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Review article

The maintenance of an oral epithelial barrier

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ABSTRACT

Oral epithelial barrier consists of closely controlled structure of the stratified squamous epithelium, which is the gateway to human bodies and encounters a huge burden of microbial, airborne and dietary antigens, as well as masticatory damage. Once this barrier is destroyed, it will trigger bone loss, tissue damage and microbial dysbiosis and lead to diseases, such as periodontitis, oral mucosal diseases and oral cancer. Recently, increasing evidences showed that different factors including microorganism, saliva, proteins and immune components have been considered to play a critical role in the disruption of oral epithelial barrier. Herein, we discussed mechanisms governing the maintenance of oral epithelial barrier. Besides, the role of oral epithelial barrier failure in oral carcinogenesis will also be talked about.

1. Introduction

The oral cavity is a special place that is challenged by a bombardment of mechanical, chemical and biological stimulation for our every lifetime. Daily diet brings nutrition but also foreign antigens and noxious molecules, not to mention the toxicity of carcinogens such as alcohol, tobacco and areca-nut [1]. In the course of food chewing, oral mucosa experiences mechanical friction. Besides, a burden of microorganism inhabiting in the oral cavity not only constitutes an integrity ecosystem that benefits the host, but microbiota dysbiosis drives the immune system of host to against virulent antigens, toxins and metabolites [2]. Oral epithelium is an important barrier in the oral cavity and is choreographed to segregate detrimental stimulus and to balance the intricate interaction between the host and exterior environment.

Oral epithelial barrier is a multitasking system to defend external stimulus. It is organized in two main components: a physical barrier which consisted of multilayered epithelial cells and cell-cell junctions, and an immune barrier that maintains immune responses or immune tolerance to microbial antigens [3,4]. The oral epithelial barrier is essential to resist against mechanical stress both physiologically and pathogenically. Additionally, the barrier is able to separate harmful microbes and toxic macromolecules and is effective in preventing chemical trauma and chronic inflammation from damaging oral epithelium [5].

Once oral epithelial barrier is disrupted, it may cause oral mucosal diseases such as oral lichen planus (OLP) and oral leukoplakia (OLK), involved in abnormal expression of keratin 4 and mucin 4 of the oral epithelia and chronic inflammation in hosts [6,7]. Destruction in gingival barrier resulted from oral microbial dysbiosis and concomitant inflammation responses leads to bone loss in settings of periodontitis, a common disease characterized by attachment loss [8]. Recently, some studies suggest that destructed oral epithelial barrier and defective keratinocytes differentiation may contribute to the development of oral squamous cell carcinoma (OSCC), which derived from self-renewing cells at the basement membrane of oral epithelium [9]. Here, we describe the composition and structure of the oral epithelial barrier, and discuss mechanisms underlying the maintenance of the oral epithelial barrier, as well as implications for oral carcinoma involved. Thus, it will provide insight into the basic mechanisms of disease occurrence relative to oral epithelial barrier.

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2. Anatomical factors maintaining oral epithelial barrier

An integrity of oral mucosa is a choreographed barrier by its multilayer cells and intercellular junctions [10]. Keratinocytes in epithelium are tightly attached with each other and are arranged into distinct layers [11]. Intercellular junction between keratinocytes is formed by desmosomes, tight junctions and adherences junctions, while adhesion between keratinocytes and basement membrane is maintained by hemidesmosomes [4]. These junctions control permeability of epithelium and can be changed by various factors such as hypoxia, drugs, radiation and microbiota dysbiosis [12]. And the dysfunctional junctions may lead to oral diseases. *Porphyromonas gingivalis*, a keystone pathogen in periodontitis, could disturb intercellular junctions through producing proteases like gingipains and collagenases. Groeger et al. demonstrated that the expression of tight junction proteins including claudin 1, claudin 2 and occludin in primary and immortalized human gingival keratinocytes infected with *P. gingivalis* disappeared and the transepithelial electrical resistance decreased to zero, while the effects were delayed by gingipain inhibitors [13]. Other researchers also suggested that *P. gingivalis* infection led to IL-13 production by mast cells, which downregulated the expression of claudin 1 in gingival epithelial cells and afterwards increased paracellular permeability in gingival barrier [14]. The recurrent or chronic oral pain may also be associated with junctional dysfunction of oral epithelial barrier, which was assessed by Yoshimoto et al., who demonstrated that epithelial cellular edema was disseminated within labial gland biopsies of patients with Sjögren's syndrome, and the intercellular molecules such as filamentous actin and E-cadherin were disarranged in the edematous areas [15]. These results suggested that junction destruction may be a crucial step in gingival barrier function failure and oral diseases (Fig. 1).

Oral epithelial barrier is made up of keratinocytes and is maintained by intercellular junctions and cornified envelope. Keratins are crucial proteins that constitute both cytoskeleton and tight junctions, among which the defects of keratin 5 (k5) and k14 result in epidermolysis bullosa simplex. Keratins could also be dissolved by proteases produced by *P. gingivalis*, leading to gingival barrier failure, attachment loss and periodontal destruction in periodontitis. The cornified envelop of stratum corneum is composed of extracellular proteins like keratins that provide for mechanical resilience, and special lipids such as ceramides which fill extracellular spaces and regulate the permeability of the oral epithelial barrier.

Keratins, which constitute 85% of a fully differentiated keratinocyte and in partly make up cytoskeletons of vertebrate epithelial cells, self-assemble into a three-dimensional array of filaments [16,17]. The structure of keratin filaments is not only choreographed for cell cohesion, but also provides mechanical resilience against stress [18]. As exemplified in epidermolysis bullosa simplex (EBS), mutations in genes coding keratin 5 and keratin 14 caused loss of an intact keratin cytoskeleton, which led to bullous lesions following mild trauma in epidermis, and even in oral mucosa [19,20]. Moreover, mutations in keratin 4 and/or keratin 13 were identified to be responsible for oral white sponge naevus, a benign disorder occurring at non-cornifying stratified squamous epithelia, whose characteristics included vacuolization of the suprabasal keratinocytes and keratin filaments in the stratum spinosum [21]. These results suggested that keratin cytoskeleton and intercellular junctions form a complex and homogeneous network to support the oral barrier.

The stratum basale is adjacent to the basal membrane and is mainly composed of mitotic cells [22]. The basal cells are undergoing proliferation, differentiation and migration to renewal and repair the integrity of epithelial barrier in danger of mechanical stress [23]. Basal cells apoptosis and extracellular matrix degrade lead to liquefaction degeneration of basal cells, a classic characteristic of OLP, speculating to be driven partly by antigen-specific immune responses [24]. As keratinocytes migrating to the surface of epithelium from stratum basale, some dead cells are retained and form a protective sheath to withstand mechanical trauma. However, over-extensive such as ill-suited denture makes the stratum corneum thinner and less keratinized, presenting as erosion or ulcer of the oral mucosa [25]. Crosslinked proteins and lipids are assembled into cornified envelope (CE) surrounding cornified cells during their terminal differentiation and migration [26]. Keratins form the majority of proteins in the stratum corneum and make up a cytoskeleton within the cells [23]. Special lipids make oral mucosa a more permeable barrier than epidermis because their shape and arrangement provide fluidity and permeability. Among them, ceramides, cholesterol, fatty acids and cholesterol sulphate filling spaces between cells are closely related to the permeability of stratum corneum [27]. In epidermis, fatty acids and ceramides are mainly cylindrical or rod in shape and highly ordered, rendering an impermeable barrier [23]. While in oral stratum corneum, some of the fatty acids and ceramides are no longer cylindrical. In addition, the stratum corneum of hard palate and gingival have significant levels of phospholipids and glycolipid, which are arranged a little disordered because of their bulky polar head [27]. Thus, keratins and special lipids in stratum corneum make the oral barrier stronger to protect against external stressors [28].

Unlike in keratinized epithelium, cell nuclei and organelles in non-keratinized epithelium are not degraded in terminally differentiated

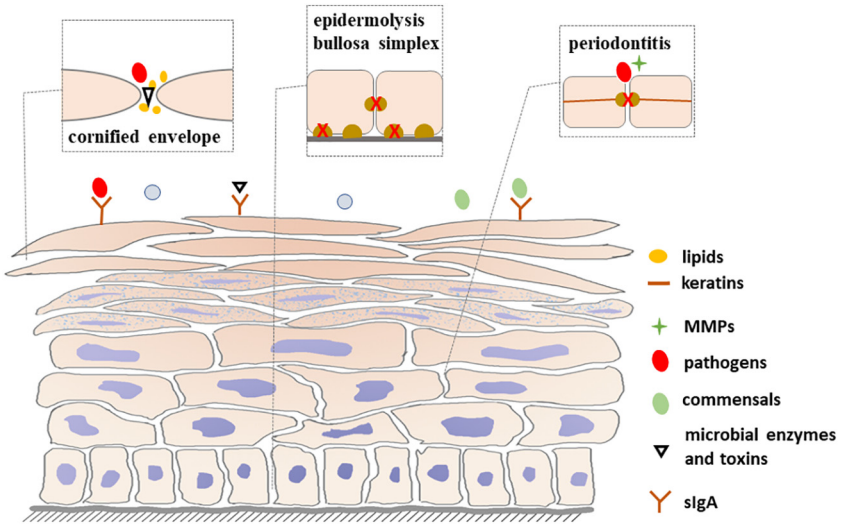

Fig. 1. Anatomic structures of the oral epithelial barrier.

cells of the surface layer [29]. The non-keratinized epithelium is weaker in defending stimulus and it may be due to the differences in cellular protein content with keratinized epithelium [30]. For instance, in keratinized oral epithelium, keratin 1 and keratin 10 can be found in suprabasal cells while nonkeratinizing tissues express keratin 4 and keratin 13[31]. On the other hand, the level of ceramides is lower in nonkeratinized epithelia which is closed related to the barrier function [27].

In conclusion, it can be concluded that the anatomical barrier is made up of keratinocytes with varying degree of keratinization and maintained by the highly fortified walls (the stratum corneum) and cement among brick (keratinocytes). The interaction between desmosomes and keratins make the oral barrier stronger to protect against mechanical and chemical stress, and forms a part of immune barrier that passively withstands microbial attack.

3. Immune factors maintaining oral epithelial barrier

The oral epithelial barrier is the gateway to human bodies and encounters a huge burden of microbial, airborne and dietary antigens, as well as masticatory damage [32]. As is the case with the gut mucosal barrier, the immune system establishes rules not only to keep pathogens at bay but also maintain immunotolerance to commensals and innocuous antigens at oral epithelial barrier [33]. Recently, the maintenance of immune barrier has been shown to strike a delicate balance to protect the body through homeostatic oral microbiome, immune composition and immune-tolerance.

The homeostatic immune responsiveness of immune barrier is tuned partly by oral microbiome. An enormous number of microbes inhabits in oral cavity after coevolution with humans for years [2]. Studies have manifested that over 600 prevalent taxa at the species level in oral cavity, with varying subsets predominating in distinct niches [34]. Commensal microbiota in gut barrier has been demonstrated to play an important part in the development of lymphoid structure, function of immune cells, and preventing metabolic and autoimmune diseases [35]. Similarly, oral microbiota may affect antimicrobial responses of hosts. Studies have demonstrated that commensal oral biofilm exposure resulted to increased epithelial thickness and stratification of 3D reconstructed human gingiva (RHG) in vitro. Moreover, the production of anti-microbial proteins and antimicrobial cytokine (such as CXCL8, CXCL1, CCL20 and IL-6) were also increased in response to biofilm exposure, suggesting that oral biofilm actively promoted oral epithelial barrier function to defense microbiomes [36]. Growth arrest specific 6 (GAS6), a ligand of the TYRO3-AXL-MERTK, is expressed in outer layers of the oral epithelium and is induced by oral microbiota dependently of myeloid differentiation primary response gene 88 (MyD88). GAS6 is an immunological regulator between host and microbiome at the oral barrier whose absence leads to intensive inflammation [37]. While others suggested a similarly oral immune network in germfree mice when compared with specific pathogen-free controls, suggesting that other mechanisms independent on oral microbiota also helped train homeostatic immunity at oral barrier [8]. On the contrary, microbiota dysbiosis triggers noxious inflammatory responses and may break oral epithelial barrier, destroy surrounding tissues and even trigger systemic inflammatory conditions. Support for this concept arises from the fact that in periodontitis, the transition of commensal bacteria to a pathogenic entity triggers uncontrolled inflammation which results in the destruction of supporting tissues [38]. In addition, periodontal pathogens may be risk factors of arthritis or atherosclerosis in susceptible individuals partly due to the production of autoantibodies [39]. Accordingly, the immune network of oral epithelial barrier that protect the hosts is maintained to some degree dependent on homeostatic oral microbiome and can be broken by microbial dysbiosis.

Oral mucosa is under protection of a barrier composed of the immune composition including dendritic cells (DCs) and T helper cells 17 (Th17). Studies have detected CD1a + DCs within the oral vestibule, bucca, hard palatum and lingua [40]. Unlike gut mucosa, typical mucosa associated lymphoid tissue in which induced immune responses, is absent in oral mucosa and DCs play a critical role in the immune response of oral mucosa [3]. Under microbial infection such as candida, CD1a + DCs can be numeric increased and distributed in all layers of the epithelium as well as the lamina propria [41]. Immune responses at oral mucosa seem to take place when DCs recognize antigens, migrate to oral lymphoid foci or local lymphoid organs and present the antigens to T cells or naïve T cells respectively [3]. Venturini et al. demonstrated that the expression of CD86, an important co-stimulus in T cell activation, was lower in DCs of hyperglycemia mice, which were susceptible to *Candida albicans* in comparison with normal mice. The results suggest the defective functional activity of DCs is favor of microbial infection [42].

Th17 are enriched in epithelial barriers and contribute to maintain the integrity of oral epithelial barrier [43]. Mechanical damage that occurs during mastication and abrasion could drive IL-6 production in gingival epithelial cells, which promoted Th17 proliferation in the gingiva [8]. Nevertheless, researches have demonstrated that germ free mice had a similar level of Th17 in oral epithelium when compared with specific pathogen free mice [32]. These investigations revealed Th17 which reside in the gingiva were developed via physiological damage of epithelial barrier during mastication, independently on microbiota [8]. Th17 have been implicated in protective inflammation toward pathogens at the oral barrier. Patients deficient in Th17 cell differentiation and function suffered from chronic mucocutaneous candidiasis [44]. Th17 are vital components in antifungal immunity via a IL-17 dependent pathway, and IL-17 has been suggested to be correlated with antimicrobial peptide β-defensin 3 expression [45]. However, excessive Th17 responses with IL-17 elevation are detrimental to the hosts, which has been demonstrated to result in bone loss, tissue damage and microbial dysbiosis in periodontitis, concomitantly barrier breaks [46]. All in all, these results highlight that Th17 that induced by local stimulus such as physiological damage can tailor immune barrier of oral mucosa (Fig. 2).

Immune-tolerance is another pivotal mechanism underlying the maintenance of oral epithelial immune barrier. Immune-tolerance is meant to denote an unresponsive state of immune system toward autologous or continuous stimulation to avoid extensive immune responses and unnecessary injury of host tissues [47]. Antigen presenting cells (APCs) and T cells play a critical part in the induction of immune-tolerance at oral mucosa. Muthukuru et al. suggested that APCs with repetitive stimulation by lipopolysaccharide (LPS) from *P. gingivalis* downregulated their expression of Toll-like receptor (TLR) 2 and TLR 4 to inhibit inflammation response. The proinflammatory cytokines produced by APCs are also decreased to avoid uncontrolled inflammation to destroy host tissues [48]. Researches also demonstrated that the oral DCs with LPS stimulation secreted immunosuppressive IL-10 and resulted in Foxp3 expression and the differentiation of regulatory T cells (Tregs), which maintain immune-tolerance by inhibiting effector T cells in vitro [49]. Other regulatory mechanisms include inducing apoptosis and functional inactivation of T cells, as well as inhibiting T cells by co-inhibitory signaling [3]. Hence, immune-tolerance of oral epithelial immune barrier is, to some degree, maintained by APCs that kept immature and limited T cell responses in the presence of commensal bacteria (Fig. 3).

Immune barrier develops and is modulated via interaction between host and oral microbiota. Barrier deterioration and bacterial translocate evoke inflammation, during which DCs recognize microbial antigens and migrate to oral lymphoid foci or local lymphoid organs to elicit adaptive immune responses. Th17 are also implicated in antimicrobial inflammation that secret IL-17 and increase the expression of antimicrobial peptides. Immune-tolerance is another crucial mechanism to maintain the oral epithelial barrier. DCs are incompetent to recognize and present commensal antigens and inhibit effector T cells. Effector T cells are also blocked by Tregs, whose polarization is induced by DCs-

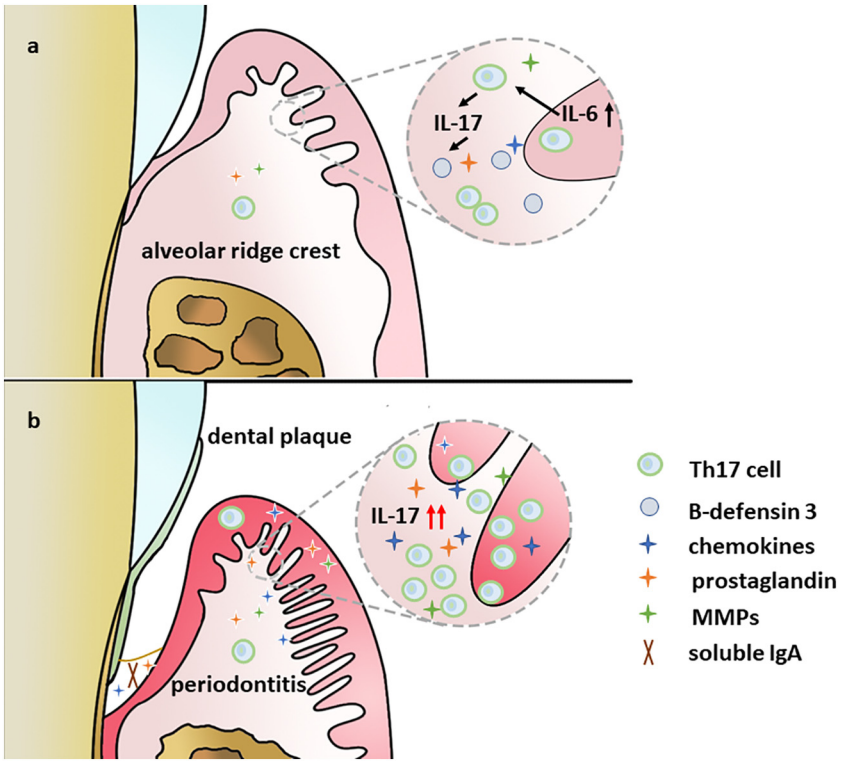

Fig. 2. The effects of Th17 on the gingival barrier.
(a). Gingival epithelial cells secrete IL-6 in response to masticatory friction and induce Th17 in the gingival. IL-17 which is secreted by infiltrated Th17 is correlated with antimicrobial peptide β-defensin 3 expression and participates in antimicrobial immunity. (b). While excessive Th17 and IL-17 result in bone loss, tissue damage and barrier breaks in settings of periodontitis.

producing IL-10.

Hence, immune barrier is invisible but functions to recognize microbial, dietary as well as tumor antigens. While falsely inactivated immune responses can trigger exaggerated or perpetuated tissue damage, as seen in periodontitis [39]. The immune barrier develops and is modulated via interaction between the host and oral microbiota. Immune populations aid in fighting pathogens, regulate host-commensal interactions, and maintain immunotolerance to preserve barrier integrity. At the same time, physiological functions such as mastication help define the immune tone of oral epithelial barrier, suggesting the tissue-specific differences with barriers of the derma or colon [8].

4. Other factors helping maintain oral epithelial barrier

4.1. sIgA

Saliva, secreted by salivary glands especially parotid gland, is important in protecting the integrity of oral epithelial barrier by rinsing and delivering antimicrobial agents to oral mucosa [50]. Patients with xerostomia (low or lack of saliva) are susceptive to oral candidiasis [32]. Saliva contains various kinds of barrier-protective factors such as electrolytes, mucus and glycoproteins as well as antimicrobial peptides and proteins [32]. Secretory immunoglobulin A (sIgA) is the largest immunologic component among immunoglobulin proteins saliva

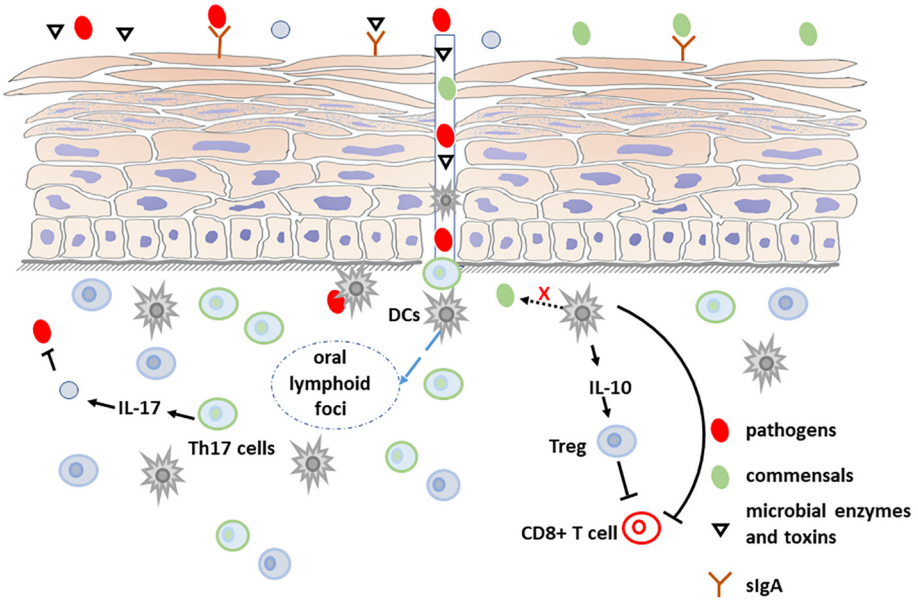

Fig. 3. Immune factors involved in maintaining oral epithelial barrier.

secrets [51]. Researches supported that sIgA was mainly secreted by plasma cells in connective tissues and lined the surfaces of oral mucosa [52].

The mechanisms of sIgA keeping potential pathogens at bay include agglutinating bacteria and neutralizing potential stimulus such as enzymes, toxins, and virus [53]. SIgA is like a fishing rod that catches and binds with foreign pathogens such as *C. albicans* and *streptococci*, to inhibit their direct contact with oral mucosal surface and restrain the penetration through epithelium as well as promote their removal, which is termed as "immune exclusion"[52,54]. SIgA can also inactivate microbial derived enzymes. Take glucosyltransferase of *streptococci* as an example, which is involved in the ability of adherence and accumulation in oral biofilm, could be blocked by sIgA through inhibiting the synthesis of extracellular polysaccharides to destabilize the binding of glucosyltransferase to substrates [52,55]. Besides, sIgA has been shown to neutralize virus by reducing the attachment to epithelial cells and to prevent their penetration [56,57]. On the other hand, sIgA could improve the activity of lactoperoxidase that is against *Streptococcus mutans* by stabilizing its enzymatic and antimicrobial activity, suggesting that sIgA may have a synergistic action with other defensive enzymes to protect oral barrier [58]. In a word, sIgA helps maintain the integrity of oral epithelial barrier by limiting microbial adherence and penetration, neutralizing virus as well as mediating microbial derived enzymes.

4.2. mucins

In addition, studies identified a cooperation between sIgA with mucins [59]. The adherence of sIgA to epithelial cells may be mediated by mucins, which forms a complex with sIgA [59]. Mucins with globular proteins (for example, sIgA) and proline-rich proteins together compose the mucosal pellicle (or salivary pellicle) that is anchored to oral epithelial cells [59]. The mucosal pellicle also helps maintain the oral epithelial barrier via protecting against abrasion or chemical xenobiotics [60]. Other factors involved in maintaining the oral epithelial barrier include fatty acid, microelement, antimicrobial peptides and salivary enzymes (Table 1).

5. Destruction of the physical and immune epithelial barrier in OSCC

OSCC is the major subtype of oral cancer from oral epithelial barrier failure, with more than 300 thousand new cases and 145 thousand mortality per year all around the world [70]. Common risk factors of OSCC include alcohol, tobacco and human papillomavirus (HPV) [71]. Paralleling a decrease in tobacco use, the incidence of HPV-negative OSCC in the United States reduced whereas incidence of HPV-positive OSCC enhanced at about 7.5% per year [72]. Recent studies have manifested HPV infection was responsible for 24% of the OSCC cases, and alcohol consumption was associated with 38.8% OSCC worldwide [73,74].

5.1. HPV

HPV is a double strand DNA virus with numerous subtypes, among which HPV16, 18, 31, 33 and 35 are highly risky to induce epithelial oncogenesis [75]. Researches have suggested that HPV16 is the most common subtype that constitutes more than 80% of HPV+ head and neck squamous cell carcinoma (HNSCC) [75,76]. Oral barrier breaks and epithelial wounds occur during mastication, which are thought to be required for HPV to infect the basal cells [77]. Then HPV virus replicate utilizing host machinery and their genome is partitioned into daughter cells. The daughter cells enter differentiation in oral epithelia and are shed with desquamated cells, rendering HPV live in latent state [78]. Once keratinocytes infected by HPV16 and HPV18 reach the superficial layer, the expression of E6 and E7 which are the main contributors to induce cancer would be markedly increased [78]. It has been widely accepted that E6 activates E6-Associated Protein (E6AP) and attenuates p53 induced apoptosis of keratinocytes [79]. And E7 binds retinoblastoma protein (pRb) and hinders its combination with transcription factors, promoting cell cycle progression and cell proliferation [80,81] (Fig. 4).

HPV could infect basal cells when oral barrier breaks or oral epithelia are wounded. Upon infection, HPV virus replicate along with infected cells and migrate to the surface layer, during which the oncoproteins interfere with pivotal signaling in host cells to promote the cell proliferation and inhibit the apoptosis of host cells, promoting epithelial oncogenesis. Besides, HPV modulates the profile of cytokines and chemokines, and the expression of IL-10, TGF-β, CXCL9, CXCL10, CXCL12, CCL17 and CCL21 is markedly increased to recruit and polarize the immune-suppressing Tregs and Th17, as well as impair the migration of DCs. It could be helpful to HPV to evade from immune surveillance and enhance tumor formation.

E6 and E7 also break immune barrier of oral epithelia to contribute to the immune evasion of HPVs and oncoproteins. At the early stage of infection, Toll-like receptors (TLRs) recognize HPVs and initiate immune responses trying to eliminate the infected cells [82]. The expression of TLR3, TLR5 and TLR8 has been verified to be increased in HPV16 E6/E7 keratinocytes, which may be an attempt to initiate antiviral immunity [83]. However, at the late stage of infection, HPVs employ various strategies to generate an anti-inflammatory microenvironment. HPV16 and HPV18 infect basal cells under protection of squamous epithelium and replicate at a low speed, thus evading immune system of host [78,84]. TLR9, which recognizes HPV-DNA and contributes to the formation of pro-inflammatory environment by producing tumor necrosis factor-α (TNF-α), IL-8, C chemokine ligand 2 (CCL2) as well as CCL20, is impaired by oncoproteins E6 and E7[83,85,86]. While the expression of IL-10, TGF-β, CXCL9, CXCL10, CXCL12, CCL17 and CCL21 is markedly increased in HPV-positive OSCC, which could recruit or polarize Tregs and Th17, and impair migration of DCs to lymph nodes [87–90]. Researches demonstrated a high infiltrating level of Th17 and Treg/CD8+T cell ratio in HPV-positive HNSCC, which suggests a high degree of immune suppression

Table 1
Other related factors in maintaining oral epithelial barrier.

Factors	Effects	Reference
10-Hydroxy-cis-12-octadecenoic acid	Inhibits *P. gingivalis* induced degradation of E-cadherin and β-catenin of gingival barrier	[61]
Estradiol	Reinforces the physical barrier by upregulating tight junction proteins	[62]
Sphingosine	Protect antimicrobial barriers	[23]
Lauric acid, sapienic acid	Control microbial growth and maintain equilibrium of oral microbiota	[23] and [63]
Calcium; Vitamin A; retinoids	Influence critical enzymes (protein kinases, etc.) in epithelial cells differentiation to maintain the integrity of barrier	[64] and [31]
B-Defensins	A group of antimicrobial peptides identified as the part of antimicrobial immune barrier	[50] and [65]
Hsp70	A cytoprotective extracellular chaperone present in human saliva that opsonize bacteria	[66]
Salivary peroxidase	maintaining the oral barrier by: (i) exerting antimicrobial effects which may be enhanced by sIgA; (ii) enhancing the cell lysis activity of lysozyme	[67], [68], and [69]

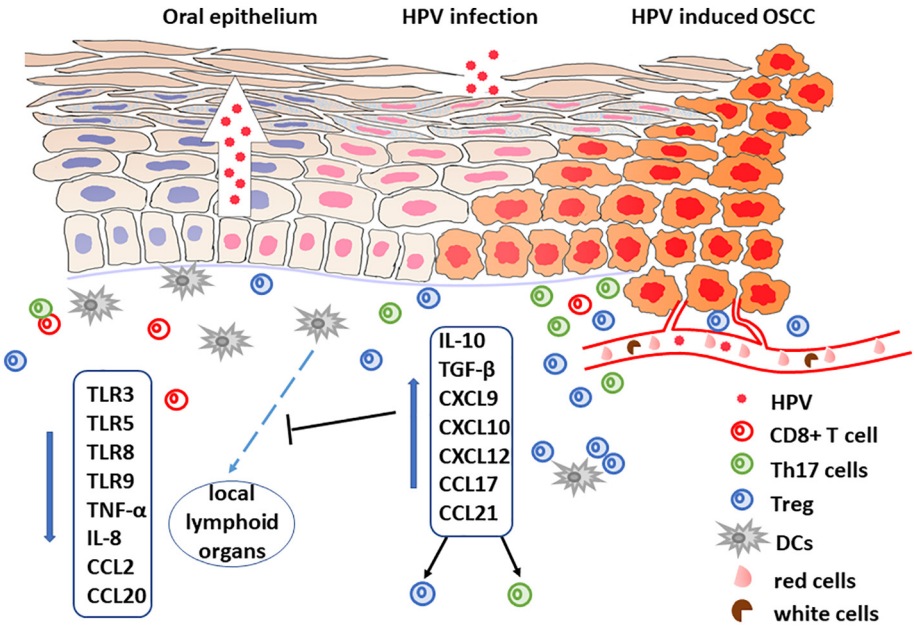

Fig. 4. HPV infection and oral epithelial barrier.

[88,91]. Thereby, E6 and E7 are crucial mediators that help HPVs and transformed cells evasion from immune surveillance and enhance tumor formation.

5.2. Alcohol and tobacco

Alcohol can dissolve lipids in oral epithelia, thus increasing the permeability of oral epithelial barrier to harmful substance [71]. Acetaldehyde, the main metabolite of alcohol, is a chemical stimulus for oral epithelia that has genotoxicity by damaging DNA and interfering with DNA repair [92]. Additionally, the risk of smokers developing oral cancer is 3 times higher than non-smokers [71]. Tobacco produces pre-carcinogens such as benzopyrenes, aromatic amines and nitrosamines that are oxidized and covalently bound to DNA in turn, and generates crucial gene mutations involved in OSCC oncogenesis, such as p53[93]. Chronic use of alcohol and cigarette is also implicated in impairing immune barrier of oral mucosa, increasing susceptibility to gingivitis, periodontitis and neoplasms [71].

6. Conclusion and perspective

Oral epithelial barrier function to protect from physical, chemical, and microbial damage in hosts, which is maintained by closely controlled structure of the stratified squamous epithelium and the immune system of host. Oral epithelium consisted of well-ordered stratified cells and tight intercellular junctions and they represent crucial means of the oral epithelial barrier maintenance. Notably, the stratum corneum, where epithelial cells lose their nucleuses and organelles and are equipped with assembled crosslinked proteins and lipids extracellularly, is a potent structure to maintain the barrier. Immune barrier is invisible but functions to recognize microbial, dietary as well as tumor antigens. While falsely inactivated immune responses can trigger exaggerated or perpetuated tissue damage, as seen in periodontitis [39]. The immune barrier develops and is modulated via interaction between the host and oral microbiota. Immune populations aid in fighting pathogens, regulate host-commensal interactions, and maintain immunotolerance to preserve barrier integrity. At the same time, physiological functions such as mastication help define the immune tone of oral epithelial barrier, suggesting the tissue-specific differences with barriers of the derma or colon [8]. Finally, the connection between oral barrier failure and HPV infection as well as consequent carcinogenesis promotion is also discussed. Persistent HPV infection requires epithelial wounds and barrier breaks. In turn, oncoproteins E6 and E7 interfere with specific cellular pathways in epithelial cells that promote tumorigenesis and impair immune barrier to induce evasion of HPV and cancer antigens from immune system.

Once it is destroyed including dysfunction of epithelial integrity and immune system, oral mucosal diseases and even oral cancers occur, during which defects in keratins, lipids and immune cells play an important role. It has been shown that the reconstruction of intestinal barrier involved in peptides, hormones, phospholipids and probiotics of epithelia [12]. In experimental colitis, transplanted intestinal stem cells have been shown to become part of naïve mucosa, give rise to self-renewing crypts with normal function and histology and even limit bacterial antigen translocation across intestinal epithelia, suggesting one possible way to regenerate damaged mucosal barrier and restore its function [94,95]. However, the reconstruction of epithelial barrier in oral cavity and intestine remain ill defined. Local tension makes dividing cells disengage from the neighbor cells transiently after mitotic exit and damages intercellular junctions. The reestablishment of the intercellular junctions is, although not entirely clear, of great importance to maintain the order of epithelial cells and restrain uncontrolled cell proliferation, which is a feature of oncogenesis [96]. Further should be done to shed light on the maintenance and reconstruction of oral epithelial barrier. As such, it holds great promise for us to look for new therapeutic targets in human diseases relating to oral epithelial barrier.

Author contribution

Sha-sha Wang and Ya-ling Tang contributed to conception and draft of the manuscript. Ya-jie Tang and Xin Pang contributed to data acquisition and assisted in writing. All the authors gave final approval and agree to be accountable for all aspects of the work.

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Conflict of interest statement

The authors declare no conflicts of interest.

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