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# *Endoplasmic Reticulum Stress in Intervertebral Disc Degeneration: Mechanisms and Research Progress*

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***Abstract.*** Intervertebral disc degeneration (IDD) is the underlying cause of many spinal diseases, such as disc herniation and chronic low back pain. The pathogenesis of IDD has been the focus of many studies, but its underling mechanisms are complex and not totally clear. Disrupted cells with deficient protein folding capacity or intracellular degradation equilibrium will elicit endoplasmic reticulum stress (ERS), and ERS has recently attracted considerable attention for its pervasive regulatory role in cell function. To respond to this stress, activation of the unfolded protein response (UPR) modifies the function of cell by tuning intracellular processes, including programmed cell death, autophagic flux, inflammatory signalling, metabolic modulation and so on. Increasing evidence has emerged indicating the role of endoplasmic reticulum stress (ERS) in promoting IDD mainly through modulating cellular integrity and extracellular matrix. Such information endows ERS as a potential target for future treatment of IDD. Collectively, we summarize current knowledge about ERS-related mechanisms in IDD and describe emerging intervention strategies, with the aim to contribute to the knowledge and to guide clinical management of IDD.

***Keywords:*** endoplasmic reticulum stress, intervertebral disc degeneration, nucleus pulposus, annulus fibrosus, cartilage endplate

## 1. Introduction

Progressive disc degeneration of intervertebral discs (IDD) is closely linked to chronic low back pain, a disabling complaint that limits functional capacity and that imposes a considerable societal and economic burden [1]. Yet despite huge advances, a full understanding of the mechanisms underlying IDD still remains limited. There is increasing evidence for the involvement of a number of cellular stress responses in IDD progression. Cells rely very much on the endoplasmic reticulum (ER), which controls protein quality control and intracellular calcium homeostasis. If the demand for protein-folding is higher than cellular capacity—because of disorders of calcium homeostasis, redox status, for example—ER activity is perturbed and the unfolded protein response (ERS) and the cellular stress response is activated to restore cellular homeostasis [2]. However, too persistent and excessive stress lead to cell death, failure in extracellular matrix metabolism and tissue damage.

ERS has been implicated in diverse pathological states such as metabolic disorders, neurodegenerative diseases and tumours, revealing its extensive influence in biological processes. In

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IDD, ERS plays distinct roles in disease progression and is related to many pathological events. In the pathogenesis of IDD, pathological responses of ERS can reflect different aspects such as increased loss of disc cells, out-of-balance extracellular matrix restructuring, and increased inflammatory responses in the local microenvironment [3]. Therefore, a better understanding of the molecular mechanisms of ERS in IDD can provide clues to potential therapeutic effects.

## 2. Molecular mechanisms and regulatory network of endoplasmic reticulum stress

### 2.1. Triggers and signaling pathways of endoplasmic reticulum stress

Protein maturation, lipid synthesis and $Ca^{2+}$ regulation are closely coupled in the ER, demonstrating its importance in maintaining cellular function [4]. Many stresses (for example, hypoxia, oxidative imbalance, and inflammatory stimuli) can interfere with ER function and result in an increase of aberrant protein production, thus inducing stress responses in ER [2].

Protein maturation disturbed by increased protein synthesis load, synthesis or expression of mutant proteins and/or inactivation of protein glycosylation, $Ca^{2+}$ imbalance, $Ca^{2+}$ storage and signalling in ER affecting the environment for protein folding all disturb the environment for protein maturation [5]. In addition, oxidative stress leads to production of superoxide, which affects the redox environment for protein maturation and disturbs ER homeostasis [6].

Onset of ER stress unleashes a programmed combination of adaptive responses, collectively known as the unfolded protein response (UPR) that rebalances cellular conditions and reestablishes normal ER function. Three ER-localized transmembrane proteins, namely IRE1α, PERK and ATF6, are the master regulators of the UPR. Using different sensing mechanisms, they read out perturbation of protein folding in the ER and engage signalling modules that attenuate the stress and restore the cell.

On activation, IRE1α uses both its kinase and its endoribonuclease activity to splices XBP1 mRNA to give the active splice variant. As part of this response, the cell upregulates genes involved in enhancing protein handling and degradation in the ER. Likewise, PERK induces eIF2α through phosphorylation and downregulates global translation, limiting the biosynthesis of nascent polypeptides in the ER lumen. This signalling axis also drives selective ATF4 production, which drives central processes for stress adaptation and influences cell survival and cell death.

Meanwhile, under ER stress, ATF6 is translocated to the Golgi compartment and then is cleaved sequentially by S1P and S2P to yield an active N-terminal fragment. The fragment translocates to the nucleus and regulates gene expression related to stress responses. The coordinated functioning of these pathways mediate chaperone production, thus reinforcing the ER's capacity to cope with protein-folding demands. The same pathways also mediate the degradation of protein by the ER-associated degradation pathway and other mechanisms, relieving ER stress [7].

### 2.2. Endoplasmic reticulum stress and cell fate determination

ERS not only prevents the death of cells but also determines cell fate. Cellular responses to ERS have the effect of adapting cell survival or apoptosis. The balance between adaptation and apoptosis are critical in ensuring tissue homeostasis and influencing disease development [4]. The adaptive response mainly involves activation of UPR to restore the capacity for protein folding and regulating cellular metabolism to boost survival of cells. But, when ERS is persistent or persistent, cells switch from an adaptive response to apoptosis to clear irreversibly damaged cells.

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Apoptosis stimulated by ER stress is mostly elicited by CHOP and Caspase-12. Factors such as CHOP and Caspase-12 induce apoptotic responses upon ER stress, and are mostly controlled by factors (such as the CHOP generated downstream of PERK–eIF2α–ATF4). Under stress condition, CHOP is substantially induced by stress and controls transcription activities by inducing pro-death genes and repressing anti-apoptotic signals, thus contributing to cell death [8]. Caspase-12 is one particular signalling protein exists in the ER membrane, and the ER severe stress induces Caspase-12 to initiate downstream caspase activation and ultimately causes apoptosis [9].

Moreover, ERS can induce pyroptosis to intensify inflammatory responses and modify the tissue injury and healing [10]. Recently, a study shows that ERS affects the cell fate through regulating the crosstalk of autophagy and apoptosis. Early in ERS, autophagy protects cells by breaking down misfolded protein and damaged organelles. However, persistent ERS stress or low level and even high level of autophagy activity promote cell apoptosis. Moreover, ERS can modulate immune responses and inflammatory microenvironment, regulate the progression of many diseases and cell fate.

## 3. Mechanisms of ERS in IDD

### 3.1. ERS-induced apoptosis of intervertebral disc cells

Loss of intervertebral disc cells is a central pathology of IDD, and ER stress–mediated apoptosis is an important driving force in the development of IDD. Previous studies showed that ERS induced disc cell apoptosis by the PERK signalling pathway to induce CHOP expression [11]. In particular, PERK signalling pathway activation causes eIF2α to be phosphorylated, thus inhibiting global protein translation, decreasing protein-folding load of ER and increasing stress protein translation (such as activated ATF4 and CHOP). CHOP functions downstream of ER stress and drives apoptosis by shifting the transcriptional control towards the pro-death pathways, suppressing antipathogenic defences and increasing apoptosis sensitivity.

Other related papers indicated that, under the mechanical stretching condition, the ROS content of AF cells is increased, along with obvious activation of the PERK–CHOP pathway and the strong enhancement of apoptosis of disc cells. Downregulation of CHOP activity—either with RNA interference or with the ER stress inducer 4-PBA—could reverse the apoptosis of disc cells, and downregulate proteins involved in ER stress signalling. Such results would functionally prove the functional role of the PERK–CHOP pathway to the apoptosis of disc cells [12].

Apoptosis-induced loss of disc cells in IDD lowers the regenerative potential and the capacity for homeostatic function of discs, leading to degradation of disc structure and disc dysfunction. Besides, the signals derived from apoptotic cells can induce inflammation of the surrounding cells and exacerbate degenerative change. Research results on the markers of ERS in vivo, apoptosis markers and the clinical symptoms of disc degeneration are markedly up-regulated and accompanied by disc degeneration pathological changes [13]. These results in vitro also suggest that mechanical stress or high glucose-induced ERS of disc cells can lead to disc cell apoptosis, but ERS inhibitor can reverse the induction of disc cell apoptosis in disc cells and further reinforce the relation between ERS and disc cell apoptosis [14].

### 3.2. ERS-mediated inflammatory response and IDD

Besides causing cell death, ERS also stimulates cytokines to elicit inflammatory response and hence promotes IDD progress. Among all the pathways, the NF-κB signalling pathway is one of the key

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signalling pathways that drive the inflammation induced by ERS. Studies have shown that after inducing ERS, ER stress sensor molecule IRE1α can activate the NF-κB pathway through downstream mediator molecule TRAF2 and other molecules, increasing the amount of IL-1β and TNF-α [15]. In addition, ERS can induce oxidative stress and abnormal calcium homeostasis, further promote the production of inflammatory factors, producing positive feedback aggravating tissue damage.

Immune cells impact IVD cell function and induce ECM degradation of IVD cells, thus promoting damage and loss of structure and function of the disc. For example, IL-1β and TNF-α can induce IVD cell expression of matrix metalloproteinase (MMP) to accelerate collagen and proteoglycans degradation and alter ECM homeostasis. Immune cell infiltration is another feature of inflammation of degenerated discs. ERS impairs macrophage function and cytokine release that in turn regulate immune cell infiltration and activation of disc cells, contributing to the inflammatory microenvironment of disc degeneration [16].

### 3.3. Effects of ERS on extracellular matrix metabolism in intervertebral discs

Metabolic balance of the ECM is important for structural stability and function of the intervertebral disc. By changing the balance between the activity of MMP and TIMP-mediated inhibition, ERS contributes to disrepair of ECM remodeling, which facilitates the onset and progression of IDD. Research has shown that after activation of ERS, expression of MMP3 and MMP9 of disc cells increases and TIMP decreases, leading to over-expression of collagen and proteoglycans [17]. In this way, the mechanical strength of the disc is decreased and protective role of ECM is destroyed. Meanwhile, the inflammatory cytokines are increased and the oxidative stress is worsened, which aggravate ERS, forming a vicious circle. ERS also affects ECM production. ERS can decrease the matrix protein expression level-associated gene synthesis by different transcription factors and different pathways, leading to reduced ECM synthesis. Recent studies showed that activation of ERS-related protein CHOP not only leads to cell apoptosis, but also inhibits collagen synthesis and induces collagen imbalance in terms of ECM synthesis and degradation [18].

In addition, ERS is closely related to autophagy as well. Mild autophagy could alleviate ERS and keep the balance of ECM homeostasis, but sustained and exaggerated ERS might suppress autophagic activity, leading to intracellular accumulation of damaged proteins and debris with metabolic waste, which further induces ECM degradation and cell dysfunction and induces IDD further [19].

## 4. ERS-related therapies and future prospects

### 4.1. Current status of drug development targeting ERS

ERS contributes to initiating and eliciting many diseases. In the past few years, advances have been made for designing drugs to tune ERS. Present studies suggest that there is therapeutic potential for the ERS inhibitors for some models of diseases. Studies show that the ER stress inhibitors 4-PBA and TUDCA are 'chemical chaperones' that aid folding of proteins, attenuate accumulation of misfolded proteins and relieve ER stress and hence prevent apoptosis and tissue injury. Zhang et al. [20] reported in a model of retinal degenerative disease that 4-PBA and TUDCA reduced ER stress-associated inflammation and death by enhancing protein-folding capacity and implying a promising therapeutic potential. Similarly, a potential clinical value of targeting ER stress strategy is clear from studies for heart failure.

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Along with traditional chemical chaperones, a series of small molecule compounds and natural compounds with potential effects on ERS emerge. Multiple bioactive natural products have been shown to protect by altering the signalling pathway of ER stress-related events. Teng et al. [12] showed that the extract of brown seaweed fucoxanthin could protect against ER stress and delay the development of IDD by upregulation of the expression of Sirt1 and suppression of PERK–eIF2α–ATF4–CHOP signalling pathway.

Some natural compounds (such as quercetin and pinosylvin) have also been shown to modulate ER stress and signalling pathways that cause ER stress in an anti-inflammatory, antioxidant and cytoprotective manner. Some of the synthetic small-molecule drugs with anti-cancer properties also induce ER stress as an antitumour effect in cancer treatment. Pharmacological compounds that interfere with ER stress sensors (for example, XBP1 and IRE1) have also been developed as therapeutic strategies for lung and breast cancer [21].

Despite these advances, we have other challenges still towards development of ERS-targeted therapies, such as safety, efficacy and clinical issues. Many compounds for ER stress targeting, such as inhibitors of the activity of an ER stress-related IRE1 RNase, produce undesired side effects in clinical trials and therefore cannot be used further. Another challenge of ER stress signalling pathways is complexity, that can lead to drug resistance or undesired drug effects. Hence, effective and safe modulation of ER stress without damaging the normal cell activity remains the major challenge in future development of drugs.

### 4.2. Gene regulation and cell-based therapeutic strategies

Gene regulation technologies provide promising opportunities for the ERS-related therapies. Among gene-editing technologies, the CRISPR-Cas9 gene editing technology is the gene regulation tool for precise regulation of ER stress-related genes. Gene target knockout or modification of key genes, CHOP and XBP1, regulates cellular stress response, alleviate cell apoptosis and promote regeneration of tissues. It has been shown to regulate the PERK/NOXA/MCL-1 axis in IDD models effectively to reduce the ERS-induced apoptosis and retard progress of disc degeneration [18]. Besides, gene regulation strategy can also have a positive impact on stem cell-based therapy.

Recently, the combination of stem cell therapy and ER stress reduction has been given special attention. MSC and its exosomes have been shown to reduce ER stress through different mechanisms, and facilitate cell survival and tissue repair. The exosomes prepared by MSCs were shown to inhibit stress-induced ERS and apoptosis of disc cells through AKT and ERK signalling pathways, and gradually ameliorate the degeneration of the intervertebral discs [11]. Exosomes derived from urine stem cells could attenuate the ER stress and protect disc cells, with promising clinical applications. EVs, mediators of intercellular communication as described above, also regulate ER stress. EVs released by MSC (mainly miRNAs and proteins) are loaded with miRNAs and proteins to reduce expression of ER stress-regulating genes, thus inhibiting inflammation and apoptosis. MSC-derived EVs can mediate the transfer of ERS–regulating miRNAs to target cells, causing a significant decrease in apoptosis induced by ERS in human corneal endothelial cells, thus deserving a therapeutic application [22].

Gene regulation and cell-based therapies both have promising prospects, however, at present many challenges remain, such as safety, delivery and immune response. Efforts for further studies should be focused on improving the precision and safety of the gene editing technology and enhancing the targeting delivery and functional stability of stem cells and their EVs for clinical application in the next stage.

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## 5. Conclusion

ERS plays an important role in maintenance of intervertebral disc homeostasis by modulating apoptosis, inflammation and matrix turnover, but it also participates in progression of IDD by multiple signalling mechanisms when deregulated. Differences might be seen in reported pathway activation and regulated targets due to some different used models and sample heterogeneities. Further research on this subject should use multicentre and multimodal studies to better delineate the dynamic changes of ERS and the interactive effects with other cellular stress responses. From the perspective of translation, inhibiting ERS can relieve apoptosis, inflammation and matrix imbalance. The evidence at present is mostly preclinical, and more clinical evidence is required. Complete modulation of ERS and reducing side effects remains challenging. Advanced techniques and other interdisciplinary methods might also help to translate ERS-targeting therapies into clinics and upgrade IDD therapies.

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