



# The role of endoplasmic reticulum stress in the pathogenesis of oral diseases

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**Abstract** (J Korean Assoc Oral Maxillofac Surg 2024;50:177-188)

The endoplasmic reticulum (ER) is crucial for protein synthesis, transport, and folding, as well as calcium storage, lipid and steroid synthesis, and carbohydrate metabolism. Endoplasmic reticulum stress (ERS) occurs when misfolded or unfolded proteins accumulate in the ER lumen due to increased protein secretion or impaired folding. While the role of ERS in disease pathogenesis has been widely studied, most research has focused on extraoral diseases, leaving the role of ERS in intraoral diseases unclear. This review examines the role of ERS in oral diseases and oral fibrosis pathogenesis. A systematic search of literature through July 2023 was conducted in the MEDLINE database (via PubMed) using specific terms related to ERS, oral diseases, and fibrosis. The findings were summarized in both table and narrative form. Emerging evidence indicates that ERS significantly contributes to the pathogenesis of oral diseases and fibrosis. ERS-induced dysregulation of protein folding and the unfolded protein response can lead to cellular dysfunction and inflammation in oral tissues. Understanding the relationship between ERS and oral disease pathogenesis could offer new therapeutic targets for managing oral health and fibrosis-related complications.

**Key words:** Endoplasmic reticulum stress, Fibrosis, Oral pathology, Pathogenesis-related proteins, Unfolded protein response

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## I. Background

The endoplasmic reticulum (ER) is a cellular organelle that plays an important role in proteogenic synthesis and conveyance, protein conformational maturation, calcium sequestration, biosynthesis of lipids and steroids, and metabolic processes related to carbohydrates<sup>1</sup>. Due to its multiple functions, the ER is closely connected to the preservation of cellular balance and the delicate equilibrium between well-being and disease<sup>2</sup>. Endoplasmic reticulum stress (ERS) is characterized by an overload of misfolded or unfolded proteins in the ER lumen due to increased protein secretion or impaired ER protein folding.

The unfolded protein response (UPR) in eukaryotic cells is a complex signaling system that modulates gene transcription, translation of mRNA, and post-translational alterations

of proteins. The UPR mitigates the buildup of unfolded or misfolded proteins and restores proteostasis by ensuring accurate protein folding and preserving the proper ER function<sup>3</sup>. When activated, UPR signaling pathways can trigger intercellular inflammatory signals. In chronic conditions this may lead to the development of many diseases and is associated with the progression of degenerative and fibrotic ailments in several organs<sup>4,5</sup>. The role of ERS in disease pathogenesis has been described previously. However, most such studies focused only on extraoral diseases, and the role of ERS in intraoral diseases is unclear. This review examines the role of ERS in oral diseases and oral fibrosis pathogenesis.

## II. Methods

This review was structured based on Arksey and O'Malley<sup>6</sup> methodological framework for a scoping review.

### 1. Focal question

Does ERS contribute to oral diseases and oral fibrosis pathogenesis?

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## 2. Identification of relevant studies

A systematic search of relevant literature published through July 2023 was conducted in the MEDLINE database (via PubMed) using the following controlled-vocabulary terms combined with Boolean operators: (endoplasmic reticulum stress) OR (unfolded protein response) AND (disease), (endoplasmic reticulum stress) OR (unfolded protein response) AND (fibrosis). To investigate the role of ERS in the pathogenesis of disease affecting the oral maxillofacial region, the following MeSH, Emtree, DeCS/MeSH, and other free terms combined with Boolean operators were used: (endoplasmic reticulum stress) OR (unfolded protein response) AND (oral disease).

## 3. Selection

The articles were selected based on titles and abstracts. Inclusion criteria included *in vitro*, *in vivo*, and clinical studies on ERS in oral disease. Literature reviews, irrelevant studies, non-English articles, and articles published in non-peer review journals were excluded. A manual search was also performed using the reference list of selected articles.

# III. Results

The flow of the search is shown in Fig. 1. The search resulted in 396 articles. After excluding 386 duplicate and irrelevant articles, 10 articles were analyzed by reading the titles, abstracts, and full manuscripts. Two articles were added after reading the reference lists of the selected articles, resulting in 12 articles (Table 1) categorized into the following topics: gingival and periodontal diseases (7 articles), salivary gland disease and malignancy (2 articles), oral squamous cell carcinoma (OSCC) (3 articles) and our summarized data regarding contributory proteins in ERS, including UPR, apoptosis, necroptosis, autophagy, angiogenesis, inflammatory signaling, and epithelial-mesenchymal transition.

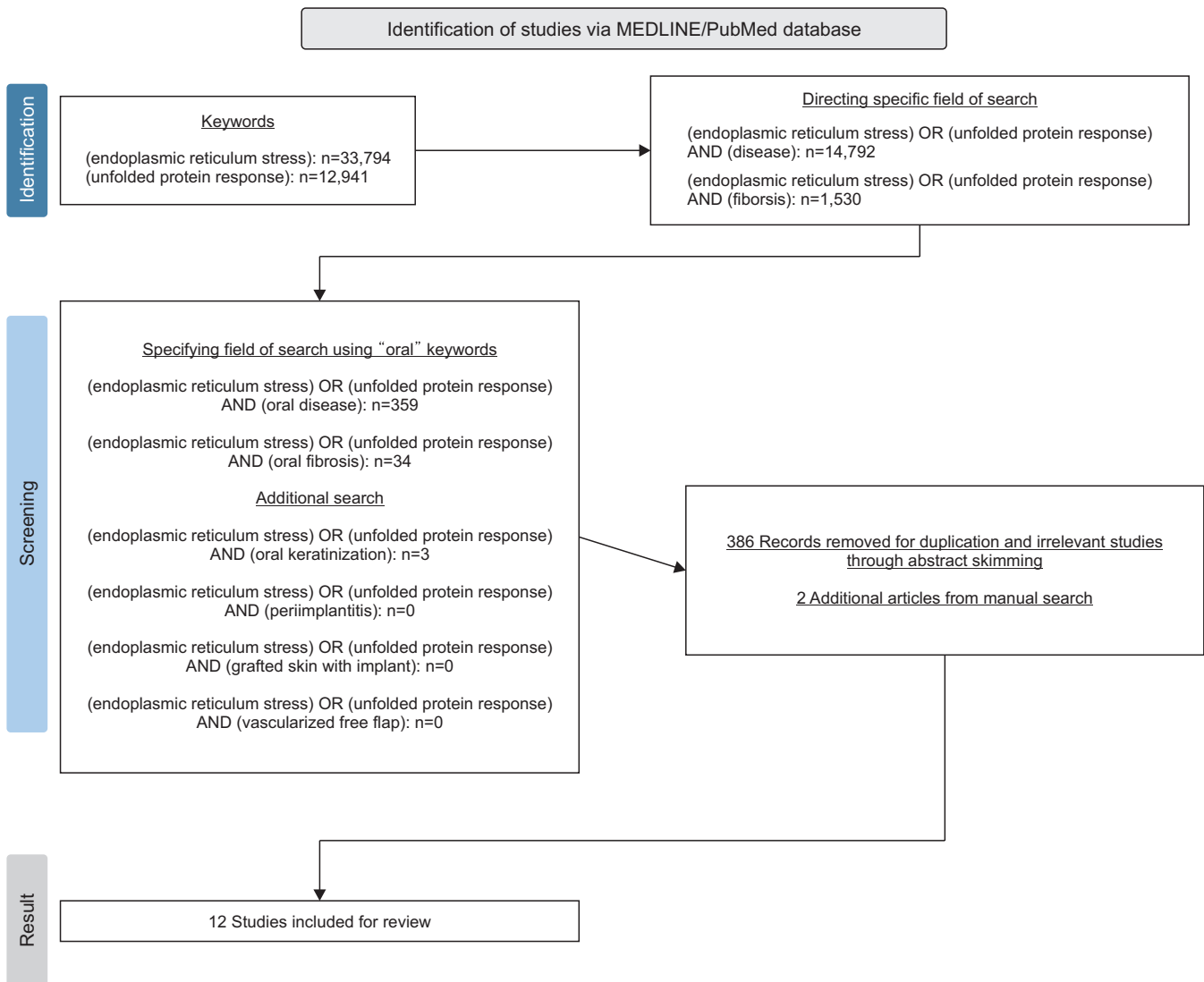
## 1. Gingival and periodontal disease

During periodontal and gingival inflammation, various stressors such as microbial pathogens and inflammatory mediators can induce ERS and UPR. In a study by Kim et al.<sup>7,8</sup> of thapsigargin (TG)-induced ERS in human gingival fibroblast cells, p38 mitogen-activated protein kinase was shown to play a significant role in cell death and autophagy, with

increased expression of beclin-1 and microtubule-associated protein 1 light chain 3 II (LC3II) as well as the formation of autophagic vesicles. Furthermore, selenoprotein S (SEPS) and heat shock protein 60 were highly expressed in the periodontitis, and the presence of *Porphyromonas gingivalis* independently aggravated alveolar bone resorption and significantly correlated with increased glucose-regulated protein (GRP) 78, X-box binding protein 1 spliced form (XBP1s), triiodothyronine receptor auxiliary protein, and cathepsin K expression<sup>9,10</sup>. Elevated expression of activating transcription factor (ATF) 6 $\beta$  was evident during tunicamycin-induced ERS in periodontal mice, with increased expression of the receptor activator of nuclear factor-kappa B (NF- $\kappa$ B) ligand (RANKL) in periodontal ligament cells. These biomarkers were associated with increased resorption of periodontal bone, and treatment using microRNA (miR)-1260b and ATF6 $\beta$  small interfering RNA (siRNA) with polyethyleneimine nanoparticles significantly inhibited periodontal bone resorption<sup>11</sup>. In drug-induced gingival hyperplasia, cyclosporine can increase the expression of CCAAT/enhancer-binding protein homologous protein (CHOP), GRP78, XBP1s, vascular endothelial growth factor (VEGF), connective tissue growth factor (CTGF), B-cell lymphoma 2 (Bcl-2), and cyclophilin D while decreasing cytochrome c, and shift gingival metabolism equilibrium toward an anabolic state, resulting in overgrowth and fibrosis<sup>12,13</sup>. In addition, treatment using 4-phenylbutyric acid, melatonin, and simvastatin were shown to downregulate the expression of ERS markers, mitochondrial apoptosis markers, and autophagy<sup>8,12</sup>.

## 2. Salivary gland disease and malignancy

In a study by Katsiogiannis et al.<sup>14</sup>, TG-induced ERS led to autophagy, as evidenced by the expression of LC3II and apoptosis in human salivary gland cells. In quiescent cells, Ro/SSA and La/SSB autoantigens are localized predominantly to the cytoplasm. However, in apoptotic cells, these autoantigens underwent relocalization and were found on the cell membrane and blebs in the apoptotic membrane. Kaira et al.<sup>15</sup> reported the involvement of ERS in adenoid cystic carcinoma (ACC) through the identification of positive GRP78/BiP expression in ACC specimens. This is indicative of an unfavorable prognostic biomarker, demonstrating a significant association with increased cellular proliferation and angiogenesis.



**Fig. 1.** Identification of relevant literature.

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### 3. Oral squamous cell carcinoma

In OSCC cells, heightened protein synthesis and changes in the tumor microenvironment (TME) can trigger ERS. These changes initiate an UPR, promote cell survival and facilitate tumor growth. However, persistent or unresolved ERS can also contribute to the advancement of OSCC by stimulating tumor-cell invasion, migration, and resistance to therapeutic interventions<sup>16</sup>.

Sufficient ERS can induce signal transducers and activators of transcription 3 (STAT3), NF- $\kappa$ B signaling, and interleukin (IL)-6. Under tunicamycin-induced ERS, normal oral keratinocytes showed significant upregulation of genes for STAT3 and leukemia inhibitory factor receptor (LIF-R), IL-6 receptor (IL-6R), and IL-18R1. Conversely, in OSCC

tissue, significantly more cyclic AMP-responsive element-binding protein 3-like 3 (CREB3L3), STAT3, IL-6R, and sterol regulatory element-binding protein (SREBP) 1 were expressed<sup>17,18</sup>. The activation of STAT3 and NF- $\kappa$ B were activated in tunicamycin-induced ERS in OSCC cells through the upregulation of IL-5, IL-22, and LIF-R<sup>17</sup>. LIF-R is expressed by cancer-associated fibroblasts (CAFs) and plays an important role in the activation of STAT3 in the TME of OSCCs, promoting the invasion of cancer cells<sup>19</sup>. In addition, ERS can change gene-expression profiles from regulators of lipid metabolism to controllers of apoptosis<sup>18</sup>.

Cancer-associated fibroblasts are a heterogeneous population of activated fibroblasts originating from mesenchymal cell lines within the TME. Due to the absence of distinctive biomarkers, determining the source of CAFs remains chal-

**Table 1.** Studies on ERS in the oral and maxillofacial regions

No.	Disease	Possible mechanism of ERS	Possible implications of ERS in the disease pathomechanism	Intervention
Gingival and periodontal diseases				
1.	Periodontal and gingival inflammation	TG-induced ERS induced by increasing several ERS-inducible, UPR-related proteins including GRP78, GRP94, C/EBP homologous protein, phospho-eIF-2 $\alpha$ , eIF-2 $\alpha$ , phospho-JNK1 (p46), phospho-JNK2/3 (p54), JNK1, IRE1 $\alpha$ , PERK, sXBP-1, beclin-1, LC3II, and autophagic vacuoles <sup>8</sup>	p38 mitogen-activated protein kinase participates in ERS-associated cell death and autophagy of gingival fibroblasts <sup>7</sup>	4PBA decreased the ERS markers and inhibited the autophagy induced by ERS <sup>8</sup>
2.	Periodontitis	High expression levels of XBP1, ATF4, SEPS1, CHOP, and HSP 60 <sup>9</sup> <i>Porphyromonas gingivalis</i> significantly increases GRP78, XBP1s, TRAP, and cathepsin K and insignificantly CHOP levels <sup>10</sup> Induction of ERS in periodontal mouse model was accompanied by enhanced ATF6 $\beta$ expression Within PDL cells, the ER stimulant tunicamycin augmented expression of RANKL <sup>11</sup>	An inflammatory reaction could exert a significant impact on the UPR <sup>9</sup> ERS triggered by <i>P. gingivalis</i> contributes to alveolar bone loss in mice through mechanisms that are separate from the involvement of inflammatory cytokines <sup>10</sup> Interaction between PDL cells and osteoclasts plays a role in Regulation of ERS-induced periodontal bone resorption <sup>11</sup>	Not applicable 4PBA suppresses the UPR-related genes (GRP78, XBP1s, CHOP, IRE1 $\alpha$ ) and osteoclastic differentiation (TRAP, and cathepsin K) <sup>10</sup> The application of miR-1260b and ATF6 $\beta$ siRNA via PEI-NPs locally resulted in substantial reduction of bone resorption in the periodontal area miR-1260b downregulated ATF6 $\beta$ leading to inhibition of RANKL. Additionally, the conditioned media from PDL cells activated by miR-1260b/ATF6 $\beta$ -axis exhibited the ability to hinder osteoclast formation in CD14+ monocytes derived from human peripheral blood <sup>11</sup>
3.	Drug-induced gingival overgrowth	Cyclosporine increases ERS markers (CHOP, GRP78 <sup>13</sup> , XBP1s), matrix protein markers (VEGF and CTGF), and mitochondrial apoptosis markers (Bcl-2 and cyclophilin D), and decreases cytochrome c <sup>12</sup>	Cyclosporine, although inducing ERS, shifts the balance of gingival metabolism toward an anabolic state leading to overgrowth <sup>12,13</sup>	4PBA, melatonin, and simvastatin decreased ERS and matrix protein markers where PBA further decreased mitochondrial apoptosis markers <sup>12</sup>
Salivary gland disorder and malignancy				
4.	Sjögren syndrome	GRP78/BiP expression was observed in acinar and ductal epithelial cells within salivary glands of both patients and sicca controls Treatment with TG led to autophagy activation, as evidenced by the heightened LC3II protein levels; furthermore, TG treatment prompted an increase in XBP-1 protein levels, indicative of UPR, accompanied by a decrease in GRP78/BiP levels. Notably, TG treatment also induced apoptosis in human salivary glands Ro/SSA and La/SSB autoantigens were primarily situated within the cytoplasm in quiescent cells, yet in apoptotic cells, they underwent relocalization to the cell membrane and exhibited formation of membrane blebs <sup>14</sup>	ERS-induced apoptosis in human salivary gland cells leads to cell surface and apoptotic bleb relocalization of Ro/SSA and La/SSB autoantigens <sup>14</sup>	Not applicable
5.	ACC	Elevated GRP78/BiP expression showed a substantial correlation with both PERK activation and cell proliferation, as indicated by the Ki-67 labeling index <sup>15</sup>	The pivotal involvement of GRP78/BiP and PERK is evident in driving the aggressiveness and advancement of ACC tumor growth <sup>15</sup>	Not applicable

Table 1. Continued

No.	Disease	Possible mechanism of ERS	Possible implications of ERS in the disease pathomechanism	Intervention
OSCC 6.	OSCC	<p>Normal oral keratinocytes response to tunicamycin-induced ERS involving significant upregulation of STAT3 and LIF-R proteins as well as IL6R and IL18R1 genes, both of which are STAT3 and NFκB signaling activators</p> <p>ERS induces STAT3 and NFκB signaling and upregulates IL-6; both STAT3 and IL-6R proteins were expressed to significantly higher extent in OSCC tissue. OSCC cells responded to tunicamycin-induced ERS caused by upregulation of IL-5 and IL-22<sup>17</sup></p> <p>Both OSCC cases, with or without tunicamycin-induced ERS, exhibited noteworthy upregulation of SREBP1 and CREB3L3</p> <p>In OSCC, a notably elevated level of SREBP1 transcriptional activation was observed; on ERS induction, apoptotic genes (DDIT3, HTRA4, and HSPA1L) displayed significantly upregulated in OSCC<sup>18</sup></p> <p>In OSCC cells that were transiently transfected and maintained without puromycin, the suppression of DSPP led to a significant reduction in the mRNA expression of key genes, including GRP78, SERCA2b, PERK, IRE1, ATF6, and MMP-20</p> <p>DSPP silencing also led to diminished cell viability and migration, accompanied by heightened apoptotic events. Moreover, DSPP knockdown resulted in decreased levels of PCNA and Bcl-2 levels, while promoting increased levels of Bax and cytochrome c proteins within OSCC cells<sup>25</sup></p>	<p>Tunicamycin-induced ERS upregulated tumor-promoting cytokines IL5 and IL22 in OSCC. IL5 and IL22 further activated STAT3 and/or NFκB. In addition, LIF-R plays an important role in STAT3 activation in OSCC<sup>17</sup></p> <p>In response to ERS, OSCC cells manifest a more concentrated UPR in comparison to normal oral keratinocytes, which includes modulation of lipid metabolism regulators</p> <p>Tunicamycin-induced ERS brought about distinctive variations in the regulation of UPR genes, shifting from those governing lipid metabolism to those influencing apoptosis<sup>18</sup></p> <p>DSPP may participate in ERS processes within OSCC</p> <p>The suppression of DSPP within OSCC cells resulted in notable changes in the abundant of key ERS-related proteins, subsequently leading to the disruption of the UPR mechanism<sup>25</sup></p>	Not applicable

(ERS: endoplasmic reticulum stress, TG: thapsigargin, UPR: unfolded protein response, GRP: glucoseregulated protein, C/EBP: CCAAT/enhancer-binding protein, eIF: eukaryotic initiation factor, JNK: c-Jun N-terminal kinase, IRE1: inositol-requiring enzyme type 1, PERK: protein kinase R [PKR]-like endoplasmic reticulum kinase, XBP: X-box binding protein, LC3: microtubule-associated protein 1A/1B-light chain 3, 4PBA: 4-phenylbutric acid, ATF: activating transcription factor, SEPS: selenoprotein S, CHOP: C/EBP homologous protein, HSP: heat shock protein, TRAP: triiodothyronine receptor auxiliary protein, PDL: periodontal ligament, ER: endoplasmic reticulum, RANKL: receptor activator of NF-κB ligand, miR: microRNA, siRNA: small interfering RNA, PEI-NPs: polyethylenimine nanoparticles, VEGF: vascular endothelial growth factor, CTGF: connective tissue growth factor, Bcl-2: B-cell lymphoma 2, XBPs: X-box binding protein spliced, ACC: adenoid cystic carcinoma, OSCC: oral squamous cell carcinoma, STAT: signal transducer and activator of transcription, LIF-R: leukemia inhibitory factor receptor, IL: interleukin, IL [number] R: interleukin [number] receptor, NF-κB: nuclear factor-kappa B, SREBP1: sterol regulatory element-binding protein 1, CREB3L3: cyclic AMP responsive element-binding protein 3-like 3, DDIT: DNA damage inducible transcript, HTRA: high-temperature requirement A, DSPP: dentin sialophosphoprotein, SERCA: sarco/endoplasmic reticulum Ca<sup>2+</sup>-ATPase, MMP: matrix metalloproteinase, PCNA: proliferating cell nuclear antigen)

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lenging. The prevailing view suggests that regular fibroblasts arise from primitive mesenchymal cells, and CAFs emerge from activated fibroblasts in nearby tissues, bone marrow-derived mesenchymal precursor cells, and endothelial and epithelial cells, some of which are stimulated by cytokines

such as TGFβ<sup>20,21</sup>.

Several inflammatory mediators may stimulate activation of CAFs. For example, IL-1 triggers CAF activation via the NF-κB pathway, and IL-6 primarily acts on signal transducers and STAT. Positive feedback loops and crosstalk involv-



ing Janus kinase (JAK)-STAT signaling, changes in the contractile cytoskeleton, and modifications in histone acetylation further contribute to CAF activation. Physical alterations in the extracellular matrix (ECM) can also serve as stimuli for CAF activation<sup>22</sup>.

The reverse Warburg effect is considered a hallmark of CAF regulation. Metabolite transfer from CAFs to cancer cells is important element of cancer cell growth and survival. In addition to CAF regulation, prolonged hypoxia can cause glycolysis-related genes in fibroblasts to undergo hypomethylation, indicating that metabolic interactions with epigenetic processes promote the buildup of pro-glycolytic CAFs<sup>23</sup>. Because hypoxia is associated with a UPR, a strong relationship likely exists between the ERS and CAF, and future studies are warranted.

Due to the complexity of OSCC pathogenesis, numerous studies have excluded the potential contribution of proteins and genes. Dentin sialophosphoprotein (DSPP), which facilitates dentin and bone matrix mineralization, is reportedly involved in cancer pathogenesis. DSPP is present in non-mineralizing metabolically active ductal epithelial cells of various glands, such as salivary glands, nephrons, and eccrine sweat glands, and helps repair pericellular matrix and ECM proteins damaged by free radicals generated during intense metabolic activity<sup>24</sup>. In OSCC cells transiently transfected and not exposed to puromycin, silencing of DSPP resulted in significant downregulation of GRP78, sarco/ER Ca<sup>2+</sup>-ATPase 2b (SERCA2b), protein kinase R (PKR)-like ER kinase (PERK), inositol-requiring enzyme type 1 (IRE1), ATF6, and matrix metalloproteinase (MMP)-20. Silencing DSPP can lead to reduced cell viability and migration accompanied by increased apoptosis in OSCC cells. In addition, DSPP knock-down resulted in decreased levels of proliferating cell nuclear antigen, an indicator of cell proliferation, and Bcl-2, an anti-apoptotic protein. Conversely, levels of Bax, a pro-apoptotic protein, and cytochrome c were elevated in DSPP-silenced OSCC cells<sup>25</sup>.

#### 4. Contributory proteins in endoplasmic reticulum stress

##### 1) Unfolded protein response

- IRE1: inositol requiring enzyme 1
- PERK: protein kinase RNA-activated (PKR-like) ER kinase
- ATF6: activating transcription factor 6
- GRP78: glucose-regulated protein 78
- XBP1: X-box-binding protein 1

- PDIA5: protein Disulphide Isomerase 5
  - PDIA6: protein Disulphide Isomerase 6
- ##### 2) Apoptosis
- CHOP/GADD153: CCAAT-enhancer-binding protein homologous protein/Growth arrest-and DNA damage-inducible gene 153
  - PUMA: p53-up regulated modulator of apoptosis
  - Noxa: pro-apoptotic member of the Bcl-2 protein family
  - BIM: Bcl-2 interacting mediator of cell death
- ##### 3) Necroptosis
- RIPK1: receptor-interacting protein kinase 1
  - RIPK3: receptor-interacting protein kinase 3
  - MLKL: mixed-lineage kinase domain-like protein
- ##### 4) Autophagy
- TRAF2: TNF receptor-associated factor 2
  - JNK: c-Jun N-terminal kinases
  - ASK1: apoptosis signal-regulating kinase 1
  - LC3: microtubule-associated protein 1 light chain 3
- ##### 5) Angiogenesis
- VEGF: vascular endothelial growth factor
  - IL-8: interleukin 8
  - MMP2: matrix metalloproteinase 2
  - MMP9: matrix metalloproteinase 9
  - ANG-2: angiopoietin 2
  - HIF-1: hypoxia-inducible factor
  - FGF2: fibroblast growth factor 2
- ##### 6) Inflammatory signaling
- NF-κB: nuclear factor kappa light-chain-enhanced activated B-cells
  - AP-1: activator protein 1
  - NLRP3 inflammasome: nucleotide-binding domain (NOD)-, leucine-rich repeat (LRR)-, and pyrin domain-containing protein 3
  - IL1β: interleukin 1 beta
  - IL18: interleukin 18
- ##### 7) Epithelial-mesenchymal transition
- TGFβ: transforming growth factor beta
  - αSMA: α-smooth muscle actin
  - E-cadherin: epithelial cadherin
  - N-cadherin: neural cadherin
  - Vimentin
  - Fibronectin
  - miR-150: microRNA 150

## IV. Discussion

### 1. Structure of the oral mucosa

The oral mucosa consists of a stratifying squamous epithelium that is largely covered by a keratinized epithelium over a dense connective tissue or lamina propria rich in type I collagen. This structural arrangement serves as a protective barrier against external microorganisms, pathogens, and mechanical stress, particularly in the gingiva and hard palate<sup>26</sup>. For flexibility in deglutition, mastication, and speech, the floor of the mouth and buccal mucosa are composed of a nonkeratinizing epithelium. In addition, the dorsum of the tongue is covered by a specialized mosaic of keratinized and nonkeratinized epithelium that attaches tightly to the tongue muscle<sup>27</sup>.

Keratins are the main structural proteins in the keratinizing stratified epithelial cytoskeleton. Basal cells, which form the actively dividing layer of the epithelium, connect to the lamina densa of the lamina basalis via hemidesmosomes. The spinous cell layers play a crucial role in facilitating cell-cell connections through numerous desmosomes and gap junctions. The stratum granulosum contains membrane-coating granules, keratohyalin granules, and abundant tonofibrils, leading to an abrupt transition to the stratum corneum. The flattened cornified squames form a relatively thick protective layer. To maintain their function, the stratified epithelia of the oral mucosa use tight cell-cell adhesion in viable cells combined with intercellular tight and adherens junctions that connect to the actin cytoskeleton<sup>28,29</sup>.

During the healing process in response to oral mucosa injury following hemostasis, the formation of fibrin-rich granulation tissue initiates the inflammatory phase. Next, the wound-healing process enters a proliferative phase characterized by the migration of keratinocytes and fibroblasts to the wound bed. Fibroblasts actively secrete ECM components, which contribute to remodeling of granulation tissue, and keratinocytes play a crucial role in re-establishing the protective barrier function of the tissue. Unlike skin, oral mucosa heals better and typically results in rapid and scarless healing. Distinct variations in wound healing occur within the oral environment contingent on the specific location. Wounds in the non-keratinized mucosa may lead to scarring, and wounds in the tongue or gingiva and hard palate heal uneventfully without scarring. These dissimilarities can be ascribed to differences in the characteristics of resident fibroblasts<sup>26,30</sup>.

Nikoloudaki et al.<sup>26</sup> suggested periostin may influence cell behavior during the proliferative phase of healing by iden-

tifying intracellular proximal localization between periostin and fibronectin in the ER of fibroblast cells. As a response to injury, the periostin enhances secretion of fibronectin from the ER into the ECM, leading to fibrosis and scarring. Periostin has also been identified in several pathologic conditions, including fibrous dysplasia<sup>31</sup>, odontogenic tumors of mixed epithelial/mesenchymal origin<sup>32</sup>, and OSCC<sup>33</sup>. This strengthens the hypothesis that intracellular ERS, such as in oral fibroblasts, can influence the secretion and expression of several proteins into the ECM, resulting in the development of oral disease and fibrosis.

### 2. UPR and ERS

During ERS, three transmembrane proteins in the ER membrane (IRE1, PERK, and ATF6) are activated to initiate a UPR<sup>34</sup>. Typically, the ER resident chaperone HSP A5 keeps the three ERS sensors in an inactive state. This chaperone is also referred to as GRP78 and binds to immunoglobulin protein (BiP). However, an accumulation of misfolded proteins in the ER lumen leads to engagement of BiP, releasing the three sensors to initiate the UPR<sup>2</sup>.

#### 1) IRE1 pathway

IRE1 possesses both serine/threonine kinase and endoribonuclease (RNase) domains in its cytoplasmic region. Comparisons between yeast IRE1 and its mammalian homologs, IRE1 $\alpha$  and IRE1 $\beta$ , have demonstrated a significant degree of conservation. IRE1 $\alpha$  is expressed in various cells and tissues, and IRE1 $\beta$  expression is mainly limited to the epithelial cells of the gastrointestinal tract<sup>35</sup>. On encountering ERS, the release of GRP78/BiP from IRE1 $\alpha$  leads to its preferential binding to unfolded or misfolded proteins, resulting in dimerization and autophosphorylation. This process activates IRE1 $\alpha$ , transforming it into an active endoribonuclease<sup>36</sup>. The activated IRE1 initiates unconventional splicing of the XBP1 mRNA, which is later translated into the potent transcription factor XBP1s<sup>3</sup>. Specifically, XBP1s contains a basic leucine zipper (bZIP) domain in the C terminus and serves as a transcription factor for UPR-related genes, including those for ER chaperones, ER-associated degradation (ERAD) components, and lipid synthesis enzymes<sup>35</sup>. XBP1s regulates the expression of various genes involved in ER protein folding and ERAD, enhancing folding capacity and clearing misfolded proteins, including molecular chaperones BiP and transcription factors such as CHOP<sup>36,37</sup>. IRE1 $\alpha$  degrades mRNA as

well as microRNAs (miRs), which regulate cellular functions, including proliferation, differentiation, and apoptosis, and abnormal miR expression can be found in various human diseases, including fibrosis. In a study by Heindryckx et al.<sup>37</sup>, miR-150 exhibited an anti-fibrotic function that suppressed the expression of c-Myb and TGF $\beta$ -induced  $\alpha$ SMA, and activated IRE1 $\alpha$ -degraded miR-150, resulting in the formation of myofibroblasts.

## 2) PERK pathway

An immediate adaptive response to ERS is initiated by PERK. Similar to IRE1 $\alpha$  activation, PERK is activated when GRP78/BiP is released from its binding site in the ER lumen<sup>36</sup>. PERK phosphorylates eukaryotic initiation factor 2 $\alpha$  (eIF2 $\alpha$ ), a crucial component of protein translation machinery. Phosphorylated eIF2 $\alpha$  has a dual effect on protein synthesis: it reduces the entire protein-synthesis process and selectively enhances the translation of ATF4 and other specific mRNAs. ATF4 triggers the transcription of genes associated with the equilibrium of cellular oxidation-reduction processes, amino acid metabolism, protein synthesis, apoptosis, and autophagy, giving cells the ability to adapt to the stress or undergo apoptosis if the stress becomes overwhelming<sup>3</sup>. ATF4 can bind to the C/EBP-ATF site in the CHOP/GADD153 promoter region. ATF4 and CHOP function as transcription factors that directly stimulate genes associated with protein synthesis and the UPR. However, upregulation of protein synthesis by ATF4 and CHOP can deplete ATP, generating oxidative stress and ultimately cell death<sup>2</sup>. PDI is an essential enzyme found in the ER lumen, where it ensures nascent (newly synthesized) proteins acquire their functional three-dimensional structures as they fold. PDI functions as a redox regulator, helping the ER maintain the appropriate redox environment for disulfide bond formation and other redox-dependent processes. The role of PDI in protein folding and redox homeostasis is closely associated with activation of the PERK pathway during ERS<sup>38</sup>. In a study by Eletto et al.<sup>39</sup>, PDIA6 was shown to regulate the deactivation of the UPR sensor IRE1 $\alpha$  by binding directly to its luminal domain through the formation of a disulfide bond. Because the luminal domains of IRE1 and PERK are homologous, interaction between PDIA6 and PERK was also observed.

## 3) ATF6 pathway

Under ERS, ATF6 migrates from the ER to the Golgi ap-

paratus, where it is proteolytically cleaved by site-1 and site-2 proteases, resulting in an active bZIP transcription factor known as ATF6p50<sup>3</sup>. Under stress conditions, PDIA5 facilitates the reorganization of disulfide bonds in ATF6 $\alpha$ , promoting the translocation of ATF6 $\alpha$  from the ER to the cell nucleus<sup>40</sup>. The active ATF6 enters the nucleus and upregulates genes for chaperones and other ER-resident proteins, including BiP, GRP94, calreticulin, and ERAD system components, further supporting protein folding and clearance<sup>5</sup>.

## 3. ERS and inflammatory signaling

NF- $\kappa$ B plays a pivotal role in inflammation response and is typically confined within the cytoplasm by the inhibitor of NF- $\kappa$ B (I $\kappa$ B). During inflammation, various stimuli, including pro-inflammatory cytokines, activate I $\kappa$ B kinases, leading to phosphorylation and degradation of I $\kappa$ B<sup>41</sup>. Under ERS, a UPR induces the degradation of I $\kappa$ B through the IRE1 $\alpha$  pathway and tumor necrosis factor receptor-associated factor 2 (TRAF2). In addition, activation of JNK by IRE1 $\alpha$  induces the expression of activator protein (AP-1)<sup>42</sup>. The primary function of AP-1 is to bind to specific DNA sequences in the promoter regions of target genes and regulate their transcription, particularly during inflammation and apoptosis. ERS can also modify the phenotype of macrophages by activating the NOD-like receptor (NLR) family, pyrin domain-containing protein 3 (NLRP3) inflammasomes<sup>5</sup>. When activated, NLRP3 can induce activation of caspase-1, which then processes pro-inflammatory cytokines, including IL-1 $\beta$  and IL-18, into their active forms<sup>43</sup>. In addition, ERS through IRE1 $\alpha$  is required for the maturation and differentiation of plasma and dendritic cells as well as polarization of Th17 cells<sup>5</sup>.

## 4. ERS and apoptosis, necroptosis, and autophagy

Apoptosis involves initiation, signaling, and execution. Key players in the apoptotic pathway include members of the Bcl-2 proteins, which are divided into pro-apoptotic (e.g., Bax, Bak) and anti-apoptotic (e.g., Bcl-2, Bcl-XL) proteins<sup>44</sup>. The BH-3-only members of the Bcl-2 family, including p53-upregulated modulator of apoptosis (PUMA), NOXA, and Bcl-2 interacting mediator of cell death BIM, are significant in ERS-induced apoptosis<sup>45</sup>. Pro-apoptotic proteins promote the release of cytochrome c from the mitochondria into the cytoplasm, where it forms a complex with apoptotic protease-activating factor 1 (Apaf-1) and procaspase-9, ultimately producing apoptosomes<sup>46</sup>. This complex activates caspase-9,



which in turn activates downstream effector caspases (e.g., caspase-3 and caspase-7), leading to the cleavage of various cellular substrates and ultimately, cell death<sup>47</sup>. In addition to direct ER-mitochondrial interactions, CHOP/GADD153 is involved in the regulation of apoptosis as the apoptosis inducer by activating BIM and PUMA as well as repressing several anti-apoptotic members of the Bcl-2 family<sup>2</sup>.

Necroptosis is a programmed form of necrosis that represents an alternative cell-death pathway when apoptotic pathways are inhibited or unavailable. Necroptosis is characterized by the rapid and uncontrolled breakdown of cellular membranes, leading to the release of cellular contents and inflammation. The molecular machinery involved in necroptosis includes RIPKs, and RIPK1 and RIPK3 in particular. These kinases form a complex, the necrosome, when apoptosis is blocked, resulting in phosphorylation of MLKL<sup>48</sup>. Phosphorylated MLKL translocates to the plasma membrane and disrupts its integrity, resulting in cell swelling, membrane rupture, and the release of intracellular contents<sup>49</sup>. In a study using a mouse fibroblast cell line, TNFR1 mediated ERS-induced necroptosis by activating caspase. The MLKL served as an effector of ERS and repression of RIPK1 shifted the ERS-induced necroptosis to apoptosis<sup>50</sup>.

In addition to ERAD, lysosome-mediated protein degradation by autophagy is another protein degradation pathway during ERS<sup>42</sup>. Bernales et al.<sup>51</sup> reported that ERS induces abundant cell-accumulated autophagosome-like structures enclosed by two membranes and containing densely packed, closely arranged membrane cisternae. Autophagy is induced by ERS by at least two UPR pathways, PERK-eIF2 $\alpha$  and IRE1 $\alpha$ . The IRE1 $\alpha$  pathway involves TRAF2, ASK1, and JNK. The PERK-eIF2 $\alpha$  pathway induces autophagy through ATF4-driven transcriptional regulation by inducing vesicle elongation. Ca<sup>2+</sup> release from the ER lumen through the inositol 1,4,5-trisphosphate receptor (IP<sub>3</sub>R) can activate calcium/calmodulin-dependent protein kinase and relieves mammalian target of rapamycin inhibition on the Unc-51-like kinase 1 complex<sup>2,52</sup>.

## 5. ERS and angiogenesis

The interplay between ERS and angiogenesis is complex and involves various signaling pathways. Hypoxia-inducible factor 1 plays a key role in cellular responses to changes in oxygen levels, specifically hypoxia, and plays a role in angiogenesis. Under ERS conditions, the activation of PERK and IRE1 branches of the UPR can lead to increased HIF-1 $\alpha$

stabilization and transcriptional activity. Subsequently, HIF-1 $\alpha$  promotes the expression of pro-angiogenic factors, including VEGF, erythropoietin (EPO), angiopoietin 2 (ANG-2), and MMPs, to stimulate angiogenesis<sup>53</sup>. In a study by Ghosh et al.<sup>54</sup>, VEGF expression during ERS was promoted by the activation of ATF4, XBP1s, and cleaved ATF6, independent from HIF-1. Under ERS, IL-8 is also upregulated through the PERK pathway by ATF4<sup>55</sup>. As a pro-angiogenic cytokine, IL-8 activity further induces the expression of MMP-2 and MMP-9, which are critical players in angiogenesis, by mediating ECM remodeling and promoting endothelial cell migration and proliferation while decreasing endothelial cell apoptosis<sup>56</sup>. In addition to VEGF and IL-8, FGF 2 and angiogenin, potent pro-angiogenic factors that contribute to endothelial cell proliferation and tube formation, are upregulated<sup>57</sup>.

## 6. ERS and EMT

During epithelial-mesenchymal transition, epithelial cells lose their cell-cell adhesion characteristics and acquire a migratory and invasive phenotype characteristic of mesenchymal cells. This process is regulated by various complex signaling pathways and transcription factors. In addition to the loss of adherens junctions, EMT also includes downregulation of cytokeratin and E-cadherin and increases of fibronectin, N-cadherin, and vimentin<sup>58</sup>. UPR activation can alter the function of fibroblasts by promoting TGF $\beta$ -mediated myofibroblast differentiation<sup>5</sup>; one such mechanism is through degradation of miR-150 by activated IRE1 $\alpha$  that consecutively regulates  $\alpha$ SMA expression<sup>37</sup>. The IRE1-XBP1 pathway can also negatively regulate E-cadherin and upregulate N-cadherin<sup>2</sup>. On PERK activation, the epithelial cells are subjected to EMT, and the process of invasion and metastasis depend on eIF2 $\alpha$  phosphorylation<sup>59</sup>. Additional pathways have also been suggested to induce EMT, such as autophagy and the activation of c-SRC kinase in tubular epithelial cells as well as the compensatory activation of nuclear factor erythroid 2-related factor 2 and heme oxygenase-1 (NRF-2/HO-1) antioxidative stress response pathway in colorectal adenocarcinoma cell lines<sup>60,61</sup>.

## V. Conclusion

Emerging evidence suggests that ERS plays a crucial part in the pathogenesis of oral diseases and fibrosis. ERS-induced dysregulation of protein folding and the UPR can lead to cellular dysfunction and inflammation in oral tissues.

In addition, ERS-related alterations in autophagy, apoptotic pathways, and activation of CAFs may further exacerbate tissue damage, impair wound healing, and facilitate favorable TME for further tumor growth and metastasis. Understanding the intricate interplay between ERS and oral disease pathogenesis will provide new insights potential therapeutic targets for managing oral health and fibrosis-related complications.

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## Authors' Contributions

K.R.M. wrote the manuscript. M.Y.E. helped prepare and edit the manuscript. S.M.K. designed the study and coordinated and carefully reviewed and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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