Mitochondrial quality control in intervertebral disc degeneration

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Intervertebral disc degeneration (IDD) is a common and early-onset pathogenesis in the human lifespan that can increase the risk of low back pain. More clarification of the molecular mechanisms associated with the onset and progression of IDD is likely to help establish novel preventive and therapeutic strategies. Recently, mitochondria have been increasingly recognized as participants in regulating glycolytic metabolism, which has historically been regarded as the main metabolic pathway in intervertebral discs due to their avascular properties. Indeed, mitochondrial structural and functional disruption has been observed in degenerated nucleus pulposus (NP) cells and intervertebral discs. Multilevel and well-orchestrated strategies, namely, mitochondrial quality control (MQC), are involved in the maintenance of mitochondrial integrity, mitochondrial proteostasis, the mitochondrial antioxidant system, mitochondrial dynamics, mitophagy, and mitochondrial biogenesis. Here, we address the key evidence and current knowledge of the role of mitochondrial function in the IDD process and consider how MQC strategies contribute to the protective and detrimental properties of mitochondria in NP cell function. The relevant potential therapeutic treatments targeting MQC for IDD intervention are also summarized. Further clarification of the functional and synergistic mechanisms among MQC mechanisms may provide useful clues for use in developing novel IDD treatments.

INTRODUCTION

Low back pain (LBP) is an extremely prevalent musculoskeletal disorder worldwide, and almost everyone suffers an acute or chronic episode of LBP during their lifetime1. According to the statistical analysis of the Global Burden of Disease Study 2017, LBP was consistently the leading contributor to the increase in years lived with a disability2. Intervertebral disc degeneration (IDD), which results in progressive spinal deformity, stenosis, and the inflammatory response, has been identified as a well-known contributor to LBP3,4. Nevertheless, current clinical therapeutic strategies, known as conservative treatment and surgical intervention, aimed at alleviating symptoms rather than targeting IDD directly5. Further clarifying the molecular mechanism of IDD will provide a new approach for precise intervention strategies for LBP.

Normal intervertebral discs consist of gelatinous nucleus pulposus (NP) as the central structure, surrounded by lamellar annulus fibrosus (AF) and sandwiched by superior and inferior cartilaginous endplates (CEPs)6. The gelatinous NP tissue is critical for the physiological function of intervertebral discs to absorb and disperse mechanical loadings during spinal motion, such as flexion, extension, bending, and rotation7. Currently, NP cells are identified as the main cell group that undergoes anabolic and catabolic metabolism and maintains extracellular matrix homeostasis. Mounting evidence has demonstrated that the loss of function of NP cells through senescence, apoptosis, necroptosis, inflammatory response, or phenotypic change plays important roles in inducing the dehydration of NP tissue and promoting IDD progression6–8.

Although the intervertebral disc has been identified as the largest avascular organ and found to generate energy through anaerobic glycolysis9,10, a critical role for mitochondria in promoting metabolic adaptation has been suggested11,12. In addition to material and energy metabolism, mitochondria also participate in regulating the function of second messengers, such as reactive oxygen species (ROS) and calcium, and the activation of various signaling pathways, which play important roles in regulating cellular function and determining cell fates13. In IDD progression, structural and functional abnormalities in mitochondria have been observed in NP cells5,14,15. Mitochondrial quality control (MQC), involving molecular, organellar, and cellular level mechanisms, is considered a critical surveillance and protective system for limiting mitochondrial damage and ensuring mitochondrial integrity14 (Fig. 1). Dysfunctional MQC strategies and aggravated mitochondrial damage are considered major contributing factors in promoting NP cell function loss6,17.

In this review, we summarize defective MQC strategies linked to mitochondrial dysfunction that contribute greatly to NP cell function loss and IDD progression. Relevant molecular strategies with clinical translational potential that might be developed for the prevention and treatment of IDD progression are also discussed.
MITOCHONDRIAL DYSFUNCTION AND IDD PATHOGENESIS

Although in some studies, few mitochondria were detected in adult NP tissue specimens, well-developed mitochondria exist in NP cells, especially in fetal NP cells. Multiple studies have confirmed that the etiological factors in IDD pathogenesis are involved in endogenous genetic predisposition and exogenous stressors, such as decreased nutrient transport, mechanical overloading, diabetes, smoking, infection, and aging. Interestingly, all these etiological mechanisms are associated with mitochondrial damage, which has been proposed to underlie the pathophysiology of NP cell function loss and IDD progression.

First, the early degenerative process of notochord-like NP cells due to phenotypic changes or cell death was partially attributed to loading, avascularity, and the hypoxic and hyperglycemic microenvironment, in which increased mitochondrial fission, fragmentation, mitophagy and mitochondrial damage play adaptive and aggravating roles. Due to the origination of the notochord, NP cells present notochord markers, also called notochord-like NP cells, and are regarded as indicative of the initial cell phenotype in NP tissue. Defective MQC strategies aggravate intervertebral disc morphologic disruption and fail to maintain mitochondrial homeostasis and exhibit mitochondrial fragmentation, low mitochondrial membrane potential, high ROS levels, and poor NP cell status. Interpretively, intervertebral disc morphology was defined on the basis of T2-weighted magnetic resonance imaging, mitochondrial structure as assessed with MitoTracker Red CMXRos staining, mitochondrial membrane potential as determined by JC-1 assay, ROS levels as measured using 2′,7′-dichlorofluorescin diacetate staining, and NP cell status as assessed using senescence-associated β-galactosidase staining.

Fig. 1 The molecular, organellar, and cellular levels of MQC strategies that maintain mitochondrial homeostasis. With increasing stress magnitude, multilevel and well-orchestrated MQC strategies are implemented. Mitochondrial proteostasis is monitored by UPRmit activity and executed by ATF5, which mainly promotes the expression of mitochondrial chaperones and proteases that conduct the refolding or proteolysis of misfolded and damaged proteins. Under primary and secondary oxidative stress, mitochondrial antioxidant members (SOD2, Gpx1/4, Prx3, Trx1, Trx2, TrxR2) eliminate superoxide radicals and maintain redox homeostasis. Further damage can induce the selective separation of healthy and injured mitochondria by Drp1-dependent fission. The remaining intact daughter mitochondria are replenished by mitochondrial biogenesis involving mitochondrial transcription factor-mediated (TFAM) mtDNA and nuclear transcription factor-mediated (PGC-1, NRFs, ERRs, PPARs) DNA expression and integrated by OPA1/MFN-dependent fusion, while the disrupted daughter mitochondria are swallowed and degraded by mitophagy, which depends on ubiquitinated mitochondrial substrates (S) in the PINK1/Parkin ubiquitin pathway or other mitophagy receptors (BNIP3/NIX, FUND1C1, or cardiolipin). Finally, irreversible damage to mitochondria induces devastating effects on cellular bioactivities and results in apoptosis. Healthy MQC strategies succeeded in maintaining good intervertebral disc morphology (A1) and mitochondrial homeostasis through mitochondrial elongation and integral structure (B1), high mitochondrial membrane potential (C1), low ROS levels (D1), and fine-tuned NP cell status (E1). Defective MQC strategies aggravate intervertebral disc morpologic disruption (A2), low mitochondrial membrane potential (C2), high ROS levels (D2), and poor NP cell status (E2). Interpretively, intervertebral disc morphology was defined on the basis of T2-weighted magnetic resonance imaging (A1/A2), mitochondrial structure as assessed with MitoTracker Red CMXRos staining (B1/B2), mitochondrial membrane potential as determined by JC-1 assay (C1/C2), ROS levels as measured using 2′,7′-dichlorofluorescin diacetate staining (D1/D2), and NP cell status as assessed using senescence-associated β-galactosidase staining (E1/E2).
| Study (year) | Models | Key findings |
|-------------|--------|--------------|
| **Mitochondrial proteostasis**<br>Chooi et al.65 | NP cells in 3D collagen | Longer loading duration resulted in a continuous upregulation of the Hsp70 gene, which might play a role in cell survival following mechanical stress. |
| Chooi et al.66 | Disc organ culture | Static loading induced higher Hsp70 expression than dynamic loading in NP cells. |
| Gosage et al.67 | NP cell culture | Hsp70, HIFs, and TonEBP form a regulatory loop to adapt the NP cells to the unique hypoxic and hyperosmolar microenvironment. |
| Tasi et al.68 | NP cell culture | Hypertonicity enhanced the expression of Hsp70 via the activation of the ERK and p38-MAPK pathways. |
| **Mitochondrial antioxidants**<br>Chen et al.77 | NP cell culture | TNF-α treatment led to the reduction in SOD and GSH-PX activity levels, which can be reversed by bioactive extract Rg3. |
| Jin et al.78 | Rat disc | Ovariectomized rats showed decreased activities of SOD and GSH-Px and an increased GSSG/GSH ratio. |
| Song et al.6 | AGEs | AGE treatment decreased the protein levels of SOD2, TRX2, TRXR2 and catalase in NP cells. |
| Chen et al.49 | NP cell culture | Mechanical loading induced a downward trend in SOD activity. |
| Jiao et al.79 | NP cell culture | Hyperosmolarity culture significantly decreased the total SOD activity compared with the in situ-osmolarity culture. |
| Gu et al.80 | NP cell culture | NP cells treated with LPS exhibited reduced SOD and catalase activity levels. |
| Tang et al.81 | NP cell culture | Honokiol pretreatment significantly reversed the H2O2-suppressed expression of the SOD and Gpx1 genes. |
| He et al.82 | NP cell culture | Melatonin pretreatment restored higher levels of GSH and SOD activity under H2O2 conditions. |
| Chu et al.83 | NP cell culture | Plumbagin significantly increased the GSH content, as well as the activity of catalase, SOD and GSH-Px. |
| Dong et al.84 | NP cell culture | Plumbagin pretreatment attenuated the increase in SOD induced by lipopolysaccharides challenge in a concentration-dependent manner. |
| **Mitochondrial dynamics**<br>Xu et al.17 | Mice disc and NP cell culture | NP cells showed the increased expression level of Drp1 and decreased levels of Mfn1/2 in the progerin group, indicating less fusion and more fission in mitochondria. |
| Kang et al.52 | Disc organ and NP cell culture | Mechanical loading promoted the mitochondrial translocation of Drp1 and upregulated Mfn1, Mff and Fis1 protein levels, whereas MitoQ could alleviate this process. |
| Xu et al.50 | NP cell culture | NaHS pretreatment significantly decreased the mitochondrial translocation of Drp1 induced by IL-1β in NP cells. |
| **Mitophagy**<br>Kang et al.52 | Disc organ and NP cell culture | MitoQ promotes Parkin-mediated mitophagy and repairs defective mitophagic flux in TNF-α-stimulated NP cells. |
| Zhang et al.104 | NP cell culture | Parkin was upregulated in degenerative NP tissues in vivo as well as in TNF-α stimulated NP cells in vitro, and salidroside could enhance Parkin expression and eliminate mitochondria damage. |
| Chen et al.105 | Rat disc and NP cell culture | Mfn2 overexpression stimulates an ROS-dependent mitophagy via Parkin/FIP200 pathway in TBHP-treated rat NP cells. |
| Chen et al.106 | NP cell culture | TBHP suppressed mitophagic activity, while melatonin effectively reversed TBHP-induced NP cell apoptosis via Parkin-dependent mitophagy induction. |
| Xie et al.107 | TBHP/circERCC2 | |
Table 1 continued

| Study (year) | Stressors/Interventions | Models | Key findings | Refs |
|--------------|-------------------------|--------|--------------|------|
| Wang et al.108 | TBHP/Honokiol | NP cell culture | Honokiol can facilitate the colocalization of LC3 and Bnip3L and enhance mitophagy in TBHP-treated NP cells by enhancing SIRT3. | 108 |
| Xu et al.32 | TBHP | NP cell culture | TBHP induced parkin-dependent excessive mitophagy that was detrimental for NP cell survival. | 32 |

**Mitochondrial biogenesis**

| Study (year) | Stressors/Interventions | Models | Key findings | Refs |
|--------------|-------------------------|--------|--------------|------|
| Hu et al.117 | H2O2/ICariin | NP cell culture | Icarin activates the NRF1/2 and TFA1 signaling pathways and mitochondrial biogenesis. | 117 |
| Song et al.6 | AGEs | Rat disc and NP cell culture | AGE treatment decreased the activation of the AMPK/PGC-1α pathway in NP cells. | 6 |
| Kang et al.52 | Mechanical loading/MitoQ | Disc organ and NP cell culture | MitoQ inhibited Keap1 expression, which activated the Nrf2 signaling cascade in human NP cells. | 52 |
| Wang et al.108 | TBHP/Honokiol | NP cell culture | Honokiol can effectively upregulate SIRT3 expression via the AMPK-PGC-1α signaling pathway in NP cells. | 108 |

The MQC system in IDD pathogenesis

Generally, the unfolded protein response (UPR) is a protective signaling pathway that diverts unfolded and misfolded proteins from the endoplasmic reticulum (ER) to the mito-ochondrial network (UPR mt). The UPR mt can also unfold and disaggregate misfolded proteins, which help maintain ER homeostasis. This response seems to lay a better foundation for controlling the production of mitochondrial-derived danger molecules. Presumably, this control of mitochondrial metabolism, incidental mitochondrial damage, and mitochondrial regeneration. Some studies have attempted to investigate precise MQC strategies and elucidate the corresponding therapeutic targets (Table 1).
the Hsp70 level and had little influence on the apoptosis ratio of the NP cells, which indicated a protective effect following mechanical stress. In addition, this research team also used adult bovine caudal discs to construct an organ culture model and found that Hsp70 expression appeared to be upregulated immediately after loading and was decreased upon resting following a repeated loading cycle in NP cells but not in AF cells. In addition, a hypoxic or hypertonic microenvironment showed dramatic effects on mitochondrial function in NP cells, in which the levels and function of the mitochondrial chaperone Hsp70 presented a corresponding response. Shilpa et al. found that toxicity enhancer-binding protein (TonEBP) and HIFs are involved in some interaction that leads to the regulation of Hsp70 levels, while Hsp70 function also negatively regulates HIF-1α protein stability and transcriptional activity. Studying the mitochondrial surface is the principal mechanisms of mitochondrial dysfunction and oxidative stress conditions. In quiescent cells, increased mitochondrial fission converts functionally mature mitochondrial networks into immature states that are applicable for conditions of low metabolic demand and reduced oxidative exposure. Under stress or proliferative conditions, however, activated mitochondrial fusion activity can maximize the oxidative capacity for energy demand and increase the degree of cross-complementation for attenuating defective mitochondria, enhancing their response capacity. A healthy balance of dynamic mitochondrial activity is well regulated by large dynamin-related guanosine triphosphatases (GTPases). Long-form optic atrophy 1 (L-Opa1) and short-form Opa1 (S-Opa1) are correspondingly critical for outer and inner mitochondrial membrane fusion, and dynamin-like protein (Drp1) and short-form Opa1 (S-Opa1) are correspondingly critical for outer and inner mitochondrial membrane fission. In addition, other factors have also been found to assemble the fusion and fission machinery, such as mitoPLD, FIS1, MFF, MID49, and MTP18. Both innate mutations and acquired stressors that disturb the healthy fusion and fission machinery can induce pathological mitochondrial dynamics.

Mitochondrial antioxidant system. Along with mitochondrial respiration and metabolism, ROS are commonly generated, such as superoxide anion and hydrogen peroxide (H$_2$O$_2$). The antioxidant system in mitochondria largely contributes to monitoring and controlling cellular ROS levels. Multiple antioxidant enzymes participate in the construction of the mitochondrial antioxidant system, including superoxide dismutases (SODs), glutathione peroxidases (Gpxs), peroxiredoxins (Prxs), and some enzymes that exhibit redundant actions. SODs can dismutate superoxide anions to H$_2$O$_2$ and SOD2 is mainly located in mitochondria. Subsequently, Gpxs/Prxs can catalyze H$_2$O$_2$ to H$_2$O, mainly through Gpx1/4, Prx3, Trx2, and TrxR2, in mitochondria. A healthy antioxidant system is crucial in determining whether ROS are playing “friends” or “foes” roles, which partially depends on their concentration, location, and functional context. Appropriate or low ROS levels contribute to multiple essential biochemical signaling processes ranging from cell metabolism to microorganism defense. Excessive generation and/or inadequate elimination of ROS results in oxidative damage to molecules and oxidative stress, which has been implicated in various pathologies and, in the case of cancer, in roles that protect tumors from elimination.

In IDD pathogenesis, it has been demonstrated that various risk factors, such as mechanical overloading, AGE accumulation, nutrient deprivation, and inflammatory cytokines, can promote IDD events by inducing oxidative stress. Under compression conditions, NP cells showed significantly decreased protein levels of SOD2, which could be rescued by MitoQ treatment, and they showed antioxidant function. It was found that the reduction in SOD and Gpx activity levels was involved in TNF-α-induced oxidative stress in human NP cells and that the rescue of SOD and Gpx activity levels by administration of ginsenoside Rg3 reversed this degenerative process. In ovariectomized animal models, IDD progression was associated with disrupted redox homeostasis involving the functional loss of SOD, Gpx, and GSSG/GSH balance. Estrogen supplementation can enhance antioxidant capacity and correct redox imbalance stress. In addition, the partial or whole functional deficiency of mitochondrial antioxidant enzymes is also critical in many other IDD processes induced by hyperosmolarity, mechanical overloading, AGE accumulation, or lipopolysaccharide. The effects of biologically active components used to treat IDD have greatly improved in recent years. It has been confirmed that honokiol, nicotinamide mononucleotide, melatonin, plumbagin, and pilose antler peptide can efficiently enhance the catalytic activity of SOD and/or Gpx, which contributes substantially to resistance to oxidative stress and IDD progression. More investigation and clarification targeting the mitochondrial antioxidant system will provide clearer strategies for IDD intervention.

Mitochondrial dynamics. Dynamic mitochondria are identified by high fusion and fission activities, ensuring their efficient response to changing requirements for energy production, calcium homeostasis, lipid biogenesis, fatty acid synthesis, and responses to stress conditions. In quiescent cells, increased mitochondrial fission converts functionally mature mitochondrial networks into immature states that are applicable for conditions of low metabolic demand and reduced oxidative exposure. Under stress or proliferative conditions, however, activated mitochondrial fusion activity can maximize the oxidative capacity for energy demand and increase the degree of cross-complementation for attenuating defective mitochondria, enhancing their response capacity. A healthy balance of dynamic mitochondrial activity is well regulated by large dynamin-related guanosine triphosphatases (GTPases). Long-form optic atrophy 1 (L-Opa1) and short-form Opa1 (S-Opa1) are correspondingly critical for outer and inner mitochondrial membrane fusion, and dynamin-like protein (Drp1) and short-form Opa1 (S-Opa1) are correspondingly critical for outer and inner mitochondrial membrane fission. In addition, other factors have also been found to assemble the fusion and fission machinery, such as mitoPLD, FIS1, MFF, MID49, and MTP18. Both innate mutations and acquired stressors that disturb the healthy fusion and fission machinery can induce pathological mitochondrial dynamics.

It has been proven that disrupted mitochondrial dynamics are also closely related to mitochondrial dysfunction and oxidative stress in the IDD process. Xu et al. found that progerin accumulation in human NP tissues was associated with IDD progression, and further study confirmed that progerin stimulation can shift mitochondrial dynamics toward fission events by decreasing the levels of mitochondrial fusion factors Opa1 and Mfn1/2 and increasing the levels of the mitochondrial fission factor Drp1. By rescuing the balance of mitochondrial dynamics, sulforaphane can significantly attenuate progerin-induced mitochondrial dysfunction and NP cell senescence. Using a mechanical overloading model of IDD, Kang et al. observed that the migration of Drp1 from the cytoplasm to mitochondria was significantly enhanced. Similarly, the total protein levels of Drp1, Mff, and Fis1 were significantly upregulated and those of Opa1 and Mfn1/2 were downregulated by mechanical overloading, which largely contributed to NP cell damage and was ameliorated by MitoQ intervention. Similarly, hydrogen sulfide treatment can also decrease the mitochondrial membrane location of Drp1 and mitochondrial dysfunction induced by proinflammatory factors. These results may suggest that rebalancing healthy mitochondrial fusion/fission dynamics is critical for IDD intervention.

Mitophagy. In contrast to bulk autophagy, in which cellular components are recycled to meet nutrient demand, selective autophagy functions to clear unwanted and damaged substances. Autophagy that is specific to mitochondria is referred to as mitophagy, which is crucial for the elimination of damaged or superfluous mitochondria. The principal mechanisms of selective autophagy rely on the use of specialized cargo-binding adaptor proteins, also called selective autophagy receptors. Members of the PARK family, PARK2 and PARK6, which encode the E3-ub ligase PARKIN and the mitochondrial-targeted kinase PINK1, respectively, were shown to be key mediators of mitophagy and mitochondrial surveillance. The accumulation of PINK1 on the mitochondrial surface is the first step to sensing mitochondrial...
stressing the mitochondrial membrane, decreasing its potential, prevents the import of PINK1 through the mitochondrial membrane and secondary proteolytic cleavage, which leads to the effective accumulation of full-length PINK1 and its activating autophosphorylation. Activated PINK1 can phosphorylate ubiquitin and elicit PARKIN recruitment to the mitochondrial surface. Ultimately, the PINK1-PARKIN pathway results in ubiquitinated mitochondrial substrates (S), autophagy receptor recruitment, and clearance of damaged mitochondria.102,103. In addition to the PINK1-PARKIN pathway, several selective mitochondrial autophagy receptors have been identified: BNIP3/NIX, FUNDC1, NLRX1, and PHB.102,103,104. Some lipid autophagy receptors have also been identified.102,103. Cardiolipin, a lipid unique to mitochondria, has recently been reported to promote mitophagy.110

It has been observed that the mitophagy process in NP cells can be induced by mechanical loading, TNF-α expression, and exogenous hydroperoxide treatment, which is beneficial for alleviating NP cell senescence, preventing cell death, and correcting imbalances in anabolic/catabolic metabolism.105. Based on this, targeting the PINK1-PARKIN pathway by natural extracts, such as salidroside and melatonin, may promote effective mitophagy and its beneficial effects. Noncoding RNAs targeting molecules upstream of the PINK1-PARKIN pathway have also been shown to exert a positive effect on mitophagy.107. In addition, other mitophagy receptors, such as BNIP3, were found to mediate the selection and elimination of damaged mitochondria and promote the resistance of NP cells to oxidative stress.108. The outcome of mitophagy as beneficial or detrimental in disease progression and/or intervention is a cellular factor- and context-dependent. Under strong oxidative conditions, excessive mitophagy is induced in NP cells, which contributes greatly to the promotion of apoptotic cell death. This study also identified the critical role of HIF-1α/NDUFA4 L2 in repressing excessive mitophagy and alleviating NP cell apoptosis. Thus, more clarification of mitophagy mechanisms in IDD progression may provide precise therapeutic targets for driving the beneficial effect of mitophagy in IDD intervention.

Mitochondrial biogenesis. Mitochondrial biogenesis is an important process that promotes the synthesis of new mitochondria through expansion and division of pre-existing mitochondria, which reach and maintain mitochondrial homeostasis by obtaining a balance between mitochondrial fission and fusion. As semiautonomous organelles, mitochondrial proteins not only transcribe and translate nuclear and mitochondrial genomes but also synchronize and coordinate their expression. Multiple transcription factors and coactivators have been shown to orchestrate genome expression during mitochondrial biogenesis. Nuclear respiratory factors (NRF1/2) were the first nuclear transcription factors found to be involved in the transcription of several mitochondrial genes that mainly encode subunits of mitochondrial respiratory chain complexes. Members of the nuclear receptor (NR) superfamily, mainly peroxisome proliferator-activated receptors (PPARs) and estrogen-related receptors (ERRs), are also important for controlling the transcription of nuclear genes encoding mitochondrial substrates involved in FAO, the TCA cycle, and ETC/OXPHOS. In peroxisome proliferator-activated receptor-gamma coactivator-1 (PGC-1) coactivators build regulatory circuitry and serve as central components to control the transcriptional activities of NRF and NR family proteins. PGC-1/NRF1 coactivation is also critical for the expression of TFAM, a transcription factor of the mitochondrial genome encoding 13 components of OXPHOS system complexes. Hua et al. observed that icariin can significantly rescue mitochondrial function in human NP cells by activating the NRF1/2 and TFAM pathways and promoting mitochondrial biogenesis. Other studies have also observed the functions of PGC-1 and NRFs in protecting mitochondria against damage in NP cells, but whether mitochondrial biogenesis is involved in this protection remains to be elucidated.

Cellular elimination of mitochondria. In the case of sustained mitochondrial stress and irreversible mitochondrial damage, the cellular quality control mechanisms that rely on apoptosis and the turnover of entire cells are engaged to ensure the homeostasis of the organism. Otherwise, damaged mitochondria would be transferred to neighboring cells, and malfunctioning cells can accumulate and lead to tumor development and other pathological conditions. Indeed, extensive mitochondrial damage promotes prolonged mitochondrial outer membrane permeabilization (MOMP), which can contribute to the release of proapoptotic molecules such as cytochrome c, Diablo, Htra2, and AIF from the mitochondrial intermembrane space into the cytosol, resulting in caspase activation and apoptosis. The well-characterized mechanism that invokes MOMP is dependent on Bax-Bak oligomerization and translocation to the mitochondrial outer membrane where pores or channels are formed to generate MOMP. In addition, this process is also affected by pro-survival members of the Bcl-2 family (Bcl-2, Bcl-xl), which either bind to Bax-Bak and prevent their oligomerization or are “neutralized” by the restraint of BH3-only proteins (Bid and Bad); the outcome of Bcl-2 family proteins dictates whether a cell survives or undergoes apoptosis. Another model of channel formation is mediated by voltage-dependent anion channel (VDAC), the most abundant protein of the mitochondrial outer membrane. Furthermore, crosstalk between VDAC and members of the Bcl-2 (homology) family have also detected and found to function together to mediate cytochrome c release and cell apoptosis. Thus, damaged mitochondrial substrates promote cell apoptosis that eliminates whole cell contents, including damaged mitochondria, at the cellular level of MQC. In the progression of IDD, mitochondria-derived signals have been confirmed to promote Bax-Bak oligomerization and further induce MOMP and NP cell apoptosis in various risk factor-induced degenerative models. However, recent studies have mostly focused on the effect of damaged mitochondria on NP cell apoptosis, but not the other forms of cell death. Recently, multiple studies demonstrated various cell death models in the IDD process, including ferroptosis, pyroptosis, and necroptosis, all of which are closely associated with mitochondrial damage. Cells commit suicide at the appropriate time as part of the natural cell turnover process that is essential to optimal tissue functioning, while more investigation and clarification between mitochondria-associated cell death and the cellular level of MQC are needed.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

MQC is tightly associated with adaptive changes in mitochondrial metabolism and the timely elimination of mitochondrial damage. Multiple levels of MQC action and surveillance strategies were involved in the mitochondrial adaptive response and defective mitochondrial elimination for the maintenance of mitochondrial homeostasis. Indeed, well-coordinated coordination and balance within MQC functional strategies efficiently maintain healthy mitochondrial metabolism (Fig. 2). For instance, eliminating damaged mitochondrial proteins by proteases or mitophagy and renewing components by adding protein and lipids through biogenesis or UPR enables the monitoring and regulation of mitochondrial protein quality. The mitochondrial network can be fragmented and segregated by fission, which requires synergistic fusion of healthy fragments and selective mitophagy to eliminate damaged mitochondrial fragments. In addition, mitophagy must be coordinated with new mitochondrial production through fusion/fission and biogenesis to control mitochondrial mass.
Abnormal MQC function was consistently observed in the IDD process. Each mechanism of MQC, including UPRmt, mitochondrial antioxidants, mitochondrial dynamics, mitophagy, and biogenesis, functions in regulating NP cell death, senescence, the inflammatory response, and anabolic and catabolic metabolism. Targeting one or several mechanisms of MQC has shown therapeutic potential for IDD intervention. However, the relative contribution of each mechanism to IDD progression remains largely unknown. In addition, crosstalk between different mechanisms also exists, and it is essential to identify the molecular underpinnings that regulate and coordinate these processes to achieve optimal MQC, thereby reducing NP cell function loss and IDD progression. Further investigation aiming to understand the molecular mechanisms and develop therapeutic strategies individually or in combination that target efficient MQC processes is expected.

DATA AVAILABILITY
The authors confirm that all data are fully available without restriction. All relevant data are described within the paper.

REFERENCES
1. Deyo, R. A. & Mirza, S. K. CLINICAL PRACTICE. Herniated Lumbar Intervertebral Disk. The. N. Engl. J. Med. 374, 1763–1772 (2016).
2. Collaborators GDAllAP. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392, 1789–1858 (2018).
3. Vlaeyen, J. W. S. et al. Low back pain. Nat. Rev. Dis. Prim. 4, 52 (2018).
4. Risbud, M. V. & Shapiro, I. M. Role of cytokines in intervertebral disc degeneration: pain and disc content. Nat. Rev. Rheumatol. 10, 44–56 (2014).
5. Roughley, P. J. Biology of intervertebral disc aging and degeneration: involvement of the extracellular matrix. Spine 29, 2691–2699 (2004).
6. Song, Y. et al. Sirtuin 3-dependent mitochondrial redox homeostasis protects against AGES-induced intervertebral disc degeneration. Redox Biol. 19, 339–353 (2018).
7. Kang, L. et al. Restoration of autophagic flux rescues oxidative damage and mitochondrial dysfunction to protect against intervertebral disc degeneration. Oxid. Med. Cell. Longev. 2019, 7810320 (2019).
8. Song, Y. et al. Advanced glycation end products regulate anabolic and catabolic activities via NLRP3-inflammasome activation in human nucleus pulposus cells. J. Cell. Mol. Med. 21, 1373–1387 (2017).
9. Grunhagen, T., Wilde, G., Soukane, D. M., Shirazi-Adl, S. A. & Urban, J. P. Nutrient supply and intervertebral disc metabolism. J. Bone Jt. Surg. Am. 88(Suppl 2), 30–35 (2006).
10. Urban, J. P., Smith, S. & Fairbank, J. C. Nutrition of the intervertebral disc. Spine J. 29, 2700–2709 (2004).
11. Martin, J. A. et al. Mitochondrial electron transport and glycolysis are coupled in articular cartilage. Osteoarthr. Cartil. 20, 323–329 (2012).
12. McEvoy, G. S. & Chandel, N. S. Mitochondria control acute and chronic responses to hypoxia. Exp. cell Res. 356, 217–222 (2017).
13. Görlach, A., Bertram, K., Huděcova, S. & Krízanova, O. Calcium and ROS: a mutual interplay. Redox Biol. 6, 260–271 (2015).
14. Hartman, R. et al. Age-dependent changes in intervertebral disc cell mitochondria and bioenergetics. Eur. Cells Mater. 36, 171–183 (2018).
15. Fernando, H. N. et al. Mechanical loading affects the energy metabolism of intervertebral disc cells. J. Orthop. Res. 29, 1634–1641 (2011).
16. Andreux, P. A., Houtkooper, R. H. & Auwerx, J. Pharmacological approaches to restore mitochondrial function. Nat. Rev. Drug Discov. 12, 465–483 (2013).
17. Xu, X. et al. Progerin accumulation in nucleus pulposus cells impairs mitochondrial function and induces intervertebral disc degeneration and therapeutic effects of sulforaphane. Theranostics 9, 2252–2267 (2019).
18. Gan, J. C., Ducheyne, P., Vresilovic, E. J., Swaim, W. & Shapiro, I. M. Intervertebral disc tissue engineering I: characterization of the nucleus pulposus. Clin. Orthopaedics Related Res. 411, 305–314 (2003).
19. Meachim, G. & Comah, M. S. Fine structure of juvenile human nucleus pulposus. J. Anat. 107, 337–350 (1970).
20. Trout, J. J., Buckwalter, J. A., Moore, K. C. & Landas, S. K. Ultrastructure of the human intervertebral disc. I. Changes in notochordal cells with age. Tissue Cell 14, 359–369 (1982).
21. Madhu, V. et al. Hypoxic regulation of mitochondrial metabolism and mitophagy in nucleus pulposus cells is dependent on HIF-1α-BNIP3 axis. J. Bone Mineral Res. 35, 1504–1524 (2020).
22. Zhao, C. Q., Wang, L. M., Jiang, L. S. & Dai, L. Y. The cell biology of intervertebral disc aging and degeneration. Ageing Res. Rev. 6, 247–261 (2007).
23. Guehringer, T., Nerlich, A., Kroeber, M., Richter, W. & Omlor, G. W. Sensitivity of notochordal disc cells to mechanical loading: an experimental animal study. Eur. Spine J. 19, 113–121 (2010).
24. Guehringer, T. et al. Notochordal intervertebral disc cells: sensitivity to nutrient deprivation. Arthritis Rheumatism 60, 1026–1034 (2009).
48. Liu, J., Yuan, C., Pu, L. & Wang, J. Nutrient deprivation induces apoptosis of nucleus pulposus cells via activation of the BNP3/Alf signalling pathway. Mol. Med. Rep. 16, 7253–7260 (2017).

49. Chen, S. et al. Critical contribution of RIPK1 mediated mitochondrial dysfunction and oxidative stress to compression-induced rat nucleus pulposus cells necroptosis and apoptosis. Apoptosis 23, 299–318 (2018).

50. Xu, D. et al. Hydrogen sulfide protects against endoplasmic reticulum stress and mitochondrial injury in nucleus pulposus cells and ameliorates intervertebral disc degeneration. Pharmacol. Res. 117, 357–369 (2017).

51. Zhao, L. et al. Hydrogen peroxide induces programmed necrosis in rat nucleus pulposus cells through the RIP1/RIP3-PARP-AIF pathway. J. Orthop. Res. 36, 1269–1282 (2018).

52. Kang, L. et al. The mitochondria-targeted anti-oxidant MitoQ protects against intervertebral disc degeneration by ameliorating mitochondrial dysfunction and redox imbalance. Cell Prolif. 53, e12779 (2020).

53. Jiang, L. et al. Activation of autophagy via Ca2+–dependent AMPK/mTOR pathway in rat notochordal cells is a cellular adaptation under hyperosmotic stress. Cell Cycle 14, 867–879 (2015).

54. Liu, Y. et al. Aspirin-mediated attenuation of intervertebral disc degeneration by ameliorating reactive oxygen species in vivo and in vitro. Oxid. Med. Cell. Longev. 2019, 7189854 (2019).

55. Feng, C. et al. ROS: crucial intermediators in the pathogenesis of intervertebral disc degeneration. Oxid. Med. Cell. Longev. 2017, 5601593 (2017).

56. Smith, H. L. & Mallucci, G. R. The unfolded protein response: mechanisms and therapy of neurodegeneration. Brain 139, 2113–2121 (2016).

57. Yung, H. W. et al. Noncanonical mitochondrial unfolded protein response impacts placental oxidative phosphorylation in early onset preeclampsia. Proc. Natl Acad. Sci. USA 116, 18109–18118 (2019).

58. Harnett, N. U. & Haynes, C. M. Signaling and regulation of the mitochondrial unfolded protein response. Cold Spring Harbor Perspect. Biol. 11, a033944 (2019).

59. Melber, A. & Haynes, C. M. UPR(mt) regulation and output: a stress response mediated by mitochondrial-nuclear communication. Cell Res. 28, 281–295 (2018).

60. Liu, Y., Samuel, B. S., Breen, P. C. & Ruvkun, G. Gaenorhabditis elegans pathways that surveil and defend mitochondria. Nature 508, 406–410 (2014).

61. Kim, S. & Sieburth, D. Sphingosine kinase activates the mitochondrial unfolded protein response and is targeted to mitochondria by stress. Cell Rep. 24, 2932–2945.e2934 (2018).

62. Pérez, M. et al. Loss of function of the mitochondrial peptidase PTMR1 induces proteotoxic stress and Alzheimer’s disease-like pathology in human cerebral organoids. Mol. Psychiatry (2020).

63. Kenny, T. C. et al. Selected mitochondrial DNA landscapes activate the SIRT3 axis of the UPR(mt) to promote metastasis. Oncogene 36, 4393–4404 (2017).

64. Seli, E., Wang, T. & Horvath, T. L. Mitochondrial unfolded protein response: a stress response with implications for fertility and reproductive aging. Fertil. Steril. 111, 197–204 (2019).

65. Chooi, W. H. & Chan, B. P. Compression loading-induced stress responses in intervertebral disc cells encapsulated in 3D collagen constructs. Sci. Rep. 6, 26449 (2016).

66. Chooi, W. H., Chan, S. C. W., Ganntenbein, B. & Chan, B. P. Compression loading induced cellular stress response of intervertebral disc cells in organ culture. Glob. Spine J. 6, s0036-5826(15)-s180036-1582604 (2016).

67. Gogate, S. S., Fujita, N., Skubutyte, R., Shapiro, I. M. & Risdal, M. V. Tonicity enhancer binding protein (TonEBP) and hypoxia-inducible factor (HIF) coordinate heat shock protein 70 (Hsp70) expression in hypoxic nucleus pulposus cells: role of Hsp70 in HIF-1α degradation. J. Bone Miner. Res. 27, 1106–1112 (2012).

68. Tsai, T. T. et al. MEX/ERK signaling controls osmoregulation of nucleus pulposus cells of the intervertebral disc by transactivation of TonEBP/OREBP. J. Bone Miner. Res. 22, 965–974 (2007).

69. Wang, W. et al. Superoxide flashes in single mitochondria. Cell 134, 279–290 (2008).

70. Apostolova, N. & Victor, V. M. Molecular strategies for targeting antioxidants to mitochondria: therapeutic implications. Antioxid. Redox Signal. 22, 686–729 (2015).

71. Gogate, S. S., Fujita, N., Skubutyte, R., Shapiro, I. M. & Risdal, M. V. Tonicity enhancer binding protein (TonEBP) and hypoxia-inducible factor (HIF) coordinate heat shock protein 70 (Hsp70) expression in hypoxic nucleus pulposus cells: role of Hsp70 in HIF-1α degradation. J. Bone Miner. Res. 27, 1106–1112 (2012).

72. Tsai, T. T. et al. MEX/ERK signaling controls osmoregulation of nucleus pulposus cells of the intervertebral disc by transactivation of TonEBP/OREBP. J. Bone Miner. Res. 22, 965–974 (2007).

73. Wang, W. et al. Superoxide flashes in single mitochondria. Cell 134, 279–290 (2008).

74. Apostolova, N. & Victor, V. M. Molecular strategies for targeting antioxidants to mitochondria: therapeutic implications. Antioxid. Redox Signal. 22, 686–729 (2015).

75. Murphy, M. P. Mitochondrial thiols in antioxidant protection and redox signaling: distinct roles for glutathionylation and other thiol modifications. Antioxid. Redox Signal. 16, 476–495 (2012).

76. Baldasari, S., Awad, M., Harrington, E. O., Selike, F. W. & Abid, M. R. Subcellular reactive oxygen species (ROS) in cardiovascular pathophysiology. Antioxidants 7, 14 (2018).

77. Trachootham, D., Lu, W., Ogasawara, M. A., Nilas, R. D. & Huang, P. Redox regulation of cell survival. Antioxid. Redox Signal. 10, 1343–1374 (2008).

78. Miyazaki, S. et al. Recombinant human SIRT1 protects against nutrient deprivation-induced mitochondrial apoptosis through autophagy induction in...
human intervertebral disc nucleus pulposus cells. Arthritis Res. Ther. 17, 253 (2015).
76. Li, K. et al. Resveratrol protects against sodium nitroprusside induced nucleus pulposus cell apoptosis by scavenging ROS. Int. J. Mol. Med. 41, 2485–2492 (2018).
77. Chen, J. et al. Protective effects of ginsenoside Rg3 on TNF-α-activated human nucleus pulposus cells through inhibiting NF-κB signaling pathway. Life Sci. 216, 1–9 (2019).
78. Jin, L. Y. 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, 7890291 (2018).
79. Jiao, S. et al. Nuclear pulposus cell apoptosis is attenuated by CDMP-2 through regulating oxidative damage under the hyperosmotic environment. Biosci. Rep. 38, e0201176 (2018).
80. Guo, R. et al. Moracin attenuates LPS-induced inflammation in nucleus pulposus cells via Nrf2/HO-1 and NF-κB/TGF-α pathway. Biosci. Rep. 39, e020191673 (2019).
81. Tang, P. et al. Honokiol alleviates the degeneration of intervertebral disc via suppressing the activation of TXNIP–NLRP3 inflammasome signal pathway. Free Radic. Biol. Med. 120, 368–379 (2018).
82. He, R. et al. Melatonin resists oxidative stress-induced apoptosis in nucleus pulposus cells. Life Sci. 199, 122–130 (2018).
83. Chu, H., Yu, H., Ren, D., Zhu, K. & Huang. H. Plumbagin exerts protective effects in nucleus pulposus cells by attenuating hydrogen peroxide-induced oxidative stress, inflammation and apoptosis through NF-κB and Nrf-2. Int. J. Mol. Med. 37, 1669–1676 (2016).
84. Dong, Y. et al. Pilose antler peptide attenuates LPS-induced inflammatory reaction. Int. J. Biol. Macromol. 108, 272–276 (2018).
85. Hoppins, S. The regulation of mitochondrial dynamics. Curr. Opin. Cell Biol. 29, 46–52 (2014).
86. Prieto, J. et al. Early ERK1/2 activation promotes DRP1-dependent mitochondrial fission necessary for cell reprogramming. Nat. Commun. 7, 11124 (2016).
87. Yao, C. H. et al. Mitochondrial fusion supports increased oxidative phosphorylation during cell proliferation. eLife 8, e41351 (2019).
88. Li, J. et al. Mitochondrial elongation-mediated glucose metabolism reprogramming is essential for tumour cell survival during energy stress. Oncogene 36, 4090–4092 (2017).
89. Youle, R. J. & van der Bliek, A. M. Mitochondrial fission, fusion, and stress. Science 337, 1062–1065 (2012).
90. Wai, T. & Langer, T. Mitochondrial dynamics and metabolic regulation. Trends Endocrinol. Metab. 27, 105–117 (2016).
91. Yang, L. et al. Metformin alleviates lead-induced mitochondrial fragmentation via AMPK/Nrf2 activation in SH-SY5Y cells. Redox Biol. 36, 101626 (2020).
92. Acín-Perez, R. et al. Ablation of the stress protease OMA1 protects against heart failure in mice. Sci. Transl. Med. 10, (2018).
93. Amartuvshin, O. et al. Aging shifts mitochondrial dynamics toward mitochondrial fusion. Aging cell 17, 446–454 (2018).
94. Wright, D. C. et al. Exercise-induced mitochondrial biogenesis begins before the increase in muscle PGC-1α expression. J. Biol. Chem. 282, 194–199 (2007).
95. Dorn, G. W. 2nd, Vega, R. B. & Kelly, D. P. Transcriptional integration of mitochondrial biogenesis. Trends Endocrinol. Metab. 23, 459–466 (2012).
96. Scarpulla, R. C., Vega, R. B. & Kelly, D. P. Transcriptional regulation of mitochondrial biogenesis. Physiology 36, 208–217 (2021).
97. Martin, S. J. Cell biology. Opening the cellular poison cabinet. Science 330, 1330–1331 (2010).
98. Kroemer, G., Galluzzi, L. & Brenner, C. Mitochondrial membrane permeabilization in cell death. Physiol. Rev. 87, 99–163 (2007).
99. Kale, J., Osterlund, E. J. & Andrews, D. W. BCL-2 family proteins: changing partners in the dance towards death. Cell Death Differ. 25, 65–80 (2018).
100. Chen, D. et al. Metformin protects against apoptosis and senescence in nucleus pulposus cells and ameliorates disc degeneration in vivo. Cell Death Differ. 7, e2441 (2016).
101. Lu, S. et al. Ferroportin-dependent iron homeostasis protects against oxidative stress-induced nucleus pulposus cell ferroptosis and ameliorates intervertebral disc degeneration in vivo. Oxid. Med. Cell. Longev. 2021, 6570497 (2021).
102. Zhao, K. et al. Acid-sensing ion channels regulate nucleus pulposus cell inflammation and pyroptosis via the NLRP3 inflammasome in intervertebral disc degeneration. Cell Prolif. 54, e12941 (2021).
103. Cai, X. et al. ROS-mediated lysosomal membrane permeabilization is involved in bupivacaine-induced death of rabbit intervertebral disc cells. Redox Biol. 18, 65–76 (2018).
104. Shirihai, O. S., Song, M. & Dorn, G. W. 2nd How mitochondrial dynamism orchestrates metabolism. Circulation Res. 116, 1835–1849 (2015).
105. Palkar, K., Lionaki, E. & Tavernarakis, N. Coordination of mitophagy and mitochondrial biogenesis during ageing in C. elegans. Nature 521, 525–528 (2015).
106. Palkar, K., Lionaki, E. & Tavernarakis, N. Coupling mitogenesis and mitophagy for longevity. Autophagy 11, 1428–1430 (2015).

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Author contributions

S.Y. conceived the manuscript. S.Y., L.S.D., G.W., and F.X.B. were all involved in writing the text, and all authors contributed to manuscript revision and approved the submitted version.
COMPETING INTERESTS
The authors declare no competing interests.

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