Cai2+, HIF-1α, Nrf2 and autophagy. *Front Immunol*. 2025;16. doi:10.3389/fimmu.2025.1558263.
15. Ding X, Zhu C, Wang W, Li M, Ma C, Gao B. SIRT1 is a regulator of autophagy: implications for the progression and treatment of myocardial ischemia-reperfusion. *Pharmacol Res*. 2024;199:106957. doi:10.1016/j.phrs.2023.106957
16. Shintani T, Klionsky DJ. Autophagy in health and disease: a double-edged sword. *Science*. 2004;306:990–995. doi:10.1126/science.1099993
17. Dong Y, Li C, Tu S, et al. Phosphatidylethanolamine protects nucleus pulposus cells from oxidative stress-induced cellular senescence and extracellular matrix degradation by promoting autophagy. *JOR Spine*. 8;2025. doi:10.1002/jsp2.70058
18. Cheng Z, Gan W, Xiang Q, et al. Impaired degradation of PLCG1 by chaperone-mediated autophagy promotes cellular senescence and intervertebral disc degeneration. *Autophagy*. 2025;21:352–373. doi:10.1080/15548627.2024.2395797
19. Yurube T, Ito M, Kakiuchi Y, Kuroda R, Kakutani K. Autophagy and mTOR signaling during intervertebral disc aging and degeneration. *JOR spine*. 2020;3:e1082. doi:10.1002/jsp2.1082
20. Ito M, Yurube T, Kakutani K, et al. Selective interference of mTORC1/RAPTOR protects against human disc cellular apoptosis, senescence, and extracellular matrix catabolism with akt and autophagy induction. *Osteoarthr Cartil*. 2017;25:2134–2146. doi:10.1016/j.joca.2017.08.019
21. Ojalvo-Pacheco J, Yakhine-Diop SMS, Fuentes JM, Paredes-Barquero M, Niso-Santano M. Role of TFEB in huntington's disease. *Biology*. 2024;13:238. doi:10.3390/biology13040238
22. Chong C-M, Ke M, Tan Y, et al. Presenilin 1 deficiency suppresses autophagy in human neural stem cells through reducing γ-secretase-independent ERK/CREB signaling. *Cell Death Dis*. 2018;9:879. doi:10.1038/s41419-018-0945-7
23. Zhang K, Zhu S, Li J, et al. Targeting autophagy using small-molecule compounds to improve potential therapy of Parkinson's disease. *Acta Pharm Sin B*. 2021;11:3015–3034. doi:10.1016/j.apsb.2021.02.016
24. Leytens A, Benítez-Fernández R, Jiménez-García C, et al. Targeted proteomics addresses selectivity and complexity of protein degradation by autophagy. *Autophagy*. 2025;21:460–475. doi:10.1080/15548627.2024.2396792

25. Zhao D, Qiang L, Lei Z, et al. TRIM27 elicits protective immunity against tuberculosis by activating TFEB-mediated autophagy flux. *Autophagy*. 2024;20:1483–1504. doi:10.1080/15548627.2024.2321831
26. Zheng B, Wang Y, Zhou B, et al. Urolithin a inhibits breast cancer progression via activating TFEB-mediated mitophagy in tumor macrophages. *J Adv Res*. 2025;69:125–138. doi:10.1016/j.jare.2024.04.010
27. Chen M, Liu G, Fang Z, et al. Buddleoside alleviates nonalcoholic steatohepatitis by targeting the AMPK-TFEB signaling pathway. *Autophagy*. 2025;21:1316–1334. doi:10.1080/15548627.2025.2466145
28. Yang J, Yuan L, Li L, et al. Trehalose activates autophagy to alleviate cisplatin-induced chronic kidney injury by targeting the mTOR-dependent TFEB signaling pathway. *Theranostics*. 2025;15:2544–2563. doi:10.7150/thno.102559
29. Abokyi S, Ghartey-Kwansah G, Tse DY. TFEB is a central regulator of the aging process and age-related diseases. *Ageing Res Rev*. 2023;89:101985. doi:10.1016/j.arr.2023.101985
30. Napolitano G, Ballabio A. TFEB at a glance. *J Cell Sci*. 2016;129:2475–2481. doi:10.1242/jcs.146365
31. Trojani M-C, Santucci-Darmanin S, Breuil V, Carle GF, Pierrefite-Carle V. Autophagy and bone diseases. *Joint Bone Spine*. 2022;89:105301. doi:10.1016/j.jbspin.2021.105301
32. Sakurai M, Kuwahara T. Canonical and noncanonical autophagy: involvement in Parkinson's disease. *Front Cell Dev Biol*. 2025;13. doi:10.3389/fcell.2025.1518991.
33. Feng C, Hu Z, Zhao M, et al. Region-specific mitophagy in nucleus pulposus, annulus fibrosus, and cartilage endplate of intervertebral disc degeneration: mechanisms and therapeutic strategies. *Front Pharmacol*. 2025;16. doi:10.3389/fphar.2025.1579507
34. Wang L, Klionsky DJ, Shen H-M. The emerging mechanisms and functions of microautophagy. *Nat Rev Mol Cell Biol*. 2023;24:186–203. doi:10.1038/s41580-022-00529-z
35. Pan Z, Huang X, Liu M, Jiang X, He G. Research advances in chaperone-mediated autophagy (CMA) and CMA-based protein degraders. *J Med Chem*. 2025;68:2314–2332. doi:10.1021/acs.jmedchem.4c02681
36. Wang S, Long H, Hou L, et al. The mitophagy pathway and its implications in human diseases. *Sig Transduct Target Ther*. 2023;8. doi:10.1038/s41392-023-01503-7
37. Liu L, Li Y, Chen G, Chen Q. Crosstalk between mitochondrial biogenesis and mitophagy to maintain mitochondrial homeostasis. *J Biomed Sci*. 2023;30. doi:10.1186/s12929-023-00975-7.
38. Liu S, Yao S, Yang H, Liu S, Wang Y. Autophagy: regulator of cell death. *Cell Death Dis*. 2023;14:648. doi:10.1038/s41419-023-06154-8
39. Wu Z, Liu Y, Song W, Zhou K, Ling Y, Zhang H. Role of mitophagy in intervertebral disc degeneration: a narrative review. *Osteoarthr Cartil*. 2025;33:27–41. doi:10.1016/j.joca.2024.09.013
40. Palmer JE, Wilson N, Son SM, et al. Autophagy, aging, and age-related neurodegeneration. *Neuron*. 2025;113:29–48. doi:10.1016/j.neuron.2024.09.015
41. Niu X, You Q, Hou K, et al. Autophagy in cancer development, immune evasion, and drug resistance. *Drug Resist Updat*. 2025;78:101170. doi:10.1016/j.drup.2024.101170
42. Yang S, Zhang F, Ma J, Ding W. Intervertebral disc ageing and degeneration: the antiapoptotic effect of oestrogen. *Ageing Res Rev*. 2020;57:100978. doi:10.1016/j.arr.2019.100978
43. Liu Y, Dou Y, Sun X, Yang Q. Mechanisms and therapeutic strategies for senescence-associated secretory phenotype in the intervertebral disc degeneration microenvironment. *J Orthop Transl*. 2024;45:56–65. doi:10.1016/j.jot.2024.02.003
44. Xu J, Shao T, Lou J, Zhang J, Xia C. Aging, cell senescence, the pathogenesis and targeted therapies of intervertebral disc degeneration. *Front Pharmacol*. 2023;14:1172920. doi:10.3389/fphar.2023.1172920
45. Silwal P, Nguyen-Thai AM, Mohammad HA, et al. Cellular senescence in intervertebral disc aging and degeneration: molecular mechanisms and potential therapeutic opportunities. *Biomolecules*. 2023;13:686. doi:10.3390/biom13040686
46. Yue C, Wu Y, Xia Y, et al. Tbxt alleviates senescence and apoptosis of nucleus pulposus cells through Atg7 mediated autophagy activation during intervertebral disc degeneration. *Am J Physiol Cell Physiol*. 2023;327:C237–C253. doi:10.21203/rs.3.rs-3481551/v1
47. Wang Z, Ma J, Sun Y, et al. Isorhapontigenin delays senescence and matrix degradation of nucleus pulposus cells via PI3K/AKT/mTOR-mediated autophagy pathway in vitro and alleviates intervertebral disc degeneration in vivo. *Int Immunopharmacol*. 2024;139:112717. doi:10.1016/j.intimp.2024.112717
48. Chen J, Xie -J-J, Jin M-Y, et al. Sirt6 overexpression suppresses senescence and apoptosis of nucleus pulposus cells by inducing autophagy in a model of intervertebral disc degeneration. *Cell Death Dis*. 2018;9. doi:10.1038/s41419-017-0085-5
49. Zhou W, Shi Y, Wang H, et al. Exercise-induced FNDC5/irisin protects nucleus pulposus cells against senescence and apoptosis by activating autophagy. *Exp Mol Med*. 2022;54:1038–1048. doi:10.1038/s12276-022-00811-2
50. Lin J, Zhuge J, Zheng X, et al. Urolithin A-induced mitophagy suppresses apoptosis and attenuates intervertebral disc degeneration via the AMPK signaling pathway. *Free Radic Biol Med*. 2020;150:109–119. doi:10.1016/j.freeradbiomed.2020.02.024
51. Bai X, Jiang M, Wang J, et al. Cyanidin attenuates the apoptosis of rat nucleus pulposus cells and the degeneration of intervertebral disc via the JAK2/STAT3 signal pathway *in vitro* and *in vivo*. *Pharm Biol*. 2022;60:427–436. doi:10.1080/13880209.2022.2035773
52. Zhang S, Liang W, Abulizi Y, et al. Quercetin alleviates intervertebral disc degeneration by modulating p38 MAPK-mediated autophagy. *Biomed Res Int*. 2021;2021:6631562. doi:10.1155/2021/6631562
53. Wang D, He X, Wang D, et al. Quercetin suppresses apoptosis and attenuates intervertebral disc degeneration via the SIRT1-autophagy pathway. *Front Cell Dev Biol*. 2020;8:613006. doi:10.3389/fcell.2020.613006
54. Wang C, Zhang -Z-Z, Yang W, et al. MiR-210 facilitates ECM degradation by suppressing autophagy via silencing of ATG7 in human degenerated NP cells. *Biomed Pharmacother*. 2017;93:470–479. doi:10.1016/j.biopha.2017.06.048
55. Yurube T, Buchser WJ, Zhang Z, et al. Rapamycin mitigates inflammation-mediated disc matrix homeostatic imbalance by inhibiting mTORC1 and inducing autophagy through Akt activation. *JOR Spine*. 2024;7:e1303. doi:10.1002/jsp2.1303
56. Yi W, Wen Y, Tan F, et al. Impact of NF-κB pathway on the apoptosis-inflammation-autophagy crosstalk in human degenerative nucleus pulposus cells. *Aging*. 2019;11:7294–7306. doi:10.18632/aging.102266
57. Bahar ME, Hwang JS, Lai TH, Byun J-H, Kim D-H, Kim DR. The survival of human intervertebral disc nucleus pulposus cells under oxidative stress relies on the autophagy triggered by delphinidin. *Antioxidants*. 2024;13:759. doi:10.3390/antiox13070759

58. Yu H, Teng Y, Ge J, et al. Isoginkgetin-loaded reactive oxygen species scavenging nanoparticles ameliorate intervertebral disc degeneration via enhancing autophagy in nucleus pulposus cells. *J Nanobiotechnol*. 2023;21:99. doi:10.1186/s12951-023-01856-9
59. Lu Y, Zhou L, He S, Ren H-L, Zhou N, Hu Z-M. Lycopene alleviates disc degeneration under oxidative stress through the Nrf2 signaling pathway. *Mol Cell Probes*. 2020;51:101559. doi:10.1016/j.mcp.2020.101559
60. Ma K-G, Shao Z-W, Yang S-H, et al. Autophagy is activated in compression-induced cell degeneration and is mediated by reactive oxygen species in nucleus pulposus cells exposed to compression. *Osteoarthr Cartil*. 2013;21:2030–2038. doi:10.1016/j.joca.2013.10.002
61. Huang D, Peng Y, Li Z, et al. Compression-induced senescence of nucleus pulposus cells by promoting mitophagy activation via the PINK1/PARKIN pathway. *J Cell Mol Med*. 2020;24:5850–5864. doi:10.1111/jcmm.15256
62. Zhou L-P, Kang L, Zhang Z-G, et al. RBX1 mitigates ferroptosis by inhibiting NCOA4-mediated ferritinophagy and contributes to the attenuation of intervertebral disc degeneration. *J Transl Med*. 2025;23:514. doi:10.1186/s12967-025-06412-7
63. Chen Y, Yang L. Cellular senescence in renal ischemia-reperfusion injury. *Chin Med J*. 2025;138:1794–1806. doi:10.1097/CM9.0000000000003698
64. Kang L, Zhang H, Jia C, Zhang R, Shen C. Epigenetic modifications of inflammation in intervertebral disc degeneration. *Ageing Res Rev*. 2023;87:101902. doi:10.1016/j.arr.2023.101902
65. Gu Y, Han J, Jiang C, Zhang Y. Biomarkers, oxidative stress and autophagy in skin aging. *Ageing Res Rev*. 2020;59:101036. doi:10.1016/j.arr.2020.101036
66. Jin L-Y, Lv Z-D, Wang K, et al. Estradiol alleviates intervertebral disc degeneration through modulating the antioxidant enzymes and inhibiting autophagy in the model of menopause rats. *Oxid Med Cell Longev*. 2018;2018:7890291. doi:10.1155/2018/7890291
67. Chen H, Gong S, Zhang H, et al. From the regulatory mechanism of TFEB to its therapeutic implications. *Cell Death Discov*. 2024;10. doi:10.1038/s41420-024-01850-6
68. Takla M, Keshri S, Rubinsztein DC. The post-translational regulation of transcription factor EB (TFEB) in health and disease. *EMBO Rep*. 2023;24. doi:10.15252/embr.202357574.
69. Puertollano R, Ferguson SM, Brugarolas J, Ballabio A. The complex relationship between TFEB transcription factor phosphorylation and subcellular localization. *EMBO J*. 2018;37:e98804. doi:10.15252/embj.201798804
70. Franco-Juárez B, Coronel-Cruz C, Hernández-Ochoa B, et al. TFEB; beyond its role as an autophagy and lysosomes regulator. *Cells*. 2022;11:3153. doi:10.3390/cells11193153
71. Nonninger TJ, Mak J, Gerisch B, et al. A TFEB–TGFβ axis systemically regulates diapause, stem cell resilience and protects against a senescence-like state. *Nat Aging*. 2025;5:1340–1357. doi:10.1038/s43587-025-00911-4
72. Linehan WM, Ricketts CJ, Crooks DR, Schmidt LS. The critical role of FLCN, TFE3, and TFEB in bioenergetic and nutrient sensing, renal cancer tumorigenesis and metabolic health. *Eur Urol*. 2025;88:274–276. doi:10.1016/j.eururo.2025.05.003
73. Tang H, Hou H, Song L, et al. The role of mTORC1/TFEB axis mediated lysosomal biogenesis and autophagy impairment in fluoride neurotoxicity and the intervention effects of resveratrol. *J Hazard Mater*. 2024;467:133634. doi:10.1016/j.jhazmat.2024.133634
74. Migliore L, Cianfanelli V, Zevolini F, et al. An AMBRA1, ULK1 and PP2A regulatory network regulates cytotoxic T cell differentiation via TFEB activation. *Sci Rep*. 2024;14. doi:10.1038/s41598-024-82957-9
75. Napolitano G, Di Malta C, Esposito A, et al. A substrate-specific mTORC1 pathway underlies birt–hogg–dubé syndrome. *Nature*. 2020;585:597–602. doi:10.1038/s41586-020-2444-0
76. Wen W, Zheng H, Li W, et al. Transcription factor EB: a potential integrated network regulator in metabolic-associated cardiac injury. *Metabolism*. 2023;147:155662. doi:10.1016/j.metabol.2023.155662
77. Tan A, Prasad R, Lee C, Jho E. Past, present, and future perspectives of transcription factor EB (TFEB): mechanisms of regulation and association with disease. *Cell Death Differ*. 2022;29:1433–1449. doi:10.1038/s41418-022-01028-6
78. Li Y, Xu M, Ding X, et al. Protein kinase C controls lysosome biogenesis independently of mTORC1. *Nat Cell Biol*. 2016;18:1065–1077. doi:10.1038/ncb3407
79. Miller AJ, Levy C, Davis IJ, Razin E, Fisher DE. Sumoylation of MITF and its related family members TFE3 and TFEB. *J Biol Chem*. 2005;280:146–155. doi:10.1074/jbc.M411757200
80. Zheng G, Pan Z, Zhan Y, et al. TFEB protects nucleus pulposus cells against apoptosis and senescence via restoring autophagic flux. *Osteoarthr Cartil*. 2019;27:347–357. doi:10.1016/j.joca.2018.10.011
81. Liang H, Luo R, Li G, et al. Lysine methylation of PPP1CA by the methyltransferase SUV39H2 disrupts TFEB-dependent autophagy and promotes intervertebral disc degeneration. *Cell Death Differ*. 2023;30:2135–2150. doi:10.1038/s41418-023-01210-4
82. Chen Y, Wu C, Zhao X, et al. 20-deoxyingenol alleviates intervertebral disc degeneration by activating TFEB in nucleus pulposus cells. *Biochem Pharmacol*. 2023;218:115865. doi:10.1016/j.bcp.2023.115865
83. Liu S, Hu Y, Xu W, et al. Restoration of lysosomal function attenuates autophagic flux impairment in nucleus pulposus cells and protects against mechanical overloading-induced intervertebral disc degeneration. *Autophagy*. 2025;21:979–995. doi:10.1080/15548627.2024.2440844
84. Xie C, Shi Y, Chen Z, et al. Apigenin alleviates intervertebral disc degeneration via restoring autophagy flux in nucleus pulposus cells. *Front Cell Dev Biol*. 2022;9:787278. doi:10.3389/fcell.2021.787278
85. Jiang W, Zhao P, Zhang X. Apelin promotes ECM synthesis by enhancing autophagy flux via TFEB in human degenerative NP cells under oxidative stress. *Biomed Res Int*. 2020;2020:1–8. doi:10.1155/2020/4897170
86. Yu H, Chen K, Li X, et al. Palmatine activation of TFEB enhances autophagy and alleviates endoplasmic reticulum stress in intervertebral disc degeneration. *Phytomedicine*. 2025;139:156431. doi:10.1016/j.phymed.2025.156431
87. Liang H, Liu Z, Wang Y, Wang D, Tian J. Transcription factor EB mediates oxidative stress-induced intervertebral disc degeneration via the NF-κB signaling pathway. *Ann Transl Med*. 2021;9. doi:10.21037/atm-21-3756
88. Zhou L, Cai F, Zhu H, et al. Immune-defensive microspheres promote regeneration of the nucleus pulposus by targeted entrapment of the inflammatory cascade during intervertebral disc degeneration. *Bioact Mater*. 2024;37:132–152. doi:10.1016/j.bioactmat.2024.03.020
89. Ren J, Li J, Tang H, Hao L, Yang K. TFEB alleviates periodontitis by activating autophagy and inhibiting inflammation. *Transl Res*. 2024;273:127–136. doi:10.1016/j.trsl.2024.08.003
90. Fang Q, Jing G, Zhang Y, et al. Erbin accelerates TFEB-mediated lysosome biogenesis and autophagy and alleviates sepsis-induced inflammatory responses and organ injuries. *J Transl Med*. 2023;21:916. doi:10.1186/s12967-023-04796-y

91. Wang Z, Gao Z, Zheng Y, et al. Melatonin inhibits atherosclerosis progression via galectin-3 downregulation to enhance autophagy and inhibit inflammation. *J Pineal Res*. 2023;74:e12855. doi:10.1111/jpi.12855
92. Jin Y, Wu O, Chen Q, et al. Hypoxia-preconditioned BMSC-derived exosomes induce mitophagy via the BNIP3–ANAX2 axis to alleviate intervertebral disc degeneration. *Adv Sci*. 2024;11:2404275. doi:10.1002/advs.202404275
93. Niu Z, Tang G, Wang X, et al. Trigonochinene E promotes lysosomal biogenesis and enhances autophagy via TFEB/TFE3 in human degenerative NP cells against oxidative stress. *Phytomedicine*. 2023;112:154720. doi:10.1016/j.phymed.2023.154720
94. Chen J, Ma Y, Yang Z, et al. TNFAIP3 ameliorates the degeneration of inflammatory human nucleus pulposus cells by inhibiting mTOR signaling and promoting autophagy. *Aging*. 2020;12:24242–24254. doi:10.18632/aging.104160
95. Xie P-L, Zheng M-Y, Han R, Chen W-X, Mao J-H. Pharmacological mTOR inhibitors in ameliorating Alzheimer's disease: current review and perspectives. *Front Pharmacol*. 2024;15:1366061. doi:10.3389/fphar.2024.1366061
96. Tramutola A, Lanzillotta C, Di Domenico F. Targeting mTOR to reduce Alzheimer-related cognitive decline: from current hits to future therapies. *Expert Rev Neurother*. 2017;17:33–45. doi:10.1080/14737175.2017.1244482
97. Occhiuzzi MA, Lico G, Ioele G, De Luca M, Garofalo A, Grande F. Recent advances in PI3K/PKB/mTOR inhibitors as new anticancer agents. *Eur J Med Chem*. 2023;246:114971. doi:10.1016/j.ejmech.2022.114971
98. Zhang W, Wang J, Yang C. Celastrol, a TFEB (transcription factor EB) agonist, is a promising drug candidate for Alzheimer disease. *Autophagy*. 2022;18:1740–1742. doi:10.1080/15548627.2022.2046437
99. Song J, Malampati S, Zeng Y, et al. A small molecule transcription factor EB activator ameliorates beta-amyloid precursor protein and tau pathology in Alzheimer's disease models. *Aging Cell*. 2020;19:e13069. doi:10.1111/acel.13069
100. Song J-X, Sun Y-R, Peluso I, et al. A novel curcumin analog binds to and activates TFEB in vitro and in vivo independent of MTOR inhibition. *Autophagy*. 2016;12:1372–1389. doi:10.1080/15548627.2016.1179404
101. Song H-C, Chen Y, Chen Y, et al. GSK-3β inhibition by curcumin mitigates amyloidogenesis via TFEB activation and anti-oxidative activity in human neuroblastoma cells. *Free Radic Res*. 2020;54:918–930. doi:10.1080/10715762.2020.1791843
102. Fang Z, Xu Y, Liu G, et al. Narirutin activates TFEB (transcription factor EB) to protect against Acetaminophen-induced liver injury by targeting PPP3/calcineurin. *Autophagy*. 2023;19:2240–2256. doi:10.1080/15548627.2023.2179781
103. Jeong S-J, Stitham J, Evans TD, et al. Trehalose causes low-grade lysosomal stress to activate TFEB and the autophagy-lysosome biogenesis response. *Autophagy*. 2021;17:3740–3752. doi:10.1080/15548627.2021.1896906
104. Genedy HH, Humbert P, Laoulaou B, et al. MicroRNA-targeting nanomedicines for the treatment of intervertebral disc degeneration. *Adv Drug Deliv Rev*. 2024;207:115214. doi:10.1016/j.addr.2024.115214
105. Liu W, Ma Z, Wang Y, Yang J. Multiple nano-drug delivery systems for intervertebral disc degeneration: current status and future perspectives. *Bioact Mater*. 2023;23:274–299. doi:10.1016/j.bioactmat.2022.11.006
106. Guo H, Pu M, Tai Y, et al. Nuclear miR-30b-5p suppresses TFEB-mediated lysosomal biogenesis and autophagy. *Cell Death Differ*. 2021;28:320–336. doi:10.1038/s41418-020-0602-4