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REVIEW

Role of Autophagy and Pyroptosis in Intervertebral Disc Degeneration

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Abstract: Intervertebral disc degeneration is a chronic degenerative disease caused by the interaction of genetic and environmental factors, mainly manifested as lower back pain. At present, the diagnosis of intervertebral disc degeneration mainly relies on imaging. However, early intervertebral disc degeneration is usually insidious, and there is currently a lack of relevant clinical biomarkers that can reliably reflect early disease progression. Pyroptosis is a regulatory form of cell death triggered by the activation of inflammatory bodies and caspase, which can induce the formation of plasma membrane pores and cell swelling or lysis. Previous studies have shown that during the progression of intervertebral disc degeneration, sustained activation of inflammasomes leads to nuclear cell pyroptosis, which can occur in the early stages of intervertebral disc degeneration. Moreover, intervertebral disc nucleus pulposus cells adapt to the external environment through autophagy and maintain cellular homeostasis and studying the mechanism of autophagy in IDD and intervening in its pathological and physiological processes can provide new ideas for the clinical treatment of IDD. This review analyzes the effects of pyroptosis and autophagy on IDD by reviewing relevant literature in recent years, in order to explore the relationship between pyroptosis, autophagy and IDD.

Keywords: intervertebral disc degeneration, pyroptosis, autophagy

Introduction

Intervertebral disc degeneration (IVDD) is a main factor contributing to the chronic lower back pain (LBP). During IVDD, aberrant apoptosis, senescence and pyroptosis of disc cells, degradation of extracellular matrix (ECM), and infiltration of immune cells are the main molecular variants. Changes at the tissue level usually do not occur until the late stages of IVDD. Ectopic growth of nerves within the annulus fibrosus (AF) and nucleus pulposus (NP) tissues is considered as the main cause of IVDD.

Overview of IVDD

Disc degeneration is a major risk factor for low back pain. IVDD usually has no obvious symptoms.[1] However, as the disease progresses, there will be disc herniation, lumbar spondylolisthesis and even spinal stenosis, which makes IVDD and lead to chronic disability.[2] In addition, IVDD can present with neurological symptoms, including neuralgia, numbness, muscle weakness, and even paralysis.[3] To date, most VIDDs have been treated with conservative treatments, such as bed rest, nonsteroidal anti-inflammatory drugs and analgesics, and surgical interventions such as lumbar discectomy and interbody fusion.[4,5] These approaches focus on temporary relief of symptoms rather than targeting pathogenesis, so the progression of IVDD cannot be reversed. Hence, developing biotherapeutics is critical for the early recovery of IVDD.

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Physiological Structure of IVDD

The intervertebral disc consists of the NP (nucleus pulposus) and the peripheral AF (annulus fibrosis) act as a buffer against pressure.[6,7] NP is a highly hydrated gelatinous tissue composed of water, proteoglycans, and collagen, and it also contains large amounts of elastin, fibrin and laminin.[8] Located around the nucleus pulposus, the annulus fibrosus is a circular structure composed of fibrous tissue rich in type I collagen.[9] The CEP (cartilaginous endplate) consists of a layer of hyaline cartilage, which plays an important role in nutrient diffusion and metabolic waste expulsion of the intervertebral disc.[9] (Figure 1).

Pathophysiology of IVDD

The nutrients required for NP (including oxygen, glucose, matrix generated substrates, amino acids and sulfate) are the roots in the permeation of vertebral capillaries through the CEP. The energy metabolism of NP is mainly performed through glycolysis, so glucose is necessary for the survival of the disc cells.[10] However, in response to smoking, decreased blood supply, subchondral osteosclerosis, nutrients are reduced in NP, manifested by high lactate, low oxygen levels, and PH value indicated acidic. On account of the low natural cell density of NP and AF, it is believed that an enough nutrient supply is needful to maintain cellular activities. Cells in the intervertebral disc function gradually changes at high lactate levels, low oxygen and acidic pH, resulting in excessive apoptosis.[11] The oxygen pressure subsequently decreases below 5%, which will greatly inhibit matrix synthesis.[12] Meanwhile, under acidic pH environment, the matrix synthesis was suppressed and the matrix fracture rate was enhanced.

Intervertebral discs can undergo aging and degenerative degeneration over lifetime of a person.[13] IVDD occurs as early as age 11, and develops with age.[14,15] Slight microscopic degenerative changes, including aging and proliferation of NP cells, slight crack formation, changes in cell density, and degeneration of the CEP matrix were observed by 2 years. Latterly, the CEP undergoes cracking and thinning eventually leading to disc herniation and even spinal canal stenosis.[16] Meanwhile, different genetic or environmental factor can damage NP, AF, or EP, leading to the development of IVDD.[17] IVDD is characterized by abnormal extracellular matrix (ECM) metabolism, expedited cartilage and bone remodeling, shaped tissue fibrosis, resulting in the release of proinflammatory cytokines.[18] Smoking, accidental trauma, tissue infection, genetic factors, and metabolism related diseases also further accelerate IVDD[19–25] (Figure 2).

Autophagy Biology

In all cells, there are usually two ways to regulate energy supply. One approach is to obtain extracellular nutrients regulated by growth factor signaling pathways.[26] Extracellular hormones stimulate this system to fortify nutrient uptake, thereby offering the cell with oxidizable substrates to support adenosine triphosphate production and biosynthesis via

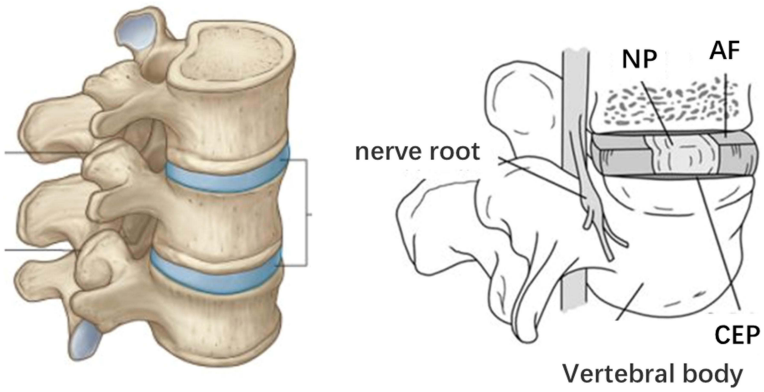

Figure 1 The Physiological structure of IVDD. The cell density of gel shaped nucleus pulposus tissue is low, and the extracellular matrix mainly includes type II collagen and proteoglycan. Protein polysaccharides (mainly aggregated proteoglycans and hyaluronic acid) can maintain intervertebral disc moisture, maintain disc height, and buffer axial loads on the spine. The fibrous ring is the fibrous tissue surrounding the nucleus pulposus, consisting of two layers: 1) the inner fibrous ring, and 2) the outer fibrous ring. The outer fibrous ring plays an important role in maintaining the integrity of intervertebral discs. The cartilage endplate contains abundant type II collagen and chondrocytes, which attach the intervertebral disc to the vertebral body and provide nutrients for the intervertebral disc. Blood vessels and nerves are only distributed in the outer fibrous ring of the intervertebral disc in healthy adults. Nutrients passively diffuse to the deep nucleus pulposus. The nerves in the scar in the degenerative intervertebral disc are the main cause of discogenic pain.

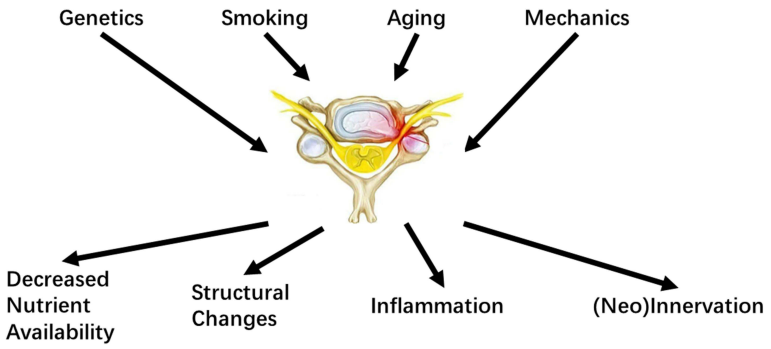

Figure 2 Risk factors for IVDD. Smoking, aging, genetics and mechanics related diseases also further accelerate IVDD.

anabolism. In the presence of attenuated growth factor signaling, autophagy at this stage can provide amino acids required for static cellular biosynthesis as well as cytoplasmic ATP.

Maintaining the integrity of organelles can help the cells adapt to various environmental changes.[27] Autophagy can remove dysfunctional and excess organelles including peroxisomes, mitochondria, nucleus, lysosomes, and ribosomes to maintain cell survival. Autophagosomes can provide nutrients to the cell during the removal of these organelles. Lipid degradation in autophagosomes/lysosomes supplies fatty acids for mitochondrion oxidation, which generates acetyl-CoA. Amino acids are substrates not only for the synthesis of new proteins, but also for mitochondrial oxidation in the tricarboxylic acid (TCA) cycle. Alanine and glutamate can generate ATP through the TCA to provide energy for the cell.

Normally, autophagy is related to apoptosis as well as the mechanism of cell death.[28,29] There is a complex cross-regulation between autophagy and apoptosis, involving a variety of common regulatory factors and signal transduction pathways.[30] The initiation of autophagy protects cells from apoptosis in IVDD, highlighting its major cytoprotective role.[31] With no other types of cell death, independent autophagy induced cell death, called autophagy cell death.[32] Apoptosis was most commonly observed at some time after autophagy was upregulated, in this case, autophagy death may play a role in protecting and restoring tissue balance by clearing out cells with irreversible damage.

Expression and Mechanism of Autophagy in IVDD

Autophagy is regulated by many factors, including the serine/threonine protein kinase ULK1 complex, beclin1 complex, positive regulation of AMPK and PINK1/Parkin, and negative regulation of mTOR targets. Genes involved in autophagy (Beclin-1, Atg8, Atg12, Cathepsin B, Presenilin 1, and p62) were prominently upregulated in degenerative disc tissue compared with healthy disc tissue.[33] Meanwhile, more autophagic vacuoles and upregulation of LC3-II as well as lysosomal associated membrane glycoprotein 2 (LAMP-2A) were also found in disc tissues with the age of rats.[34] In addition, numerous studies have found increased expression and phosphorylation levels of mTOR, p70/S6K, and Akt.[35]

mTOR Signaling

Recently, in a review of IVDD, Yurube et al described the mechanism by which the mTOR pathway regulates autophagy.[3] mTOR is a member of the phosphatidylinositol 3-kinase family. In mammals, m can form two complexes with other proteins, mTORC1 or mTORC2. mTORC1 is mainly a complex sensitive to rapamycin, and mTORC2 is vice versa. mTORC2 is involved in the assembly of mTORC2 complexes that are resistant to rapamycin. Ito et al verified that the interference with targeted RNA against mTORC1 and mTORC2 could obviously enhance the autophagy process in NP cells.[36] PI3Ksare lipid kinases that can convert phosphatidylinositol to 3,4,5-trisphosphate (PIP3). Afterwards, The combined interaction of PIP3 and Akt can fully activate Akt and promote the activation of mTORC1, leading to the inhibition of autophagy.[37] Moreover, morpholino M could activate autophagy in NP cells, which further reversed LPS-induced IL-1β, TNF-α and IL-6 Morpholino M can reduce the activity of PI3K/Akt/mTOR by down-regulating the ratio of pPI3K/PI3K, p-Akt/Akt and p-mTOR/mTOR, which leads to the reduction of PI3K/Akt/ mTOR activity and induces autophagy in NP cells.[38]

PINK1/Parkin Signaling

PINK1 encodes a 581 amino acid residues PINK1 protein. The mature PINK1 protein has kinase activity and is cleaved from its precursor protein through the cytoplasm to the mitochondria. PINK1 is located in mitochondria and interacts with Parkin to maintain the integrity of mitochondrial structure and function, which is the main regulatory pathway of mitophagy.[39] Down-regulation of PINK1 in NP cells could obviously inhibit mitochondrial phagocytosis and accelerate oxidative stress-induced apoptosis of NP cells.[40] Zhang et al found that salicylic acid can promote Parkin expression in vivo and in vitro, and upregulation of Parkin can promote mitophagy and further inhibit TNF- α caused apoptosis of nucleus pulposus cells and ROS production.[41] In parallel, Parkin-mediated mitophagy was verified to be essential in the elimination of mitochondrial dysfunction and apoptosis in NP cells.[42] The current study identified a total of 12 immunoglobulins involved in the regulation of autophagy process in age-related diseases.[43]

AMPK Signaling

AMP-activated protein kinases are sensors that stabilize the body's energy and can link cellular metabolic stress to energy homeostasis by controlling several homeostatic mechanisms such as autophagy and protein degradation.[44] AMPK/mTOR signaling pathway can regulate autophagy activation. AMPK directly activates ULK1 via phosphorylation of Ser317 to promote autophagy.[45] Active mTORC1 prevents ULK1 activation and inhibits autophagy by phosphorylating a specific ULK1 site (Ser757) and disrupting the interaction between ULK1 and AMPK.[46] Activation of the AMPK/mTOR pathway in vitro is associated with intercellular Ca2+ levels and inhibits apoptosis of human notochord cells by inducing autophagy. Using Ca2+ inhibitors, AMPK/mTOR pathway activation induced reduced autophagy and p62/SQSTM1 deposition, leading to accelerated apoptosis of human notochord cells.[47] In a separate experiment, researchers verified that curcumin activates the AMPK/mTOR/ULK1 pathway and leads to autophagy activation and autophagic flux increase., removing TBHP - induced apoptosis, ECM degradation, and senescence.[48] Nevertheless, other scholars confirmed that activation of the AMPK/mTOR pathway can facilitate autophagy and accelerate apoptosis, and ECM breakdown in human NP cells.[49]

Autophagy Plays a Protective Role in IVDD

Protective Role of Autophagy in IVDD

Autophagy plays a twofold role in IVDD, activation of autophagy is a protective effect for IVDD.[50] Autophagy can be rapidly activated in response to oxidative stress, starvation, inflammation, and hypoxia. After intervention with sirolimus (an mTORC1 inhibitor), the levels of P70/S6K kinases were distinctly decreased. However, Akt phosphorylation and LC3-II expression were upregulated, which promoted autophagy.[23] Melatonin synthesis in the pineal gland is mainly regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus. A positive correlation between serum melatonin concentration and IVDD in patients was demonstrated in clinical studies.[51] Experiments have suggested that removal of the pineal gland in chickens will induce the disease of IVDD.[52] Melatonin could increase sSirt1 expression and activity, promote autophagy in inner plate chondrocytes. The protective effects of melatonin on apoptosis and calcification of lamellar chondrocytes were abolished by autophagy inhibitor 3-methyladenine (3-MA).[53] In addition, activation of the autophagy pathway can attenuate oxidative stress-induced mitochondrial dysfunction and inhibit apoptosis and senescence in NP cells. In addition, it regulates the expression of type II collagen, proteoglycans and matrix metalloproteinases in the intervertebral disc to maintain a stable level of extracellular matrix.[54]

Autophagy Promotes IVDD

Excessive activation of autophagy can promote excessive degradation and self-digestion of important cellular components.[55] Researches verified that activation of autophagy facilitated apoptosis and senility in NP cells. Applying 1 MPa of the autophagy inhibitor 3-MA to mouse NP cells significantly increased the death of NP cells compared with NC group, and the promotion death effect of 3-mA was clearly reduced.[56] This research suggests that appropriate autophagy is beneficial for the survival of NP cells, but when the stimulus accumulates to a certain limit, the significantly increased autophagic flow may accelerate the apoptosis of NP cells.

Basal cell autophagy may avoid or delay the progression of intervertebral disc herniation by reducing or inhibiting cell apoptosis, ECM degradation, osteogenic differentiation and inflammatory response. The increase of autophagy flow can promote the apoptosis and senescence of intervertebral disc cells, thereby accelerating the development of IVDD.[57]

Scorch Death and IVDD

Pyrogenic Cell Biology

Pyroptosis is an inflammatory programmed cell death mode found in macrophages in recent years that depends on the activation of caspase-1. In addition to causing a large number of immune cells to decrease, pyroptosis can also trigger excessive inflammatory response of the body, cause tissue and organ damage and even lead to death.[58,59]

Study of Focal Death in IVDD

Mechanism of Pyroptosis in the Progression of IVDD

The inflammatory response is mediated by the formation of the inflammatory body complex, which is a cell membrane heptamer consisted of nucleotide binding domains and leucine-rich repeat (NLR) pattern recognition receptors. NLR or NLR3 is a redox-sensitive cell membrane sensor that causes docking and activation of procaspase-1, which clefts proIl-1β into its mature form IL-1β at 17kDa. Latest research have speculated that both chronic inflammation and innervation are key factors in disc degeneration.[60] In contrast to apoptosis, focal death during intervertebral disc degeneration has not been well studied.

In general, exogenous deleterious stimuli activate innate immune-dependent PRRS, which in turn activate various inflammatory bodies, including NLRP3, producing caspase-1 and gasdermin D (GSDMD), which ultimately mediate programmed death.[61] Bai et al verified that hydrogen peroxide could increase the ROS level in human NP cells leading to increased pyroptosis. Compared with the control group, the expressions of NLRP3, cleaved IL-1, and PYCARD in the hydrogen peroxide treatment group reached the maximum at 3 h.[62] Transfection of NLRP3-shrna and PYCARD-shRN reduced the thermal damage of NP cells. Zhang et al showed that pyroptosis in NP cells is mediated by LPS-induced upregulation of NLRP3, caspase-1, and GSDMD.[63] The expression of NLRP3, caspase-1 and GSDMD was down-regulated after the intervention of MSCs-derived exosomes, and miR-410 could significantly down-regulate their expression, thereby inhibiting pyroptosis. We also found that P. acnes activated NLRP3 inflammasome through TXNIP-NLRP3 pathway, which promoted pyroptosis of NP cells and ultimately led to IVDD.[64]

IL-1β secretion is associated with pyroptosis and the NLRP3 inflammatory factor triggers the coking process.[65] In addition, pyroptosis was found to be related to proinflammatory processes of intervertebral disc degeneration mediated by Propionibacterium acnes. The expression of NLRP3, IL-1β and GSDMD in NPC was up-regulated after co-culture with Propionibacterium acnes.[64]

The canonical inflammasome activation pathway needs to include the initiating event of the binding of proinflammatory cytokines to their receptors, such as by triggering pattern recognition receptors (PRRS).[66,67] In response to PAMPs or DAMPs, the inflammasome complex assembles leading to caspase 1 activation, IL-1β cleavage and pyroptosis. In addition, ROS also control pyroptosis of NPCs via the NLRP3/PYCARD pathway and are negatively regulated by promoting autophagy and the transcription factor erythrocytic 2-like 2 (NFE2L2).[62]

Pyroptosis Promotes IVDD

Focal death of resident intervertebral disc cells promotes the progression of IVDD.[64] Inflammatory cytokines or ROS accumulate in senescent or degenerated intervertebral disc cells, thereby activating the NLRP3 inflammasome and caspase-1. Activated caspase-1 in the case of cleavage of GSDMD and release of the GSDMD-N fragment leads to membrane pore formation and cell death.[68] Knockout of GSDMD can inhibit the inflammatory response, thereby protecting the organ damage caused by the stimulation.[69] It was also shown that delivery of NLRP3 inflammasome inhibitor to degenerated rat intervertebral discs can effectively delay the progression of IDD.[70] In addition, caspase-1 inhibitors reduced GSDMD expression and ameliorated disc degeneration in vivo.[71]

Strategies Targeting Autophagy and Pyroptosis in IVDD

Autophagy and Pyroptosis in IVDD

Some studies have shown that autophagy inhibits inflammasome activation and reduces the secretion of inflammatory cytokines.[72,73] Previous researches have confirmed that activation of autophagy protects NP cells from stress-induced cell death, whereas inhibition of autophagy has the opposite effect.[74] Autophagy has been reported to be activated during ROS-induced pyroptosis of NP cells, with negative regulatory and self-protective effects.[62] The effect of increased ROS levels on pyroptosis may vary depending on the difference in autophagy levels in the inability cell lines. A study assessing the relationship between oxidative stress and pyroptosis in NP cells showed that ROS induced pyroptosis in NP cells via the NLRP3/PYCARD inflammasome and formed a negative regulatory relationship with NFE2L2 by activating autophagy.

Currently, some studies have shown that autophagy can inhibit the activation of inflammasome, and indicate the protective effect of autophagy on pyroptosis.[75] Bai et al showed that autophagy was activated in the process of pyroptosis induced by ROS, and inhibition of autophagy could aggravate pyroptosis.[62] Since autophagy enzymatically hydrolyses its contents, its activation could remove some pyrogen inducers or remove damaged organelles to re-establish cellular balance.[75–77] Similarly, increased autophagy markers led to pyroptosis, which was associated with terminal activation of autophagy and lysosomal instability, while autophagy inhibitors reduced pyroptosis. Since autophagy is a dynamic activity at different stages, the relationship between autophagy and pyroptosis is still controversial.

In fact, activation of inflammasomes, including NLRP3, plays an important role in pyroptosis.[78] It has been shown that activation of autophagy down-regulates NLRP3 expression and cleaved caspase-1 production.[79,80] Houtman et al verified colocalization between NLRP3 and LC3-labeled structures, suggesting a selective degradation mechanism of NLRP3.[81] In addition, mTOR signaling pathway is involved in autophagy activation. Autophagy intervention may regulate NLGRP3 activation by regulating mTOR and NLGRP3 binding.[79] Perforation of the plasma membrane is a sign of pyroptosis. Plasma membrane perforation leads to the leakage of cell contents and the release of inflammatory cytokines.[82] Lysosomes can act as a membrane repair mechanism under autophagy activation.[83,84] With the activation of small GTP-enzymes, lysosomes fuse with the plasma membrane and release degradation products via extravasation pathways that may repair thermalized perforations and promote cell survival.[85]

Impaired autophagy accelerates PS-induced pyroptosis of NP cells.[86] VX-765, an inhibitor delivering caspase-1, inhibits inflammatory body activation and pyrogenesis, hence improving the progression of intervertebral disc degeneration in vivo. These studies indicate the deleterious role of pyroptosis in intervertebral disc degeneration and the protective role of autophagy in pyroptosis of NP cells.

Treatment of IVDD with Traditional Chinese Medicine

The treatment of LIDH, especially the treatment of traditional Chinese medicine is very important and necessary. At present, although a large number of conservative treatments are available, LIDH patients are still well treated. In addition, there are certain national characteristics in the conservative treatment of LIDH in different countries, but it is still difficult to widely apply these methods. How to select a conservative treatment method with less side effects and low cost has become a common concern for doctors and patients with LIDH. Among the non-surgical treatment methods, some TCM therapies such as acupuncture, massage, and Chinese herbal medicine are especially favored by patients with LIDH. Chinese medicine has developed its own unique theory, diagnosis and treatment system in Asian countries, especially China, after thousands of years of development. In the past few decades, these TCM therapies have been increasingly used worldwide and are known for their important role in the prevention and treatment of various diseases including LIDH.[87]

Under various adverse stimuli, NP cells enhance their ability to clear damaged tissues through autophagy, suggesting that autophagy plays a key role in protecting the survival of NP cells and delaying the course of IVDD. Studies have shown that traditional Chinese medicine YQHXR can promote the absorption of ruptured lumbar disc herniation to a certain extent.[88] Dai Feng et al studied the protective effect of Yiqi Huoxue recipe on IVDD by promoting autophagy, which provided a reference for the clinical treatment of IVDD with Yiqi Huoxue recipe. Fu et al found that lumbar spine

instability (LSI) in mice caused histological changes of intervertebral disc degeneration, interrupted stroma metabolism, activated Wnt signaling in VD tissues, promoted apoptosis of IVD cells, sensory nerve invasion into the annulus fibrosus, and induced focal death.[89] Maltol can improve IVDD by inhibiting the PI3K/AKT/NF-κB pathway and regulating NLRP3 inflammasome-mediated focal disc death.[90]

IVDD is a complex pathological process, which is affected by nutritional factors, mechanical factors and body metabolism. The specific mechanisms in the disease process of IVDD have not been fully elucidated. Autophagy and pyroptosis play a key role in the occurrence and development of IVDD. In recent years, the experimental research on the mechanism of delaying IDD through the signaling pathway of traditional Chinese medicine has become more and more in-depth. Moreover, the balance of autophagy in intervertebral disc cells and the effect of autophagy on pyrocytosis will not only expand the knowledge of molecular pathogenesis of IVDD, but also provide new ideas for the treatment and prevention of intervertebral disc degeneration and the exploration of the therapeutic value of traditional Chinese medicine.

Conclusions

The traditional treatment methods of IDD can no longer meet the patient's expectations for prognosis and their needs for quality of life. In recent years, autophagy has attracted widespread attention and in-depth exploration as a research hotspot. At present, most studies are still in the in vitro trial stage, and their exact clinical effects still need to be verified. How to regulate the levels of pyrocytosis and autophagy of intervertebral disc cells to the optimal level to minimize cell apoptosis is a major challenge in clinical application. However, it can be foreseen that therapies targeting pyrocytosis and autophagy related pathways will provide more options for the clinical treatment of IDD.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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