J Turk Spinal Surg 2024;35(2):85-91
DOI: 10.4274/jtss.galenos.2024.81300

COULD PHARMACOLOGICAL TARGETING MITOPHAGIC OR LYSOPHAGIC SIGNALING PATHWAYS BE A NEW HOPE IN THE TREATMENT OF INTERVERTEBRAL DISC DEGENERATION?

İbrahim Yılmaz[1], Halil Can Küçükyıldız[2], Gazi Akkurt[3], Ali Dalgıç[2]

[1]İstanbul Rumeli University Faculty of Medicine, Vocational School of Health Services, Department of Medical Services and Techniques, İstanbul, Turkey
[2]Ankara Medicana International Hospital, Clinic of Neurosurgery, Ankara, Turkey
[3]Ankara Medicana International Hospital, Clinic of Anesthesiology, Ankara, Turkey

ABSTRACT

The relationship between mitophagy, a selective form of macroautophagy/autophagy that targets dysfunctional or excessive amounts of irregular mitochondria for degradation, and mycophagy, a selective autophagy mechanism for the removal of dysfunctional/unwanted lysosomes, in the context of intervertebral disc degeneration (IVDD) has not been sufficiently elucidated. This study was conducted to investigate the question, "Can IVDD be delayed or halted through pharmacological targeting of mitophagic or dysphagic signaling pathways?". For this purpose, systematic searches were conducted in the PubMed electronic database without country or language restrictions until March 21, 2024, using sequential searches with keywords related to the topic using "and/or" combinations to select high-evidence studies. Findings from studies meeting the research criteria and undergoing full-text assessment were compiled into an Excel spreadsheet using Microsoft Office. Results are presented in counts and/or frequencies (%). Following a comprehensive literature search, 12.720 studies were encountered, with 11.49% being reviewed. Although no clinical research related to the topic was found, no studies fully encompassed the inclusion criteria or the keywords "mitophagy"/"lysophagy" with "IVDD". Based on the existing literature, it is impossible to determine the level of evidence regarding the effect of mitophagic and/or dysphagic signaling pathways on IVDD or to discuss the effectiveness and reliability of targeting these pathways in treating degeneration. To establish evidence-based conclusions on this research topic, findings from multicenter, double-blind, randomized, and clinical trials involving a larger number of cases in different populations need to be evaluated.

Keywords: E3 ubiquitin, G3BP1, mitochondrial dynamics, Parkin, PINK1, sequestrotomy

INTRODUCTION

Mitophagy is a process whereby cells selectively degrade and remove damaged or dysfunctional mitochondria[1]. Mitochondria, the organelles responsible for energy production within cells, can generate harmful byproducts when damaged. Mitophagy is believed to play a central role in mitochondrial quality control, including processes such as mitochondrial biogenesis and dynamics. It is considered the most effective way to eliminate damaged or unwanted mitochondria. By eliminating damaged or dysfunctional mitochondria, mitophagy helps maintain cellular health, preventing the accumulation of harmful substances. It has been proposed as a crucial mechanism to maintain cellular homeostasis and prevent diseases related to mitochondrial dysfunction[2].

Recent research suggests that dysregulation of mitophagy may contribute to intervertebral disc (IVD) degeneration (IVDD) by disrupting cellular homeostasis, increasing oxidative stress, and promoting inflammation and cell death in IVD cells[3,4].

Additionally, it is suggested that dysfunctional or impaired mitophagy may promote disc degeneration by leading to the accumulation of damaged mitochondria, increased oxidative stress, and inflammation in nucleus pulposus (NP) cells[5]. Fundamental mechanisms proposed in the literature for mitophagy include the involvement of mitochondrial quality control mechanisms, such as phosphatase and tensin homolog-induced putative kinase 1 (PINK1) and Parkin, which play significant roles in tagging damaged mitochondria for removal when triggered by various cellular stressors such as oxidative damage, depolarization of mitochondrial membrane potential, or accumulation of damaged mitochondrial proteins[6].

Address for Correspondence: İbrahim Yılmaz, Tekirdağ Dr. İsmail Fehmi Cumalıoğlu City Hospital, Tekirdağ, Turkey
Phone: +90 632 701 28 58 **E-mail:** dryilmazi@yahoo.com **Received:** 02.04.2024 **Accepted:** 22.04.2024
ORCID ID: orcid.org/0000-0003-2003-6337

Another mechanism involves the effects on autophagosome formation, where autophagy receptors such as p62/Sequestosome-1 (SQSTM1) and nuclear domain 10 protein 52 (NDP52) are proposed to bind to damaged mitochondria, leading to the formation of autophagosomes around them, facilitating their recognition by autophagy receptors for degradation[7].

NDP52 plays important roles in ubiquitin-mediated protein degradation. It is well known that the ubiquitin-proteasome system is another important degradation system in host cells. Following ubiquitylation, invading pathogens can be cleared by host cells via autophagy. Autophagy receptors such as NDP52 and SQSTM1 play intermediate roles in autophagy and ubiquitylation[8].

Furthermore, a mechanism involving fusion with lysosomes is reported, where autophagosomes containing damaged mitochondria fuse with lysosomes to form autolysosomes, leading to the degradation of engulfed mitochondria by acidic environments and lysosomal enzymes.

In the recycling of degraded components, the breakdown products such as amino acids and fatty acids that emerge after degradation are recycled for cellular processes or excreted from the cell[9].

The breakdown products are then recycled or expelled from the cell for cellular processes. Lysophagy, conversely, is a selective form of autophagy that targets unhealthy and unwanted lysosomes for removal in normal mammalian cells[10].

In lysophagy, several basic steps target damaged or dysfunctional lysosomes for removal. Damaged or dysfunctional lysosomes are typically identified through oxidative stress, nutrient deficiency, or other insults. Once identified, damaged lysosomes are captured by double-membrane vesicles called autophagosomes, which aim to degrade cellular components targeted for degradation[11]. Like mitophagy, in lysophagy, autophagosomes containing damaged lysosomes merge with functional lysosomes, forming autolysosomes. As a result, the acidic environment and lysosomal enzymes within autolysosomes facilitate the degradation of damaged lysosomal contents, including proteins, lipids, and other macromolecules. The breakdown products are recycled for cellular processes or expelled from the cell after degradation. Overall, lysophagy helps maintain cellular homeostasis by removing damaged lysosomes and preventing the accumulation of toxic cellular remnants, contributing to cellular function and health[12]. Dysregulation of lysophagy can lead to cellular dysfunction and contribute to various pathological conditions.

In this systematic review, based on the hypothesis that maintaining appropriate mitophagy/lysophagy to prevent degenerative changes associated with IVDD could be crucial for preserving IVDD health and function, a systematic review is planned to be conducted.

MATERIALS AND METHODS

The study adhered to the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines[13,14].

Search Strategy

Systematic searches were conducted on the PubMed electronic database up to March 21, 2024, to evaluate published studies examining mitophagic/lysophagic signaling pathways associated with IVDD. Searches were conducted sequentially using the keywords "mitophagy", "lysophagy", in combination with "annulus fibrosus", "NP", and "IVDD" without country or language restrictions. Additionally, manual literature searches were performed by examining the reference lists of significant articles to identify other relevant studies.

Selection Criteria

The inclusion criteria for studies were as follows:

Studies conducted on humans and preclinical studies conducted on live mammalian subjects *in vivo* or *in vitro* cell cultures were included.

Clinical trials, if available, were considered, excluding non-randomized and non-blinded trials.

Exclusion criteria encompassed comments, editorials, letters to the editor, protocols, guidelines, meta-analyses, systematic reviews, and reviews.

The studies were selected based on their evidence level, which was determined according to the criteria set by Lijmer et al.[15-17].

After evaluating studies meeting the inclusion criteria following the keyword searches, information such as publication year range, examined signaling pathways, and characteristics related to tested pharmaceutical or pharmacological agents were recorded.

If the authors disagreed, the issue was discussed, and the senior author's (A.D.) opinion prevailed.

Figure 1 (PRISMA 2009 flow diagram) depicts the screening process for studies that did not meet the inclusion criteria and were thus excluded from our systematic review[18].

Statistical Analysis

After systematic literature searches, data were compiled in an Excel spreadsheet using Microsoft Office Program (version 10). While initially planned to assess heterogeneity using the

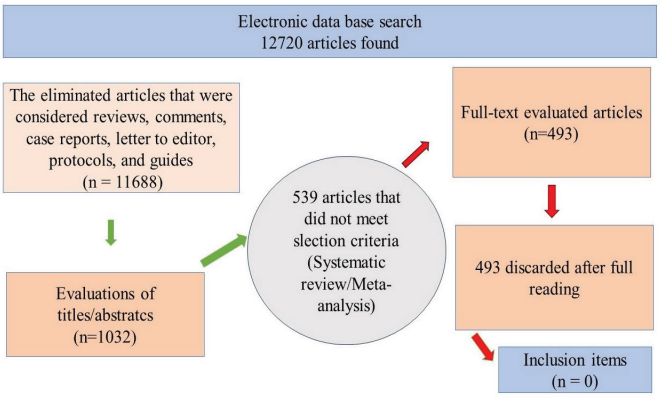

Figure 1. Flowchart of selection of studies for inclusion in umbrella review

Cochrane Q test, statistical evaluation could not be performed due to the absence of high-level clinical trials meeting the inclusion criteria. Descriptive statistics were used to analyze the obtained data, and the results were presented in counts and/or percentages (frequency, %).

RESULTS

Using the keyword "IVD", 41.698 results from 1890-2024 were found, of which 12.614 were identified as studies associated with disc degeneration between 1942 and 2024 (Table 1).
After a comprehensive literature search, no clinical trials or studies fully covering the topic of interest, "mitophagy"/"lysophagy" and "IVDD", were found.

DISCUSSION

All members of the Ras protein family belong to a class of proteins called small guanosine triphosphate (GTP) ases and play a role in transmitting signals within cells (signal transduction). Ras, the prototype member of the Ras protein family, is activated "ON" by incoming signals, subsequently activating other proteins and genes related to cell growth, proliferation, differentiation, and survival. Mutations in Ras genes can produce persistently active Ras proteins, resulting in unwanted and overly active signaling within cells, even without incoming signals. Therefore, Ras inhibitors are being intensively researched to treat various diseases with Ras overexpression, primarily cancer types and many other neurological conditions[19,20].
A study investigating the relationship between autophagy, ferroptosis, and potentially related molecules reported that compression pressure induces excessive iron accumulation and ferroptosis in human NP cells by inactivating autophagy and inducing lysosomal damage. Specifically, Ras GTPase-activating protein-binding protein 1 (G3BP1), primarily located in lysosomes, coordinates lysophagy activity through the G3BP1 and tuberous sclerosis complex (TSC)2 signaling pathways[10]. Functional impairment of G3BP1/TSC2 accelerates lysosomal damage and ferroptosis in NP cells. Additionally, inhibition of the mammalian target of rapamycin (mTOR) signaling by rapamycin improves lysosomal damage and protects cell ferroptosis[10]. *In vivo* experiments also demonstrate the role of G3BP1/mTOR signaling in the progression of IVDD. G3BP1 coordinates lysophagic activity to protect against cell ferroptosis associated with compression during IVDD. These findings demonstrate the relationship between lysophagy and compression-induced cell ferroptosis, while also indicating the positive role of G3BP1, which may provide potential targets for IVDD treatment[10].
In a study reporting that hypoxia-inducible factor-1-alpha (HIF-1α) alleviates compression-induced apoptosis of NP-derived stem cells by regulating autophagy, the dependence of BNIP3-like protein (BNIP3L) on HIF-1α-dependent expression, known as B-cell lymphoma-2 and adenovirus E1B 19 kDa-interacting protein-3 (BNIP3), and Nix, a proapoptotic gene regulated by histotoxic hypoxia, has been widely accepted as the fundamental mechanism of hypoxia-induced autophagy. Depletion of both components completely abolishes mitophagy and significantly increases cell death[21].
The mitochondrion is the center for bioenergetic processes, where substrates from the cytoplasm are utilized for fatty acid oxidation, the tricarboxylic acid (TCA) cycle, the electron transport chain, and respiration. Additionally, the mitochondrion serves as a platform for the biosynthesis of amino acids, lipids, nucleotides, heme, and iron-sulfur clusters and functions as its antioxidant defense through nikotinamid adenin dinükleotid fosfat.

Table 1. Searches performed before a detailed examination of the full texts of the articles

Keywords (year range of publication)	Case reports (amount)	Clinical trial (amount)	Review (amount)	Systematic review (amount)	Meta analysis (amount)	Total (amount)
IVDD (1942-2024)	434	493	1454	285	254	12619
IVDD + Mitophagy (2013-2024)	0	0	6	0	0	49
Lysophagy (2011-2024)	0	0	1	0	0	11
Mitophagy + AF (2019-2024)	0	0	0	0	0	3
Mitophagy + NP (2018-2024)	0	0	0	3	0	37
Lysophagy + AF (2013)	0	0	0	0	0	1
Lysophagy + NP (2011-2024)	0	0	0	0	0	9
IVDD + Mitophagy + Lysophagy	0	0	0	0	0	0

IVDD: Intervertebral disc degeneration, NP: Nucleus pulposus, AF: Annulus fibrosus

A study emphasizing that BNIP3 translocation to mitochondria mediates hypoxia-induced mitophagy in NP cells, but whether BNIP3 also regulates mitochondrial function and metabolism in hypoxic NP cells remains unknown, reported that BNIP3 degradation enhances mitochondrial morphology[22]. In a study reporting that BNIP3 deficiency in NP cells reduces glycolytic capacity, reflecting lower lactate/H+ production and lower adenozin trifosfat production rates, the authors have reported that loss of BNIP3 redirects glycolytic flux into pentose phosphate and hexosamine biosynthesis, as well as into pyruvate, leading to increased TCA flux using 1-2-13C-glucose. They observed increased autophagic flux, decreased disc height index, and abnormal expression of collagen type-X (an early sign of disc degeneration) in young adult BNIP3 knockout mice. These findings indicate that in addition to regulating mitophagy, BNIP3 also plays a role in preserving mitochondrial function and metabolism, and disruption of mitochondrial homeostasis may support disc degeneration[22].

CsA-induced mitophagy inhibition partially abolished the protective effects of melatonin against NP cell apoptosis, highlighting mitophagy's role in mediating melatonin's protective effect on IVDD[17]. Additionally, melatonin has been shown to inhibit the expression of extracellular matrix (ECM) degradation enzymes such as matrix metalloproteinase-13 and a disintegrin and metalloproteinase with thrombospondin motifs 5, while preserving the ECM content of collagen type-II, aggrecan, and Sox9. *In vivo*, melatonin treatment has been reported to improve degeneration in a puncture-induced experimental rat IVDD model[23]. These results suggest that melatonin protects NP cells against apoptosis through the induction of mitophagy and improved disc degeneration, potentially providing a therapeutic strategy for IVDD[23].

In previous studies, it was reported that mitochondrial dysfunction contributes to apoptosis and urolithin A (UA) specifically triggers mitophagy[24]. The protective effect of UA-induced mitophagy against tert-butyl hydroperoxide (TBHP)-induced apoptosis in NP cells was demonstrated in vitro. and was investigated in the *in vivo* experimental IVDD rat model. They have been reported that UA can activate mitophagy in primary NP cells, and UA treatment inhibits TBHP-induced mitochondrial dysfunction and the intrinsic apoptosis pathway. Mechanistically, UA has also been mentioned to promote mitophagy by activating 5' adenosine monophosphate (AMP)-activated protein kinase (AMPK) signaling in TBHP-induced NP cells. It has been shown *in vivo* that UA effectively alleviates the progression of puncture-induced experimental IVDD in rats, and they argue that UA may be a new and effective therapeutic strategy for IVDD[24].

In a study where the interaction between circular RNAs CircERCC2 and the miR-182-5p/Sirtuin (SIRT)-1 axis was investigated, it was reported that downregulation of circERCC2 increased miR-182-5p levels and decreased SIRT1 levels in degenerative NP and TBHP-stimulated NP *in vitro*[25]. They provided the first evidence that circERCC2 activates mitophagy and inhibits apoptosis through the miR-182-5p/SIRT1 axis, suggesting that circERCC2 could be a potential therapeutic target for IVDD[25].

In 2021, it was reported that zinc finger protein/tumor necrosis factor α-induced protein-3 (A20) can inhibit the activation of the nuclear factor kappa-B (NF-κB) signaling pathway and promote autophagy[26]. Therefore, it has been reported that A20 can improve IVDD by regulating inflammation through autophagic pathways mediated by NF-κB in human NP cells[26]. Subsequently, in 2023, it was reported that A20 promotes mitophagy, weakens pyroptosis, and inhibits ECM degradation, thus significantly improving IVDD. Mechanistically, it was reported in a study that A20 reduces pyroptosis and further suppresses cellular mTOR activity. In a study reporting that A20-induced mTOR inhibition promotes mitophagy through the AMPK signaling pathway activated by AMP, it was further reported that A20 suppresses mTOR pathway activation induced by lipopolisakkarit (LPS), supporting BNIP3-mediated mitophagy, thereby inhibiting LPS-induced pyroptosis. These findings suggest that A20 may regulate IVDD through mitophagy and ECM degradation inhibition[27].

Additionally, in the literature, using live mammalian subjects and *in vitro* tissue and cell models, it is mentioned that nucleotide-binding oligomerization domain (NOD)-like receptor family member X1 (NLRX1) can facilitate mitochondrial quality by combining mitophagy activity and mitochondrial dynamic factors such as dynamin 1-like protein, which is involved in the division of mitochondria and peroxisomes. It is reported that in NP cells with NLRX1 damage, mitochondrial collapse occurs and the compensatory PINK1-Parkin RBR E3 Ubiquitin Protein Ligaz (PRKN) signaling pathway is activated, leading to excessive mitophagy and aggressive NP cell senescence[28]. NLRX1 has been shown to initially interact with the zinc transporter SLC39A7 and modulate mitochondrial Zn2+ through the formation of an NLRX1-SLC39A7 complex on the mitochondrial membrane of NP cells, subsequently regulating mitochondrial dynamics and mitophagy and improving IVD[28].

Sestrin2 (Sesn2), a highly conserved, stress-responsive protein, can be triggered by a variety of noxious stimuli such as hypoxia, DNA damage, oxidative stress, endoplasmic reticulum stress, and inflammation. Many transcription factors, including Hif-1α, p53, nuclear factor E2-related factor 2 (Nrf2), activating transcription factor (ATF)-4, ATF-6, regulate Sesn2 expression. Upon induction, Sesn2 generally leads to activation of AMPK and inhibition of the mechanistic target of mTOR1C. To maintain cellular homeostasis, Sesn2 and its downstream molecules directly scavenge reactive oxygen species (ROS) or indirectly influence the expression patterns of key genes associated with redox, macroautophagy, mitophagy, endoplasmic reticulum stress, apoptosis, protein synthesis and inflammation[29].

In a study reported that Sesn2 functions as a regulator between the mitochondrial unfolded protein response (UPRmt) and mitophagy in IVDD[30], it has been mentioned that the mitochondrial UPRmt can induce mitophagy to protect the

cell from unfolded protein. In the study reported that Sesn2 is considered to be a key molecule that transmits UPRmt and mitophagy in the IVD, it is mentioned that silencing Sesn2 can reverse the protective effects of nicotinamide riboside (NR) on NP cells and inhibit mitophagy induced by UPRmt[30]. Sesn2 has also been mentioned to promote the translocation of cytosolic Parkin and SQSTM1 to damaged mitochondria, respectively, thus increasing mitophagy. They have been reported that NR, Sesn2-/- mice do not completely attenuate IVDD, but UPRmt may attenuate IVDD through regulation of Sesn2-induced mitophagy[30].

Additionally, the literature mentions that NOD-like receptor family member X1 (NLRX1) can facilitate mitochondrial quality by combining mitochondrial dynamic factors and mitophagy activities, thereby regulating mitochondrial division in vascular tissues. It is reported that in NP cells with NLRX1 damage, the compensatory PINK1-PRKN signaling pathway is activated, resulting in mitochondrial collapse and aggressive NP cell aging. NLRX1 is shown to interact with the zinc transporter SLC39A7 and modulate mitochondrial Zn2+, subsequently regulating mitochondrial dynamics and mitophagy, thus alleviating IVDD[31].

In a study using a hydrogen peroxide (H_2O_2)-induced NP cell aging model and a rat acupuncture IVDD model to investigate the role of cannabinoid type 2 receptor (CB2R) in IVDD, p16INK4a expression was shown to increase with a decrease in CB2R expression[32]. They reported that CB2R activation significantly reduced the number of SA-β-gal positive cells and suppressed the expression of p16INK4a and senescence-associated secretory phenotypes and the high mobility group[32]. Additionally, activation of CB2R has been reported to promote the expression of collagen type-II and Sox9, inhibit collagen type-X, and restore the balance of the ECM. It has also been shown that CB2R plays a role in the aging or regulation of the AMPK/GSK3β signaling pathway and NP cells in the rat experimental IVDD model. It has been stated that activation of CB2R may attenuate IVDD[32].

Selenophosphate synthetase-1 (SEPHS1) has been reported to play an important role in reducing oxidative stress in an osteoarthritis model by reducing ROS production, thereby delaying the occurrence and development of osteoarthritis. Overexpression of SEPHS1 and inhibition of Hippo-Yap/Taz have been reported to alleviate IVDD in rats[33].

In a study reporting that SIRT3 expression decreased in degenerated NP cells but increased in H2O2-derived NP, it was emphasized that upregulation of SIRT3 reduced oxidative stress, delayed cellular aging, and reduced IVDD via the AMPK/PGC-1α signaling pathway[34]. There is also a claim in the literature that hyaluronic acid improves IVDD by promoting mitophagy activation[35]. A study reported that MitoQ, through the PINK1/Parkin signaling pathway, restores mitochondrial dynamic balance, alleviates the disruption of mitophagosome-lysosome fusion and lysosomal function, and increases Nrf2 activity, thus eliminating damaged mitochondria, improving redox balance, and increasing cell survival. It has been reported to represent a promising therapeutic strategy for IVDD[36].

In a study in which optineurin (OPTN), a selective mitophagy receptor, was tested in a rat disc degeneration model[37], it was emphasized that H_2O_2-induced cellular senescence was significantly inhibited and ECM-related protein expression increased in NP cells. They demonstrated that OPTN attenuates oxidative stress-induced NP cellular senescence and ECM degeneration by promoting mitophagy to clear damaged mitochondria and excess ROS, thereby slowing the progression of IVDD[37].

Following lentivirus (LV)-shLRRK2 transfection in human degenerative NP and rat NP cells, the therapeutic effects of LV-shLRRK2 on IVDD were evaluated. In the study reporting that LRRK2 expression increased in degenerative NP cells[38], it was reported that LRRK2 deficiency significantly suppressed oxidative stress-induced mitochondria-dependent apoptosis in NP cells and promoted mitophagy. The study revealed that LRRK2 plays a role in the pathogenesis of IVDD and that knockdown of LRRK2 inhibits oxidative stress-induced apoptosis through mitophagy, emphasizing that inhibition of LRRK2 may be a promising therapeutic strategy for IVDD[38].

Vitamin D receptor (VDR) is a steroid hormone receptor that can regulate autophagy. In a study that sought to answer the question of whether VDR alleviates IVDD by promoting autophagy, a negative correlation was reported between VDR expression and IVDD. It was also reported in the study that overexpression of VDR promoted mitophagy and prevented apoptosis and mitochondrial damage under oxidative stress, and that mitophagy inhibition by 3-methyladenine, an autophagy inhibitor, eliminated the protective effect of VDR activation. The study revealed that VDR activation ameliorates oxidative damage and reduces NP cell apoptosis by promoting PINK1/Parkin-dependent mitophagy, indicating that VDR may serve as a promising therapeutic target in the management of IVDD[39].

It has been hypothesized that downregulation of vascular endothelial growth factor A creates a new effect in non-vascular tissues through mitophagy regulation, and it has also been reported in the literature that it accelerates NP degeneration mediated by advanced glycation end products by inhibiting protective mitophagy in high glucose environments[40].

In summary, research into the molecular mechanisms underlying IVDD has identified multiple pathways and molecules involved in regulating cellular processes, such as autophagy, mitophagy, apoptosis, ferroptosis, and ECM degradation. These findings provide valuable insights into potential therapeutic targets for the treatment of IVDD, although further research is needed to elucidate the complex interactions and signaling pathways involved fully.

CONCLUSION

In the context of IVDD, lysophagy may play a role in maintaining cellular homeostasis by clearing damaged components within disk cells such as NP and annulus fibrosus dysregulation

of lysophagy may contribute to the progression of IVDD by impairing the ability of IVDD cells to remove cellular debris and maintain tissue integrity. Mitophagy, particularly within disk cells in the avascular and nutrient-deprived IVD environment, is believed to play a crucial role in preserving mitochondrial quality control and cellular homeostasis in IVDD. Dysregulation of mitophagy has been implicated in the pathogenesis of IVDD, as impaired mitophagy can contribute to the degenerative process by accumulating dysfunctional mitochondria, increased oxidative stress, and, ultimately, cell death. Therefore, promoting healthy mitophagy may hold therapeutic potential for mitigating the progression of IVDD. However, further research is needed to fully understand the relationship between lysophagic or mitophagic signaling pathways and IVDD.

Ethics

Authorship Contributions

Surgical and Medical Practices: İ.Y., H.C.K., G.A., A.D., Concept: İ.Y., A.D., Design: İ.Y., A.D., Data Collection or Processing: İ.Y., H.C.K., G.A., Analysis or Interpretation: İ.Y., A.D., Literature Search: İ.Y., G.A., Writing: İ.Y., H.C.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Li X, Huang L, Lan J, Feng X, Li P, Wu L, et al. Molecular mechanisms of mitophagy and its roles in neurodegenerative diseases. Pharmacol Res. 2021;163:105240.
2. Wang XL, Feng ST, Wang ZZ, Chen NH, Zhang Y. Role of mitophagy in mitochondrial quality control: Mechanisms and potential implications for neurodegenerative diseases. Pharmacol Res. 2021;165:105433.
3. Pan C, Hou W, Deng X, Liu J, Chi R, Shang X, et al. The pivotal role of Nrf2 signal axis in ıntervertebral disc degeneration. J Inflamm Res. 2023;16:5819-33.
4. Sun K, Jing X, Guo J, Yao X, Guo F. Mitophagy in degenerative joint diseases. Autophagy. 2021;17:2082-92.
5. Xin J, Wang Y, Zheng Z, Wang S, Na S, Zhang S. Treatment of ıntervertebral disc degeneration. Orthop Surg. 2022;14:1271-80.
6. Nguyen TN, Padman BS, Lazarou M. Deciphering the molecular signals of PINK1/parkin mitophagy. Trends Cell Biol. 2016;26:733-44.
7. Lippai M, Lőw P. The role of the selective adaptor p62 and ubiquitin-like proteins in autophagy. Biomed Res Int. 2014;2014:832704.
8. Fan S, Wu K, Zhao M, Zhu E, Ma S, Chen Y, et al. The role of autophagy and autophagy receptor NDP52 in microbial ınfections. Int J Mol Sci. 2020;21:2008.
9. Liu Y, Zhou T, Hu J, Jin S, Wu J, Guan X, et al. Targeting selective autophagy as a therapeutic strategy for viral ınfectious diseases. Front Microbiol. 2022;13:889835.
10. Li S, Liao Z, Yin H, Liu O, Hua W, Wu X, et al. G3BP1 coordinates lysophagy activity to protect against compression-induced cell ferroptosis during intervertebral disc degeneration. Cell Prolif. 2023;56:13368.
11. Kudriaeva AA, Sokolov AV, Belogurov AAJ. Stochastics of degradation: the autophagic-lysosomal system of the cell. Acta Naturae. 2020;12:18-32.
12. Ward C, Martinez-Lopez N, Otten EG, Carroll B, Maetzel D, Singh R, et al. Autophagy, lipophagy and lysosomal lipid storage disorders. Biochim Biophys Acta. 2016;1861:269-84.
13. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
14. Han YH, Bo JQ, Liu LX. Neoadjuvant immunotherapy for resectable hepatocellular carcinoma: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2023;27:7134-47.
15. Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, van der Meulen JH, et al. Empirical evidence of design-related bias in studies of diagnostic tests. JAMA. 1999;282:1061-6.
16. Karaarslan N, Yilmaz I, Ozbek H, Caliskan T, Topuk S, Sirin DY, et al. Systematic evaluation of promising clinical trials-gene silencing for the treatment of glioblastoma. Turk Neurosurg. 2019;29:328-34.
17. Topuk S, Akyuva Y, Karaaslan N, Mutlu CA, Yilmaz I, Isyar M, et al. Is it Possible to treat osteosarcoma using oligonucleotides confined into controlled release drug delivery systems? Curr Pharm Biotechnol. 2017;18:516-22.
18. Lozano-López MT, Gamonal-Limcaoco S, Casado-Espada N, Aguilar L, Vicente-Hernández B, Grau-López L, et al. Psychosis after buprenorphine, heroin, methadone, morphine, oxycodone, and tramadol withdrawal: a systematic review. Eur Rev Med Pharmacol Sci. 2021;25:4554-62.
19. Colicelli J. Human RAS superfamily proteins and related GTPases. Sci STKE. 2004;2004:RE13.
20. Wang D, Shang Q, Mao J, Gao C, Wang J, Wang D, et al. Phosphorylation of KRT8 (keratin 8) by excessive mechanical load-activated PKN (protein kinase N) impairs autophagosome initiation and contributes to disc degeneration. Autophagy. 2023;19:2485-503.
21. He R, Wang Z, Cui M, Liu S, Wu W, Chen M, et al. HIF1A alleviates compression-induced apoptosis of nucleus pulposus derived stem cells via upregulating autophagy. Autophagy. 2021;17:3338-60.
22. Madhu V, Hernandez-Meadows M, Boneski PK, Qiu Y, Guntur AR, Kurland IJ, et al. The mitophagy receptor BNIP3 is critical for the regulation of metabolic homeostasis and mitochondrial function in the nucleus pulposus cells of the intervertebral disc. Autophagy. 2023;19:1821-43.
23. Chen Y, Wu Y, Shi H, Wang J, Zheng Z, Chen J, et al. Melatonin ameliorates intervertebral disc degeneration via the potential mechanisms of mitophagy induction and apoptosis inhibition. J Cell Mol Med. 2019;23:2136-48.
24. Lin J, Zhuge J, Zheng X, Wu Y, Zhang Z, Xu T, et al. Urolithin a-induced mitophagy suppresses apoptosis and attenuates intervertebral disc degeneration via the AMPK signaling pathway. Free Radic Biol Med. 2020;150:109-19.
25. Xie L, Huang W, Fang Z, Ding F, Zou F, Ma X, et al. CircERCC2 ameliorated intervertebral disc degeneration by regulating mitophagy and apoptosis through miR-182-5p/SIRT1 axis. Cell Death Dis. 2019;10:751.
26. Zhang Y, Yi W, Xia H, Lan H, Chen J, Yang Z, et al. A20 regulates inflammation through autophagy mediated by NF-κB pathway in human nucleus pulposus cells and ameliorates disc degeneration in vivo. Biochem Biophys Res Commun. 2021;549:179-86.
27. Peng X, Zhang C, Gao JW, Wang F, Bao JP, Zhou ZM, et al. A20 ameliorates disc degeneration by suppressing mTOR/BNIP3 axis-mediated mitophagy. Genes Genomics. 2023;45:657-71.
28. Song Y, Liang H, Li G, Ma L, Zhu D, Zhang W, et al. The NLRX1-SLC39A7 complex orchestrates mitochondrial dynamics and mitophagy to rejuvenate intervertebral disc by modulating mitochondrial Zn2+ trafficking. Autophagy. 2023:1-21.
29. Lu C, Jiang Y, Xu W, Bao X. Sestrin2: multifaceted functions, molecular basis, and its implications in liver diseases. Cell Death Dis. 2023;14:160.

30. Xu WN, Liu C, Zheng HL, Xu HX, Yang RZ, Jiang SD, et al. Sesn2 Serves as a regulator between mitochondrial unfolded protein response and mitophagy in ıntervertebral disc degeneration. Int J Biol Sci. 2023;19:571-92.
31. Yan X, Ding JY, Zhang RJ, Zhang HQ, Kang L, Jia CY, et al. FSTL1 accelerates nucleus pulposus cell senescence and ıntervertebral disc degeneration through TLR4/NF-κB pathway. Inflammation. 2024.
32. Du J, Xu M, Kong F, Zhu P, Mao Y, Liu Y, et al. CB2R attenuates ıntervertebral disc degeneration by delaying nucleus pulposus cell senescence through AMPK/GSK3β pathway. Aging Dis. 2022;13:552-67.
33. Hu T, Shi Z, Sun Y, Hu F, Rong Y, Wang J, et al. SEPHS1 attenuates intervertebral disc degeneration by delaying nucleus pulposus cell senescence through the Hippo-Yap/Taz pathway. Am J Physiol Cell Physiol. 2024;326:386-99.
34. Lin J, Du J, Wu X, Xu C, Liu J, Jiang L, et al. SIRT3 mitigates intervertebral disc degeneration by delaying oxidative stress-induced senescence of nucleus pulposus cells. J Cell Physiol. 2021;236:6441-56.
35. Zhang F, Wang S, Gao M, Li B, He Z, Tang T, et al. Hyaluronic acid ameliorates intervertebral disc degeneration via promoting mitophagy activation. Front Bioeng Biotechnol. 2022;10:1057429.
36. Kang L, Liu S, Li J, Tian Y, Xue Y, Liu X. The mitochondria-targeted anti-oxidant MitoQ protects against intervertebral disc degeneration by ameliorating mitochondrial dysfunction and redox imbalance. Cell Prolif. 2020;53:12779.
37. Hu Z, Wang Y, Gao X, Zhang Y, Liu C, Zhai Y, et al. Optineurin-mediated mitophagy as a potential therapeutic target for intervertebral disc degeneration. Front Pharmacol. 2022;13:893307.
38. Lin J, Zheng X, Zhang Z, Zhuge J, Shao Z, Huang C, et al. Inhibition of LRRK2 restores parkin-mediated mitophagy and attenuates intervertebral disc degeneration. Osteoarthritis Cartilage. 2021;29:579-91.
39. Lan T, Yan B, Guo W, Shen Z, Chen J. VDR promotes nucleus pulposus cell mitophagy as a protective mechanism against oxidative stress injury. Free Radic Res. 2022;56:316-27.
40. Wu D, Huang W, Zhang J, He L, Chen S, Zhu S, et al. Downregulation of VEGFA accelerates AGEs-mediated nucleus pulposus degeneration through inhibiting protective mitophagy in high glucose environments. Int J Biol Macromol. 2024;262:129950.