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Perspective

Oral Dysbiosis and the Hallmarks of Aging: A Perspective on Mechanisms and Therapeutic Opportunities

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ABSTRACT: Aging is characterized by progressive decline in cellular and tissue functions, markedly increasing susceptibility to age-related diseases (ARDs) such as neurodegenerative diseases, cardiovascular diseases, metabolic diseases, and musculoskeletal disorders. The twelve aging hallmarks proposed in 2022 have clarified the underlying mechanisms linking aging to ARDs. As the second-largest microbiome in the body, oral dysbiosis has been associated with aging-related phenotypes and may influence systemic aging and ARDs. Available evidence, derived largely from observational and preclinical studies, suggests that oral dysbiosis may be associated with selected aging-related processes, including cellular senescence, altered intercellular communication, mitochondrial dysfunction, and loss of proteostasis via virulence factors, metabolites, etc. Here, we summarize epidemiological observations linking oral microbiota to ARDs, and offer a perspective centered on core aging hallmarks to delineate how oral dysbiosis may serve as a plausible modulator of systemic aging and ARD progression. We also introduce promising interventions such as plaque control, targeted antimicrobials, and probiotics as research opportunities. Finally, we discuss current limitations and highlight future directions including microbial biomarkers and machine learning-based aging prediction models to identify whether oral microbiota related biomarkers can improve risk stratification and mechanistic studies of biological aging.

Key words: Oral microbiota, Age-related diseases (ARDs), Aging hallmarks, Cellular senescence

1. Introduction

Aging is a gradual and irreversible pathophysiological process characterized by progressive decline in tissue and cell function, which significantly heightens susceptibility to various age-related diseases (ARDs) such as neurodegenerative disorders, cardiovascular diseases, metabolic syndromes, and malignancies, and constitutes a primary contributor to the burden of these conditions. Aging is shaped by interconnected biological processes commonly summarized as the canonical hallmarks of aging: cellular senescence, loss of proteostasis, altered intercellular communication, mitochondrial dysfunction, and epigenetic changes [1]. These hallmarks are susceptible to genetic background [2], environmental exposure [3], and lifestyle factors [4]. Among them, dysbiosis of the microbiome has emerged as a key etiological factor attracting increasing attention. As the largest microbiome in the human body, the gut microbiome dysbiosis has been associated with aging-related phenotypes and ARDs, with immunosenescence, systemic low-grade chronic inflammation (inflammaging), metabolic dysregulation, and barrier dysfunction proposed as candidate intermediary processes. The mechanism has been reviewed [1]. As the second-largest microbiome, the oral microbiome has also

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been associated with the onset and progression of ARDs as well as the aging process.

The oral microbiome contains more than 700 microbial taxa (Human Oral Microbiome Database), including bacteria, viruses, fungi, and archaea, which colonize the main anatomical niches such as the oral mucosa, hard palate, and gingiva, as well as microenvironments like saliva and dental plaque [5]. Under physiological conditions, the oral microbiome co-evolves with the host, which is essential for maintaining local and systemic homeostasis. However, perturbations in the host's genetic background, immune status, or external environment can lead to oral dysbiosis, defined by the abnormal proliferation of opportunistic pathogens and diminished abundance of commensal beneficial bacteria, which in turn contributes to local oral diseases such as dental caries and periodontitis [6]. More importantly, the oral dysbiosis, along with their virulence factors and metabolites may contribute to functional alterations in distant tissues, such as activation of cellular senescence phenotype and loss of proteostasis, hallmarks of aging that have been proposed to accompany organismal decline. These new findings have broadened our understanding of how the oral microbiome may be linked to ARDs, and also highlighted the necessity of constructing a theoretical framework based on the perspective of aging hallmarks to analyze the association between oral dysbiosis and ARDs.

This article provides a narrative synthesis of the clinical epidemiology and of the mechanisms that have been proposed to link oral dysbiosis with systemic aging and ARDs, outlining how the oral microbiome may influence core aging hallmarks. It aims to refine the framework for how oral dysbiosis may influence aging processes and ARDs onset and to highlight future opportunities for oral-microbiota-targeted interventions and early ARDs prevention.

2. Clinical evidence: The Association Between Oral Microbiome and Aging-related Phenotypes

Multiple recent cohort investigations have identified statistical associations between oral microbiota-associated pathologies and systemic aging acceleration, yet the evidence hierarchy remains predominantly observational and causal inference is constrained by study design, confounding, and reverse-causation risks.

2.1 The Correlation Between Oral Diseases and Biological Aging Biomarkers

One prospective birth cohort (94 % retention, follow-up from birth to age 45 years) built a quantitative model of biological aging velocity using circulatory and metabolic indicators, including blood pressure and cholesterol levels and reporting that individuals with childhood caries lesions exhibited a 0.1-year advancement in biological age compared to caries-free counterparts in midlife [7]. Analogously, participants with periodontitis displayed a 0.41-0.57 year elevation in biological aging pace relative to those without the condition [8]; this estimate was derived from a cross-sectional analysis of NHANES 2009-2014 supplemented by Mendelian randomization (MR). In another study based on NHANES III with up to 31 years of mortality follow-up, periodontitis was associated with a higher all-cause mortality risk ($P = 0.012$) [9]. Together, these observations are consistent with an association between oral disease burden and long-term prognosis, but do not establish causality.

Given the intimate relationship between telomere attrition and systemic aging, cross-sectional studies have preliminarily demonstrated that the severity of periodontitis is closely associated with telomere length attrition [10, 11], alongside a notable association between persistent oral viral and shortened human telomeres [12]. Nevertheless, these investigations failed to delineate the specific oral microbial components that may be associated with systemic aging acceleration.

Although these cohort studies provide population-level epidemiological evidence for the association between oral diseases and systemic aging, such research still has limitations. On one hand, it is difficult to fully eliminate confounding: most studies cannot exclude factors such as smoking, socioeconomic status, oral hygiene practices, and underlying chronic diseases, which can simultaneously affect oral microbial homeostasis and biological aging, leading to residual confounding bias. On the other hand, current cross-sectional designs cannot rule out reverse causality: aging-related immune dysfunction and diminished tissue repair capacity can themselves increase susceptibility to caries and periodontitis, making it challenging to precisely delineate the temporal causal order between oral dysbiosis and systemic aging.

2.2 Diversity and Metabolic Shifts of the Oral Microbiome and Aging-Related Outcomes

However, advances in metagenomic sequencing technologies have enabled investigators to dissect and begin to elucidate the mechanisms underlying oral dysbiosis leveraging extensive existing epidemiological data in aging processes, including compositional and metabolic alterations. The primary observation is that reduced oral microbial α-diversity has been associated with several aging-related outcomes. A cross-sectional study based on NHANES 2009-2012 comprising 7,716 participants reported a significant inverse association between oral microbiome α-diversity and accelerated

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biological aging [13]. A substantial prospective cohort investigation demonstrated that, following adjustment for smoking and other confounders, diminished salivary microbial α-diversity was associated with a ~10% heightened risk of lung cancer [14]. A nested case-control study limited to never-smokers in Shanghai similarly validated the association between microbial diversity and cancer, but was constrained by geographic and ethnic homogeneity, single sampling, and limited sample size, warranting replication [15]. Within the same line of investigation, reduced salivary microbial α-diversity was associated with a 17-21% elevated risk of all-cause mortality [16], particularly mortality from diabetes and cardiovascular conditions.

Regarding the expansion of oral pathogenic lineages, elevated abundance of established periodontal pathogens, including *Porphyromonas gingivalis (P. gingivalis), Tannerella forsythia (T. forsythia), Treponema denticola (T. denticola), Fusobacterium nucleatum (F. nucleatum), Prevotella intermedia (P. intermedia), and Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans),* have been implicated in regulating the onset and progression of ARDs, such as diabetes mellitus and Alzheimer's disease (AD) [17]. Notably, recent work has identified elevated abundance of *Veillonella parvula*, a *Firmicutes* phylum member and periodontal pathogen, as positively associated with neurodegenerative progression and cardiovascular conditions [18, 19].

Furthermore, dynamic shifts in microbial metabolic activity are intricately linked with aging. Illustratively, oral microbiota dysbiosis has been linked to ARDs by perturbing nitric oxide (NO) homeostasis and FoxO metabolism pathways [20], thereby potentially contributing to cellular senescence and oxidative damage. This phenotype is largely characterized by reduced abundance and functional activity of nitrate-reducing bacteria, including *Neisseria spp., Rothia spp., Streptococcus spp., and Haemophilus spp.* [21-24]. It should be noted that these intervention studies lacked salivary sampling at the initiation of each intervention period, leaving the washout-phase kinetics of microbiome recovery unresolved; moreover, enhanced oral nitrate-reducing capacity was inferred from plasma nitrite levels rather than measured directly in vivo.

2.3 Tissue and Histology Evidence: Biological Plausibility

The above epidemiological associations are also supported by direct biological evidence. Researchers have found that the oral microbiota in age-related cancer tissues significantly increases [25, 26]. Saliva derived *F. nucleatum* strain was detected in digestive tract cancer tissue [27]. Oral cavity bacterial DNA and gingipain antigen were detected in both brain and cerebrospinal fluid samples of AD patients [28]. In addition, researchers successfully isolated and identified 23 commensal oral bacteria, including *P. gingivalis* and *A. actinomycetemcomitans*, in non-diseased vascular tissues [29] and atherosclerotic plaques of patients undergoing coronary artery bypass surgery [30-33]. These findings support the biological plausibility of oral microbiota as possible promoters of aging and their capacity for translocation to distal organs. Nevertheless, these post-mortem and surgical-tissue studies are inherently cross-sectional and cannot resolve temporal ordering: it remains unclear whether microbial colonization precedes disease onset or occurs secondarily to barrier breakdown and impaired clearance in advanced disease.

2.4 Limitations, Considerations, and Machine Learning Prospects in Oral-Dysbiosis-Aging Associations

Most current studies focus on the oral microbiome after the onset of ARDs, but lack systematic investigation into two key stages: the subclinical asymptomatic phase and the post-intervention restoration phase. This gap limits our understanding of the microbiome's role in ARDs progression. Early subclinical microbial changes may act as prognostic biomarkers, while post-treatment microbiome reconfiguration and its long-term effects on aging remain unclear. Filling this gap will clarify the full dynamic lifecycle of the oral microbiome and provide a basis for early risk stratification, personalized prevention and treatment, and prognostic evaluation of ARDs.

With advances in machine learning, 16S rRNA sequencing data from salivary microbiome samples has enabled the development of non-invasive, accessible, and generalizable models for aging risk prediction. A recent study trained a LightGBM model on 7,268 salivary microbial samples (70% training cohort, 30% validation cohort), using relative microbial abundances as predictors and chronological age as the target [34]. The resulting continuous MicroAge estimator achieved an R^2 of 0.7983 and a root mean square error of 9.34 years, translating salivary microbiome profiles into precise quantitative age estimates. Meanwhile, generative AI integrates the oral microbiome into large-scale multi-omics modeling. The AURORA framework covers 581,763 samples from 425,258 individuals across seven modalities including oral tongue-coat metagenomes [35]. It corrects batch effects and imputes missing data via cross-modal generation, building multimodal aging clocks with ~2.5-year prediction error and chronic disease risk models (AUC 0.79-0.88), validated in longitudinal cohorts. The reported performance illustrates the potential utility of salivary microbial profiles for age prediction, but external

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validation, calibration across populations, and assessment of clinical utility remain necessary.

3. Potential mechanisms linking oral dysbiosis with selected aging hallmarks

The underlying molecular and cellular mechanisms have been further clarified in light of clinical correlations between the oral microbiota and their virulence factors may translocate to distal systemic tissues via invasion portals, including the lower respiratory tract [36], digestive tract [37], nervous system [38, 39], and circulatory system [40-42]. These pathogens and their products could modulate the aging process by interfering with key aging-associated pathways, which might contribute to features such as cellular senescence, loss of proteostasis, altered intercellular communication, mitochondrial impairment. The core mechanisms derived from recent investigations will be delineated in the following section.

3.1 Cellular Senescence

Cellular senescence denotes stable growth arrest with preserved metabolism, characterized by persistent irreversible G1/S arrest and the senescence-associated secretory phenotype (SASP). G1/S arrest is governed primarily by the p53-$p21^{CIP1}$ and $p16^{INK4A}$-Rb axes. p53 induces CDKN1A (p21) to suppress CDK2-Cyclin E and CDK4/6-Cyclin D, whereas $p16^{INK4A}$ competitively inhibits CDK4/6. Both keep Rb hypophosphorylated, repressing E2F-driven proliferative gene transcription and locking cells at the G1-S boundary [43]. SASP, controlled by cGAS-STING, NF-κB and MAPK cascades, upregulates inflammatory, chemotactic and matrix-remodeling genes. Its secretome includes proinflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8, TNF-α), chemokines (CCL2, CXCL1, CXCL2, CXCL10), growth factors (TGF-β, PDGF, FGF, VEGF) and MMPs (MMP-1, MMP-3, MMP-9). These factors remodel the microenvironment and propagate senescence signals; together with G1/S arrest, they define cellular senescence [44].

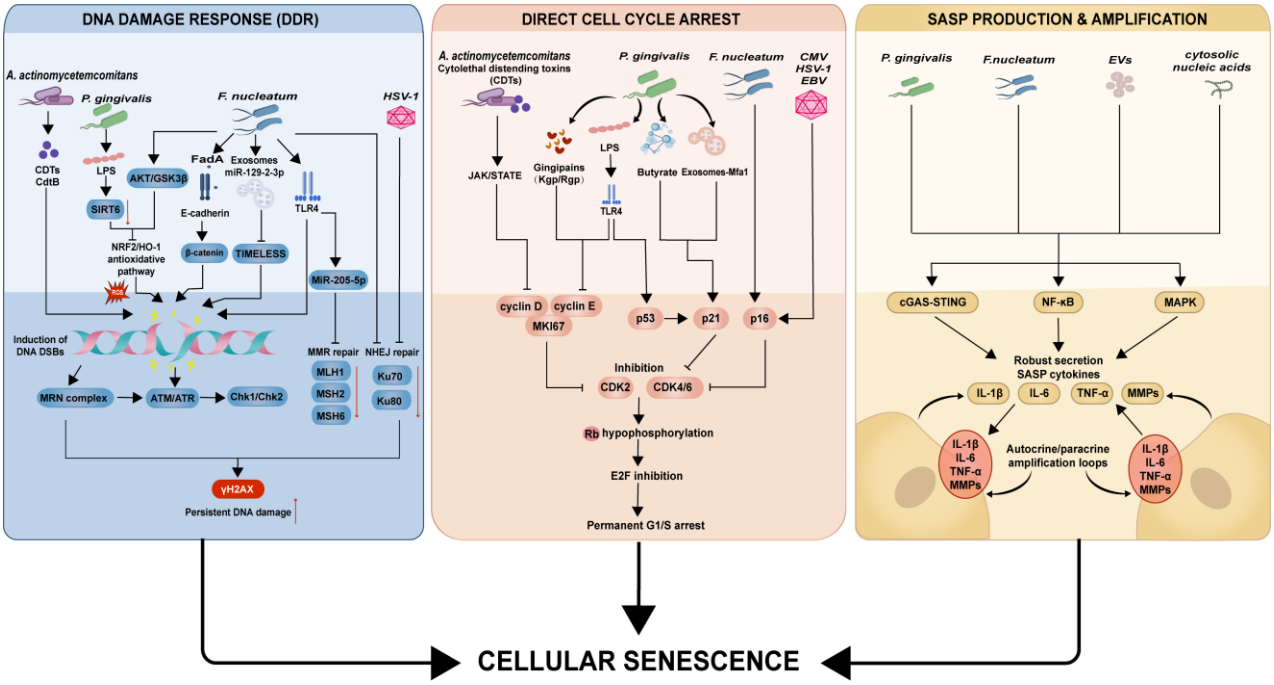


Figure 1. Proposed Mechanisms Linking the Oral Microbiota to Cellular Senescence. Mechanisms reported in experimental studies by which oral bacteria, viruses and derived virulence factors may trigger cellular senescence via three core pathways. The left panel shows accumulated DNA double-strand breaks and impaired DDR signaling. The middle panel depicts cell cycle perturbation through cyclin/CDK dysregulation and p53/p16 activation, which has been associated with permanent G1/S arrest. The right panel illustrates SASP secretion and amplification mediated by cGAS-STING, NF-κB and MAPK cascades.

Existing studies indicate that oral dysbiosis could be associated with modulation of senescence phenotypes in different host cells via integrated processes such as sustained DNA damage, aberrant cell-cycle regulation, and amplified SASP signaling; however, most evidence to

date comes from in vitro systems and animal models, with limited human data (Fig. 1).

3.1.1 Persistent DNA damage response (DDR)

The DDR is observed as a central upstream factor linked to cellular senescence. Sustained DDR signaling has been associated with the p53-p21^{CIP1} and p16^{INK4A}-Rb cell cycle inhibitory pathway, which can favour irreversible cell cycle arrest [45]. Upon oral dysbiosis, periodontal pathogens, oral viruses, and its virulence factors have been described as capable of maintaining DDR state by directly cleaving DNA double strands, increasing oxidative stress, inhibiting DNA repair, which may be compatible with cellular senescence in experimental contexts.

DNA double strand breaks (DSBs) represent one-activating stimulus associated with oral microbiota challenge. Oral bacteria and their virulence factors may disrupt host genomic homeostasis through intracellular invasion and toxin secretion. Animal studies demonstrate that *F. nucleatum* invades carcinoma cells via its surface FadA adhesin [46], whereas *A. actinomycetemcomitans* secretes the tripartite cytolethal distending toxin (CDT) complex, which enters host cells through dynamin-dependent endocytosis; its catalytic subunit CdtB translocates into the nucleus in a cellugyrin-dependent fashion [47]. These pathogens have been associated with DNA damage signaling events, including recruitment of repair sensors MRN and RPA to accumulate ATM and ATR kinases at lesion sites and activation of the MRN-ATM-Chk1/Chk2 signaling cascade [45]. Sustained cascade activation could further elevate the DNA damage marker γH2AX, increases senescence-associated β-galactosidase (SA-β-Gal), and engages the p53-p21^{CIP1} and p16^{INK4A}-Rb to promote cellular senescence.

Furthermore, some observations suggest that oral microbiota may also indirectly elevate DNA damage through extracellular vesicles (EVs) and microRNAs, possibly supporting paracrine p53-p21^{CIP1} activation. In vitro evidence shows that *F. nucleatum*-infected intestinal epithelial cells secrete exosomes. Upon internalization by neighbouring epithelial cells, these exosomes release miR-129-2-3p into the cytoplasm to suppress the clock gene TIMELESS, potentially activating the ATM/ATR/p53-dependent DDR and may contribute to senescence in intestinal epithelial cells [48].

Besides, oxidative stress and excessive accumulation of reactive oxygen species (ROS) are important pathways for oral microbiota to indirectly engage DDR and cellular senescence, mainly through dysregulated NOX4/NRF2/HO-1 signaling. In vitro experiment demonstrates that *F. nucleatum* infection activates the AKT/GSK3-β pathway and disrupts NOX4/NRF2 redox homeostasis in endothelial cells [49]. Moreover, lipopolysaccharide derived from *P. gingivalis* (*P. gingivalis*-LPS) has been reported to downregulate SIRT6 expression in human gingival fibroblasts through TLR4, thereby repressing the NRF2-HO-1 antioxidant cascade [50].

With respect to DNA repair, oral microbiota may amplify DNA damage signaling by suppressing the non-homologous end-joining (NHEJ) and DNA mismatch repair (MMR) pathways. In the NHEJ repair pathway, *F. nucleatum* has been observed to downregulate the expression of the key repair protein Ku70 [51]; *HSV-1* infection may contribute to ubiquitination-dependent degradation of Ku80, impairs DSB repair capacity, and sustains accumulation of the DNA-damage marker γH2AX to reinforce senescence signaling [52]. In the MMR repair pathway, in vitro assays and clinical tissue specimens from head and neck squamous cell carcinoma reveal that *F. nucleatum* infection could upregulate miR-205-5p via the TLR4/MYD88 signaling axis. This microRNA silences MMR-related genes including MLH1, MSH2 and MSH6, which could be compatible with genomic instability and cellular senescence [53].

3.1.2 Altered abundance of cell cycle-regulatory proteins

In addition to DDR-associated arrest, some evidence suggests that oral microbiota components (LPS, gingipains, metabolites) may be associated with changes in cell-cycle regulators, potentially contributing to cell-cycle perturbations linked to cellular senescence.

On the one hand, the microbiota may downregulate proliferation proteins, such as cyclin and MKI67 in cellular models. Kato et al. found that gingipains notably the Lysine-specific gingipain (Kgp) of *P. gingivalis* hydrolyze of Cyclin D and Cyclin E when infection of murine ST2 stromal cells, plausibly inducing premature G1 phase arrest [54]. Following *A. actinomycetem-comitans* infection of macrophages, cyclin D1 undergoes degradation via the JAK/STAT signaling axis, associated with G1 phase arrest [55]. Concurrently, oral epithelial cells exposed to *A. actinomycetemcomitans* virulence factors such as cytolethal distending toxins (CDTs) may exhibit sustained G2/M phase arrest, which could progress towards a senescent state [47]. Additionally, *P. gingivalis*-LPS and the oral virus *CMV* are reported to elicit senescence in periodontal ligament stem cells and renal epithelial cells via downregulation of mRNA expression of the proliferation marker MKI67 [56, 57]. This phenotype is evidenced by cytoplasmic enlargement, elevated SA-β-Gal activity, and impaired proliferative capacity.

On the other hand, some data suggest that oral microbiota may elevate the expression of cell cycle inhibitors $p16^{INK4A}$ and $p21^{CIP1}$ to disrupt normal cell cycle progression, culminating in sustained arrest and senescence. For example, *P. gingivalis* via its fimbrial adhesin Mfa1 invades dendritic cells (DCs) [58], and its metabolite butyrate acts on colon epithelial cells [59], both of which significantly increase intracellular expression of $p21^{CIP1}$ and $p16^{INK4A}$, and may contribute to cellular senescence. In addition, *P. gingivalis*-LPS, together with a high-glucose microenvironment, may alter mitochondrial structure and function. It is linked to p53 stabilization and $p21^{CIP1}$ upregulation via the AMPK metabolic stress axis, alongside oxidative stress associated with CDKN2A de-silencing, sustained $p16^{INK4A}$ elevation and cell-cycle arrest [60]. Similarly, *F. nucleatum* might promote cellular senescence by upregulating the $p16^{INK4A}$ and downregulating the protective p14 expression [61].

Following infection with the oral virus *HSV-1*, significant upregulation of $p16^{INK4A}$ expression and cellular senescence can be observed in the spinal trigeminal tract and locus coeruleus of the brainstem [62]. The inflammatory factor TNF-α produced after latent infection of cells by *Epstein-Barr virus* (*EBV*) may raise expression of $p16^{INK4A}$ and $p21^{CIP1}$ in neighboring primary human tonsillar epithelial cells and human nasopharyngeal carcinoma (CNE1) cells, possibly triggering paracrine senescence [63].

3.1.3 SASP-Mediated Amplification of Cellular Senescence

Pre-clinical evidence supports a hypothetical model whereby oral dysbiosis may activate inflammatory pathways to promote sustained SASP release, forming a self-amplifying positive-feedback loop that could maintain and exacerbate cellular senescence in experimental systems. Oral pathogenic bacteria represented by *P. gingivalis* and *F. nucleatum*, as well as their extracellular vesicles, have been shown in cell culture to release a large number of cytoplasmic pathogen related molecular patterns (c-PAMPs) that activate the host cGAS-STING pathway and trigger the activation of NF-κB and MAPK signaling axes, thereby initiating the transcription and protein secretion of a series of SASP effector genes such as IL-1β, IL-6, TNF-α, MMPs, etc., and might stably sustain the cellular senescence phenotype.

In experimental systems, the oral-microbiota-associated SASP response could simultaneously act on immune cells and tissue parenchymal cells, which may contribute to local and systemic pathological damage. On the one hand, this pathological process could favor the senescence of innate immune cells such as dendritic cells and macrophages [58, 64], reducing the immune surveillance efficacy of the body against oral pathogens [65]; on the other hand, it has also been reported to induce senescence-like changes in various tissue parenchymal cells, and to accompany local and systemic aging-related injury in these models [57, 66-68]. Moreover, SASP autocrine may reinforce senescence and paracrine has been reported to induce peripheral cell cycle arrest, suggesting a putative microbiota-SASP-senescence loop that remains to be verified in vivo.

However, a single biomarker is insufficient to determine the oral microbiota-related cellular senescence. For example, short-term pathogenic bacterial stimulation could temporarily activate DDR and increase the damage marker γH2AX; transient upregulation of p16 and p21 is not by itself sufficient to indicate irreversible cycle arrest; inflammatory factors such as IL-6 and TNF-α are common in acute inflammation and SASP. Future studies should combine complementary assessments of DNA damage, durable proliferative arrest, lysosomal or SA-β-gal changes, and SASP, while distinguishing senescence from acute stress, cytotoxicity, and reversible quiescence.

Beyond the main mechanisms mentioned above, heightened apoptotic resistance constitutes another key mechanism linked to cellular senescence [69]. Dysfunctional cells cannot be cleared through the apoptotic pathway, leading to continuous accumulation of damage and might finally progress the cells into a senescent state. *P. gingivalis* Ndk and infection have been reported to alter apoptosis-related signaling, including phosphorylate heat shock protein 27 (HSP27)/cytochrome-c and anti-apoptotic protein (BCL-2)-associated responses [70, 71]. These observations raise the possibility that oral pathogens could influence the survival or clearance of damaged cells; however, direct evidence that these anti-apoptotic effects increase senescent-cell accumulation is currently lacking.

3.2 Loss of Proteostasis

Proteostasis denotes the dynamic equilibrium state maintained within the cellular proteome, a process including the synthesis, folding, unfolding, post-translational modification, and degradation of proteins [72]. The collapse of this homeostatic system, also termed loss of proteostasis, represents a well-established pathological hallmark in a spectrum of ARDs [1]. Experimental studies suggest that the oral microbiota may be associated with changes in protein processing, aggregation, and clearance. Reported examples include amyloid-β (Aβ) plaques, tau, and α-synuclein pathology; however, most mechanistic evidence derives from cellular

and animal models, and a causal contribution to human ARDs remains to be established (Table 1).

Table 1. Evidence that oral bacteria-associated mechanisms may promote proteostasis collapse, leading to accumulation of misfolded proteins and contributing to aging or ARD progression.

Misfolded Protein	Oral microbiota	Mechanism	Experimental Site/Model	Outcome	Ref
Aβ peptides	P. gingivalis	Upregulates APP and BACE1 expression; activates P38 MAPK signaling	Hippocampus	Aβ plaques, neuroinflammation and neurodegeneration	[73, 74]
	P. gingivalis	Triggers type I interferon (IFN-β) upregulation in brain; induces IFITM3 expression, which modulates γ-secretase activity to enhance Aβ production;	C57BL/6J and APP/PS1 mice, brain in vivo	Aβ deposition, cognitive decline, neuroinflammation	[79]
	P. gingivalis-LPS	Activates caspase-4-dependent noncanonical inflammasome (caspase-4–NLRP3–caspase-1–GSDMD); upregulates APP and presenilin-1	Human neuronal and microglial cell lines in vitro	Aβ secretion, neuroinflammation, oxidative stress	[78]
	P. gingivalis msRNA P.G_45033	Enhances glycolysis and histone lactylation	Macrophages in vitro	Aβ plaques, exacerbates AD pathology	[80]
	P. gingivalis PGDHC	Upregulates Aβ42 secretion and APP expression via TLR-independent pathway	CHO-7WD10 cells in vitro	Aβ42 secretion, APP upregulation	[68]
	T. denticola	Upregulates BACE1 and PS1 (γ-secretase)	Hippocampus	Aβ plaques, neuroinflammation	[75]
	A. actinomycetemcomitans	Triggers pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) via microglial M1 phenotype and increases Aβ42 secretion	Primary microglia and mixed hippocampal cell cultures in vitro	Aβ42 secretion, pro-inflammatory response, neurite shrinking	[76]
	HSV-1	US7 binds γ-secretase, elevates Ca^{2+} and activates GSK-3, and promotes APP phosphorylation at Thr668	Cortical neurons in vitro	Aβ plaques, synaptic dysfunction	[77]
Phosphorylated Tau	P. gingivalis OMVs	Activates NLRP3 inflammasome, elevates IL-1β and induces tau phosphorylation at Thr231	BV2 microglia in vitro	NFTs, neuronal death and memory deficits	[84]
	P. gingivalis-LPS	Inhibits PP2A, activates GSK-3β and regulates TNF-α/AKT pathway	microglia and neurons in vitro	NFTs, learning and memory deficits	[81]
	F. nucleatum	Activates MyD88/p38/JNK signaling, stimulates microglial activation, and proinflammatory cytokine release	Hippocampus; cortex in vitro	NFTs, cognitive impairment	[83]
	T. denticola	Activates hippocampal neuroinflammation and GSK-3β, then induces tau phosphorylation at Thr181, Thr231, Ser396	BV2 and N2a neurons in vitro	NFTs, neuroinflammation	[85]
	P. gingivalis-LPS	P. gingivalis-LPS downregulates GRK5	SH-SY5Y neuroblastoma cells	NFTs, oxidative damage and cell death	[82]
α-Syn	P. gingivalis Gingipains (Kgp)	Kgp cleaves α-syn to generate aggregation-prone fragments	Dopaminergic neurons	Lewy bodies, mitochondrial dysfunction and dopaminergic neuron death	[87]

Abbreviations: *P. gingivalis*, *Porphyromonas gingivalis*; *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*; *F. nucleatum*, *Fusobacterium nucleatum*; *T. denticola*, *Treponema denticola*; Aβ, amyloid-beta; AD, Alzheimer's disease; AKT, protein kinase B; APP, amyloid precursor protein; APP/PS1, amyloid precursor protein/presenilin-1 transgenic mice; ARD, age-related disease; α-Syn, alpha-synuclein; BACE1, beta-

site amyloid precursor protein cleaving enzyme 1; GRK5, G protein-coupled receptor kinase 5; GSDMD, gasdermin D; GSK3β, glycogen synthase kinase 3 beta; HSV-1, herpes simplex virus type 1; IFITM3, interferon-induced transmembrane protein 3; IFN-β, interferon-beta; IL-1β, interleukin-1 beta; IL-6, interleukin-6; JNK, c-Jun N-terminal kinase; Kgp, lysine-specific gingipain; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; msRNA, small non-coding RNA; MyD88, myeloid differentiation primary response 88; NFTs, neurofibrillary tangles; NLRP3, NLR family pyrin domain containing 3; OMVs, outer membrane vesicles; PGDHC, phosphoglycerol dihydroceramide; PP2A, protein phosphatase 2A; PS1, presenilin-1; TLR, toll-like receptor; TNF-α, tumor necrosis factor-alpha.

3.2.1 Promotion of Aβ Plaque Formation

Amyloid precursor protein (APP) processing illustrates one route through which microbial-associated signals could intersect with proteostasis. APP can undergo non-amyloidogenic or amyloidogenic processing; the latter involves sequential cleavage by β-secretase (BACE1) and γ-secretase (PS1) and generates Aβ peptides. An imbalance between Aβ production, aggregation, and clearance may contribute to Aβ accumulation, a pathological feature of Alzheimer's disease (AD).

Experimental studies have examined whether oral microbial components affect APP abundance, phosphorylation, or cleavage. In mouse models, exposure to *P. gingivalis*-derived phosphoglycerol dihydroceramide (PGDHC), *T. denticola*, or serotype b LPS from *A. actinomycetemcomitans* was reported to be associated with increased cerebral APP expression [68, 73-76]. Additionally, HSV-1 infection has also been linked to Ca^{2+}-dependent GSK-3β activation and APP phosphorylation at the Thr668 residue, potentially contributing to accelerated intraneuronal Aβ accumulation [77].

Other cell-based studies have investigated the APP-cleaving enzymes (BACE1, PS1) and oral microbiota-related inflammatory pathways. In SH-SY5Y cells, *P. gingivalis* LPS was reported to increase BACE1 and PS1 expression in association with TLR4/NF-κB signaling. Another separate study linked PS1 upregulation to a caspase-4-dependent non-canonical pyroptosis pathway [78]. Notably, Kong L et al. identified a transcription-independent regulatory mechanism of enzyme activity: *P. gingivalis* might elevate type I interferon responses and markedly upregulate interferon-induced transmembrane protein 3 (IFITM3) in glial cells. IFITM3 binds to the γ-secretase complex and induces conformational changes, directly enhancing its catalytic efficiency without altering PS1 expression levels, and consequently amplifying the production of toxic Aβ plaque [79].

A further proposed mechanism involves peripheral Aβ production and its potential relationship to cerebral Aβ burden. In vitro, uptake of the *P. gingivalis* small RNA msRNA P.G_45033 by macrophages was associated with altered glycolysis and histone lactylation, alongside increased Aβ production [80]. This finding incorporates bacterial non-coding RNAs into the regulatory network of APP proteostasis dysregulation, suggesting a potential pathogenic mechanism whereby oral pathogens may disturb proteostasis by affecting host metabolic reprogramming and epigenetic remodeling. Meanwhile, Pollreisz et al. showed that *P. gingivalis* may target brain endothelial cells and modulate RAGE upregulation via the CatB/NF-κB pathway, enabling efficient influx of peripheral Aβ into the brain, which is associated with cerebral Aβ proteostasis breakdown [71].

3.2.2 Promotion of NFTs Formation

In addition to Aβ plaques, neurofibrillary tangles (NFTs) represent another hallmark pathological feature of AD and multiple tauopathies. They are formed by the aberrant aggregation and assembly of microtubule-associated tau protein after its hyperphosphorylation. Research indicates that oral pathogenic bacteria may disrupt tau protein homeostasis at two levels: imbalanced tau phosphorylation and direct proteolytic cleavage, which might collectively promote the pathogenesis of NFTs.

Tau hyperphosphorylation arises primarily from elevated activity of the neuronal kinase glycogen synthase kinase 3β (GSK-3β), accompanied by suppressed activity of protein phosphatase 2A (PP2A). Oral pathogens and their virulence factors have been shown to activate GSK-3β via multiple pathways, including Toll-like receptor (TLR) signaling, the NLRP3 inflammasome, and microglia-mediated inflammatory responses, thereby modulating tau hyperphosphorylation. In the TLR-dependent pathway, *P. gingivalis*-LPS has been reported to act on TLR2/4 on the neuronal surface, activate the AKT/GSK-3β signaling axis, which could contribute to tau hyperphosphorylation at Ser202, Thr231, and Ser396 [81]. Meanwhile, Wu et al. found that *P. gingivalis*-LPS stimulation of SH-SY5Y cells downregulates G protein-coupled receptor kinase 5 (GRK5) via TLR2/4, relieving the inhibitory effect of GRK5 on the p53/GSK-3β pathway and inducing tau phosphorylation at Ser396 [82]. Live *F. nucleatum* infection in 5XFAD mice has been revealed to potentially activate the MyD88/p38/JNK pathway, which is linked to neuroinflammation and phosphorylated tau accumulation; however, this study used a pan-phospho-tau antibody for detection and did not identify specific phosphorylation sites [83].

Regarding the NLRP3 inflammasome pathway, *P. gingivalis* OMVs administered by oral gavage may also penetrate the blood-brain barrier and accumulate in the hippocampus and cortex of C57BL/6 mice. By activating the microglial NLRP3 inflammasome to promote IL-1β

release, they specifically induce tau phosphorylation at Thr231 in the hippocampal region [84]. In addition, oral pathogens can indirectly activate neuronal GSK-3β and stimulate tau hyperphosphorylation through microglia-mediated inflammatory responses. *P. gingivalis*-LPS stimulation of murine microglia has been shown to trigger TNF-α secretion, which in turn activates the neuronal AKT/GSK-3β signaling axis, resulting in tau hyperphosphorylation at Ser202, Thr231, and Ser396 in the cortex [81]. After oral infection of C57BL/6 mice, live *T. denticola* colonizes the hippocampus, activates microglia to secrete IL-1β, IL-6, and TNF-α, and enhances GSK-3β kinase activity, mediating tau phosphorylation at Thr181, Thr231, and Ser396 [85]. Although these experimental findings from cellular and animal models are mutually consistent, only a correlation between *P. gingivalis* load and tau phosphorylation levels has been observed in clinical samples, and a causal relationship remains to be further validated by clinical studies.

At the proteolytic level, Dominy et al. have also found that gingipain from *P. gingivalis* can hydrolyze tau protein and generate tau fragments containing the common motifs of "VQIINK" and "VQIVYK" hexapeptides in vitro experiments [28]. These fragments have been discussed in relation to NFTs formation by forming paired helical filaments (PHF) [86]. Whether this proteolytic event occurs in the human brain or contributes to tau aggregation in vivo remains unknown.

3.2.3 Promotion of Lewy bodies Formation

Similarly, limited in vitro and clinical-pathological observations raise the possibility that oral microbiota may induce the formation of Lewy bodies, which are key pathological features of neurodegenerative diseases. The co-localization of *P. gingivalis* gingipain and phosphorylated α-synuclein (α-Syn) aggregates was revealed through ultrastructural analysis of dopaminergic neuron mitochondria in PD patients. Further in vitro enzymatic and cellular experiments showed that *P. gingivalis* Kgp specifically hydrolyzes α-Syn into fragments with aggregation-related properties, which contain the non-amyloid component region [87, 88]. Given the established evidence regarding oral microbiota-associated phosphorylation modification of APP and tau protein, we note that there are currently few studies directly linking α-Syn pathological modifications to oral microbiota, representing a notable research gap. While a clinical study detected elevated levels of Ser129-phosphorylated α-synuclein in the oral mucosa and saliva of patients with PD and proposed this measure as a potential non-invasive biomarker [89], the study has not explored the correlation between elevated phosphorylation of α-Syn and oral microbiota, and cannot demonstrate the involvement of oral microbiota in this modification process.

Protein aggregation is only one manifestation of altered proteostasis; the capacity to refold or clear misfolded proteins is also important. Protein quality-control (PQC) pathways, including molecular chaperones such as heat-shock proteins (HSPs), the ubiquitin–proteasome system (UPS), and endoplasmic-reticulum stress responses such as the unfolded protein response (UPR) may therefore represent a shared mechanistic link between microbial-associated stress and protein accumulation. Although oral microbial effects on these pathways have been examined in local periodontal disease [90, 91], their relevance to systemic aging and ARDs remains unclear. In particular, it is not yet known whether oral microbiota or infection-associated inflammation alter neuronal PQC capacity or the clearance of potentially toxic protein species in vivo. Therefore, a deeper mechanistic inquiry into PQC dysregulation holds potential to unveil novel pathophysiological insights into how oral microbiota may accelerate aging processes.

3.3 Altered Intercellular Communication

Coordinated communication between cells and the extracellular matrix (ECM), as well as between neighboring cells, is essential for tissue homeostasis. Pathological remodeling of cell-to-extracellular matrix (Cell-to-ECM) and cell-to-cell (Cell-to-Cell) communication networks has been shown to disrupt tissue homeostasis and further raises the risk of a range of aging-related disorders [92]. Experimental studies suggest that oral dysbiosis or its products may alter these signaling networks, with potential implications for matrix remodeling and the propagation of inflammatory or senescence-associated signals in local and distal tissues (Fig. 2).

3.3.1 Dysregulated Cell-to-ECM Communication

Cell-to-ECM communication coordinates matrix synthesis, degradation, and remodeling through pathways that include TGF-β/Smad, ERK, and β-catenin signaling. Preclinical studies have associated exposure to *P. gingivalis, F. nucleatum*, or their products with changes in these pathways and with increased expression of selected profibrotic markers in several tissues [93-96]. These observations raise the possibility that oral microbial signals may influence ECM remodeling beyond the oral cavity, although the extent and direction of these effects may depend on the tissue and experimental model.

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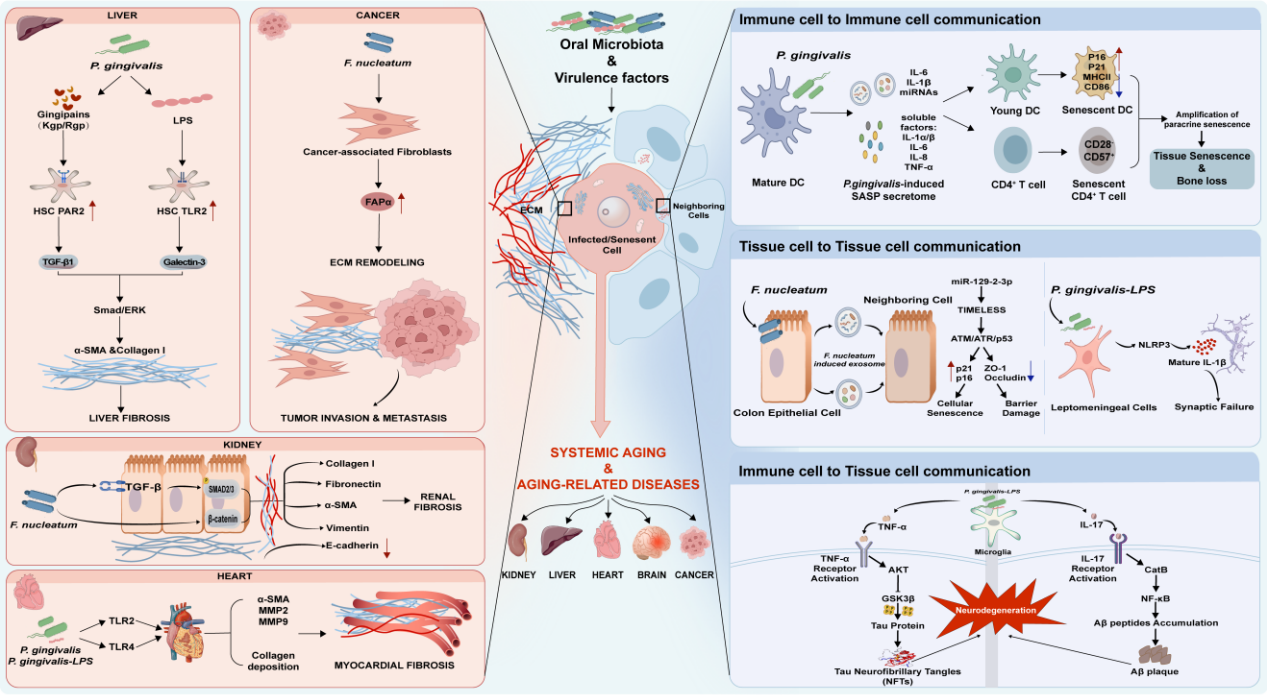


Figure 2. Oral Microbiota-Associated Modulation of Altered Intercellular Communication in ARDs. Oral microbiota and virulence factors have been reported, largely in cell and animal models, to modulate systemic aging via regulating Cell-to-ECM communication (red) and Cell-to-Cell communication (blue). As for Cell-to-ECM communication, *P. gingivalis* has been shown to activate HSCs PAR2/TLR2 pathways, inducing TGF-β1/galectin-3 and driving ECM deposition in liver and triggers TLR2/4 signaling, promoting collagen deposition via α-SMA/MMP9 in the myocardium. *F. nucleatum* has been reported to remodel the tumor microenvironment via $FAP^{\alpha+}$ cancer-associated fibroblasts and disrupts renal ECM through TGF-β/SMAD3 signaling. As for Cell-to-Cell communication, oral microbiota may induce cell senescence and SASP secretion (IL-1, IL-6, IL-8, IL-17, TNF-α, insoluble exosomes), which may amplify senescence to neighboring cells and induce immune senescence and inflammaging. These mechanisms remain to be validated in humans.

Liver models provide one of the more detailed examples [97]. *P. gingivalis* gingipain has been noted to promote the production of TGF-β1 by upregulating the expression of protease-activated receptor 2 (PAR2) in hepatic stellate cells (HSCs); meanwhile, *P. gingivalis*-LPS also promotes the production of galectin-3 by upregulating the expression of TLR2 in HSCs. Both TGF-β1 and galectin-3 activate the Smad and ERK pathways in quiescent HSCs through autocrine or paracrine pathways, leading to higher expression of liver fibrosis markers such as α-SMA and type I collagen [98]. Notably, macrolide antibiotics like azithromycin (AZM), administered locally or systemically to target *P. gingivalis*, have been reported to suppress galectin-3 phosphorylation and reduce the number of hepatic crown-like structures (hCLS) [99]. Similarly, *F. nucleatum*-infected murine livers show more pronounced fibrosis and collagen deposition, with upregulated expression of key fibrogenic genes *TGFB1* and *ACTA2* [100].

Beyond the liver, preclinical data suggest *F. nucleatum* may activate TGF-β/SMAD2/3 and β-catenin cascades, which may upregulate profibrotic proteins (collagen I, fibronectin, vimentin, α-SMA) and contribute to renal interstitial fibrosis, a hallmark of renal senescence [101]. In animal models, *P. gingivalis* or its LPS has also been shown to increase myocardial profibrotic markers (α-SMA, MMP2, MMP9) and collagen deposition via TLR2/4 signaling, potentially facilitating myocardial fibrotic responses [102-104]. Taken together, these studies suggest a possible association between oral microbial exposure and fibrotic remodeling across tissues; however, many rely on marker expression or collagen deposition, and the causal contribution of altered Cell-to-ECM signaling remains to be clarified.

Oral microbial signals may also intersect with tumor-stromal communication, possibly creating a more immunosuppressive and invasive tumor milieu. In experimental studies, *F. nucleatum* has been associated with altered cancer-associated fibroblast phenotypes, including changes in fibroblast activation protein-α (FAPα) expression [105]; while this phenotypic transition may enhance ECM remodeling and promote metastasis and invasion in vitro [106, 107]. This mechanism extends microbial interference in Cell-to-ECM communication

into tumor biology, although their contribution to invasion or metastasis and their relevance to therapeutic strategies require further validation.

Current studies have mainly reported changes in fibrosis-associated markers or collagen deposition. By comparison, potential effects on ECM organization, collagen crosslinking, and tissue mechanical properties, including matrix stiffness remain poorly characterized. Because ECM function depends on its composition as well as its architecture and mechanics, future work should determine whether oral microbial exposures alter these properties and whether such changes contribute to tissue remodeling.

3.3.2 Dysregulated Cell-to-Cell Communication

The oral microbiota, beyond modulating Cell-to-ECM communication, may also alter the Cell-to-Cell communication networks through cellular secretion of EVs and soluble factors, thereby potentially establishing an amplification mechanism for the transmission of aging-associated signals [92].

In experimental models, oral microbiota has been associated with the release of cytokines and other SASP-related factors that may affect neighboring cells [58, 66, 68], thereby establishing an amplifying mechanism for the spread of senescence between cells [92].

For example, animal studies showed that *P. gingivalis*-LPS could activate microglia to secrete pro-inflammatory factors such as TNF-α and IL-17, which then act on neighboring neuronal cells via paracrine signaling. TNF-α could induce AKT/GSK3-β-dependent hyperphosphorylation of tau protein in adjacent neurons [81], while IL-17 could induce CatB/NF-κB-dependent aggregation and deposition of Aβ peptides in neuronal cells [108]. *P. gingivalis*-LPS activates the NLRP3 inflammasome in leptomeningeal cells and secretes mature IL-1β that may affect neighboring neurons and impair neural connectivity [109]. In addition to bacteria, *CMV* infection may contribute to primary renal proximal tubular epithelial cells (RPTECs) to senescence, enhance SA-β-gal activity, and increase SASP secretion, which then mediates paracrine senescence through IL-6, upregulating the expression of nuclear NF-κB and DNA damage marker γH2AX in neighboring uninfected RPTECs, indicating further expansion of senescence [57].

Beyond soluble factors, EV-mediated signaling provides a second potential route for intercellular communication. Oral microbiota has been shown to exploit the vesicle-carrier function of exosomes to mediate the efficient transmission of senescence signals. Compared with free soluble factors that are readily diluted and degraded in body fluids, exosomes encapsulate inflammatory factors and functional miRNAs within lipid bilayer structures, conferring cargo stability and the capacity for long-distance transport through body fluid circulation; they might thus not only amplify paracrine senescence effects locally within tissues but also mediate the dissemination of senescence signals to the immune system and distal organs throughout the body [92].

On the one hand, some studies described that dendritic cells (DCs) undergo endocytosis of *P. gingivalis*, producing a characteristic *P. gingivalis*-induced exosomal senescence-associated secretory phenotype (PgexoSASP). This SASP is enriched in inflammatory cytokines such as IL-6 and IL-1β, as well as regulatory microRNAs. Through paracrine pathways, PgexoSASP not only upregulates the expression of senescence markers such as $p16^{INK4A}$ and $p21^{CIP1}$ in bystander young DCs (yDCs), consistent with premature cellular senescence, but also downregulates the expression of maturation markers such as MHC II and CD86. This impairment abrogates the maturation functionality of yDCs, hindering their capacity to stimulate antigen-specific T cell proliferation and manifesting as immune senescence [58]. Related work has also linked PgexoSASP exposure to increased senescence-associated $CD28^{-}CD57^{+}$ T-cell populations, which could propagate senescence to adjacent healthy cells [110]. On the other hand, EVs released from *F. nucleatum*-exposed colon epithelial cells (Fn-Exo) have been reported to paracrinally act on neighboring colon epithelial cells and activate the ATM/ATR/p53 signaling pathway through the miR-129-2-3p/TIMELESS axis, culminating in the upregulation of key senescence markers expression, such as p53, $p16^{INK4A}$ and $p21^{CIP1}$, promoting intestinal epithelial cell senescence and changing tight junction proteins ZO-1 and barrier function in vitro, suggesting possible implications for intercellular communication [48].

Collectively, exosomes serve not only as potential amplification mediators of local paracrine senescence orchestrated by oral microbiota but also as potential core vehicles for the dissemination of senescence signals to the immune system and systemic organs. Nevertheless, direct in vivo experimental evidence for the long-distance transport and cross-organ targeted delivery of exosomes remains lacking, and the underlying molecular mechanisms warrant further investigation.

Some work has described non-contact paracrine senescence via soluble factors and exosomes, and emerging observations propose juxtacrine senescence via Notch signaling as a possible mechanism, breaking through the limitations of the traditional SASP paracrine. Senescent cells upregulate surface expression of Notch ligands and bind to the Notch receptors of adjacent cells, triggering receptor cleavage and the release of the intracellular domain (NICD). The translocated NICD

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subsequently induces the senescence of neighboring cells by upregulating cell cycle inhibitors such as CDKN1A (p21) and CDKN2B (p15), as well as activating downstream target genes like connective tissue growth factor (*CTGF*) and fibrous collagens (*COL1A1*, *COL3A1*). This juxtacrine senescence phenotype is marked by the accumulation of senescence markers such as γH2AX and SA-β-Gal, as well as the formation of senescence-associated heterochromatin foci (SAHF) [111, 112]. Notably, gingipain secreted by *P. gingivalis* has also been linked to Notch1-mediated juxtacrine signaling in studies of gingival epithelial cell migration [113]; whether this interaction also affects senescence transmission between neighboring cells is an open question requiring direct experimental testing.

3.4 Mitochondrial Dysfunction

Preclinical studies suggest that oral microbiota related stimuli may alter host cell energy supply, redox balance, and damage signal release by affecting mitochondrial dynamics, biogenesis, mitochondrial autophagy, and tricarboxylic acid cycle-oxidative phosphorylation (TCA-OXPHOS) metabolism, and participate in various age-related pathological processes such as alveolar bone resorption, cognitive decline, and vascular sclerosis. These changes have been associated with altered ROS levels, aberrant opening of the mitochondrial permeability transition pore (mPTP), mitochondrial-derived damage-associated molecular patterns (mt-DAMPs), inflammation, and tissue-specific pathological phenotypes [114, 115] (Fig. 3).

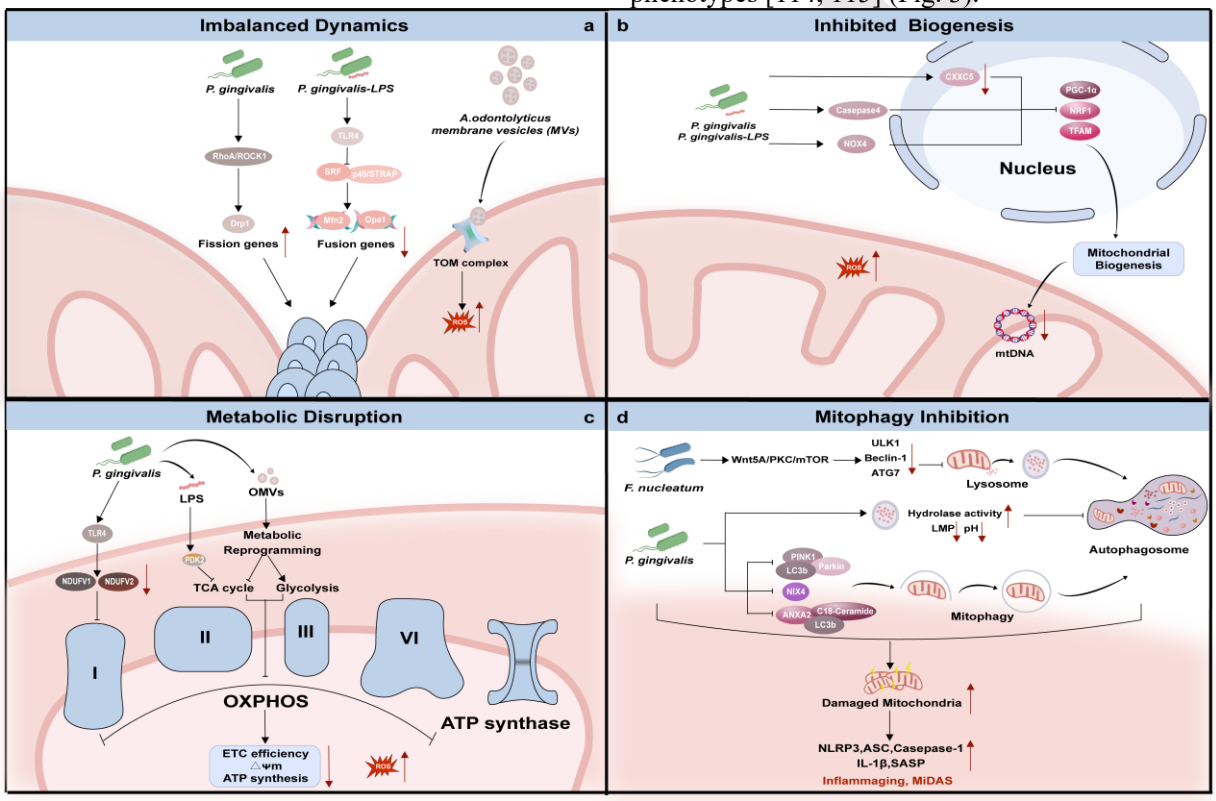


Figure 3. Potential Mechanisms by Which Oral Dysbiosis May Impair Mitochondrial Homeostasis. Proposed mechanisms reported in experimental studies by which oral microbiota may induce mitochondrial dysfunction: **(a)** Imbalanced Dynamics: P. gingivalis has been shown to increase fission gene (Drp1) via RhoA/ROCK1/Drp1 and its LPS decreases fusion genes (Mfn2, Opa1) via SRF/p49/STRAP, while A. odontolyticus membrane vesicles (MVs) have been reported to compromise mitochondrial import through the TOM complex. **(b)** Inhibited Biogenesis: P. gingivalis and LPS have been shown to suppress nuclear biogenesis factors (PGC-1α, NRF1, TFAM) and reduce mtDNA copy number via casepase-4-dependent, CXXC5, NOX4 signaling, abrogating mitochondrial biogenesis. **(c)** Metabolic Disruption: Oral bacteria and OMVs have been reported to reprogram metabolism towards glycolysis and inhibit OXPHOS/ATP synthase efficiency, leading to energy depletion. **(d)** Mitophagy Inhibition: Pathogens have been described to diminish the fusion of lysosomes with autophagosomes containing damaged mitochondria and block PINK1-Parkin-LC3, NIX, ANXA2-mediated mitophagy, which may result in the accumulation of damaged mitochondria and instigation of the NLRP3 inflammasome.

3.4.1 Disrupting mitochondrial dynamic balance

Mitochondrial function depends in part on a balance between fission and fusion, which contributes to organelle

distribution, function, and quality control. Preclinical studies have associated oral microbiota with changes in fission- and fusion-related proteins, including dynamin-related protein 1 (Drp1), mitochondrial fission protein 1 (Fis1), Mitofusin (Mfn), and optic atrophy 1 protein (Opa1) [116-121].

In a mouse model of osteoporosis, *P. gingivalis*-derived EVs have been observed to enter the bone marrow through the bloodstream and target osteoblasts. These vesicles upregulate the fission-related proteins Drp1 and Fis1 while down-regulating the fusion-related proteins Mfn1 and Opa1, triggering excessive mitochondrial fission. It is proposed that such mitochondrial morphological perturbation further represses carnitine palmitoyltransferase 2 (Cpt2)-dependent fatty acid oxidation (FAO), impairing the ATP supply required for osteogenic differentiation [116]. Similarly, *P. gingivalis*-LPS has been shown to bind to TLR4 on human SH-SY5Y neuronal cells in vitro, repress the SRF/p49/STRAP complex, down-regulate Mfn2 and Opa1 expression, and augment mitochondrial fission [117].

As an anaerobic bacterium closely associated with periodontitis, *Actinomyces odontolyticus* releases lipoteichoic acid (LTA)-rich OMVs. These vesicles have been revealed to target the outer mitochondrial membrane protein TOMM20 of human colonic epithelial cells through dynamin-dependent and clathrin-dependent endocytosis in vitro, which are associated with mitochondrial fragmentation and accumulated DNA damage [118]. When live *P. gingivalis* is co-cultured with vascular endothelial cells in vitro, it specifically activates the RhoA/ROCK1 pathway to promote Drp1 recruitment to the mitochondrial outer membrane. Phosphorylation of Drp1 at the Ser616 site facilitates the dissociation of the voltage-dependent anion channel 1 (VDAC1) -hexokinase 2 (HK2) complex. This dissociation relieves the inhibitory constraint on the mPTP, a change that has been associated with mitochondrial oxidative stress and endothelial cell injury-senescence in vitro [119-121].

These studies suggest that oral microbiota may affect mitochondrial dynamics across several cell types, but they differ in exposure, model, and measured outcome. It remains uncertain how oral microbiota reach distal tissues in vivo and whether the observed mitochondrial changes are pathogen-specific or partly secondary to systemic inflammation. These issues should be resolved before organ-specific findings are interpreted as a common causal pathway.

3.4.2 Reducing mitochondrial biogenesis

Mitochondrial biogenesis is predominantly governed by the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), nuclear respiratory factor 1 (NRF1), and transcription factor A (TFAM), which orchestrates mitochondrial biogenesis, antioxidant enzyme and respiratory chain transcription. Existing evidence indicates that oral dysbiosis and its virulence factors may target and repress PGC-1α dependent mitochondrial biogenesis [78, 117, 122, 123]. This further provokes oxidative stress imbalance, aberrant mPTP opening, and robust release of mt-DAMPs, which in turn elevates chronic low-grade inflammation and contributes to the progression of neural-related and bone-related degenerative disorders. Reported examples include changes in the TLR4-SRF/p49/STRAP axis, non-canonical caspase-4 mediated inflammasome signaling, NOX4 driven oxidative stress, and CXXC5 dependent osteogenic regulatory signaling.

In vitro assays revealed that *P. gingivalis*-LPS could activate TLR4 signaling, suppress the activity of SRF/p49/STRAP, a master transcriptional complex for mitochondrial biogenesis and dynamics [117]. Consistently, Verma et al. identified that *P. gingivalis*-LPS could trigger the caspase-4 non-canonical inflammatory pathway in neurons and microglia to repress the transcription of PGC-1α, NRF1 and TFAM [78]. In central microglia, *P. gingivalis* has been reported to elevate NADPH oxidase subunit NOX4 to block the PPAR-α/PGC-1α pathway, changes that have been associated with ferroptosis and mediate hippocampal neuroinflammation and neuronal injury [122]. In cementoblasts, *P. gingivalis* has been revealed to inhibit the PGC-1α-Nrf1/2-TFAM signaling by downregulating CXXC5, an upstream activator of PGC-1α, which is associated with osteogenic differentiation impairment in mice [123].

Notably, in the neurodegeneration-related studies discussed here, several mechanistic experiments have relied on tumor-derived cell lines. Because tumor cell lines differ substantially from primary cells under physiological conditions, particularly in baseline PGC-1α expression levels and constitutive SRF pathway activity, thus experimental system bias may be introduced. Therefore, these mechanistic conclusions require further validation through primary cell models and in vivo animal experiments.

3.4.3 Inhibition of mitophagy

Mitophagy contributes to mitochondrial quality control by removing damaged organelles. Oral microbiota might also suppress mitophagy at more than one stage, including mitochondrial recognition or initiation, autophagosome formation, and lysosomal processing. Reported changes involve the canonical ubiquitin-dependent PINK1/Parkin pathway, the hypoxia-inducible NIX-mediated pathway,

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and the ANXA2-ceramide lipid-dependent pathway, as well as lysosomal function. In experimental models, such suppression has been associated with accumulation of impaired mitochondria, subsequent opening of the mPTP and release of mt-DAMPs [124-126].

On the one hand, inflammatory gingival tissue samples and cell experiments showed that *P. gingivalis* infection significantly downregulates the expression of mitophagy-related proteins PTEN-induced kinase 1 (PINK1), Parkin, and microtubule-associated protein 1A/1B-light chain 3B (LC3B) in bone marrow macrophages, thereby inhibiting mitophagic flux and exacerbating local periodontal inflammation [127]. On the other hand, Sheridan M et al. showed that *P. gingivalis* downregulates NIX signaling in osteoblasts under hyperglycemic microenvironments to trigger alveolar bone degeneration and disrupts the ANXA2-ceramide molecular scaffold required for mitophagy initiation, contributing to senescence and premalignant transformation of oral epithelial cells in vitro [128].

Moreover *F. nucleatum* has been described to invade oral mucosal fibroblasts and activate the Wnt5A/PKC/mTOR signaling cascade. This activation is associated with reduced expression of core mitophagy proteins ULK1, Beclin-1 and Atg7, and co-occurs with lowered LC3 II/I ratio and autophagosome biogenesis, and may result in defective mitochondrial clearance, MiDAS senescence and impaired mucosal regenerative capacity in fibroblasts [129].

Beyond the specific mitophagy cascades mentioned above, studies suggest oral microbiota may also block mitochondrial clearance processes via interfering with autophagosome maturation and inhibiting autophagic vesicle synthesis. Liu et al. observed that *P. gingivalis* infection of gingival epithelial cells may trigger lysosomal exocytosis, which could compromise autolysosomal degradation, disrupt epithelial barriers and potentially induce cellular senescence in vitro [130]. When *P. gingivalis* is internalized by vascular endothelial cells, it may induce lysosomal dysfunction, causing lysosomal membrane permeabilization and hydrolase activity reduction. This blocks the fusion of mitophagosomes with lysosomes, stalls mitophagy flux, and promotes the accumulation of damaged mitochondria in experimental settings [131].

3.4.4 Disruption of mitochondrial TCA-OXPHOS energy metabolism pathway

Animal and cellular studies suggest that oral dysbiosis plausibly target the structure and function of the mitochondrial tricarboxylic acid cycle (TCA) and electron-transport chain (ETC), suppress the tricarboxylic acid cycle-oxidative phosphorylation (TCA-OXPHOS) energy-metabolism program, and provoke persistent cellular energy metabolic dysfunction.

Taking *P. gingivalis* as an example, *P. gingivalis* and its secreted OMVs have been reported to impact metabolic reprogramming in macrophages by down-regulating key TCA cycle related genes and up-regulating glycolysis-associated genes, a shift that could favor a glycolytic phenotype and sustained energy stress [132]. Meanwhile, *P. gingivalis*-LPS down-regulates the expression of pyruvate dehydrogenase kinase 2 (PDK2), a key rate-limiting enzyme of the TCA cycle, which might perturb TCA cycle substrate metabolism and cellular redox balance [133]. In endothelial cells, *P. gingivalis* infection appears to reduce the protein level of mitochondrial deacetylase sirtuin-3 (Sirt3), impairing its deacetylation regulation of the mPTP core protein cyclophilin D (CypD) at the K167 site. This potentially alters mitochondrial permeability and downstream energetics [134]. In addition, *P. gingivalis* represses the expression of NDUFV1 and NDUFV2, which encode subunits of mitochondrial complex I in neurons. This plausibly influences ETC electron-transfer efficiency, triggers cellular energy exhaustion and mitochondrial dysfunction, contributing to energy imbalance and neuroinflammatory changes in neuronal cells [117].

Overall, preclinical studies implicate oral microbiota in several components of mitochondrial quality control, including dynamics, biogenesis, mitophagy, and energy metabolism. The evidence remains heterogeneous across microbes, host-cell types, and experimental systems. An important priority is to distinguish direct effects of intracellular or organelle-targeting oral microbiota from indirect effects mediated by host inflammatory signaling, and to establish whether the observed mitochondrial changes causally contribute to senescence or tissue dysfunction.

Collectively, the preceding sections have mapped the associations between oral dysbiosis and four core hallmarks of aging: cellular senescence, loss of proteostasis, altered intercellular communication, and mitochondrial dysfunction; while the bulk of current mechanistic research has centered on microbial taxa and their virulence factors, leaving the contribution of microbial metabolites largely underexplored. Oral microbiota-derived metabolites including short-chain fatty acids, amino acids, and lipid species are potential mediators of host-microbiota interactions [135]. Among these, *P. gingivalis*-associated PGDHC has been preliminarily investigated in preclinical models of senescence and age-related pathology [68, 136]. Further work should determine how oral microbial metabolites influence these aging-related processes and whether their effects are distinct from or shared with those of microbial virulence factors.

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4. Therapeutic Research Opportunities Involving Oral Microbiota in the Context of Aging

Building on the aforementioned mechanistic insights, microbiota targeted interventions represent a promising research frontier for investigating aging processes linked to oral dysbiosis. Current intervention focuses on two major directions: microbial homeostasis management and targeting oral microbiota-mediated aging signaling pathways triggered by virulence factors of oral microbiota. To date, relevant investigations remain predominantly pre-clinical basic research and small-scale observational studies. Evidence of therapeutic efficacy via large-scale, multicenter clinical trials is still lacking, leaving substantial translational gaps before routine clinical implementation (Fig. 4).

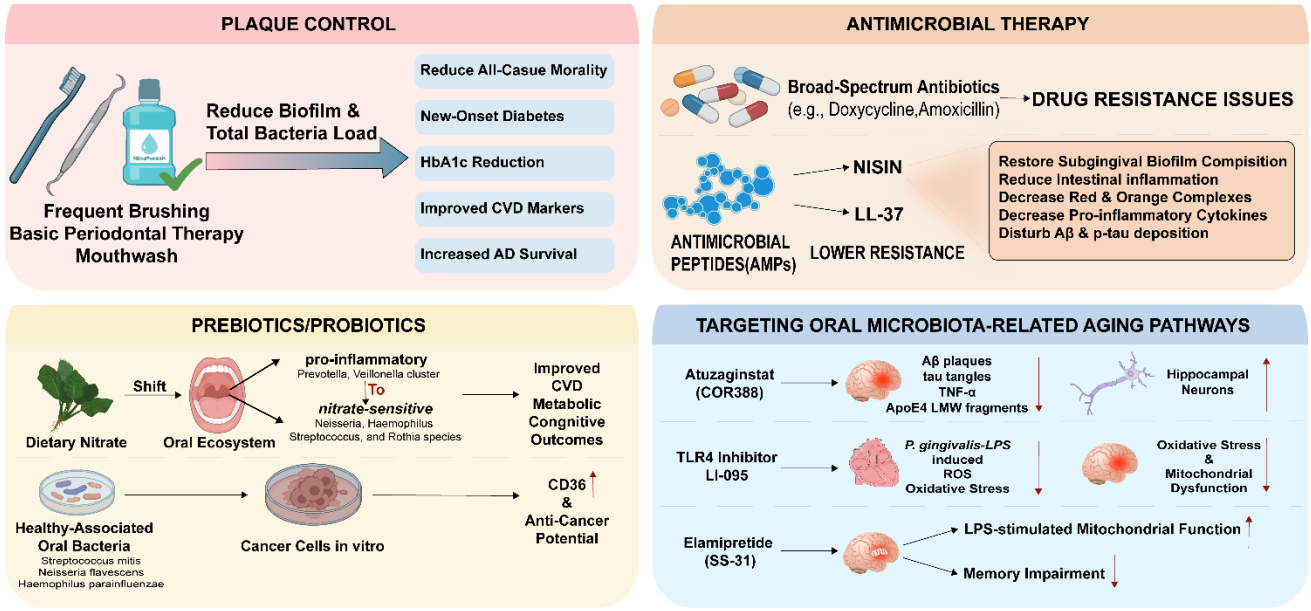


Figure 4. Research Opportunities For Targeting Oral Microbiota-Related Aging. Schematic depicting potential approaches to alleviate aging pathologies associated with the oral microbiota, as supported by current experimental and clinical evidence. (Plaque Control): Frequent brushing/mouthwash has been reported to reduce biofilm load, improving HbA1c, CVD markers, and AD survival. (Antimicrobial Therapy): Broad-spectrum antibiotics carry resistance risks; while antimicrobials (NISIN, LL-37) restore oral microbiome balance and reduce inflammation in animal models. (Prebiotics/Probiotics): Dietary nitrate has been reported to shift the oral ecosystem toward health-associated bacteria, improving metabolic/cognitive outcomes, while healthy-associated oral bacteria inhibits cancer cell growth in vitro. (Pathway Targeting): Inhibitors (Atuzaginstat, LI-095) and peptides (Elamipretide) may block TLR4 signaling, reduce oxidative stress, restore mitochondrial function, and alleviate neuroinflammation and memory impairment, primarily in preclinical studies.

4.1 Strategies for Oral Microbial Homeostasis Management: Preliminary Evidence from Basic and Observational Studies

At present, there are three main approaches used experimentally to reshape the homeostasis of the oral microbiota and to investigate aging-related mechanisms: plaque control, antibiotic therapy, and prebiotic/probiotic intervention. These approaches may offer potential therapeutic opportunities to mitigate systemic aging-related outcomes.

4.1.1 Plaque Control

Mechanical plaque control, which encompasses toothbrushing, non-surgical periodontal therapy, and mouthwash use, may represent a potential therapeutic opportunity to assess whether restoring oral homeostasis can modify ARD risk. Characterized by simplicity, high accessibility and ease of popularization, plaque control measures hold promise for integration into comprehensive prevention-management regimens for ARDs. Observational cohort data suggest potential population-level benefits. A 14-year prospective cohort study demonstrated that frequent toothbrushing (≥2 times/day) was significantly associated with reduced all-cause mortality (adjusted hazard ratio [HR] 0.86) and lower cause-specific mortality from cardiovascular disease, stroke, and respiratory diseases [137, 138]. Moreover, more intensive toothbrushing (≥3 times/day) was linked to an 8% relative reduction in incident type 2 diabetes risk (HR 0.92; $p<0.001$) [139].

Similarly, non-surgical periodontal therapy aimed at plaque control has been associated with improved outcomes in ARDs. For instance, it reduces glycated hemoglobin (HbA1c) levels in patients with type 2 diabetes by 0.24-1.21 percentage points [140, 141], lowers cardiovascular risk biomarkers (C-reactive protein [CRP], interleukin-6 [IL-6], systolic blood pressure) [142], and enhances 17-year cumulative survival in individuals with AD (83.5% vs. 71.5%, $p<0.05$) [143]. Furthermore, periodontal therapy has been reported to improve prodromal AD symptoms [144], suggesting its potential to modify disease progression at preclinical stages, and exerted favorable effects on pre-clinical pathological manifestations of AD.

Mouthwash rinses have been associated with reduced abundance of highly virulent periodontal pathogens, including *P. gingivalis*, *T. denticola*, and *T. forsythia,* and with less hyperglycemia in patients with type 2 diabetes, particularly in younger individuals [145]. However, chronic overuse of these agents may disturb the ecological homeostasis of the oral microbiota [146]. For example, broad-spectrum antimicrobial formulations can inhibit oral nitrate-reducing bacteria (NRB), thereby decreasing circulating nitrite levels, a key mediator of NO bioavailability, which has been associated with higher blood pressure [147] and with worsened glycaemia [148]. The above clues suggest that developing mouthwash formulations capable of targeting pathogenic bacteria while preserving commensal beneficial bacteria may represent a potential therapeutic opportunity to delay aging process. Nevertheless, the effects of such interventions on aging-related biomarkers, systemic outcomes, and safety remain insufficiently validated, warranting prudent evaluation before clinical translation.

4.1.2 Antimicrobial Therapy

Beyond plaque control, antibiotics are empirically employed as adjunctive therapies for managing or preventing oral dysbiosis [149], including local drug-delivery systems and systemic combination. Traditional broad-spectrum agents such as doxycycline and amoxicillin have only shown weak and transient improvement effects on some aging-related biomarkers in small-scale short-term trials [150, 151]. However, the widespread emergence of microbial resistance greatly limits its long-term research value in exploring the aging trajectory associated with oral dysbiosis.

Given these limitations, antimicrobial peptides (AMPs) exhibiting low resistance profiles hold promise as alternative therapeutics. The existing preclinical experimental data at the in vitro and animal levels suggest that nisin, a naturally occurring AMP produced by lactic acid bacteria, has demonstrated efficacy in modulating oral dysbiosis and may provide a useful opportunity for preclinical investigation. In vivo studies reveal that nisin disrupts the formation, structure, and viability of subgingival plaque biofilms, restoring the periodontal microbial community from dysbiosis to homeostasis [152]. Further research on animal intervention suggests that oral administration of nisin mitigates small intestinal inflammation and hepatic lipid accumulation, both induced by oral dysbiosis, thereby reducing liver-related pathological phenotypes in a preclinical model [153]. Nisin has also emerged as a preclinical tool for oral microbiota dysbiosis-associated Alzheimer's disease [154]. Mechanistically, nisin reduces the levels of red and orange complexes in dental plaque, the key periodontal pathogenic consortia and suppresses pro-inflammatory cytokine mRNA expression (IL-1β, IL-6, TNF-α) in the mouse brain. It further restores the loss of proteostasis by decreasing Aβ and p-tau deposition, thereby attenuating brain senescence. Beyond neuroprotective effects, nisin has been shown to inhibit the proliferation of head and neck squamous cell carcinoma (HNSCC) cells in cell and animal experiments, suppress tumorigenesis, and prolong survival in murine cancer models [155].

Similarly, the endogenous antimicrobial peptide LL-37, encoded by the *CAMP* gene, exhibits antifungal, antibacterial, and anti-biofilm activities in *in vitro* cell and biological models. It inhibits biofilm formation by *Actinomyces* species and restricts the growth of *F. nucleatum* [156, 157], while also reducing the invasion of viable *P. gingivalis* into host cells [158]. However, the application of LL-37 in preventing microbiota dysbiosis-induced ARDs remains largely unexplored, necessitating further investigation. Meanwhile, comprehensive evaluation of the safety profiles and optimization of administration regimens for antimicrobial peptides are critical for their clinical translation.

However, the evidence related to antimicrobial peptides is mostly limited to in vitro and animal experiments, and there is a lack of population intervention data. There are multiple gaps in extrapolating from in vitro, animal to human models. Oral microbial configurations in animals inherently differ from those in humans, and dysbiosis induction in animal models deviates from naturally occurring chronic infection in human subjects. Moreover, critical concerns regarding human-relevant stability, immunogenicity and administration safety of antimicrobial peptides remain unresolved. Currently, they can only be regarded as mechanism research tools and candidate compounds and are not yet ready for clinical anti-aging implementation.

4.1.3 Prebiotics and Probiotics

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In addition to plaque control and antibiotic therapy, microbial homeostasis management also encompasses the use of prebiotics and probiotics. Extensive reviews have summarized studies on delaying aging and treating ARDs through prebiotic/probiotic-mediated modulation of gut microbiota homeostasis [159]. However, research on regulating oral microbiota to delay aging is still in its infancy.

In recent years, research on prebiotic/probiotic interventions for aging delay via oral microbiota homeostasis regulation has gained significant momentum. Limited human interventional and pre-clinical studies represent promising avenues for mechanistic research of oral-microbiome-targeted prebiotics and probiotics. For instance, Streptococcus salivarius strains K12 and M18, which produce salivaricin, are orally administered probiotics classified as GRAS (Generally Recognized as Safe) by the U.S. FDA and exert bidirectional regulatory effects on the oral cavity and systemic health [160, 161]. Human double-blind clinical trials have further confirmed that a single administration of strain K12 increases circulating regulatory T cells and the anti-inflammatory cytokine IL-10, while moderately elevating the immunomodulatory factor IL-12. This strain has been associated with reduced systemic chronic low-grade inflammation via the gut-oral axis; however, causal evidence from large-sample, long-term clinical investigations remain to be consolidated [162].

Meanwhile, a randomized crossover human intervention trial showed that short-term dietary supplementation with nitrate-rich prebiotics shifts the oral ecosystem from a pro-inflammatory *Prevotella-Veillonella cluster* to a nitrate-sensitive community dominated by *Neisseria*, *Haemophilus*, *Streptococcus*, and *Rothia species*. This transition enhances the nitrite-NO axis function, thereby improving cardiovascular, metabolic, and cognitive parameters [21, 22]. Observational population data and preclinical cellular and animal model studies reveal that the oral probiotic *Lactobacillus salivarius* generates the tryptophan metabolite indole-3-acetic acid (IAA). This metabolite activates the aryl hydrocarbon receptor (AHR) in intestinal epithelial cells and transcriptionally upregulates the expression of DNA damage repair protein PARP1, thereby enhancing DNA damage repair, suppressing intestinal epithelial cellular senescence, and ameliorating intestinal barrier dysfunction and chronic inflammation [163]. Nevertheless, human randomized intervention trials are still lacking in verifying the practical efficacy of this microbiota-targeted regulatory strategy in elderly populations.

Recently, health-associated oral microbiota, including *Streptococcus mitis*, *Neisseria flavescens*, and *Haemophilus parainfluenzae,* have demonstrated in vitro anticancer potential [164]. These taxa significantly reduce CD36 expression, a protein closely linked to tumor growth and metastasis in cancer cells, inhibiting tumor cell proliferation in vitro.

The foregoing evidence suggests that these probiotics hold considerable potential for microecological interventions in ARDs and for the development of oral biomaterials incorporating probiotic delivery systems. However, microbiome heterogeneity and strain specificity constitute formidable challenges in prebiotic and probiotic research: substantial functional divergence exists across strains within the same species; individual baseline microbiota composition critically determines intervention response; and the absence of standardized criteria for strain selection, dosing regimens, treatment duration, and delivery vehicles severely compromises cross-study comparability.

4.2 Targeting Aging Pathways related to Oral Microbiota

As previously outlined, the oral microbiota and its virulence factors may influence aging processes and ARDs by modulating cellular senescence, disrupting proteostasis, and altering intercellular communication. Therefore, small molecule inhibitors designed for oral microbiota virulence factors and related aging pathways have emerged as candidates for precision intervention against dysbiosis-associated aging, including gingipain inhibitors (e.g., Atuzaginstat [COR388]), TLR4 inhibitors (e.g., LI-095), which have shown the potential opportunities to alleviate oral microbiota related aging phenotypes in preclinical models.

Both *in vitro* cell experiments and rodent models suggest that the small-molecule inhibitor Atuzaginstat (COR388), structurally derived from the Kgp of *P. gingivalis* and its binding pocket, exerts multifaceted neuroprotective effects. It not only reduces Aβ plaque deposition and tau tangle formation but also attenuates neuroinflammation by suppressing pro-inflammatory cytokine TNF-α expression, thereby rescuing hippocampal neurons [28, 165] and slowing AD progression in these models. Notably, a 28-day COR388 regimen significantly decreased low-molecular-weight (LMW) ApoE4 fragments in the cerebrospinal fluid of AD patients [166], while ApoE4 is the strongest genetic risk factor for AD. Although the Phase 2/3 clinical trial of COR388 was discontinued due to dose-dependent hepatotoxicity [165], the translational insights obtained from this study still provide valuable research directions for the development of small molecule drugs targeting oral microbiota virulence factors in the future.

Beyond targeting bacterial virulence factors, blockade of upstream microbiota-associated

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inflammatory signaling pathways also confers robust protection against aging related pathological insults. The TLR4-specific inhibitor LI-095 was found to not only alleviate *P. gingivalis*-LPS induced myocardial ROS production and oxidative stress by inhibiting the TLR4-NOX4 pathway [103], but also counteract *P. gingivalis*-LPS induced oxidative stress and mitochondrial dysfunction associated with AD [117] in vitro cell and rodent preclinical experiments. However, in vivo bioavailability, tissue targeting, and long-term safety of these molecules have not been validated, creating substantial translational barriers prior to standardized clinical antiaging deployment.

Given that oral virulence factors may accelerate aging via mitochondrial dysfunction, Elamipretide (SS-31), a novel mitochondria-targeted antioxidant, has been shown to ameliorate LPS-induced hippocampal mitochondrial dysfunction, thereby mitigating memory impairment in murine models [167]. Collectively, the basic research results provide a clear research and development approach for the design of small molecule formulations targeting aging pathways related to oral microbiota. Subsequent candidate molecules can be structurally optimized around neuronal mitochondrial homeostasis as the core target, with mitochondrial oxidative stress and energy metabolism pathways as the main intervention directions, to specifically block neurotoxic reactions associated with oral dysbiosis.

Current approaches to plaque control and antibiotic therapy are constrained by inherent limitations, including antimicrobial resistance and pronounced dysbiosis, which compromise the sustainability of long-term anti-aging interventions. In this context, quorum quenching (QQ) has emerged as a promising research opportunity for modulating microbial community homeostasis via targeted disruption of bacterial quorum sensing (QS) systems. Unlike broad-spectrum antibiotics that indiscriminately eliminate bacteria, QQ selectively interferes with QS pathways by either degrading signaling molecules (e.g., acyl-homoserine lactones [AHLs], autoinducer-2 [AI-2]) or antagonizing receptor proteins (e.g., LuxR-family transcriptional regulators). This mechanism suppresses virulence factor expression, such as biofilm formation and extracellular polysaccharide secretion in pathogenic taxa while preserving microbial diversity [168], positioning QQ as a translational bridge linking oral microbiota equilibrium to aging intervention. Notably, existing QQ agents, including plant-derived natural compounds such as coumarin and curcumin have demonstrated life-extending effects in model organisms [169]. Moving forward, priority should be given to elucidating the anti-aging potential of QQ-mediated modulation of oral microbiota. Key directions include structural optimization of QQ agents to enhance their targeting specificity and bioavailability within the oral niche, as well as development of oral delivery platforms for sustained local modulation with systemic implications.

5. Key unresolved questions

In conclusion, the involvement of oral microbiota and its virulence factors in regulating aging is being extensively studied. Compared with the gut microbiome, the oral microbiome features non-invasive sampling and sensitive responsiveness to aging phenotypes, making it an ideal target for developing non-invasive systemic aging assessment and early warning systems. However, given the current landscape of fragmented associative evidence, incomplete causal frameworks, and limited translational progress, future research should advance across five pillars: cohort development, multi-omics analysis, AI-driven modeling, mechanistic validation, and clinical translation, to establish an integrated research and application framework for oral microbiome modulation of systemic aging (Fig. 5).

Firstly, large-scale, multi-regional, longitudinal cohorts spanning all age groups with standardized sampling, preservation, nucleic acid extraction, and sequencing workflows are urgently needed to ensure reproducibility and cross-cohort comparability; concurrently, account for heterogeneity across oral niches and control confounders such as periodontal disease, denture use, diet, medications, and chronic conditions.

Secondly, multi-omics integration should become routine. In addition to 16S rRNA/metagenomic sequencing, combine oral and peripheral metabolomics, aging biomarkers such as telomere length, SASP, epigenetic clocks, etc., to construct a multidimensional co-variation network linking microbiota, metabolism, and host aging. Meanwhile, causal inference methods including Mendelian randomization, mediation analysis, and cross-lagged panel models should be applied to dissect the microbiota-metabolism-host aging regulatory network and strengthen population-level causal evidence.

Thirdly, AI and machine learning-driven quantitative aging models remain limited in reliability and interpretability. AI modeling based on multi-omics data should emphasize temporality and biological priors, avoiding purely statistical associations that yield false positives; require external validation across diverse populations and provide interpretable analyses (e.g., SHAP) to achieve individualized aging predictions and intervention responses [34]. Multi-modal aging clocks remain conceptual, with modality imputation, batch correction, and intervention response prediction models all requiring further optimization [35].

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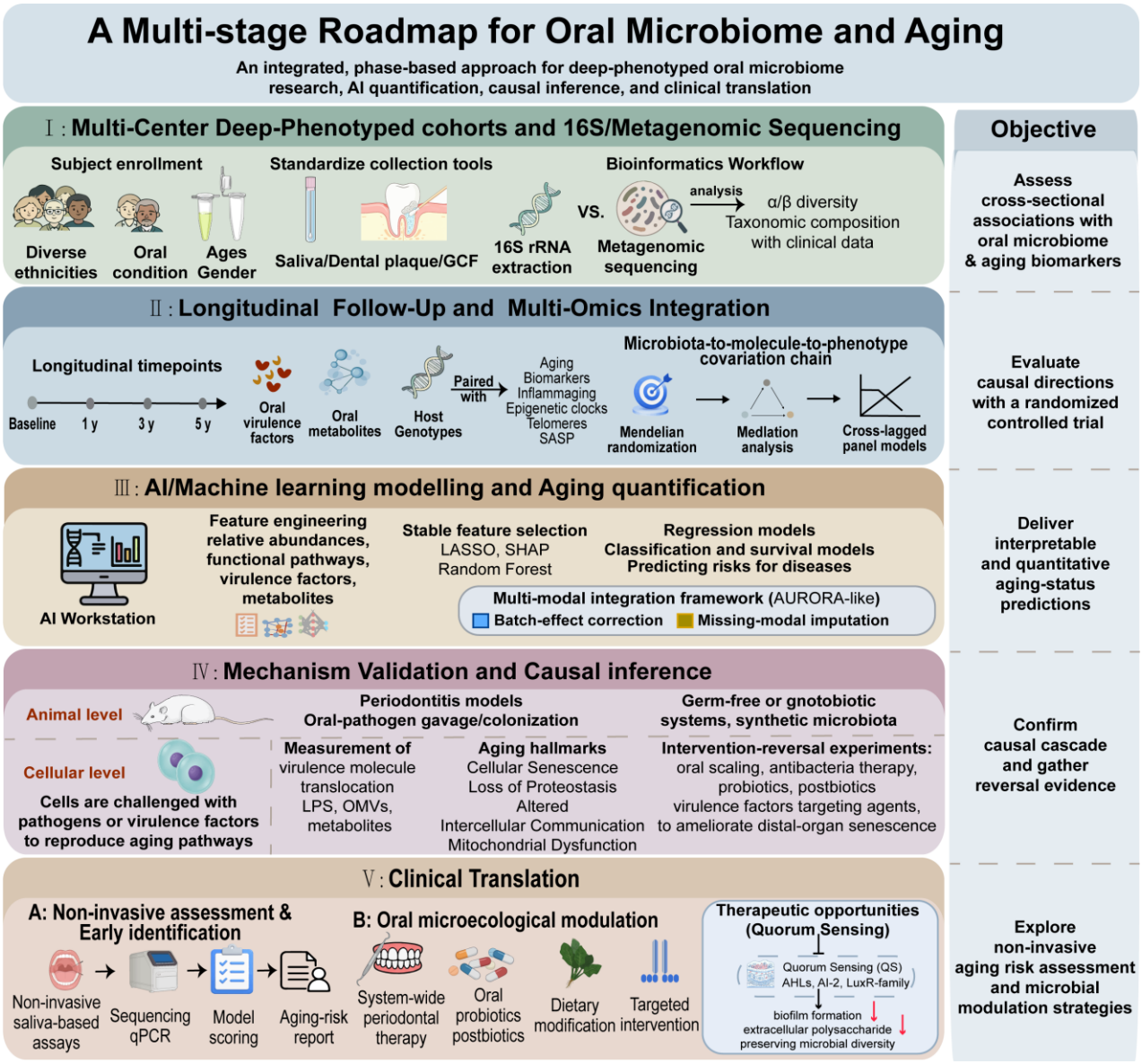


Figure 5. A Multi-Stage Roadmap for Oral Microbiome and Aging: From Deep Phenotyping to Clinical Translation. An infographic outlining a five-stage, integrative roadmap for studying the link between the oral microbiome and aging. The horizontal, color-coded panels (I-V) depict: I) multi-center deep-phenotyped cohorts with 16S/metagenomic sequencing and bioinformatics analyses to assess cross-sectional associations; II) longitudinal follow-up with multi-omics integration and causal inference workflows (Mendelian randomization, mediation analysis, cross-lagged models); III) AI/machine learning models and aging quantification, featuring multi-modal data integration and interpretable feature selection; IV) mechanism validation and causal inference using animal and cellular models, periodontal disease models, and reversal interventions; V) clinical translation, including non-invasive aging risk assessment and microbiome-targeted interventions. The legend notes a right-hand "Objective" column summarizing the goal of each stage, and icons illustrate sampling, sequencing, models, pathogens, and interventions.

Moreover, mechanism research should move beyond single-strain interventions toward multi-microbial or synthetic communities, and include sterile animal models, organotypic cultures, and multi-layer in vivo systems to delineate core virulence factors and host aging pathways; and conduct reversal intervention studies to confirm causal effects of oral microbial ecology on multi-organ aging.

Finally, a translational clinical framework centered on oral microbiome modulation is needed, including standardized diagnostic platforms, risk thresholds, long-term interventional trials, and integrated evaluation systems to bridge scientific theory and clinical practice.

6. Conclusion

This perspective summarizes clinical epidemiology and experimental evidence suggesting that oral dysbiosis may act as an upstream risk factor associated with systemic biological aging and ARDs. Persistent oral dysbiosis has been associated with a higher systemic aging burden relative to age-matched peers, reframing oral health beyond a local dental and periodontal paradigm and supporting oral dysbiosis as a potential modulator of multisystem comorbidity and aging. This perspective provides a novel theoretical framework for the co-pathogenesis of aging-related multimorbidity.

Dysregulated oral microorganisms and their virulence factors may translocate to distant organs, comprehensively activate core host aging programs via multiple signaling pathways, potentially contributing to multi-organ degenerative damage and accelerating systemic aging. Unlike prior studies that largely reported fragmented associations between oral microbiota and individual ARDs, this work integrates the canonical aging hallmarks to construct a complete cascade regulatory framework linking localized oral dysbiosis to accelerated systemic biological aging, filling a gap in mechanistic understanding.

This perspective further summarizes exploratory opportunities for strategies that may mitigate biological aging, involving reconstitution of the oral microbiome and targeting aging pathways, and highlights the practical advantage of non-invasive oral sampling for monitoring. Meanwhile, this work objectively appraises current limitations, acknowledges that the prevailing evidence is largely correlative, and clarifies the need for robust causal validation through prospective cohorts, deeper mechanistic dissection, and targeted interventions. The findings provide a conceptual basis for foundational research and future clinical translation of oral microbiome-targeted intervention strategies.

Author contributions

SY is the corresponding author responsible for the overall conception, framework design, and revision of the review. LHL and XWQ are the co-first authors. LHL and XWQ contributed to the in-depth analysis of key topics. YSR and HCY led the literature collection and preliminary screening, as well as the creation of schematic diagrams, ensuring the accuracy and readability of the information presented. CYH, ZXY and RQQ refined the language of the review draft, enhancing the article's fluency. All authors read and approved the final manuscript.

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Competing interests

The authors declare no competing interests.

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