Endoplasmic Reticulum and Its Significance in Periodontal Disease

Qi Ming ZHAI[1,2#], Bei LI[1#], Xiao Ning HE[1], Jia GUO[1,2], Xiao LEI[1,2], Fang JIN[2], Yan JIN[1]

The endoplasmic reticulum has emerged as a modulator that is essential for cellular homeostasis and human health. It is an extensive membranous organelle that acts as a hub for the physiological and pathological processes. In recent years, it has become a topic of interest in studies on the relationship between endoplasmic reticulum homeostasis and system diseases. Periodontal disease is a prevalent chronic disease that affects tooth-supporting tissues, initiated by the interaction between pathogenic bacterial infection and immune defence and resulting in tooth loss. The endoplasmic reticulum participates in the responses to the fluctuating microenvironments in periodontal pathogenesis and regulates periodontal homeostasis. In this review, we present an overview of the significance of endoplasmic reticulum regulation as a multidimensional mediator in periodontal disease and highlight the potential strategies for periodontal regeneration.

Key words: *endoplasmic reticulum, periodontal disease, periodontal regeneration*
Chin J Dent Res 2021;24(2):79–84; doi: 10.3290/j.cjdr.b1530481

The periodontium is a highly organised group of tissues that support the teeth and consists of gingival tissue, the cementum, the periodontal ligament (PDL) and alveolar bone[1]. As an important complex structure that is essential for maintaining tooth stability, the periodontium undergoes constant remodelling throughout life in various microenvironments[2]. Periodontal diseases are highly prevalent worldwide and comprise a wide variety of inflammatory conditions of the periodontium[3]. This kind of disease begins with localised inflammation of the gingiva, known as gingivitis. If the inflammation persists, untreated gingivitis may progress to periodontitis, characterised by destruction of the PDL and alveolar bone resorption, and eventually lead to tooth loss. Interestingly, periodontitis correlates with several system disorders, such as diabetes and hypertension[4,5].

In recent years, regulation of the endoplasmic reticulum (ER) has attracted remarkable attention in relation to many diseases, such as diabetes and neurodegenerative and inflammatory diseases[6-8]. Meanwhile, accumulating evidence has demonstrated that ER is a multidimensional modulator in the pathogenesis of periodontal disease. Currently identified as a sophisticated system that mediates an array of biosynthetic signalling processes and organelle dynamics[9-11], the critical function of ER in determining periodontal modelling continues to be revealed. ER compromise has further demonstrated impacts on the proliferation, differentiation and apoptosis of stem cells[12]. Accordingly, medication targeting the ER may support dental tissue regeneration,

1 State Key Laboratory of Military Stomatology; National Clinical Research Center for Oral Diseases; Shaanxi International Joint Research Center for Oral Diseases; Center for Tissue Engineering, School of Stomatology, Fourth Military Medical University, Xi'an, Shaanxi Province, P.R. China.
2 Department of Orthodontics, School of Stomatology, Fourth Military Medical University, Xi'an, Shaanxi Province, P.R. China.

# These authors contributed equally to this work.

Corresponding authors: Prof Yan JIN, Center for Tissue Engineering, School of Stomatology, Fourth Military Medical University, Xi'an, Shaanxi 710032, P.R. China. Tel: 86-29-84776471. Email: yanjin@fmmu.edu.cn

Dr Fang JIN, Department of Orthodontics, School of Stomatology, Fourth Military Medical University, Xi'an, Shaanxi 710032, P.R. China. Tel: 86-29-84776137. Email: fangjin191@163.com

This work was supported by grants from the National Natural Science Foundation of China (Nos. 81870768 and 81991504 to Bei LIi, 81870796 to Fang JIN and 81930025 to Yan JIN) and the Guangzhou Science, Technology and Innovation Commission (201803040008 to Bei LI).

aiming to further elucidate the contribution of the ER to periodontal homeostasis, disorders and regeneration.

The ER: A hub of physiological and pathological processes

The ER is a membranous organelle, a large hub that extends from the nuclear membrane to the plasma membrane, establishing a certain connection with other organelles such as mitochondria, the Golgi apparatus and lysosomes[11]. It is divided into the smooth ER and rough ER, which are distinguished according to whether there are (granular) ribosomes on the envelope[13].

The ER is involved in calcium storage responsible for intracellular calcium homeostasis and secreted proteins are synthesised and folded there. ER homeostasis can be disrupted by diverse environmental stresses including hypoxia, oxidative stress, malnutrition and intracellular pathogens, under which circumstances the cells carry out a series of adaptive and protective reactions to overcome the ER stress, called unfolded protein response (UPR). UPR is a complex and coordinated cellular response. It is regulated by three transmembrane receptors in the endoplasmic reticulum: protein kinase receptor-like ER kinase (PERK), activating transcription factor 6 (ATF6) and inositol-requiring enzyme1 (IRE1), also known as ERN1. It is essential for alleviating cellular stress, which accurately responds to reduce the accumulation of unfolded proteins and restore the normal function of the ER. Beyond ER proteostasis, it also participates in various biological processes such as autophagy, cytoskeleton dynamics and reactive oxygen species (ROS) production[6]. Additionally, ER communicates with other organelles, in which it mediates the regulation of mitochondria dynamics, cellular calcium oscillations and autophagosome formation[14,15].

Association of ER with periodontal disease

Previous genome-wide associated studies have found that the ER membrane as the top gene set is correlated with severe periodontitis[16]. Levels of UPR-related gene expression are higher in periodontitis lesions than in gingivitis lesions. Additionally, a study found the percentage of cells expressing heat shock protein 60 (HSP60), chaperones of intracellular proteins during protein folding, was greater in the periodontitis group than the gingivitis group[17]. Russell bodies (RBs) are indigested proteins accumulated in dilated ER, which correlates with ER occurrence in periodontal inflammation[18]. Furthermore, dilated ER and upregulated UPR genes have been found in PDL stem cells (PDLSCs) isolated from periodontitis patients[19-21].

The ER is notably related to risk factors for periodontal disease. Smoking is considered one of the major risk factors for periodontitis[22]. Nicotine-induced cytotoxicity and extracellular matrix (ECM) degradation by matrix metalloproteinases (MMPs) in human PDL cells (hPDLCs) have been proven to be mediated by the ER stress pathway[23]. Diabetes is the most studied systemic disease that predisposes periodontitis[22,24-26]. ER stress could be induced by advanced glycation end products (AGEs) in PDSLCs[27]. In high glucose concentrations, proteomic analysis of PDL fibroblasts (PDLFs) revealed an increased abundance of chaperonins and E3 ubiquitin ligases involved in misfolded protein degradation[28]. Force-induced cell death is also an important mediator of periodontal connective tissue destruction. PERK has been proven to mediate force-induced apoptosis in mouse embryonic fibroblasts[29]. Mechanical strain could downregulate cell viability and increase the level of expression of UPR-related genes[30]. Ageing is also a trigger of alveolar bone resorption. The expression of several ER stress markers is higher in osteocytes from bones of old compared to adult mice[31].

ER regulation in the pathogenesis of periodontal disease

As examples of local inflammation, chronic gingivitis and periodontitis are triggered and sustained by periodontopathic bacteria[32]. Porphyromonas gingivalis may be the indicative species for progressive periodontitis[33], while Aggregatibacter actinomycetemcomitans are associated with aggressive forms of periodontal disease[34]. Meanwhile, it is widely recognised that the interaction between subgingival dental plaque and the host immune response contributes to the occurrence and development of periodontitis. In the following section, we describe how periodontal pathogens interact with the ER, and how the latter contributes to immune responses against invading pathogens. In such situations, the ER plays a significant role in local inflammation and indeed homeostasis in the entire organism.

ER responses to periodontal pathogen invasion

Human primary gingival epithelial cells (GECs) are the first line of oral mucosa defence, which is vital for the success of pathogen invasion. Porphyromonas gingivalis (P. gingivalis) is closely associated with ER structures and exploits ER networks as an excellent subcellular niche for intracellular location in human GECs[35]. The following investigation studied the intracellular trafficking of

P. gingivalis in GECs and revealed that a large quantity of P. gingivalis localise to perinuclear ER regions and are encapsulated in ER-rich/LC3-positive double membrane vacuoles. As a result, P. gingivalis might utilise ER-rich autophagosomes to escape from antimicrobial mechanisms[36]. ER-associated degradation (ERAD) is a physiological process that transfers misfolded proteins from the ER lumen and membrane to the cytoplasm for further degradation by the proteasome. The components of the ERAD pathway are implicated in host cell entry and the toxicity of A. actinomycetemcomitans cytolethal distending toxin (AaCDT)[37]. Consistently, several ER-associated genes were found to be required for AaCDT toxicity in genome-wide screening in a yeast model[38].

Bacterial toxins can also induce UPR. Lipopolysaccharide (LPS), a component of gram-negative bacteria, has been applied widely to simulate the process of periodontal pathogen stimulation in vitro. The ER stress signalling pathway was activated by P. gingivalis LPS stimuli in hPDLCs[39]. Beyond the local invasion, oral administration of P. gingivalis significantly increased expression of glucose-regulated protein 78 (GRP78) and IRE1a/X-box binding protein-1 (XBP1) participating in UPR pathways was detected in the gingival tissue[40].

ER and periodontal immune response

The invasion of pathogens elicits immune responses, dedicated to killing bacteria with immune cell infiltration into the periodontium. It has been reported that ER stress modifies the gene expression associated with transcription of proinflammatory cytokines in B cells[41]. In addition, ER stress could be one of the pathological mechanisms in periodontal disease, evidenced by the colocalisation of HSP60/HSP70 cells and B cells in gingival biopsies from periodontitis patients[17].

Indeed, inflammatory cytokines can trigger UPR in periodontal tissues. The long-term rather than short-term inflammatory stimulation by tumour necrosis factor alpha (TNF-α) or interleukin-1β (IL-1β) could activate the prolonged UPR[19]. ER stress is also detected in a hypoxia microenvironment accompanied by inflammatory infiltration in aberrant vascularisation in periodontal tissues[42].

Conversely, ER stress can manipulate the release of proinflammatory cytokines with multiple proinflammatory signalling pathways including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Salubrinal (elF2α phosphorylation modulator/ERS antagonist) treatment successfully repressed the secretion of proinflammatory cytokines IL-6 and IL-8 in hPDLCs induced by LPS[39]. Consistently, IL-8 expression was elevated by thapsigargin, a selective inhibitor of the sarco/endoplasmic reticulum calcium ATPase for ER stress activation[43]. Moreover, ER stress is also attributed to intracellular calcium overload and increased oxidative stress in periodontal inflammatory conditions[44].

ER dysfunction in periodontal destruction

Periodontal destruction occurs owing to dysbiosis of the host to external stimuli[45]. The initial gingivitis will develop into severe chronic inflammation,and result in degradation of ligament fibres by MMPs and alveolar bone resorption by osteoclasts. When the ER fails to recover, the sustained ER dysfunction may lead to irreversible damage to the periodontal tissue. Uncovering the mechanisms of ER in periodontium destruction will facilitate the application of precision treatment to periodontal tissue regeneration.

ER dysregulation in the gingiva

ER stress induces autophagy and cell apoptosis via c-Jun activated protein kinase/stress-activated protein kinase (JNK/SAPK or p38 MAPK) in human gingival cells[46]. Human gingival fibroblasts (HGFs) are essential for oral wound healing. Functional impairment to the HGFs and damage to the gingiva in the acidic intraoral environment are attributed to the excessive Ca^{2+} released from ER mediated by OGR1/phospholipase C signalling[47]. Zoledronic acid (ZA), a bisphosphonate, can affect the viability of HGFs with irregularly shaped nuclei, dilated rough ER and numerous vacuoles[48]. Cyclosporine can significantly augment ER stress and induce overgrowth of human gingiva via the prominent anti-apoptotic action[49]. 4-phenylbutyric acid (4-PBA) attenuates the gingival hyperplasia by suppressing both the fibrotic and vascular components by blocking ER stress and matrix protein markers including TGF-α, connective tissue growth factor (CTGF) and vascular endothelial growth factor (VEGF) in HGFs[44].

ER and ECM degradation

MMP-mediated ECM degradation plays an important role in periodontal destruction[36-38]. The ER triggers expression of MMPs by activating CCAAT enhancer binding protein beta (C/EBP β) expression in hPDLCs[39]. Inhibition of ER stress by salubrinal and C/EBP homologous protein (CHOP)/GADD153 small interfering RNA (siRNA) eliminates ECM degradation and MMP pro-

duction in nicotine-treated PDLCs. Furthermore, ER stress contributes to PDLC apoptosis and periodontal connective tissue destruction via the Akt, ERK, p38, JNK, MAPK and NF-κB pathways in PDLCs[23,29,30]. As a result, ER stress seems to play a regulatory role in PDLC apoptosis and ECM degradation in PDL destruction.

Role of ER in alveolar bone resorption

Alveolar bone homeostasis is sustained by the balance between osteoblastogenesis and osteoclastogenesis. An overwhelming amount of bone resorption over formation contributes to alveolar bone loss in periodontal disease. Alveolar bone loss is mainly modulated by the function of osteoblasts, osteoclasts and osteocytes. It has been reported that the ER stress activator thapsigargin or tunicamycin contributes to alveolar bone loss in experimental periodontitis mice[19].

Furthermore, ER-associated pathways and activities have been shown to participate in modulating the function of these bone cells, suggesting that ER plays a crucial role in alveolar bone homeostasis. Aberrant osteocyte activity can lead to bone loss[50,51]. General communication takes place between osteocytes through their dentritic network. Interestingly, osteocytes can share their mitochondria transferred by the ER from the donor to recipient cells[20]. The degree of ER stress has been found to affect the viability and osteogenic differentiation of osteoblasts. ER stress can weaken the osteogenesis of primary calvarial osteoblasts (POBs). Additionally, salubrinal can restore the ER stress–induced decreased viability of POBs in a dose-dependent manner[52]. It has been reported that the PERK-eIF2a and IRE1a–XBP1 pathways also participate in osteoclastic differentiation of bone marrow macrophages[40].

The ER is the largest organelle for intracellular Ca^{2+} storage. Calcium oscillations, which can be modulated by the calcium receptors on the ER membrane, are well-recognised in reactive oxygen species and receptor activator of NF-κB ligand (RANKL)–induced osteoclastogenesis and bone resorption via calcineurin[53]. The production of RANKL in osteoblasts and PDLCs has been detected in periodontitis with the occurrence of alveolar bone damage[54].

ER mechanisms of periodontal regeneration

The ultimate goal of periodontal therapy is to regenerate the lost tissues. Notably, irreversible alveolar bone absorption as an outcome of periodontal disease is mainly attributed to the destruction of stemness of PDSLCs. The effectiveness of periodontal treatment based on PDLSCs has been widely supported in recent studies, as reported in a review[55]. PDLSCs have the ability to differentiate into osteoblasts, cementoblast-like cells and collagen-forming cells, and thus can regenerate the periodontal tissues destroyed by chronic periodontitis[56]. Given that ER dysfunction was found to be involved in the onset and progress of periodontal disease, treatments targeting the recovery of ER homeostasis in PDSLCs may present a novel strategy for the reconstruction of periodontal tissue.

ER stress inhibitors such as 4-PBA can directly recover the alveolar bone level in periodontitis models with their functions by improving the differentiation ability of PDLSCs[19,40]. Low-intensity pulsed ultrasound (LIPUS) enhances the osteogenic ability of PDLSCs and rescues the alveolar bone loss in periodontitis mice by downregulating ER stress, which makes it a promising noninvasive strategy to reconstruct the periodontal tissues[21]. Given the essential role played by PERK in the differentiation of hPDLSCs into osteoblast-like cells, the PERK inhibitor GSK2606414 can facilitate the formation of alveolar bone[19,57]. CirkCDK8 silencing rescues impaired PDLSC osteogenesis under hypoxic conditions by alleviating the ER-associated autophagy[42], which indicates a novel therapeutic strategy to manipulate intracellular dynamics via the ER pathway.

Conclusion

The periodontium plays a crucial role in maintaining dental health. The main aim of periodontology is to rehabilitate the periodontal tissues. In recent years, ER has emerged as a regulator of cell function and trigger of periodontal disorders. Accordingly, ER-targeting therapy is increasingly harnessed to support regenerative therapeutics. With the help of technological advances, research focused on ER intracellular regulation and manipulating ER dynamics hold the prospect of safeguarding periodontal homeostasis and regeneration.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

This review article was conceived by Profs Yan JIN and Fang JIN; Drs Qi Ming ZHAI and Bei LI were responsible for the preparation and revision of the initial

draft; Drs Xiao Ning HE, Jia GUO and Xiao LEI were involved in reviewing each draft and approving the final manuscript.

(Received Jan 31, 2021; accepted Feb 20, 2021)

References

1. Wei X, Liu Q, Guo S, Wu Y. Role of Wnt5a in periodontal tissue development, maintenance, and periodontitis: Implications for periodontal regeneration (Review). Mol Med Rep 2021;23:1–7.
2. Hodjat M, Khan F, Saadat KASM. Epigenetic alterations in aging tooth and the reprogramming potential. Ageing Res Rev 2020;63:101140.
3. Peres MA, Macpherson LMD, Weyant RJ, et al. Oral diseases: A global public health challenge. Lancet 2019;394:249–260.
4. Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, et al. Causal association between periodontitis and hypertension: Evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. Eur Heart J 2019;40:3459–3470.
5. Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: A tale of two common interrelated diseases. Nat Rev Endocrinol 2011;7:738–748.
6. Hetz C, Zhang K, Kaufman RJ. Mechanisms, regulation and functions of the unfolded protein response. Nat Rev Mol Cell Biol 2020;21:421–438.
7. Celli J, Tsolis RM. Bacteria, the endoplasmic reticulum and the unfolded protein response: Friends or foes? Nat Rev Microbiol 2015;13:71–82.
8. Hetz C, Mollereau B. Disturbance of endoplasmic reticulum proteostasis in neurodegenerative diseases. Nat Rev Neurosci 2014;15:233–249.
9. Westrate LM, Lee JE, Prinz WA, Voeltz GK. Form follows function: The importance of endoplasmic reticulum shape. Annu Rev Biochem 2015;84:791–811.
10. Joshi AS, Zhang H, Prinz WA. Organelle biogenesis in the endoplasmic reticulum. Nat Cell Biol 2017;19:876–882.
11. Zhang H, Hu J. Shaping the endoplasmic reticulum into a social network. Trends Cell Biol 2016;26:934–943.
12. Tavasolian F, Hosseini AZ, Mirzaei A, et al. Unfolded protein response-mediated modulation of mesenchymal stem cells. IUBMB Life 2020;72:187–197.
13. Shibata Y, Voeltz GK, Rapoport TA. Rough sheets and smooth tubules. Cell 2006;126:435–439.
14. Arruda AP, Pers BM, Parlakgül G, Güney E, Inouye K, Hotamisligil GS. Chronic enrichment of hepatic endoplasmic reticulum-mitochondria contact leads to mitochondrial dysfunction in obesity. Nat Med 2014;20:1427–1435.
15. Nakatogawa H. Mechanisms governing autophagosome biogenesis. Nat Rev Mol Cell Biol 2020;21:439–458.
16. Rhodin K, Divaris K, North KE, et al. Chronic periodontitis genome-wide association studies: Gene-centric and gene set enrichment analyses. J Dent Res 2014;93:882–890.
17. Domon H, Takahashi N, Honda T, et al. Up-regulation of the endoplasmic reticulum stress-response in periodontal disease. Clin Chim Acta 2009;401:134–140.
18. Seo B, Coates DE, Seymour GJ, Rich AM. Unfolded protein response-related gene regulation in inflamed periodontal tissues with and without Russell bodies. Arch Oral Biol 2016;69:1–6.
19. Xue P, Li B, An Y, et al. Decreased MORF leads to prolonged endoplasmic reticulum stress in periodontitis-associated chronic inflammation. Cell Death Differ 2016;23:1862–1872.
20. Gao J, Qin A, Liu D, et al. Endoplasmic reticulum mediates mitochondrial transfer within the osteocyte dendritic network. Sci Adv 2019;5:eaaw7215.
21. Li H, Deng Y, Tan M, et al. Low-intensity pulsed ultrasound upregulates osteogenesis under inflammatory conditions in periodontal ligament stem cells through unfolded protein response. Stem Cell Res Ther 2020;11:215.
22. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Dis Primers 2017;3:17038.
23. Lee SI, Kang KL, Shin SI, Herr Y, Lee YM, Kim EC. Endoplasmic reticulum stress modulates nicotine-induced extracellular matrix degradation in human periodontal ligament cells. J Periodontal Res 2012;47:299–308.
24. Teles F, Wang Y, Hajishengallis G, Hasturk H, Marchesan JT. Impact of systemic factors in shaping the periodontal microbiome. Periodontol 2000 2021;85:126–160.
25. Wang X, Wang H, Zhang T, Cai L, Kong C, He J. Current knowledge regarding the interaction between oral bone metabolic disorders and diabetes mellitus. Front Endocrinol (Lausanne) 2020;11:536.
26. Chow KF. A review of excessive sugar metabolism on oral and general health. Chin J Dent Res 2017;20:193–198.
27. Xu J, Xiong M, Huang B, Chen H. Advanced glycation end products upregulate the endoplasmic reticulum stress in human periodontal ligament cells. J Periodontol 2015;86:440–447.
28. Ashour A, Xue M, Al-Motawa M, Thornalley PJ, Rabbani N. Glycolytic overload-driven dysfunction of periodontal ligament fibroblasts in high glucose concentration, corrected by glyoxalase 1 inducer. BMJ Open Diabetes Res Care 2020;8:e001458.
29. Mak BC, Wang Q, Laschinger C, et al. Novel function of PERK as a mediator of force-induced apoptosis. J Biol Chem 2008;283:23462–23472.
30. Firth FA, Milne TJ, Seo B, Farella M. An in-vitro mechanical strain three-dimensional culture model: Periodontal ligament cell viability, apoptosis, and endoplasmic reticulum stress response. Eur J Oral Sci 2020;128:120–127.
31. Chalil S, Jaspers RT, Manders RJ, Klein-Nulend J, Bakker AD, Deldicque L. Increased endoplasmic reticulum stress in mouse osteocytes with aging alters Cox-2 response to mechanical stimuli. Calcif Tissue Int 2015;96:123–128.
32. Darveau RP. Periodontitis: A polymicrobial disruption of host homeostasis. Nat Rev Microbiol 2010;8:481–490.
33. Amaliya A, Laine ML, Delanghe JR, Loos BG, Van Wijk AJ, Van der Velden U. Java project on periodontal diseases: periodontal bone loss in relation to environmental and systemic conditions. J Clin Periodontol 2015;42:325–332.
34. Haubek D, Ennibi OK, Poulsen K, Vaeth M, Poulsen S, Kilian M. Risk of aggressive periodontitis in adolescent carriers of the JP2 clone of Aggregatibacter (Actinobacillus) actinomycetemcomitans in Morocco: A prospective longitudinal cohort study. Lancet 2008;371:237–242.
35. Choi CH, DeGuzman JV, Lamont RJ, Yilmaz Ö. Genetic transformation of an obligate anaerobe, P. gingivalis for FMN-green fluorescent protein expression in studying host-microbe interaction. PLoS One 2011;6:e18499.
36. Lee K, Roberts JS, Choi CH, Atanasova KR, Yilmaz Ö. Porphyromonas gingivalis traffics into endoplasmic reticulum-rich-autophagosomes for successful survival in human gingival epithelial cells. Virulence 2018;9:845–859.
37. Eshraghi A, Dixon SD, Tamilselvam B, et al. Cytolethal distending toxins require components of the ER-associated degradation pathway for host cell entry. PLoS Pathog 2014;10:e1004295.
38. Denmongkholchai S, Katare P, Choochuay S, et al. Genome-wide identification of host genes required for toxicity of bacterial cytolethal distending toxin in a yeast model. Front Microbiol 2019;10:890.

39. Bai Y, Wei Y, Wu L, Wei J, Wang X, Bai Y. C/EBP β mediates endoplasmic reticulum stress regulated inflammatory response and extracellular matrix degradation in LPS-stimulated human periodontal ligament cells. Int J Mol Sci 2016;17:385.
40. Yamada H, Nakajima T, Domon H, Honda T, Yamazaki K. Endoplasmic reticulum stress response and bone loss in experimental periodontitis in mice. J Periodontal Res 2015;50:500–508.
41. Wheeler MC, Rizzi M, Sasik R, Almanza G, Hardiman G, Zanetti M. KDEL-retained antigen in B lymphocytes induces a proinflammatory response: A possible role for endoplasmic reticulum stress in adaptive T cell immunity. J Immunol 2008;181:256–264.
42. Zheng J, Zhu X, He Y, et al. CircCDK8 regulates osteogenic differentiation and apoptosis of PDLSCs by inducing ER stress/autophagy during hypoxia. Ann N Y Acad Sci 2021;1485:56–70.
43. Son A, Shin DM, Hong JH. Peptidoglycan induces the production of interleukin-8 via calcium signaling in human gingival epithelium. Korean J Physiol Pharmacol 2015;19:51–57.
44. Rao SR, Subbarayan R, Ajitkumar S, Murugan Girija D. 4PBA strongly attenuates endoplasmic reticulum stress, fibrosis, and mitochondrial apoptosis markers in cyclosporine treated human gingival fibroblasts. J Cell Physiol 2018;233:60–66.
45. Hajishengallis G, Lamont RJ. Beyond the red complex and into more complexity: The polymicrobial synergy and dysbiosis (PSD) model of periodontal disease etiology. Mol Oral Microbiol 2012;27:409–419.
46. Kim DS, Kim JH, Lee GH, et al. p38 Mitogen-activated protein kinase is involved in endoplasmic reticulum stress-induced cell death and autophagy in human gingival fibroblasts. Biol Pharm Bull 2010;33:545–549.
47. Kim MS, Shin DM, Kim MS. Acidification induces OGR1/Ca^{2+}/calpain signaling in gingival fibroblasts. Biochem Biophys Res Commun 2018;496:693–699.
48. Zafar S, Coates DE, Cullinan MP, Drummond BK, Milne T, Seymour GJ. Zoledronic acid and geranylgeraniol regulate cellular behaviour and angiogenic gene expression in human gingival fibroblasts. J Oral Pathol Med 2014;43:711–721.
49. Rao SR, Sundararajan S, Subbarayan R, Murugan Girija D. Cyclosporine-A induces endoplasmic reticulum stress and influences pro-apoptotic factors in human gingival fibroblasts. Mol Cell Biochem 2017;429:179–185.
50. Nakashima T, Hayashi M, Fukunaga T, et al. Evidence for osteocyte regulation of bone homeostasis through RANKL expression. Nat Med 2011;17:1231–1234.
51. Huang X, Xie M, Xie Y, et al. The roles of osteocytes in alveolar bone destruction in periodontitis. J Transl Med 2020;18:479.
52. Chen Y, Guo Y, Li J, et al. Endoplasmic reticulum stress remodels alveolar bone formation after tooth extraction. J Cell Mol Med 2020;24:12411–12420.
53. Okada H, Okabe K, Tanaka S. Finely-tuned calcium oscillations in osteoclast differentiation and bone resorption. Int J Mol Sci 2020;22:180.
54. Tsukasaki M. RANKL and osteoimmunology in periodontitis. J Bone Miner Metab 2021;39:82–90.
55. Zhai Q, Dong Z, Wang W, Li B, Jin Y. Dental stem cell and dental tissue regeneration. Front Med 2019;13:152–159.
56. Seo BM, Miura M, Gronthos S, et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. Lancet 2004;364:149–155.
57. Yang S, Hu L, Wang C, Wei F. PERK-eIF2α-ATF4 signaling contributes to osteogenic differentiation of periodontal ligament stem cells. J Mol Histol 2020;51:125–135.