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Review Article

Virulence Factors of Periodontal Pathogens and Their Specific Targets in the Oral Epithelial Barrier

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Abstract

Background: The exploration of the epithelial targets of periodontal pathogens is crucial for our understanding of the underlying mechanisms of the host immune response and periodontal disease pathogenesis. ***Objective***: To comprehensively review the current knowledge and key findings from relevant studies that contribute to this understanding. ***Source***: PubMed database of the US National Library of Medicine. ***Study selection***: Original articles (*in vitro studies*) published in the English language only and available as free text were included. ***Conclusions***: Periodontal pathogen virulence factors are capable of directly targeting keratinocyte adhesion proteins, leading to the deterioration of epithelial barrier integrity, resulting in disease progression.

Keywords: Epithelial barrier integrity; Epithelial junctions, Keratinocyte; Periodontal pathogen; Virulence factor.

عوامل الضراوة لممرضات اللثة وأهدافها المحددة في الحاجز الظهاري الفموي

الخلاصة

الخلفية: يعد استكشاف الأهداف الظهارية لممرضات اللثة أمرا بالغ الأهمية لفهمنا للآليات الأساسية للاستجابة المناعية للمضيف ومسببات أمراض اللثة. **الهدف**: مراجعة شاملة للمعرفة الحالية والنتائج الرئيسية من الدراسات ذات الصلة التي تساهم في هذا الفهم. **المصدر**: قاعدة بيانات PubMed التابعة للمكتبة الوطنية للطب الأمريكية. **اختيار الدراسة**: تم تضمين مقالات أصلية (دراسات مختبرية) منشورة باللغة الإنجليزية فقط والمتاحة كنص حر. **الاستنتاجات**: عوامل الضراوة لممرضات اللثة قادرة على استهداف بروتينات التصاق الخلايا الكيراتينية مباشرة، مما يؤدي إلى تدهور سلامة الحاجز الطلائي، و يؤدي إلى تقدم المرض.

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INTRODUCTION

Epithelial tissues represent a distinctive barrier layer that separates the underlying tissues and organs from the outer environment. Depending on location, they perform various functions but always serve to protect the internal underlying tissues from environmental stresses, chemical damage, and bacterial infection. Keratinocytes, the fundamental cells of epithelial tissue, exhibit distinctive structural characteristics, including cellular stratification and cornification, along with specific cell-to-cell communication, enabling them to function as a barrier against harmful microbes and toxic substances. These protective properties effectively prevent chemical injuries and long-term inflammation in the oral epithelium [1]. Epithelial barrier homeostasis is regulated by the cytoskeleton. Keratinocyte junctional proteins constitute the structural barrier of the epithelial tissue and serve as targets for a variety of periodontal pathogen virulence factors, which aim to invade the underlying connective tissue. Notably, *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Treponema denticola*, and *Escherichia coli* can elicit chronic inflammatory reactions that result in attachment loss and damage to the periodontal tissue [2,3]. Damage to the oral epithelial barrier can result in several diseases, such as inflammation, cancer, and autoimmune and developmental diseases [4]. During periodontitis pathogenesis, gingival epithelial barrier destruction resulting from the microbial ecological imbalance and associated inflammation ultimately progresses to loss of both the clinical attachment and alveolar bone in the periodontitis patient [5,6]. In addition to periodontitis development, recent studies have shown that a compromised oral epithelium barrier and aberrant keratinocyte differentiation contribute to oral squamous cell carcinoma (OSCC) pathogenesis, which originates from self-renewing cells at the epithelial basement membrane interface [7-10]. An understanding of the epithelial barrier homeostasis/disruption-related mechanisms is the cornerstone for several research fields, including cancer therapy, inflammatory/infectious diseases, and pharmaceutical research. Consequently, this review aims to provide a general overview of oral epithelium barrier disruption caused by periodontal pathogens' virulence arsenals along with the possibility of reversing this disruption by using recently discovered therapeutic agents. Findings from recent reviews and related research publications will be highlighted to provide the reader with a thorough understanding of the subject area.

Search strategy

An electronic literature search was performed in the PubMed database of the US National Library of Medicine (https://pubmed.ncbi.nlm.nih.gov/) for articles published with the following search queries: (“periodontal pathogen” OR “periodontal pathogen virulence“) AND (“oral epithelium” OR “oral epithelial barrier disruption”),"*Porphyromonas gingivalis*" AND ("epithelial barrier" OR “oral epithelial barrier"), "periodontal virulence" AND "epithelial barrier”, “tight junction" AND "periodontal pathogen”, “Adherens junctions" AND "periodontal pathogen” ”cadherin" AND " periodontal pathogen”, “Aggregatibacter actinomycetemcomitans" AND "Epithelial barrier”, “*Treponema denticola*" AND "epithelial barrier” “E.coli". Reviews, case reports, editorials and expert opinions were excluded. After conducting the preliminary search, duplicates were removed, resulting in 278 articles being retrieved. Subsequently a “manual” screening was then completed to ensure the relevance of selected publications to the aims of this study. Original in vitro articles published between 2000 and 2024 were included if they were written in English, available as free text, focused on the role of periodontal pathogens in compromising oral epithelial barrier integrity, and provided in vitro evidence related to the disintegration of the oral keratinocyte’s junctional proteins under the influence of periodontal pathogens’ virulence factors. Eventually, this narrative review identified 18 key peer-reviewed articles for inclusion.

Keratinocyte cell junctions

The integrity of the gingival epithelium is critical for its function as a physical barrier; this integrity is defined by the unique cobblestone architectural arrangement of keratinocytes bounded tightly together by intercellular junctions. These structures comprise multi-protein cell junction complexes composed of transmembrane, cytosolic, and cytoskeletal proteins. They are symmetrical formations located between cells that are critical for maintaining the physical and functional integrity of the tissue [11]. They are classified into 3 groups known as subapical tight junctions (TJs), scattered lateral gap junctions (GJs), and anchoring junctions, namely lateral desmosomes, adherens junctions (AJs), and hemidesmosomes that mediate adhesion between keratinocytes and the underlying basement membrane [12]. These structures are illustrated in Figure 1.

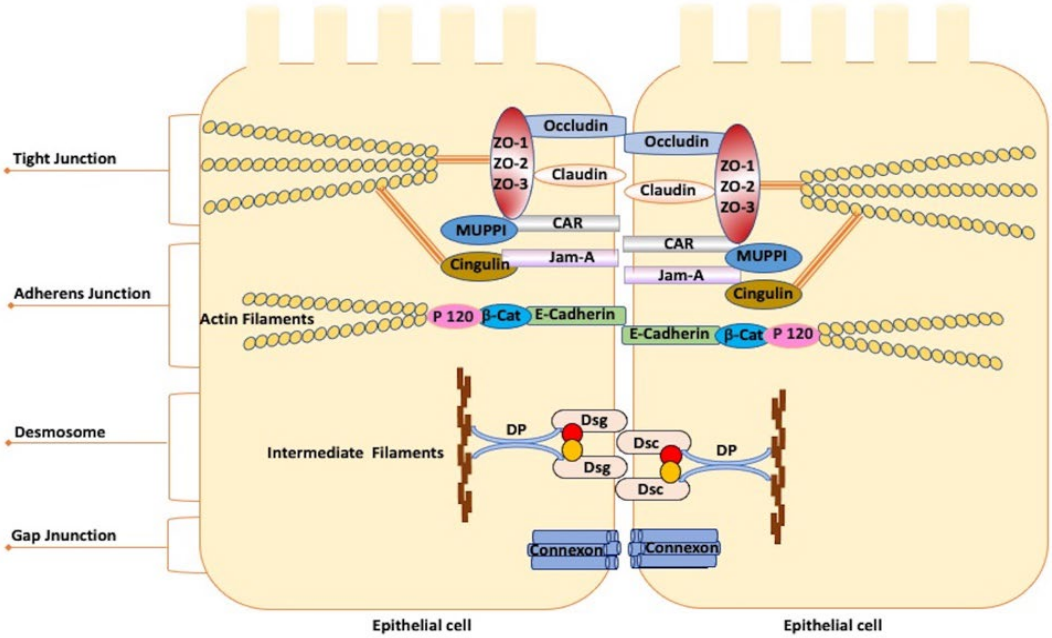

Figure 1: Schematic Illustration of oral epithelial cellular junctions along with associated proteins complexes . From top : tight junction the closest to the apical area of epithelial cells junction, formed by transmembrane proteins claudin and occludin connected to intracellular zonula occludens (ZO) proteins, while Junctional adhesion molecules (JAM)/coxsackievirus and adenovirus receptor (CAR), as transmembrane glycoproteins, bind to cingulin and/or multi-PDZ domain protein 1 (MUPP1). CAR is also attached to ZO-1. ZO proteins and cingulin link the tight junction structure to the actin filament. Adherens junctions are responsible for cellular junction stability by forming a belt like structure , classical cadherins like E-cadherin are paired to intracellular actins via α-catenin and β-catenin. Desmosomes are the structures responsible for cellular mechanical strength. Several proteins families make up desmosomes namely desmogleins (Dsgs), desmocollins (Dscs), armadillo proteins and plankin proteins, such as Desmoplakin (DP).Gap junctions: represent neighboring cells’ transcellular portal of communication, having the structure of hemichannels named (connexon), connexons are built by 6 connexin proteins. [14].

Bacterial influence on cell–cell junctions and the gingival epithelial barrier

Several studies have provided evidence for direct and indirect methods by which periodontal pathogens influence epithelial barrier function [1, 12, 13]. Microorganisms or their products mostly mediate the direct impact, affecting genes and proteins related to barrier function. Table 1 provides information on the in vitro evidence supporting the role of periodontal pathogens’ virulence factor in loss of oral keratinocyte junctional proteins and subsequent deterioration of epithelial barrier functions. Interestingly, even after removal of the periodontal pathogen, its indirect effect

on periodontal tissue homeostasis is seen to remain. Indeed, it has been shown that oral keratinocytes have sustained prolonged elevation of specific inflammatory markers after three days of eradication of periodontal pathogens, and these changes can affect the integrity of epithelial barrier function [14].

Table 1 : Periodontal pathogen virulence factors and their specific targets in the oral epithelial barrier.

Pathogen	ATCC Strain	Virulence	Study cells	Junctional protein(s)	Assay	Reference/ (year)
P. g	AT33277	WT	OECs	E-Cad	IF, WB	[34] (2017)
P. g	AT33277	WT	MDCK	Claudin, E-Cad	IF, WB	[61] (2000)
P. g	AT33277	WT	IHGK	ZO-1, Occludin	IF	[29] (2018)
P. g	AT33277	WT	IOEC B11	ZO-1, Occludin	IF	[31] (2021)
P. g	AT33277	WT	MDCK	E-Cad	WB	[35] (2002)
P. g	AT33277, W83, KDP 136	WT	IHGK	Claudin 1,2, Occludin	IHC, IF	[28] (2010)
P. g	AT33277 KDP136 TDC60	WT	IHGE	JAM-1	WB	[33] (2019)
P. g	AT33277	WT	IHGK	Occludin	IF	[32] (2020)
P. g		LPS	IHGE	E-Cad	IF	[36] (2017)
P. g	AT33277	WT LPS	H413	Occludin, Cluadin1,4,15, Jam-A, Zo-1	IF, WB RT-PCR	[39] (2018)
A. a		Heat Killed	HGEC	E-Cad	IHC RT-PCR WB	[43] (2010)
A. a		Whole live	HGEC	CHX 43, ZO-1	RT-PCR WB	[44] (2006)
A. a		Whole live OMP29	HGEC	CHX 43	WB	[45] (2005)
A. a		Cdt	HGEC	E-Cad, β-Cat	IF RT-PCR	[46] (2013)
T. d	WT 35405, ATCC35405, prtP mutant K1	WT	HEp-2 EC	ZO-1	IF	[62] (2003)
T. d	WT 35405, ATCC35405, prtP, mutant K1	WT	MDCK	ZO-1, Caudin-1 Occludin	IF, WB	[54] (2018)
T. d	WT 35405, ATCC 35405, DMSP3, mutant K1	WT	MDCK	Zo-1	WB	[56] (2022)
E. Coli		LPS	EC, PDL	Claudin 1	IHC, FCM	[59] (2012)

P. g: *Porphyromonas gingivalis*, A. a: *actinomycecomitans,* T. d: *Treponema denticola, E.coli*: *Escherichia coli,* KDP 136: gingipains-deficient P. g strain, WT: Wild Type, ATCC: American type culture collection, prtP: prolyl-phenylalanine-specific protease (dentilisin), DMSP3 : msp-deficient mutant 3, LPS: Lipopolysaccharides, OMP29: outer membrane protein 29, Cdt: Cytolethal Distending Toxin, OECs: oral epithelial cells, MDCK: Madin-Darby Canine Kidney cell, IHGK: Immortalized Human Gingival Keratinocytes, IHGE : immortalized gingival epithelial cells , H413 : squamous cell carcinoma of the buccal mucosa cell line , IOEC B11:immortalized oral epithelial cells B11, HGEC: human gingival epithelial cells, EC: Rat's sulcular epithelial cell , PDL: Porcine periodontal ligament epithelial cell, E-Cad: epithelial cadherin, β-Cat: beta catenin, ZO-1:zonula occludens-1, JAM-1: junctional adhesion molecule 1 CHX 43:connexin 43, IF: immunofluorescence, WB: western blot, IHC: immunohistochemistry, RT-PCR: Reverse transcription polymerase chain reaction, FCM: flow cytometry.

Porphyromonas gingivalis

P. gingivalis is a member of the "red complex," and these bacteria are considered the primary microbiological factors important in the pathogenesis of periodontitis. It has recently been described as a 'keystone pathogen' [15,16]. *P. gingivalis* (ATCC 33277) is one of the most well-characterized clinically isolated bacterial strains that expresses fimbriae [17], is able to produce gingipains [18], and can invade and internalize in oral cells [19]. In contrast, fimbriae-deficient *P. gingivalis* strains also exist, including the W83 strain, and this variant shows low adherence to human gingival fibroblasts and produces gingipains [20]. While a third strain commonly used in studies is KDP 136, and this lacks both fimbria & gingipains [21]. The gingipains are a group of cysteine proteases with selectivity for arginine- or lysine-containing peptide bonds and are the most widely studied *P. gingivalis* proteases [22-24]. These proteases have been linked to a variety of important disease-associated roles, including hemagglutination, cytokine modulation, and antibody and epithelial cell-cell junctional complex destruction [18,25-27]. The impact of gingipains on epithelial tight junction integrity was recently investigated by Groeger *et al*. [28], who compared the influence of three *P. gingivalis* strains, which differ in their gingipain profiles, on the integrity of the epithelial barrier using a transepithelial electrical resistance (TER) reduction assay. It was found that infection of immortalized human gingival keratinocytes (IHGK) with *the P. gingivalis* strain ATCC 33277 influenced TER similarly to infection with the W83 strain. In contrast, the KDP 136 strain showed a minimal effect on epithelial barrier function. In the same study, the damaging effects of gingipains were prevented by the specific Kgp and Rgp inhibitors Z-Phe-Lys-2,4,6-trimethylbenzoyloxymethyl ketone and H-D-Phe-Phe-Arg-chloromethyl ketone, and unexpectedly the TER reduced to zero after an initial transitory rise. This decrease in TER might be attributable to *P. gingivalis* ability to synthesize a variety of different proteolytic enzymes equivalent to gingipains, which are detrimental to junctional complexes. These include eight endopeptidases and a number of exopeptidases [24]. Tight junctions are intercellular proteins that are a target of gingipain proteolytic effects. Infection of the gingival keratinocyte monolayer with the ATCC 33277 strain of *P. gingivalis* resulted in reduced expression of ZO-1

and occludin accompanied by reduced TER values. Interestingly, these deleterious effects on epithelial integrity were reversed by the combination of green and black tea extract and epigallocatechin-3-gallate [29,30]. This protective effect may be in part related to the ability of tea catechins to inhibit the protease activities of *P. gingivalis*. Recently, the tart cherry phenolic extract (*Prunus cerasus*) was also shown to exert a protective effect on epithelial barrier integrity in an in vitro model infected with *P. gingivalis* (ATCC 33277) [31]. Prunus cerasus extract caused a cessation of TER reduction as well as the destruction of tight junction proteins of ZO-1 and occludin. Furthermore, highbush blueberry extract was also shown to protect the integrity of the gingival keratinocyte barrier by reversing *P. gingivalis*-mediated damage via inhibiting proteinase activity as determined by TER analysis and visualization of occludin expression [32]. Collectively, these results provide a promising array of natural therapeutics for the treatment of periodontitis due to their ability to attenuate the virulence properties of *P. gingivalis* and thereby restrict the ability of this pathogen to impair oral epithelial barrier function. Wild-type *P. gingivalis*-secreted gingipains have the ability to degrade the tight junction M1 protein (JAM1) in gingival epithelial cells, resulting in increased permeability of the gingival epithelium to the microbial virulence factors of lipopolysaccharide and proteoglycan. A similar effect was shown upon infection with the TDC60 strain clinically isolated from periodontal pockets. In contrast, the *P. gingivalis* strain lacking gingipains (KDP136) showed impaired degradation of JAM1, indicating the pivotal role of the secreted gingipains in disrupting the barrier function of stratified squamous epithelium via degradation of its tight junction protein (JAM1). Consequently, this damage would allow further bacterial virulence factors to penetrate into the subepithelial tissues [33]. Data on cadherin-based adherens junctions indicates that infection of primary oral epithelial cells with *P. gingivalis* ATCC 33277 results in loss of the junctional protein e-cadherin. Notably, the decrease detected was positively linked with the period of infection [34]. Similar results were found when Madin-Darby canine kidney (MDCK) cells were infected with the ATCC 33277 strain with the evident disruption of adherens junction proteins of E-cadherin, beta1-integrin, and the tight junction, occludin [27]. Interestingly, the immunoprecipitated occludin and E-cadherin proteins from the MDCK cell lysates were degraded by *P. gingivalis*, suggesting that these bacterial proteases are capable of cleaving epithelial junction transmembrane proteins. It is important to note that in the aforementioned study, both basolateral and apical exposure to bacteria resulted in cell-cell connection disruption. Notably, the latter effect manifested over a longer time period compared with the former, emphasizing the importance of an intact epithelial barrier. *P. gingivalis* gingipains exhibit varying levels of proteolytic activity. Indeed, in the study by Katz *et al*. [35], MDCK epithelial cell cultures were treated with the three arginine- and lysine-specific gingipains of *P. gingivalis* (i.e., HRgpA, RgpB, and Kgp, respectively) to compare their E-cadherin hydrolyzing effect. As determined by western blotting, all gingipains resulted in efficient and comparable hydrolysis of the e-cadherin protein. Kgp, in particular, was the most efficient in hydrolyzing the E-cadherin molecules at the adherens junction. Furthermore, the degradative capability of the whole gingipain Kgp was evaluated in comparison to its catalytic domain alone. Although both had catalytic activity, Kgp was more effective than its catalytic domain at a 500 nM concentration, but not at the lower concentration of 250 nM. These findings indicate that the Kgp hemagglutinin domain plays a degradative role in a dose-dependent manner. Another important virulence factor of *P. gingivalis* is the endotoxin, LPS. This microbial toxic product represents a powerful antigen to gingival epithelium cells by triggering the production of a wide array of inflammatory molecules, including cytokines, prostaglandins, proteolytic enzymes, and reactive oxygen species (ROS). Consequently, these molecules induce the destruction of the periodontal tissues. It has been shown that following incubation of human gingival epithelial cells with *P. gingivalis*-LPS, epithelial barrier function is disrupted, and this was related to decreased immunofluorescence expression of E-cadherin in the infected cells. Consequently, this initial reduction in E-cadherin enabled accelerated penetration of *P. gingivalis* LPS through the epithelial cell monolayer [36]. In addition, to attempt to reverse this damage, antioxidants such as vitamins C and E and L-ascorbic acid 2-phosphate magnesium salt (APM), applied as major ROS scavengers, were supplemented into cultures. In accordance with evidence from other cell studies, the added antioxidants demonstrated the potential to restore the impaired epithelial barrier function by scavenging harmful ROS as evidenced by modulating E-cadherin expression back to pre-infection levels [36-38]. The effect of LPS in contrast to the whole pathogen has also been investigated on tight junction protein differential expression, including claudin-1, claudin-15, ZO-1, JAM-A, and claudin-4. Following challenges with whole *P. gingivalis, P. gingivalis* LPS, and the danger/damage signal (ATP) [39], data demonstrated that *P. gingivalis* LPS alone had a more powerful effect on disrupting the epithelial barrier compared with the whole bacterium. ATP stimulation enhanced the reaction of TJ proteins to *P. gingivalis* invasion and LPS destruction and also modulated inflammatory mediators and cytokine secretion [40].

Aggregatibacter actinomycetemcomitans

A. actinomycetemcomitans is a Gram-negative facultative periodontal pathogen that colonizes the oral cavity [41]. *A. actinomycetemcomitans* is highly genetically diverse and expresses a wide range of virulence factors closely associated with periodontitis pathogenesis [42]. The potential capacity of whole *A. actinomycetemcomitans* for modulating the expression of adherens, gap, and tight junction proteins has also been investigated [43-45]. Whole live *A. actinomycetemcomitans* application to rat gingival sulcus and cultured human gingival epithelial cells

(HGECs) decreased the number of cells positive for E-cadherin and for gene and protein expression of both zonula occludens-1 (ZO-1) and connexin-43 (CX43). *A. actinomycetemcomitans* has a unique cytolethal distending toxin (Cdt) that is exclusively found in this bacterium. Cdt is expressed by 66% to 86% of *A. actinomycetemcomitans* strains, and its presence has been linked to periodontal disease etiology [74]. When HGECs were treated with recombinant Cdt from *A. actinomycetemcomitans*, morphological changes in the epithelial compartment of the human gingival explant included detachment of the keratinized outer layer, distention of spinous and basal cells in the oral epithelium, and disruption of rete pegs [46]. Furthermore, there was an increase in the expression and cytosolic distribution of E-cadherin, which was accompanied by an increase in the levels of the intracellular scaffolding proteins, beta-catenin and beta-actin. These data indicated that Cdt induced remodeling of adherens junctions, and this may impact the barrier function of the gingival epithelium. *A. actinomycetemcomitans* outer membrane proteins (OMPs) play an important role in antigen transport. The twenty-nine kilodalton OMP (OMP29) of *A. actinomycetemcomitans* is an antigenic determinant to which IgG antibodies in the sera of many advanced-stage periodontitis patients react [47]. Hence, OMP29 is recognized as a major virulence factor for the pathogenesis of periodontal disease. It has been demonstrated that infection of cultured HGECs with *A. actinomycetemcomitans* and its virulence factor OMP29 reduced the production of both phosphorylated and non-phosphorylated versions of the gap junction protein CX43 [45]. Interestingly, it has been shown that the treatment of cultured HGECs with an anti-gastric ulcer agent (irsogladine maleate) halts *A. actinomycetemcomitans*-induced changes in junctional protein expression due to its ability to modulate inflammation. Data demonstrated the suppressive effect of irsogladine maleate on the local production of the cytokines IL-8, CXCL-1, CXCL-2, CXCL-3, CXCL-6, and CXCL-8 with subsequent inhibition of neutrophil migration and recovery of pre-infection junctional protein levels mediated by the p38 MAP kinase and ERK pathways [45, 48].

Treponema denticola

Along with other proteolytic pathogens, *T. denticola* forms the “red complex” with *P. gingivalis* and *T. forsythia* [49]. Peptidoglycans, outer-sheath-associated peptidases, chymotrypsin-like and trypsin-like proteinases, major surface protein (MSP), hemolytic and hemagglutinating activity, adhesins that attach to matrix proteins and cells, and an outer-sheath protein with pore-forming properties represent the virulence components that enable this microbiome to be a successful periodontal pathogen that elicits a wide array of destructive effects on the periodontal tissues [50]. *T. denticola* is able to induce several cytopathic effects, such as membrane blebbing, vacuolization, inhibition of motility, and loss of epithelial cell contacts [51]. Virulent peptidoglycans account for 0.1% of the dry weight of T. denticola and were previously considered an inert molecule responsible for the spirochetes' coiled shape [52]. Incubation of epithelial cells with *T. denticola* peptidoglycan resulted in peripheral vesicle formation accompanied by loss of cell junction visualized using electron microscopy [53]. Upon infection, Treponema shed their chymotrypsin-like proteinase (Dentisilin), which rapidly penetrates the infected cell layers and causes increased permeability of the epithelium [51]. The effects of the whole *T. denticola* and its dentisilin on human periodontal cell cultures were confirmed when infected epithelial multilayers lost their lateral cellular connections, the intercellular gaps collapsed, and the permeability increased following infection. Moreover, immunogold electron microscopy demonstrated the ability of *T. denticola* to transport dentisilin into newly formed large intracellular vacuoles within the infected epithelial layers [51]. The effect of dentisilin on epithelial barrier integrity was confirmed in a study that compared epithelial monolayer infection with wild-type and dentisilin-mutant *T. denticola*. The wild-type form disrupted TER and penetrated deeply into the epithelium. In contrast, the dentisilin mutant altered the monolayer minimally and exhibited limited entry into the epithelial monolayer. Furthermore, immunofluorescence analysis indicated that *T. denticola*-induced TER change was mediated by dentisilin degradation of the tight junctional protein, ZO-1 [54]. An additional virulence factor, MSP, the predominant component of the T. denticola outer sheath, exists as a complex with the surface protein dentisilin [55]. *T. denticola* MSP mediates microbial adhesion to different types of matrix proteins, such as fibronectin, laminin, and keratin, as well as to host cells, including fibroblasts and epithelial cells. It exerts a cytopathic effect similar to that of dentisilin [50]. In accordance with the previous study, it was shown that infection of MDKC with wild-type and the MSP mutant *T. denticola* resulted in degradation of the ZO-1 protein in contrast to cells infected with dentisilin mutants alone [56].

Escherichia coli

The identification of extra-intestinal pathogenic *E. coli* strains and their interactions with the mucosal immune system supports the need for more investigations into their influence on oral epithelial barrier integrity [57]. Bacterial cell surface-associated virulence factors include flagellum, capsular lipopolysaccharide, and other outer membrane proteins, while hemolysin and siderophores represent secreted virulence factors [58]. It has been shown that the topical daily administration of *E. coli* LPS to the rat gingival sulcus for 8 weeks resulted in a reduction in claudin-1 protein expression. In parallel, persistent *E. coli* LPS treatment of porcine epithelial cell cultures for 3 weeks lowered TER and claudin-1 gene and protein expression [59]. Furthermore, 8 days of exposure of H400 oral keratinocytes to *E. coli* LPS, heat-killed *P. gingivalis*, and *F. nucleatum* resulted in a significant down-regulation of E-cadherin and β-catenin compared with the unstimulated control, with the highest β-catenin

down-regulation detected with *E. coli* LPS exposure alone [60].

Conclusion

Collectively, these studies demonstrate that the integrity or deterioration of the oral epithelial barrier results from the complex interplay between host cells, the immune system, and microbial virulence factors. An understanding of these interactions is crucial for determining the molecular and cellular dynamics that underpin periodontal health and disease status. Consequently, this knowledge is essential for developing successful disease management and preventive and therapeutic strategies, particularly for individuals at high risk of periodontitis progression. This includes emphasizing the importance of periodic periodontal examination for early disease detection and delivering full periodontal therapeutic protocols to ensure eradication of the highly pathogenic periodontal pathogens. To date, the potential of utilizing therapeutic agents in reversing the disruption of the oral epithelial junction remains largely confined to experimental and preclinical studies, with the existing research being primarily centered on cancer-related contexts.

Conflict of interests

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Data sharing statement

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