Cellular senescence: A new perspective on the suppression of periodontitis (Review)

XUE-JING LIN[1,2], QING YUAN[1,2], JIE ZHOU[1,2], YU-LEI DONG[1,2], DIWAS SUNCHURI[3] and ZHU-LING GUO[1,4]

[1]School of Dentistry, Hainan Medical University, Haikou, Hainan 571199, P.R. China;
[2]Department of Dentistry, The First Affiliated Hospital of Hainan Medical University, Haikou, Hainan 570100, P.R. China;
[3]School of International Education, Hainan Medical University, Haikou, Hainan 571199, P.R. China;
[4]Department of Health Management Center, The First Affiliated Hospital of Hainan Medical University, Haikou, Hainan 570100, P.R. China

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Abstract. Cellular senescence, characterized by cell cycle arrest, can result in tissue dysfunction when senescent cells persist and accumulate. Periodontitis, a chronic inflammatory condition caused by the interaction between bacteria and the immune system of the host, primarily manifests as damage to periodontal tissues. Aging and inflammation are interlinked processes that exacerbate each other. The progression of localized chronic periodontal inflammation is often accelerated in conjunction with tissue and organ aging. The presence of senescent cells and release of inflammatory cytokines, immune modulators, growth factors and proteases that are associated with the senescence-associated secretory phenotype contribute to the deterioration of periodontal tissues. The present review aimed to elucidate the mechanisms of cellular senescence and its potential impact on periodontitis, offering novel insights for modulating the inflammatory microenvironment of periodontal tissues.

Contents

Correspondence to: Dr Zhu-Ling Guo, School of Dentistry, Hainan Medical University, 3 Xueyuan Road, Haikou, Hainan 571199, P.R. China
E-mail: hy0210026@hainmc.edu.cn

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1. Introduction

Aging encompasses a gradual decline in physiological and pathological functions. Physiological aging involves the natural deterioration of organs and systems over time, while pathological aging is influenced by diseases, environmental factors or other abnormal causes, including chronic disease, inflammation and genetic mutation (1). There is not an absolute boundary between physiological and pathological aging and both can influence the onset of cellular senescence (2,3). Cellular senescence is the irreversible halting of cell division, which is induced by external pro-senescence factors. IGFBP5 actively contributes to promoting senescence and can induce senescence in neighboring cells. The senescence-associated secretory phenotype (SASP) contributes to this process through the secretion of interleukins (ILs), tumor necrosis factor (TNF)-α, prostaglandin E2, interferon (INF)-β and IFN-γ. Periodontitis, a chronic inflammatory disease, disproportionately affects the patients aged 60-65 years, with aging being a notable risk factor that exacerbates alveolar bone and tooth loss (4). In developing countries, periodontal disease is common in the elderly, with 62-97.00% having mild periodontitis and 20.00 to 48.00% having severe periodontitis (5). Various stimuli such as oxidative stress, proinflammatory factors, microbial infections or activation of signaling pathways can induce senescence in cells that is independent of telomere shortening. Due to cell cycle arrest, senescent cells exhibit altered expression profiles of proteins and transcription factors that are associated with the regulation of the cell cycle (6). While bacteria may induce inflammation, the immune response of the host is the primary driver of periodontal tissue destruction. Cellular senescence can compromise bacterial clearance and immune defenses (7). Targeting cellular senescence presents a novel approach to understanding the mechanisms and clinical management of periodontitis. The present review investigated the mechanisms of cellular senescence and the characterization of periodontal tissues during cellular senescence (Fig. 1).

2. Mechanisms of cellular senescence

Oxidative stress. Aging is characterized by progressive degeneration, which is influenced by alterations in the

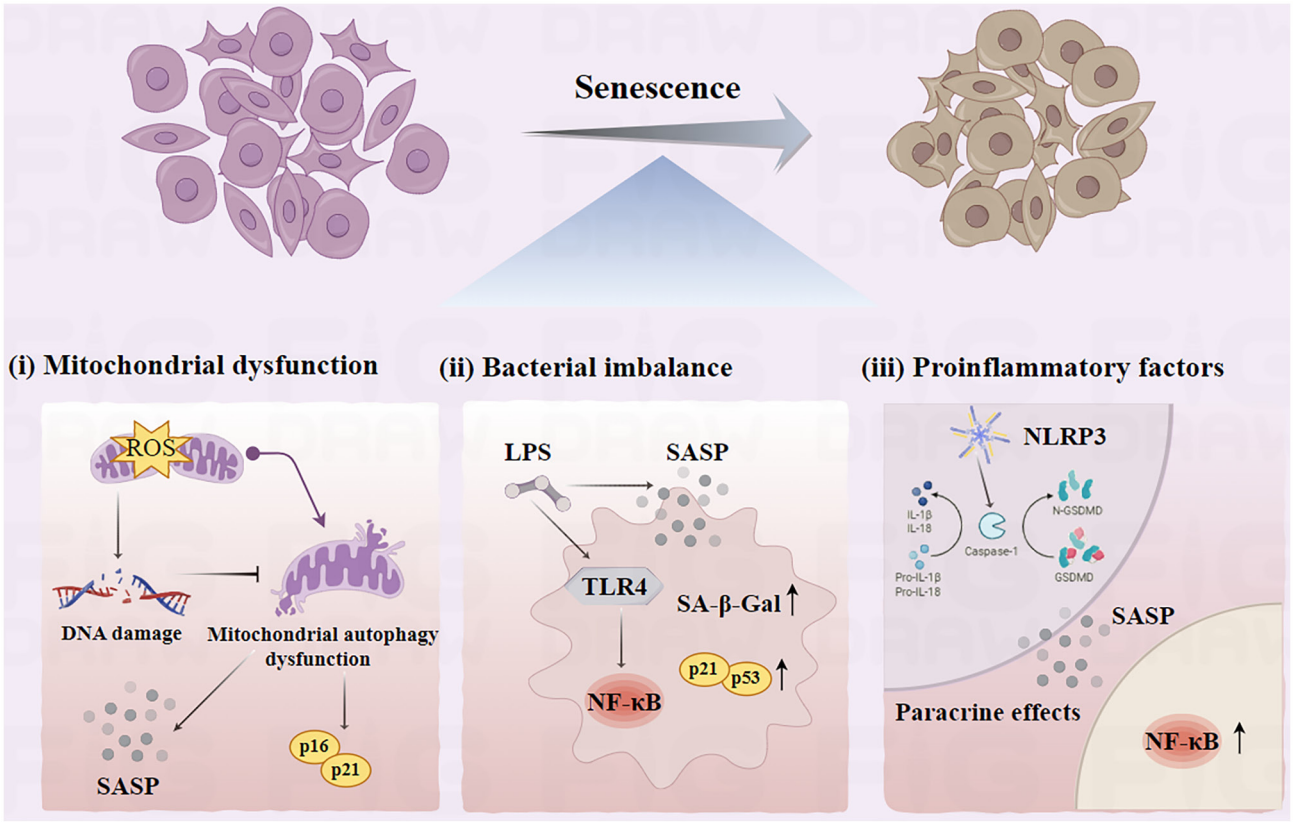

Figure 1. Mechanisms of cellular senescence. (i) Impaired scavenging of reactive oxygen radicals causes DNA damage. This leads to an accumulation of senescence-associated lipofuscin, and inhibits mitochondrial autophagy, which increases protein expression of the cellular senescence markers p16 and p21. (ii) Bacterial flora imbalance can lead to an increase in the secretion of SASP-associated proteins and an activation of the downstream NF-κB pathway via TLR4. This promotes the release of inflammatory cytokines, which in turn promotes cell injury. (iii) NLRP3 recognizes caspase-1, which converts IL-1β and IL-18 precursors to mature IL-1β and IL-18, triggering pyroptosis. Senescent cells secrete SASP-associated protein (such as IL-1α, IL-1β, IL-6 and IL-8), which affect the functions of neighboring cells through paracrine and autocrine signaling mechanisms. SASP, senescence-associated secretory phenotype; TLR4, Toll-like receptor 4; NLRP3, NOD-like receptor pyrin domain-containing protein 3; Caspase-1, cysteinyl aspartate specific proteinases-1; IL, interleukins; ROS, reactive oxygen species; LPS, lipopolysaccharides; SA-β-Gal, senescence-associated β-galactosidase; GSDMD, gasdermin D.

oxidation-reduction status and inflammatory responses triggered by oxidative stress (8). This results in an increased production of reactive oxygen species (ROS) within the body, leading to abnormal levels of oxidative stress. Specific increases in the levels of ROS are hypothesized to serve an important role in initiating and perpetuating the cellular aging processes. The accumulation of ROS can result in DNA damage and subsequent cell cycle arrest (9). DNA damage can further lead to telomere shortening, DNA methylation, histone deacetylation and mitochondrial dysfunction, thereby instigating transcriptome alterations that are associated with aging (10,11).

Mitochondrial dysfunction is a hallmark of aging (12). Mitochondrial autophagy, vital for maintaining mitochondrial quality control, eliminates dysfunctional mitochondria to maintain cellular homeostasis. It can modulate the cellular senescence phenotype by suppressing transcription of SASP-associated genes (13). The accumulation of lipofuscin is a distinctive feature of senescent cells, and oxidative stress-induced DNA damage during senescence promotes its accumulation (14). Moreover, it is associated with impaired mitochondrial autophagy function, exhibiting a positive association with the expression levels of cell aging markers p16 and p21 (11,15,16). Oxidative stress-induced senescence (SIPS) is implicated in the pathogenesis of age-associated macular degeneration and is known to increase secretion of SASP-associated proteins (15,16). In periodontal tissue, increases in the SIPS levels have detrimental effects that are comparable to inflammatory factors and promote the secretion of SASP-associated proteins (17). Targeting mitochondrial autophagy pathways in mesenchymal stem cells in various degenerative conditions, such as intervertebral disc degeneration (IVDD) and osteoarthritis (OA), may enhance cartilage repair and regeneration capabilities (18-20).

Bacterial imbalance. Aging is associated with alterations in the composition of microbial communities. For example, in the gut, the microbiota can influence the aging of gut cells by regulating the intestinal epithelial barrier, gut immune system and gut metabolism. In the skin, the microbiota can influence skin cell senescence by regulating the integrity of the stratum corneum, the skin immune system and skin metabolism. Previous studies reveal a shift in the microbiome with age, demonstrating a positive association between aging and the presence of gram-negative bacteria such as *Porphyromonas gingivalis* (21,22). Furthermore, aging is characterized by an increased responsiveness of periodontal cells to the oral microbiota and mechanical stress (23). A previous study indicates that bacterial lipopolysaccharides (LPS) can induce cellular senescence and increase expression levels of SASP-associated genes (24). Prolonged exposure to *P. gingivalis* LPS can prompt periodontal cell senescence due to the activation

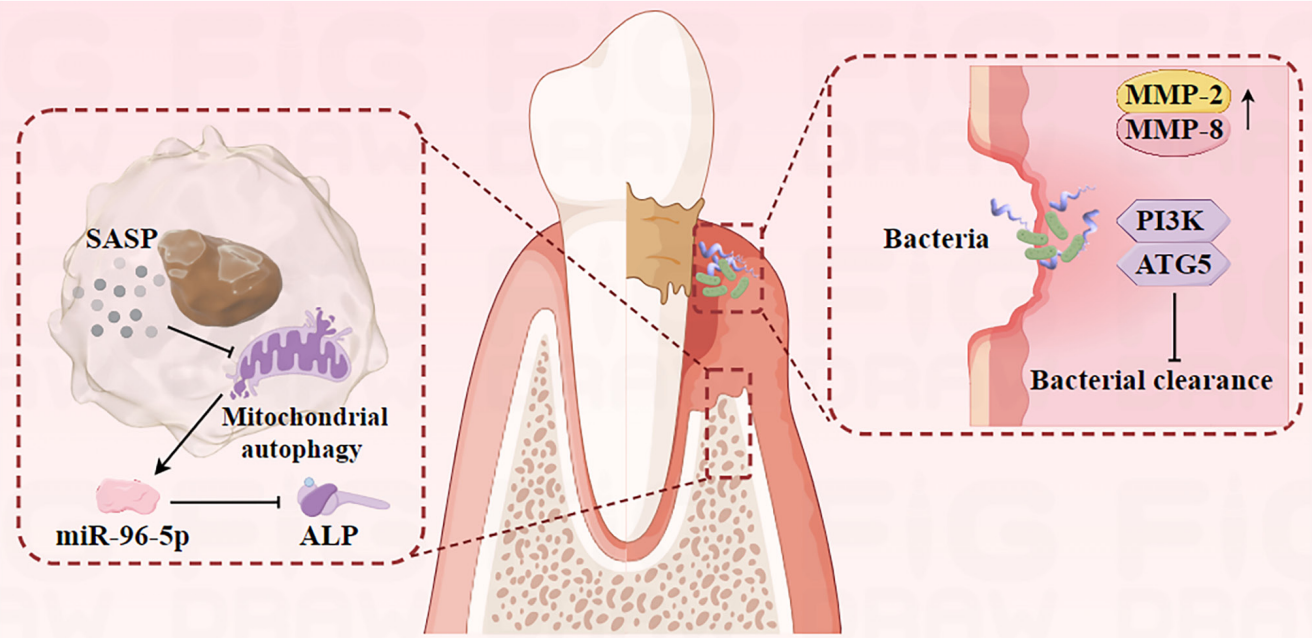

Figure 2. Cellular senescence affects alveolar bone metabolism through secretion of SASP-associated proteins. MiR-96-5p promotes osteoblast senescence, leading to decreased bone differentiation. Senescence-associated dysbiosis compromises the integrity of the epithelial barrier and further destroys deeper tissues. Decreased levels of developmental endothelial locus-1, PI3K and ATG5 affect periodontal bacterial clearance, thus exacerbate periodontal inflammation. SASP, senescence-associated secretory phenotype; miR-96-5p, micro-RNA-96-5p; ALP, alkaline phosphatase; MMP, matrix metalloproteinases; ATG5, autophagy-related protein 5.

of the cell cycle arrester molecule p53 (25). LPS also mediate microglia activation and ischemic brain injury via the NF-κB signaling pathway (26). Additionally, LPS from *Escherichia coli* is indicated to increase the activity of senescence-associated β-galactosidase, increase the expression levels of cell cycle inhibitor proteins p21 and p53, and impede human pulp stem cell growth (25,27,28). Increased expression of LPS by *P. gingivalis* may stimulate NF-κB activation in periodontal ligament stem cells (PDLSCs), exacerbate the high glucose microenvironment and increase the expression of proinflammatory cytokines (namely, ILs, TNF and INF) and matrix metalloproteinases (MMPs) such as MMP-1 (29,30). LPS can also trigger the downstream NF-κB pathway via Toll-like receptor 4, prompting the release of inflammatory cytokines such as TNF-α, IL-6 and IL-1β that contribute to cellular damage. Activation of NF-κB also results in an increased expression of p53 and p21 in the PDLSC nucleus, which is pivotal in promoting cellular aging (31,32).

Proinflammatory factors. A potential feedback loop exists between inflammatory cytokines and cellular senescence, which could hasten the progression of the senescence of inflammatory cell (33). Senescent cells are more vulnerable to harm from external stimuli, including proinflammatory factors and bacterial virulence factors. The NOD-like receptor pyrin domain-containing protein 3 inflammasome recognizes pathogen-associated molecular patterns or damage-associated molecular patterns, activating cysteinyl aspartate specific proteinases-1 (Caspase-1) (34). Caspase-1 cleaves the protein Gasdermin D, which then converts the precursor forms of IL-1β and IL-18 into mature forms, thereby initiating pyroptosis (35,36). IL-1β can promote paracrine cellular senescence and NF-κB activation, activating a cascade of an inflammatory-induced senescence (37). The accumulation of pyroptotic macrophages (MΦs) in gingival tissue under high-glucose conditions can stimulate IL-1β secretion and paracrine senescence in neighboring cells (38). Furthermore, proinflammatory cytokines (such as ILs, TNF and INF) generate the ROS themselves and then the ROS induce epithelial cell senescence, the ROS activate the Eotaxin-1/CCL11 pathway leading to fibroblast senescence (39,40).

Senescent cells, with a SASP, release various proinflammatory factors (such as IL-1α, IL-1β, IL-6 and IL-8), growth factors (such as hepatocyte growth factor, TGF-β and granulocyte macrophage colony-stimulating factor), chemokines [such as chemokine (C-X-C motif) ligand (CXCL)-1/3 and CXCL-10] and MMP-8 and MMP-9. The SASP can promote chronic inflammation through paracrine effects, affecting neighboring stem cells, fibroblasts, immune cells, epithelial cells and endothelial cells via paracrine and autocrine signaling mechanisms (41). In the aging heart, MMP-9 activates the transition of the MΦ phenotype to the proinflammatory M1 subtype can induce inflammation due to its increased secretion of TNF-α, IL-1β, IL-6 and other inflammatory factors (42). Activation of the SASP initiates a milieu of chronic inflammation in addition to the age-induced stressors, leading to a self-perpetuating cycle of senescent cell accumulation (43).

3. Senescence-associated alterations in the periodontal microenvironment

Alveolar bone remodeling ability and cellular senescence. PDLSCs possess self-renewal and multi-directional differentiation capabilities, which are important for periodontal tissue regeneration and osteogenic differentiation (44). The senescence of PDLSCs reduces their osteogenic potential, leading to periodontal tissue destruction via inflammation and the induction of the SASP (Fig. 2). This process reduces

the regenerative capacity of periodontal tissues in periodontitis. In patients with diabetes, oxidative stress induces telomere dysfunction and PDLSC senescence, reducing periodontal bone tissue regeneration and increasing bone loss in periodontitis (45-47).

Aging impacts the proliferation and differentiation of bone marrow mesenchymal stem cells (BMSCs), with senescent cells involved in senile osteoporosis-related bone loss (48). Sirtuin (SIRT), a NAD-dependent deacetylase family member, is a potential therapeutic target for age-related diseases (49). SIRT1, an upstream regulator of mitochondrial autophagy, can inhibit age-related degenerative changes in IVDD and OA (18,50). The SIRT1/PTEN-induced kinase 1/Parkin pathway-mediated mitophagy activation reduces renal tubular epithelial cell senescence (51). The balance between osteoblast and osteoclast activity maintains bone mass, and osteoblasts are important in bone formation through matrix synthesis, substance secretion and tissue mineralization. Upregulation of SIRT1 expression levels activates the PI3K/Akt/mTOR pathway to promote mitophagy, enhancing osteoblast proliferation and viability (52).

Inhibition of micro (mi)RNA-96-5p expression levels in osteoblasts markedly downregulates the mRNA of alkaline phosphatase (the bone differentiation factor), which indicates that miRNA-96-5p promotes osteoblast senescence, leading to decreased bone differentiation. miRNA-96-5p is likely crucial in regulating osteoblast degenerative changes during aging (53,54). The accumulation of senescent cells in the alveolar bone can stimulate the secretion of SASP-associated protein, which exerts a potent paracrine effect on osteoblasts, inhibiting their function and reducing bone regeneration in periodontitis (23,55). Inflammatory bone loss in periodontitis, characterized by osteoclast activity, is exacerbated by aging, which enhances osteoclast production (56). Osteoblast-secreted osteoprotegerin (OPG) mitigates bone loss by inhibiting the receptor activator of NF-κB (RANK) ligand/RANK pathway. However, the reduction in osteoblast numbers with aging reduces OPG levels, contributing to osteoclast-induced bone loss (57,58). These findings underscore the causal role of senescent cells and their SASPs in alveolar bone loss and suggest that targeting senescent cells could increase the alveolar bone remodeling capabilities.

Bacterial clearance capacity and cellular senescence. Gingival fibroblasts (GFs) are predominant cells within the gingival connective tissue and serve an important role in regulating periodontal inflammation. The proliferative capacity of GFs and the mitotic activity of PDLSCs may reduce with age. This reduction is associated with increased mRNA levels of MMP-2 and MMP-8, leading to the increased degradation of the extracellular matrix (59). Chronic bacterial assaults can induce a reduction in the amount of epithelial growth, compromising the integrity of the epithelial barrier (60). Once this barrier is breached, bacteria and their virulence factors such as endotoxin and exotoxin, can penetrate deeper connective tissues, exacerbating periodontal tissue damage (61).

Neutrophils are important for pathogen clearance in the immune response to periodontitis. Age-related neutrophil dysfunction may disrupt the neutrophil homeostasis in periodontal tissues, impairing bacterial clearance and resulting in subsequent damage to periodontal tissues (62). Previous studies demonstrate developmental endothelial locus-1 mRNA and protein expression levels are downregulated in the periodontal tissue of aged mice compared with that of young mice (63,64). This downregulation leads to an excessive recruitment of neutrophils and inflammatory bone resorption. Furthermore, in elderly hosts aged >65 years, excessive or dysregulated PI3K activity impairs the accuracy of neutrophil migration (65,66). Aging mice have a deficiency in autophagy-related protein 5, resulting in decreased autophagy levels and impaired release of neutrophil extracellular traps (NETs) (67-69). This impairment hinders the clearance of pathogenic bacteria and their metabolites in the gingival sulcus by NETs. In summary, cellular senescence reduces the clearance of existing periodontal bacteria, compromising the integrity of the epithelial barrier and exacerbating local periodontal inflammation.

Organizational defense effectiveness and cellular senescence. MΦs serve an important role in the innate immunity as the initial defense against pathogenic microorganisms. Monitoring periodontitis activity may rely on the phenotypic polarization of MΦs in order for them to modulate the immune response to the subgingival biofilm and mitigate alveolar bone loss (70). Aging-related M1 to M2 repolarization failure can lead to an increase in osteoclast activation, a reduction in osteoblast formation, an increase in bone resorption and a decrease in bone formation. Senescent MΦs are implicated in perpetuating chronic inflammation during bone remodeling, as well as inducing a senescent state in young BMSCs and diminishing their osteogenic potential (71). MΦ M1 polarization is associated with PDLSC senescence in diabetic periodontitis microenvironments. By contrast, M2 polarization potentially increases the expression levels of osteogenesis-related cytokines, such as runt-related transcription factor 2, alkaline phosphatase and osteocalcin, exerts anti-aging effects and facilitates the osteogenic differentiation of PDLSCs (72,73). Additionally, the paracrine factors released by PDLSCs can stimulate the expression of CD163, a surface marker associated with M2-MΦs, which contributes to macrophage M2 polarization (74).

Dendritic cells (DCs) represent a diverse cell population and inhibiting their function results in reduced responses of the adaptive immune system as well as an increased susceptibility to periodontal disease. A previous study indicates that the quantity of DCs in the peripheral blood fluctuates with age, potentially contributing to the increased vulnerability of older patients to infection compared with younger patients (75). Furthermore, alterations in the functionality of DCs contribute to immune dysregulation and the onset of chronic inflammation. *In vitro*, infection of DCs by the non-living oral pathogen *P. gingivalis* triggers activation of the SASP and subsequent bone loss (76).

Langerhans cells (LCs), a subset of DCs located in the oral mucosal epithelium, likely serve a role in initiating and perpetuating periodontal diseases (77). A decrease in the number of epithelial LCs and their dendritic structures in elderly individuals aged >75 years with periodontitis, which are distinct compared with those in adults, may compromise their removal

of pathogenic bacteria (78,79). Reducing LCs in the aging epidermis impairs the immunoregulatory functions of the skin and compromises barrier integrity, antimicrobial defenses and overall cell protection capabilities (80,81). Consequently, immune cell senescence may disrupt the homeostasis of periodontal defense mechanisms.

4. Conclusions and prospects

In conclusion, the prevalence and severity of periodontitis are associated with cellular senescence. The intricate changes in cellular senescence can impair the effective removal of pathogens by immune cells. The interaction of intracellular and extracellular aging environments can lead to the deterioration of cells and factors involved in bone metabolism, tissue defense and immune response in periodontal tissues, which exacerbates the progression of periodontitis. Furthermore, a comprehensive literature review underscores the complexity of the association between cellular senescence and inflammation. The precise nature of the association between cellular senescence and inflammation is yet to be completely understood, with the possibility of a causal or bidirectional association.

The current understanding suggests that the cascade of changes triggered by cellular senescence serves a role in the development of periodontal disease, potentially explaining the increased prevalence of this condition among the elderly aged >65 years. Increasing the understanding of the association between cellular senescence and periodontitis could offer a novel approach to preventing and treating periodontal diseases in older individuals. Further investigation is required to assess the applicability of these mechanisms to other age-related diseases such as hypertension, diabetes in clinical settings.

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Availability of data and materials

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Authors' contributions

ZG conceived and designed the present review. XL wrote most of the manuscript. DS, JZ, YD and QY edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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