Developments in the connection between epithelial-mesenchymal transition and endoplasmic reticulum stress (Review)

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Abstract. Endoplasmic reticulum stress (ERS) and epithelial-mesenchymal transition (EMT) have important roles in fibrosis and tumour development. Moderate ERS activates cellular defence mechanisms in response to noxious stimuli; however, sustained or overly strong ERS induces apoptosis. In this disease process, EMT induces epithelial cells to acquire the ability to migrate and invade. Reportedly, ERS directly or indirectly regulates EMT processes through multiple mechanisms (such as key transcription factors, signalling pathways, ferroptosis, autophagy and oxidative stress), and both processes form a complex network of interactions. Given the critical roles of ERS and EMT in disease, targeted intervention of these two processes has emerged as a potential therapeutic strategy. In the present study, the molecular interaction mechanism of ERS and EMT was systematically explored, research progress in fibrotic and neoplastic diseases was reviewed and the potential application prospects of related targeted therapies were examined, which may provide new ideas for the development of drugs to reverse fibrosis and treat tumours.

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Abbreviations: ERS, endoplasmic reticulum stress; EMT, epithelial-mesenchymal transition; UPR, unfolded protein response; PERK, protein kinase R-like endoplasmic reticulum kinase; IRE1, inositol-requiring enzyme 1; ATF6, activating transcription factor 6; GRP78, glucose-regulated protein 78; CHOP, C/EBP homologous protein; TGF-β, transforming growth factor β; MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor κB; XBP1, x-box binding protein 1

Key words: endoplasmic reticulum stress, epithelial-mesenchymal transition, unfolded protein response, tumours, fibrotic disease, apoptosis, autophagy, ferroptosis, oxidative stress, inflammation

Contents

1. Introduction

Endoplasmic reticulum (ER) stress (ERS) is a pathological state in which the normal function of the ER is impaired, leading to the accumulation of unfolded or misfolded proteins and disruption of Ca^{2+} homeostasis. To manage ERS, cells activate an adaptive mechanism known as the unfolded protein response (UPR) to restore metabolic balance and protein folding capacity within the ER (1). On the other hand, epithelial-mesenchymal transition (EMT) is a process in which epithelial cells, stimulated by specific cytokines or microenvironmental signals, lose their polarity and cell-cell adhesion properties, gradually transforming into mesenchymal cells with migratory and invasive capabilities. This transformation contributes considerably to pathological processes such as tissue remodelling, fibrosis and tumour metastasis (2). As two core processes in the field of cell biology, ERS and EMT substantially influence the initiation, progression and metastasis of fibrotic diseases and tumours (3,4). However, the specific mechanisms by which ERS directly or indirectly regulates EMT have not yet been fully elucidated and related research remains limited. Therefore, the aim of this study was to systematically explore the research progress and targeted therapeutic strategies of ERS and EMT in fibrotic diseases and tumours, and to elucidate the molecular connections and regulatory mechanisms between the two processes. Another objective was to provide a theoretical foundation to further reveal the interactions between these complex processes in the future, as well as to offer new insights and directions for the innovation of clinical treatment strategies.

2. Overview of ERS

A heat shock protein called glucose-regulated protein 78 (GRP78)/immunoglobulin heavy chain-binding protein (BiP)

dissociates from the transmembrane receptor, binds and processes the unfolded proteins and activates the UPR, which is the cell's protective pathway (5). Any factor that disrupts protein function, such as hypoxia, nutrient deprivation or oxidative stress, can cause the accumulation of misfolded/unfolded proteins in the ER, a crucial organelle involved in Ca^{2+} storage and release in the lumen of the ER (6). As shown in Fig. 1, to maintain ER homeostasis and restore ER function, the UPR mediates three transmembrane protein pathways: Activating transcription factor 6 (ATF6), the protein kinase RNA-like ER kinase (PERK) and inositol-requiring enzyme 1α (IRE1α) (7). Furthermore, ERS activation can result in either cell survival or death, depending on the length and severity of the stress (4). This is because when cells are exposed to ERS, the UPR shows two distinct results. However, cells that are exposed to weak or short-term ERS will trigger adaptive and pro-survival signalling, which will restore ER homeostasis to a physiological level. Conversely, prolonged or severe ERS will trigger autophagy and apoptosis-associated signalling across several pathways, changing the UPR from a pro-survival network to a pro-apoptotic system, which promotes apoptosis and eventually causes illness (8,9).

3. Overview of EMT

EMT is a dynamic process in which epithelial cells undergo a series of complex molecular modifications to transdifferentiate into mesenchymal cells (2). Based on their biological context and functions, EMTs are categorized into three subtypes: Type I EMT is associated with embryonic development, Type II is linked to tissue repair and organ fibrosis and Type III is related to cancer invasion and metastasis. These subtypes contribute significantly to various physiological and pathological conditions (2,10,11). EMT initiation depends on multiple inducing signals and involves the activation of numerous signalling pathways. Simultaneously, EMT is regulated by several key transcription factors, such as Snail family transcriptional repressor 1 (SNAIL1) and SNAIL2, zinc finger E-box-binding homeobox 1 (ZEB1) and ZEB2 and the TWIST transcription factor. These transcription factors suppress the expression of epithelial marker genes and activate genes associated with the mesenchymal phenotype, playing crucial roles in development, fibrosis and cancer (11,12).

The induction of EMT involves complex interactions between signalling pathways and transcription factors, and its core regulatory mechanisms depend on the coordinated regulation of signalling pathways such as transforming growth factor-β (TGF-β), Wnt and Notch (13). Among these, TGF-β1 critically induces EMT. TGF-β activates both canonical (Smad-dependent) and non-canonical (Smad-independent) signalling pathways by binding to its receptors TβRI and TβRII (14). The canonical signalling pathway is the primary route through which TGF-β regulates EMT: TβRII recruits and phosphorylates TβRI, which in turn phosphorylates the key signal transducers Smad2 and Smad3. Subsequently, the phosphorylated Smad2/3 forms heterodimeric or trimeric complexes with Smad4, which translocate into the nucleus and recruit co-activators such as CREB-binding protein or P300 to regulate the target genes' transcription (15). Additionally, TGF-β mediates non-canonical signalling pathways through mechanisms such as phosphorylation, acetylation, ubiquitination and protein-protein interactions. These non-Smad signalling branches can either independently execute TGF-β-mediated biological functions or modulate the canonical Smad signalling pathway, thereby synergistically influencing the EMT process (16). As shown in Fig. 2, EMT is a reversible process in which cells can be restored to the epithelial state by mesenchymal-epithelial transformation (MET) (17), a feature that provides new insights for developing related therapeutic strategies.

4. The role of ERS and EMT in disease

ERS and EMT in fibrotic disease. Necrosis of organ parenchymal cells and excessive extracellular matrix deposition result in fibrosis, a pathological process that causes connective tissue growth and, in certain cases, organ sclerosis (18). Various organs can be affected by fibrosis, and in developed nations, mortality rates may reach 45% (19). Substantial evidence reveals that ERS is associated with fibrosis in numerous organs. For instance, ERS in fibrotic lung tissue is thought to contribute significantly to aggravating the development of pulmonary fibrosis, a chronic progressive disease in the lungs (20). A considerable increase in ERS markers in the alveolar epithelial type II cells has been progressively verified in patients in various studies with various fibrotic lung disorders, such as interstitial lung disease, asbestosis and silicosis (21). Findings from a study showed that the UPR can accelerate the development of liver fibrosis by inducing transporter and Golgi organization 1-mediated hepatic stellate cell collagen I production in an x-box binding protein 1 (XBP1)-dependent manner (22). Recently, in numerous investigations, the pathogenic function of ERS in myocardial fibrosis in the heart has been demonstrated. For instance, using microarray and bioinformatics analysis, Li *et al* (23) investigated genetic changes in cardiac fibrosis and discovered putative biomarkers linked to ERS. In the hearts of pathologically cardiometabolically hypertrophied mice, Zhang *et al* (24) discovered that interferon gene stimulating drugs also induce fibrosis and inflammation through ERS.

Currently, controlling ERS and chaperone function may be a possible treatment strategy for fibrosis. Ghafoor *et al* (25) revealed that lung fibroblasts had higher expression levels of zinc finger CCCH-type containing 4 protein (ZC3H4) and sigma 1 receptor (sigmar1), two novel members of the zinc-finger protein family, and that silica-enhanced fibroblast activation was reduced by ZC3H4 knockdown and ERS inhibition. Based on their findings, Sigmar1 and ZC3H4 may be new therapeutic targets for silicosis (25). In addition, Chen *et al* (26) showed that crystalline silica-induced lung fibrosis is reduced when ERS is inhibited by focusing on the IRE1α-thioredoxin domain containing 5 pathway. Sun *et al* (20) reported that lactic acid causes cellular fibrosis by activating caspase-12 via the ATF4-C/EBP homologous protein (CHOP) axis mechanism. Since caspase-12 induces apoptosis and promotes fibrosis, ERS inhibitors can successfully prevent pulmonary fibrosis and alveolar epithelial cell death, providing a new possible treatment target for pulmonary fibrosis. Thalidomide has anti-inflammatory and immunomodulatory properties. It reduces inflammatory responses and the ERS and Toll-like

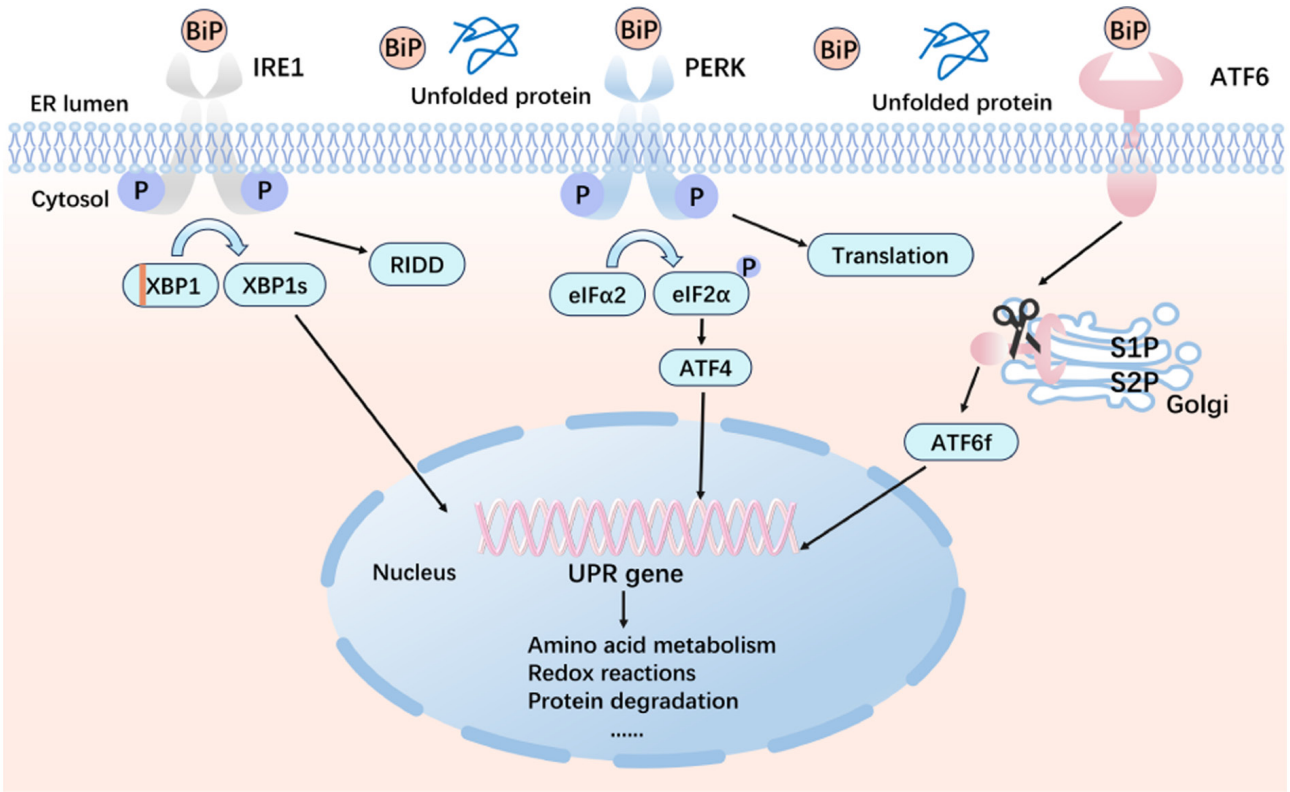

Figure 1. Schematic displaying the unfolded protein response signalling pathway. When ER stress occurs, GRP78/BiP dissociates from the transmembrane receptor, binds and processes unfolded proteins, and activates the cell's protective pathway, the UPR mediates three transmembrane protein pathways, namely IRE1α, PERK and ATF6, to maintain ER homeostasis and restore ER function. ER, endoplasmic reticulum; IRE1α, inositol requiring enzyme 1α; PERK, protein kinase RNA-like ER kinase; ATF6, activating transcription factor 6; UPR, unfolded protein response; BiP, binding immunoglobulin protein; XBP1, x-box binding protein 1; RIDD, regulated IRE1α-dependent decay; eIF2α, eukaryotic initiation factor 2α; ATF4, activating transcription factor 4; S1P, sphingosine 1-phosphate.

receptor 4-nuclear factor κB (NF-κB) pathways in mice with silicosis and silica-stimulated alveolar macrophage cell line MH-S cells (27). Yang *et al* (28) reported in their study that ERS contributes to lung fibrosis by altering lung-resident mesenchymal/stromal cells (LR-MSC) and converting them into myofibroblasts. C/EBP homologous protein (CHOP) plays a crucial role in this process, and the findings reveal that medications that target CHOP or treatments involving the use of CHOP to knock down LR-MSC may be effective ways to treat lung fibrosis. Severe ERS is associated with liver fibrosis and cirrhosis, which activate PERK and IRE1α, contributing to the disease pathology. Therapeutic inhibition of the UPR pathway reduces the severity of cirrhosis and liver fibrosis (29). Diacerein improves rat liver damage caused by cholestasis by blocking the high-mobility group box 1/receptor for advanced glycation end-products/NF-κB/JNK pathway and ERS fibrosis (30). Therefore, ERS modulation may be a promising therapeutic approach to halt the advancement of fibrosis as the understanding of the connection between ERS and fibrosis continues to develop.

EMT is a natural process of organ development and wound repair through finely programmed processes (31). Reports show that numerous fibrotic diseases are also associated with EMT, which has been linked to inflammatory bowel disease, in which recurrent intestinal inflammatory stimuli set off mucosal repair responses that result in the deposition of extracellular matrix and the establishment of fibrosis (32). The molecular pathogenesis of subretinal fibrosis in neovascular age-related macular degeneration is a complex process in which the EMT of retinal pigment epithelium plays a critical role (33). Researchers have discovered that fibrosis is considerably decreased when transcription factors or signalling associated with EMT are inhibited (34). For instance, in a laser-induced animal model, luteolin suppresses Smad2/3 and Yes-associated protein signalling, thereby preventing EMT in the retinal pigment epithelium (35). EMT in diabetic nephropathy is driven by lactate through the H3K14la/Kruppel-like factor (KLF)5 pathway. Furthermore, renal-specific knockdown and pharmacological inhibition of KLF5 decreased EMT formation and mitigated the fibrosis associated with diabetic nephropathy (36). The catalytic subunit of the DNA-dependent protein kinase prevents EMT in radiation-induced lung fibrosis through the ubiquitination and degradation of Twist1 (37). By controlling Smad-dependent and non-dependent signalling pathways in proximal tubular cells that depend on TGF-β1 for EMT, chrysin has been shown to prevent cyclosporine A-induced renal tubulointerstitial fibrosis (38). Targeting TGF-β signalling appears to be a promising therapeutic approach because of the crucial role that TGF-β and its downstream molecules play in fibrosis and cancer development (34).

ERS and EMT in cancer. ERS is essential for the development, spread and treatment response of cancer. High levels of expression and activation of ERS indicators, including IRE1,

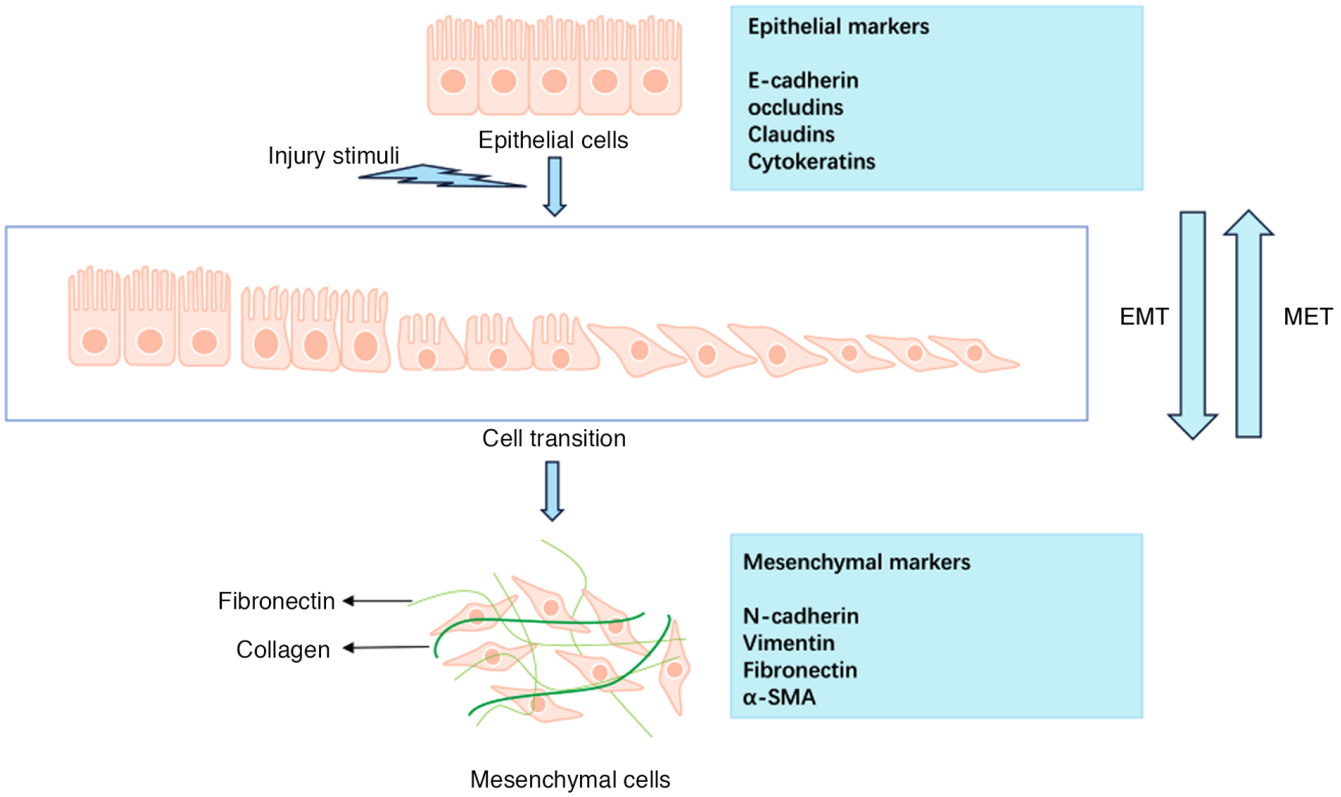

Figure 2. Bidirectional transition between EMT and MET and the different markers of each state. EMT, epithelial-mesenchymal transition; SMA, smooth muscle actin.

PERK, ATF6 and GRP78, have been observed in various human malignancies, as reported in several studies (39-43). ERS is produced when tumour cells are exposed to both extrinsic and intrinsic factors that can change protein homeostasis. Prolonged ERS of greater than moderate intensity can, among other effects, promote cancer cell transformation and proliferation, which in turn control tumour growth and metastasis, among others (44). A current strategy to mitigate the protective effects of ERS on cancer would be to target ERS (44). The ERS-related IRE1/CHOP pathway may be the mechanism by which Tongguanteng injection combats osteosarcoma (45). Through ERS and mitochondrial malfunction, laminarin, a β-1,3-glucan obtained from brown algae, suppresses the development of ovarian cancer cells (46). Currently, numerous compounds are being created to target the three UPR sensors. However, the elements that influence which sensors behave as pro- or anti-apoptotic signals are unknown. Tumorigenesis, progression, metastasis, immunological escape and radiation resistance are all signs that cancer cells are using adaptive responses to survive overstimulation. Nevertheless, tumour death results from prolonged or severe stimulation (47). The complexity of the UPR as a therapeutic target is highlighted by its dual roles in adaptation and disease. Hence, effective modulation of these pathways may delay disease progression and provide useful possibilities for establishing novel therapeutic approaches by restoring ER function or inducing controlled apoptosis in cancer cells.

EMT, in which tumour cells change from an epithelial to a mesenchymal form, gaining motility, invasion and metastasis, is a defining feature of tumour plasticity (48). Reportedly, the function of EMT is driven by conserved zinc finger transcription factors, including Snail, Zeb-1 and Slug, which are regulated by upstream TGF-β activity. Cells that receive EMT grow and degrade from the surrounding microenvironment before migrating from the original site (49). Clinically, focusing on EMT can have several advantages, including lowering chemotherapy resistance and preventing metastases (50). Inhibiting important EMT signalling pathways, preventing interactions with the tumour microenvironment (TME) and reversing EMT by promoting MET are possible therapeutic approaches (51). A well-known strategy to counter EMT is to interfere with TGF β signalling. By blocking the EMT process, galunisertib, a tiny TGF-βR1 inhibitor, can be potentially used for treating several malignancies. Findings from clinical trials have shown its effectiveness, e.g., when combined with sorafenib for hepatocellular carcinoma and gemcitabine for advanced pancreatic cancer (52). By altering the matrix metalloproteinase and adenosine monophosphate-activated protein kinase (AMPK)/NF-κB pathways, specifically the upregulation of epithelial E-calmodulin and the downregulation of mesenchymal waveform protein, the natural compound methyl gallate prevents the proliferation, migration, invasion and EMT of hepatocellular carcinoma cells (51). However, targeting cancer-associated EMT specifically while preserving normal EMT processes that are essential for tissue regeneration and repair is a challenge; nonetheless, a thorough understanding of EMT mechanisms may offer fresh insights to develop future medications and therapeutic approaches.

5. Interrelationship between ERS and EMT

Evidence in favour of the relationship: Experimental studies. As shown in Fig. 1, GRP78 is a marker protein for ERS activity (50). Fig. 2 shows that the loss of E-cadherin and laminin 1 and the resulting conversion to N-cadherin, α-smooth muscle actin, fibroblast-specific protein-1 and vimentin are the primary characteristics of EMT. ERS is recognized as a key mechanism for controlling EMT in various experimental investigations. For instance, when chemotherapeutic medications that are frequently used for treatment activate ERS, EMT-like states are also activated. These states persist as long as ERS is present and seem to diminish once ERS is removed; however, they still persist, indicating that ERS-induced EMT has a long-term effect (53). Delbrel *et al* (54) treated hypoxic alveolar epithelial cells with the ERS inhibitor 4-phenylbutyrate ester (4-PBA) and discovered that it inhibited the increase of TGF-β1, ZEB1 and Twist1 mRNA levels induced by hypoxia. Gong *et al* (55) discovered that IL-32 could induce alveolar epithelial cells to produce ERS, which in turn caused EMT formation. Furthermore, by producing ERS, Liang *et al* (56). discovered that advanced oxidation protein products may induce EMT in human glomerular endothelial cells. Both ERS and EMT were then reversed after administering salubrinal, an ER stress inhibitor, to human glomerular endothelial cells (56). In diabetic nephropathic mice and renal tubular epithelial cells treated with high glucose, Han *et al* (57) discovered that *Ginkgo biloba* leaf extract EGB761 improved extracellular matrix and EMT accumulation by inhibiting ERS. Zhou *et al* (58) reported that the 4-PBA may prevent this impact, whereas tunicamycin, a chemoinducer of ERS, could encourage cell migration and E-cadherin downregulation in human lens epithelial cells. Furthermore, high calcium concentrations of 1.75 and 2.25 mmol/l activated ERS, which in turn increased EMT in human peritoneal mesothelial cells, according to a recent experimental investigation by Guo *et al* (59). This evidence suggests a strong association between ERS and EMT.

Mechanisms for linking ERS to EMT

ERS-UPR-EMT. ERS regulates the EMT process through three core pathways of UPR (IRE1-XBP1, PERK-eIF2α and ATF6), and this regulatory network demonstrates high conservation and specificity across different disease models (60). Substantial evidence indicates a complex regulatory network between ERS and EMT: Chemotherapeutic agents such as cisplatin induce significant upregulation of ERS markers (Bip, Chop, protein disulfide-isomerase) and EMT markers (Vimentin, Snail) in multiple tissues (lung, liver, kidney), a phenomenon also observed in primary lung adenocarcinoma patient samples, confirming the universality of ERS-induced EMT (53). At the molecular level, lysyl oxidase-like 2 overexpression activates the IRE1-XBP1 pathway, leading to the spliced form of XBP1 (XBP1s) specifically recognizing and binding to the unfolded protein response element core motif (ACGTG) in the promoter regions of key EMT transcription factors (SNAI1, SNAI2, ZEB2 and transcription factor 3 (TCF3). Through chromatin immunoprecipitation and luciferase reporter assays, researchers precisely mapped XBP1s binding sites at SNAI1 (-550 bp), SNAI2 (-526 bp), ZEB2 (-2,269/-658 bp) and TCF3 (-2,230 bp) promoters, demonstrating that this binding significantly enhances transcriptional activity (61). Similar regulatory mechanisms have been identified in various cancers: In breast cancer, XBP1 promotes EMT and invasion by directly activating the Snail promoter and is significantly associated with poor prognosis; in glioblastoma multiforme, the IRE1-XBP1 axis not only upregulates EMT markers (Vimentin, ZEB1) but also promotes the secretion of chemokines (C-X-C motif chemokine ligand 2 and C-C motif chemokine ligand 2) (62); in hepatocellular carcinoma, a XBP1s/Twist/Snail cascade regulatory axis is formed (63). Notably, viral infections such as respiratory syncytial virus can also activate this pathway by inducing SNAI1 expression (5.8-fold mRNA increase) through IRE1α-XBP1s, a process specifically inhibited by the IRE1α inhibitor KIRA8 (64). Beyond the IRE1-XBP1 pathway, the PERK-eIF2α axis promotes EMT by upregulating ZEB1 in fibrotic diseases (65,66), while the ATF6 pathway drives EMT through distinct mechanisms in cervical and colorectal cancers (67,68). As shown in Fig. 3, these findings systematically revealed the core mechanism of the ERS-UPR-EMT regulatory network: The XBP1s drive the EMT process by either directly binding to EMT transcription factor promoters or regulating intermediate signaling pathways (TGF-β/Smad, NF-κB, SRC, etc.). Based on these findings, several targeted intervention strategies have shown therapeutic potential, including ginsenoside's getinoblastoma 1-mediated inhibition of the BiP/eIF2α/CHOP axis (69), mesenchymal stem cells modulating the IRE1α branch (70) and luteolin-induced EMT reversal through regulation of E-cadherin/N-cadherin expression (71). These studies not only systematically elucidate the core regulatory mechanisms of the ERS-UPR-EMT network but also provide a crucial theoretical foundation for developing precise therapeutic strategies for fibrosis and cancer.

ERS-TGFβ/Smad-EMT. The TGF-β/Smad signaling pathway establishes a complex bidirectional interaction network between ERS and EMT through a multilevel molecular regulatory mechanism. When TGF-β ligand binds to TβRII receptor, it induces the phosphorylation of the GS structural domain of TβRI, which in turn specifically catalyzes the phosphorylation of the C-terminal SSXS motif of Smad2/3, promotes the formation of its complex with Smad4 and translocates it to the nucleus, and regulates the expression of key transcription factors of EMT (such as SNAIL1/2, ZEB1/2 and TWIST) expression (72-74). Notably, ERS can activate this pathway through multiple mechanisms: PM2.5 exposure induces ERS-dependent TGF-β1/Smad3 signaling activation by decreasing caveolin 1 protein levels (75); Grp78 knockdown leads to its dissociation from TβRI, which deregulates the inhibition of receptor activation (76); and cadmium exposure activates Smad3 signaling directly by phosphorylating IRE1α. These findings reveal an important role for ERS as an upstream regulator of the TGF-β/Smad pathway (77). However, the direction of regulation varies significantly in different tissues: In endometrium and ovarian granulosa cells, ERS explicitly acts as an upstream activator of the TGF-β/Smad pathway, whereas in other models of fibrosis, a positive feedback loop may develop, whereby activation of the TGF-β/Smad pathway in turn leads to a further induction of ERS (78,79). This tissue specificity may arise from cell-type-specific differences in the regulator's expression or

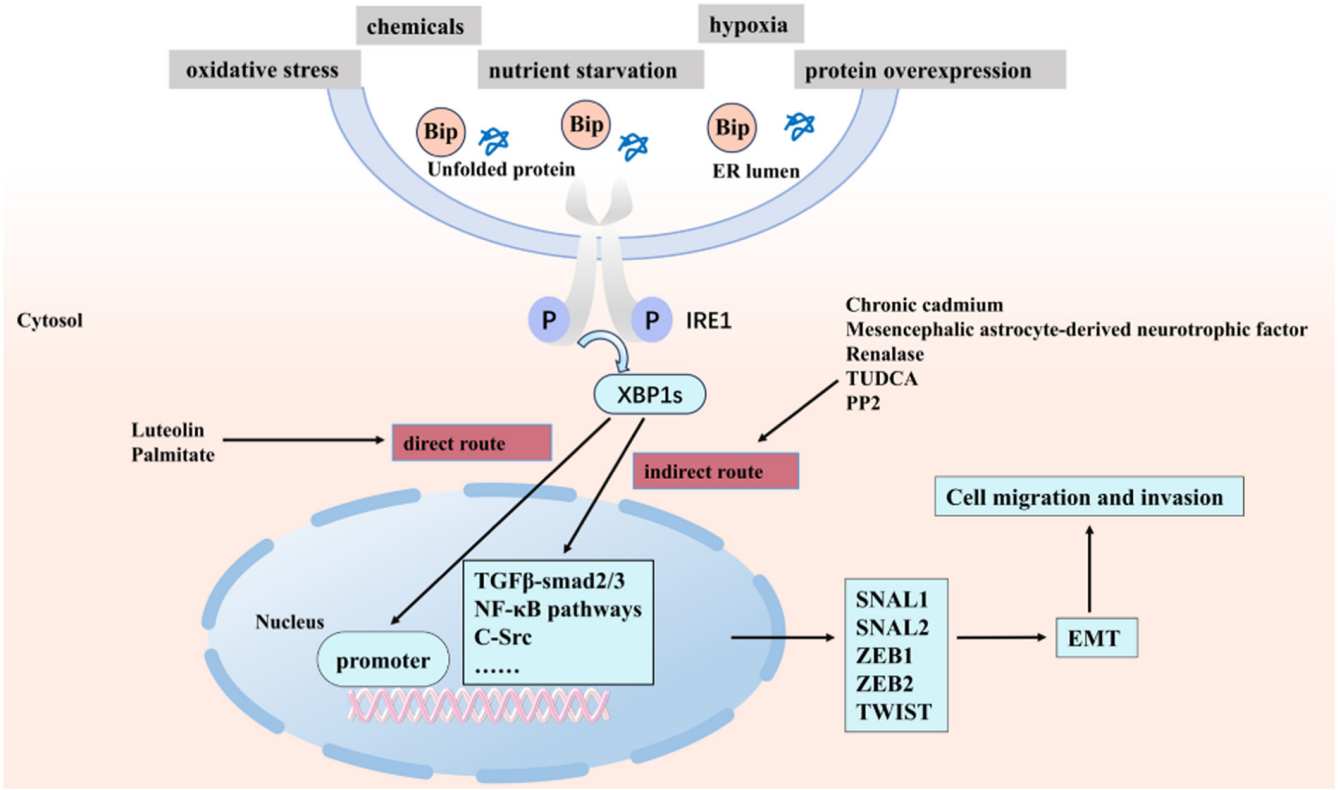

Figure 3. Schematic of the promotion of EMT by XBP1. The IRE1-XBP1 signalling pathway is key in regulating EMT. This pathway can directly (e.g., binding to the promoters of EMT transcription factors) or indirectly (e.g., activating downstream signalling pathways such as TGF-β/Smad2/3, NF-κB or c-Src (a 60 kDa nonreceptor tyrosine kinase encoded by the SRC gene) regulate the expression of EMT-associated transcription factors, which can promote the EMT process, and enhance the migration and invasive ability of cells. Notably, indirect regulatory pathways (e.g., TGF-β/Smad and NF-κB, etc.) dominate the process. IRE1α, inositol requiring enzyme 1α; ER, endoplasmic reticulum; EMT, epithelial-mesenchymal transition; BiP, binding immunoglobulin protein; XBP1, x-box-binding protein 1; SNAL1, snail family transcriptional repressor 1; ZEB1, zinc finger E-box-binding homeobox 1; TWIST, the transcription factor twist; TGF-β, transforming growth factor β; smad, small mother against decapentaplegic; NF-κB, nuclear factor κB; C-Src, Src kinase; TUDCA, tauroursodeoxycholic acid; PP2, Phloem protein 2.

microenvironmental differences. Of particular interest is the finding that SIRT7 activates the IRE1α-XBP1 axis to promote PD-L1 expression while inhibiting classical TGF-β signaling through deacetylation of SMAD4, a finding that provides a new idea for the development of combined therapeutic strategies targeting the ERS-TGFβ-EMT network (80). Future studies need to deeply resolve the molecular basis of the differences in the direction of regulation in different tissues and develop novel modulators that can specifically intervene in pathological interactions without affecting physiological functions.

Nrf2 (NF-E2-related factor 2) reactive oxygen species (ROS)-ERS-EMT. Nrf2, a core regulator of cellular antioxidant defence, maintains redox homeostasis by coordinating the dynamic balance of the kelch-like ECH-associated protein 1 (Keap1)-E3 ubiquitin ligase scaffold cullin 3 (Cul3) ubiquitination system (81). Under homeostatic conditions, Keap1 promotes ubiquitination degradation of Nrf2 by binding to the ETGE/DLG motifs of Nrf2 through its Kelch structural domain (82); whereas, when the PERK pathway is activated, it induces the expression of ATF4 by phosphorylating eIF2α, which directly binds to the antioxidant-responsive elements of the Nrf2 promoter and upregulates Nrf2 transcription. Meanwhile, PERK kinase activity also blocks Keap1 interactions with Nrf2 by phosphorylating the Ser40 site of Nrf2, a dual mechanism that synergistically stabilizes the Nrf2 protein (1,83). This protective mechanism is hijacked in the TME: In lung cancer models, KRAS mutations enhance Nrf2 nuclear translocation through activation of PI3K-AKT signaling, leading to abnormally low ROS levels, which in turn promotes EMT through the mechanisms of i) ROS-dependent downregulation of the pro-apoptotic factor raf kinase inhibitor protein, and ii) upregulation of the expression of SNAIL1 promoter by direct binding to it via ATF4 to create a pro-metastatic phenotype (84-86). ROS is not only a core mediator of the ERS-EMT network, but its dynamic balance of production and clearance determines cell fate. In a cadmium exposure-induced EMT model of prostate cancer, chronic ROS accumulation activates the ERS-Smad pathway through the following pathways: i) ROS induces oxidative modification of the Cys931 site of the IRE1α kinase structural domain, which triggers its autophosphorylation and tumor necrosis factor receptor associated factor 2 (TRAF2) recruitment, and then activates the JNK/NF-κB pathway to synergistically upregulate TGF-β1; ii) mitochondrial ROS are activated through the activation of the apoptosis signal-regulating kinase 1 (ASK1)-MAPK kinase 4 pathway phosphorylates the linker region (Thr179/Ser204) of Smad3, promoting its nuclear translocation and binding to the Snail promoter. This TGF-β-independent Smad activation mechanism can be specifically blocked by N-acetylcysteine (NAC), confirming

the critical role of the ROS-ERS axis (77). A similar mechanism is seen in environmental toxicology models: the PM2.5 component 1-nitropyrene activates the PERK-ATF4-CHOP axis via NADPH oxidase 4-dependent ROS generation, inducing downregulation of GRP78 expression in alveolar epithelial cells and dissociation of the E-cadherin/β-catenin complex, leading to EMT and interstitial fibrosis, a process that can be reversed by NAC or 4-PBA (ERS inhibitors) to reverse the process (87). Therapeutic strategies targeting this pathway need to take into account tissue specificity: In KRAS-mutant tumors, lignans restore ROS levels and induce pro-apoptotic signaling by competitively binding to the Neh1 structural domain of Nrf2 and disrupting its heterodimerization with musculoaponeurotic fibrosarcoma proteins (86); whereas, in liver fibrosis, short hairpin RNAs targeting mitochondrial calcium uniporter regulator 1 inhibit the ROS/Nrf2/Notch1 axis and the EMT processes (88). These findings systematically reveal a sophisticated regulatory network between redox homeostasis and EMT plasticity, providing a molecular basis for the development of precision therapies based on the Nrf2-ROS-ERS node.

ERS-EMT and programmed cell death. Programmed cell death is an actively regulated cellular process initiated under specific physiological and pathological conditions, primarily comprising three major forms: Apoptosis, autophagy and ferroptosis (89). Apoptosis serves as a crucial mechanism for eliminating abnormal or damaged cells (90), while autophagy represents a highly conserved process that maintains intracellular homeostasis by degrading dysfunctional cellular components such as protein/DNA aggregates and abnormal organelles (91), and ferroptosis is a distinctive form of iron-dependent regulated cell death driven by lipid peroxidation (92). These cell death modalities, together with ERS and EMT, constitute a complex regulatory network that plays pivotal roles in fibrosis and tumor progression.

Over time, the activated UPR engages multiple cellular signaling pathways that largely determine cell fate decisions, including autophagy, apoptosis, ferroptosis and inflammation (93). Studies in inflammatory stress models demonstrate synchronous activation of all three UPR sensors (ATF6, IRE1α, PERK) in conjunctival epithelial cells and fibroblasts, accompanied by upregulation of inflammatory and apoptotic markers (IL-1β, BAX, caspase-3), along with increased expression of autophagy-related protein light chain 3A/B in epithelial cells and lysosomal marker lysosome-associated membrane protein 1 in fibroblasts. These findings confirm the molecular mechanisms through which ERS remodels cell fate by integrating multiple stress signaling pathways (94). Under physiological conditions, the UPR precisely balances survival and death signals to determine cellular outcomes. However, disruption of this equilibrium through chronic UPR activation or functional impairment may contribute to tumorigenesis (95).

In apoptosis regulation, persistent ERS activates pro-apoptotic UPR pathways. Substantial evidence demonstrates that two key UPR kinases, PERK and IRE1α, promote apoptosis through distinct mechanisms (96,97). Specifically, chronic ERS triggers pro-apoptotic programs via the PERK-eIF2α-ATF4 signaling axis: ATF4 directly binds to C/EBP-ATF response elements in the CHOP promoter to enhance its transcription, while CHOP suppresses the anti-apoptotic protein Bcl-2 and induces pro-apoptotic proteins building information modelling/p53 upregulated modulator of apoptosis, ultimately leading to mitochondrial membrane potential collapse and caspase-9/3 cascade activation. Concurrently, IRE1α recruits TRAF2 through kinase domain autophosphorylation to form the IRE1α-TRAF2-ASK1 complex, thereby activating JNK (Thr183/Tyr185 phosphorylation) and promoting c-Jun-mediated transcription of pro-apoptotic genes, establishing a dual apoptotic driving mechanism (98-100). Notably, certain natural compounds such as the aqueous extract of Descuraniae Semen can alleviate inflammation and apoptosis by modulating proteasomal degradation and UPR pathways (101).

TGF-β serves as a central regulatory hub with dual roles in EMT and apoptosis. Shenkang injection and rosiglitazone ameliorate diabetic tubulopathy by inhibiting EMT and ERS-induced apoptosis (102). The EMT process is regulated by various molecular pathways that also control autophagy. Research reveals that autophagy exhibits bidirectional regulatory effects: It can facilitate EMT progression (103), while also attenuating EMT by suppressing SNAIL/SLUG overexpression and ROS-NF-κB-hypoxia-inducible factor-1α pathway activation, indicating the potential therapeutic value of autophagy modulators (104).

Multiple pharmacological agents and nanomaterials further demonstrate the complexity of this regulatory network. Amlodipine exerts therapeutic effects by inducing ERS-mediated apoptosis and inhibiting EMT (105). Piperine displays anticancer activity in colorectal adenocarcinoma by modulating arf-like protein 3 expression to influence cell cycle progression, EMT pathways and ERS (106). Zinc oxide nanoparticles suppress malignant progression and chemoresistance in tumor cells by activating ERS and promoting autophagy (107). Additionally, C1q/TNF-related protein 4 alleviates high glucose-induced apoptosis and ERS while normalizing EMT markers through AMPK/autophagy-mediated signaling (108). ZC3H4, a member of the CCCH zinc finger protein family, influences pulmonary fibrosis progression via ERS and autophagy-induced endothelial-mesenchymal transition (109).

Ferroptosis, as a newly discovered cell death modality, shows close associations with both ERS and EMT. Altered expression of key EMT transcription factors can modulate tumor cell susceptibility to ferroptosis, while ERS participates in ferroptosis regulation through oxidative stress and iron metabolism (110,111). In diabetic nephropathy, the ERS-XBP1-HMG-CoA reductase degradation 1-Nrf2 pathway has been shown to promote EMT progression via ferroptosis (112), providing novel insights into disease mechanisms. Ginsenoside Rg1 ameliorates cigarette smoke-induced ferroptosis in chronic obstructive pulmonary disease by suppressing ERS through modulation of the PERK/ATF4 axis (113). Mechanistically, ferroptosis can induce ERS and promote apoptosis through multiple pathways, whereas persistent ERS leads to accumulation of ROS and Fe^{2+} (essential for ferroptosis) via UPR and disrupts redox homeostasis to enhance ferroptosis sensitivity (114,115).

In conclusion, the ERS-EMT-programmed cell death network forms a sophisticated regulatory axis in various diseases. Elucidating the dynamic mechanisms underlying

this network and developing novel therapeutic strategies that simultaneously target multiple pathways will open new avenues for precision medicine. Future research should focus on deciphering the intricate interactions between different forms of programmed cell death and exploring their clinical translation potential.

Metabolic reprogramming and the TME. The TME is the environment that tumour cells live in during tumorigenesis, development and metastasis. A hostile TME changes the ER's ability to fold proteins, which promotes the build-up of misfolded or unfolded proteins and, ultimately, ERS (116). It can be caused by either intrinsic tumour characteristics (such as high metabolic demand, hypoxia, nutrient limitation and acidosis) or external stressors (such as chemotherapy and radiation). By altering the TME, ERS can reduce the effectiveness of anticancer therapies, such as immunotherapy (117). In the TME, ERS can impact immune cell function and tumour growth (118). Through their influence on cellular communication and immunological responses, tiny extracellular vesicles can play a critical function in controlling the TME, and ERS contributes to the evolution of hepatocellular carcinoma (118). Different stromal cell types in the TME, together with biochemical and biophysical variables, have been shown to impact the EMT program, influencing tumour growth (119,120). The release of catecholamines in the TME can also regulate the EMT and metabolic changes in cancer cells by activating EMT transcription factors such as ZEB1, Snail or Slug/SNAI2 (121). Maintaining a healthy TME and developing therapeutic or multidrug resistance depends on the protein kinase C, Notch and TGF-β signalling pathways (117). EMT is reciprocally triggered by exosomes generated from the TME in tumour cells, leading to metastasis and treatment resistance (39). *In vitro*, enzymes that support EMT, migration and invasion of cancer cells are activated by extracellular ATP and adenosine in the TME, which bind to specific receptors (122). Findings from studies reveal that cancer therapy is made possible by focusing on EMT-induced signals in the TME (119). There is a strong relationship between TME and both ERS and tumour cell EMT.

Metabolic reprogramming within the TME is a critical adaptive feature exhibited by tumour cells in response to microenvironmental changes. This reprogramming serves as a key driver of tumour progression (123). SEC63, a novel regulator of metabolism in hepatocellular carcinoma, has been shown to considerably contribute to maintaining ER homeostasis through its mediation of metabolic reprogramming. In the nucleus, SEC63 activates UPR targets and increases the acetylation of SMAD3, inducing Snail1 expression and promoting cancer cell metastasis (124). In animal models of chronic colitis transitioning to colon cancer, combining ERS and metabolic reprogramming drives the malignant transformation of chronic inflammation (125). In colorectal cancer, the loss of stromal interaction molecule 2 alters ER Ca^{2+} levels and activates the cMyc and PERK/ATF4 branches of the ERS pathway, leading to transcriptional reprogramming and metabolic remodelling, which in turn drive tumour growth and metastasis (126). Activating STING, a stimulator of interferon genes, is closely associated with ERS induction and related inflammatory responses. The STING-dependent pathway is involved in the metabolic reprogramming of macrophages and contributes to the establishment and maintenance of a robust inflammatory phenotype (127). Metabolic reprogramming in cancer cells alters the use of energy sources and regulates the expression of genes associated with EMT (128). The mesenchymal stem cell-like phenotype generated by EMT enables cancer cells to detach from the primary tumour site, acquiring motility associated with metastatic and invasive capabilities. Research findings indicate that metabolic reprogramming is a core driver of EMT initiation and propagation (129). Additionally, changes in glycolysis, mitochondrial function, lipid metabolism and choline metabolism functionally promote TGF-β-induced EMT (130). EMT reshapes metabolic pathways by switching metabolic reprogramming, which supports transcription regulated by epigenetic mechanisms and reduces the risk of ferroptosis (131). Cellular processes such as metabolic reprogramming, EMT and ERS significantly increase the complexity of cancer by driving uncontrolled cell proliferation, metastasis and therapy resistance (132). Metabolic reprogramming, EMT and ERS drive tumour progression through complex interactions within the TME. However, their molecular mechanisms should be further elucidated. In addition, their potential applications in cancer therapy should be explored. Targeting these intricate cellular processes may provide novel therapeutic strategies to halt cancer progression.

6. Conclusion and outlook

From the perspective of molecular mechanisms, the bidirectional regulation of EMT by ERS depends on the dynamic balance of three key pathways: i) The IRE1α-XBP1 branch directly recognizes the UPRE core motif (ACGTG) in the promoter regions of EMT transcription factors through its spliced form XBP1s, with its binding affinity regulated by the methylation status of CpG islands; ii) the PERK-eIF2α-ATF4 axis requires sustained activation to induce EMT via ZEB1; and iii) the ATF6 pathway exhibits a rapid response in cervical cancer but requires prolonged activation in colorectal cancer. This spatiotemporal specificity in regulation provides an important basis for developing targeted drugs, as exemplified by β-asarone, which selectively activates the ATF6 branch (without affecting the IRE1α and PERK pathways) to inhibit bladder cancer EMT (133).

In terms of therapeutic strategies, a multi-tiered intervention approach has been developed based on in-depth understanding of the ERS-EMT network: First-generation ERS modulators (e.g., 4-PBA, tauroursodeoxycholic acidnon-specifically inhibit EMT by maintaining ER homeostasis); second-generation targeted drugs (e.g., galunisertib) precisely block the kinase domain of TGF-β receptor I; the most promising prospect lies in achieving synergistic therapy by simultaneously modulating UPR (e.g., inhibiting IRE1α RNase activity) and EMT signaling (e.g., blocking ZEB1 nuclear translocation), which would represent a breakthrough in treating fibrosis, tumors and other diseases (70,106,134-136). Notably, metabolic reprogramming in the TME significantly impacts treatment efficacy, as SEC63-mediated SMAD3 acetylation can increase tumor cell sensitivity to ERS inhibitors by 3-5-fold (124).

Despite these advances, several key scientific questions remain unanswered: The structural basis for the marked selectivity of XBP1s in recognizing different EMT transcription factor promoters (its binding affinity for SNAIL is 7-fold higher than for TWIST) is still unclear; the crosstalk between the TGF-β pathway and UPR exhibits tissue specificity, showing linear activation in endometrial cells but forming a positive feedback loop in pulmonary fibrosis and the molecular determinants of these differences need to be elucidated; and the mechanisms by which epigenetic regulation influences the reversibility of ERS and EMT require further exploration.

This review provides an in-depth analysis of the molecular regulatory network between ERS and EMT, revealing multi-layered precise regulatory mechanisms. Based on these molecular mechanisms, various targeted intervention strategies have demonstrated therapeutic potential. For instance, ginsenoside Rb1 specifically inhibits the BiP/eIF2α/CHOP axis, luteolin modulates E-cadherin/N-cadherin expression and lignan compounds competitively bind to the Neh1 domain of Nrf2 (35,69,86). These interventions precisely target key regulatory nodes at the molecular level. Future research needs to further elucidate the structural basis of regulatory direction differences in various tissue microenvironments and develop novel modulators that can specifically intervene in pathological interactions without affecting physiological functions, thereby providing more effective strategies for precision therapy.

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HC was the main contributor in writing the original draft. SY performed investigation. YG and QH were responsible for resources. WS acquired funding. All authors were involved in reviewing and editing the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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