

REVIEW

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# Insights into the underlying pathogenesis and therapeutic potential of endoplasmic reticulum stress in degenerative musculoskeletal diseases

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## Abstract

Degenerative musculoskeletal diseases are structural and functional failures of the musculoskeletal system, including osteoarthritis, osteoporosis, intervertebral disc degeneration (IVDD), and sarcopenia. As the global population ages, degenerative musculoskeletal diseases are becoming more prevalent. However, the pathogenesis of degenerative musculoskeletal diseases is not fully understood. Previous studies have revealed that endoplasmic reticulum (ER) stress is a stress response that occurs when impairment of the protein folding capacity of the ER leads to the accumulation of misfolded or unfolded proteins in the ER, contributing to degenerative musculoskeletal diseases. By affecting cartilage degeneration, synovitis, meniscal lesion, subchondral bone remodeling of osteoarthritis, bone remodeling and angiogenesis of osteoporosis, nucleus pulposus degeneration, annulus fibrosus rupture, cartilaginous endplate degeneration of IVDD, and sarcopenia, ER stress is involved in the pathogenesis of degenerative musculoskeletal diseases. Preclinical studies have found that regulation of ER stress can delay the progression of multiple degenerative musculoskeletal diseases. These pilot studies provide foundations for further evaluation of the feasibility, efficacy, and safety of ER stress modulators in the treatment of musculoskeletal degenerative diseases in clinical trials. In this review, we have integrated up-to-date research findings of ER stress into the pathogenesis of degenerative musculoskeletal diseases. In a future perspective, we have also discussed possible directions of ER stress in the investigation of degenerative musculoskeletal disease, potential therapeutic strategies for degenerative musculoskeletal diseases using ER stress modulators, as well as underlying challenges and obstacles in bench-to-beside research.

**Key words** Endoplasmic reticulum stress, Degenerative musculoskeletal diseases, Pathogenesis, Treatment

## Background

Degenerative musculoskeletal diseases refer to the structural and functional failures of muscle, bone, cartilage, joint, and surrounding connective tissue, resulting in weakness and motor dysfunction in patients[1]. Osteoarthritis (OA), osteoporosis (OP), intervertebral disc degeneration (IVDD), and sarcopenia (SP) are common musculoskeletal degenerative diseases with similar age-related risk factors[2-5]. OA, the most common degenerative joint disease globally, is characterized by pain and constrained activity, leading to a significant reduction in the quality of life[2,6]. OP is a dominating public health concern worldwide with distinguishing features of reduced bone mass, microstructural degeneration, decreased bone rigidity, and

high risk of fracture[3,7]. As the major contributor to low back pain and disability, IVDD is generally believed to be caused by the structural damage and low-grade inflammation of intervertebral disc (IVD) elicited by senility[4,8]. SP is a systemic and deteriorating skeletal muscle disease that clinically manifests an accelerated decrease in muscle mass and strength, further increasing the risk of physical function decline[5]. With the acceleration of the global aging process, degenerative musculoskeletal diseases are becoming increasingly prevalent, which has created additional social and economic burden. Meanwhile, the rapid development of the economy and society promotes the human desire for health and longevity, making aging research unprecedentedly prosperous[9]. Unfortunately, there is still a lack of treatments for delaying or halting the progression of degenerative musculoskeletal diseases in clinical practice. Although a large number of studies have been carried out and a series of tremendous advances have emerged in the past few decades, the detailed pathogenesis of degenerative

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musculoskeletal disease is still not fully understood, hindering the research and development of effective and safe therapeutic approaches.

Endoplasmic reticulum (ER) is mainly responsible for protein synthesis, folding, and structural maturation, maintaining the activity and function of more than one-third of proteins in eukaryotic cells[10]. ER stress occurs when the aforementioned faculties of the ER are impaired and brings about the accumulation of misfolded or unfolded proteins in the ER[11]. Of note, since the ER is in charge of intracellular calcium ( $\text{Ca}^{2+}$ ) storage, perturbations of  $\text{Ca}^{2+}$  homeostasis can also contribute to ER stress[12]. To protect themselves from ER stress, eukaryotic cells have developed an evolutionarily conserved adaptive mechanism, including the unfolded protein response (UPR) and the ER-associated degradation (ERAD) pathways[13]. Both of these intracellular adaptive responses are triggered by ER stress in response to malfunctions during protein synthesis, folding, and structural maturation, serving as protein quality control programs[14]. Upon mild ER stress, the UPR and ERAD are activated and restore ER homeostasis by removing misfolded and unfolded proteins. However, excessive ER stress beyond the compensatory capacity of UPR and ERAD pathways gives rise to cellular dysfunction and even cell death[14]. Given its decisive role in cellular function and fate, ER stress has increasingly emerged as a significant contributor to the pathogenesis of various diseases, including neurodegenerative disorders, atherosclerosis, diabetes, and cancers[11,15-17]. In recent years, there has been a growing focus on unraveling the implications of ER stress in degenerative musculoskeletal diseases and their treatment.

Herein, we will compile a comprehensive and thorough summary of updated research findings regarding ER stress in the pathogenesis and progression of degenerative musculoskeletal diseases (including OA, OP, IVDD, and SP) to clarify the underlying mechanisms involved and put forward several prospects for future research in this field. We will also discuss the therapeutic potential of treating degenerative musculoskeletal diseases by regulating ER stress and the remaining challenges in bench-to-beside investigations to provide novel strategies and solid rationale for the future development of curative means for degenerative musculoskeletal diseases.

### ER stress signaling pathways

ER is the largest membrane-bound organelle in eukaryotic cells and is mainly responsible for protein and lipid synthesis, detoxification, and intracellular  $\text{Ca}^{2+}$  storage[18]. The initial steps of protein maturation that occur in the ER are essential

for protein synthesis, and more than one-third of proteins in eukaryotic cells are folded and structurally matured in the ER[10]. Because of its robust protein-processing capacity, the ER bears a significant workload in cells with high secretory demands, making these cells more susceptible to ER stress[16]. Usually, pro-inflammatory cytokines, oxidative stress, hypoxia, nutritional deficiency, and low pH easily induce ER stress[6,14]. Once ER stress is activated by the aforementioned stimuli, intracellular adaptive responses, including UPR and ERAD, are triggered to eliminate misfolded and unfolded proteins and reestablish ER homeostasis[14]. The UPR alleviates ER stress primarily by inhibiting protein synthesis and increasing chaperone expression to aid in the refolding of misfolded and unfolded proteins, whereas ERAD mainly degrades misfolded and unfolded proteins through the ubiquitin-proteasome pathway.

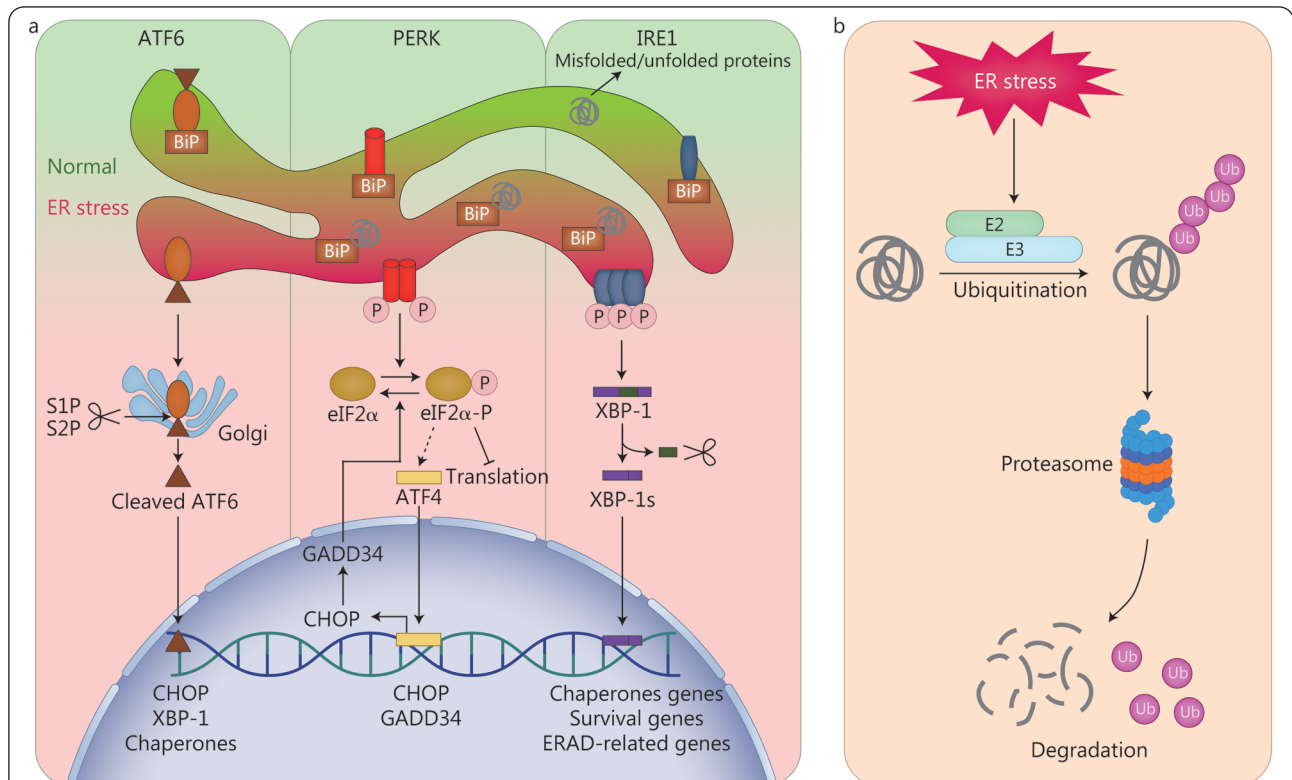
Generally, three transmembrane proteins located on the ER membrane, including activating transcription factor 6 (ATF6), protein kinase R-like ER kinase (PERK), and inositol-requiring enzyme 1 (IRE1), are responsible for mediating the activation of the UPR induced by ER stress[19] (Fig. 1a). All of these stress sensors of the UPR share a similar structure consisting of an ER luminal domain for sensing stress, a transmembrane domain, and a cytoplasmic domain with enzymatic activity[20]. Glycoprotein 78 kD glucose-regulated protein (GRP78), also known as binding immunoglobulin protein (BiP), is a major ER chaperone[21]. Under physiological conditions, GRP78/BiP binds to the ER luminal domains of ATF6, PERK, and IRE1 to inactivate UPR[19]. Upon the protein-processing function of the ER is impaired, GRP78/BiP dissociates from the stress sensors and interacts with misfolded and unfolded proteins to prevent their aggregation and assist them in refolding accurately, which in turn activates three UPR branches[22]. Furthermore, all the UPR branches can be sensitized by the direct combination of stress sensors to unfolded proteins as well[23].

ATF6 is a transcription factor that is transferred to the Golgi complex and cleaved by site-1 and -2 membrane proteases upon activation[24]. Cleaved ATF6 exhibits transcriptional activity and facilitates the transcription of genes encoding C/EBP homologous protein (CHOP), X-binding protein 1 (XBP-1), and chaperones in the nucleus[25]. In the second branch of the UPR, translation initiation is blocked by PERK through phosphorylation of the  $\alpha$ -subunit of eukaryotic translation initiation factor 2 (eIF2 $\alpha$ ), which reduces the risk of continued accumulation of misfolded and unfolded proteins to exacerbate ER stress[26]. However, activating transcription factor 4 (ATF4) mRNA is preferentially translated *via* escaping PERK-

mediated translational blockade[27]. Consequently, ATF4 and its downstream target, CHOP, are upregulated whereas other proteins are downregulated[28]. CHOP modulates the expression of several UPR-related genes in response to ER stress by interacting with other transcriptional regulators; it is also a key determinant of cell fate[11,29]. Growth arrest and DNA damage-inducible protein 34, a substrate-specific regulatory subunit of the holo-phosphatase complex induced by CHOP, can dephosphorylate phosphorylated eIF2 $\alpha$ , thereby restoring protein translation and inhibiting ATF4 translation[11]. IRE1 is the most conserved component of the UPR in evolution because it exists in animals, plants, and *Saccharomyces cerevisiae*[30]. In IRE1 branch, misfolded and unfolded proteins are cleared by the upregulation of chaperones and ERAD-related proteins to mitigate ER stress. The cytoplasmic domain of IRE1 possesses serine/threonine kinase and endoribonuclease activities[31]. Upon activation, IRE1 unconventionally splices mRNA encoding XBP-1 through its highly sequence-specific serine/threonine kinase and endoribonuclease activities[32]. Spliced XBP-1 (XBP-1s) encourages the translation of chaperones genes,

survival genes, and ERAD-related genes, while unspliced XBP-1 suppresses their translation[23]. IRE1 can also attenuate protein translation and induce cell death by degrading mRNAs localized on the ER membrane through its serine/threonine kinase and endoribonuclease activities, which is called regulated IRE1-dependent decay[33]. Additionally, phosphorylated IRE1 is capable of binding to tumor necrosis factor receptor-associated factor 2 to recruit apoptosis signal-regulating kinase 1, which in turn activates the c-Jun N-terminal kinase (JNK) pathway[34]. The IRE1-apoptosis signal-regulating kinase 1-JNK pathway is activated by excessive ER stress and is closely related to apoptosis[35].

In the ERAD pathway, misfolded and unfolded proteins are transported into the cytoplasm and ubiquitinated by E2 ubiquitin-conjugating enzymes and E3 ubiquitin ligases[36]. Subsequently, the cytoplasmic 26 S proteasome system recognizes and degrades misfolded and unfolded proteins labeled by ubiquitination[36] (Fig. 1b). Apart from the UPR and ERAD, ER stress activates autophagy, which is another protein degradation pathway[37]. During autophagy, damaged macromolecules and organelles are encapsulated in vesicles and



**Fig. 1 Mechanisms of the UPR (a) and ERAD (b) pathways.**

ATF4. Activating transcription factor 4; ATF6. Activating transcription factor 6; BiP. Binding immunoglobulin protein; CHOP. C/EBP homologous protein; eIF2 $\alpha$ .  $\alpha$ -subunit of eukaryotic translation initiation factor 2; ER. Endoplasmic reticulum; ERAD. ER-associated degradation; GADD34. Growth arrest and DNA damage-inducible protein 34; IRE1. Inositol-requiring enzyme 1; P. Phosphorylated; PERK. Protein kinase R-like ER kinase; S1P. Site-1 membrane proteases; S2P. Site-2 membrane proteases; XBP-1. X-binding protein 1; XBP-1s. Spliced XBP-1; Ub. Ubiquitin

transported to lysosomes for degradation and recycling[13]. Excessive ER stress or suppressed UPR, ERAD, and autophagy may contribute to cellular dysfunction or apoptosis.

### ER stress in the pathogenesis of OA

As the most prevalent joint disease worldwide, OA is the leading causation of pain and disability[2]. Although previously considered as a degenerative disease of cartilage, increasing evidence has transformed the general understanding of OA into a whole-joint disease covering cartilage degeneration, synovitis, meniscal lesion, subchondral bone remodeling, ligament degeneration, and skeletal muscle degeneration[38] (Fig. 2a). The risk factors for OA are numerous, including aging, obesity, gender, diabetes, and injury, among which aging is the most critical[39]. About 10% of men and 18% of women over 60 years old are affected by OA, and the prevalence of OA increases rapidly with age, resulting in an enormous socioeconomic burden due to increased medical needs and disability-induced early retirement[2,6]. So far, the clinical treatment for OA is symptomatic and mainly consists of pain management in the early stages and artificial joint replacement in the advanced stages, without diseasemodifying drugs currently available for OA[40]. In spite of the rapid development of research on the pathogenesis and treatment of OA, a limited amount of progress is available for clinical use. In recent years, many studies have found an increase in ER stress biomarkers—GRP78, CHOP, ATF6, PERK, and IRE1—in cartilaginous tissues of patients with OA and have reported that this increase is positively correlated with cartilage degeneration[41,42]. Furthermore, modulation of ER stress using ER stress inhibitors or small-molecule chemical chaperones can protect against OA *in vitro* and *in vivo*[43,44]. These above results enlighten that ER stress is at least partially involved in OA pathogenesis. In the following sections, we will elaborate on the roles of ER stress in the pathogenesis of cartilage degeneration, synovitis, meniscal lesion, and subchondral bone remodeling, respectively.

#### ER stress in cartilage degeneration

Cartilage degeneration is the predominant pathological change in OA that causes OA progression[45]. Cartilage is an avascular tissue without sufficient nutrients and supplying cells, making the repair of degenerative cartilage extremely burdensome[46]. Chondrocytes are the only resident cells in cartilage and are primarily responsible for regulating the synthesis-degradation balance of the extracellular matrix (ECM)[47]. Disturbance of this balance caused by chondrocyte dysfunction or death can result in cartilage degeneration. Thus, as a switch that determines the function and fate of chondrocytes, ER stress

may play a dominant role in the onset and progression of OA[6]. Insulin-like growth factor-1 (IGF-1) is a growth factor that increases ECM synthesis, including type II collagen, proteoglycans, and other matrix components[48]. ER stress-induced upregulation of tribbles homolog 3 reduced the sensitivity of chondrocytes to IGF-1 by inhibiting protein kinase B (Akt)[49]. In addition, ER stress triggered by palmitate repressed the chondrogenic function of IGF-1 in chondrocytes by activating JNK[50]. Other than inhibiting ECM synthesis, ER stress accelerated ECM degradation in cartilage by upregulating matrix metalloproteinase-13 expression *via* the p38 mitogen-activated protein kinase (MAPK) pathway[51]. Furthermore, as a biomarker of ER stress, CHOP has been shown to upregulate the expression of sirtuin1 (SIRT1) by directly acting on the promoter region of SIRT1 or indirectly promoting the activation of AMP-activated protein kinase- $\alpha$ , ultimately inhibiting chondrogenic differentiation and ECM production[52].

Moderate ER stress could protect chondrocytes from apoptosis by activating autophagy through the GRP78 pathway, whereas severe ER stress could boost chondrocyte apoptosis, revealing a complicated crosstalk between ER stress, autophagy, and apoptosis[53]. To figure out the mechanisms involved, Yang *et al.*[54] proposed and demonstrated that the IRE1-mechanistic target of rapamycin complex 1 (mTORC1)-PERK signaling pathway synergistically regulated autophagy and apoptosis in OA temporomandibular joint chondrocytes (Fig. 2b). IRE1-mediated autophagy and PERK-mediated apoptosis were activated simultaneously in response to anomalous mechanical loading. However, IRE1 signaling diminished over time, leading to the activation of mTORC1, which subsequently activated PERK and inhibited autophagosome formation. The sensitized PERK resulted in apoptosis and restrained the fusion of autophagosome and lysosome. Furthermore, decreased Dishevelled, EGL-10 and pleckstrin domain-containing mechanistic target of rapamycin-interacting protein inhibited translocation in renal cancer from chromosome 8 ubiquitination-proteasome degradation in OA chondrocytes, leading to the accumulation of translocation in renal cancer from chromosome 8, excessive ER stress, and OA progression[55]. Ubiquitin-specific peptidase 7, a widely studied deubiquitinase, promoted chondrocyte proliferation and suppressed tumour necrosis factor- $\alpha$  (TNF- $\alpha$ )-induced apoptosis and inflammation *via* inhibiting eIF2 $\alpha$ -ATF4-CHOP signaling and nuclear factor-kappa B (NF- $\kappa$ B)/p65 signaling, thereby preventing the occurrence of OA[56,57].

Among the numerous risk factors for OA, aging is the most significant[58]. And the prevalence of OA increases

sharply with age[59]. Many hypotheses have revealed the processes by which aging leads to OA, and ER stress may be one of them, serving as a bridge linking aging and OA. Aging is closely associated with decreased chaperones, chaperone dysfunction, perturbations of critical regulatory molecules in ER stress, and increased senescence-related biomarkers, all of which can elicit excessive ER stress[60-64]. Tan *et al.*[65] compared knee cartilage obtained from young (6 to 11 years old) and aged cynomolgus monkeys (20 to 34 years old), and found that the expression of chaperones was downregulated in aged cynomolgus monkeys, while ER stress and apoptosis markers were upregulated and could be partially restored by PERK inhibitor. Senescence-related dysfunction of chaperones also contributed to ER stress, for example, BiP ATPase activity and protein disulfide isomerase enzyme function were significantly reduced in hepatocytes of senescent mice[66]. However, whether a similar mechanism exists in chondrocytes remains to be verified. Furthermore, *PERK* mRNA expression was statistically decreased in the hippocampus of senescent rats and increased the risk of ER stress[61]. Senescence-associated  $\beta$ -galactosidase, the most widely used biomarker of senescence, was increased in OA chondrocytes and decreased after the inhibition of ER stress[62,67]. Advanced glycation end products (AGEs), a group of compounds synthesized by nonenzymatic glucose-protein condensation (also known as the Maillard reaction), are inevitable products of senescence and accumulate in various cells[63,68]. Yamabe *et al.*[64] unveiled that the accumulation of AGEs in chondrocytes induced ER stress and apoptosis by modifying UPR-related proteins, thereby hastening OA progression. Rasheed *et al.*[69] further demonstrated that AGEs mediated ER stress in human chondrocytes *via* eIF2 $\alpha$ , p38 MAPK, and NF- $\kappa$ B pathways. Nevertheless, the associations between ER stress and other senescence-related biomarkers or senescence-associated secretory phenotype (a toxic microenvironment in which cells stop dividing and begin to secrete chemokines, cytokines, and extracellular matrix proteins, resulting in DNA damage) in chondrocytes still wait for further exploration[70].

As mentioned earlier, obesity is another pathogenic factor of OA. The mechanisms of obesity causing OA may be the accumulation of free fatty acids in non-adipose tissues, which is called lipotoxicity, rather than mechanical-associated pathogenesis[71,72]. Tan *et al.*[73] observed that high-fat diet facilitated chondrocyte apoptosis and OA progression by mediating ER stress. Interestingly, the type of dietary fat affects the onset of OA caused by obesity. Palmitate (a kind of saturated fatty acid) instead of oleate (a kind of monounsaturated fatty acid) promoted chondrocyte

apoptosis by inducing ER stress both *in vivo* and *in vitro*[74,75]. Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by intestinal L cells that regulates energy metabolism homeostasis by combining with GLP-1 receptor (GLP-1R)[76]. Chen *et al.*[77] revealed that the activation of GLP-1R with liraglutide could inhibit ER stress and apoptosis by activating the phosphatidylinositol-4,5-bisphosphate 3-kinase/Akt pathway *in vitro* and mitigate cartilage degeneration *in vivo*.

Notably, gender is also reported to be one of the risk factors for OA[78]. Incidence of OA in women increases significantly around the age of 50 and knee OA is more severe in women after menopause[79,80]. Dreier *et al.*[81] found that estrogen at physiological concentrations could inhibit ER stress and ER stress-induced apoptosis in ER protein 57 (*ERp57*)-knockout C28/I2 chondrocytes. This study preliminarily illuminated that estrogen could affect OA progression by regulating ER stress, however, the concrete mechanisms through which estrogen decreases ER stress and whether gender accelerates OA progression by regulating ER stress in other ways remains undetermined.

#### **ER stress in synovitis**

The synovium consists of two layers: the lining layer is composed of numerous fibroblast-like synoviocytes (FLSs) and synovial macrophages, and the sub-lining layer contains mainly connective tissue and few cellular components[82]. Contrary to cartilage, synovium is rich in vascular, neural, and cellular components, responsible for secreting synovial fluid and maintaining joint homeostasis[83]. The latest view suggests that synovitis may be the initial pathological change preceding cartilage degeneration and is mainly responsible for OA pain[84]. Because the synovium participates more in systemic circulation than cartilage without blood vessels, and is more sensitive to serum modulators, it may be the pathological tissue and curative target of diabetes-related OA[85]. In rat FLSs, high glucose stimulation upregulated the expression of glucose transporter 1 (GLUT1) and the accumulation of AGEs through hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ), thus forwarding ER stress and the release of pro-inflammatory mediators[86]. Besides, the combination of AGEs and the receptor for AGEs can activate HIF-1 $\alpha$  signaling in various tissues, hence there may be HIF-1 $\alpha$ -GLUT1-AGEs-HIF-1 $\alpha$  loop and lead to diabetes-related OA[86,87] (Fig. 2c). The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome consists of NLRP3, adaptor apoptosis-associated specklike protein, and procaspase-1, serving as a key factor in initiating the inflammatory cascade of amplification[88]. The upregulation of thioredoxin-interacting protein (TXNIP) elicited by the PERK-CHOP

pathway activated the NLRP3 inflammasome[89]. In OA rat models and lipopolysaccharide-treated FLSs, Liu *et al.*[90] unveiled that the ER stress/TXNIP/NLRP3 signaling pathway could mediate synovitis and the release of pro-inflammatory mediators including interleukin (IL)-1 $\beta$  and IL-18. Moreover, the GRP78-NF- $\kappa$ B pathway is involved in IL-1 $\beta$ -induced pro-inflammatory mediator release from FLSs and synovial macrophage polarization, which are pivotal factors in the pathogenesis of synovitis[91].

#### **ER stress in meniscal lesion**

The meniscus is mainly composed of water (72%) and organic matter (28%), including meniscus cells and ECM[92]. As one of the essential components of joints, meniscus plays a significant role in alleviating OA progression by absorbing shock and stabilizing joints, and is exposed to the biomechanical and biochemical microenvironment similar to cartilage[42,92]. However, OA has long been considered a degenerative disease of cartilage, rather than a degenerative disease of meniscus[40]. Recently, meniscus has been proposed to be more susceptible to the catabolic effect of adipokines than cartilage, indicating that meniscus may be the major tissue affected in obesity-related OA[93]. However, palmitate, rather than oleate, has been shown to induce ER stress and prompt apoptosis in meniscus cells[42]. Furthermore, palmitate could restrain autophagy and stimulate apoptosis of meniscus cells by degrading autophagy-related 5 (ATG5) through ERAD pathway [94] (Fig. 2d).

#### **ER stress in subchondral bone remodeling**

Subchondral bone usually refers to the bony component located at the distal end of calcified cartilage, which consists of subchondral bone plate and trabecular bone[95,96]. Remodeling of the subchondral bone microstructure is closely related to cartilage degeneration during OA progression[97]. Subchondral bone and cartilage contribute to subchondral bone remodeling and cartilage degeneration through biomechanical coupling and interactions, forming a vicious cycle accelerating OA progression[98]. Targeted inhibition of subchondral bone remodeling relieves OA symptoms and protects cartilage from degradation[99]. Osteoblasts, osteoclasts, osteocytes, and bone marrow mesenchymal stem cells (BMSCs) all participate in subchondral bone remodeling[100]. Among the four cell types, the coupling of osteoblast-mediated bone formation and osteoclast-mediated bone resorption mainly regulate subchondral bone remodeling[101]. Subchondral bone remodeling in OA is usually accompanied by containment of osteoblast mineralization, which can be partially restored by inhibiting ER stress[102]. PERK mediates osteoclast

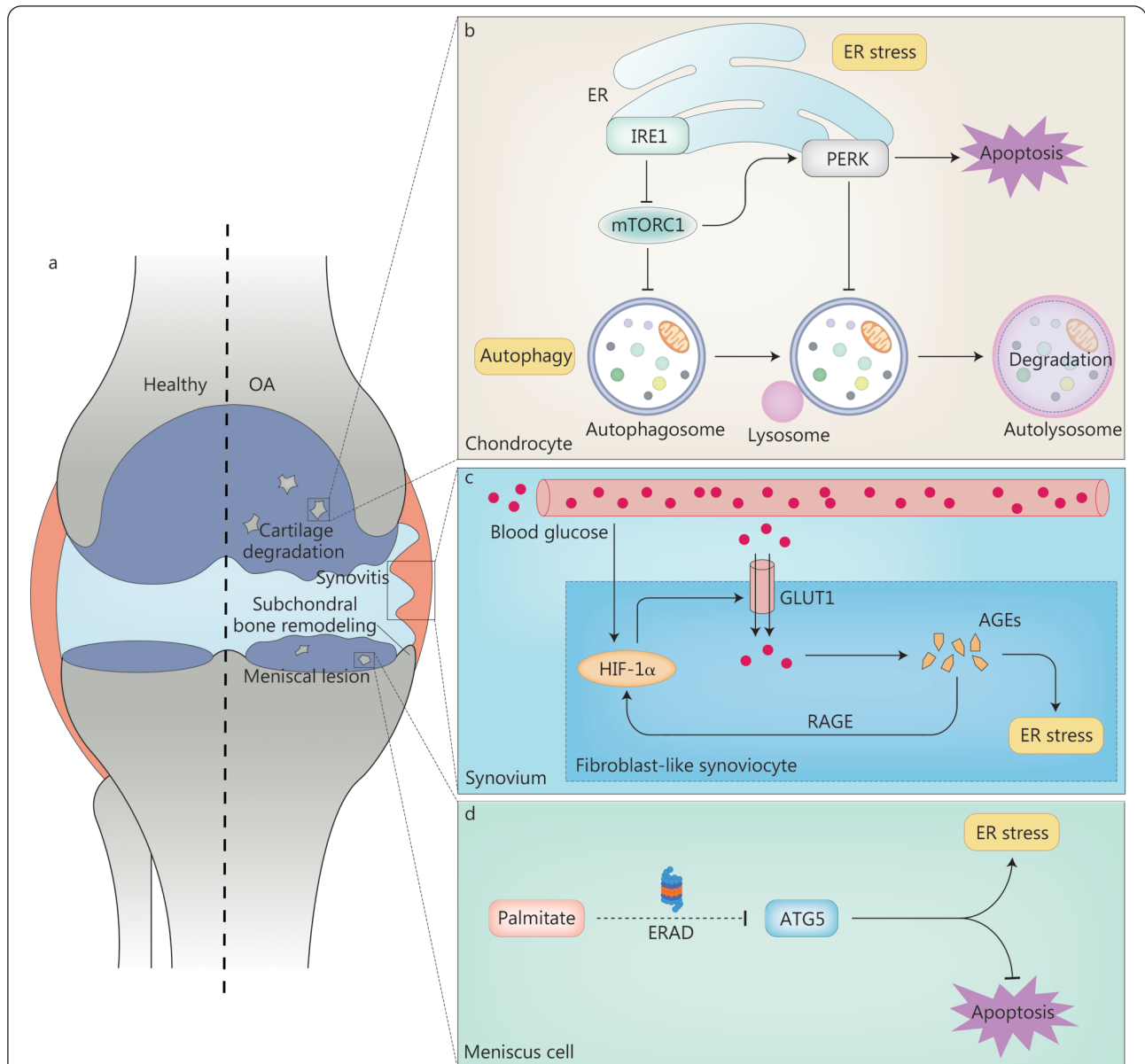
differentiation and bone resorption, while inhibiting PERK curtails osteoclastogenesis and mitigates bone loss in ovariectomized mouse models[103]. Osteocytes are the terminally differentiated osteoblasts embedded in the bone matrix, which affect osteoclastogenesis by regulating the expression of receptor activator of NF- $\kappa$ B ligand (RANKL) in response to mechanical stimuli[100]. Inhibition of ER stress alleviates cell death and diminishes intracellular reactive oxygen species (ROS) levels in osteocytes induced by oxygen-glucose deprivation[104]. Because osteocytes are as old as the embedded bone packet, osteocytes may be more susceptible to excessive ER stress compared to the short-lived osteoblasts and osteoclasts[105]. However, no experiments have been performed to confirm whether cellular lifespan affects ER stress. BMSCs are a heterogeneous population of cells with self-renewal capacity and multidirectional differentiation potential[106]. ER stress and impaired autophagy elicited inflammation-mediated bone loss *via* the activation of Rho-associated protein kinase 1 in BMSCs[107].

#### **ER stress in ligament degeneration**

Ligament connects two bones or fibrous cartilages to bone and functions by balancing abnormal mechanical forces within the joint[108]. Furthermore, because ligament comprises a mass of ECM, poor blood supply, and low cellular contents, it is prone to degeneration and tears (especially aging ligaments with lower cellular components)[108]. Impaired ligament can destabilize the joint and accelerate OA progression. Ligament containing free nerve endings are involved in OA pain along with other innervated tissues including synovium[109]. Li *et al.*[110] observed that dexamethasone led to calcification and degeneration of anterior cruciate ligament cells through ER stress, increasing the risk of injury. In addition, Shi *et al.*[111] found that ER stress might facilitate mechanical stress-induced ossification of the posterior longitudinal ligament through the MAPK signaling pathway. Unfortunately, research on the roles of ER stress in ligament degeneration of OA is lacking.

#### **ER stress in skeletal muscle degeneration**

Skeletal muscle structure and function are related to the onset and progression of OA[112]. Currently, relevant study has concentrated on the relationship between muscle strength and OA progression[112]. In addition to skeletal muscle function, skeletal muscle constitution, biochemical and molecular interactions are considered to be the underlying mechanisms[112]. Kim *et al.*[113] reported that valdecoxib, a non-steroidal anti-inflammatory drug, could relieve lipid-induced skeletal muscle insulin resistance by inhibiting inflammation and ER stress. However, there have been no



**Fig. 2 ER stress in the pathogenesis of OA.**

a. Pathological changes in OA regulated by ER stress; b. IRE1-mTORC1-PERK signaling pathway synergistically regulates autophagy and apoptosis in OA chondrocytes. Attenuation of IRE1 signaling activates mTORC1, converting protective autophagy to apoptosis; c. Mechanisms through which ER stress accelerates OA progression in synovitis. A vicious cycle of HIF-1 $\alpha$ -GLUT1-AGEs-HIF-1 $\alpha$  may exist in the fibroblast-like synoviocyte of patients with diabetes-related OA, aggravating OA progression; d. ER stress is involved in meniscal lesion to accelerate OA progression. Palmitate degrades ATG5 through the ERAD pathway to inhibit autophagy and promote meniscus cell apoptosis. AGEs. Advanced glycation end products; ATG5. Autophagy-related 5; ER. Endoplasmic reticulum; ERAD. ER-associated degradation; GLUT1. Glucose transporter 1; HIF-1 $\alpha$ . Hypoxia-inducible factor-1 $\alpha$ ; IRE1. Inositol-requiring enzyme 1; mTORC1. Mechanistic target of rapamycin complex 1; OA. Osteoarthritis; PERK. Protein kinase R-like ER kinase; RAGE. Receptor for AGEs

studies on ER stress in the skeletal muscle degeneration of OA.

**ER stress in OA neuropathic pain**

Pain is the most significant symptom of OA and a major determinant of clinical decision-making and patient counseling[114]. Poor pain management is also the main cause of disability and artificial joint replacement in OA

patients[115]. OA pain includes nociceptive, inflammatory, and neuropathic pain (referring to pain caused by diseases of the central and peripheral nervous systems). ER stress in the peripheral nervous system has been identified as an important driver of neuropathic pain in diabetes[116]. Mao *et al.*[117] demonstrated that ER stress contributed to bone cancer pain

in a mouse model and inhibition of ER stress in spinal neurons relieved bone cancer pain by modulating neuroinflammation. Nevertheless, there are few studies on the role of ER stress in OA neuropathic pain.

### ER stress in the pathogenesis of OP

OP is a systemic skeletal disorder characterized by reduced bone mass, microstructural degeneration, decreased bone rigidity, and high risk of fracture[7]. Risk factors of OP include aging, menopause, iatrogenic factors (excessive use of glucocorticoids is the most common), behavior, nutrition, and genetics[3]. Due to the aging of the world population, OP is estimated to affect 200 million people globally, especially those over 60 years of age[118]. Osteoporotic fracture is the most serious clinical consequence of OP, with hip fracture being the most dangerous[3]. Statistically, one in five people die in the first year after a hip fracture, and less than a third fully return to normal[3]. In the United States, more than 1.5 million people are diagnosed with osteoporotic fractures each year, at a cost of about \$17 billion and projected to reach \$50 billion annually by 2040[3]. The magnitude of socioeconomic burden and health risks urge researchers to explore the pathogenesis of OP and develop effective curative tactics. Due to the relatively high demand of osteoblasts to secrete bone matrix, ER stress may determine the cell function and fate of osteoblasts, and play a decisive role in the progression of OP. In the following, we will summarize the latest findings that ER stress not only affect osteoblasts, but also osteoclasts, osteocytes, BMSCs, and vascular endothelial cells to mediate OP pathogenesis.

#### ER stress in bone remodeling

Bone remodeling constitutes a dynamic equilibrium between bone formation and resorption, serving as the primary mechanism for bone renewal and adaptation to changes in load-bearing demands. This intricate process hinges predominantly on the synergy of osteoblast-mediated bone formation and osteoclast-mediated bone resorption, accompanied by the regulatory influence of osteocytes[119] (Fig. 3a). Both decreased bone formation and increased bone resorption during bone remodeling contribute to OP. Therefore, ER stress-induced cellular dysfunction and aberrant apoptosis of osteoblasts, osteoclasts, and osteocytes might underlie the development of OP. Indeed, ER stress has been shown to participate in OP by inducing osteoblast apoptosis and facilitating osteoclast differentiation, migration, and adhesion, as observed both *in vivo* and *in vitro*[120]. Moreover, considering the capacity of BMSCs and bone marrow hematopoietic cells to differentiate into osteoblasts and osteoclasts, it is plausible that ER stress could play a role

in the initiation and progression of OP by modulating their differentiation processes.

The signal transducer and activator of transcription 3 is a transcription factor boosting cell survival and differentiation[121]. Signal transducer and activator of transcription 3 were reported to upregulate the expression of miR-205, which could directly target the 3'-untranslated region of the *CHOP* gene to downregulate its expression and in turn, inhibited the apoptosis of osteoblasts[122]. In addition, GRP78 was increased in osteoblasts and adipocytes of aged and ovariectomy-induced OP mice, and GRP78 negatively regulated osteoblast differentiation and facilitated adipogenic differentiation in C3H10T1/2 cells[123]. Glutathione peroxidase 7 is a highly conserved member of the glutathione peroxidase family that functions as an antioxidant together with superoxide dismutase[124]. Glutathione peroxidase 7 deficiency might suppress the mechanistic target of rapamycin pathway by upregulating ER stress, thereby reducing the osteogenic potential of BMSCs[125].

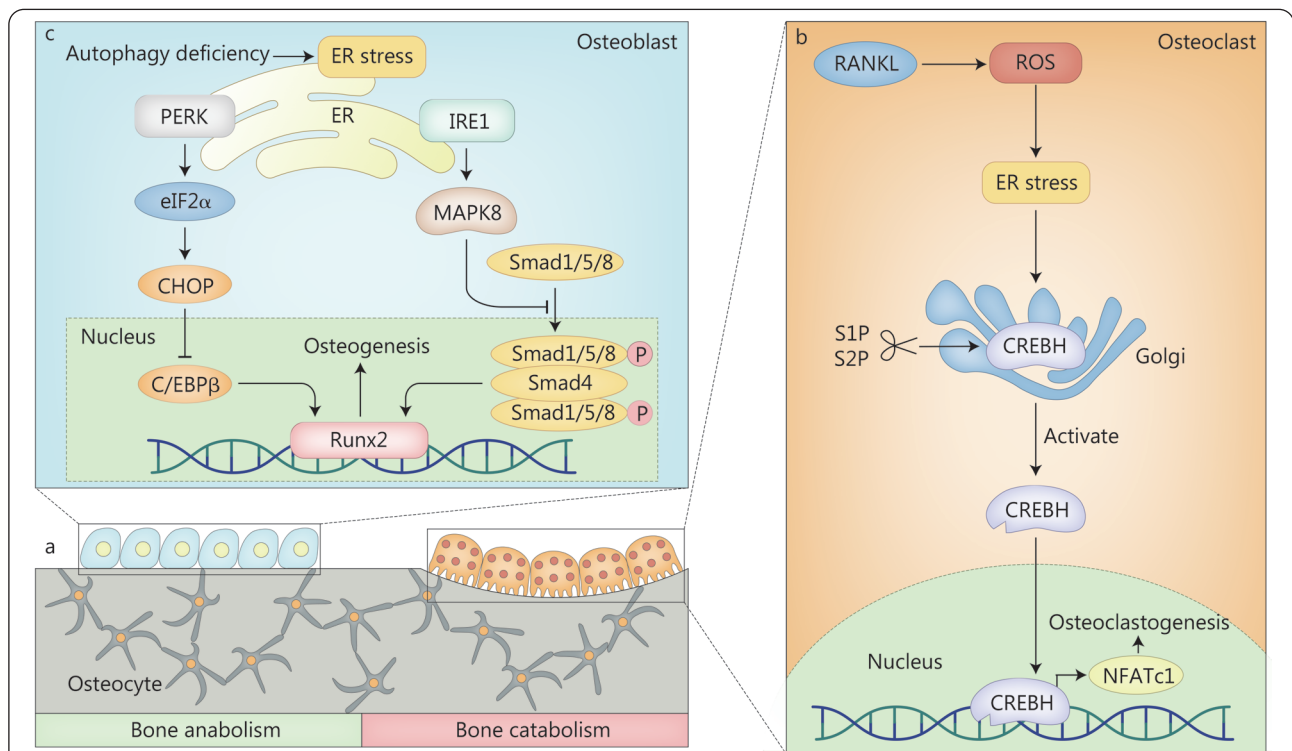
RANKL is essential for osteoclast differentiation, survival, and activation [126]. RANKL binds to the receptor activator of NF- $\kappa$ B located on the membrane of osteoclast precursors, leading to the activation of *c-Fos*, NF- $\kappa$ B, and nuclear factor of activated T cells cytoplasmic 1 (NFATc1) by recruiting signaling adaptor molecules tumor necrosis factor receptor-associated factor[127]. NFATc1 in turn upregulates the expression of various osteoclast-specific genes and is indispensable for osteoclast differentiation[128]. Lee *et al.*[129] testified a crucial role of excessive ER stress in RANKL-induced NFATc1 activation and osteoclast differentiation mediated by IL-1 $\beta$ . cAMP response element-binding protein H is a transcription factor activated by UPR-dependent proteolytic cleavage and then translocated to the nucleus to regulate the transcription of target genes[130]. RANKL activated cAMP response element-binding protein H through the ROS/ER stress signaling pathway to prompt the transcription of NFATc1, ultimately leading to increased osteoclastogenesis[126] (Fig. 3b).

Similar to chondrocytes, a tangled crosstalk of ER stress, autophagy, and apoptosis exists in osteoblasts and osteoclasts as well. Yang *et al.*[131] reported that ER stress attenuated oxidative damage and apoptosis in osteoblasts by enhancing autophagy. Autophagy-related 7 (ATG7) is an essential autophagy effector enzyme that acts in coordination with other ATG proteins to regulate autophagy, apoptosis, and cell cycle[132]. Li *et al.*[133] found that autophagy deficiency induced by conditional *Atg7* deletion inhibited mineralization, and promoted ER stress and apoptosis in osteoblasts. Bone

morphogenetic protein signaling, a key regulator of embryonic bone development and postnatal bone homeostasis, binds to its receptor and functions through both small mother against decapentaplegic (Smad)-dependent and Smad-independent signaling pathways[134]. In the Smad-dependent pathway, two phosphorylated R-Smads (Smad1/5/8) bind to a co-Smad (Smad4) and co-translocate to the nucleus, where they recruit Runt-related transcription factor 2 (Runx2) to regulate osteoblast-specific gene expression. PERK activation induced by autophagy deficiency upregulated the expression of CHOP by phosphorylating of eIF2 $\alpha$ , and the increased CHOP formed a heterodimer with CCAAT/enhancer binding protein  $\beta$  (C/EBP $\beta$ ) to inhibit the Runx2-binding activity of C/EBP $\beta$ , leading to the downregulation of osteogenic gene expression[133]. Moreover, the activation of IRE1 triggered by autophagy deficiency inhibited the bone morphogenetic protein-Smad1/5/8 pathway *via* MAPK8, thereby constricting Runx2-mediated osteoblast-specific gene expression (Fig. 3c). Furthermore, site-1 membrane proteases (S1P) depletion in

bone marrow monocytes inhibited ATF6 and sterol response element binding protein 2 (SREBP2) maturation, which subsequently blocked CHOP/SREBP2 complex-induced autophagy, thereby suppressing osteoclast differentiation[135].

OP can be categorized into primary (including the senile and postmenopausal OP) and secondary OP (including glucocorticoids-induced OP), with primary OP being more common[136]. Senile OP, which occurs in the elderly over 70 years old, has now become a focus of global health care concern. The pathogenesis of senile OP has not been fully elucidated, and cellular senescence is a possible mechanism. Suzuki *et al.*[137] observed that AGEs accumulated in osteoblasts with aging could elicit apoptosis through ER stress. However, the association between ER stress and other senescence-associated biomarkers (such as senescence-associated  $\beta$ -galactosidase) or senescence-associated secretory phenotype, remains unclear. Postmenopausal OP is caused by estrogen deficiency in postmenopausal women. 17 $\beta$ -estradiol, a major estrogen, was reported to protect



**Fig. 3 ER stress in the pathogenesis of OP.**

a. Bone remodeling is mainly regulated by the coupling of osteoblast-mediated bone formation and osteoclast-mediated bone resorption, and osteocytes have also been reported to participate in bone remodeling in OP; b. RANKL activates CREBH through ROS/ER stress signaling pathway to promote the transcription of NFATc1, ultimately leading to increased osteoclastogenesis; c. Autophagy deficiency induced by conditional *Atg7* deletion inhibits mineralization and promotes ER stress and apoptosis in osteoblasts. CHOP. C/EBP homologous protein; CREBH. cAMP response element-binding protein H; C/EBP $\beta$ . CCAAT/enhancer binding protein  $\beta$ ; eIF2 $\alpha$ .  $\alpha$ -subunit of eukaryotic translation initiation factor 2; ER. Endoplasmic reticulum; IRE1. Inositol-requiring enzyme 1; MAPK8. Mitogen-activated protein kinase 8; NFATc1. nuclear factor of activated T cells cytoplasmic 1; PERK. Protein kinase R-like ER kinase; RANKL. receptor activator of NF- $\kappa$ B ligand; ROS. Reactive oxygen species; Runx2. Runt-related transcription factor 2; S1P. Site-1 membrane proteases; S2P. Site-2 membrane proteases; Smad. Small mother against decapentaplegic

osteoblasts from ER stress-induced apoptosis by promoting Ras-ERK1/2 signaling pathway dependent transcription factor II-I activity to upregulate the expression of GRP78, which could inhibit apoptosis by binding to procaspases-7 and procaspases-12[138]. This contradicts the typical role of GRP78 as a pro-apoptotic molecule for reasons that are still not known. Glucocorticoids are widely used in inflammatory and autoimmune diseases, and long-term administration of large amounts of glucocorticoids may lead to glucocorticoids-induced OP[139]. Glucocorticoids accelerated the apoptosis of osteoblasts and osteocytes partly through ER stress, and the inhibition of eIF2 $\alpha$  dephosphorylation protected osteoblasts and osteocytes from apoptosis induced by glucocorticoids *in vitro* and *in vivo*[140]. Further study has shown that glucocorticoids induce ER stress-mediated apoptosis by increasing CHOP expression in osteoblasts[141].

In addition, due to the global epidemic of diabetes, the morbidity of diabetic OP caused by chronic hyperglycemia, AGEs, and oxidative stress has gradually increased[142]. ER stress was implicated in the progression of diabetic OP *in vivo* and *in vitro* by increasing CHOP expression in osteoblasts[143]. Obesity has recently been found to be strongly associated with the onset of OP, which may be an additional risk factor for OP[144]. In obese patients, serum free fatty acids are often increased due to lipid accumulation and reduced utilization of fatty acids (FAs), leading to lipotoxicity in BMSCs and osteoblasts[145]. Palmitate was proven to induce the apoptosis of BMSCs and osteoblasts through ER stress, which was alleviated by oleate[146]. Homocysteine, a sulfur-containing amino acid, is now considered a risk factor for OP and is commonly found in hyperhomocysteinemia, an inherited disorder of amino acid metabolism[147]. Park *et al.*[147] observed that homocysteine induced apoptosis through ER stress in osteoblasts. Besides, exercise is known to increase bone rigidity by improving bone mineral content and structure, and the mechanism is thought to be at least through affecting osteogenic and adipogenic differentiation balance of BMSCs[148]. Styner *et al.*[149] reported that mechanical stimulation upregulated BiP and downregulated CHOP expression to alleviate ER stress and inhibit adipogenesis by inhibiting C/EBP $\beta$  expression in BMSCs. However, C/EBP $\beta$  overexpression did not restore the suppression of adipogenesis by mechanical stimulation, suggesting that mechanical sensitivity of C/EBP $\beta$  is not the primary site of adipogenesis regulation in BMSCs. In addition, ER stress reduced the response of osteocytes to mechanical stimulation and then contributed to low bone mass[150].

Bone marrow hematopoietic cells, including macrophages

and neutrophils, exert an indirect influence on bone remodeling[151,152]. Exhibiting remarkable heterogeneity and plasticity, macrophages shift from non-activated M0 macrophages to pro-inflammatory M1 phenotype when triggered by lipopolysaccharide or interferon- $\gamma$ , while they can alternatively assume an anti-inflammatory M2 phenotype under the influence of IL-4, IL-13, or IL-10[153-155]. The co-culture of M1 and M2 macrophages enhanced the osteogenic capacity of MC3T3 cells, as demonstrated by increased alkaline phosphatase activity and matrix mineralization[156]. After IL-4 treatment, which induced the repolarization of M1 macrophages into the M2 subset, the osteogenic capacity of M1-MC3T3 co-cultures was further elevated[156]. Interestingly, the direct effect of IL-4 on MC3T3 cells did not result in an increase in osteogenic capacity, implying that the increased osteogenic capacity could potentially be ascribed to the secretion of osteoblastic cytokines by M2 macrophages[157]. Within tumor cells, ER stress promoted the repolarization of macrophages into the M2 phenotype by modulating the secretion of extracellular vesicles[158,159]. The SIRT1/ER stress signaling pathway was also recognized to participate in the modulation of macrophage polarization[160]. However, further investigations are required to establish whether ER stress can impact the progression of OP by regulating macrophage polarization. Neutrophils, a vital cell type within the innate immune system, arise from hematopoietic stem cells and progenitor cells in the bone marrow[161]. Within the context of rheumatoid arthritis, activated neutrophils contributed to osteoclast-mediated bone resorption by promoting the expression of RANKL in inflamed joints[162,163]. Moreover, neutrophils expressing RANKL were increased in male patients with chronic obstructive pulmonary disease and were associated with low bone density, suggesting their potential role in bone resorption[164]. One of the three branches of ER stress, IRE1 $\alpha$ , plays a crucial role in the heightened activity of neutrophils in lupus[165]. Nonetheless, whether ER stress contributes to OP by influencing the function and fate of neutrophils remains to be conclusively determined.

#### **ER stress in angiogenesis**

The onset of OP is associated with a decrease in bone marrow microvessels, and the encouragement of angiogenesis exhibited therapeutic effect on OP[166]. Therefore, ER stress may accelerate OP progression by mediating dysfunction or apoptosis of vascular endothelial cells and BMSCs. Naringin inhibited the apoptosis of vascular endothelial cells by blocking ER stress, which might delay OP progression[167]. Bisphosphonates are the most common anti-resorptive

drugs used to treat OP. Alendronate is a nitrogen-containing bisphosphonate that exerts an anti-resorptive effect by binding to and inhibiting the activity of farnesyl diphosphate synthase[168]. Recent study has shown that preosteoclasts hardly resorb bone matrix and even facilitate angiogenesis by secreting platelet-derived growth factor-BB[169]. Ding *et al.*[170] proposed that the lack of selectivity of alendronate in inhibiting preosteoclasts and mature osteoclasts could lead to peroxisome dysfunction in preosteoclasts, further inducing ER stress and apoptosis. Since decreased angiogenesis increases the risk of OP, how to retain proangiogenic preosteoclasts while depleting mature osteoclasts is a problem worth investigating, and targeted drug delivery systems may be a suitable solution.

### ER stress in the pathogenesis of IVDD

The IVD is the largest avascular fibrocartilaginous organ that acts to absorb shock and provide flexibility to the spine, consisting of the gel-like nucleus pulposus (NP) in the center, the annulus fibrosus (AF) around it, and the cartilaginous endplate (CEP) that anchors the IVD to the corpus vertebrae[171]. IVDD is characterized by the degeneration of local physiological structures, including decreased hydration of the NP, destruction of the AF, and calcification of the CEP, which is a major cause of low back pain[172] (Fig. 4a). Approximately 700 million individuals worldwide suffer from low back pain, which reduces the quality of life of IVDD patients and may eventually lead to disability[173]. At the same time, low back pain caused by IVDD is also the most common reason for patients visits[174]. Increased absence from work, decreased productivity and massive consumption of medical resources caused by low back pain place huge burdens on society[173]. IVDD has many known risk factors, including abnormal mechanical loading, obesity, aging, genetics, and poor diet[8]. ECM in NP mainly consists of proteoglycan and type II collagen, which is highly hydrated and contributes to resisting axial mechanical load; while in AF, ECM is mainly composed of type I collagen, which is helpful to withstand lateral mechanical stimulation[175,176]. The balance between ECM anabolism and catabolism plays a pivotal role in maintaining IVD homeostasis[172]. Hence, the disturbance of ECM anabolism and catabolism caused by ER stress may lead to the biomechanical imbalance of IVD and accelerate the progression of IVDD. Furthermore, the expression of ER stress biomarkers, such as GRP78 and CHOP, was increased in NP from IVDD patients[177]. The expression of GRP78 and CHOP was positively correlated with the Pfirrmann grades of IVDD[178]. Targeted inhibition

of IRE1 restrained the degeneration of NP cells and postponed the progression of IVDD in a puncture rat model[179]. Notably, a recent single-cell RNA sequencing analysis of NP cells from patients with IVDD showed that late degenerative NP cells were predominantly composed of cell types associated with ER stress, inflammatory response, and fibrocartilaginous activity, which might be major contributors to the late progression of IVDD[180]. These findings all suggest that ER stress is involved in the pathogenesis of IVDD.

### ER stress in NP degeneration

NP is the most hydrated part of the IVD and develops from the embryonic notochord[181]. ECM secreted by NP cells, including type I collagen, type II collagen, and proteoglycan, enables IVD to absorb mechanical loading and maintain physiological function[182]. Anomalous mechanical loading beyond IVD affordability is a critical pathogenic factor in the pathogenesis and progression of IVDD[175]. Excessive mechanical loading has been reported to facilitate pro-inflammatory mediator production and apoptosis of NP cells, leading to NP degeneration and IVDD[183,184]. Xiang *et al.*[185] observed a significant increase in ER stress markers (GRP78 and CHOP) over time in high-pressure gas-treated NP cells. Moreover, ER stress induced by compression promoted NP cell apoptosis[186]. Interestingly, necroptosis (also called programmed necrosis), a programmed cell death triggered by death receptors independent of caspase, was also caused by compression-induced ER stress in NP cells[186,187]. Lin *et al.*[188] further unveiled compression-enhanced ER stress and ER stress-induced  $Ca^{2+}$  influx from ER to mitochondria *via* inositol 1,4,5-trisphosphate receptor-glucose-regulated protein 75-voltage-dependent anion-selective channel 1 complex. Consequently, increased ER-mitochondria  $Ca^{2+}$  crosstalk elicited necroptosis of rat NP cells through the poly(ADP-ribose) polymerase/apoptosis-inducing factor pathway (Fig. 4b).

Crosstalk between ER stress, autophagy, and apoptosis is another potential pathogenesis of IVDD. Hydrogen peroxide promoted NP cell apoptosis by stimulating ER stress and ER stress-dependent autophagy *via* the IRE1/JNK pathway[189]. PERK/eIF2 $\alpha$  pathway promoted NP cell survival in response to TNF- $\alpha$  stimulation by activating autophagy[190]. Moderate ER stress and low levels of ROS induced by short-term glucose deprivation protected NP cells from apoptosis through autophagy, whereas excessive ER stress and ROS production caused by late glucose deprivation contribute to the apoptosis of NP cells[191]. These abovementioned findings are suggestive of a double-edged role of ER stress and autophagy in regulating cell survival. Apart from autophagy, another particular type of selective autophagy, ER-phagy (also called

reticulophagy), has attracted our attention[192]. Glucose deprivation induced senescence and apoptosis of human NP cells and resulted in IVDD through ER stress[193]. At the same time, enhanced ER stress could induce reticulophagy regulator 1-mediated ER-phagy in response to glucose deprivation, which in turn prevented glucose deprivation-induced cell senescence and apoptosis by inhibiting ER stress in human NP cells[193].

IVDD is associated with increased expression of pro-inflammatory cytokines that promote ECM degradation, chemokine secretion, and alterations in cell phenotype, resulting in imbalance between ECM anabolism and catabolism[4]. Krupkova *et al.*[194] reported that ER stress mediated IL-6 release *via* p38 MAPK and CHOP in primary IVD cells. In turn, pro-inflammatory mediators (IL-1 $\beta$  and TNF- $\alpha$ ) significantly upregulated IRE1 and PERK expression, but not ATF6, thereby amplifying the inflammatory cascade[195]. TNF- $\alpha$  increased CHOP expression through the JNK/ERK/MAPK and NF- $\kappa$ B signaling pathways, and then promoting NP cell apoptosis[196]. However, in contrast, Chen *et al.*[197] found that PERK/eIF2 $\alpha$  and IRE1/XBP1 enhanced the survival and proliferation of rat NP cells following TNF- $\alpha$  stimulation. This also indicates that ER stress possesses two opposite pro-apoptotic and pro-survival effects.

Hypercholesterolemia is becoming a global public health problem owing to a high-fat diet and an unhealthy lifestyle[198]. Sprague-Dawley rats on a high-cholesterol diet showed more severe IVDD than rats on a normal diet[199]. Statins, a class of drugs recommended by professional guidelines and widely used worldwide to lower blood cholesterol, were found to alleviate IVDD *in vivo* and *in vitro*[199-201]. Pyroptosis, unlike apoptosis, is a specific programmed cell death mediated by gasdermin[202]. Yan *et al.*[199] reported that cholesterol accumulation induced pyroptosis of NP cells *via* the mature form of SREBP1 (mSREBP1)-mediated ER stress (Fig. 4b). The results of these studies extend our understanding of IVDD pathogenesis and provide a novel therapeutic approach for the IVDD from the perspective of improving systemic metabolic disorders.

Aging is a major risk factor for IVDD, but the pathogenesis leading to IVDD during aging remains uncertain[203]. AGEs accumulate in IVD with age, especially in diabetic patients, leading to increased ECM degradation and cellular apoptosis, which is considered to be one of the mechanisms of aging-induced IVDD[204,205]. Liao *et al.*[178] demonstrated that AGEs induced ER stress to promote NP cell apoptosis. Luo *et al.*[206] further reported that AGEs accumulation resulted in excessive ER stress and the subsequent NP cell apoptosis by

increasing the expression of ER-resident Ca<sup>2+</sup>-release channels inositol 1,4,5-triphosphate receptor and ryanodine receptor, and decreasing the expression of ER Ca<sup>2+</sup>-reuptake pumps sarco/ER Ca<sup>2+</sup>-ATPase (Fig. 4b).

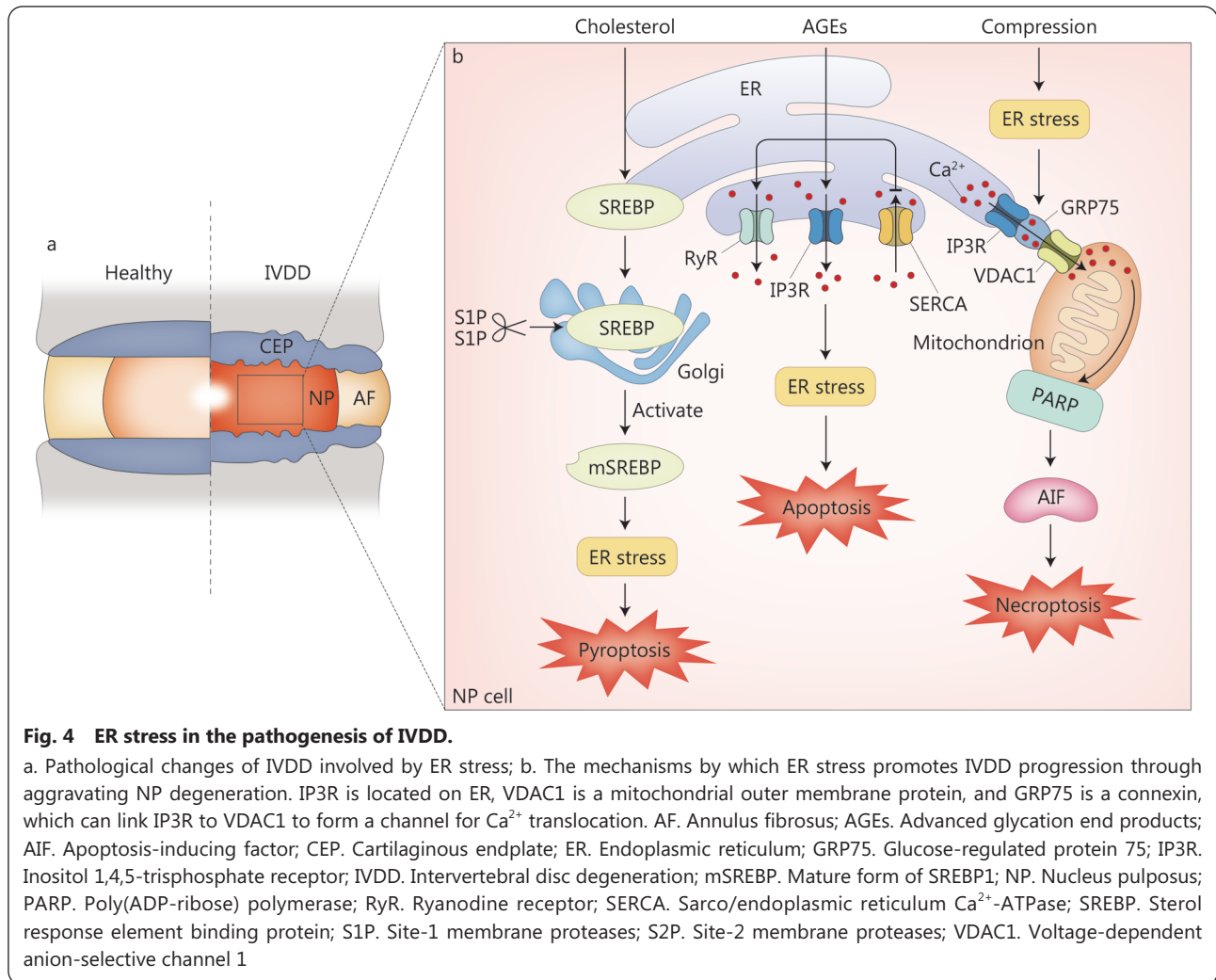
The nutrients and oxygen of IVD are mainly derived from the capillary network of CEP[207]. Due to diffusion, the oxygen tension gradually decays from the surrounding AF to the central NP, forming an anoxic microenvironment. As a result, glycolysis becomes the main energy supply mode for NP cells, through which large amounts of lactate are produced and result in a low pH microenvironment[208]. Zhu *et al.*[209] found that ER stress inhibited acidic microenvironment-induced senescence of NP cells by activating autophagy. Whereas Xie *et al.*[210] proclaimed that acidic microenvironment promoted apoptosis of NP cells through activation of acid-sensing ion channel 1a and acid-sensing ion channel 1a-mediated ER stress. The different effects of ER stress may be caused by different stimuli to NP cells.

#### **ER stress in AF rupture**

AF is the peripheral structure of IVD with a zonal distribution of phenotypically distinct cells[211]. The ECM produced by the outer AF cells contained abundant type I collagen and a small amount of proteoglycan, while the ECM produced by the inner AF was mainly composed of type II collagen and proteoglycan. The structural integrity of AF is critical for limiting NP movement and maintaining physiological IVD pressure under aberrant mechanical loading, and thus plays a vital role in the biomechanical properties of IVD and NP[212]. In AF of IVDD patients, tears and cracks are commonly present, which may be caused by excessive ER stress in AF cells. Abnormal mechanical loading facilitated apoptosis of AF cells through nitric oxide-mediated ER stress[213]. Chen *et al.*[214] found that autophagy and apoptosis were mediated by ER stress in AF cells of mechanical loading-related IVDD model rats, suggesting that mechanical loading was involved in IVDD through crosstalk among ER stress, autophagy, and apoptosis in AF cells. Moreover, diabetes is a pivotal risk factor of IVDD, and the hyperglycemia is caused by diabetes induced apoptosis of AF cells through ER stress[215].

#### **ER stress in CEP degeneration**

As discussed above, CEP is the main blood supply to IVD. Degeneration of CEP can severely hinder blood and nutrient supply to IVD, and then lead to IVDD[216]. Aberrant endplate chondrocyte apoptosis and calcification are two principal alterations in CEP degeneration[217]. ER stress may be an underlying mechanism leading to apoptosis and calcification of endplate chondrocytes; however, ER stress has not yet been linked to CEP degeneration.



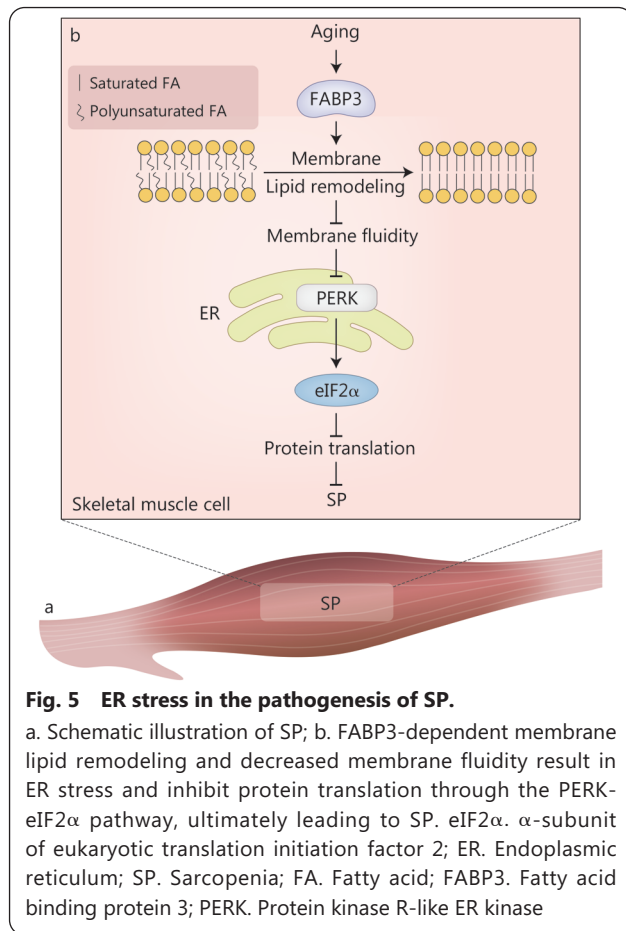
**Fig. 4 ER stress in the pathogenesis of IVDD.**

a. Pathological changes of IVDD involved by ER stress; b. The mechanisms by which ER stress promotes IVDD progression through aggravating NP degeneration. IP3R is located on ER, VDAC1 is a mitochondrial outer membrane protein, and GRP75 is a connexin, which can link IP3R to VDAC1 to form a channel for  $Ca^{2+}$  translocation. AF. Annulus fibrosus; AGEs. Advanced glycation end products; AIF. Apoptosis-inducing factor; CEP. Cartilaginous endplate; ER. Endoplasmic reticulum; GRP75. Glucose-regulated protein 75; IP3R. Inositol 1,4,5-trisphosphate receptor; IVDD. Intervertebral disc degeneration; mSREBP. Mature form of SREBP1; NP. Nucleus pulposus; PARP. Poly(ADP-ribose) polymerase; RyR. Ryanodine receptor; SERCA. Sarco/endoplasmic reticulum  $Ca^{2+}$ -ATPase; SREBP. Sterol response element binding protein; S1P. Site-1 membrane proteases; S2P. Site-2 membrane proteases; VDAC1. Voltage-dependent anion-selective channel 1

### ER stress in the pathogenesis of SP

The term SP, first coined by Irwin Rosenberg in 1989, comes from the Greek “sarx”, meaning flesh, and “penia”, meaning loss[218] (Fig. 5a). SP is a new disease that was recognized as an independent disease in 2016 by the International Classification of Diseases-10 code[219]. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) published a definition of SP based solely on low muscle mass[220]. Subsequently, EWGSOP2 added low muscle strength as a primary criterion for SP to the new definition developed in 2018, as muscle strength is a more accurate predictor of adverse clinical outcomes in SP, such as falls, physical functional decline, frailty, impaired quality of life, increased health care costs, and mortality[5,221]. At the same time, EWGSOP2 proposed a stepwise diagnostic method for SP by comprehensively measuring muscle mass, muscle strength, and physical performance[5]. According to the study, among the elderly hospitalized, hospitalization costs were more than five times higher for those with SP at the time

of admission than for those without SP[222]. Unfortunately, there are still limited reports on the pathophysiology of SP. The heavy clinical burdens of SP prompt us to explore the pathogenesis of SP in depth. Etiologies of SP include neurological disorders, hormonal disturbances, nutritional disorders, immune factors, redox status of skeletal muscle, and reduced physical activity[223,224]. From a cellular and molecular point of view, a mismatch in protein synthesis and degradation is the predominant factor contributing to SP[225]. Furthermore, a specialized ER network, called the sarcoplasmic reticulum, exists in skeletal muscle cells, and  $Ca^{2+}$  released from the sarcoplasmic reticulum plays a critical role in the process of skeletal muscle contraction[226]. ER stress may accelerate SP progression by affecting protein metabolism and  $Ca^{2+}$  release in skeletal muscle cells. It has been reported that the expression of ER stress biomarkers (ATF6, PERK, and IRE1) was significantly upregulated in SP skeletal muscle of lung cancer patients with cachexia[227]. Indoxol sulfate, a uremic toxin of chronic kidney disease, was used to construct



a model of premature aging to study the pathogenesis of SP[225]. XBP1 and phosphorylated eIF2 $\alpha$  played a promyogenic and anti-myogenic role in the differentiation of mouse myoblast C2C12 cells treated with indoxyl sulfate, respectively[225].

During aging, some critical molecules of the UPR, such as chaperones and enzymes, exhibit decreased expression and activity, leading to enhanced ER stress[228]. The expression of chaperones, including endoplasmic reticulum protein 29, 70 kD heat shock protein, and calreticulin, was decreased in skeletal muscle of 32-month-old rats compared with 6-month-old rats, whereas the expression levels of ER stress and apoptosis markers were increased[229]. Aging-related impairment of mitochondrial function and integrity could also lead to cellular oxidative stress, which then triggered ER stress in C2C12 myotubes[230]. On the other hand, aging-caused decrease in autophagy aggravated ER stress-induced loss of muscle mass[231]. Muscle RING Finger 1 is a muscle-specific E3 ubiquitin ligase whose transcription is increased in response to various stimuli inducing muscle loss[232]. Muscle RING Finger 1 has been reported to reduce muscle mass in aging mice by upregulating CHOP expression and

inhibiting proteasome activity[233]. Fatty acid binding protein 3 (FABP3) is highly expressed in aged muscle and is considered a lipid chaperone that regulates fatty acid solubility, mobility, and utilization[234]. FABP3 overexpression in young muscle remodeled membrane lipid composition to that of senescent muscle and reduced membrane fluidity by replacing unsaturated FAs with saturated FAs[235]. FABP3-dependent membrane lipid remodeling and decreased membrane fluidity resulted in ER stress and inhibited protein translation through the PERK-eIF2 $\alpha$  pathway, ultimately leading to SP (Fig. 5b). In sedentary and inactive individuals, optic atrophy 1 (OPA1), which is responsible for the fusion of the outer and inner mitochondrial membranes, showed an age-related decline, which was associated with the onset and progression of SP[236]. Ablation of *Opa1* resulted in ER stress, which induced catabolic processes and mass loss in skeletal muscle through UPR and forkhead box transcription factors[236]. Older adults are less responsive to anabolic stimuli, known as anabolic resistance, and may play an important role in the pathogenesis of SP[237-239]. Decreased phosphorylation of protein kinase B induced by ER stress led to low phosphorylation of proline-rich Akt substrate of 40 kD and allosteric inhibition of mTORC1[240]. The mTORC1 pathway is indispensable in response to anabolic stimuli, and its inhibition is one of the mechanisms involved in anabolic resistance in skeletal muscle during aging[218]. Moreover, it is noteworthy that the loss of muscle strength is greater than the loss of muscle mass in older individuals[241]. Reduced Ca<sup>2+</sup>-releasing capacity and increased markers of ER stress have been found in aged sarcoplasmic reticulum[242,243]. Therefore, ER stress-induced impairment of sarcoplasmic reticulum Ca<sup>2+</sup> release may be another possible reason for the inhibition of muscle strength during SP.

Obesity is known to increase the risk of mortality in patients with SP[244]. Bryner *et al.*[245] revealed that palmitate mediated ER stress and apoptosis in C2C12 cells. Alleviation of ER stress could ameliorate palmitate-induced apoptosis in myotubes[246]. Excessive intake of lipids in mice was reported to cause ER stress in skeletal muscle[247]. However, the molecular processes by which obesity triggers ER stress remain unknown.

### Treatments regulating ER stress for degenerative musculoskeletal diseases

There are currently no effective and safe treatments to delay or halt the progression of degenerative musculoskeletal diseases, making them an unmet medical need and a clinical problem urgently required to be addressed. Nevertheless, the severe

socioeconomic burden of degenerative musculoskeletal diseases and the desire of patients for health and longevity call for effective and safe therapeutic approaches. Excessive ER stress is one of the causative factors involving in the pathogenesis of degenerative musculoskeletal diseases. Hence, regulation of ER stress may be a potential and prospective therapeutic strategy to alleviate degenerative musculoskeletal diseases. Thereinafter, we will provide a systematic summary of therapeutic tactics modulating ER stress from two main perspectives: decreasing the production of misfolded and unfolded proteins (including assisting protein folding and

blocking protein synthesis) and facilitating the degradation of misfolded and unfolded proteins (Table 1 [129,206,248-253]). Unfortunately, ER stress modulators are not currently in clinical trials for the treatment of degenerative musculoskeletal diseases, even though there have been clinical trials validating the efficacy and safety of ER stress modulators for the treatment of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease (NCT03533257, NCT02046434). Furthermore, possible hurdles in the journey from bench to bedside are discussed as well.

Chemical chaperones are reagents that regulate ER stress by

**Table 1 Therapeutic reagents targeting ER stress to alleviate degenerative musculoskeletal diseases**

| Therapeutic reagents | Effects in targeting ER stress   | Roles in degenerative musculoskeletal diseases   | Level of evidence | References |
|----------------------|--|--|-------------------|------------|
| 4-PBA                | Assist protein folding   | Inhibit ER stress, apoptosis, and cartilage degradation in anterior cruciate ligament transection rat models   | <i>In vivo</i>    | [248]      |
|                      |  | Inhibit ER stress-mediated osteoclast differentiation in IL-1 $\beta$ -treated BMSCs   | <i>In vitro</i>   | [129]      |
|                      |  | Protect NP cell from AGEs-induced apoptosis  | <i>In vitro</i>   | [206]      |
| TUDCA                | Assist protein folding   | Recover cell proliferation, reduce apoptosis and increase expression of type II collagen in OA chondrocyte   | <i>In vitro</i>   | [249]      |
|                      |  | Alleviate compression-induced apoptosis and necroptosis of NP cells  | <i>In vitro</i>   | [250]      |
| Salubrinal           | Inhibit eIF2 $\alpha$ dephosphorylation                                | Inhibit ER stress-mediated upregulation of MMP13   | <i>In vitro</i>   | [251]      |
|                      | Inhibit protein translation  | Stimulate the osteoblastogenesis of MC3T3 E1 and inhibit the osteoclastogenesis of RAW264.7  | <i>In vitro</i>   | [252]      |
| Guanabenz            | Inhibit eIF2 $\alpha$ dephosphorylation<br>Inhibit protein translation | Stimulate the osteoblastogenesis of MC3T3 E1 and inhibit the osteoclastogenesis of RAW264.7  | <i>In vitro</i>   | [252]      |
| CBZ                  | Increase autophagy   | Reduce ER stress, improve hypertrophic chondrocyte differentiation, accelerate bone growth rate, and decrease skeletal dysplasia in metaphyseal chondrodysplasia type Schmid mouse model | <i>In vivo</i>    | [253]      |

ER. Endoplasmic reticulum; 4-PBA. 4-phenylbutiric acid; BMSCs. Bone marrow mesenchymal stem cells; NP. Nucleus pulposus; AGEs. Advanced glycation end products; TUDCA. Tauroursodeoxycholic acid; OA. Osteoarthritis; eIF2 $\alpha$ .  $\alpha$ -subunit of eukaryotic translation initiation factor 2; MMP13. Matrix metalloproteinase-13; CBZ. Carbamazepin

assisting proper protein folding, such as 4-phenylbutiric acid (4-PBA) and tauroursodeoxycholic acid (TUDCA). 4-PBA, a small molecule chemical chaperone, was reported to suppress ER stress, apoptosis, and damage of cartilage in anterior cruciate ligament transection rats with OA[248]. Moreover, 4-PBA restrained ER stress-mediated osteoclast differentiation in IL-1 $\beta$ -treated BMSCs and protected NP cells from AGEs-induced apoptosis by inhibiting ER stress[129,206]. Currently, 4-PBA is mainly recommended for clinical treatment of inherited urea cycle disorders; whereas, there are no clinical trials on 4-PBA for the treatment of degenerative musculoskeletal diseases[254]. TUDCA is another chemical chaperone playing a critical role in controlling ER stress. Compared with tunicamycin-treated chondrocytes, TUDCA-treated chondrocytes exhibited reduced levels of ER stress markers, recovered cell proliferation, decreased apoptosis, and increased expression of type II collagen[249]. Moreover,

TUDCA alleviated compression-induced apoptosis and necroptosis of NP cells by reducing ER stress[250]. TUDCA has been approved by the Food and Drug Administration for primary biliary cholangitis therapy in modern clinical practice. Considering that TUDCA is transported into cells *via* the Na<sup>+</sup>/taurocholate co-transporting peptides mainly expressed on the membrane of hepatocytes, the clinical application of TUDCA in non-liver diseases such as degenerative musculoskeletal diseases may be somewhat confined by off-target effects[255]. Furthermore, blocking protein synthesis is another approach to avoid the accumulation of misfolded and unfolded proteins in the ER and subsequently regulate ER stress. Salubrinal is a selective inhibitor of eIF2 $\alpha$  phosphatase that interdicts protein synthesis by increasing eIF2 $\alpha$  phosphorylation and ultimately suppresses ER stress[256]. Hamamura *et al.*[251] found that salubrinal downregulated ER stress-mediated matrix metalloproteinase-13 expression by suppressing p38

MAPK in tunicamycin-treated chondrocytes. In addition, salubrinal and guanabenz (another selective inhibitor of eIF2 $\alpha$  dephosphorylation) were demonstrated to not only stimulate the osteoblastogenesis of MC3T3 E1, but also inhibit the osteoclastogenesis of RAW264.7[252]. Another strategy to manipulate ER stress is through degradation of misfolded and unfolded proteins accumulated in the ER, which is similar to ERAD. As a clinically approved autophagy stimulant used for the treatment of epileptic seizures and bipolar disorder, carbamazepine was testified to relieve ER stress and improve hypertrophic differentiation of chondrocytes in metaphyseal chondrodysplasia type Schmid mouse model, giving rise to an accelerated bone growth rate and decreased skeletal dysplasia[253]. However, it has not yet been determined, even in preclinical studies, whether carbamazepine can delay the progression of degenerative musculoskeletal diseases by mitigating ER stress.

With the vigorous development and expansion of translational medicine, it has always been the long-cherished desire of clinical and pharmaceutical workers to facilitate the achievements of basic and academic research to clinical application and marketing. Despite tremendous strides have been made in the regulation of ER stress for the treatment of degenerative musculoskeletal diseases, significant knowledge gap still lies in the bench-to-beside research and the journey to the clinic is not as smooth as expected. Firstly, more comprehensive and in-depth *in vitro* and *in vivo* experiments are required to expound the pathogenic and protective roles of ER stress in degenerative musculoskeletal diseases. As previously suggested, mild ER stress is protective, whereas excessive ER stress leads to disturbed ER homeostasis, cellular dysfunction, and even cell death. A better understanding of ER stress in the pathogenesis of degenerative musculoskeletal diseases is warranted for the development of pharmacological avenues to modulate ER stress for the prevention and treatment of degenerative musculoskeletal diseases. Secondly, the targets alternative to modulate ER stress are various, but the most appropriate ones for designing drugs remain to be identified. Thirdly, disease phenotypes in rodent models (generally referring to mice and rats) with degenerative musculoskeletal diseases are not always concordant with humans, thus potent modulators of ER stress in rodent models are not necessarily effective in patients. Because pathogenesis is more complicated and represents significant heterogeneity in humans, ER stress modulators that have been validated for efficacy and safety *in vivo* are not directly available for clinical trials. Further investigations of ER stress modulators in larger animal models, such as pigs and bovines, which are more similar to humans

in terms of anatomy, body size, and physiological status, are needed. Next, reasonable drug concentrations, dosage forms, routes and frequency of administration for clinical trials have not been determined. Eventually, the poor selectivity of free ER stress modulators results in the susceptibility to aggregate in tissue or cells at non-disease sites, causing potential systemic side effects, decreased bioavailability, and reduced efficacy. TUDCA, for example, is transported into the cell *via* the Na<sup>+</sup>/taurocholate co-transporting peptides highly expressed on hepatocytes and is therefore prone to off-target effects. The use of drug delivery systems loaded with ER stress regulators allows for targeted, long-lasting and safe delivery of drugs to disease sites, which is a promising curative strategy.

## Conclusions

Degenerative musculoskeletal diseases (including OA, OP, IVDD, and SP) are becoming increasingly prevalent as the aging population increases worldwide. Degenerative musculoskeletal diseases not only increase the global health care burden, but also result in absenteeism owing to their symptoms and adverse clinical outcomes, which imposes a huge direct and indirect socioeconomic burden on families and society. Meanwhile, rapid economic and social development has promoted the desire of the elderly for health and longevity. However, our understanding of the pathogenesis of degenerative musculoskeletal diseases remains limited, hindering the advancement of effective and safe treatments. The imbalance between pursuing health and the low efficacy and safety of existing therapies provides a catalyst for the research of degenerative musculoskeletal diseases. Through sophisticated molecular mechanisms, ER stress is able to influence cartilage degeneration, synovitis, meniscal lesion, subchondral bone remodeling of OA, bone remodeling and angiogenesis of OP, NP degeneration, AF rupture, CEP degeneration of IVDD, and SP, contributing to degenerative musculoskeletal diseases. Regulation of ER stress can slow the progression of degenerative musculoskeletal diseases by regulating cartilage degeneration, bone remodeling, and NP degeneration to a certain extent *in vitro* or *in vivo*. Moreover, we have presented the possible future research directions of ER stress in degenerative musculoskeletal diseases, the latent challenges that will be encountered in the clinical translation of ER stress modulators, and the corresponding solutions. Although no ER stress modulators have yet entered clinical trials, these preliminary findings set the stage for further evaluation of the feasibility, efficacy, and safety of modulating ER stress for the treatment of human musculoskeletal degenerative diseases.

## Abbreviations

AF: Annulus fibrosus; AGEs: Advanced glycation end products; Akt: Protein kinase B; ATF4: Activating transcription factor 4; ATF6: Activating transcription factor 6; BiP: Binding immunoglobulin protein; BMSCs: Bone marrow mesenchymal stem cells; Ca<sup>2+</sup>: Calcium; CEP: Cartilaginous endplate; CHOP: C/EBP homologous protein; C/EBPβ: CCAAT/enhancer binding protein β; ECM: Extracellular matrix; eIF2α: α-subunit of eukaryotic translation initiation factor 2; ER: Endoplasmic reticulum; ERAD: ER-associated degradation; EWGSOP: European Working Group on Sarcopenia in Older People; FABP3: Fatty acid binding protein 3; FAs: Fatty acids; FLSs: Fibroblast-like synoviocytes; GLP-1: Glucagon-like peptide-1; GLUT1: Glucose transporter 1; GRP78: Glycoprotein 78 kD glucose-regulated protein; HIF-1α: Hypoxia-inducible factor-1α; IGF-1: Insulin-like growth factor-1; IL: Interleukin; IRE1: Inositol-requiring enzyme 1; IVD: Intervertebral disc; IVDD: Intervertebral disc degeneration; JNK: c-Jun N-terminal kinase; MAPK: Mitogen-activated protein kinase; mTORC1: Mechanistic target of rapamycin complex 1; NFATc1: Nuclear factor of activated T cells cytoplasmic 1; NF-κB: Nuclear factor-kappa B; NLRP3: NOD-like receptor family pyrin domain containing 3; NP: Nucleus pulposus; OA: Osteoarthritis; OP: Osteoporosis; PERK: Protein kinase R-like ER kinase; RANKL: Receptor activator of NF-κB ligand; ROS: Reactive oxygen species; Runx2: Runt-related transcription factor 2; SIRT1: Sirtuin1; Smad: Small mother against decapentaplegic; SP: Sarcopenia; SREBP: Sterol response element binding protein; TUDCA: Tauroursodeoxycholic acid; UPR: Unfolded protein response; XBP-1: X-binding protein 1; 4-PBA: 4-phenylbutyric acid.

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## Authors' contributions

YSL and GHZ conceived this article. ZQW and JL drafted and revised the manuscript. WQX and YHS prepared the table and figures. All authors read and approved the final manuscript.

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## Availability of data and materials

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## Declarations

### Ethics approval and consent to participate

Not applicable.

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### Competing interests

The authors declare that they have no competing interests.

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