Review Article

Turning Barrier Cells into Invaders: The Epithelial-Mesenchymal Transition Signature of *Porphyromonas gingivalis*

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Abstract | *Porphyromonas gingivalis* has been considered as one of the most important keystone pathogens in the pathogenicity of periodontitis by virtue of its capacity to modify the host's immune response and the subgingival microbiota. There is increasing evidence that Epithelial-Mesenchymal Transition (EMT) is a fundamental biological process in development, inflammation, and fibrosis and may represent an essential link in the relationship between microbial insult and epithelial barrier damage in periodontal tissue. The present review aims to integrate current information regarding how *P. gingivalis* and its major virulence factors (*i.e.*, gingipains, lipopolysaccharide, and outer membrane vesicles) stimulate and perpetuate EMT in gingival epithelial cells with particular focus on the interaction between the virulence mechanisms of *P. gingivalis* and the conventional EMT associated signaling pathways (e.g. TGF-β/ Smad, Wnt/ β catenin, and NF-κB). The role of EMT in maintaining chronic inflammation, enhancing bacterial invasion, promoting pathological fibrosis, and disrupting the integrity of epithelial barriers, which ultimately define the progression of the disease, is also outlined. Clinical relevance of EMT mediated pathology is addressed in relation to potential biomarkers used for assessing disease activity and novel host modulation therapies to prevent EMT mediated tissue damage. Understanding the contribution of *P. gingivalis* induced EMT represents a paradigmatic shift in the knowledge of periodontal pathogenesis and identifies new areas of interest for both diagnostics and therapeutics.

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Introduction

Periodontitis is an extremely common multifactorial oral disease, induced by a dysbiotic microbial biofilm which initiates a chronic inflammatory reaction, thereby causing the gradual deterioration of the periodontium, including the gingiva, periodontal ligament, and alveolar bone (Harbood *et al.*, 2024; Abd Alhussien and Mahmood, 2025; Albuslutan *et al.*, 2025). If untreated, the degradation of tissues will eventually result in the loss of teeth, ultimately resulting in the loss of oral function and the quality of life of the patient (Fadhil *et al.*, 2022; Harbood *et al.*, 2024; Reyes-Garita *et al.*, 2024). The etiology of the disease is complex and represents a chronic feedback loop among the virulence factors of the pathogenic

bacteria mediating a dysregulated host immune response (Sharaf and Hijazi, 2022). There are many members of the consortia of periodontal pathogens, but among them, the Gram-negative anaerobic bacterium *Porphyromonas gingivalis* has been designated as a "keystone pathogen" (Hajishengallis *et al*., 2012; Kareem *et al*., 2022). *P. gingivalis* at low population density can induce the host immune system to respond abnormally and create a dysbiotic shift in the commensal microbiota to generate an inflammatory environment that promotes tissue destruction (Zenobia and Hajishengallis, 2015; Chen *et al*., 2023). Maintaining the integrity of the gingival epithelium, is important for preserving the periodontal health, since it provides the first line of defense against the constant onslaught of the subgingival biofilm from a physical and immunological standpoint (Takahashi *et al*., 2019; Kareem *et al*., 2022). Disruption of this barrier is an essential initial event in the onset and progression of periodontitis. Recent studies have identified a basic biological process known as, epithelial-mesenchymal transition (EMT), as a plausible method through which barrier dysfunction and subsequent tissue pathology occur in periodontitis (Abdulkareem, 2017; Abdulkareem *et al*., 2018; Saliem *et al*., 2022, 2023; Alanbari *et al*., 2025).

EMT is a dynamic and reversible program of cellular differentiation, in which polarized epithelial cells undergo a series of molecular transformations to lose cell-cell junctions and apical-basal polarity in order to acquire a mesenchymal cell phenotype (Saliem *et al*., 2022). Through undergoing this transition, these cells become more capable of migration, invasion, and resistance to apoptosis than before. Although type 1 EMT is an obligatory process during embryonic development and wound healing, dysfunctional EMT (types 2 and 3) has recently been identified as a potential initiator of pathologies in chronic inflammatory diseases, fibrotic diseases, and cancer (Škovierová *et al*., 2018; Zou *et al*., 2025).

Recent compelling evidence now clearly indicates that *P. gingivalis* infection causes EMT induction in periodontal epithelial cells (Abdulkareem *et al*., 2018). Due to its numerous virulence factors, *P. gingivalis* may easily disrupt host cell signaling pathways to initiate the EMT program. Thus, *P. gingivalis*-induced cellular programming is another part of the periodontitis disease causation puzzle that has not been previously explored until now, and therefore, provides a mechanism to explain how a protozoal insult results in impaired barrier function, increased bacterial invasion, dysregulation of pathological tissue remodeling and chronic inflammation over time.

The objective of this paper is to present a complete review of the role of *P. gingivalis* in the induction of EMT during periodontitis. First, we will describe the primary characteristics and virulence factors of *P. gingivalis* responsible for creating the host microenvironment. Next, we will outline the fundamental molecular mechanisms of EMT. Most of this study will focus on reviewing and integrating the evidence supporting *P. gingivalis*-induced EMT and describing the specific signaling pathways involved. Finally, we will discuss the pathological and physiological implications of this process for the progression of periodontitis and possibly identify some areas for future diagnostic and therapeutic approaches.

Porphyromonas gingivalis: The master manipulator of the periodontal microenvironment

Porphyromonas gingivalis is a black-pigmented, asaccharolytic, Gram-negative anaerobic bacterium historically considered as one of the primary etiological agents of chronic periodontitis (Mysak *et al*., 2014). The pathogenicity of *P. gingivalis* is not due to overwhelming the host defence mechanisms by sheer numbers, but rather it is an example of a keystone pathogen, being able to subvert and manipulate the host immune response, and creating a dysbiotic and inflammatory environment from which it and other pathogens benefit (Xu *et al*., 2020). This manipulation occurs through a variety of virulence factors that directly and indirectly help with the destruction of periodontal tissues (Aleksijević *et al*., 2022). At the forefront of these virulence factors are the gingipains, a class of virulent cysteine proteases that can either be secreted or remain attached to the cell surface. Gingipains are classified as arginine-specific (RgpA, RgpB) and lysine-specific (Kgp) (de Diego *et al*., 2014). Their proteolytic actions are extensive and pleiotropic, as they degrade collagen and fibronectin, process bacterial surface proteins for adherence, and most importantly, they disassemble integral components of the host immune system (de Diego *et al*., 2014). Gingipains can degrade immunoglobulins, complement components, cytokines, and ultimately paralyze both innate and adaptive immunity (Zenobia and Hajishengallis, 2015). They can also activate host metalloproteinases (MMPs) that ultimately contribute to the cascade of connective tissue degradation

(Chen *et al.*, 2023). *Porphyromonas gingivalis'* ability to adhere to and invade host cells, which allows for the persistent presence of this bacterium, is dependent on the formation of fimbriae. The long (major) fimbriae are made up of FimA subunits and provide an opportunity for attachment to host cells, other bacteria in the biofilm and extracellular matrix proteins (Pandit *et al.*, 2015). This attachment, in addition to anchoring the bacterium, leads to the activation of a series of intracellular signaling events in the host epithelial cells, resulting in the modulation of the host's cellular function in favor of the bacterial pathogen (Pandit *et al.*, 2015).

The outer membrane of *P. gingivalis* also serves as a reservoir of virulence factors including lipopolysaccharide (LPS) (Jia *et al.*, 2019). *P. gingivalis* LPS is a potent pro-inflammatory factor that interacts with host toll-like receptors (TLRs), especially TLR2 and TLR4 on immune and epithelial cells (Jia *et al.*, 2019). This interaction activates intracellular signaling via the transcription factor nuclear factor-kappa B (NF-κB), resulting in the expression of a multitude of pro-inflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α) and chemokines (Liao *et al.*, 2025). This prolonged inflammatory signaling is a feature of the periodontitis lesion and contributes directly to tissue destruction (Figure 1).

In addition to individual molecules, *P. gingivalis* releases outer membrane vesicles (OMVs). OMVs are proteoliposomes having a size range of 50-250 nm. They are a heterologous and very effective long-range delivery vehicle. OMVs are packed with a concentrated and diverse cargo of gingipains, LPS, other proteins, and lipid virulence factors (Liao *et al.*, 2025). They can fuse with host cells and deliver these virulence factors directly into the cytoplasm of the host cell. In this way, the virulence factors are protected from host degrading enzymes and can elicit a pathogenic response well beyond the local area of the bacterium (How *et al.*, 2016, Hamid *et al.*, 2025). *P. gingivalis* utilizes these approaches and more, to successfully evade host defenses, establish chronic inflammation, and directly mediate the destruction of periodontal tissues (How *et al.*, 2016).

Epithelial-mesenchymal transition: A cellular reprogramming process

Epithelial-Mesenchymal Transition (EMT) is a highly conserved cellular program characterized by a process whereby fully differentiated epithelial cells undergo phenotypic conversion to a mesenchymal-like cell

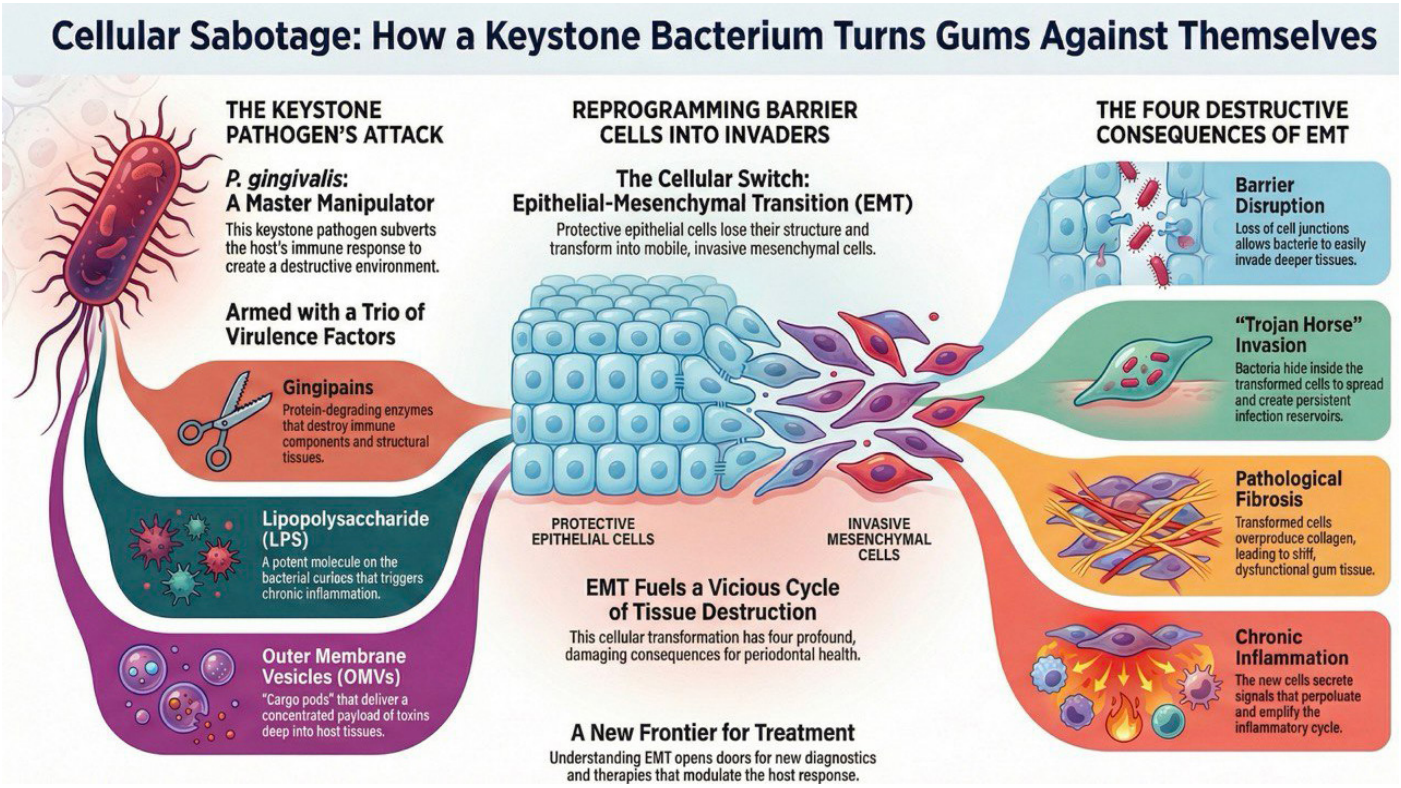

Figure 1: *Porphyromonas gingivalis virulence factors may trigger EMT in gingival epithelial cells, converting the protective barrier cells into invasive mesenchymal-like cells. This shift likely weakens the epithelial barrier and promotes persistent infection, fibrosis, and chronic inflammation in periodontitis.*

(Abdulkareem *et al.*, 2018; Saliem *et al.*, 2022, 2023; Kazem *et al.*, 2025). The transition from an epithelial phenotype to a mesenchymal phenotype will result in all aspects of cellular structure being altered and may alter the gene expression profile of the cell (Hosseinirad *et al.*, 2025). The apico-basal polarity characteristic of the epithelial cells will be lost, in addition to the disruption of tight junctions between the cells, which are responsible for the cells forming a cohesive sheet of epithelial tissue (Abdulkareem, 2017). EMT also results in cells acquiring different functional and morphological characteristics (Kazem *et al.*, 2025). Specifically, the cells become spindle-shaped, lose their stationary nature, and acquire greater ability to migrate and invade (Abdulkareem, 2017). At the molecular level, EMT is regulated through established transcriptional programs. In particular, downregulation of the epithelial adhesion proteins occurs with downregulation of E-cadherin being identified as the defining event of EMT (Hosseinirad *et al.*, 2025). E-cadherin is a transmembrane protein; a key component of adherens junctions, responsible for cell-cell adhesion and maintaining structural integrity of the epithelium (Asl *et al.*, 2025; Kazem *et al.*, 2025).

E-cadherin repression is typically accompanied by decreased expression of other junctional proteins such as claudins and occludins. At the same time, a coordinated process upregulates mesenchymal markers, including N-cadherin (which promotes transient cell-cell interactions), vimentin (an intermediate filament protein), and extracellular matrix (ECM) components such as fibronectin and type I collagen (Nie *et al.*, 2025).

Transcriptional reprogramming is governed by a core set of EMT-driving transcription factors (EMT-TFs), which consist of members of the Snail (Snail1/2), zinc finger E-box binding homeobox (ZEB) (ZEB1/2), and Twist families. These transcription factors are master regulators, acting by direct binding to the promoter of the E-cadherin gene (*CDH1*) to repress transcription. Activation of the EMT-TFs is dependent on the integration of multiple major signaling pathways. The transforming growth factor (TGF)-β pathway is one of the best studied and most robustly characterized inducers of EMT (Lien *et al.*, 2024). Upon ligand binding to TGF-β receptors, intracellular activation and nuclear translocation of Smad proteins occur to regulate the expression of EMT-TFs. Other key pathways include Wnt/β-catenin, in which nuclear translocation of β-catenin activates transcription of EMT-related genes (Zhang *et al.*, 2025).

Crucially, EMT should not be regarded as a binary, on-off switch, but rather an active continuum, where cells can exist in intermediate (partial-EMT) states, co-expressing both epithelial and mesenchymal markers (Wesseling *et al.*, 2018). Depending on the biological context, EMT is broadly classified in three types: (1) Type 1 EMT typically occurs during embryogenesis and development; (2) Type 3 EMT is linked to cancer progression and metastasis; and (3) Type 2 EMT, is related to wound healing and tissue regeneration, and is also linked to fibrosis and chronic inflammation, making it the most relevant type in the context of periodontitis pathogenesis (Škovierová *et al.*, 2018).

P. gingivalis as a robust inducer of EMT in periodontal tissues

This concept reflects a remarkable paradigm shift that a periodontal pathogen could trigger a cellular process as fundamental to host cells as EMT (Asl *et al.*, 2025). A growing body of evidence from *in vitro* and *in vivo* studies strongly suggests that *P. gingivalis* is a robust inducer of EMT in gingival and oral epithelial cells (Liao *et al.*, 2025). The bacterium activates this process through a dual approach: (1) by direct receptor engagement of host cell receptors via its virulence factors; and (2) through indirect stimulation by generating a pro-inflammatory and permissive microenvironment for EMT. Direct induction mechanisms involve direct interactions between *P. gingivalis* components and epithelial cells. In this regard, it has been shown that *P. gingivalis* infection or exposure to OMVs can promote EMT in oral epithelia (Liao *et al.*, 2025). One of the key pathways involved in EMT is the exposure of TLRs to LPS binding which then activates the NF-κB signaling cascade. While NF-κB is recognized for its role in the promotion of cell inflammation, it also has the ability to directly promote the expression of EMT-TFs such as Snail and ZEB1, which in turn will activate the EMT program. In addition, gingipains have been demonstrated to cleave E-cadherin and disrupt adherens junctions, which in turn liberates β-catenin, allowing it to translocate to the nucleus and activate the Wnt signaling pathway (Liao *et al.*, 2025). The dual ability to induce EMT TFs while directly disrupting cell to cell adhesions is a

particularly potent mechanism for promoting EMT-like epithelial remodeling.

Indirectly, the influence of *P. gingivalis* creates an inflammatory microenvironment rich in host-derived EMT inducers (Lee *et al*., 2017). The chronic inflammation induced by *P. gingivalis* results in prolonged release of pro-inflammatory cytokines and growth factors from both infiltrating immune cells (e.g., macrophages, lymphocytes) and resident stromal cells (e.g., fibroblasts). Among many others, tumor growth factor beta (TGF-β) is a potent EMT inducing cytokine. *P. gingivalis* has been shown to stimulate the TGF-β signaling that drives EMT *via* the canonical Smad pathway (Gao *et al*., 2023). Similarly, the inflammatory mediators such as interleukin-6 (IL-6) are elevated in periodontitis and can be induced by *P. gingivalis*, and are also known to promote EMT, in part through the action of the STAT3 signaling pathway (Chen *et al*., 2022). In this way, a vicious cycle is established where a bacterial infection can initiate inflammation, which in turn can induce EMT, and the EMT-transformed cells may produce greater amounts of pro-inflammatory factors, propagating the cycle. This prolonged feedforward cycle is a common feature of chronic inflammation and represents an important feature of chronic periodontitis pathology. The ability of *P. gingivalis* to influence core biological processes regulating cell cycling and EMT explains its position in inducing the pathogenic alterations of the host epithelium (Abdulkareem *et al*., 2018).

Pathophysiological consequences of EMT in periods of periodontitis progression

Induction of EMT in the gingival epithelium is not merely a benign cellular event; rather, it carries profound and deleterious effects that unequivocally contribute to the hallmark pathological features of periodontitis (Abdulkareem, 2017). By inducing epithelial cells to acquire a migratory and invasive phenotype, *P. gingivalis* destabilizes the primary barrier to the periodontium and contributes to the cycle of tissue destruction (Asl *et al*., 2025).

The first impact of EMT is catastrophic disruption of the epithelial barrier. As EMT leads to loss of E-cadherin and degradation of tight and adherens junctions, the paracellular permeability increases (Saliem *et al*., 2022). Compromise in barrier function permits bacterial ingress and virulence factors, starting from subgingival plaque to the connective tissues of the periodontium (Ji and Choi, 2020). Increased exposure of connective tissues to bacterial products, such as LPS, may magnify an inflammatory response and greater recruitment of host immune components, in addition to increased production of tissue destructive enzymes like MMPs and mediators (Sell *et al*., 2017).

A second effect of EMT is that the migratory and invasive phenotype afforded to EMT transformed cells promotes deeper penetration of the bacteria (Saliem *et al*., 2022). *P. gingivalis* can invade and survive in epithelial cells, protecting itself from the host response and antibiotic therapy (Holt and Ebersole, 2005). When these cells undergo EMT, they gain the ability to migrate from the epithelial layer into the connective tissue. This may permit a "Trojan horse" mechanism by the pathogen, allowing it to migrate deeper into periodontal tissues and create persistent reservoirs of infection. Moreover, this may offer a possibility to access the systemic circulation (Abdulkareem *et al*., 2018).

A third effect of EMT is that it allows for fibrotic and pathological remodeling of periodontal tissues. Mesenchymal cells are defined by their tremendous capacity to produce ECM components. The epithelial to fibroblast-like cell transition results in excessive deposition of collagen and fibronectin, accounting for the fibrotic, hyperplastic appearance often observed in chronic gingivitis and periodontitis (Shoker, 2022). This pathological fibrosis disrupts normal tissue's architecture and function of the periodontal ligament and creates harsh, stiff, and hypoxic microenvironments that may promote inflammation and inhibit effective repair and regeneration of tissues (Huang *et al*., 2024).

Finally, the EMT cells participate in the inflammatory response and promote the inflammatory state. Mesenchymal-like cells have an altered secretome, producing a unique profile of cytokines, chemokines, and growth factors compared to the epithelial cells. Moreover, they can secrete pro-inflammatory and pro-fibrotic mediators, which exacerbate the inflammatory response and recruit more immune cells to the infection site (Marconi *et al*., 2021). Thus, we have established a self-perpetuating loop, wherein *P. gingivalis* causes EMT, the mesenchymal cells are patterned to produce a microenvironment that

continues to promote inflammation and breakdown of periodontal tissues, thereby defining the progressive nature of periodontitis.

Clinical implications and future therapeutic directions

Defining *P. gingivalis* induced EMT as a core mechanistic mediator of periodontitis pathology has future clinical opportunities practically across the continuum of care: from diagnostics to therapeutics. Although there are many ways to consider treatments using solely an antibacterial approach to treating periodontal diseases; however, looking into the host cell's biological processes that contribute to inflammation may be a better way to inhibit the ongoing inflammatory process and promote true regeneration of periodontal tissues. During diagnosis, substances associated with the EMT process can provide potential biomarkers for determining disease activity and predicting outcomes. Using examples from these areas, detection of soluble E-cadherin fragments or increased levels of mesenchymal markers (like vimentin) within the gingival crevicular fluid could potentially determine if the patients have an active breakdown of their epithelial barrier and/or active tissue remodeling. As such, additional use of these biomarkers can be employed to help identify patients at high-risk of aggressive disease progression and monitor the effectiveness of targeted therapies at the molecular level.

The broader clinical implications are for the development of unique therapeutic strategies. Classical periodontal therapy relies on mechanical debridement to decrease the bacterial load, which may provide an advantage, but does not resolve the inflammatory state or reverse tissue damage. Host-modulation therapy aimed at modulating and tempering the destructive host response is an emerging area of research. Targeting EMT presents many potential therapeutic targets. One approach could target the specific virulence factors of *P. gingivalis* that induce EMT, such as specific inhibition of gingipains (Wu *et al.*, 2025).

Another more direct approach could be to inhibit the key host signaling pathways driving EMT. Given the importance of TGF-β in executing the EMT process, small molecule inhibitors of the TGF-β receptor or downstream signaling components may be sufficient to prevent the EMT process (Toma *et al.*, 2022). Additional potentially successful modifiers could be Wnt/β-catenin or NF-κB pathways. The short and rapid pathway to the clinic for periodontitis therapy could be repurposing drugs developed for anti-cancer or anti-fibrotic therapies that are often directed toward those pathways (Alameer *et al.*, 2024; Jia *et al.*, 2025). For example, the natural flavonoid; fisetin, has shown the ability to inhibit EMT induced by periodontal pathogens in oral cells by inhibiting the Wnt/β-catenin pathway (Zhang *et al.*, 2025). An integrated therapeutic strategy combining conventional antimicrobial approaches and host-modulating drugs specifically targeting inhibition of EMT may be more effective than either strategy alone. While the microbial trigger is removed, a combination strategy can also actively block the downstream cascade of tissue destruction, creating a more conducive environment for healing and regeneration.

Conclusions and Recommendations

Periodontitis pathogenesis results from a dysfunctional interaction between the dysbiotic oral microbiota and an abnormal host response. *Porphyromonas gingivalis,* acting as a keystone pathogen, initiates the cell destruction process and maintains it through the activation of a series of cellular responses and signaling cascades leading to a cellular transformation (EMT). The data presented in this study support the concept that *P. gingivalis's* effect on the host is not limited to an inflammatory stimulus, but rather it induces a fundamental cellular reprogramming event. This cellular reprogramming EMT event is induced by *P. gingivalis via* the activation of various virulence factor-derived signaling pathways, transforming the periodontal epithelial cells from a protective barrier state into a destructive, migratory, and profibrotic phenotype. Thus, the microorganism-induced EMT serves as a critical link connecting the microbial challenge with the hallmarks of periodontitis; mainly destruction of the epithelial barrier, increase in bacterial penetration of the epithelial layer, production of pathological fibrosis, and perpetuation of the chronic inflammation. As such, incorporation of EMT into the features of periodontitis pathogenesis will revolutionize our understanding of the disease and the therapeutic applications of periodontitis treatment. Additional work on this phenomenon could enable new EMT-informed diagnostics and host-modulating therapies that target inflammation and support periodontal repair. Future studies are recommended that may clarify whether *P. gingivalis*–

driven EMT is a true causal pathway in human periodontitis, not just an associated finding, using longitudinal and cell-resolved approaches linked to clinical outcomes

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Novelty Statement

This review highlights *P. gingivalis*–induced EMT as a plausible mechanistic link between epithelial barrier breakdown and periodontitis progression, and summarizes EMT-informed biomarkers and host-modulation opportunities to complement conventional therapy.

Author's Contribution

HMA: Conceptualization, review drafting, and final approval of the submitted version.
SSS: Revision, editing, and final approval of the submitted version.

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During the preparation of this work, the author used Quilbot premium to paraphrase. After using this tool/service, the author reviewed and edited the content as needed and took full responsibility for the content of the publication.

Conflict of interests
The authors have declared no conflicts of interest.

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