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Review Article

Role of oxidative stress in mitochondrial dysfunction and their implications in intervertebral disc degeneration: Mechanisms and therapeutic strategies

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ABSTRACT

Background: Intervertebral disc degeneration (IVDD) is widely recognized as one of the leading causes of low back pain. Intervertebral disc cells are the main components of the intervertebral disc (IVD), and their functions include synthesizing and secreting collagen and proteoglycans to maintain the structural and functional stability of the IVD. In addition, IVD cells are involved in several physiological processes. They help maintain nutrient metabolism balance in the IVD. They also have antioxidant and anti-inflammatory effects. Because of these roles, IVD cells are crucial in IVDD. When IVD cells are subjected to oxidative stress, mitochondria may become damaged, affecting normal cell function and accelerating degenerative changes. Mitochondria are the energy source of the cell and regulate important intracellular processes. As a key site for redox reactions, excessive oxidative stress and reactive oxygen species can damage mitochondria, leading to inflammation, DNA damage, and apoptosis, thus accelerating disc degeneration.

Aim of review: Describes the core knowledge of IVDD and oxidative stress. Comprehensively examines the complex relationship and potential mechanistic pathways between oxidative stress, mitochondrial dysfunction and IVDD. Highlights potential therapeutic targets and frontier therapeutic concepts. Draws researchers' attention and discussion on the future research of all three.

Abbreviations: IVDD, Intervertebral disc degeneration; IVD, Intervertebral disc; DNA, DeoxyriboNucleic Acid; LBP, Low back pain; NP, Nucleus pulposus; ECM, Extracellular matrix; NPCs, Nucleus pulposus cells; H2O2, Hydrogen peroxide; ATP, Adenosine Triphosphate; ROS, Reactive oxygen species; mtDNA, Mitochondrial DNA; SOD, Superoxide dismutase; GSH, Glutathione; ADAMTS, A disintegrin-like and metalloproteinase with thrombospondin motifs; TIMPs, Tissue inhibitors of metalloproteinases; NF-κB, Nuclear factor-kappa B; MAPK, Mitogen-activated protein kinase; MPTP, Mitochondrial permeability transition pore; Nrf2, Nuclear factor E2-related factor 2; NADH, Nicotinamide adenine dinucleotide; NADPH, Nicotinamide adenine dinucleotide phosphate; PI3K, Phosphatidylinositol 3-kinase; Drp1, Dynamin-related protein 1; Mfn1, Recombinant Mitofusin 1; Mfn2, Recombinant Mitofusin 2; AMP, Adenosine monophosphate; AMPK, AMP-activated protein kinase; SIRTs, Sirtuins; HSPs, Heat shock protein; cAMP, Cyclic adenosine monophosphate; PKA, Protein kinase A; JNK, C-Jun N-terminal kinase; 8-OHdG, 8-hydroxydeoxyguanosine; SAM, S-adenosylmethionine; DNMT, DNA Methyltransferase; CoQ10, Coenzyme Q10; RNAi, RNA interference; CDKs, Cyclin-dependent kinases; CKIs, Cyclin-dependent kinase inhibitors; NAC, N-acetylcysteine; NRF-1, Nuclear factor-1; PGC-1α, Peroxisome proliferator-activated receptor-gamma coactivator-1α; mTOR, Mammalian target protein of rapamycin; ADSCs, Adipose-derived stem cells; BMSCs, Bone marrow-derived stem cells; PSCs, Placental-derived stem cells.

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Key scientific concepts of review: Origin, development and consequences of IVDD, molecular mechanisms of oxidative stress acting on mitochondria, mechanisms of oxidative stress damage to IVD cells, therapeutic potential of targeting mitochondria to alleviate oxidative stress in IVDD.

The translational potential of this article: Targeted therapeutic strategies for oxidative stress and mitochondrial dysfunction are particularly critical in the treatment of IVDD. Using antioxidants and specific mitochondrial therapeutic agents can help reduce symptoms and pain. This approach is expected to significantly improve the quality of life for patients. Individualized therapeutic approaches, on the other hand, are based on an in-depth assessment of the patient's degree of oxidative stress and mitochondrial functional status to develop a targeted treatment plan for more precise and effective IVDD management. Additionally, we suggest preventive measures like customized lifestyle changes and medications. These are based on understanding how IVDD develops. The aim is to slow down the disease and reduce the chances of it coming back. Actively promoting clinical trials and evaluating the safety and efficacy of new therapies helps translate cutting-edge treatment concepts into clinical practice. These measures not only improve patient outcomes and quality of life but also reduce the consumption of healthcare resources and the socio-economic burden, thus having a positive impact on the advancement of the IVDD treatment field.

1. Introduction

Low back pain (LBP) is a common and widespread health problem that affects people of all ages and socioeconomic backgrounds across the globe. Over the recent years, the negative consequences of LBP on individuals and the society as a whole have become increasingly evident [1]. Indeed, according to estimates, roughly 700 million individuals worldwide are affected by LBP, which is widespread across different continents and cultures. LBP not only hampers individuals' ability to function effectively but also significantly diminishes their overall quality of life. Additionally, LBP is recognized as a prominent contributor to disability, making it a major concern for global healthcare providers who frequently encounter it as a primary reason for consultations [2–4]. The prevalence of LBP imposes a significant economic burden on society. Studies have shown that LBP accounts for more than 30 % of absenteeism, leading to a notable decrease in productivity. Additionally, direct healthcare costs associated with LBP are substantial. These expenses not only have an impact on individuals and households but also strain the social healthcare system and hinder economic development [5,6]. Furthermore, LBP is a complex condition that involves pain and disability influenced by a combination of biological, psychological, and social factors. IVDD is considered a significant contributing factor to the development of LBP(7). As individuals age, prolonged excessive usage and injuries to the back can gradually lead to IVDD, resulting in the loss of the spine's normal structure and function, ultimately causing pain and disability [8,9].

The IVD is an avascular tissue composed of the central gelatinous nucleus pulposus (NP), the peripheral annulus fibrosus, and the cartilage endplate. These structures provide the IVD with significant compressive and tensile strength, which maintains both the axial pressure of the spine and its multidirectional flexibility [10]. However, influenced by various factors such as genetics, circadian rhythms, aging, and mechanical stress, the IVD undergoes degeneration at the levels of tissue, cells, and molecules. As a result, there is a decrease in proteoglycan content within the IVD, a reduction in disc height, endplate hardening, and the formation of bone spurs, ultimately leading to the loss of the discs' ability to withstand compressive loads [11,12]. The causes and mechanisms underlying IVDD are currently unclear. The most commonly mentioned factors include cellular apoptosis, imbalance between the number of senescent cells and active cells, as well as abnormalities in the degradation of extracellular matrix (ECM) and the cascade of inflammatory reactions [7]. Recently, there has been increasing attention on the imbalance of oxidative stress within the mitochondria during the process of IVDD [13,14].

The mitochondria are a diminutive subcellular organelle within the confines of a cell, varying in size and shape from circular to spindle-like, boasting an array of functions and structural traits. It manifests as a bag-like structure comprised of inner and outer membranes, with the inner membrane featuring numerous folds referred to as cristae [15,16]. The mitochondria, among their primary functions, play a vital role in cellular energy generation. Through the process of oxidative phosphorylation during cellular respiration, mitochondria efficiently convert glucose and other organic molecules into adenosine triphosphate (ATP), providing the necessary energy for the cell. Nonetheless, the production of energy by mitochondria is accompanied by a process known as oxidative stress [17,18]. Oxidative stress refers to the excessive production of free radicals during the intrinsic redox process within mitochondria. These excessive reactive oxygen species (ROS) can cause oxidative damage to biological molecules such as nucleic acids, proteins, and lipids within the cellular environment, ultimately triggering cellular stress responses. In the context of IVDD, oxidative stress plays a significant role [19]. A multitude of factors contribute to IVDD, encompassing mechanical stress, aging, genetic predisposition, malnutrition, and occupational hazards, all of which augment the extent of oxidative stress within the IVD cells [13,20]. Oxidative stress can also induce oxidative damage to mitochondrial DNA (mtDNA), resulting in abnormal proliferation and mutations of mtDNA. This aberrant mtDNA further impairs mitochondrial function, impeding normal energy production and maintenance, ultimately leading to mitochondrial dysfunction within IVD cells and subsequently triggering a cascade of pathological changes [21].

In recent years, with further exploration of oxidative stress within mitochondria, an increasing body of evidence has shown a link between mitochondrial dysfunction and various skeletal disorders, such as osteoarthritis, osteomyelitis, and degenerative bone diseases [22–24]. Oxidative stress-induced damage is considered a significant mechanism in IVDD and one of the main causes of chronic lower back pain [20]. Recent studies have shown that during the process of IVDD, oxidative stress responses are widely activated. This activation can result in mitochondrial dysfunction, endoplasmic reticulum stress, and excessive production of ROS, further contributing to the development of IVDD. The imbalance of oxidative stress is also associated with lipid peroxidation, cell apoptosis, and inflammatory responses in the pathogenesis of IVDD [25]. In this comprehensive review, we elucidate the types and pathways of ROS generation and analyze the impact of excessive ROS on mitochondrial function. Additionally, we place particular emphasis on unraveling the mechanisms and signaling pathways through which oxidative stress activation promotes IVDD by affecting mitochondrial function. Lastly, we expound upon the potential therapeutic efficacy of targeting mitochondria to attenuate oxidative stress in the context of IVDD, thus providing vast prospects for future treatment approaches in this field.

2. Intervertebral disc degeneration

2.1. Anatomy and physiology

The IVD, situated between adjacent vertebrae, is a crucial component of the human spinal column. It plays a critical role in cushioning

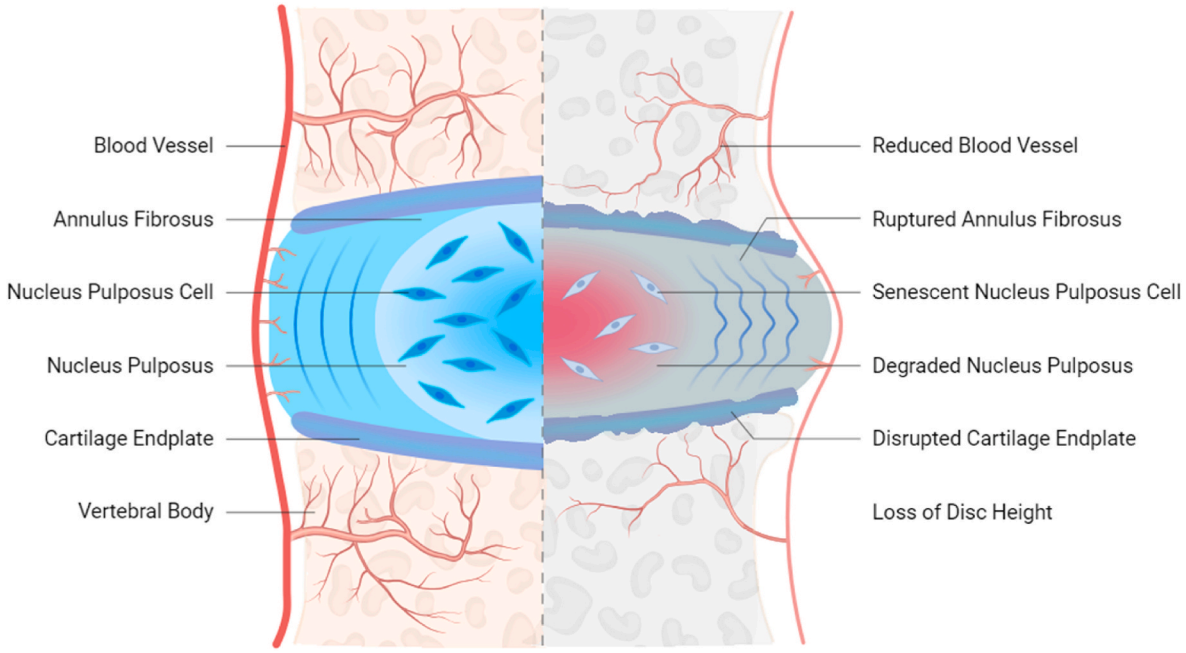

Fig. 1. Schematic illustration comparing the healthy IVD and the degenerated IVD. a) Sufficient blood supply, well-organized annulus fibrosus, active nucleus pulposus cells, rounded nucleus pulposus tissue, continuous cartilage endplate. b) Insufficient blood supply, ruptured annulus fibrosus, senescent nucleus pulposus cells, degraded nucleus pulposus tissue, disrupted cartilage endplate, loss of IVD height.

impacts, supporting the spine, and safeguarding neural structures [7]. Understanding the anatomy and physiology of IVD forms the foundation for comprehending IVDD. The structure of IVD consists of three components: the annulus fibrosus, the NP, and the cartilage endplate. The annulus fibrosus, located in the outer periphery of the disc, is composed of fibrocartilaginous tissue arranged in a circular pattern, which provides it with strong tensile strength. The annulus fibrosus is made up of layers of fiber lamellae that cross each other in different directions, enhancing the stability and strength of the disc. The outer layer of the annulus fibrosus is connected to the endplate of the adjacent vertebrae, while the inner layer contacts the NP [26,27]. The NP, situated centrally within the disc, is a gel-like substance mostly composed of water and collagen fibers. Its main function is to absorb and distribute pressure, ensuring stability and flexibility of the spine during daily activities and movement [28,29]. The cartilage endplate, responsible for the blood supply to IVD, is the hyaline cartilaginous connection between the subchondral bone and IVD [30].

The IVD is primarily composed of water, collagen proteins, and proteoglycans, among other constituents [31]. Water is one of the main components of IVD, generally occupying a significant volume of the NP. The presence of water provides the disc with excellent elasticity and shock-absorbing ability, enabling it to cushion the pressure and impact borne by the spine [32]. Collagen proteins are the main structural proteins in IVD, imparting toughness and tensile strength to the annulus fibrosus. Proteoglycans, primarily in the form of proteoglycan proteins and chondroitin sulfate, are another important component. Proteoglycans possess the ability to retain water, aiding in the maintenance of IVD's tissue structure and function [33,34].

The blood supply of IVD primarily originates from the vertebral body and adjacent vessels [35]. These vessels, through a small supporting system, transport oxygen and nutrients to the peripheral region of IVD. However, due to the dense structure and inherent characteristics of the disc itself, the blood supply to IVD is relatively insufficient. This limitation is one of the factors contributing to the restricted self-repair capability of the disc and its susceptibility to damage during degenerative processes [11]. Proper hydration of the IVD is a crucial factor in maintaining its normal function. Hydration is primarily absorbed and supplied by the capillaries and lymphatic vessels surrounding the disc. Under normal circumstances, hydration absorption and release are balanced, ensuring the ideal hydration level of the IVD. Nonetheless, the aging process and prolonged mechanical stress can lead to a decline in the disc's hydration level, resulting in dryness and increased fragility [36,37].

The cell types within IVD predominantly consist of fibroblasts, chondrocytes, and NP cells (NPCs) [38]. These cells play crucial roles in the normal metabolism and repair processes of IVD. Fibroblasts are primarily found in the annulus fibrosus, responsible for maintaining its structural integrity and functionality. Chondrocytes are mainly distributed within the NP, and involved in synthesizing and secreting matrix components such as collagen and proteoglycans. NPCs are primarily located in the central region of the NP, responsible for maintaining hydration and pressure balance within the nucleus [39,40].

2.2. *Mechanisms and etiology of disease*

IVDD is a complex process involving the interaction of multiple factors [41]. Age, genetic factors, environmental factors, and changes within IVD tissue are considered to be among the main contributing factors to IVDD [42]. As individuals age, IVD undergoes progressive degeneration. In youth, IVD is characterized by good hydration and elasticity, with well-organized annulus fibrosus, pliable NP tissue, and continuous cartilage endplate. However, with age, the disc experiences a gradual loss of hydration and elasticity. The collagen fibers within the annulus fibrosus begin to rupture and become brittle, the NP loses hydration and elasticity, and the cartilage endplate is disrupted, resulting in a reduction in disc height [43,44] (Fig. 1). Age-related changes significantly increase the susceptibility of intervertebral discs to pressure and damage, thus playing a pivotal role in the progression of degeneration. Additionally, genetic factors exert a substantial influence on an individual's susceptibility to IVDD. Various studies have reported associations between multiple genes, such as the Collagen IA1 chain, and an elevated risk of developing IVDD. Furthermore, specific genetic polymorphisms within the vitamin D receptor gene have been identified as potential contributors to the development of IVDD [45]. Moreover,

specific variants in diverse protease genes responsible for matrix degradation have been identified as correlated with varying degrees of IVDD. Environmental factors also have a notable impact on the development of IVDD. Unhealthy lifestyles, notably characterized by insufficient physical activity, prolonged periods of sitting, and poor posture, impose an increased burden and pressure on intervertebral discs, thereby exacerbating the degenerative process [46]. Furthermore, smoking has been identified as a risk factor, as it diminishes the blood supply to intervertebral discs, influencing their overall health [47]. Occupational exposures, such as heavy lifting, prolonged periods of poor posture, and exposure to vibrations, may also contribute to the development of IVDD [48,49].

The internal changes within IVD tissue are a fundamental mechanism of IVDD. In IVDD, the matrix components of the disc undergo alterations, such as degradation of collagen and proteoglycans. The collective degradation of these components alters the matrix structure of the disc, weakening its elasticity and stability, consequently reducing its ability to absorb shocks and maintain flexibility [7,50]. This renders the disc susceptible to pressure and load, leading to susceptibility to damage and degradation. IVDD also triggers inflammation reactions both within and outside of the cells, resulting in the release of inflammatory cytokines that further exacerbate damage and destruction. With the progression of IVDD, the disc tissue gradually loses its normal metabolic state and repair capacity. This restricts the disc's ability to undergo self-repair and regeneration, hindering the restoration of its normal structure and function. Additionally, the occurrence of inflammation reactions and cellular apoptosis further disrupts the local microenvironment of the disc tissue and impedes the tissue repair process [51,52].

2.3. Consequences of IVDD

IVDD is a prevalent spinal condition that can significantly impact an individual's quality of life and functional abilities. Primarily, IVDD manifests with a variety of consequences, with LBP being the most commonly reported symptom. LBP can vary in its presentation, ranging from acute and intermittent episodes to chronic and continuous discomfort. The severity and extent of LBP differ among individuals, with some experiencing mild discomfort while others endure severe pain that significantly impairs their daily activities [53]. Moreover, IVDD can lead to the radiating spread of pain from the lower back to the buttocks, thighs, and lower extremities, often resulting in sciatica-like symptoms. Apart from LBP, IVDD can also give rise to nerve root compression. When an intervertebral disc protrudes or herniates, exerting pressure on the spinal cord or spinal nerve roots, patients may experience various symptoms including radiating pain, numbness, tingling, and reduced muscle strength. Depending on the specific affected nerve root site, sensory abnormalities, muscle atrophy, and reflex abnormalities may also manifest [33].

Furthermore, IVDD is associated with a decline in disc height and spinal instability. IVDD induces structural changes in the IVD by causing degeneration of the annulus fibrosus and NP, resulting in a reduction in disc height. This reduction in disc height can impair stability of the spine, leading to increased spinal instability and greater magnitude of spinal motion [54]. The instability of the spine can give rise to complications such as osteophytes, lumbar spondylolisthesis, and degenerative spondylolisthesis, which further exacerbate symptoms and contribute to functional impairment. Moreover, IVDD can also result in diminished elasticity and flexibility of the spine, thereby affecting normal spinal motion [10,55]. This can lead to a limited range of motion, stiffness, and decreased motor function that can interfere with daily life and work. It is important to note that the condition and symptoms may vary among individuals. Some individuals may experience only mild symptoms, while for others, symptoms may be more severe and last longer. For some people with mildly degenerated discs, symptoms can be relieved with proper treatment, self-management, and rehabilitation. This may include pain relief, improved motor function, return to daily activities, and improved quality of life [41]. For patients with moderate to severe IVDD, their symptoms may require long-term management and control. This could entail the use of medications such as analgesics, nonsteroidal anti-inflammatory drugs, and muscle relaxants to mitigate pain and inflammation. Additionally, non-pharmacological therapies such as physical therapy, rehabilitation, acupuncture, and massage may also be utilized to manage symptoms [56]. In certain severe cases of IVDD, conservative treatment may prove inadequate in alleviating symptoms or improving function. In such situations, surgical intervention may become a necessary course of action. The specific type and method of surgical intervention will depend on the individual circumstances of the IVDD, such as discectomy, disc replacement, or spinal fusion, for instance. The primary objectives of surgery are to alleviate pain, stabilize the vertebral column, and restore functionality [57].

3. Basics of oxidative stress and ROS

3.1. Concepts and mechanisms of oxidative stress

Oxidative stress refers to a state of imbalance in the intracellular and extracellular environment caused by the excessive accumulation of oxidants, surpassing the regulatory capacity of intracellular antioxidative defenses. Under normal physiological conditions, the generation of oxidants, such as ROS and reactive nitrogen species, plays a vital role in cellular metabolism [58]. Under certain conditions, the production of oxidants in the body may surpass the cellular clearance capacity, resulting in oxidative stress. Oxidative stress can be triggered by various factors, including external factors like environmental pollutants, radiation, drugs, and toxins. These factors can generate free radicals or disrupt the body's internal antioxidative system, leading to oxidative stress. Internal factors also contribute to oxidative stress, such as free radicals produced during normal cellular metabolism, as well as oxidative substances generated during pathological processes like inflammation, infection, hypoxia, and tumors. These factors can further increase oxidative stress levels in the body [59].

The mechanism of oxidative stress involves multiple key processes, including the excessive generation of ROS, disturbance of antioxidant defense systems, and the occurrence of oxidative damage. First and foremost, the mechanism of oxidative stress is primarily associated with the excessive generation of ROS. ROS are highly reactive oxidants, consisting of superoxide anion (O_2·-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (·OH) [60]. Within the cellular environment, ROS are primarily generated by various sources such as mitochondria, endoplasmic reticulum, fixed oxidases, and metabolic enzymes. During the respiratory chain process in mitochondria, electrons undergo redox reactions on the mitochondrial membrane, resulting in the production of ROS. Additionally, enzymatic systems and enzymatic reactions within the cell also contribute to the generation of ROS. The production of ROS within the cell is regulated by multiple factors, including biochemical metabolism, stress stimuli, and the regulation of intracellular and extracellular signaling pathways. Furthermore, the occurrence of oxidative stress is associated with the disruption of the cell's antioxidant defense system [61]. In normal physiological conditions, cells possess a highly intricate antioxidant defense system encompassing enzymes, including but not limited to superoxide dismutase, catalase, and glutathione peroxidase, as well as small molecule antioxidants like glutathione, vitamin C, and vitamin E. The primary function of these antioxidant systems is to efficiently eliminate or neutralize ROS and maintain a state of redox homeostasis both intracellularly and extracellularly. However, during periods of heightened oxidative stress, the effectiveness of the cellular antioxidant defense system may become compromised. This impairment results in a diminished capacity to effectively eliminate ROS, thereby exacerbating the severity of oxidative stress. Ultimately, the prolonged presence of oxidative stress can induce oxidative damage, adversely affecting the structural and functional

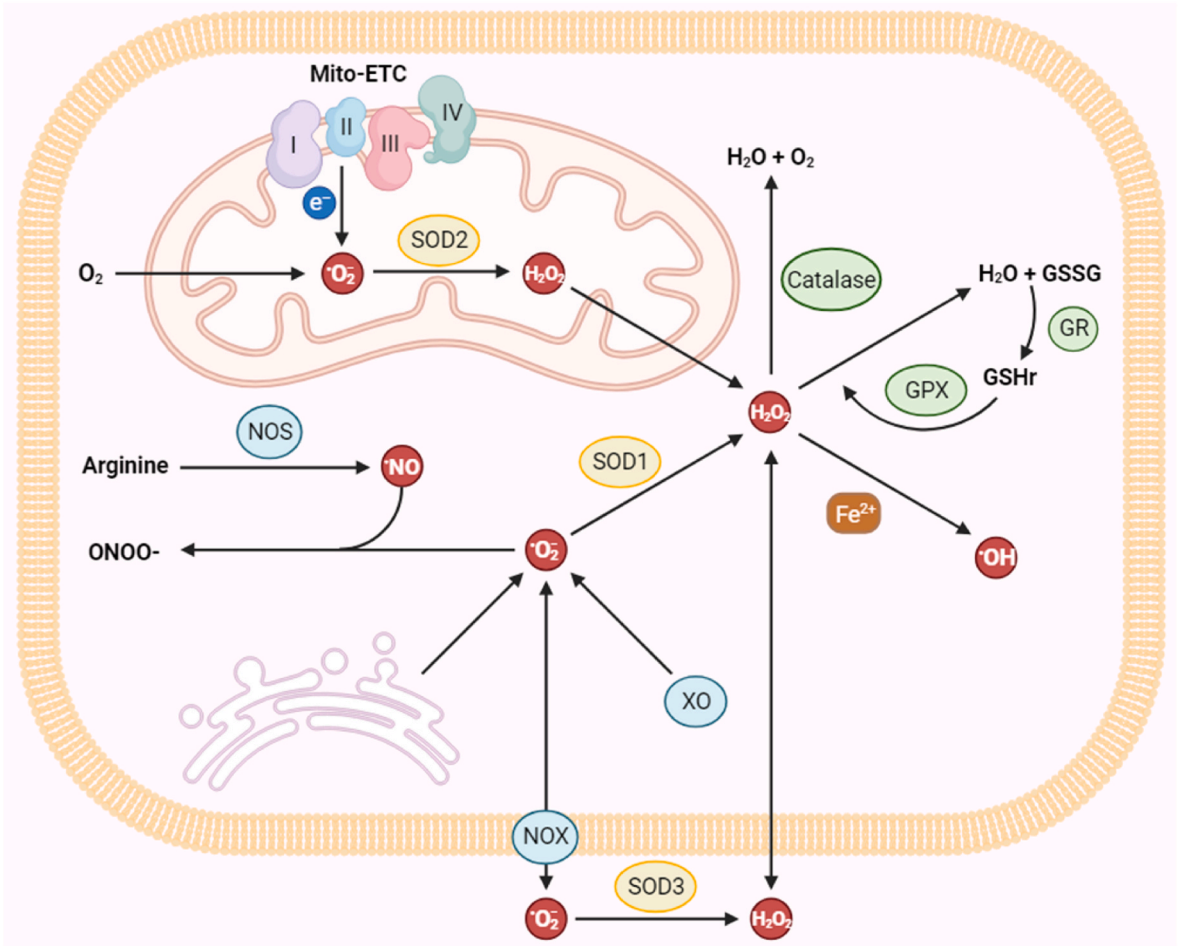

Fig. 2. Schematic illustration of redox homeostasis in IVD cells. Mito-ETC: mitochondrial electron transport chain, SOD: superoxide dismutase, GPX: glutathione peroxidase, GR: glutathione reductase, NOS: nitric oxide synthase, GSSG: glutathione (oxidized), GSHr: glutathione (reduced), XO: xanthine oxidase, NOX: NADPH oxidase.

integrity of various biomolecules within the cellular milieu [62]. Excessive ROS exhibit remarkable reactivity within cells, engaging in direct interactions with biomolecules such as proteins, nucleic acids, and lipids. These interactions provoke consequential changes in their structures and functions. For instance, excessive ROS can oxidatively modify amino acid residues within proteins, encompassing the oxidation of cysteine and tyrosine residues. Such oxidative modifications have the potential to significantly impact the structural integrity and functionality of proteins, leading to degradation, inactivation, or aberrant aggregation. Moreover, excessive ROS instigates oxidative damage to DNA, inducing base modifications, strand breaks, and oxidation of DNA deoxyribonucleotides, thereby influencing DNA stability and replication processes. Furthermore, excessive ROS can incite lipid peroxidation reactions, causing oxidative damage to cell membranes, and compromising both their integrity and functionality [63,64].

3.2. Types of ROS and generation pathways

Firstly, the O2·- is regarded as one of the earliest discovered ROS, arising from the reduction of oxygen molecule (O_2) by the loss of one electron. Within cells, O_2·- is mainly generated through the mitochondrial respiratory chain and enzymatic oxidation reactions. Within the respiratory chain of mitochondria, electrons are transferred from Complex I and Complex III to O_2, resulting in the formation of water. However, during this process, some electrons may leak and combine with O_2, giving rise to O_2·-. Furthermore, oxidases such as NADPH oxidase are responsible for transferring electrons from the reduced coenzyme NADPH to O_2, resulting in the generation of ROS, such as O_2·-. Xanthine oxidase catalyzes the oxidation of substrates, producing uric acid and free radical oxygen species, while also participating in the generation process of O_2·-. These enzymes are activated under specific conditions to convert oxygen in its reduced state into O_2·-[65,66].

Moreover, H_2O_2 constitutes another essential class of ROS. H_2O_2 is a relatively stable and diffusible molecule with significant signaling roles both intra- and extracellularly. Within cells, the primary pathways for H_2O_2 production encompass enzymatic and non-enzymatic mechanisms. Enzymatic pathways involve the activity of various enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase. These enzymes have the ability to convert O_2·- into H_2O_2, and further transform H_2O_2 into water. H_2O_2 produced through non-enzymatic catalysis is mainly implicated in processes such as saturated fatty acid oxidation, oxidative stress, and metabolic activities. The β-oxidation pathway is responsible for the metabolism of saturated fatty acids within cells, leading to the production of coenzyme A (CoA) esters and acetyl-CoA. During this oxidation process, a portion of the saturated fatty acids undergoes oxidation, resulting in the generation of H_2O_2. This non-enzymatic generation of H_2O_2 serves as a signaling molecule involved in cellular signal transduction and metabolic regulation [67,68].

In addition, the ·OH is one of the most ROS and represents an exceedingly unstable active oxygen substance. The generation of ·OH primarily relies upon the presence of Fe^{2+}. Through the Fenton and Haber–Weiss reactions, Fe^{2+} catalyzes the decomposition of H_2O_2 into ·OH and hydroxide ions OH-. Upon its production both inside and outside of cells, ·OH swiftly reacts with biomacromolecules such as DNA,

lipids, and proteins, triggering oxidative damage [69].

Finally, ·NO is a significant nitrogenous substance with reactivity. ·NO is a molecule possessing the capability of dual electron transfer, participating in a variety of physiological processes and signal transmission. In living organisms, the generation of ·NO involves the catalysis of ·NO synthase with the reaction of nitrosyl CoA and L-arginine. ·NO synthase is capable of converting L-arginine into ·NO and citrulline, termed an oxidative reaction. ·NO interacts directly with intracellular proteins such as guanylate cyclase and soluble guanylate cyclase, thus influencing signal transduction and physiological functions within cells. ROS participate in multiple physiological and pathological processes within cells through various pathways of generation [70,71] (Fig. 2).

4. Oxidative stress in IVD cells

4.1. Oxidative damage to important molecules in IVD cells by excessive ROS

Excessive levels of ROS precipitate oxidative damage to DNA within IVD cells. DNA, being a critical component of cellular genetic information, inherently demands stability for normal cellular functioning. Regrettably, the heightened oxidative stress induced by an overabundance of ROS can instigate oxidative harm to DNA bases. Specifically, the overproduction of ROS can facilitate the oxidation of DNA strand bases, such as thymine and guanine, thereby disrupting the standard base structure of DNA and potentially triggering DNA breakdowns and genetic alterations. Moreover, direct ROS exposure can result in DNA strand breaks and the formation of cross-links, exacerbating the overall impairment inflicted upon DNA integrity and stability. The progressive accrual of these oxidative DNA damages may consequently impede proper disc cell functionality and contribute to the degeneration of disc structure [72].

Furthermore, an overabundance of ROS results in oxidative impairment of proteins in IVD cells. Proteins serve as crucial regulators of IVD cellular function, and the excessive ROS-mediated oxidative damage to proteins could lead to disruption of normal cell signaling and regulation pathways. Oxidative stress triggered by excessive ROS induces oxidative modifications to proteins, such as cysteine oxidation and disulfide bond breakage. These oxidative modifications disrupt protein structure and function and may lead to abnormalities in protein aggregation and degradation. In addition, under oxidative stress conditions, kappa groups and amino acid residues within proteins undergo abnormal cross-linking reactions to form oxidized products. Also, oxidatively modified proteins are prone to abnormal aggregation and polymerization, forming aggregates, gels, or fiber-like deposits. These abnormal cross-linking and aggregation further disrupt the normal structure and function of proteins, which may ultimately interfere with the normal metabolism and intra- and extracellular signaling of IVD cells [73].

Third, excessive ROS cause oxidative damage to the lipids of IVD cells. The lipids of IVD cells include cell membrane phospholipids, cholesterol, and fatty acids. Oxidative stress induced by excessive ROS leads to the occurrence of lipid peroxidation, which in turn damages the integrity and function of the cell membrane. Excessive ROS initiate lipid peroxidation by reacting directly with lipid molecules or indirectly through free radical chain reactions. Lipid peroxidation engenders the oxidative fragmentation of lipid entities and engenders the generation of an array of oxidative byproducts, encompassing lipid peroxides and lipid peroxyl radicals. These oxidation products further initiate a lipid chain reaction and a free radical chain reaction, in which free radicals generated from one oxidized lipid molecule react and oxidize other lipid molecules to form new oxidation products and free radicals. This chain reaction continues until the reaction stops or antioxidants intervene. The free radical chain reaction leads to increased oxidative damage to lipids in the cell membrane of disc cells, further destabilizing and destabilizing the cell membrane, ultimately leading to abnormal physiological function and pathological changes in disc cells [74].

4.2. Effect of excessive ROS on the extracellular matrix of IVD cells

When exposed to oxidative stress, IVD cells can produce excessive reactive oxygen species, which can have significant implications on the ECM. These effects comprise collagen oxidation and rupture, proteoglycan degradation and abnormal accumulation, as well as the modulation of proteases associated with the ECM [8].

Collagen is one of the major components of the ECM of IVD. Excessive generation of ROS leads to oxidative damage to amino acid residues (e.g., Proline, Lysine, and Tryptophan) within the collagen molecule. These amino acid residues readily react with ROS to form oxidized collagen. Interconnections among the amino acid residues within oxidized collagen are disrupted, resulting in the impairment of the structural integrity of collagen fibers. Consequently, the stability and mechanical robustness of the collagen fibers are diminished. In addition, excessive ROS can also reduce the activity of collagen synthesis, leading to a decrease in collagen content and quality. These changes reduce the elasticity and stability of the ECM of the IVD [8,75].

Proteoglycans are an important component of the ECM of IVD, such as chondroitin sulfate and hyaluronic acid. Overproduction of ROS triggers the process of proteoglycan degradation. Active oxygen species stimulate proteoglycan degradation by activating proteases and protease-like anti-enzymes in the ECM, such as phosphatase and proteinase K. In addition, excessive ROS lead to aberrant expression and imbalance in the regulation of proteoglycan synthesis-related proteins, further promoting proteoglycan degradation. This degradation and abnormal accumulation of proteoglycans leads to a loss of hydration and decompression of the ECM, which further destabilizes IVD and its function [76].

The proteases associated with extracellular matrix (ECM) in IVD cells primarily consist of matrix metalloproteinases (MMPs) and ADAMTS proteases (a disintegrin-like and metalloproteinase with thrombospondin motifs). These groups of enzymes are responsible for the degradation and modification of the ECM in usual circumstances. However, they are activated and regulated by an abundance of ROS in environments characterized by oxidative stress. The excessive ROS promote the degradation of collagen and proteoglycans by activating the gene expression and protease activity of ECM-associated proteases [42,77]. At the same time, excessive ROS also inhibit the activity of tissue inhibitors of metalloproteinases (TIMPs), a class of proteins that interact with MMPs, which inhibit their activity mainly by binding to the catalytic region of MMPs. Under normal conditions, TIMPs are able to form a 1:1 complex with MMPs, thereby limiting the activity of MMPs and maintaining the stability of the ECM. However, when cells are exposed to oxidative stress, the overproduction of ROS inhibits the activity of TIMPs and disrupts the balance between TIMPs and MMPs. This leads to an increase in the activity of MMPs, which further increases the extent of ECM degradation. This modulation of enzyme family activity results in a decrease in the ECM and reduced stability, which accelerates the degenerative process of the IVD [78,79].

Oxidative stress also indirectly affects the structure and function of the ECM through cell–substrate interactions. Structural proteins and proteoglycans of the ECM can act as signaling molecules that interact with cell surface receptors to regulate cell adhesion, migration, and proliferation. However, the increased generation of ROS due to oxidative stress may alter the structure and function of these signaling molecules, thus affecting the normal cell–matrix interactions [80]. Furthermore, excessive ROS can alter the oxygen tension and pH of the ECM microenvironment. Under oxidative stress conditions, there is an increase in lactate and H^+ production, resulting in acidification of the ECM. The acidic conditions play a significant role in regulating ECM synthesis and degradation [50]. Under acidic conditions, the activity of acid proteases and MMPs in the ECM increases, leading to an elevation in the degradation of the ECM. Simultaneously, the acidic environment can also inhibit the activity of certain enzymes involved in the synthesis and stability of the ECM. Alterations in acidity levels can influence the

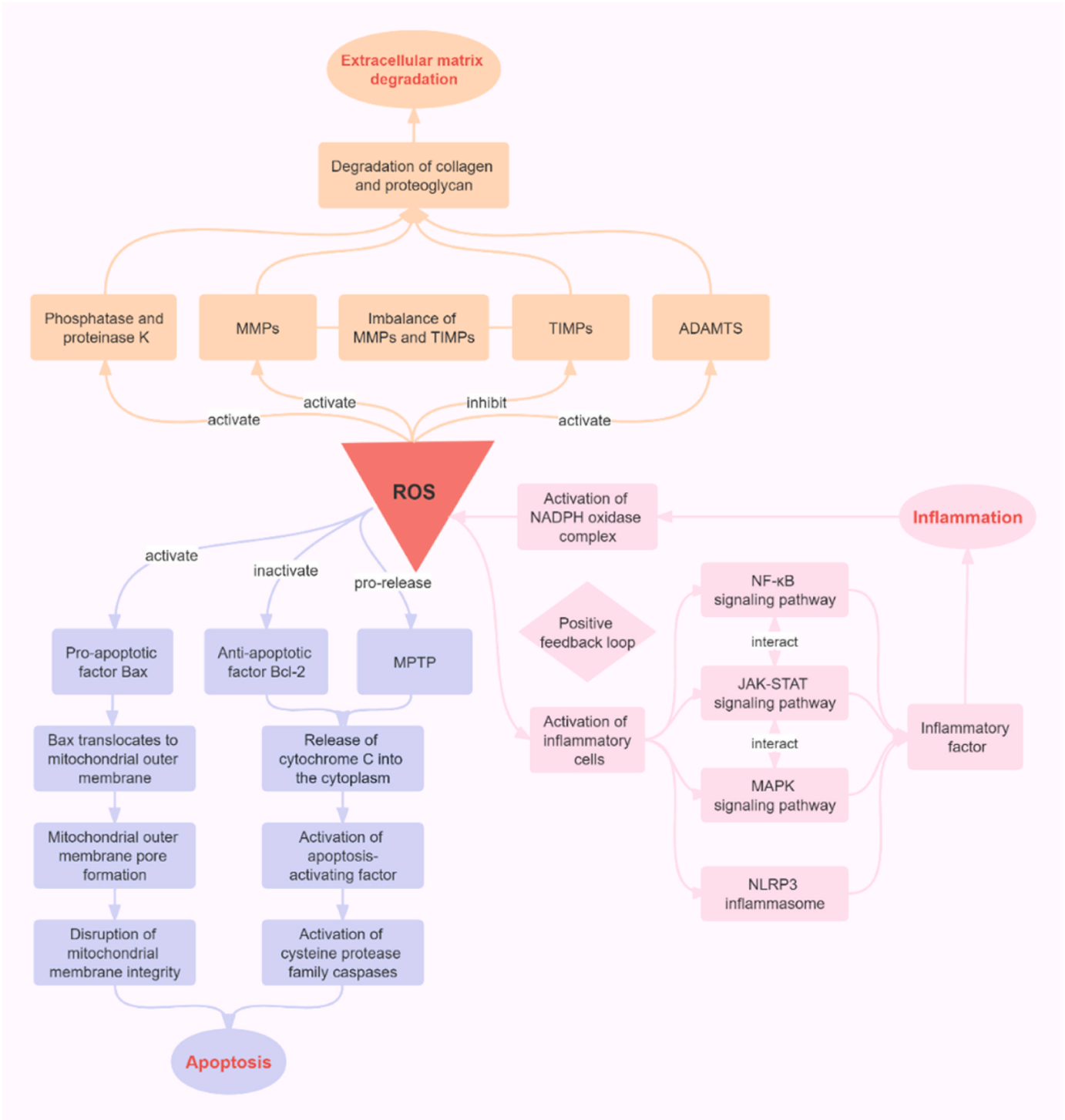

Fig. 3. Schematic illustration of the impact of excessive ROS on extracellular matrix, inflammation, and apoptosis in IVDD. MMPs: matrix metalloproteinases, TIMPs: tissue inhibitors of metalloproteinases, ADAMTS: a disintegrin-like and metalloproteinase with thrombospondin motifs, MPTP: mitochondrial permeability transition pore.

expression of genes related to the synthesis and degradation of the ECM, thereby affecting its metabolism and stability. These perturbations can impact the regulation of genes involved in ECM modulation and molecular signaling pathways, subsequently influencing its synthesis and degradation [81]. The modifications have led to the deterioration and malfunctions of the ECM, compromising the IVD's ability to endure mechanical strain.

4.3. The association between excessive ROS and inflammatory response in IVD tissue

Firstly, excessive ROS are involved in regulating the occurrence of inflammatory reactions in IVD tissue. Upon activation of intracellular inflammatory signaling pathways, specific cell types, such as IVD cells and immune cells, elevate the levels of ROS [82]. Amidst inflammatory reactions, the discharge of intracellular inflammatory modulators, such

as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), may incite the activation of the NADPH oxidase complex, resulting in the production of copious ROS. Furthermore, inflammation-induced cell apoptosis and necrosis can also result in the release of ROS. The increase in these ROS promotes the occurrence and maintenance of inflammatory reactions, establishing a positive feedback loop between excessive ROS and inflammatory responses [77].

Furthermore, excessive ROS play a pivotal role in the development of inflammatory response in IVD tissue. ROS are involved in the activation of inflammatory cells, production of cytokines, and regulation of cell adhesion molecule expression through various mechanisms during the inflammatory process. The inflammatory response in IVD tissue is closely associated with multiple signaling pathways, including nuclear factor κB (NF-κB), JAK-STAT, mitogen-activated protein kinase (MAPK), and NLRP3 inflammasome. In inflammatory regulation, the NF-κB signaling pathway plays a pivotal role. In its inactive state, NF-κB forms a complex with the inhibitory protein IκB in the cytoplasm, preventing its entry into the nucleus and activation of transcription of inflammatory genes. During an inflammatory response, IκB is phosphorylated and degraded, enabling NF-κB to enter the nucleus and regulate the expression of various inflammation-related genes, such as TNF-α and IL-1β [29,83]. Similarly, the JAK-STAT signaling pathway is also involved in the inflammatory processes of IVD tissue. Upon inflammatory stimulation, cell surface receptors bind to cytokines and activate JAK kinases, leading to the phosphorylation of intracellular STAT proteins. This phosphorylation facilitates the formation of dimers, which then translocate to the cell nucleus, thereby regulating the transcription of genes associated with inflammation. Additionally, the MAPK signaling pathway is closely associated with the inflammatory response in IVD tissue. This genealogy encompasses constituents akin to ERK, c-Jun N-terminal kinase (JNK), and p38 MAPK. These potency-metering proteins, when stimulated by inflammatory triggers, can regulate cellular growth, programmed cell death, tissue specialization, and the biosynthesis of pro-inflammatory molecules. Furthermore, the MAPK signaling pathway interacts with NF-κB and the JAK-STAT signaling pathway, forming a complex regulatory network [84,85]. The NLRP3 inflammasome also functions as a crucial inflammatory regulatory mechanism that is involved in the inflammatory response of IVD tissues. Upon inflammatory stimulation, the NLRP3 protein aggregates to form the inflammasome, subsequently activating caspase-1. Activated caspase-1 further enhances the production and release of inflammatory factors IL-1β and IL-18, exacerbating the intensity of the inflammatory response [86,87].

There exists a dynamic interaction between excessive ROS and the inflammatory response in IVD tissues. Excessive ROS actively participate in the regulation and maintenance of inflammatory reactions, while also driving the progression of inflammation through various mechanisms. The excessive generation of ROS, coupled with the oxidative stress triggered by inflammatory responses, contributes to oxidative damage of IVD tissues. Moreover, excessive ROS can modulate the expression levels of cell adhesion molecules, exacerbating the intensity of inflammatory reactions and cellular interactions. As a pivotal regulatory factor, it closely interacts with these signaling pathways, playing a crucial role in the modulation of the inflammatory response in IVD tissues [88].

4.4. The impact of excessive ROS on the apoptosis and regenerative capacity of IVD cells

Apoptosis is an intricately regulated cellular demise process, achieved by activating a series of signaling pathways. The production and accumulation of ROS can induce oxidative stress within cells, subsequently triggering apoptotic signaling pathways, and consequently impacting the viability and regeneration of IVD cells [46].

Within IVD tissue, the excessive generation of ROS plays a role in the regulation of cellular apoptosis through multiple pathways. One mechanism involves the oxidative stress of mitochondria induced by excessive ROS. The overabundance of ROS can lead to oxidative stress on the mitochondrial membrane, causing damage to mitochondrial function and the release of mitochondrial permeability transition pores. This, in turn, promotes the release of a series of apoptotic factors (such as cytochrome c) into the cytoplasm, ultimately activating the caspase family of cysteine proteases and initiating the apoptotic program [89].

Furthermore, excessive ROS can participate in the apoptosis of IVD cells by modulating the death receptor pathway. Under inflammatory stimulation, excessive ROS can promote the oxidative modification of TNF receptor-associated factors, thereby activating the apoptosis signaling pathway. This leads to the activation of Caspase-8, which in turn activates downstream members of the Caspase enzyme family, such as Caspase-3. The sequential activation process ultimately culminates in the fragmentation of vital proteins and the deterioration of cellular DNA, serving as a catalyst for a chain reaction of programmed cell death [8, 90].

Moreover, excessive ROS can participate in the regulation of cellular apoptosis by modulating the apoptosis-inhibitory protein Bcl-2 family. The Bcl-2 family members consist of anti-apoptotic factors such as Bcl-2 and Bcl-xL, as well as pro-apoptotic factors like Bcl-2 associated X (Bax) and Bcl-2 associated death promoter (Bad). Through oxidative modifications and other regulatory mechanisms, excessive ROS induce conformational changes and activation of the Bax protein. The activated Bax protein undergoes translocation from the cytoplasm to the outer membrane of mitochondria, resulting in the generation of pores on the outer mitochondrial membrane and subsequent disruption of mitochondrial membrane integrity. Moreover, excessive ROS can inactivate the anti-apoptotic protein Bcl-2, thus blocking its inhibitory action on Bax [88,91]. In this process, the cytochrome c released into the cytoplasm will activate apaf-1, the activator of apoptotic protease (caspase-9), forming a protein complex that triggers a cascade of cellular apoptosis. Due to the activation of Bax and the inactivation of Bcl-2, the integrity of the mitochondrial membrane is compromised, leading to the release of cytochrome c from the mitochondria to the cytoplasm. The release of cytochrome c activates the apoptotic protease activator and caspase-9, ultimately resulting in the activation of downstream caspase-3 and caspase-7, initiating cellular apoptosis [92,93].

In addition, the reparative capacity of IVD cells is also influenced by excessive ROS. Adequate levels of ROS can facilitate cell proliferation and synthesis of ECM components such as collagen, thereby participating in the repair process of IVD. However, excessive levels of ROS may cause damage to IVD cells and inhibit repair. An excess of ROS can lead to increased oxidative stress within cells, resulting in oxidation damage to DNA, proteins, and lipids. Such damage may induce cell apoptosis, activate inflammatory responses, and enhance matrix degradation, further impeding the repair process of IVD [94, 95] (Fig. 3).

5. Effects of excessive ROS on mitochondrial function

5.1. The oxidative damage of the mitochondrial inner membrane caused by excessive ROS

The inner membrane constitutes the intramitochondrial membrane system, harboring pivotal functionalities and architectural attributes. The generation and accumulation of ROS may incite oxidative stress within the mitochondrial inner membrane, impairing its structure and function, thereby precipitating a myriad of mitochondrial-related disorders. Primarily, the inner mitochondrial membrane is abundant with phospholipids, such as phosphatidyl CoA and phosphatidylinositol, which serve as targets for ROS, initiating lipid peroxidation. The process of lipid peroxidation inflicts harm upon the arrangement and efficacy of the lipid membrane, heightening the permeability of the membrane and enabling the entry of ions and assorted molecules. Consequently, this can lead to an imbalance in intracellular and extracellular ion concentrations, disrupting ion homeostasis and the membrane potential,

ultimately impacting mitochondrial energy production and cellular function [96]. In addition, the mitochondrial inner membrane harbors proteins rich in cysteine residues, such as Thioredoxin (a thiol oxidoreductase). Excessive ROS can oxidize the cysteine residues in mitochondrial inner membrane proteins, leading to structural alterations and loss of function. The oxidation of cysteine residues may also promote protein cross-linking and aggregation, further compromising the integrity and functionality of the mitochondrial inner membrane [97].

The oxidation damage to the inner membrane of mitochondria has a significant impact on cellular function and health. In order to counteract the oxidative damage to the mitochondrial inner membrane caused by excessive ROS, cells possess a series of antioxidant defense systems. These include antioxidant enzymes and molecules such as SOD, catalase, and GPx, as well as non-enzymatic antioxidants such as GSH and vitamin E. These antioxidant compounds actively engage in the elimination and neutralization of surplus ROS, thereby upholding the redox equilibrium of the inner mitochondrial membrane and safeguarding it against harm. Moreover, mitochondria also possess inherent regenerative capacities, consisting of DNA repair enzymes and protein quality control mechanisms, to sustain the intact structure and optimal functionality of the inner mitochondrial membrane [98].

5.2. The impact of excessive ROS on the mitochondrial respiratory chain and ATP synthesis

The mitochondrial respiratory chain is a crucial process for energy production within cells, while ATP synthesis is essential for maintaining normal cellular functions. The generation and accumulation of ROS may lead to dysfunction of the mitochondrial respiratory chain and a decrease in ATP synthesis. The mitochondrial respiratory chain consists of a series of protein complexes located on the inner membrane of mitochondria, transferring electrons from respiratory substrates (such as NADH and FADH2) to O_2, forming water, and releasing energy through the electron transfer process. This energy is used to maintain a proton gradient, which is then utilized by ATP synthase to synthesize ATP on the inner membrane of the cell [99].

The excessive generation of ROS can disrupt the normal functioning of the mitochondrial respiratory chain. Primarily, excessive ROS directly oxidizes proteins on the mitochondrial inner membrane. These proteins include components of the respiratory chain complexes, such as NADH dehydrogenase (Complex I) and cytochrome c oxidase (Complex IV), as well as other proteins associated with respiratory chain function. By oxidizing key residues in proteins, excessive ROS can induce changes in the structure and function of these complexes, thereby affecting the rate and efficiency of electron transfer. Additionally, excessive ROS can react with phospholipids present in the mitochondrial membrane, resulting in lipid peroxidation. The products of lipid peroxidation may interact with the proteins of the respiratory chain complexes, disrupting their structure and, consequently, interfering with their function [100]. Excessive ROS can also influence the expression and assembly of respiratory chain complexes. It has been observed that the expression of complexes can be altered upon ROS stimulation. Excessive ROS can activate oxidation-sensitive signaling pathways, such as nuclear factor E2-related factor 2 (Nrf2), a transcription factor that plays a crucial role in regulating oxidative stress responses within cells. Under normal cellular conditions, Nrf2 resides in the cytoplasm and interacts with the cytokine Keap1, leading to the degradation of Nrf2. However, upon stimulation by excessive ROS, Nrf2 dissociates from Keap1 and is released, subsequently translocating into the cell nucleus. Within the nucleus, Nrf2 binds to antioxidant response elements in the promoter regions and regulates the expression of a series of antioxidant response genes. Furthermore, excessive ROS can also disrupt the assembly process of complexes, triggering abnormal assembly and decreased stability of these complexes [101,102].

In the presence of disruptions in the mitochondrial respiratory chain, the oxidative stress reaction triggered by excessive ROS can destabilize the proton gradient and the process of adenosine nucleotide phosphorylation. This can result in the direct oxidation of the ATP synthase complex, impairing its functionality and reducing the efficiency of ATP synthesis. Additionally, it can interfere with the function of proton pumps and the maintenance of the proton gradient, disrupting the process of energy conversion and subsequently reducing ATP production [99,103]. In addition to directly impacting the mitochondrial respiratory chain and ATP synthesis, excessive ROS can also influence these processes by activating signal transduction pathways. Cellular physiological functions can be altered by activating the MAPK family, such as ERK, JNK, and p38 MAPK. When the phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt) signaling pathways are activated, they are able to regulate the activity of downstream targets. This, in turn, can directly or indirectly impact the modulation of gene expression and protein synthesis that pertains to respiratory chain complexes. The activation of these signaling pathways may regulate the expression and function of ATP synthase, altering the state of the mitochondrial respiratory chain and, consequently, impacting ATP synthesis [72,104].

5.3. Regulation of mitochondrial dynamics and autophagy by excessive ROS

Mitochondrial dynamics involves the dynamic alterations in the shape, distribution, and number of mitochondria, whereas autophagy is a cellular process that involves self-degradation. Excessive ROS can impact mitochondrial dynamics and autophagy by influencing mitochondrial fusion and fission, maintaining mitochondrial quality control, and affecting autophagy pathways [105].

Mitochondrial fusion and fission are crucial processes in mitochondrial dynamics. Fusion enables the merging of distinct mitochondria into a cohesive network, while fission divides mitochondria into smaller units. These processes are essential for shaping mitochondrial morphology, regulating functionality, and ensuring quality control. The balance of mitochondrial fusion and fission can be influenced by increased levels of ROS(106). On one hand, excessive ROS can modulate the process of mitochondrial fusion and fission by oxidatively regulating related proteins such as mitofusins and dynamin-related protein 1 (Drp1). The fusion proteins Mfn1 and Mfn2 interact with their corresponding proteins on the outer mitochondrial membrane through their N-terminal transmembrane domains. Subsequently, their C-termini form highly stable protein bridges that promote fusion between mitochondria. Mitochondrial fusion proteins are essential in maintaining the connectivity of the mitochondrial network. They enable the exchange of contents between mitochondria, safeguard the integrity of mitochondrial DNA, and help maintain a balanced distribution of cellular energy. The activation and oligomerization of Drp1 are critical steps in mitochondrial fission. The oligomerization of Drp1 leads to the formation of a circular or helical structure, tightly binding it to the outer mitochondrial membrane, creating a constrictive ring. The contraction of the Drp1 ring triggers mitochondrial division, resulting in the formation of two independent mitochondria. The oxidative effect of excessive ROS may disrupt the functionality of these proteins, consequently affecting the balance between fusion and fission [107,108].

ROS are closely associated with mitochondrial quality control and cellular autophagy processes. Cells maintain the healthy state of mitochondria through mechanisms of mitochondrial quality control, which include selective removal of damaged mitochondria and balancing mitochondrial biosynthesis. Excessive ROS modulates the activity of mitochondrial quality control pathways, thereby influencing mitochondrial health [106]. On one hand, increased levels of ROS can activate redox-sensitive signaling pathways, such as Nrf2, NF-κB, and p53, which regulate the expression of mitochondrial quality control genes and promote mitochondrial biosynthesis and repair. On the other hand, Excessive levels of ROS can cause oxidative damage to mitochondria. This damage can surpass the cellular repair capabilities of quality control mechanisms in the cytoplasm. As a result, it can trigger a process

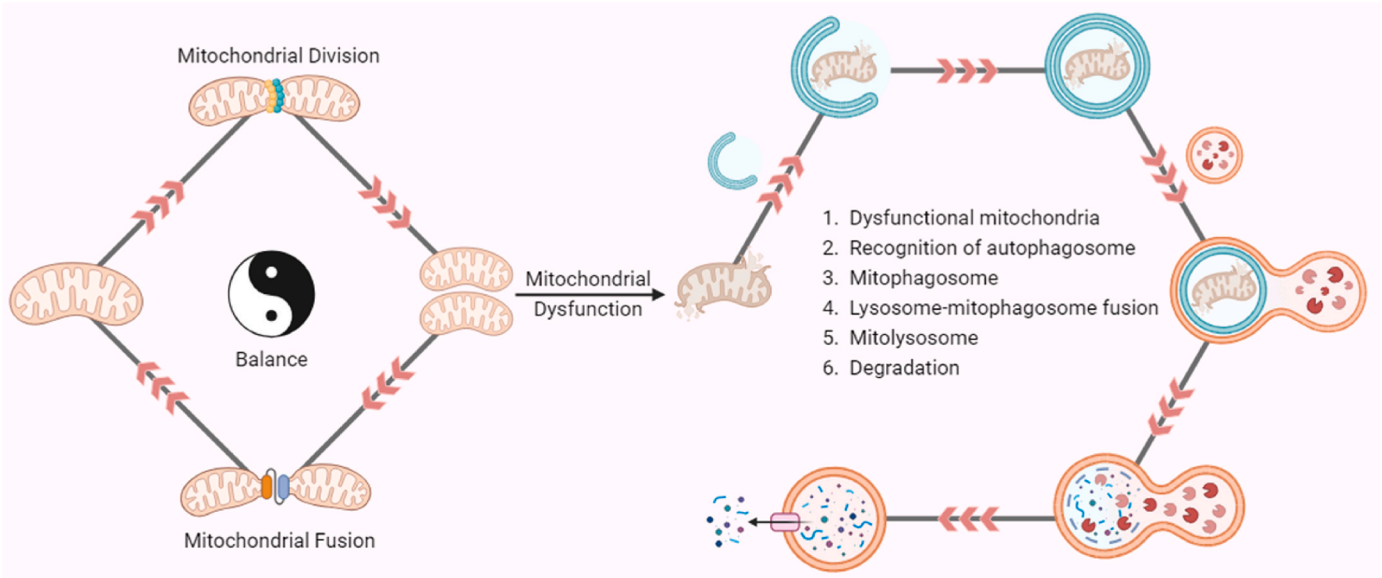

Fig. 4. Schematic illustration of mitochondrial dynamics and mitophagy homeostasis in IVD cells.

called mitophagy, which selectively removes damaged mitochondria through autophagy [42,109]. Mitophagy is a mechanism that ensures the maintenance of mitochondrial function and stability by selectively enveloping and degrading damaged or aging mitochondria. This process involves specialized signaling pathways and autophagy-related proteins, such as the PINK1/Parkin pathway and BNIP3. Additionally, an increase in ROS can activate the adenosine monophosphate (AMP) activated protein kinase (AMPK) signaling pathway, thereby promoting mitochondrial fusion and mitophagy. Excessive ROS can also interact with sirtuins (SIRTs), which are a type of cellular energy sensor. SIRTs are NAD + -dependent deacetylases that play a role in regulating protein deacetylation modifications for various cellular physiological processes. This interaction allows SIRTs to regulate mitochondrial dynamics, autophagy, and cellular metabolism [110](Fig. 4).

6. Interaction of oxidative stress and mitochondrial damage leads to IVDD

6.1. The interaction between excessive ROS and the crucial signaling pathways in IVD cells

When oxidative stress is enhanced, the complex interplay between impaired mitochondrial function and altered function of heat shock proteins (HSPs) has a significant impact on the development of IVDD. HSPs play a critical role in cellular stress response by protecting cells by aiding protein folding, stabilization and repair, preventing aberrant aggregation of damaged proteins and facilitating their degradation, thereby reducing the intracellular stress burden. However, oxidative stress-induced impairment of mitochondrial function negatively affects the function of HSPs [111,112]. Mitochondria are not only responsible for energy supply, but also involved in the synthesis and processing of HSPs. When mitochondrial function is impaired, the synthesis efficiency of HSPs is reduced, leading to their insufficient concentration in the cell and weakening their ability to repair damaged proteins. At the same time, mitochondrial damage decreases the function of the cellular antioxidant system, and the level of ROS is difficult to be effectively controlled, further exacerbating the state of oxidative stress and increasing the burden of HSPs. In addition, excess ROS have direct effects on HSPs, including through oxidative modification of their sulfur-containing amino acid residues (e.g., cysteine). Such oxidative modifications can alter the conformation and function of HSPs, interfering with their normal folding and stabilizing effects. In the case of Hsp90, for example, this molecular chaperone protein helps HSPs to fold correctly and prevents them from aggregating abnormally under normal conditions, but when ROS levels are too high, this interaction is disrupted, leading to abnormal aggregation of HSPs. Ultimately, the abnormal aggregation of HSPs and mitochondrial dysfunction work together to drive IVDD [113, 114].

In addition, when ROS are increased, it activates the JNK signaling pathway. JNK is a MAPK family member that plays an important role in cells. When ROS levels are elevated, the body normally regulates the JNK signaling pathway in response to this stressful stimulus. Excessive ROS undergo oxidative modification with specific proteins in the JNK pathway, leading to JNK activation. Moreover, excessive ROS can directly activate JNK by activating upstream protein kinase kinases (MAP3K). These MAP3K can be directly oxidized by excessive ROS and transformed into an activated state. Once the JNK signaling pathway is activated, it acts by phosphorylating downstream target proteins. These target proteins include the transcription factors c-Jun, ATF2, and p53, which are involved in regulating gene expression and cell fate decisions. The activated JNK signaling pathway can regulate apoptosis, inflammatory response, and stress response. It does so by phosphorylating specific proteins, which alters their transcriptional activity and intracellular interactions. In IVDD, oxidative modification and aberrant aggregation of heat shock proteins may interfere with the normal regulation of the JNK signaling pathway. Furthermore, oxidative modification of heat shock proteins enhances JNK activity, affecting mitochondrial function, and thus promoting apoptosis and inflammatory responses [115,116].

Excessive ROS affect the activity and function of adenylate cyclase. Adenylate cyclase catalyzes the synthesis of cyclic adenosine monophosphate (cAMP) from adenosine in mitochondria and is involved in cellular physiological processes and signaling. Excessive ROS reduce the catalytic activity and stability of adenylate cyclase by directly oxidizing the sulfur amino acid residues that modify it. The decrease in intracellular cAMP levels can disrupt normal signaling pathways, such as the cAMP-dependent protein kinase A (PKA) pathway. This disruption can interfere with the phosphorylation of target proteins downstream of PKA, which are involved in mitochondrial function, cellular energy metabolism, and the physiological regulation of IVD cells [117].

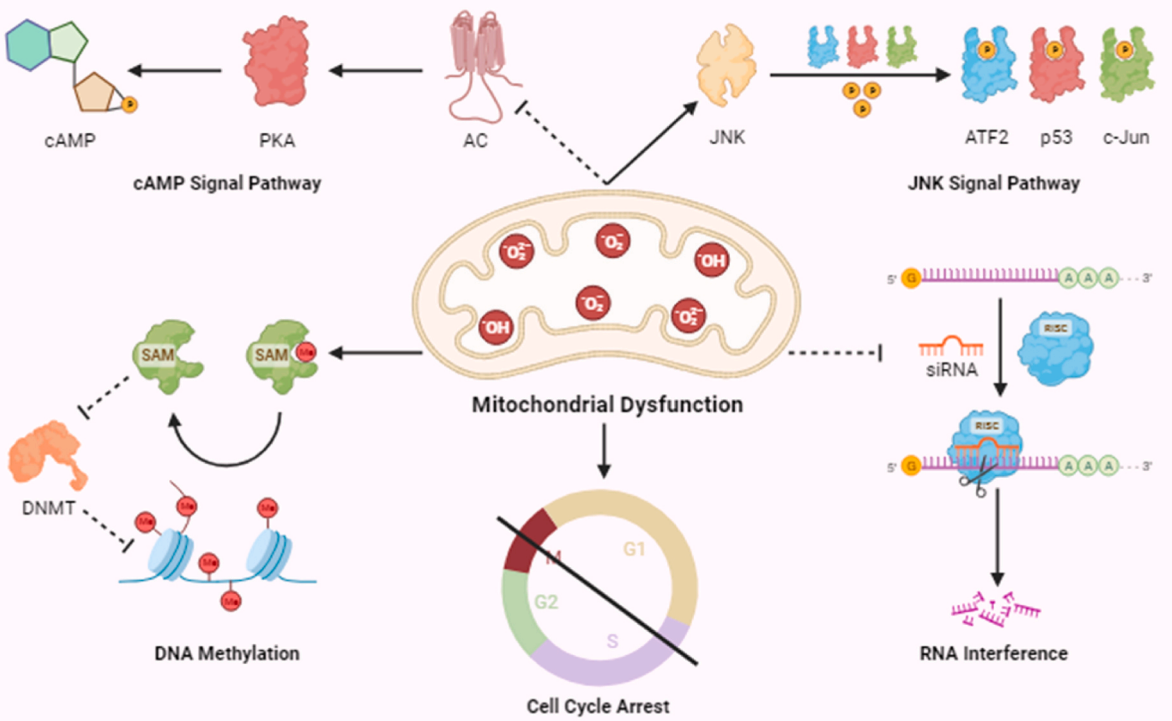

Fig. 5. Schematic illustration of excessive ROS affecting IVDD by inducing mitochondrial dysfunction.
cAMP: cyclic adenosine monophosphate, PKA: protein kinase A, AC: adenylate cyclase, JNK: c-Jun N-terminal kinase, SAM: s-adenosylmethionine.

6.2. Epigenetic regulation

A prominent epigenetic modification is DNA methylation, which involves the addition of methyl groups to DNA molecules and is often involved in maintaining gene silencing and regulating gene expression. Oxidative stress and mitochondrial dysfunction significantly alter DNA methyltransferase activity, which may lead to oxidative stress-associated DNA damage, such as 8-hydroxydeoxyguanosine (8-OHdG) formation. Mitochondrial dysfunction usually leads to elevated levels of ROS, and excessive ROS not only directly cause DNA damage but also irreversible oxidative damage to DNA methyltransferases. At the same time, excess ROS also affects the level of S-adenosylmethionine (SAM), a cofactor for DNA methyltransferases, which is a high-energy methyl donor required for DNA methylation. Increased depletion of SAM leads to reduced methylation activity of DNMT enzymes. It has been found that DNA methylation levels are abnormally elevated in IVDD tissues. Mitochondrial dysfunction exacerbates this process, further leading to aberrant DNA methylation patterns that negatively impact IVD cell function and health [118,119].

In addition, chromatin modification is an important mechanism of epigenetic regulation, referring to the process of chemical modification of DNA and histones within chromatin that can regulate gene expression by altering chromatin structure and density. Oxidative stress and mitochondrial dysfunction can alter the activity and function of chromatin-modifying enzymes through various mechanisms [121,122]. [120,121]. One approach involves adjusting the expression and stability of chromatin-modifying enzymes to affect their activity. Studies have shown that oxidative stress and mitochondrial dysfunction can modulate the activity of transcription factors such as NF-κB and AP-1, which in turn directly or indirectly regulate the gene expression of chromatin-modifying enzymes. In addition, the activity of these enzymes can also be altered by affecting their stability. Excess ROS may alter the protein structure of chromatin-modifying enzymes through oxidation, thereby affecting their stability and activity. Another mechanism involves regulating cofactors and other factors associated with chromatin-modifying enzymes to alter their activity. Excessive ROS and mitochondrial dysfunction may affect ROS production and clearance, resulting in reduced intracellular levels of coenzyme Q10 (CoQ10). Coenzyme Q10 is an important electron carrier that assists in the removal of ROS through the antioxidant mechanisms present in the mitochondria and cytoplasm. Decreased levels of CoQ10 may disrupt cellular redox homeostasis, which in turn may affect the function of chromatin-modifying enzymes. This may ultimately lead to abnormal function of IVD cells and result in IVDD [122,123].

Long non-coding RNA and microRNA are actively involved in the epigenetic regulation of IVDD. These non-coding RNA molecules, which do not encode proteins, have the ability to interact with specific gene loci and modulate gene expression and function. Recent studies have shown that oxidative stress and mitochondrial dysfunction can impact the expression levels and functionality of non-coding RNA by affecting the RNA interference (RNAi) pathway mediated by these molecules. RNAi is a mechanism of gene silencing mediated by non-coding RNA, wherein the binding of non-coding RNA to specific gene mRNA targets leads to their degradation or inhibition of translation. Excessive ROS may influence the formation and functionality of protein complexes involved in the RNAi process, subsequently affecting the efficiency and regulation of RNAi. Consequently, this cascade of events can contribute to the pathological processes occurring in IVD cells and tissues [124, 125].

6.3. Regulation of the cell cycle and cell proliferation

In IVD cells, cell cycle regulation ensures that cells are able to properly enter, pass through, and exit the G1, S, G2, and M phases through a series of precise molecular events and signaling pathways. This process is critical for IVD cell proliferation as it ensures that the cell accomplishes DNA replication and cell division at the proper time to maintain the structure and function of the IVD [126].

Firstly, excessive ROS and mitochondrial dysfunction can cause DNA damage, activating DNA damage response pathways such as the ATM-ATR signaling pathway and the activation of poly (ADP-ribose) polymerase (PARP). These signaling pathways can halt the progression of the

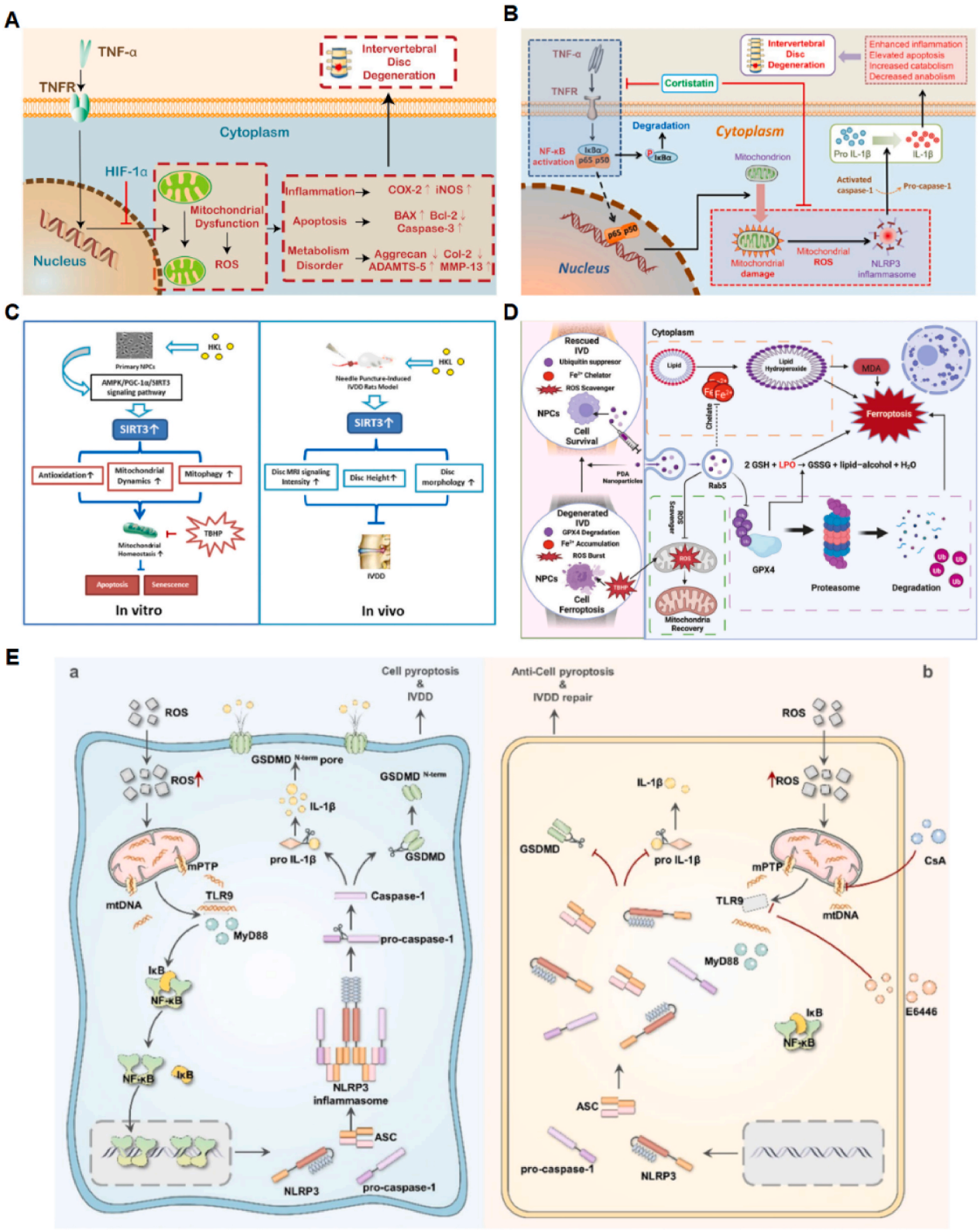

Fig. 6. Mitochondrial antioxidants and protectants ameliorate IVDD under oxidative stress. (A) Hypoxia-inducible factor-1α protected against IVDD through antagonizing mitochondrial oxidative stress [130]. Copyright 2022, Springer Nature; (B) Cortistatin ameliorated IVDD through targeting mitochondrial ROS-dependent NLRP3 inflammasome activation [88]. Copyright 2020, Weiwei Li; (C) SIRT3 ameliorated IVDD by maintaining mitochondrial homeostasis under oxidative stress [131]. Copyright 2018, Springer Nature; (D) PDA NPs targeting ferroptosis as ROS scavengers restored mitochondrial function and ameliorated IVDD (132). Copyright 2023, Wiley-VCH GmbH; (E) The antagonists of mPTP opening (CsA) and TLR9 (E6446) attenuated oxidative stress-induced NPCs pyroptosis and IVDD by inhibiting the TLR9-NF-κB-NLRP3 axis. a) MtDNA via mPTP opening release into the cytoplasm triggered TLR9-NF-κB-NLRP3 axis-dependent NPCs pyroptosis. b) The CsA and E6446 mitigated NPCs pyroptosis and IVDD by inhibiting the TLR9-NF-κB-NLRP3 axis [133]. Copyright 2023, Springer Nature;

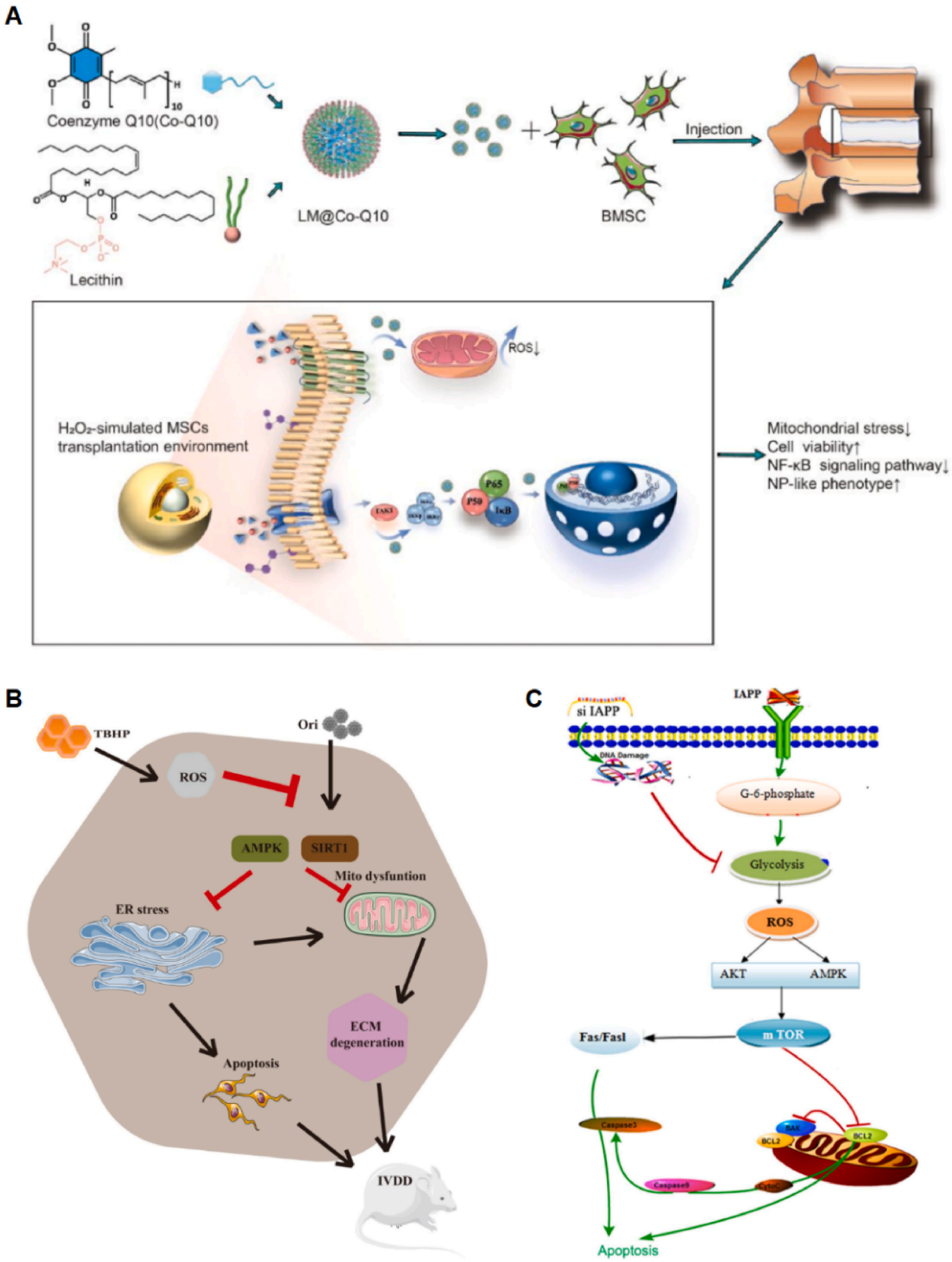

Fig. 7. Mitochondrial antioxidants and protectants ameliorate IVDD by inhibiting oxidative stress. (A) Co-Q10-loaded micelle (LM@Co-Q10) ameliorated IVDD by targeting mitochondrial ROS(137). Copyright 2023, Elsevier B.V.; (B) Orientin alleviated IVDD by downregulating oxidative stress-mediated mitochondrial dysfunction [139]. Copyright 2022, Springer Nature; (C) Islet amyloid polypeptide rescued oxidative stress-induced IVDD by inhibiting mitochondrial and death receptor pathways [140]. Copyright 2017, Elsevier B.V.;

cell cycle to ensure the repair of DNA damage or induce apoptosis. Furthermore, oxidative stress and mitochondrial dysfunction may modulate the cell cycle by affecting the expression and activation of cell cycle proteins and cyclin-dependent kinases (CDKs) [127]. Research has uncovered that excessive ROS can modulate the activity of transcription factors, thereby affecting the gene expression of cell cycle proteins and CDKs. Certain transcription factors, such as p53, NF-κB, and AP-1, can directly or indirectly regulate the expression of genes involved in cell cycle regulation. Hence, oxidative stress and mitochondrial dysfunction may disrupt the progression of the cell cycle by modulating the activity of transcription factors and controlling the expression levels of cell cycle proteins and CDKs. Additionally, the regulation of cyclin-dependent kinase inhibitors (CKIs), which are proteins associated with cell cycle regulation, can also influence cell cycle control and cellular proliferation. CKIs act as negative regulators by inhibiting CDK activity, thereby impeding the progression of the cell cycle. Excessive ROS can impact the expression levels and stability of CKIs, thereby regulating the activity of cell cycle proteins and CDKs [128].

The disruption of cell cycle regulation is closely associated with weakened cellular functions and reduced proliferative capacity. Normal cell cycle regulation ensures that cells undergo DNA replication, mitosis, and cell division in an orderly manner at specific time points. If cell cycle regulation is disrupted, cells may be in inappropriate stages or become stalled, which adversely affects their normal functions [126]. In IVD cells, oxidative stress and mitochondrial dysfunction may lead to disruptions in cell cycle regulation, resulting in cell arrest at specific phases such as G1 and G2. This can potentially impair the functionality of IVD cells, including decreased synthesis of proteins and ECM, reduced metabolic activity, and cellular sluggishness or death(Fig. 5).

7. Potential for targeting mitochondrial function and oxidative stress to treat IVDD

7.1. Mitochondrial antioxidants and protectants

Antioxidants are a category of compounds that possess the ability to counteract free radicals and alleviate oxidative stress. At the mitochondrial level, antioxidants can enhance mitochondrial function and mitigate oxidative stress. Mitochondria possess an antioxidant enzyme system to combat oxidative stress, including SOD and GSH-Px, among others. These enzymes have the ability to eliminate ROS within mitochondria, thereby reducing the severity of oxidative stress. Thus, through injection or administration of relevant compounds such as SOD and GSH-Px analogs, it is possible to enhance the antioxidant capacity of mitochondria [129]. Yang et al. demonstrated that hypoxia-inducible factor-1α protected against IVDD by reducing ROS production in mitochondria, thereby inhibiting inflammation, metabolic disorders, and apoptosis of NPCs (Fig. 6A) [130]. After knocking out the mouse cortistatin gene, Zhao et al. found that cortistatin was involved in the activation of mitochondrial ROS and NLRP3 inflammasomes in IVD degeneration, providing a new clue for therapeutic targets in IVDD (Fig. 6B) [88]. Moreover, honokiol activated SIRT3 through the AMPK-PGC-1α signaling pathway, promoting antioxidant capacity, mitochondrial dynamics, and mitophagy (Fig. 6C) [131]. Furthermore, recent scientific investigations have put forth evidence pointing towards the significant alleviation of apoptosis in IVD cells induced by oxidative stress through the application of N-acetylcysteine (NAC), an antioxidant primarily localized in mitochondria. Importantly, this treatment also ensures the preservation of mitochondrial structure and functionality. The mechanism underlying the protective effects of NAC involves its ability to regulate the clearance of ROS and vital free radicals within the mitochondrial environment, thereby mitigating oxidative stress. As a ROS scavenger, polydopamine nanoparticles could recover mitochondrial function to ameliorate IVDD (Fig. 6D) [132]. The antagonist of mPTP opening (CsA) and TLR9 (E6446) mitigated NPCs pyroptosis and IVDD by inhibiting the TLR9-NF-κB-NLRP3 axis (Fig. 6E) [133]. The application of these antioxidants has the potential to enhance mitochondrial antioxidant capacity and alleviate oxidative stress imposed on mitochondria, thereby potentially improving the survival and regeneration of IVD cells [134].

Another crucial mechanism involves mitigating oxidative stress by protecting the mitochondrial membrane. The stability of the mitochondrial membrane is vital for maintaining proper mitochondrial function. Currently, several compounds have been discovered to exhibit properties of mitochondrial membrane stabilizers. One such compound is methylene blue, a mitochondrial membrane stabilizer that has shown potential in alleviating mitochondrial damage in IVDD. Methylene blue is capable of reducing lipid peroxidation and protein oxidation in the mitochondrial membrane, thus mitigating phenomena such as mitochondrial outer membrane rupture, mitochondrial membrane potential decline, and damage to the mitochondrial respiratory chain. It accomplishes this by inhibiting the transition of mitochondrial membrane permeability and safeguarding the integrity of the mitochondrial membrane. Moreover, methylene blue has been discovered to regulate the interaction between mitochondria and the mitochondria-associated endoplasmic reticulum membrane. This regulatory effect serves to alleviate oxidative stress and promote the survival of IVD cells by enhancing communication between the mitochondria and endoplasmic reticulum [135,136].

Furthermore, mitochondrial-targeted antioxidants and protectants can also improve mitochondrial function and reduce oxidative stress by exerting an impact on the mitochondrial respiratory chain and energy metabolism. A study has revealed that supplementation of CoQ10 can enhance mitochondrial energy production and antioxidant defense capabilities. CoQ10 acts as an electron transfer mediator in the mitochondrial respiratory chain and possesses antioxidant properties. It has the ability to enhance the electron transfer rate within mitochondria, thereby promoting ATP production and alleviating mitochondrial oxidative stress [123]. Sun et al. encapsulated CoQ10 into lecithin micelles to antagonize mitochondrial ROS and exert protective effects in cell survival and differentiation (Fig. 7A) [137]. In addition, Niacin has shown the potential to improve mitochondrial function and reduce oxidative stress. Niacin, scientifically recognized as vitamin B3, plays a vital role in the intricate NADH/NAD + cycle within the mitochondrial respiratory chain. Its indispensability lies in its contribution to mitochondrial energy metabolism, fostering improved energy production and bolstering antioxidant defenses. Consequently, it holds the potential to mitigate oxidative stress, thereby enhancing overall cellular well-being [138].

Additionally, the study of antioxidants and protective agents involves a number of other compounds and strategies. Orientin alleviated oxidative stress-induced mitochondrial dysfunction and endoplasmic reticulum stress by upregulating AMPK and SIRT1 (Fig. 7B) [139]. Moreover, Wu et al. found that islet amyloid polypeptide rescued oxidative stress-induced IVDD by inhibiting mitochondrial and death receptor pathways (Fig. 7C) [140].

Certain polyphenolic compounds and natural plant extracts, such as catechins, flavonoids, and polyphenol flavonoids, neutralize free radicals and other oxidizing substances, showing mitochondrial protective and antioxidant activities. They also have anti-inflammatory effects and can reduce mitochondrial damage and exacerbation of oxidative stress by inflammatory responses [141].

7.2. Transcription factor regulation

In circumstances where cells undergo oxidative stress and consequent cellular damage, Nrf2 comes into play by activating and relocating to the nucleus, where it binds with the antioxidant response element of anti-oxidative stress response genes, initiating a chain reaction of transcription in numerous antioxidants and cytoprotective genes. In the treatment of IVDD, activation of the Nrf2 signaling pathway has been considered as a potential therapeutic approach to alleviate oxidative

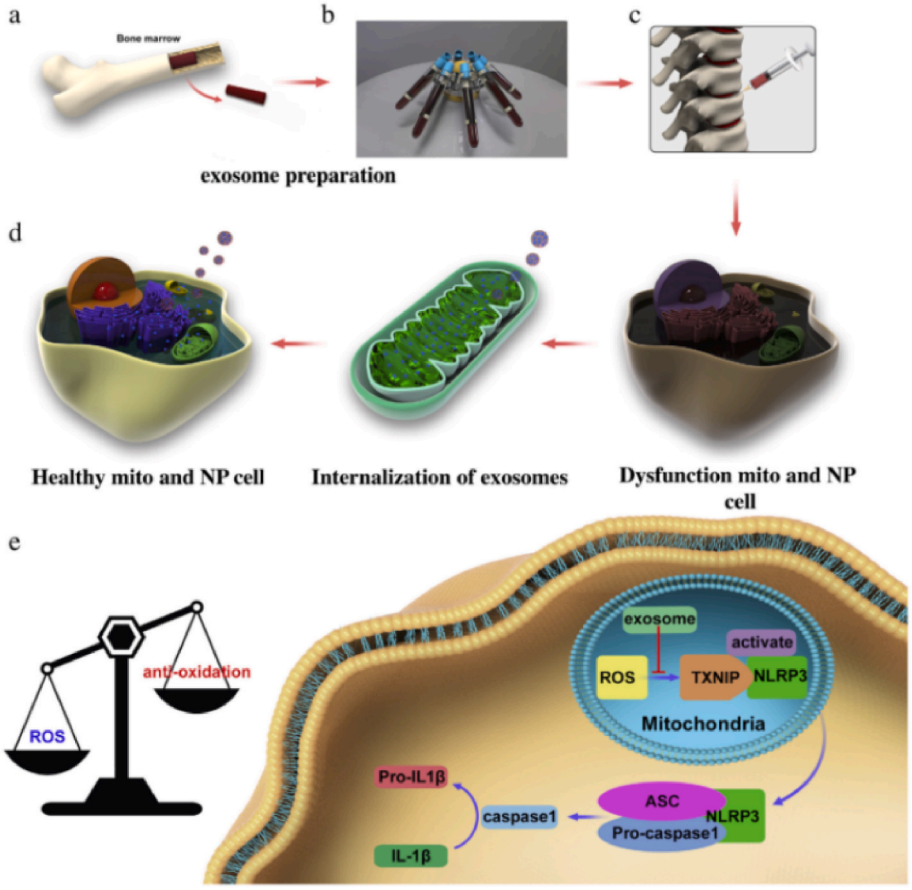

Fig. 8. Stem cells ameliorate IVDD under oxidative stress. a) BMSCs derived from C57BL/6 mice were obtained. b) Isolation of BMSC-derived exosomes. c) Exosomes were investigated in a model of IVDD. d) Enhanced mitochondrial biogenesis by exosomes. e) Possible signal pathways in the process of stem cells ameliorating IVDD (149). Copyright 2019, Elsevier Inc; To improve the effectiveness of stem cell therapy, researchers are improving treatment strategies and techniques. One common approach is to pre-differentiate stem cells into disc-like cells, which can better adapt stem cells to the environment of IVDD and increase the efficiency of differentiation into disc cells. In addition, in stem cell therapy, scaffolding materials, biomaterials, and bioprinting technologies can be combined to establish and maintain a three-dimensional microenvironment for stem cells, providing better support and guidance for disc regeneration and repair [45,56]. Although stem cell therapy shows potential in the treatment of IVDD, a number of challenges and problems remain. For example, the source of stem cells, acquisition methods, and preparation requirements need to be further studied and addressed. At the same time, the safety, viability, and maintenance time of stem cells after their introduction also need to be carefully considered and evaluated.

stress in IVD cells by increasing the antioxidant capacity and function of mitochondria [142].

Activation of Nrf2 promotes antioxidant stress responses and maintains mitochondrial health by regulating the expression and function of a range of mitochondria-related genes. First, activation of Nrf2 induces the expression of mitochondrial antioxidant enzymes, such as SOD, catalase, and GPx. These antioxidant enzymes can scavenge intracellular free radicals and harmful oxidants and attenuate mitochondrial oxidative stress. Second, Nrf2 also regulates lipid synthesis and transport processes in the mitochondrial envelope. The mitochondrial envelope is an important component of mitochondria and plays a role in protecting mitochondrial structure and function. By activating the Nrf2 signaling pathway, the synthesis and repair of mitochondrial lipids can be promoted, and the integrity and stability of the mitochondrial envelope can be enhanced [143,144]. In addition, activation of Nrf2 regulates mitochondrial DNA replication, repair, and degradation. Mitochondrial DNA is the genetic material inside mitochondria and is critical for mitochondrial function and health. By activating the Nrf2 signaling pathway, the replication and repair of mitochondrial DNA can be promoted to maintain the integrity and stability of the mitochondrial genome. Activation of Nrf2 also regulates the expression of mitochondrial adhesion proteins, transport proteins, and lipid synthases. These proteins and enzymes have important regulatory roles in mitochondrial structure and function. Activation of the Nrf2 signaling pathway promotes the synthesis and maintenance of mitochondrial proteins and enzymes, thereby enhancing mitochondrial function [145].

Several natural compounds have been demonstrated to activate the Nrf2 signaling pathway. Polyphenolic compounds such as EGCG in tea, caffeine, and sulfides like allicin in garlic have been found to possess the ability to activate Nrf2. These natural compounds can activate Nrf2 through a variety of pathways, including direct binding to Nrf2, alteration of Nrf2 transport and stability, and modulation of Nrf2 regulators [101]. Current research suggests that a number of nutrients and compounds may be able to promote Nrf2 activation indirectly or directly. For example, antioxidant vitamins such as vitamin C and vitamin E have the potential to modulate the Nrf2 pathway, but the exact mechanism of activation is still under intensive study. Similarly, some natural compounds such as isoflavones are thought to have the ability to activate Nrf2 [146]. However, more research and clinical trials are needed to validate the potential effects and side effects of these drugs. In order to precisely activate Nrf2, more in-depth studies are needed to understand the regulatory mechanisms of the Nrf2 signaling pathway and to develop specific activators and methods.

Table 1
Molecules or compounds that regulate oxidative stress through mitophagy in IVDD. NP: nucleus pulposus, AF: annulus fibrosus, BMSCs: bone marrow-derived stem cells, MitoQ: mitoquinone, OPTN: optineurin, HA: hyaluronic acid, PGC-1α: peroxisome proliferator-activated receptor-gamma coactivator-1α.

Regulators	Target cell	Pathway	Main findings	References
PINK1	Human NP cells	mitophagy↑	PINK1 clears damaged mitochondria through mitophagy and delays cell senescence to alleviate the progress of IVDD.	[182]
Parkin	Rat BMSCs	mitophagy↑	Parkin suppresses the generation of mtROS via initiating mitophagy to eliminate dysfunctional mitochondria.	[183]
MitoQ	Human NP cells	mitophagy↑	MitoQ protects against IVDD by ameliorating mitochondrial dysfunction and redox imbalance.	[184]
A20	Rat NP cells	mitophagy↑	A20 inhibits ROS production by promoting mitophagy and stabilizing mitochondrial dynamics in NP cells.	[185]
Melatonin	Rat NP cells	mitophagy↑	Melatonin activates mitophagy in a Parkin-dependent manner to ameliorate ECM degradation and apoptosis induced by oxidative stress.	[186]
Honokiol	Rat NP cells	mitophagy↑	Honokiol responds to oxidative stress in a SIRT3-dependent manner to promote anti-oxidation, mitochondrial dynamics, and mitophagy.	[131]
OPTN	Rat NP cells	mitophagy↑	OPTN attenuates oxidative stress-induced cell senescence and matrix degeneration by promoting mitophagy to scavenge damaged mitochondria and excess reactive oxygen species.	[187]
NDUFA4L2	Human NP cells	mitophagy↓	NDUFA4L2 inhibits apoptosis of human NP cells induced by oxidative stress via inhibiting mitophagy.	[188]
HA	Human NP cells	mitophagy↑	HA ameliorates TBHP-induced mitochondrial dysfunction, apoptosis, senescence, and ECM degradation by activating mitophagy.	[189]
PGC-1α	Rat AF cells	mitophagy↓	PGC-1α acts as a mediator of SIRT2 to protect annulus fibrosus from apoptosis induced by oxidative stress through restraining mitophagy.	[190]

7.3. Stem cell therapy

Stem cell therapy is regarded as a promising new approach for the treatment of IVDD. Conventional treatment methods, such as medication, physical therapy, and surgery, provide some degree of symptom relief but fail to achieve actual IVD repair. It is hoped that through the regenerative and reparative abilities of stem cells, restoration of IVD function and reconstruction of diseased tissues can be achieved [147].

Stem cells have the potential for self-renewal and multidirectional differentiation into different types of cells, including IVD cells. In stem cell therapy, commonly used stem cell sources include adipose-derived stem cells (ADSCs), bone marrow-derived stem cells (BMSCs), and placental-derived stem cells (PSCs). These stem cells can be introduced into the damaged disc area by implantation or injection to provide new cell resources for the disc. On the one hand, the introduced stem cells can differentiate into IVD cells to fill in the missing cells in the damaged region, replenish the functionally intact mitochondria, and promote the regeneration of IVD. Studies have shown that under appropriate environment and stimulation, stem cells can differentiate directionally into IVD cells and express disc-specific markers and functional proteins. This directed differentiation process helps to restore the number and function of IVD cells, which in turn improves the mechanical properties and organizational structure of the disc [148]. On the other hand, stem cells demonstrate the capability to release a diverse array of bioactive substances, including cytokines, growth factors, and extracellular vesicles, which exhibit antioxidant and anti-inflammatory properties. These bioactive substances effectively mitigate oxidative stress and inflammatory reactions within disc cells, simultaneously restoring proper mitochondrial function and enhancing cellular well-being. Among them, the antioxidant effect helps to scavenge free radicals and harmful oxidants, protecting disc cells from oxidative damage. The anti-inflammatory effect helps to inhibit the release of inflammatory cells and inflammatory factors, reducing the inflammatory response and the destruction of IVD tissue. Xia et al. supplied mitochondrial proteins to NPCs via mesenchymal stem cell-derived exosomes, and with this supplementation could repair damaged mitochondria (Fig. 8) [149]. Through these mechanisms, stem cells can promote the self-healing and repair process of IVD cells, which helps to restore the function and structure of IVD [93,150].

Targeting the regulation of mitochondrial function is an important aspect of stem cell therapy. Studies have shown that stem cells can repair and improve damaged mitochondrial function through multiple mechanisms. First, stem cells can release mitochondria-derived factors, such as mitochondrial DNA and mitochondrial RNA, which can be taken up by peripheral cells and enter the damaged mitochondria, thus promoting mitochondrial repair and regeneration [151]. Second, stem cells can also affect the metabolism and energy supply of damaged mitochondria by regulating the expression and function of mitochondria-related genes. Bioactive molecules released by stem cells, such as cytokines and growth factors, can also affect intracellular mitochondrial function through receptor-mediated pathways. In addition, stem cell therapy can modulate the mitochondrial oxidative stress response. It has been found that antioxidants and active substances released by stem cells, such as GSH and SOD, can scavenge intracellular free radicals and harmful oxidants and reduce mitochondrial oxidative stress, thus protecting mitochondria from damage [152].

7.4. Carrier delivery system

Carrier delivery systems are a widely studied method for efficiently delivering drugs or genes into mitochondria to enhance their antioxidant and mitochondrial protection. In the field of IVD repair, these systems can aid in the intracellular localization and delivery of drugs or genes to mitochondria and enhance their therapeutic efficacy [151].

A common carrier delivery system is nanoparticles. Nanoparticles have a large specific surface area and excellent stability at the nanoscale, which can accommodate and protect drugs or genes and provide an efficient pathway to direct them intracellularly and into mitochondria. The ability of nanoparticles to target cell membranes and mitochondria can be achieved by modifying their surface properties and components. Through surface modifications, nanoparticles can bind to specific receptors, thereby helping to target drugs or genes to specific types of cells and mitochondria [153]. Another common carrier is liposomes. Liposomes are composed of phospholipids and have good biocompatibility and tunability. Liposomes are capable of forming complexes with drugs or genes and directing them to intracellular and mitochondria through interactions with cell membranes. The delivery properties and stability of liposomes are optimized by modulating their components and structure. In addition, liposomes can be used to create specific functionality for targeting cell membranes and mitochondria to enhance the efficacy of drugs or genes in disc repair [154,155]. Polymers are another commonly used class of carrier materials that are versatile and tunable. By modifying the structure and physicochemical properties of polymers, the release rate and delivery efficiency of drugs or genes within cells and mitochondria can be controlled. Polymeric carrier delivery systems help to improve the stability and bioavailability of drugs or genes and facilitate their localization and release within mitochondria. In addition, polymers can be combined with other carrier materials to form composite carrier systems to further improve delivery and enable more accurate mitochondrial targeting [156].

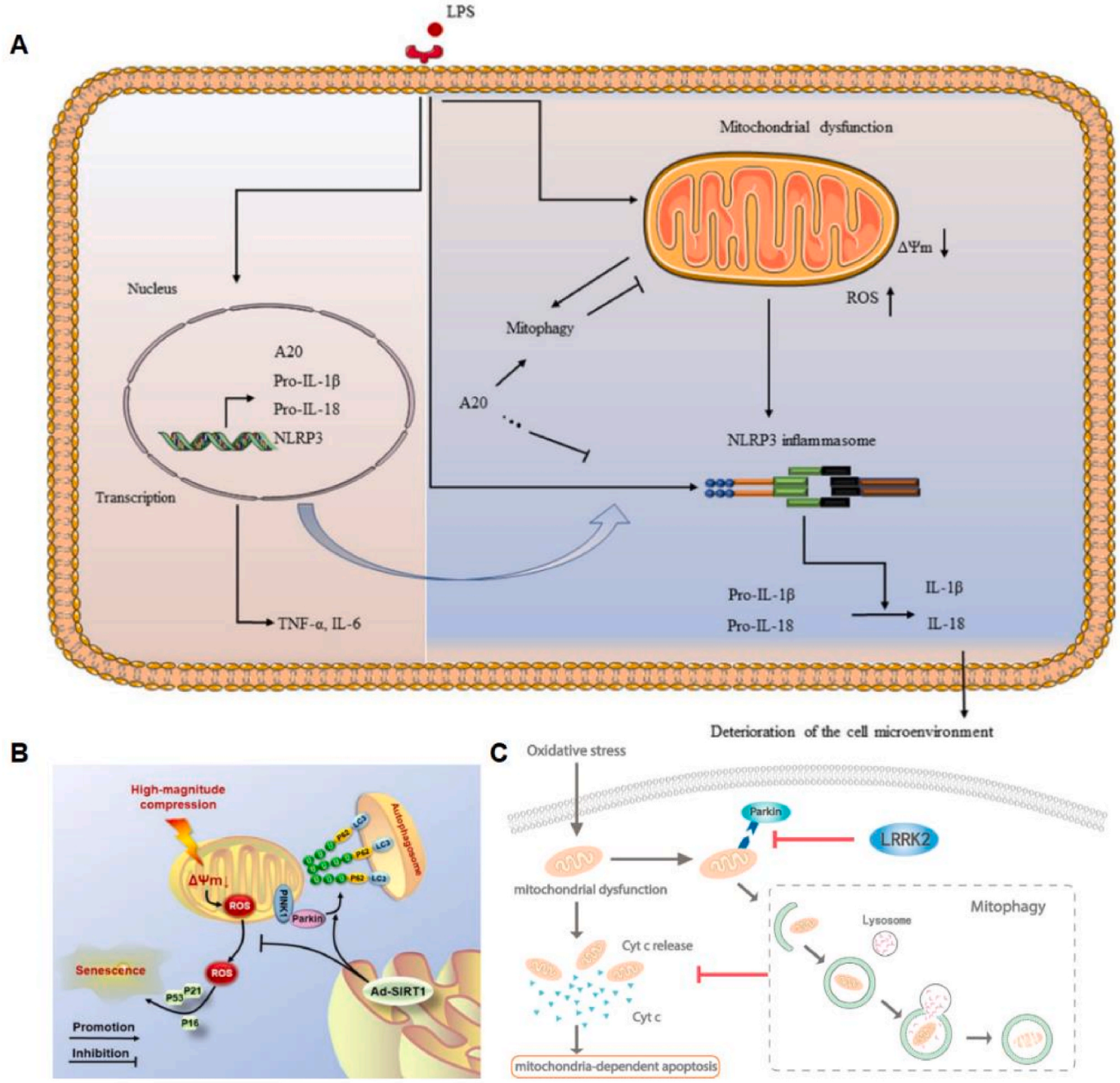

Fig. 9. Mitophagy ameliorates IVDD under oxidative stress. (A) A20 alleviated IVDD by promoting mitophagy to rescue oxidative stress-induced mitochondrial dysfunction [175]. Copyright 2022, Springer Nature; (B) SIRT1 attenuated NPCs senescence under oxidative stress via PINK1-dependent mitophagy [176]. Copyright 2020, Wang et al.; (C) Inhibition of LRRK2 attenuated oxidative stress-induced mitochondrial dysfunction by activating mitophagy to alleviate IVDD(177). Copyright 2021, Elsevier;.

Other vector delivery systems have also been developed to achieve mitochondrial delivery in disc repair, including viral vectors, carbon nanotubes, and metal nanoparticles. Viral vectors are a vector system commonly used for gene delivery. By loading drugs or genes into the genome of viral particles, researchers can utilize the self-replicating mechanism and efficient cellular delivery capabilities of viruses to deliver drugs or genes into cells and mitochondria. Different types of viruses exhibit different mitochondrial localization and delivery properties, such as adenoviruses, adeno-associated viruses, and retroviruses [157]. Viral vectors usually require rigorous safety assessment and careful control of their potential side effects in clinical applications. Carbon nanotubes are nanomaterials with unique structures and functions. They can be used as carriers of drugs or genes for efficient delivery within IVD cells and mitochondria. Carbon nanotubes have good physical and chemical stability and can be modified by modifying their surface to alter their properties and delivery capabilities. By modifying the structure and function of carbon nanotubes, more accurate and efficient mitochondrial delivery can be achieved and the effectiveness of IVD repair can be improved [158].

Metal nanoparticles are another potential class of carrier delivery systems. Due to the small size and high specific surface area of metal nanoparticles, they can efficiently carry drugs or genes and enter into cells and mitochondria. Metal polyphenol nanoparticles are a class of nanoparticles with unique advantages. They have powerful antioxidant

Table 2
Molecules or compounds that regulate oxidative stress through mitochondria in IVDD. NP: nucleus pulposus, CEP: cartilage endplate, AF: annulus fibrosus, BMSCs: bone marrow-derived stem cells, NMN: nicotinamide mononucleotide, Co-Q10: coenzyme Q10, EGCG: epigallocatechin 3-gallate, Amo: amobarbital, NAC: n-acetylcysteine, VDR: vitamin D receptor, HIF-1α: hypoxia-inducible factor-1α.

Regulators	Target cell	Pathway	Main findings	References
Icariin	Human NP cells	Nrf2 pathway↑	Icariin inhibits H_2O_2-induced mitochondria-mediated apoptosis via the Nrf2 signaling pathway.	[191]
Pinocembrin	Mice CEP cells	Nrf2 pathway↑	Pinocembrin promotes mitophagy to maintain chondrocyte homeostasis in oxidative stress conditions.	[183]
Kinsenoside	Rat NP cells	Nrf2 pathway↑	Kinsenoside alleviates apoptosis, senescence, and mitochondrial dysfunction of NP cells induced by TBHP via an Nrf2-dependent way.	[192]
Polydatin	Rat NP cells	Nrf2/HO-1 pathway↑	Polydatin attenuates ROS-mediated mitochondrial dysfunction by activating the Nrf2/HO-1 signaling pathway in rat NP cells.	[193]
Polydatin	Human CEP cells	Nrf2 and Parkin pathway↑	Polydatin protects CEP cells from H_2O_2-induced mitochondrial dysfunction, oxidative stress, and cell apoptosis.	[194]
NMN	Human NP cells	AMPK-PGC-1α pathway↑	NMN restores SIRT3 function and mitochondrial antioxidant network to alleviate oxidative stress apoptosis of human NP cells.	[91]
SIRT3	Human NP cells	AMPK-PGC-1α pathway↑	SIRT3 rescues human NP cell apoptosis and attenuates IVDD by improving mitochondrial redox homeostasis.	[91]
Co-Q10	Rat BMSCs	NF-κB pathway↓	Co-Q10 restores mitochondrial structure as well as function by antagonizing mitochondrial ROS.	[137]
Cortistatin	Human NP cells	NF-κB pathway↓	Cortistatin protects against IVDD by targeting mitochondrial ROS-dependent NLRP3 inflammasome activation.	[88]
EGCG	Human IVD cells	PI3K/Akt pathway↑	EGCG protects human IVD cells from oxidative stress-induced degeneration by inhibiting mitochondrial membrane depolarization.	[195]
Naringin	Rat NP-MSC	PI3K/Akt pathway↑	Naringin restores the ultrastructural morphology of mitochondria and reduces mitochondrial damage to alleviate H_2O_2-induced apoptosis.	[196]
Amo	Rabbit NP cells	MAPK pathway↑	Amo improves mitochondrial function and lowers TBHP-induced apoptosis and necrosis.	[183]
NAC	Rabbit NP cells	MAPK pathway↑	NAC improves mitochondrial function and lowers TBHP-induced apoptosis and necrosis.	[183]
Icariin	Human NP cells	mitochondrial pathway↓	Icariin attenuates H_2O_2-induced mitochondrial morphological changes and cell apoptosis by inhibiting the mitochondrial pathway.	[197]
Melatonin	Rat NP cells	mitochondrial apoptotic pathway↓	Melatonin inhibits the mitochondrial apoptotic pathway to protect rat NP cells from oxidative stress-induced cell apoptosis.	[198]
Lupeol	Rat NP cells	mitochondrial apoptotic pathway↓	Lupeol alleviates the mitochondrial-mediated endogenous apoptosis pathway and enhances the antioxidant stress of mitochondria to inhibit cell apoptosis.	[199]
Visomitin	Human NP cells	/	Visomitin relieves mitochondrial oxidative stress and maintains mitochondrial homeostasis in human NP cells.	[91]
Mito-TEMPO	Human NP cells	/	Mito-TEMPO relieves the mitochondrial oxidative stress and maintains mitochondrial homeostasis in human NP cells.	[91]
Mito-TEMPO	Human CEP cells	/	Mito-TEMPO inhibits oxidative stress, mitochondrial dysfunction, and apoptosis induced by H_2O_2 in human CEP cells.	[194]
Curcumin	Human NP cells	/	Curcumin alleviates TBHP-induced mitochondrial dysfunction to improve apoptosis, senescence, and ECM degradation.	[200]
VDR	Rat AF cells	/	Activation of VDR protects rat AF cells from oxidative stress-induced apoptosis by maintaining mitochondrial function.	[201]
Polydopamine	Rat NP cells	/	Polydopamine nanoparticles targeting ferroptosis as ROS scavengers restore mitochondrial function and ameliorate IVDD.	[132]
HIF-1α	Mice NP cells	/	HIF-1α protects against IVDD by reducing mitochondrial ROS production and consequent inhibition of apoptosis of MNPCs.	[185]
Exosomes	Rat NP cells	/	Exosomes provide rat NP cells with mitochondrial-related proteins and restore mitochondrial function to inhibit the production of ROS.	[149]

properties that trap and scavenge free radicals and protect cells from oxidative stress. In addition, metal polyphenol nanoparticles are biocompatible and can be chemically modified to achieve multifunctionality. They can be used as drug delivery systems to modulate drug release and improve targeting, thus enhancing drug delivery. In addition, the special optical properties of metal polyphenol nanoparticles give them potential in applications such as optical imaging and photothermal therapy, and as a potential carrier delivery system in the field of IVD repair [158,159].

7.5. Gene editing technology

Gene editing technologies, particularly the CRISPR-Cas9 system, provide an emerging approach for direct editing of the mitochondrial genome to correct mitochondrial dysfunction caused by mutations and defects in mitochondrial genes. The innovative approach proposed here is anticipated to significantly enhance mitochondrial function, effectively lowering oxidative stress within both cells and mitochondria. In the context of IVDD, DNA abnormalities and mutations within mitochondria can lead to decreased mitochondrial functionality, insufficient energy supply, and elevated levels of oxidative stress. Ultimately, these factors can significantly contribute to the progression and development of IVDD [160]. Therefore, targeting the editing and repair of mitochondrial genes has become a promising approach for IVD repair.

CRISPR-Cas9 is a gene editing technology that utilizes a programmable RNA sequence and a Cas9 protein complex to localize and cut specific regions of DNA. By directing appropriately designed RNA sequences to specific sites in the mitochondrial genome, the CRISPR-Cas9 system can selectively repair or correct mutations and defects in mitochondrial genes [161,162].In this way, CRISPR-Cas9 technology-mediated mitochondrial genome editing can correct mutations and defects associated with mitochondrial dysfunction in IVDD. CRISPR-Cas9 technology can be used to target mutation sites for cleavage and repair by designing specific gRNAs and Cas9 proteins. This restores normal mitochondrial function and improves ATP production, thereby enhancing disc cell repair. For a larger range of structural variants or deletions, CRISPR-Cas9 technology can introduce normal mitochondrial gene fragments by homologous recombination to replace defective genes, thus restoring normal mitochondrial function. In addition to direct editing of the mitochondrial genome, the CRISPR-Cas9

system can also enhance mitochondrial function and stability by regulating the transcriptional modification and expression of mitochondrial genes. For example, using CRISPRa's gRNA to target the promoter region of NRF1 in combination with an activator (e.g., dCas9-VP64) increases the transcriptional level of NRF1. Regulation of snRNA or snoRNA expression by CRISPRa or CRISPRi systems to optimize the transcription and translation processes of mitochondrial genes. Transcription of mitochondrial genes is regulated by increasing the expression of histone acetyltransferases (HATs) using the CRISPRa system or inhibiting the expression of histone deacetylases (HDACs) using the CRISPRi system. The CRISPRa system can also be used to activate the expression of AMPK or PGC-1α to enhance mitochondrial biosynthesis and function, or to inhibit the expression of mTOR to enhance mitochondrial autophagy and improve mitochondrial function [163,164].

Gene editing technology can also be applied to disc repair as a form of gene therapy. By introducing specific gene fragments or repairing defective gene sequences, gene editing can alter the phenotype and function of IVD cells and promote mitochondrial health and repair processes. This approach can be used to deliver genes that activate functions such as mitochondrial biosynthesis, reduce free radical production, and enhance oxidative stress adaptation and apoptosis protection. Gene editing technology can also be combined with stem cell therapy for cellular repair of IVDD. Gene editing can also regulate the differentiation pathway of the cells, which can lead to the specialization of stem cells into cell types suitable for IVD repair, such as chondrocytes or mesenchymal stem cells, in order to achieve the treatment and repair of IVDD [56,165].

7.6. Promotes mitochondrial dynamics and autophagy

Promoting mitochondrial dynamics and autophagy are important therapeutic strategies in the treatment of IVDD. By regulating mitochondrial biosynthesis, optimizing mitochondrial fusion and division, and activating the autophagic process to attenuate the damage of oxidative stress, we can improve the physiological activity and function of degenerated IVD tissues, thereby promoting repair and regeneration [166].

First, activating mitochondrial biosynthesis is a key therapeutic strategy. Mitochondria are the energy production centers within the cell, and they provide the energy needed by the cell through oxidative phosphorylation of metabolically produced ATP. IVDD leads to impaired mitochondrial function, which in turn leads to a reduced energy supply, preventing normal cellular metabolism and repair, while further releasing ROS and activating oxidative stress [136]. Mitochondrial biosynthetic pathways can be stimulated through the use of AMPK activators such as AICAR (5-Aminoimidazole-4-carboxamide ribonucleotide) and metformin, as well as mitochondrial biosynthesis enhancers such as NRF-1 (nuclear factor-1) and PGC-1α (peroxisome proliferator-activated receptor-gamma coactivator-1α) [167]. AMPK activators can inhibit the mammalian target protein of rapamycin (mTOR) signaling pathway by activating the AMPK signaling pathway, which in turn promotes mitochondrial biosynthesis. Mitochondrial biosynthesis enhancers, on the other hand, can increase the replication of mitochondrial DNA and the synthesis of mitochondrial proteins by activating transcription factors such as NRF-1 and PGC-1α. By increasing the number of mitochondria and improving their function, cells have access to more mitochondria for energy production and enhanced cellular adaptation to oxidative stress [168]. Furthermore, augmenting mitochondrial proliferation enhances mitochondrial division and regeneration, replenishing damaged mitochondrial structures, and facilitating efficient metabolism of severely impaired mitochondria due to oxidative stress. These mechanisms collectively contribute to the repair of damaged IVD tissues, thereby fostering the restoration of their normal function and integrity.

Moreover, optimizing mitochondrial fusion and division is also an important strategy for treating IVDD. Mitochondrial fusion and division are processes regulated by specific proteins. Mitochondrial fusion is dependent on the expression and function of the fusion proteins Mitofusin 1 and Mitofusin 2, which promote fusion between different mitochondria, thereby improving mitochondrial quality and function. Mitochondrial fission, on the other hand, is dependent on the expression and function of the fission protein Drp1, which prompts mitochondrial fission and contributes to the clearance of damaged mitochondria. By regulating the expression and function of mitochondrial fusion and division-related proteins, the dynamic balance of mitochondria can be reshaped to promote their repair and regeneration. Enhancement of mitochondrial fusion can promote the fusion of damaged mitochondria with healthy mitochondria, thus realizing the complementarity of mitochondrial DNA, protein, and phospholipids, and contributing to the repair of damaged mitochondrial structure and function [105,169]. On the other hand, mechanisms that regulate mitochondrial division can restore or maintain a healthy state of mitochondria by removing mitochondria with severe oxidative damage. Appropriate regulation of the division mechanism can prevent excessive division or inhibit division to avoid further mitochondrial damage caused by oxidative stress [170].

In terms of promoting autophagy, the treatment of IVDD can be achieved by activating the autophagic mechanism. Autophagy is a process of cellular self-cleaning and regeneration that degrades and removes damaged and aged mitochondria from the cell, thereby improving the quality and function of mitochondria [171]. The activation of autophagy involves the mTOR and AMPK signaling pathways. mTOR is a key negative regulator that down-regulates the process of autophagy when the cell is in a state of sufficient nutrition. By using mTOR inhibitors, such as Rapamycin, mTOR activity can be reduced, which in turn promotes autophagy [172]. Alternatively, AMPK activators, such as AICAR, can activate the process of autophagy by activating the AMPK signaling pathway and thereby inhibiting the mTOR signaling pathway. The regulation of these signaling pathways can synergistically enhance the formation of autophagic vesicles and the efficiency of degradation of mitochondria [173].

Mitochondrial proliferation and repair are considered promising therapeutic tools to improve the function and number of mitochondria and reduce oxidative stress. Mitochondrial primers refer to a group of compounds that enhance mitochondrial biosynthesis and division, leading to an increase in the population of healthy mitochondria. This augmentation improves the cell's capacity to combat oxidative stress [127]. These compounds work by activating signaling pathways within the cell, inducing the cell to produce more mitochondria and targeting them to the damaged disc area for repair. The mechanism of mitochondrial priming involves promoting mitochondrial biosynthesis and fission, which leads to an increase in the population of healthy mitochondria. This increase in mitochondrial numbers results in a higher supply of energy for the cell and elevates the level of antioxidant molecules produced by the mitochondria. These molecules can then reduce cellular damage caused by oxidative stress and promote the normal functioning and recovery of IVD cells. This therapeutic strategy can help improve the health of degenerating discs and slow the effects of oxidative stress [174]. An alternative approach involves the utilization of proteins associated with mitophagy (Table 1). These proteins play crucial roles in preserving mitochondrial function and health. Peng et al. found that A20 attenuated pyroptosis and apoptosis in NPCs by promoting mitophagy and stabilizing mitochondrial dynamics (Fig. 9A) [175]. In addition, PINK1 and Parkin participate in regulating the quality control mechanisms of mitochondria, including their clearance and repair. When mitochondria become damaged, excessive ROS release exacerbates intracellular oxidative stress. PINK1 can be activated and translocated to damaged mitochondria, recruiting the Parkin protein. Activation of Parkin protein can trigger the processes of mitochondrial repair or elimination. By activating PINK1 and Parkin proteins, the population of healthy mitochondria can be increased, promoting the repair or removal of damaged mitochondria. For example, SIRT1 attenuated mitochondrial dysfunction and cellular senescence through

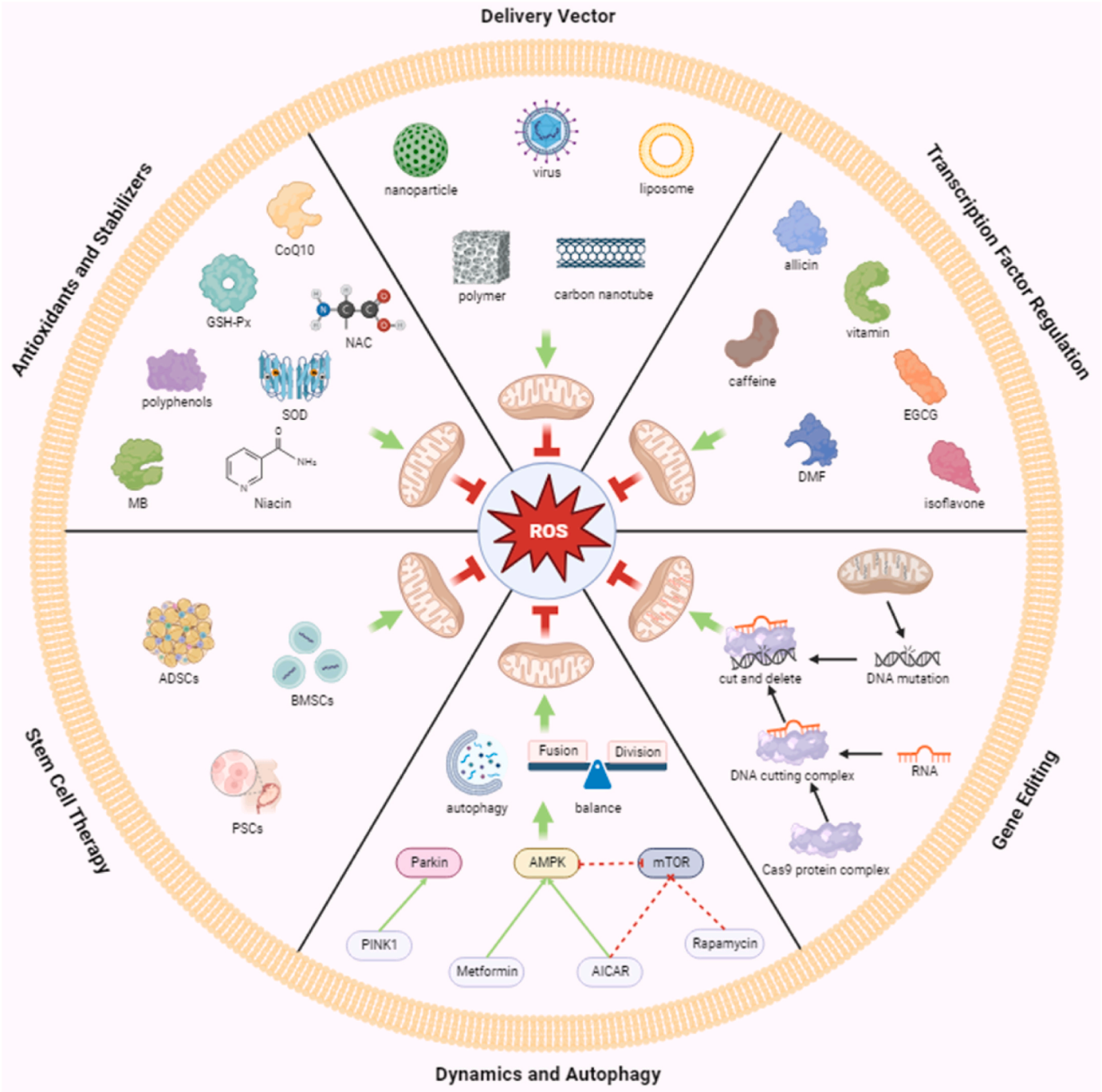

Fig. 10. Schematic illustration of the therapeutic potential of ameliorating oxidative stress-induced IVDD through mitochondria. CoQ10: coenzyme Q10, GSH: glutathione, NAC: N-acetylcysteine, SOD: superoxide dismutase, ADCSs: adipose-derived stem cells, BMSCs: bone marrow-derived stem cells, PSCs: placental-derived stem cells, EGCG: epigallocatechin 3-gallate.

PINK1-dependent mitophagy (Fig. 9B) [176]. In addition to the above proteins, the downregulation of leucine-rich repeat kinase 2 could inhibit oxidative stress-induced apoptosis via mitophagy (Fig. 9C) [177]. These, in turn, slow down the further damage caused by the release of ROS from impaired mitochondria, thereby improving IVD health [178–180] (Table 2).

In addition to the above strategies, there are other complementary approaches to further enhance mitochondrial dynamics and autophagy [93]. For example, physical therapies, such as heat, cold, and electrotherapy, can improve mitochondrial function by modulating factors such as temperature, metabolism, and electrical potential within the cell. In addition, specific pharmacological interventions targeting mitochondria are also a hot topic of research. Some herbs and natural products may have the potential to modulate mitochondrial function and autophagic pathways [181]. However, these methods are still in the research phase and require more validation and clinical practice (Fig. 10).

7.7. Research gaps and future directions

In the research on targeting mitochondria to alleviate oxidative stress in the treatment of intervertebral disc degeneration, several methods such as antioxidants, transcription factor regulation, stem cell therapy, carrier delivery systems, gene editing technologies, and

Table 3
The advantages and disadvantages of various approaches targeting mitochondria to relieve oxidative stress in the treatment of IVDD and the Research Gaps and Future Directions.

Method	Advantages	Disadvantages	Research Gaps and Future Directions
Mitochondrial antioxidants and protectants	1 Directly target mitochondria, reducing oxidative stress 2 Significantly improve the function and structure of intervertebral discs 3 Suitable for long-term treatment strategies	1 Possible non-specific effects 2 Long-term use may result in drug resistance 3 Wide variation in individual response	1 To develop a new generation of highly effective and low-toxic mitochondrial antioxidants 2 To assess the safety and side effects of long-term use 3 xplore more appropriate dosage and utilization modes
Transcription factor regulation	1 Globally regulates gene expression 2 Regulating multiple signaling pathways 3 Potential to improve the overall cellular microenvironment	1 Difficult to precisely control the regulatory network 2 May cause unpredictable side effects 3 Unstable regulatory effects	1 Discovering new transcription factors to improve the accuracy of regulation 2 Deepen the research on the mechanism of action of transcription factors 3 Developing technologies to monitor transcription factor activity in real time
Stem cell therapy	1 Capable of self-renewal and multi-directional differentiation 2 Repair and regeneration of intervertebral disc tissue 3 Potential for radical healing	1 Stem cell source and differentiation efficiency issues 2 Immune rejection and ethical issues 3 High cost of treatment	1 Exploring new stem cell sources and culture techniques 2 Researching ways to improve the efficiency and survival rate of stem cell transplantation 3 Promoting the clinical translation and standardization of stem cell therapy
Carrier delivery system	1 Enables precise drug delivery 2 Controlled release mechanism to improve treatment durability and efficacy 3 Applicable to a wide range of drugs and therapeutic regimens	1 Complex vector design and preparation technology 2 Need to ensure the biocompatibility and safety of the carrier 3 High cost, difficult to apply on a large scale	1 Developing new efficient and low toxicity carrier materials 2 Explore the best match between carriers and drugs 3 Reduce the production cost of carrier delivery systems
Gene editing technology	1 Capable of precisely modifying mitochondrial or related gene sequences 2 Capable of achieving long-lasting therapeutic effects 3 Potential for radical healing	1 High technical difficulty and off-target risk 2 Facing ethical and legal challenges 3 May cause unknown genetic problems	1 Improving the accuracy and safety of gene editing 2 Exploring best practices in the clinical application of gene editing technologies 3 Strengthening ethical and legal frameworks
Promotes mitochondrial dynamics and autophagy	1 Helps to restore mitochondrial function 2 Removes damaging substances through autophagy and reduces oxidative stress 3 Enhances the efficiency of cellular metabolism	1 The regulation mechanism is not yet fully clarified 2 The therapeutic effect may vary according to individual differences. 3 May interfere with normal cell function	1 To study in depth the regulatory mechanisms of mitochondrial dynamics and autophagy 2 To develop drugs that can accurately regulate mitochondrial dynamics and autophagy 3 Explore strategies for combining with other therapeutic agents.

modulation of mitochondrial dynamics and autophagy have shown significant potential. However, notable research gaps remain. Specifically, the long-term safety and efficacy of existing mitochondrial antioxidants and protectants require further clinical validation. The regulatory mechanisms of transcription factors still need more in-depth study. Stem cell therapy faces challenges related to cell survival, differentiation efficiency, and long-term outcomes. Carrier delivery systems need improvements in targeting accuracy and delivery efficiency. Gene editing technologies must overcome issues of precision and safety. Additionally, the mechanisms of mitochondrial dynamics and autophagy regulation are not yet fully understood. Future research should focus on optimizing treatment methods, elucidating underlying mechanisms, enhancing technological efficiency, and exploring combined therapeutic strategies to achieve more effective and safer interventions for intervertebral disc degeneration (Table 3).

8. Conclusion and future perspectives

ROS, including O2·-, H_2O_2, and ·OH, can oxidize structural proteins in mitochondria, leading to increased permeability of the mitochondrial membrane and interference with mitochondrial fusion and fission processes, consequently damaging and reducing mitochondrial function [97]. Additionally, excessive ROS can interfere with mitochondrial signaling pathways, inhibit mitophagy, and exacerbate the progression of IVDD [202]. As mitochondria serve as cellular energy production centers, the functional integrity of the mitochondrial respiratory chain is essential for normal cellular physiological activity. However, excessive ROS can inhibit energy production by oxidizing key proteins in the respiratory chain, interfering with complex assembly, etc [97]. Thus, excessive ROS affect mitochondrial function in multiple ways.

Oxidative stress plays a crucial role in the process of IVDD. The intensification of IVDD will further promote the formation of oxidative stress, creating a vicious cycle [203]. Understanding the mechanisms of oxidative stress is of great significance in the search for therapeutic strategies for IVDD. There exists a close relationship between oxidative stress and IVDD. Oxidative stress is an imbalance caused by an increase in intracellular free radicals and ROS. These free radicals and excessive ROS can damage components such as mitochondrial DNA, proteins, and lipids, resulting in mitochondrial dysfunction [204]. Impaired mitochondrial function leads to disruptions in energy metabolism and redox balance, ultimately contributing to cellular functional degradation and matrix degradation in IVD [205].

Treatment strategies targeting mitochondria for oxidative stress-induced IVDD have attracted a lot of research attention. Antioxidants are used to alleviate oxidative stress reactions and protect cells from the harmful effects of excessive ROS. Furthermore, mitochondrial protectants are being explored for their potential to repair and safeguard mitochondrial function, thereby delaying the progression of IVDD [206,207]. Nrf2, as a transcription factor, plays a crucial role in regulating oxidative stress response within cells. When cells are exposed to oxidative stress, Nrf2 is activated and translocates to the cell nucleus, initiating the transcription of a series of antioxidant and cell-protective genes. Activation of the Nrf2 signaling pathway is considered a potential therapeutic approach in the treatment of IVDD [32]. In addition, stem cells, such as ADSCs, BMSCs, and PSCs are believed to be a promising new approach for the treatment of IVDD, as they can alleviate mitochondrial oxidative stress through various mechanisms [208]. Various novel delivery systems, such as nanoparticles, viral vectors, liposomes, as well as gene editing technologies like the CRISPR-Cas9 system, are also being increasingly used for the

treatment of mitochondrial dysfunction and IVDD caused by excessive ROS [54,209,210].

In recent years, various compounds and novel carrier delivery systems have been designed to target mitochondria and ameliorate oxidative stress-induced IVDD. However, most of the research has focused only on surface-level investigations, such as in vitro studies, lacking in vivo experiments on animal models [182,189,211]. While some studies have verified the reparative effects of proteins both in vitro and in vivo, the specific molecular mechanisms remain unclear [188,189,212]. Moreover, there is a lack of evidence regarding the treatment efficacy of existing therapeutic strategies in human patients. Further clinical trials are needed to demonstrate the feasibility of targeted mitochondrial therapy for oxidative stress-induced IVDD in humans.

In summary, oxidative stress and ROS lead to cellular damage and inflammatory responses that accelerate the development of IVDD. Mitochondrial dysfunction plays a key role in this, as mitochondria are not only a major source of ROS, but also play an important role in the redox homeostasis of cells. Studies targeting mitochondria have been found to show great promise in alleviating oxidative stress-induced IVDD. Mitochondria have the ability to regulate ROS generation and scavenging; therefore, improving mitochondrial function may help to mitigate the damage of oxidative stress on intervertebral disc tissues. This direction of research not only helps to reveal the specific mechanism of oxidative stress in IVDD, but also offers the possibility of developing new therapeutic strategies, which is important for the development of effective preventive and therapeutic strategies. Interventions that target mitochondria may help slow the progression of IVDD and improve patients' quality of life. Further research will be key, aiming to delve into the specific role of mitochondria in IVDD and develop targeted therapies. This will provide IVDD patients with more effective treatment options, which in turn will improve their overall health to address this global challenge.

CRediT authorship contribution statement

Z.H., W.C.Y, J.Y.X, and W.O.Q contributed equally to this work. Hao Zhou: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. Chenyu Wu: Formal analysis, Investigation, Writing – review & editing. Yuxin Jin: Conceptualization, Writing – review & editing. Ouqiang Wu: Formal analysis, Investigation, Writing – review & editing. Linjie Chen: Investigation. Zhenyu Guo: Formal analysis. Xinzhou Wang: Conceptualization. Qizhu Chen: Formal analysis. Kenny Yat Hong Kwan: Investigation. Yan Michael Li: Methodology. Dongdong Xia: Validation. Tao Chen: Supervision, Writing – review & editing. Aimin Wu: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

Authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Some of the diagrams were created with BioRender.com.

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