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REVIEW

SPECIAL ISSUE: Oral Regional Immune Mechanisms and Systemic Homeostasis

From homeostasis to barrier failure: oral microbial dysbiosis reprograms mucosal immunity and epithelial states in oral mucosal diseases

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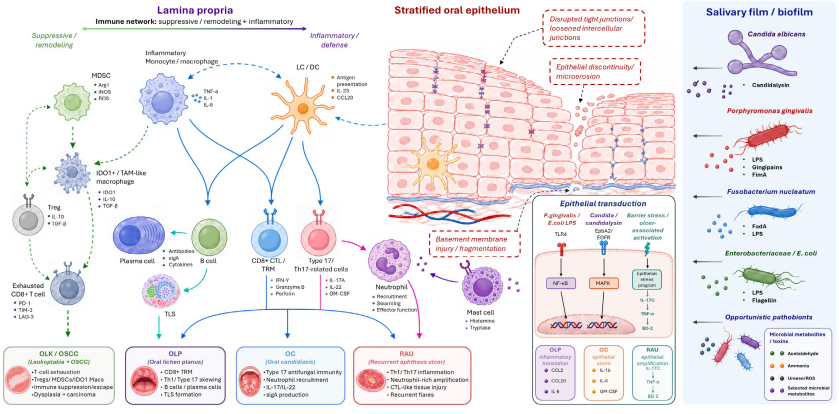
ABSTRACT: Oral mucosal diseases arise at a highly exposed barrier interface where microbial communities, mucosal immunity, and epithelial repair programs must remain dynamically balanced. Increasing evidence suggests that oral microbial dysbiosis is not merely a compositional shift, but a context-dependent functional state involving altered microbial localization, virulence programs, metabolic activity, and host sensing thresholds. In this Review, we examine oral candidiasis (OC), oral lichen planus (OLP), recurrent aphthous ulcer (RAU), oral leukoplakia (OLK), and oral squamous cell carcinoma (OSCC) as representative disease contexts along the continuum from oral homeostasis to barrier failure. We integrate microbial signals, immune remodeling, epithelial barrier states, and disease-stage transitions into an evidence-graded framework. We propose that dysbiosis may function as an initiating trigger, inflammatory amplifier, chronic maintenance factor, risk-associated ecological signal, or secondary colonization event, depending on disease context, stage, localization, and evidence certainty. OC currently has the strongest mechanistic and interventional support, whereas evidence in OLP, RAU, OLK, and OSCC remains more heterogeneous. This framework may guide future microbiota-informed risk stratification, prevention, adjunctive therapy, and supportive care.



KEYWORDS: oral mucosal diseases, oral microbiota, microbial dysbiosis, mucosal immunity, epithelial barrier

1 Introduction

Oral mucosal diseases (OMDs) constitute a heterogeneous spectrum of disorders that arise at one of the body's most exposed barrier interfaces. The oral mucosa is continuously challenged by commensal microorganisms, dietary antigens, airborne particles, mechanical forces, and salivary flow, while preserving tissue integrity and immune tolerance. Although OMDs differ in clinical presentation, histopathological features, and outcomes, they share a common ecological context in which microbial communities, mucosal immunity, and epithelial repair programs must remain dynamically coordinated[1-5]. Thus, the shared basis of OMDs is not a single etiological factor, but a vulnerable mucosal system that must continuously balance commensalism, vigilance, tolerance, and repair.

This view has shifted how OMDs are conceptualized. Models centered on a single pathogen, immune abnormality, or epithelial injury are increasingly being replaced by an integrated view of OMDs as disorders of host-microbiota-barrier crosstalk[1,3,4]. In this context, microbial dysbiosis is not defined simply by community composition. It also involves altered colonization niches, disrupted intermicrobial interactions, changes in virulence programs and

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metabolic output, recalibrated host-sensing thresholds, and impaired epithelial-interface functions[1,5,6]. Importantly, these changes do not carry the same biological meaning in every disease setting. Depending on disease context and stage, dysbiosis may be linked to susceptibility to opportunistic infection, chronic inflammatory amplification, recurrent ulceration with defective repair, remodeling of a premalignant niche, or progression within a tumor-associated ecosystem[1,5,6].

Despite growing interest in oral microbiome–host interactions, several conceptual gaps remain. Compared with barrier tissues such as the intestine and skin, the oral field still lacks a clear framework for interpreting when dysbiosis acts as a driver, amplifier, maintainer, risk-associated ecological signal, or secondary colonization event. The temporal sequence and causal direction among microbial changes, immune-network remodeling, and epithelial-interface instability remain incompletely defined. It is also difficult to distinguish mechanisms that are shared across OMDs from those that are disease-specific, site-specific, or stage-dependent[1,5,6]. These uncertainties are particularly important because the strength of evidence differs markedly across disease contexts, ranging from mechanistically supported microbial state switching to association-based or tumor-ecology-confounded observations.

In this Review, we use oral candidiasis (OC), oral lichen planus (OLP), recurrent aphthous ulcer (RAU), oral leukoplakia (OLK), and oral squamous cell carcinoma (OSCC) as representative clinical contexts along a homeostasis-to-barrier-failure continuum. These diseases were selected because they represent clinically distinct but biologically connected states: fungal opportunistic infection, chronic immune-mediated inflammation, recurrent ulcerative barrier failure, potentially malignant epithelial disorder, and invasive carcinoma. This cross-disease comparison allows us to examine how microbial cues, mucosal immune remodeling, epithelial barrier dynamics, and disease-stage transitions are connected, while preserving differences in causality, evidence certainty, and translational maturity. We propose that oral microbial dysbiosis should be interpreted as a context-dependent functional state rather than a fixed pathogenic label. Within this framework, dysbiosis may contribute to disease initiation in mechanistically supported settings, amplify or maintain inflammation in unstable mucosal tissues, mark risk-associated ecological remodeling in premalignant lesions, or emerge as secondary colonization within remodeled tumor ecosystems.

1.1 Literature selection and scope

This article was designed as a narrative review rather than a systematic review or meta-analysis. To improve transparency in literature selection, we performed a structured but non-systematic search of PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar for English-language articles published from 2000 to April 2026. The search combined disease-related terms, including oral candidiasis, oral lichen planus, recurrent aphthous ulcer, oral leukoplakia, and oral squamous cell carcinoma, with microbiome-related terms such as oral microbiota, oral microbiome, dysbiosis, biofilm, Candida, Porphyromonas gingivalis, and Fusobacterium nucleatum. These terms were further combined with host-response and barrier-related terms, including mucosal immunity, epithelial barrier, epithelial permeability, tight junction, IL-17, Th17, macrophage, neutrophil, and Treg. Additional topic-specific searches were conducted for mechanistic and translational evidence, including single-cell RNA sequencing, spatial transcriptomics, metabolomics, probiotics, antifungal adjunctive therapy, and microbiota-targeted therapy. Relevant studies were also identified by screening the reference lists of key reviews and primary research articles.

We prioritized studies that provided mechanistic, tissue-level, longitudinal, multi-omics, animal-model, *in vitro* functional, interventional, or reversibility evidence linking microbial changes to immune remodeling, epithelial barrier dysfunction, or disease progression. Human studies were included when they examined saliva, plaque, mucosal swabs, biopsies, or tumor tissues in the selected disease contexts. Studies were excluded if they were not directly related to oral mucosal diseases, focused primarily on dental caries or periodontitis without relevance to mucosal barrier disease, lacked sufficient methodological detail, were limited to broad taxonomic description without disease-contextual interpretation, or were not available in English. Because the available evidence differs substantially across diseases, we interpreted findings according to study design, tissue context, disease stage, and evidence strength. Particular attention was given to whether a study provided association-based, tissue-localization, mechanistic, longitudinal, interventional or reversibility evidence.

2 Homeostatic baseline

The oral mucosa does not maintain health by excluding microorganisms or remaining immunologically silent. Instead, it functions as a dynamic barrier ecosystem that continuously integrates microbial, mechanical, metabolic, dietary, and environmental inputs while preserving immune tolerance, epithelial integrity, and rapid repair capacity. Earlier models of oral homeostasis mainly emphasized a static balance among the epithelial barrier, salivary clearance, and resident microbial communities. Recent studies employing single-cell omics, spatial transcriptomics, reconstructive tissue models, and mechanobiology now suggest that oral homeostasis is an actively organized state, orchestrated through spatial compartmentalization, ecological selection, mechanical cueing, tonic low-amplitude immune surveillance, and metabolic repair programs[7-10](Fig. 1). This active baseline provides the reference state for understanding dysbiosis: barrier failure may emerge when normally constrained microbial cues exceed local sensing thresholds, disrupt tissue organization, or prevent timely immune resolution and epithelial repair.

2.1 The oral mucosal interface: from passive coverage to active organization

Recent studies have driven an important conceptual shift in how the oral mucosa is understood. Rather than serving as a uniform physical covering, the oral mucosa functions as a spatially organized barrier interface with site-specific epithelial, stromal, and immune programs. Using a human oral mucosal single-cell atlas, Williams *et al.* demonstrated that epithelial and stromal cells in healthy oral mucosa harbor intrinsic programs related to antimicrobial defense, neutrophil chemotaxis, and regulation of local inflammatory thresholds. Gingival tissue exhibited a higher baseline propensity for immune responses than other oral sites[7]. These findings suggest that oral homeostasis is not a uniformly low-response program across all regions, but an anatomically patterned state in which local tissues are differentially primed for microbial exposure and immune surveillance.

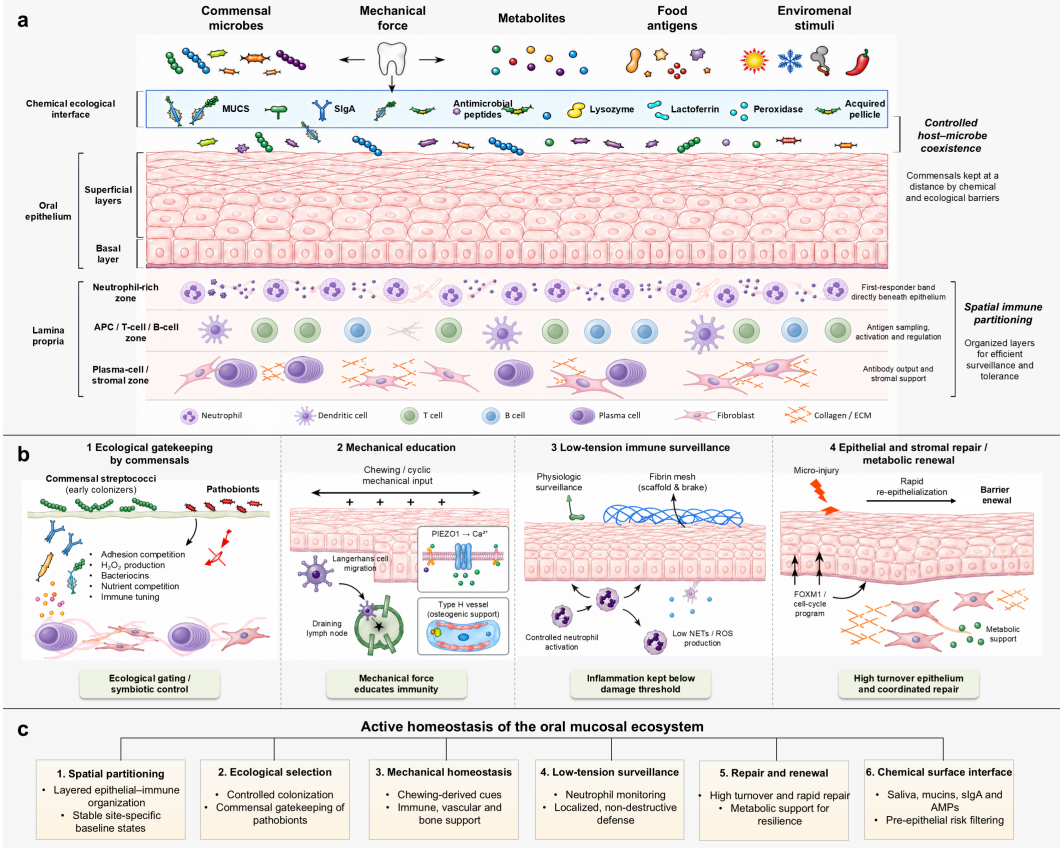

Figure 1 Active homeostasis of the oral mucosal ecosystem. (a) Under physiological conditions, the oral mucosa acts as a dynamic host–environment interface rather than a passive barrier. Commensal microbes, mechanical forces, metabolites, food antigens, and environmental stimuli are first buffered by a pre-epithelial chemical–ecological interface composed of mucins, secretory IgA, antimicrobial peptides, lysozyme, lactoferrin, peroxidases, and the acquired pellicle. Beneath this surface layer, the epithelium and lamina propria are spatially organized into superficial and basal epithelial compartments, a neutrophil-enriched first-responder zone, an APC/T-cell/B-cell regulatory zone, and a deeper plasma-cell/stromal support zone. (b) Homeostasis is maintained by coordinated ecological, mechanical, immune, and repair programs. Commensals contribute to ecological gatekeeping through adhesion competition, antimicrobial metabolite production, nutrient competition, and immune tuning. Cyclic mechanical input from mastication supports mucosal adaptation, vascular homeostasis, and stromal remodeling. Low-amplitude immune surveillance restrains microbial invasion while limiting excessive NET/ROS-mediated tissue injury. After micro-injury, rapid re-epithelialization, stromal repair, and metabolic renewal restore barrier integrity. (c) Together, spatial partitioning, ecological selection, mechanical homeostasis, low-amplitude surveillance, chemical surface defense, and rapid repair define an active homeostatic program that maintains stable coexistence, controlled vigilance, and rapid recovery at the oral mucosal interface.

This view has been strengthened by higher-resolution spatial studies. Theofilou et al. generated a multi-omic spatial map of human gingiva, revealing that tooth-associated epithelium is thin, non-keratinized, and highly permeable. Despite this high level of exposure, the tissue maintains a stable immune architecture. A neutrophil-rich zone lies directly beneath the epithelium, with underlying areas enriched in antigen-presenting cells and lymphocytes. During disease, inflammatory zones do not undergo complete spatial reorganization. Instead, they expand along a pre-existing framework and can further organize into immature tertiary lymphoid structures[10]. Thus, oral barrier resilience depends not only on epithelial integrity, but also on pre-established immune geography that localizes microbial sensing, inflammatory amplification, and tissue repair.

A developmental perspective further supports this view. Zubeidat and Hovav proposed that oral homeostasis is not simply the result of long-term microbial adaptation in adulthood. It is also shaped postnatally by stratified epithelium, which gradually educates the immune system and organizes the microbial ecosystem[8]. The homeostatic baseline should therefore be viewed as a tissue- and site-specific program shaped by development, environmental exposure, and local anatomy. This spatially organized baseline provides an important reference for interpreting dysbiosis: disease-associated microbial changes may have different consequences depending on where they occur and which epithelial, stromal, or immune compartments they engage.

2.2 Ecological selection and commensal gatekeeping by microbes

At the microbial level, oral homeostasis is governed by ecological selection rather than microbial elimination. Healthy oral microbiota do not colonize oral surfaces randomly. Instead, site-specific commensal networks are established through colonization sequence, nutritional cross-feeding, oxygen gradients, and selective adhesion molecules. Within these networks, early colonizers function as ecological gatekeepers that shape which organisms can persist, which virulence programs are restrained, and how strongly host tissues are exposed to microbial signals. Oral streptococci and other early colonizers are now recognized as homeostatic gatekeepers rather than background organisms. Reviews by Baty et

al. and Bloch et al. both emphasize that oral commensal streptococci, as primary early colonizers, shape subsequent microbial succession through adhesion, hydrogen peroxide production, bacteriocin secretion, metabolic competition, and modulation of host immune responses. In doing so, they restrain the overgrowth of potential pathogens and contribute to the maintenance of oral homeostasis[11,12].

Experimental models further support commensal gatekeeping. In an in vitro model simulating the healthy gingival interface, Adelfio et al. observed that host tissues and microbes can remain viable over prolonged co-culture while epithelial barrier integrity, host phenotypic function, and functional host-microbe interactions are preserved[13]. These findings indicate that oral health is not defined by a low microbial burden alone, but by a controlled form of host-permitted microbial activity within defined spatial and temporal boundaries. In this sense, commensals help maintain a homeostatic "set point" by limiting pathogen access, constraining excessive inflammatory stimulation, and supporting epithelial compatibility.

Commensal microbes also participate in immune balance. In the context of Sjögren's syndrome, Tseng et al. reported that a reduction in the oral commensal *Haemophilus parainfluenzae* was associated with disease. Oral supplementation with this bacterium improved oral microbial diversity, attenuated IFN-γ-skewed T-cell responses, and limited CD8+ T-cell expansion in epithelial-cell models[14]. Although this example comes from a disease context outside the main OMD spectrum discussed in this Review, it illustrates a broader homeostatic principle: commensals can shape local T-cell polarization and inflammatory thresholds rather than simply occupying epithelial surfaces.

The microbial dimension of oral homeostasis has also expanded beyond the bacteriome. Xu et al. established a human oral virome catalog and demonstrated that oral viral diversity, virus-bacterium associations, and oral-gut virome connections are markedly altered in individuals with obesity, with or without type 2 diabetes[15]. Future definitions of oral homeostasis should therefore incorporate bacterial, phage, fungal, and viral networks, as well as their functional interactions with host tissues. Overall, the oral microbial ecology under homeostatic conditions is best defined as a host-permitted commensal network. Its core is not a fixed list of "healthy" species, but the controlled nature of microbial localization, intermicrobial interactions, functional outputs, and host immune exposure.

2.3 Mechanical force as a homeostatic factor

Compared with barrier tissues such as the intestine and lung, the oral mucosa is uniquely exposed to cyclic mechanical stimulation generated by mastication, friction, swallowing, hygiene practices, and occlusion. These forces can cause epithelial microdamage when excessive or poorly regulated, but under physiological conditions they also provide homeostatic cues that shape epithelial adaptation, immune development, and tissue remodeling. In a study of postnatal oral homeostasis, Jaber et al. showed that oral Langerhans cells respond primarily to mechanical forces generated by chewing during weaning. These forces promote the migration of Langerhans cells to draining lymph nodes and thereby support adaptive immune development required for epithelial integrity[9]. Thus, immune maturation at the oral barrier is not solely microbe driven; it is also instructed by mechanical input.

Mechanical regulation also extends beyond the mucosal surface to the integrated soft–hard tissue interface formed by the periodontal ligament, vasculature, and alveolar bone. Physiological occlusal force can maintain type H angiogenesis in the periodontal ligament via the PIEZO1/Ca2+/HIF-1α/SLIT3 axis, supporting osteogenesis-coupled tissue activity, while PIEZO1 activation in osteoblasts promotes bone-maintaining programs and osteoclast apoptosis[16,17]. These findings illustrate a broader principle: oral homeostasis is maintained by coordinated epithelial, stromal, vascular, immune, and skeletal responses to mechanical load.

Mechanical force and periodontal homeostasis provide a broader tissue-level context. Wang et al. noted that appropriate mechanical force can regulate immune defense, extracellular matrix metabolism, periodontal ligament stem-cell behavior, bone metabolism, and non-coding RNA networks. Excessive force and force deprivation can both shift tissues outside the homeostatic range[18]. For oral mucosal diseases, this means that barrier instability should not be interpreted only as a microbial or immune event. It may also reflect failure to convert daily mechanical stress into controlled adaptive and repair signals.

2.4 Tonic low-amplitude immune surveillance

At the immune level, healthy oral mucosa is not immunologically quiescent. It is maintained in a tonic, low-amplitude, spatially localized surveillance state that allows rapid microbial sensing without persistent tissue injury. The stromal-neutrophil regulatory axis identified by Williams et al. indicates that stromal cells in healthy gingiva participate directly in neutrophil recruitment and tissue immunity[7]. Theofilou et al. further showed that, beneath tooth-associated epithelium, neutrophil bands, T-cell and B-cell zones, antigen-presenting cell aggregates, and deeper plasma-cell-associated regions establish a clear vertical architecture that persists across health and disease[10]. These findings suggest that oral immune homeostasis is not defined by absence of inflammation, but by spatially organized inflammatory readiness.

Our understanding of neutrophils has also changed. Neutrophils were previously viewed mainly as inflammatory cells. In a Science study, Silva et al. showed that commensal microbes can induce extravascular fibrin deposition in the oral mucosa. Fibrin subsequently regulates neutrophil activation through the αMβ2 integrin, promoting reactive oxygen species generation and neutrophil extracellular trap (NET) formation. Under normal fibrinolytic conditions, these responses are immunoprotective; when fibrinolysis is impaired, they become tissue-damaging[19]. Thus, the boundary between protective surveillance and pathological inflammation depends not only on immune-cell activation, but also on local tissue constraints that determine whether the response resolves or persists.

Systemic metabolic conditions can further shift this surveillance program outside the physiological range. Wang et al. reported in 2024 that hyperglycemia induces metabolic reprogramming of gingival neutrophils. Enhanced GLUT1-mediated glucose uptake and glycolysis promote excessive NET release and ultimately damage the oral mucosal barrier[20]. Inflammatory tone also varies among individuals even under comparable microbial challenge. In an experimental gingivitis study, Bamashmous et al. showed that, despite similar plaque accumulation, individuals segregated into high, low, or slow inflammatory responders[21]. Together, these findings indicate that oral homeostasis operates through individualized immune set points. Barrier failure may emerge when microbial, mechanical, or metabolic inputs exceed the local capacity to constrain immune activation and restore tissue integrity.

2.5 Epithelial and stromal cells execute repair programs

The oral mucosa can withstand high exposure, intense friction, and rapid turnover because its structural cells possess intrinsic repair and remodeling capacity. Using single-cell transcriptomics of healthy human oral soft tissues, Caetano et al. showed that oral homeostasis depends on coordinated communication among epithelial, mesenchymal, and immune cells. During disease progression, epithelial and mesenchymal subsets involved in tissue maintenance are among the first affected populations[22]. This indicates that oral homeostasis is not protected by the immune system alone; it also depends on epithelial and stromal programs that preserve tissue architecture, coordinate repair, and restore barrier continuity after injury.

Host–microbe interactions also contribute to epithelial maintenance. Long et al. compared tongue tissues from germ-free and conventionally housed mice and found that microbiota influence not only local immune responses and mitochondrial metabolism, but also keratinization programs, cell-adhesion molecule expression, and epithelial permeability. Chronic stress further exacerbated these differences[23]. Thus, commensal exposure helps tune the basal structural and metabolic state of the oral epithelium, whereas stress can shift this host–microbe relationship toward barrier vulnerability.

Recent studies of epithelial wound repair further indicate that oral mucosal homeostasis depends upon adequate metabolic supply and cell-cycle control. For example, α-ketoglutarate promotes re-epithelialization of palatal wounds and increases collagen deposition through FOXM1-mediated cell-cycle activation[24]. The healthy oral mucosa is therefore a metabolically active tissue with high renewal and rapid repair capacity. Barrier failure may occur when epithelial–stromal repair programs can no longer match the cumulative burden of microbial stimulation, mechanical injury, metabolic stress, and unresolved inflammation.

2.6 The chemical-ecological interface

The oral mucosa is not directly exposed to microbial communities as a bare epithelial surface. Its outermost surface is covered by a pre-epithelial chemical-ecological layer composed of saliva, acquired pellicle, mucins, secretory IgA, antimicrobial peptides, lysozyme, lactoferrin, peroxidases, and related molecules. This layer provides lubrication, clearance, and physical coverage. It also regulates microbial access to the epithelial surface. By limiting microbial adhesion, controlling nutrient availability, trapping or neutralizing microbial components, and maintaining local antimicrobial tone, it determines which microbes can transiently remain, which can stably colonize, and which potential pathogens are excluded before epithelial contact[25]. Oral mucosal homeostasis therefore begins before microbes reach the epithelial cell layer. This surface chemical barrier mediates primary filtering and risk partitioning. Barrier breakdown should consequently include not only disruption of cell junctions or epithelial integrity, but also loss of control over microbial adhesion, virulence expression, and community succession.

In summary, recent studies allow oral mucosal homeostasis to be defined more precisely. It is not a static combination of normal microbiota, intact barrier, and low inflammation. It is an active equilibrium maintained by spatial compartmentalization, ecological gatekeeping, mechanical cueing, tonic low-amplitude immune surveillance, cellular repair programs, and surface humoral and chemical defenses. The healthy oral mucosa coexists with complex microbial communities by converting stimulation into controlled signals, keeping local inflammation within a physiological vigilance range, and limiting tissue injury to a repairable level.

3 Oral microbial dysbiosis and mucosal immune remodeling

Oral microbial dysbiosis can alter mucosal immunity by changing the location, intensity, duration, and functional quality of microbial cues encountered by the host. Under homeostatic conditions, the oral mucosa receives spatially restricted and amplitude-controlled commensal signals. When colonization sites, tissue proximity, community interactions, virulence programs, and metabolic outputs change, these inputs may shift toward danger-associated cues that trigger immune sensing and polarization[5,6]. Across the representative disease contexts discussed below, the strength and type of evidence differ substantially. OC provides the clearest mechanistic model of microbial state switching, whereas OLP, RAU, OLK, and OSCC are supported by different combinations of human association studies, tissue-localization findings, multi-omics correlations, experimental models, and limited interventional evidence.

3.1 Rewiring of upstream microbial signals during dysbiosis

Oral candidiasis is caused mainly by Candida albicans, yet colonization does not always progress to disease. Oral Candida carriage can be detected in healthy individuals, while colonization and infection increase in denture wearers, long-term care populations, patients receiving radiotherapy, chemotherapy, or immunosuppression, and hosts with xerostomia or low salivary flow[26,27]. At the ecological level, OC is best understood as pathogenic state switching within a permissive niche rather than simple fungal overgrowth. Reduced salivary flow, local pH shifts, denture-associated hypoxia and mechanical stress, weakened bacterial competition after antibiotic exposure, and therapy-induced mucosal fragility favor beta-glucan exposure, hyphal formation, candidalysin release, non-albicans Candida expansion in selected hosts, and mixed bacterial-fungal biofilms[27-30]. Frois-Martins et al. further showed that hypha-associated programs and candidalysin contribute to pathogenicity and niche maintenance; when IL-17-mediated constraints are weakened, Candida is more likely to adopt a highly pathogenic phenotype[29,31]. Thus, OC provides the clearest disease context in which microbial state switching is mechanistically linked to epithelial sensing, immune activation, and disease initiation.

In OLP, microbial changes do not indicate expansion of a single pathogen. Current evidence instead supports a tissue-localized dysbiosis-associated inflammatory niche that may amplify and maintain disease activity. Saliva- and plaque-based 16S rRNA sequencing studies show that patients with OLP differ from healthy controls, and that erosive and non-erosive subtypes can be partially stratified by microbial profiles. Porphyromonas, Solobacterium, Fusobacterium, Leptotrichia, Capnocytophaga, and Escherichia-Shigella have been reported as enriched in different cohorts, whereas Streptococcus and Haemophilus are often reduced[32-34]. Mucosal sampling further suggests a field-like pattern, because lesional and adjacent clinically normal mucosa may resemble each other more than healthy mucosa[33]. Importantly, tissue-level studies

show that salivary microbiota cannot be assumed to represent lesion-associated microbial communities. Paired saliva-biopsy analyses show that tissue microbiota cannot be inferred from saliva alone, and bacterial signals can penetrate deep epithelium and lamina propria[35]. Choi et al. observed bacteria within the epithelium and lamina propria, associated with CD4+ and CD8+ T-cell infiltration[36]. Li et al. reported Candida and Aspergillus enrichment and weakened or reversed bacterial-fungal correlations in OLP, especially erosive lesions[35,37]. These findings support microbial participation in tissue-localized immune amplification, although direct microbial causality remains less definitive than in OC.

RAU shows episodic microbial instability linked to disease activity rather than a stable initiating pathogen. Kim et al. reported increased interindividual variation in mucosal communities, reduced Streptococcus salivarius, and increased Acinetobacter johnsonii, with A. johnsonii inhibiting oral epithelial proliferation in vitro[38]. Stehlikova et al. compared active ulcer, peri-lesional, unaffected, healed, and healthy sites and found that dysbiosis was most pronounced on lower labial mucosa; healed mucosa did not completely return to a healthy state[39]. Yang et al. similarly observed increased Escherichia coli and Alloprevotella and reduced Streptococcus in ulcerated mucosa compared with matched normal mucosa[40]. Cross-kingdom findings, including Malassezia dominance in active ulcers, are intriguing but currently rely mainly on a single study and require independent replication[39]. Metabolome-microbiome analysis also showed reduced salivary microbial diversity, stronger microbial interactions, and abnormalities in amino acid, lipid, nucleotide, and caffeine metabolism[41]. RAU-associated dysbiosis is therefore best interpreted as a flare-associated ecological signal that may lower or prolong the mucosal inflammatory threshold, rather than as a confirmed initiating cause[38-41].

In premalignant and tumor-associated lesions, upstream cues acquire risk-associated or tumor-associated properties, but causal interpretation is more complex. In OLK, microbiome signatures are associated with dysplasia grade and are shaped by smoking and tooth loss[42]. Rothia mucilaginosa isolates from OLK can produce acetaldehyde, a metabolic feature related to DNA damage and pro-carcinogenic microenvironments[43]. In a prospective case-control study, baseline oral microbiome features were associated with subsequent head and neck squamous cell carcinoma risk, suggesting that some microbial risk signals may precede clinical tumor formation[44]. In OSCC, integrated 16S datasets show that cancer tissues and adjacent tumor tissues resemble each other more than healthy mucosa, supporting an ecological field effect[45]. Proliferative verrucous leukoplakia also resembles OSCC more closely than conventional leukoplakia in salivary microbial structure[46], and OSCC-associated dysbiosis is coupled with host transcriptomic and DNA methylation abnormalities[47]. These findings suggest risk-associated ecological selection and tumor-permissive remodeling, but must be interpreted alongside smoking, alcohol exposure, periodontal disease, dysplasia, tumor hypoxia, necrosis, and treatment effects[42-47].

Overall, upstream microbial rewiring has different stage-dependent meanings across oral mucosal diseases: pathogenic fungal switching in OC, chronic inflammatory amplification in OLP, episodic threshold crossing in RAU, and risk-associated ecological selection or tumor-associated remodeling in OLK/OSCC (Fig. 2, Table 1).

This hierarchy also affects how causal language should be used. In OC, fungal morphogenesis, epithelial sensing, and IL-17-mediated restriction can be discussed as a relatively direct pathogenic sequence. In OLP and RAU, microbial signals are better described as amplifying tissue inflammation or flare susceptibility unless supported by intervention or longitudinal validation. In OLK and OSCC, microbial signals should be interpreted within premalignant or tumor ecology, where host epithelial

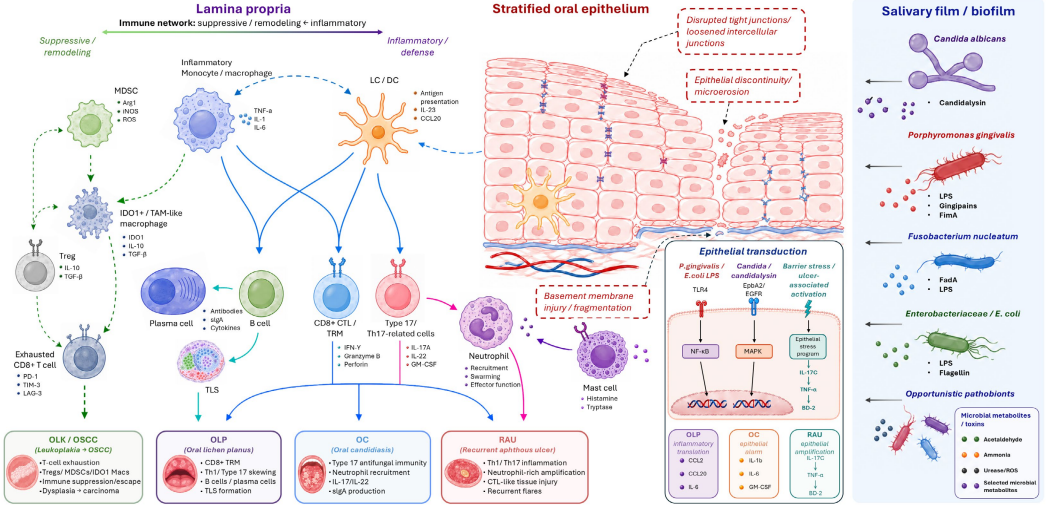

Figure 2 Oral microbial dysbiosis and remodeling of mucosal immune networks. Under dysbiotic conditions, pathobionts, fungi, microbial metabolites, and virulence factors within the salivary pellicle and biofilm can increase epithelial exposure to microbial danger signals. In mechanistically supported settings, these inputs activate epithelial signal-transduction programs; in other contexts, they are associated with loosened intercellular junctions, microerosion, epithelial discontinuity, and, in advanced lesions, basement membrane injury. Epithelial and microbial signals are linked to lamina propria immune-network remodeling involving LC/DCs, inflammatory monocytes/macrophages, type 17/Th17-related cells, neutrophils, CD8+ CTL/TRM cells, B cells/plasma cells/TLS, MDSCs, IDO1+/TAM-like macrophages, Tregs, and exhausted CD8+ T cells. These immune modules are differentially assembled across disease contexts, giving rise to fungal defense and epithelial injury in OC, cytotoxic chronic inflammation in OLP, episodic ulcerative inflammation in RAU, and immunosuppressive or tumor-permissive niches along the OLK-OSCC continuum.

Table 1 Evidence-graded synthesis of microbial signals, immune remodeling, epithelial barrier states, and stage-dependent roles of dysbiosis across oral mucosal diseases.

Disease context	Microbial signal, sample type, and evidence basis	Immune remodeling module	Barrier abnormalities/ epithelial state	Strength of evidence and interpretive caution	Stage-dependent role of dysbiosis
OC	C. albicans carriage becomes pathogenic when ecological constraints are weakened Hyphal transition, candidalysin release and beta-glucan exposure Non-albicans Candida expansion in selected hosts Mixed bacterial-fungal biofilms reshape host-facing danger cues [26-31]	Epithelial EphA2/EGFR-MAPK signaling IL-1alpha/beta, GM-CSF and IL-8 output Myeloid IL-1beta/IL-6/IL-23 signaling Langerhans-cell antigen presentation gamma delta T/natural Th17-derived early IL-17 Protective Th17/IL-17/IL-22 immunity Treg-assisted immune contraction and B-cell/IgA boundary maintenance [31,48-57,85-90]	Hyphal penetration and candidalysin-associated epithelial injury EphA2/EGFR-linked epithelial danger sensing Transcellular traversal and hidden structural bypass Barrier fragility when IL-17-mediated antifungal containment is impaired [48,52,119,120]	Strength: Strong mechanistic support from experimental, tissue-level and functional evidence for fungal state switching, epithelial sensing, type 17 immunity and antifungal containment. Caution: Susceptibility is modified by host immune status, xerostomia, denture use, antibiotics, cancer therapy, non-albicans ecology and antifungal exposure.	Commensal-to-pathogenic switching Infection initiation and immune containment
OLP	Salivary, plaque, mucosal and tissue dysbiosis Porphyromonas, Fusobacterium, Leptotrichia, Escherichia-Shigella and other taxa enriched in different cohorts Candida/Aspergillus mycobiome changes in selected studies Tissue-localized bacterial signals and altered bacterial-fungal networks [32-37]	Epithelial TLR4/NF-kappaB activation CCL2/CCL17/CCL20/IL-6 production pDC activation through cathepsin K-related pathways Macrophage/DC remodeling and inflammatory fibroblast niches CD8+ TRM accumulation near the basement membrane IFN-gamma/TNF-alpha/IL-17 networks B-cell/plasma-cell activation and TLS formation [58-68,91-98]	Tight-junction downregulation and increased epithelial permeability Basal-layer injury and chronic erosive wound-like state Basement membrane disruption linked to keratinocyte-derived MMP9/JNK signaling Barrier effects influenced by corticosteroid exposure and lesion subtype [121,127]	Strength: Moderate tissue-level and mechanistically plausible support from human association, tissue-localization, single-cell/spatial and in vitro evidence. Caution: Microbial causality remains less definitive. Interpretation is affected by cross-sectional designs, lesion subtype, medication exposure, sampling site and treatment status.	Inflammatory amplification Chronic maintenance rather than proven initiation
RAU	Active ulcer-, peri-lesional-, healed- and site-specific microbial differences Reduced S. salivarius with increased opportunistic taxa such as A. johnsonii, E. coli and Alloprevotella Salivary metabolic remodeling Malassezia-associated signal remains exploratory [38-41]	Hyper-reactive epithelial interface IL-17C-IL-17RA/RE signaling TNF-alpha and BD-2 induction Mast-cell accumulation and edema before ulceration Neutrophil aggregation IL-6/Th17-neutrophil inflammatory circuit Active-phase Th1/Th17 and CTL-like injury; B-cell/TLS programs less established [39,71-74,99]	Non-keratinized mucosal vulnerability and microfissure-associated antigen entry Acute epithelial disruption, fibrinous exudation and ulceration Incomplete return of healed mucosa to a healthy microbial/barrier state Delayed repair may sustain recurrence susceptibility [39,71-74]	Strength: Low-to-moderate support, mainly from stage-associated human microbiome studies and limited mechanistic evidence. Caution: Pre-lesional longitudinal and interventional evidence remains scarce. RAU is multifactorial and episodic, and the Malassezia finding requires independent replication.	Episodic flare amplification Incomplete post-healing restoration Not a confirmed initiating trigger
OLK	Dysplasia-associated microbiome signatures Acetaldehyde-producing taxa such as Rothia mucilaginosa Periodontal/pathobiont-related signals Field-effect ecology shaped by smoking, tooth loss, periodontal status and lesion site [42,43]	Early suppressive myeloid remodeling IDO1+ macrophages in premalignant lesions MDSC recruitment Epithelial-stromal inflammatory niche PTGES/PGE2-linked macrophage polarization during progression Treg increase with dysplasia grade Exhausted-like CD8+ T cells and PD-1/PD-L1-related programs Early TLS/B-cell relevance remains context-dependent [75-77,81,82,100-103]	Dysplastic epithelial field with epithelial-stromal remodeling Early basement-membrane vulnerability and chronic wound-like tissue instability Candida/opportunistic niche susceptibility supported by altered fibroblast-epithelial signaling Barrier interpretation confounded by dysplasia and field cancerization [42,76,128]	Strength: Context-dependent and partly exploratory, with human tissue, single-cell and experimental evidence suggesting immune remodeling before invasion. Caution: Causal direction is difficult to assign because smoking, alcohol use, periodontal disease, dysplasia grade, lesion site and epithelial barrier disruption may all shape the microbiome.	Risk-associated ecological selection Premalignant immune remodeling

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(Continued)

Disease context	Microbial signal, sample type, and evidence basis	Immune remodeling module	Barrier abnormalities/ epithelial state	Strength of evidence and interpretive caution	Stage-dependent role of dysbiosis
OSCC	Tumor and adjacent-tissue microbiome field Association with Fusobacterium, Treponema, Peptostreptococcus and related taxa Microbial metabolites such as kynurenine Coupling with host transcriptomic, methylation, adhesion, migration and proliferation programs [44-47,75]	TAM/SPP1+ macrophage programs PTGES-migrasome-PGE2 cascade MDSCs, pDCs and tumor-associated neutrophils NK-TAM communication modules in immunosuppressive and remodeling fields CD8+ T-cell exhaustion Treg and Breg-mediated suppression PD-1/PD-L1 axis TLSs and TCL1A-high B cells often associated with better prognosis [77-83,100-107]	Tumor-associated barrier collapse with epithelial-stromal boundary loss Partial EMT, weakened adhesion and increased epithelial plasticity Invasion-associated basement membrane and ECM remodeling Hypoxia, necrosis and treatment exposure promote opportunistic colonization [47,118,129,130]	Strength: Tumor-associated and mechanistically suggestive, supported by multi-omics, tissue studies, animal models and immunotherapy-related experimental data. Caution: Causality is complex because tumor hypoxia, necrosis, tissue destruction, treatment exposure, tumor stage, periodontal status and sampling site may shape the microbiome.	Tumor-permissive ecology Immune suppression Possible secondary colonization

Note: "Strong mechanistic support" refers to convergent experimental, tissue-level and functional evidence. "Moderate" or "low-to-moderate" support indicates that evidence is mainly associative, stage-associated, tissue-localized or mechanistically suggestive, but lacks robust longitudinal or interventional validation.

transformation, stromal remodeling, and secondary colonization may all shape the observed microbiome.

3.2 Microbial signals and innate immune remodeling

Perturbed fungal and bacterial signals, mixed biofilms, metabolites, and aberrant tissue localization can engage epithelial, myeloid, stromal, and innate-like immune cells. The outcome of this sensing is highly context dependent. In different disease settings, dysbiotic cues may support defensive clearance, chronic inflammatory maintenance, hyper-reactive ulceration, or immunosuppressive and pro-carcinogenic remodeling[1,3,4,25]. Thus, innate immune remodeling should be interpreted not simply by which pathways are activated, but by whether the response remains protective, becomes unresolved, or is reorganized within a premalignant or tumor-associated tissue environment.

In OC, innate immune remodeling is driven primarily by beta-glucan exposure, hyphal formation, and candidalysin release. Swidergall et al. showed that oral epithelial cells recognize fungal beta-glucan through EphA2, which cooperates with EGFR; Als3 promotes endocytosis, whereas candidalysin accumulates locally and sustains EphA2/EGFR activation[48]. Ho et al. further demonstrated that candidalysin activates a MAPK danger-response program through EGFR[49]. This epithelial response has a defined transcriptional architecture: candidalysin induces IL-1alpha release and upregulates GM-CSF and IL-8 through IkappaBalpha/IkappaBzeta-related pathways[50], while EGR1 determines cytokine-output patterning after C. albicans stimulation[51]. At the tissue level, oral epithelial cells orchestrate local innate type 17 responses to Candida through candidalysin[52]. Myeloid and antigen-presenting cells amplify this alarm by producing IL-1beta, IL-6, and IL-23, and oral Langerhans cells regulate intraepithelial Tc17 abundance through MHC-II antigen presentation[28,53,54]. Early IL-17 is rapidly supplied by tongue-resident gamma delta T cells and natural Th17 cells[55], and neutrophil swarming limits local fungal infection[56]. An emerging oral megakaryocyte-platelet axis also contributes to antifungal defense: IL-17 deficiency impairs oral megakaryocyte expansion, while candidalysin can directly activate megakaryocytes to release antifungal platelets[57]. Together, these findings define OC as the strongest example of protective innate remodeling, in which fungal state switching is coupled to epithelial alarm, type 17 activation, and antifungal containment.

In OLP, dysbiosis is better framed as a chronic inflammatory amplifier than as an acute infectious trigger. Lesion-enriched bacterial components from P. gingivalis, E. coli, and other tissue-localized organisms may be detected by epithelial and myeloid cells and translated into chemokines, inflammatory cytokines, and antigen-presentation-related signals. P. gingivalis-related studies show TLR4 upregulation in OLP epithelium and excessive CCL2 expression through TLR4/NF-kappaB signaling, supporting monocyte and macrophage recruitment[58]. In vitro work using E. coli or its LPS shows activation of TLR4/NF-kappaB signaling in keratinocytes and OLP-derived T cells, with increased IL-6, IL-17, CCL17, CCL20, T-cell migration, and keratinocyte apoptosis[59,60]. Epithelial cathepsin K connects pDCs with the Th17 axis by enhancing TLR9+CD123+ pDC activation and inducing IL-6, IL-23, and TGF-beta[61]. Single-cell studies identify pDCs, conventional dendritic cells, macrophage subsets, inflammatory fibroblast states, MAIT-cell activation, and mast-cell-associated markers in OLP lesions[62-68]. These findings support a tissue-localized innate inflammatory circuit involving epithelial sensing, myeloid recruitment, stromal activation, and innate-like lymphocyte responses. However, most evidence remains associative or mechanistically supportive rather than directly causal.

RAU is best interpreted as a flare-associated, hyper-reactive innate interface rather than a disease with a stable microbial initiator. Bacterial and fungal remodeling during active disease, metabolic fluctuations, and microfissures in non-keratinized mucosa may jointly lower the inflammatory threshold across onset, persistence, and repair[38-41,69,70]. RAU lesions highly express IL-17C and IL-17RA/IL-17RE, and in vitro data suggest that IL-17C can induce TNF-alpha transcription[71]. Beta-defensin 2 is markedly increased in acute RAU epithelium, and TNF-alpha and IL-17C synergistically induce BD-2 in epithelial cells[72]. Classical pathology and recent mechanistic work further link subepithelial mononuclear infiltration, mast-cell accumulation, IL-6-driven neutrophil infiltration, and the IL-6/Th17-neutrophil axis to local tissue injury[73,74]. Thus, RAU innate immunity is better described as flare-associated amplification at a vulnerable barrier interface, with limited evidence for microbial initiation.

In OLK and OSCC-associated lesions, innate immune remodeling resembles a chronic pro-carcinogenic or tumor-permissive inflammatory field. Acetaldehyde-producing microbes, periodontal anaerobes, tumor-enriched bacteria, and kynurenine may create pressure for DNA damage, oxidative stress, inflammation, and immunosuppressive metabolism[42-47,75]. Single-cell studies show that IDO1+ macrophages are enriched in premalignant OLK and coexist with exhausted-like T cells and Tregs, suggesting that immunosuppressive niches can begin before invasive carcinoma[76]. SPP1+ macrophages are associated with tumor progression, stromal remodeling, and immunosuppression[77-80]. In mechanistic studies, PTGES-enriched migrasomes released by OLK and OSCC epithelial cells can be taken up by macrophages, amplify the PGE2 cascade, induce an SPP1+ phenotype, and promote premalignant progression-related phenotypes[77]. MDSCs, pDCs, neutrophils, and NK cell-TAM communication modules further contribute to this field[78-83]. Overall, innate remodeling in OLK/OSCC is mechanistically suggestive and biologically plausible, but its interpretation remains constrained by premalignant and tumor ecology, tissue destruction, treatment exposure, and secondary colonization.

Taken together, innate immune remodeling should be interpreted according to disease timing, tissue localization, and evidence certainty. The best-supported sequence is antifungal containment in OC; OLP and RAU are better described as inflammatory amplification or flare-associated threshold crossing; and OLK/OSCC involve tumor-permissive or immunosuppressive myeloid remodeling, with interpretation constrained by premalignant or tumor ecology.

3.3 Microbial signals and adaptive immune differentiation

Adaptive immunity reflects the persistence, spatial organization, and functional interpretation of microbial signals over time. The direction of T-cell, B-cell, and lymphoid-like responses depends not only on microbial antigens, virulence programs, metabolites, and exposure patterns, but also on epithelial, stromal, and myeloid shaping of antigen presentation, co-stimulation, cytokine signaling, and metabolic context.

In OC, adaptive immunity remains centered on Th17/IL-17 responses. When C. albicans shifts toward hyphal growth and high

candidalysin expression, epithelial cells and antigen-presenting cells establish a type 17-polarizing environment. IL-17 receptor signaling in oral epithelium and Langerhans-cell regulation of intraepithelial Tc17 abundance represent site-specific mucosal defense against fungal danger inputs[52,54,55,84-87]. During early infection, IL-17 is mainly produced by tongue-resident gamma delta T cells and natural Th17 cells[55]. Classical Th17 cells subsequently mediate long-term protection. Hernandez-Santos et al. showed that Th17 cells confer long-term adaptive immunity to oral Candida infection, and Aggor et al. demonstrated that IL-17 and IL-22 have non-redundant cooperative functions in inducing keratinocyte effector molecules and improving antifungal capacity[86,87]. Frois-Martins et al. further showed that IL-17 maintains colonizing Candida in a low-pathogenic state; when IL-17 is absent, Candida shows increased hyphal growth, hypha-associated gene expression, barrier damage, and worsened inflammation, partly through reduced calprotectin and impaired zinc sequestration[31]. Tregs also have stage-dependent functions, promoting IL-17 production during infection and later supporting immune contraction through TGF-beta1-related mechanisms[88,89]. B cells and IgA responses contribute to mucosal boundary control, because persistent Candida colonization upregulates IgA-related pathways and increases B cells, plasmablasts, and plasma cells at colonized sites[90]. Thus, these findings define OC as the clearest adaptive immune model in which type 17 immunity, regulatory contraction, and IgA-mediated boundary control cooperate to contain fungal pathogenicity.

In OLP, adaptive immunity reflects tissue-level chronicity, cytotoxic residency, and lymphoid organization. Classical histopathology shows CD8+ T cells closer to the basal layer and CD4+ T cells in deeper lamina propria. Single-cell and spatial transcriptomic studies show that CD8+ tissue-resident memory T cells expand in erosive OLP and localize near the basement membrane, accompanied by IFN-gamma, TNF-alpha, and IL-17 networks[62,91]. cDC2A cells can serve as an IL-15 source, remain spatially adjacent to CXCL13+CD8+ T cells, and promote cytotoxic enhancement through TNFRSF9-related programs[92]. Some T-cell subsets acquire exhaustion-like features, suggesting persistent but ineffective local inflammation[93]. B cells and plasma cells are increasingly recognized in OLP: CD20+ B-cell and CD138+ plasma-cell infiltration can be observed in diagnostic OLP lesions[94], and single-cell profiling identifies BCR clonal expansion[62]. TLS studies show that CCL19+ fibroblasts are associated with TLS formation, and TLSs display humoral activation with CD20+ B cells, CD38+ plasma cells, IRF4, and TNFRSF17 upregulation; this activation is associated with erosive disease, recurrence, and poorer outcomes[95,96]. B-cell-enriched lesions may also show poorer corticosteroid responses[97], and IgA-seq suggests reduced IgA targeting of Leptotrichia, Fusobacterium, and Streptococcus despite limited change in total salivary IgA[98]. These data support a model in which adaptive immunity in OLP is organized around chronic CD8+ TRM, Th17-related inflammation, B-cell/plasma-cell activation, and TLS-like organization. However, microbial signals are best interpreted as potential amplifiers or organizers of this chronic immune architecture rather than as proven primary causes.

RAU provides a temporally restricted adaptive pattern that intensifies during active ulceration and partially contracts during repair. Classical studies link RAU to T-cell-mediated injury, and Streptococcus-like antigens or heat-shock-protein homology suggest possible cross-reactive T-cell activation at mucosal breaks[39,73]. Cytokine evidence shows elevated salivary IL-2, IL-5, IL-6, IL-12, and TNF-alpha, elevated serum IL-6, TNF-alpha, and IFN-gamma, and reduced IL-10, indicating pro-inflammatory T-cell skewing with insufficient regulation[99]. The IL-6-Th17-neutrophil axis may further connect adaptive and innate inflammation during ulceration[74]. Together, these findings support active-phase Th1/Th17-skewed and cytotoxic amplification in RAU. In contrast to OLP, there is less evidence for stable tissue-resident, TLS-like, or durable B-cell organization, and the initiating hierarchy among host predisposition, epithelial microdamage, microbial change, and immune activation remains unresolved.

In premalignant and tumor-associated lesions, adaptive immunity is shaped by risk-associated microbial communities, microbial metabolites, epithelial dysplasia, stromal remodeling, and tumor ecology. Chronic restraint stress has been reported to drive dysbiotic oral microbiota toward kynurenine production and CD8+ T-cell exhaustion in experimental settings[75]. Dynamic studies show that inhibitory receptors on CD4+ and CD8+ T cells progressively increase from normal epithelium to dysplasia and cancer[100]. Exhausted-like CD8+ T cells and IDO1+ macrophages are already spatially adjacent in premalignant OLK, while Treg infiltration increases with dysplasia grade; CD8+ effector T cells and PD-1/PD-L1 expression also increase as disease progresses, indicating coexistence of effector and suppressive programs[76,100,101]. In the 4NQO model, anti-PD-1 therapy reduces oral lesions and prevents progression to invasive carcinoma, supporting immune dysfunction as an actionable premalignant event[102]. B-cell effects remain context-dependent: CD19+IL-10+ regulatory B cells can induce FoxP3+ Tregs[103], whereas TLSs and TCL1A-high B cells in OSCC are generally associated with better prognosis[104-107].

Overall, adaptive immune remodeling ranges from protective type 17 antifungal immunity in OC, to chronic resident cytotoxicity and humoral organization in OLP, episodic Th1/Th17-cytotoxic injury in RAU, and mixed exhaustion-suppression-TLS programs in OLK/OSCC. These patterns should not be interpreted as equivalent causal outputs of dysbiosis. They reflect different evidence levels, tissue contexts, and stage-dependent roles, as summarized in Table 1.

4 Oral microbial dysbiosis and the epithelial barrier

4.1 The surface chemical barrier

The oral mucosa does not encounter microbes as a bare epithelial surface. Instead, microbial access is first regulated by a surface chemical barrier composed of saliva, acquired pellicle, mucins, secretory antibodies, and antimicrobial molecules. Membrane-bound mucin 1 (MUC1) participates in surface protection and signal regulation. Secreted mucins MUC5B and MUC7 provide lubrication, anti-adhesive capacity, and decoy-binding functions. Secretory IgA (sIgA), lysozyme, lactoferrin, peroxidases, secretory leukocyte protease inhibitor (SLPI), histatins, and related molecules further help determine which microbes can transiently remain and which are excluded or constrained in low-virulence states[1,2,25,108,109]. Thus, the surface chemical barrier functions as a pre-epithelial filter that controls microbial proximity, adhesion, and host exposure.

During dysbiosis, this surface filtering system may weaken before overt cellular barrier breakdown. Streptococcus oralis can bind salivary mucins and cleave MUC5B-associated structures, suggesting that mucins may become ecological resources under

dysbiotic conditions[110]. P. gingivalis proteases reduce LL-37 activity in the salivary environment, while its OmpA-like proteins help the bacterium tolerate LL-37 killing[111,112]. Hyphal invasion by C. albicans can suppress beta-defensin expression and reduce antifungal tone at the epithelial surface[113]. Low salivary flow or glandular injury can further weaken clearance and humoral supply[25,114]. These examples indicate that surface barrier dysfunction is not simply a late consequence of epithelial damage. It can represent an early ecological failure in which microbial adhesion, proteolytic activity, virulence expression, and weakened salivary defense increases microbial access to epithelial and immune compartments.

4.2 Cell junctions and paracellular permeability

When the surface chemical barrier is weakened, the capacity of the epithelial interface to maintain controlled permeability depends mainly on the cell junction system. Tight junctions, composed of claudin family proteins, occludin, and ZO proteins, mainly restrict paracellular passage of solutes and microbial products. Adherens junctions, centered on the E-cadherin/β-catenin complex, maintain stable cell-cell adhesion, epithelial polarity, and stratified architecture. Desmosomes provide resistance to friction and shear stress through desmosomal cadherins and intermediate filament networks. More importantly, these three junctional systems are not isolated static components. They are dynamic systems continuously coupled to the actin cytoskeleton, cellular tension, and epithelial transcriptional programs. Barrier instability therefore does not simply mean reduced expression of a single protein. It usually reflects a coordinated process involving increased paracellular permeability, loosened cell polarity, reduced mechanical stability, and sustained inflammatory signaling[1,115].

Dysbiosis-associated barrier changes often progress from reversible epithelial stress to sustained junctional instability. In experimental models, persistent P. gingivalis exposure downregulates occludin, claudin-1, and claudin-4 and lowers transepithelial electrical resistance, consistent with a shift toward a leaky state[116,117]. P. gingivalis also suppresses the epithelial transcription factor GRHL2, supporting the possibility that microbial stimulation can weaken transcriptional maintenance of desmosomes and junction-related molecules[118]. These findings support a mechanism in which selected bacterial stimuli impair epithelial barrier integrity not only by altering individual junctional proteins, but also by disrupting the regulatory programs that maintain junctional architecture.

Fungal invasion provides a distinct mechanism. C. albicans does not always cross the epithelium through direct lysis; virulence factors activate the EphA2-EGFR axis, and candidalysin targets sulfated glycosaminoglycans, which may indirectly destabilize junctional and cytoskeletal organization[48,119]. Hyphae can also traverse epithelial cells through transcellular tunnel-like structures without immediate membrane rupture[120]. Thus, Candida-associated barrier disturbance may begin as structural bypass and functional instability before overt epithelial permeability failure becomes apparent.

Junctional abnormalities also occur in chronic inflammatory lesions. In OLP, CLDN1, CLDN4, OCLN, and TJP1 downregulation is associated with disease severity[121]. Conversely, S. salivarius and its cell-free supernatant can inhibit P. melaninogenica-induced barrier disruption and partially restore ZO-1 and tight junction-related molecules[122]. These findings suggest that both pathogenic and commensal signals can influence junctional homeostasis. However, disease-specific causality remains incompletely established, and future studies should determine whether junctional changes precede inflammation, result from chronic immune injury, or represent reversible barrier states shaped by microbial exposure.

4.3 Chronic wound-like epithelial state

Physiological oral mucosa frequently experiences minor injury, but homeostasis depends on rapid re-epithelialization, early inflammatory resolution, and limited scarring[123,124]. The pathological issue is therefore not epithelial injury itself, but failure to terminate the wound-repair program. When microbial stimulation, inflammatory mediators, and mechanical stress persist, epithelial cells may remain in a chronic wound-like state characterized by delayed migration, impaired proliferation, prolonged cytokine exposure, and incomplete barrier restoration.

Available evidence suggests that microbial load and composition can influence this repair trajectory. Bacterial exposure can inhibit oral epithelial cell migration and proliferation and delay wound closure[125], while higher bacterial load and patient-specific microbial composition are linked to impaired healing in chemotherapy-associated mucositis models[126]. These findings suggest that dysbiosis may interfere with epithelial repair not only by damaging the barrier directly, but also by preventing timely exit from a wound-response program.

Recurrent ulceration in RAU and persistent erosion in OLP may therefore reflect contexts in which microbial and inflammatory signals are associated with delayed exit from a wound-like epithelial state. In RAU, this may contribute to delayed ulcer resolution or incomplete restoration of a healthy mucosal state after healing. In OLP, persistent epithelial injury and immune activation may maintain erosive lesions in a non-resolving repair state. However, whether dysbiosis initiates these wound-like programs or secondarily prolongs them remains disease- and stage-dependent and requires longitudinal and interventional validation.

4.4 Basement membrane disruption and premalignant-to-malignant transition

Persistent epithelial injury can extend barrier abnormalities to the epithelial-stromal boundary. The basement membrane maintains polarity, attachment, and stratified architecture; sustained degradation therefore marks a deeper stage of barrier failure, shifting lesions from superficial permeability defects to structural instability. In OLP, MMP9 is upregulated in basal-layer keratinocytes and is associated with JNK activation, suggesting that keratinocytes may participate in basement membrane degradation rather than acting only as passive targets of inflammatory injury[127]. In leukoplakia-related settings, reduced CX3CL1 secretion by OLK-associated fibroblasts increases adhesion, invasion, and survival support for C. albicans, suggesting that epithelial-stromal remodeling may create a niche more permissive to opportunistic fungal persistence and signals[128].

Partial EMT-like changes represent one route through which epithelial-state instability may acquire invasive features. Among oral bacteria, P. gingivalis has relatively strong experimental support in this context: long-term infection impairs GRHL2, weakens junctional protein maintenance, decreases E-cadherin, increases vimentin, and enhances epithelial migratory capacity[118,129]. Coinfection and signal-integration studies further suggest that

periodontal pathogens can enhance invasive phenotypes through integrin/FAK, TLR/MyD88, and downstream inflammatory pathways[130]. These findings support a mechanistic link between selected microbial stimuli and EMT-like barrier instability, but should not be generalized to all dysbiotic communities or interpreted as sufficient evidence that dysbiosis directly drives malignant transformation.

In OSCC, tumor-enriched bacteria are associated with host adhesion-migration programs rather than proving direct causality. Integrated tissue analysis linked F. nucleatum, T. medium, P. stomatis, and related bacteria with host genes involved in adhesion, migration, and proliferation, and suggested that F. nucleatum may upregulate SNAI2 through E-cadherin/beta-catenin, TNF-alpha/NF-kappaB, and extracellular matrix remodeling[47]. Similarities among microbial communities in conventional leukoplakia, proliferative verrucous leukoplakia, and OSCC further support coordinated ecological and structural remodeling, but these observations should be interpreted within premalignant and tumor ecology[46]. Thus, along the OLK-OSCC continuum, microbial signals are best viewed as components of a remodeled epithelial-stromal ecosystem that may reinforce tissue instability, immune suppression, or invasive programs, rather than as isolated causal agents.

Immune remodeling and barrier disruption are interconnected. In mechanistically supported contexts, type 17 responses support antifungal barrier defense in OC by inducing epithelial antimicrobial programs and neutrophil recruitment. In chronic inflammatory lesions, persistent IL-17-, TNF-alpha-, IL-6-, chemokine-, and neutrophil-associated signals may instead amplify epithelial stress and junctional instability. In OLP, keratinocyte-derived MMP9 induced through JNK activation provides a direct example linking immune-inflammatory signaling to basement membrane degradation. Thus, immune-mediated barrier injury should be interpreted according to disease context, duration, tissue localization, and evidence level, rather than as a uniform consequence of dysbiosis[52,55,71,74,121,127,131,132].

5 The role of the oral microbiota during disease progression

During disease progression, the oral microbiota does not have a single fixed role. The meaning of dysbiosis depends on when it appears, where it is located, which epithelial, stromal, or immune compartments it engages, and whether microbial modulation can alter disease activity. Therefore, dysbiosis should be evaluated across four dimensions: temporal sequence, tissue localization, mechanistic evidence, and reversibility after intervention (Fig. 3). This evidence-graded framework helps distinguish microbial initiation, inflammatory amplification, chronic maintenance, risk-

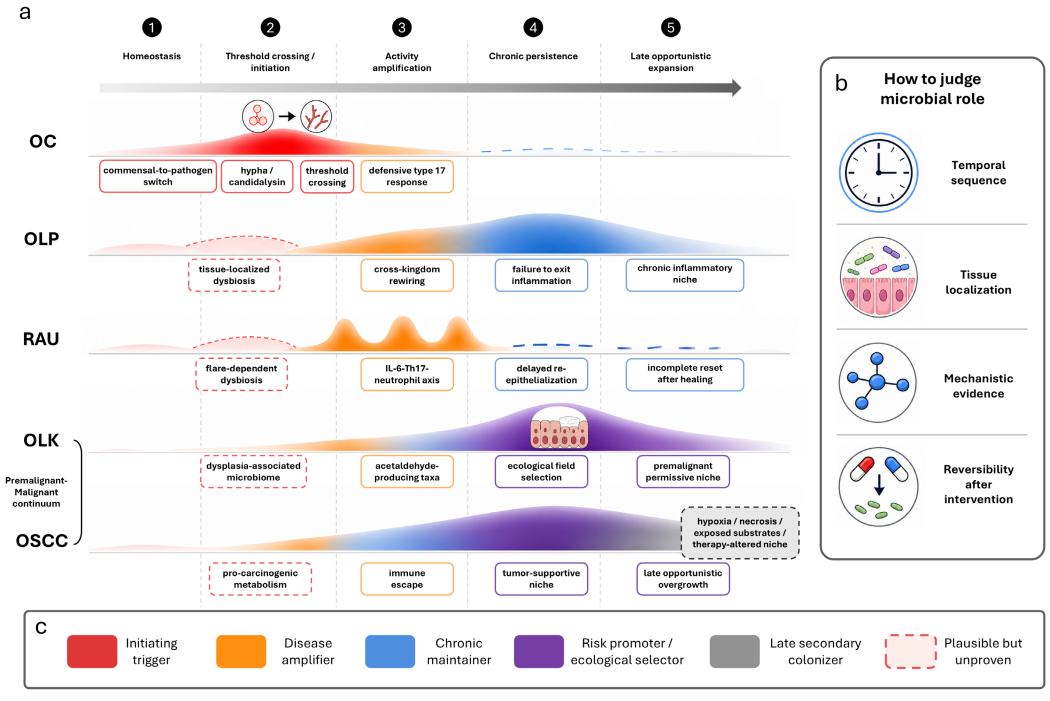

Figure 3 Stage-dependent roles of oral microbiota in oral mucosal disease progression. (a) A unified disease timeline illustrates how microbial roles vary across homeostasis, threshold crossing, disease-activity amplification, chronic persistence, and late-stage opportunistic expansion. In OC, the best-supported initiating event is the transition of Candida from commensal colonization to pathogenic invasion, accompanied by hyphal growth, candidalysin activity, and induction of type 17 antifungal immunity. In OLP, tissue-localized bacterial and fungal dysbiosis more plausibly amplifies immune activity and helps sustain a chronic inflammatory niche. In RAU, microbial effects appear flare-dependent and are consistent with episodic inflammatory amplification, neutrophil recruitment, delayed re-epithelialization, and incomplete post-ulcer reset. In OLK, dysbiosis is associated with risk-related ecological selection, including dysplasia-linked microbial shifts, acetaldehyde-producing taxa, and formation of a premalignant permissive niche. In OSCC, microbial signals may further support immune escape, stromal remodeling, and tumor-permissive ecology, with secondary opportunistic expansion emerging under hypoxic, necrotic, exposed, or therapy-altered conditions. (b) Microbial roles should be interpreted using four complementary criteria: temporal sequence, tissue localization, mechanistic evidence, and reversibility after intervention. Integrating these criteria helps distinguish microbial initiation, disease-activity amplification, chronic maintenance, risk-associated ecological selection, and late-stage secondary colonization. (c) Colors indicate the proposed microbial role categories. Dashed boxes denote biologically plausible but not yet sufficiently proven links.

associated ecological selection, and secondary colonization, while avoiding the assumption that dysbiosis has equivalent causal significance across OC, OLP, RAU, OLK, and OSCC.

5.1 Initiation and state switching

Among the disease contexts reviewed here, OC most closely fits a microbial initiation and state-switching model. *Candida albicans* is a resident member of the oral microbiota; therefore, the key issue is not whether it is present, but when the host microenvironment permits it to enter hyphal growth, increased virulence, and closer tissue contact. Reduced salivary flow, denture-associated niches, impaired bacterial competition, epithelial fragility, or weakened IL-17-mediated restraint can promote hyphal growth, beta-glucan exposure, candidalysin release, and closer epithelial contact[29,31]. Therefore, in OC, microbial dysbiosis is not merely associated with infection; it directly participates in crossing the threshold from commensalism to pathogenicity.

This level of causal support has not yet been established for most non-OC lesions. In OLP, microbial changes are better interpreted as tissue-localized inflammatory amplifiers unless longitudinal or interventional evidence shows that they precede lesion development. In RAU, dysbiosis appears more episodic and activity-associated, and may lower the threshold for ulcerative flares rather than serve as a stable initiating cause[41,133-136]. Thus, microbial initiation should be assigned cautiously and reserved for contexts in which temporal sequence, tissue localization, mechanistic plausibility, and reversibility evidence converge.

5.2 Amplification and chronic maintenance

For many non-OC lesions, current evidence more strongly supports amplification or maintenance roles for the oral microbiota than a primary initiating role. In RAU, microbial and metabolic disturbances appear most closely linked to active disease, where they may interact with epithelial microinjury, IL-6–Th17–neutrophil inflammation, and delayed re-epithelialization to intensify or prolong ulcerative episodes[41,74,136]. This pattern is best interpreted as activity-phase amplification rather than stable microbial initiation.

OLP more closely fits a chronic-maintenance model. Lesion-associated dysbiosis, altered microbial interactions, tissue-localized bacterial or fungal signals, and functional microbial outputs may reinforce epithelial stress, cytotoxic inflammation, B-cell/plasma-cell activation, and non-resolving erosive disease[133-135]. Treatment-related ecological shifts, including subsequent Candida overgrowth in some settings, further suggest that the OLP microbial niche is dynamic and influenced by local immune status and therapy exposure. Thus, in OLP, dysbiosis is best viewed as part of a self-reinforcing inflammatory barrier niche, although whether it precedes disease onset remains unresolved.

5.3 Risk-associated ecological selection and progression

In premalignant-to-malignant settings, microbial findings should be interpreted as risk-associated ecological signals unless stronger causal or interventional evidence is available. In OLK, microbiome features are associated with dysplasia grade and local immunosuppressive programs, suggesting that microbial shifts may mark or reinforce an ecological field permissive for high-risk epithelial states[42,76]. Microbial metabolites such as acetaldehyde, together with periodontal anaerobes, barrier disruption, and altered epithelial–stromal signaling, may further contribute to a pro-inflammatory or pro-carcinogenic niche[43].

In OSCC, prospective and multi-omic studies link oral microbiome features with later head and neck squamous cell carcinoma risk and cancer-related host transcriptional or epigenetic programs[44,46,47]. However, these associations remain embedded within tumor ecology, where epithelial transformation, stromal remodeling, hypoxia, necrosis, immune suppression, treatment exposure, and secondary colonization can all shape microbial composition and function. Thus, along the OLK-OSCC continuum, dysbiosis is best viewed as a component of risk-associated ecological selection and tumor-permissive remodeling, rather than as a stand-alone driver of malignant progression.

5.4 Secondary colonization and stage transition

Late-stage lesions often acquire opportunistic microbes as barrier opening, necrosis, hypoxia, nutrient exposure, and treatment effects reshape the niche. In advanced OSCC or long-standing chronic lesions, expanding taxa may therefore reflect adaptation to a remodeled tissue environment rather than early driver mechanisms. This distinction is important because the same microbial signature may have different meanings across stages: it may mark early ecological risk in premalignant tissue, reinforce inflammation or immune suppression during progression, or simply expand after tissue destruction has created permissive niches. Stage-specific interpretation remains essential.

Overall, OC has the strongest causal and interventional support, whereas evidence in OLP, RAU, and OLK remains dominated by cross-sectional association, tissue-localization findings, multi-omics correlations, in vitro or animal-model data, and limited longitudinal or reversibility evidence[29,31,48-57,137-149]. For OSCC, microbial signals should be interpreted within tumor ecology, where epithelial transformation, stromal remodeling, hypoxia, necrosis, treatment exposure, and secondary colonization may shape the observed microbiome[44-47,75-83].

6 Microbiota-informed strategies: translational maturity and clinical boundaries

Microbiota-informed approaches for OMDs can operate at several levels, including reduction of pathogen burden, inhibition of adhesion or biofilm formation, supplementation of commensal organisms with ecological gatekeeping functions, and use of postbiotics or bacteria-derived metabolites to regulate inflammation and barrier function. However, these approaches should be interpreted according to disease-specific translational maturity rather than grouped as a single therapeutic category. At present, clinical evidence is most developed for Candida-related conditions, particularly oral candidiasis and denture-associated stomatitis, where probiotics or commensal-based approaches have mainly been evaluated as adjuncts to conventional antifungal therapy or denture hygiene. In OLP and RAU, available data suggest possible symptom-modifying or adjunctive effects, but the results remain heterogeneous and do not yet support probiotics as stand-alone disease-modifying treatments. For OLK and OSCC, microbiota-targeted strategies remain largely exploratory. Current evidence is more relevant to risk stratification, ecological monitoring, management of opportunistic colonization, and supportive care during cancer therapy than to prevention of malignant transformation, antitumor efficacy, or survival improvement[1,5] (Table 2).

Table 2 Translational Maturity and Evidence Positioning of Microbiota-Informed Strategies in Oral Mucosal Diseases.

Disease/Clinical Setting	Microbiota-Informed Approach and Representative Evidence	Major Endpoints and Results	Translational Maturity and Caution
Overall evidence for oral candidiasis (OC)	Clinically tested adjunctive or preventive probiotic approach; the systematic review included 13 randomized controlled trials covering diagnosed OC, related high-risk populations, and different formulations.	Major endpoints included Candida detection/colonization risk and OC-related clinical outcomes. Overall, probiotics were associated with lower oral Candida detection or colonization risk, indicating that adjunctive treatment evidence has already emerged [137].	Relatively higher translational maturity among OMDs, but still best interpreted as adjunctive rather than replacement therapy. Optimal strains, formulations, treatment duration, recurrence prevention, and ecological recovery remain to be defined.
Representative clinical trials in Candida-associated stomatitis/OC	Topical probiotics combined with conventional antifungal therapy; representative regimens included Bifidobacterium longum, Lactobacillus bulgaricus, Streptococcus thermophilus, or Streptococcus salivarius K12 combined with nystatin.	After 4 weeks, Candida detection in the combination group decreased from 100% to 8.21%, compared with 34.6% in the control group. S. salivarius K12 plus nystatin also showed a higher mycological cure rate and shorter treatment duration, supporting an "antifungal therapy + ecological restoration" model rather than a simple microbicidal strategy [138,139].	These findings support a clinically plausible combination model with high translational potential in selected Candida-related settings, but multicenter validation, strain-specific protocols, and recurrence endpoints are still needed.
Denture wearers/risk of denture-associated stomatitis	Preventive multispecies probiotic intervention, often considered together with control of mixed Candida-bacterial biofilms on denture surfaces.	A randomized trial in new complete-denture wearers suggested that multispecies Lactobacillus and Bifidobacterium preparations may reduce the risk of new denture-associated oral candidiasis, indicating that high-risk ecological niches can be targeted preventively [140].	This is best positioned as a preventive adjunct for high-risk denture wearers and should be evaluated together with denture hygiene, surface treatment, and standardized oral-care measures.
Post-antifungal phase in OC	Post-treatment ecological reconstruction and follow-up, rather than focusing only on fungal burden reduction.	Longitudinal profiling showed that although antifungal therapy improved clinical infection, the post-treatment oral microbiota did not necessarily return fully to a healthy state, indicating that "clinical cure" and "ecological recovery" are not equivalent [141].	The evidence is currently mainly observational. Its translational implication is endpoint design: OC trials should evaluate ecological recovery and recurrence risk rather than fungal reduction alone.
Oral lichen planus (OLP): stand-alone microbiota-targeted intervention	Broad-spectrum multispecies probiotics used alone; the CABRIO trial evaluated VSL#3 in symptomatic OLP. Additional exploratory work focused on Streptococcus salivarius-related intervention.	VSL#3 was safe and well tolerated but did not significantly improve pain, clinical activity, quality of life, or oral microbiota composition. S. salivarius-related intervention suggested possible effects on local ecology and symptoms, although the evidence remains preliminary [142,143].	Low and inconsistent clinical maturity. These findings indicate that "safe" does not equal "effective" in OLP, and stand-alone probiotics should not be presented as a strong independent or disease-modifying treatment modality.
OLP combination-treatment setting	Probiotics combined with topical immune therapy; this included Lactobacillus reuteri-related strategies and multispecies probiotics combined with 0.05% clobetasol propionate.	L. reuteri-related studies failed to stably reshape the oral microbiome; however, multispecies probiotics plus clobetasol led to greater reductions in pain scores and Thongprasom scores at 2 and 4 weeks, while Candida burden remained similar between groups. This suggests that benefit may derive more from inflammatory/barrier modulation than from direct antifungal effects [144–146].	Exploratory adjunctive combination model. This setting is better positioned as "microbiota modulation + topical immune therapy" and requires larger randomized trials before clinical generalization.
Overall evidence for recurrent aphthous ulcer (RAU)	Probiotics alone or combined with conventional therapy; the meta-analysis included 7 randomized controlled studies.	Overall, probiotics used alone showed a relatively clear signal for pain relief, but results for ulcer severity and recurrence control were inconsistent. When combined with topical corticosteroids, anesthetics, or antimicrobial gels, the improvement was more evident [147].	Evidence supports possible short-term symptomatic benefit, but heterogeneity is high. Current data do not establish durable recurrence prevention, and acute symptom relief should be separated from long-term disease modification.
Representative RAU clinical trials	Probiotic lozenges, Lactobacillus reuteri-derived topical nano-formulations, and topical Bacillus clausii as adjunctive therapy.	Studies in adults and children reported reduced pain, smaller ulcer area, and, in some cases, lower recurrence frequency. The topical nano-formulation outperformed a standard analgesic mouthwash within 7 days, while Bacillus clausii mainly improved short-term pain, erythema, and local symptoms [148–150].	Current value mainly lies in acute-phase adjunctive therapy and symptom relief. Longer follow-up, recurrence endpoints, and patient stratification are required before broader clinical recommendations.

(To be continued on the next page)

(Continued)

Disease/Clinical Setting	Microbiota-Informed Approach and Representative Evidence	Major Endpoints and Results	Translational Maturity and Caution
Cancer therapy-associated oral mucositis	Supportive-care probiotic strategies for cancer therapy-associated oral mucositis, including evidence from systematic review/meta-analysis and randomized trials of Lactobacillus brevis CD2 lozenges.	Meta-analysis showed that probiotics reduced the risk of severe oral mucositis without a clear signal for major safety problems. An early single-center trial suggested that L. brevis CD2 reduced grade III–IV mucositis and improved treatment completion, but a later multicenter study failed to reproduce this benefit [151–153].	Relatively stronger supportive-care direction in oral cancer-related settings, but not evidence of anticancer efficacy. Results remain inconsistent and are influenced by strain selection, control regimen, baseline oral care, and chemoradiotherapy protocol.
The OLK/OSCC premalignant-to-malignant continuum	Exploratory and supportive approaches, including high-risk microbial/metabolic monitoring, management of opportunistic colonization, ecological support during cancer therapy, and hypothesis generation for future combination trials.	There is currently no prospective clinical evidence showing that microbiota-targeted intervention can reduce OLK malignant transformation, enhance antitumor immunity, improve immunotherapy response, or prolong survival in OSCC. Current evidence mainly supports risk stratification, complication management, supportive care, and mechanistic hypothesis generation [42–47,75,76,151–153].	Exploratory/risk-stratification/supportive-care stage only. It should not be described as an established anticancer strategy or as a proven strategy for preventing malignant transformation.

Abbreviations: OC, oral candidiasis; OLP, oral lichen planus; RAU, recurrent aphthous ulcer; OLK, oral leukoplakia; OSCC, oral squamous cell carcinoma.
Note: Microbiota modulation should be positioned according to disease-specific evidence maturity. It is best supported as an adjunctive strategy in Candida-related diseases, as a possible symptom-modifying adjunct in OLP and RAU, as supportive care in cancer therapy-associated oral mucositis, and as exploratory/risk-stratification-oriented in OLK and OSCC rather than as a replacement for standard antifungal, anti-inflammatory, chemoradiotherapeutic, or antitumor treatment.

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OC and denture-associated stomatitis remain the closest to clinical translation because they have clearer microbial targets and therapeutic endpoints, including erythema, pain, Candida detection, fungal burden, and recurrence. A 2025 systematic review of 13 randomized controlled trials involving 898 participants found that probiotic interventions were associated with lower oral Candida detection or colonization risk[137].

Adjunctive probiotic preparations combined with conventional local antifungal therapy or nystatin have also been associated with lower residual Candida detection, higher mycological cure rates, or shorter treatment duration in selected studies[138,139]. In denture wearers, probiotic dairy products, lozenges, and multi-strain preparations have also been tested for Candida colonization or prevention of denture-associated oral candidiasis[137,140]. These findings support probiotics as clinically tested adjuncts in selected Candida-related settings, but not as substitutes for antifungal therapy or standardized denture hygiene.

Antifungal therapy itself can alter the oral microbiota. Longitudinal tracking after treatment for primary OC showed clinical improvement without full restoration of a healthy-like microbiota[141]. Future OC studies should therefore evaluate ecological reconstruction, recurrence risk, strain-specific formulations, and long-term outcomes in addition to fungal burden.

Microbiota-informed intervention in OLP should be described with restraint. OLP is not defined by infection with a single microorganism, and relevant endpoints should include pain, erosive area, clinical score, recurrence, and corticosteroid need rather than salivary microbiome changes alone. Current evidence best supports microbiota-targeted strategies as possible adjuncts for immuno-inflammatory modulation, not as stand-alone disease-modifying therapy. The

CABRIO trial provides an important negative result: in 30 patients with symptomatic OLP, VSL#3 was safe but did not significantly improve pain, clinical activity, quality of life, or oral microbial composition versus placebo[142]. Other exploratory studies suggest potential symptom or ecological effects from S. salivarius-related intervention, whereas Lactobacillus reuteri-related intervention in OLP with recurrent Candida-related problems did not stably reshape the oral microbiome[143-145].

Kamal et al. reported greater pain and clinical-score reduction when multi-strain probiotics were added to topical clobetasol, but Candida burden did not differ significantly from clobetasol alone[146]. Together, these findings suggest that microbiota modulation in OLP is best positioned as an exploratory adjunct to immuno-inflammatory control, not as an independent disease-modifying therapy. Future studies should prioritize larger randomized designs, lesion-level microbiome assessment, corticosteroid-sparing effects, recurrence endpoints, and stratification by erosive status and baseline microbial ecology.

In RAU, microbiota-targeted interventions should be interpreted mainly as acute-phase adjunctive strategies.

RAU trials mainly evaluate pain, ulcer size, healing rate, and recurrence frequency. A 2020 meta-analysis of seven randomized studies found a clearer signal for pain relief than for ulcer severity or recurrence control, with stronger short-term effects when probiotics were combined with conventional treatments[147].

Subsequent small studies using probiotic lozenges, Lactobacillus reuteri-derived topical nano-formulations, or topical Bacillus clausii reported short-term improvements in pain, ulcer area, erythema, or local symptoms[148-150]. These findings are encouraging but remain heterogeneous in strain, formulation, dosing, follow-up, and patient stratification. Therefore, microbiota-targeted intervention in RAU should be described as a possible adjunct for symptom relief and short-term repair, not as an established strategy for durable recurrence prevention.

Future trials should distinguish acute healing endpoints from recurrence-prevention endpoints and stratify patients by flare frequency, ulcer type, non-keratinized mucosal vulnerability, baseline microbiota, and systemic factors.

Along the premalignant-to-malignant continuum, microbiota-informed strategies require particular caution. Microbial signatures, metabolites, and tumor-associated ecological states may inform risk stratification or hypotheses, but there is currently no prospective clinical evidence that microbiota modulation prevents OLK malignant transformation, enhances antitumor immunity, improves immunotherapy response, or prolongs OSCC survival. The most appropriate current framing is exploratory risk assessment, ecological monitoring, and supportive management of opportunistic colonization and complication control during cancer therapy.

In cancer-related care, the strongest clinical signal concerns therapy-associated oral mucositis rather than prevention of OLK malignant transformation or OSCC treatment. A 2024 meta-analysis of 12 randomized trials involving 1376 patients reported reduced severe oral mucositis with probiotics[151]. However, evidence remains inconsistent: an early randomized study reported benefit with Lactobacillus brevis CD2 lozenges in head and neck cancer chemoradiotherapy, whereas a later multicenter trial did not reduce grade 3-4 mucositis compared with sodium bicarbonate mouthwash[152,153].

Therefore, evidence from radiotherapy- or chemotherapy-related mucositis should not be extrapolated to anticancer efficacy or malignant-transformation prevention. At present, microbiota-targeted intervention in OLK/OSCC-related settings is best supported as supportive care and complication management; effects on malignant transformation, immunotherapy response, survival, or antitumor combination therapy remain open questions requiring prospective trials.

7 Conclusions and perspectives

OMDs can be viewed as a continuum of diseases arising at a highly exposed and dynamically regulated barrier interface. The healthy oral mucosa does not maintain homeostasis by being sterile or inflammation-free. Instead, in the continuous presence of commensal microbiota, it preserves dynamic homeostasis through surface humoral defense, epithelial spatial organization, tonic low-amplitude immune surveillance, and rapid repair programs. Once this homeostasis is disrupted, oral microbial dysbiosis is not limited to shifts in community composition. It may reflect changes in microbial localization, virulence state, metabolic output, host-sensing thresholds, immune tone, and epithelial barrier dynamics. These changes can shift the mucosal interface from controlled vigilance toward persistent inflammation, failed repair, structural remodeling, and, in selected contexts, malignant progression.

A central conclusion of this Review is that dysbiosis does not have a single fixed pathogenic meaning across OMDs. OC provides the clearest model of microbial state switching, in which Candida pathogenicity is mechanistically linked to epithelial sensing, type 17

immunity, and antifungal containment. In contrast, OLP, RAU, OLK, and OSCC require more cautious interpretation. In these settings, dysbiosis may act as an inflammatory amplifier, a chronic-maintenance factor, a flare-associated ecological signal, a marker or component of risk-associated remodeling, or a secondary colonization event within damaged or tumor-associated tissues. Thus, microbial findings should be interpreted according to disease stage, tissue localization, mechanistic support, and reversibility after intervention, rather than being assigned equivalent causal weight across diseases.

Several limitations in the current evidence base should be acknowledged. First, pre-lesional and longitudinal samples remain scarce, making it difficult to define whether microbial changes precede lesion onset, emerge during active inflammation, or reflect secondary colonization after barrier damage. Second, many studies still rely on saliva, plaque, swab, or surface-level sampling, whereas tissue-level spatial data are needed to determine whether microbes, microbial products, or metabolites are actually located near epithelial, stromal, or immune-cell compartments. Third, much of the current evidence remains taxonomic, and functional validation of microbial virulence programs, metabolites, interkingdom interactions, and host-response circuits is still limited. Fourth, disease heterogeneity, lesion subtype, anatomical site, disease stage, and treatment status are not always sufficiently controlled, which may partly explain inconsistent microbial signatures across cohorts. Fifth, medication exposure, including antibiotics, antifungals, corticosteroids, immunosuppressants, and proton pump inhibitors, may substantially alter oral or oral-gut microbial ecosystems and should be systematically recorded and adjusted for in future studies.

The next phase of oral microbiome research should move beyond asking which taxa are altered toward asking where microbes are located, what functions they express, which host compartments they engage, and whether modifying these interactions changes disease trajectory. Future studies should combine longitudinal sampling, lesion-level spatial multi-omics, strain- or function-resolved microbial profiling, mechanistic epithelial-immune-microbial models, and interventional or reversibility designs. Such approaches will be essential for distinguishing causal mechanisms from disease-associated remodeling and for developing microbiota-informed strategies in risk stratification, prevention, adjunctive therapy, supportive care, and rational clinical trial design.

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Data available statement

All data supporting the findings of this study are available within the article or from the corresponding author upon reasonable request.

Author contribution

M.Y. and C.H. contributed to conceptualization, literature curation, evidence synthesis, manuscript drafting, figure and table preparation, and manuscript revision. Y.G., R.Y., J.L., Q.H., Y.S., Y.M.S., H.W., R.M., and Z.Z. contributed to literature searching, reference organization, evidence summarization, and manuscript revision. J.F. and Z.W. conceived and supervised the study, guided the overall framework, provided project administration and resources, critically revised the manuscript, and approved the final version. J.F. and Z.W. are the corresponding authors. All authors have read and approved the final manuscript.

Ethics approval and consent

N/A

Consent for publication

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Conflicts of interest

Author Zhi Wang is an editorial board member of this journal, but she is not involved in the peer-review or decision of this article.

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