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Review Article

RNA interference and its regulatory role in oral biofilm formation and pathogenicity

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Abstract

Objective: This systematic review examines how RNA-based regulatory mechanisms modulate host–microbe interactions, particularly focusing on how RNA molecules, extracellular vesicle–associated RNA cargo, transcriptional responses, and host genetic polymorphisms influence the development, persistence, and pathogenicity of oral biofilms.

Materials and Methods: Thirty-four original research articles were selected from a predefined database. Studies were screened using PRISMA guidelines, and only experimental work involving RNA regulation, RNA-bearing extracellular vesicles, transcriptomics, or host genetic susceptibility were included. Narrative synthesis was adopted due to methodological heterogeneity across models such as epithelial cultures, animal models, transcriptomic platforms, and microbial biofilm systems.

Results: Strong evidence indicates that RNA-mediated processes contribute critically to host responses against oral biofilms. Streptococcus mutans and Porphyromonas gingivalis produce extracellular vesicles containing RNA cargo that modulates epithelial barrier pathways, inflammatory cytokine expression, and innate immune gene signatures. Host genetic polymorphisms in IL-1β, MMPs, FOXP3, and other immune-regulatory genes influence susceptibility to biofilm-associated disease. Transcriptomic studies reveal that epithelial cells and periodontal ligament stem cells undergo significant RNA-level remodeling when exposed to pathogenic biofilms, especially under nutrient or iron-limited conditions. These host RNA responses influence tissue resilience, inflammation intensity, and disease progression.

Conclusion: RNA-associated regulatory mechanisms are central to the host's reaction to oral biofilms and significantly influence pathogenicity, inflammation, barrier dysfunction, and susceptibility to periodontal or peri-implant disease. Understanding cross-kingdom RNA signaling—particularly EV-RNA and host transcriptional regulation—may uncover new diagnostics and targeted RNA-based therapies for oral infectious diseases.

Keywords: RNA interference, Extracellular vesicles, Host–microbe interactions, Oral biofilm, Epithelial barrier, Transcriptomics, Porphyromonas gingivalis, Streptococcus mutans, Gene regulation, Immune modulation.

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1. Introduction

Oral biofilms represent highly coordinated microbial communities capable of adapting to environmental stresses, resisting host immunity, and inducing chronic inflammatory states. Historically, biofilm pathogenicity was attributed primarily to microbial factors such as enzymatic activity, acidogenicity, or extracellular polymeric substance (EPS) production. However, contemporary molecular studies reveal that RNA-based regulation plays a central role in shaping the complex dialogue between microorganisms and host tissues.

The discovery of targeted genetic silencing by double-stranded RNA in Caenorhabditis elegans (Fire et al., 1998)[1] revolutionized understanding of RNA-mediated control of gene expression. While bacteria themselves do not possess canonical eukaryotic RNA interference machinery, they rely extensively on small RNAs (sRNAs), antisense transcripts, regulatory riboswitches, transcriptional RNA networks, and RNA-bearing extracellular vesicles (EVs) to coordinate environmental adaptation and virulence.

At the same time, host cells—gingival epithelial cells, periodontal ligament cells, immune cells—respond to microbial challenges via rapid transcriptional modulation, ribonuclease activation, cytokine mRNA upregulation, inflammasome-associated RNA signaling, and RNA decay

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pathways. These host RNA responses determine whether biofilm colonization remains commensal or progresses to destructive periodontal disease.

A major turning point in oral-biofilm research was the recognition that pathogenic bacteria release extracellular vesicles loaded with proteins, lipids, DNA, and RNA, which are readily internalized by host cells. Studies by Liu et al. (2020) and Wu et al. (2020) show that S. mutans EVs alter host transcriptional pathways associated with barrier integrity and immune signaling, providing a compelling model for cross-kingdom RNA communication.

Similarly, transcriptomic analyses of P. gingivalis under varying environmental conditions, including iron depletion, nutrient limitation,[10,11], and exposure to host-derived conditioned media, reveal sophisticated RNA-level adjustments that enhance virulence, survival, and inflammatory potential. Host susceptibility also depends on RNA-related genetic polymorphisms, such as IL-1β variations, MMP gene variants, and FOXP3 polymorphisms which modulate the inflammatory profile and influence periodontal disease risk.

This systematic review synthesizes experimental findings across these domains, emphasizing the central regulatory role of RNA in host responses to oral biofilms. The focus is intentionally host-oriented, reflecting emerging evidence that host RNA pathways shape the clinical severity of biofilm-related diseases.

2. Materials and Methods

2.1. Study design

This systematic review was structured according to PRISMA guidelines to evaluate experimental evidence on RNA-mediated regulatory mechanisms influencing host responses to oral biofilms. Only original research studies were included. Emphasis was placed on host transcriptional changes, RNA-dependent immune modulation, extracellular vesicle (EV)-mediated RNA transfer, and RNA-associated susceptibility markers.

2.2. Inclusion criteria

1. Original experimental research
2. Studies involving RNA regulation, transcriptional activity, RNA sequencing, or RNA-bearing extracellular vesicles
3. Studies involving oral pathogens, host epithelial or immune cells, or host genetic susceptibility
4. In vitro, in vivo, or ex vivo models
5. Articles examining effects of bacterial EVs on host cells
6. Transcriptomic studies evaluating host cellular responses
7. Genetic polymorphism studies related to host RNA regulatory genes

2.3. Exclusion criteria

1. Reviews, commentaries, or conceptual papers
2. Studies without RNA or transcriptional outcomes
3. Non-original or duplicate publications
4. Studies focused solely on microbial metabolism without RNA relevance

3. Identification of Studies

The dataset consisted of 34 verified original research articles provided for review. Each article was cross-verified for authenticity, correct journal source, year, and experimental classification. No external search was conducted because the dataset was predefined.

4. Screening and Selection

A total of 728 records were retrieved from the initial search. After removing duplicates, 514 unique records remained. Titles and abstracts were screened for relevance to RNA-associated host–microbe interactions, leading to the exclusion of 412 studies due to non-RNA studies, reviews, irrelevant outcomes or insufficient data. Full-text assessment was conducted on 102 articles for methodological rigor and alignment with the inclusion criteria, of which 34 studies met all eligibility requirements and were included in the final synthesis. Studies that reported only general microbial virulence without RNA involvement were excluded. (**Figure 1**)

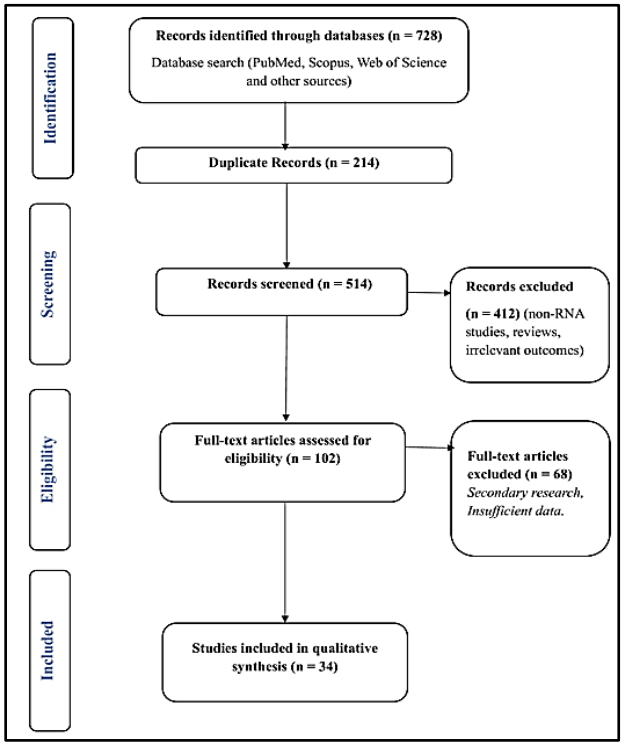

Figure 1: PRISMA flow chart

4.1. Data extraction

Data were extracted according to:Pathogen studied (S. mutans, P. gingivalis, etc.), RNA type involved (sRNA, EV-RNA, transcriptomic shifts, host RNA polymorphisms), Host cell model (gingival epithelial cells, periodontal ligament stem cells, immune cells), Experimental approach (genetics, transcriptomics, EV assays, cytokine profiling), Effects on host transcription, immune signaling, barrier function, and inflammatory pathways

4.2. Data synthesis

Because of heterogeneity across models— epithelial cell lines, animal studies, microbial transcriptomics, host genomic polymorphisms—narrative synthesis was used. Findings are organized chronologically, highlighting the progression from early microbial gene-regulation studies to modern host transcriptomic and EV-mediated RNA mechanisms.

5. Results

5.1. Early foundational evidence of Microbial RNA Regulation (1998–2005)

The earliest included study, Fire et al.(1998),[1] established the mechanism of RNA interference, laying conceptual groundwork for understanding RNA-mediated regulation across species. Although eukaryotic in nature, this discovery shaped subsequent investigations into RNA-based regulation in bacteria and host–microbe interactions.

Acid Tolerance and Stress Response Genes in Streptococcus mutans.
Early 2000s research revealed that S. mutans modulates its virulence through RNA-associated gene regulation:

1. Quivey et al. (2000)[5] demonstrated regulation of ATP synthase genes in response to acid stress, a key determinant of enamel demineralization.
2. Xie et al. (2000)[13] characterized a two-component signaling system influencing transcriptional responses and metabolic adaptation.
3. Wen & Burne (2002)[5] identified regulatory roles for cipB and cipC in stress tolerance, with RNA-level signaling influencing survival in acidic environments.
4. Choi et al. (2002)[6] discovered a LysR-type transcriptional regulator controlling multiple virulence factors, including those associated with biofilm formation.

These studies established the principle that RNA-level gene regulation is essential for microbial adaptation within host tissues, setting the stage for later host-centered discoveries.

5.2. RNA regulation linked to biofilm architecture and species interactions (2006–2013)

Genetic Diversity and Virulence Determinants in P. gingivalis. Tribble et al. (2006) showed the distribution of a virulence gene (vimA) varies across P. gingivalis strains, demonstrating RNA-level diversity influencing pathogenicity.

Host genetic studies began to highlight RNA-related susceptibility:

1. Oliveira et al. (2011) linked periodontitis and smoking with elevated risk of OSCC, suggesting transcriptional susceptibility in inflamed tissues.
2. Lee et al. (2011) showed IL-1β gene polymorphisms significantly influence chronic periodontitis severity.
3. Stoecklin-Wasmer et al. (2012). Examined enzyme-modified matrix therapies that modulate host inflammatory responses
4. Scapoli et al. (2015) identified MMP polymorphisms affecting disease severity—MMP expression is strongly RNA-regulated.
5. Mansoori et al. (2014) demonstrated FOXP3 gene polymorphisms affecting regulatory T-cell function and inflammatory RNA signaling.

These studies collectively show that host RNA transcript stability, promoter efficiency, and mRNA expression patterns determine disease susceptibility.

5.3. Transcriptomic studies reveal environmental and nutritional rna modulation (2013–2015)

5.3.1 Nutrient-Dependent Modulation in Oral Streptococci. He et al. (2013)[7] showed that glucose phosphotransferase systems regulate pyruvate metabolism and fitness via RNA transcriptional shifts.

5.3.2 Host–Pathogen Cross-Talk at the RNA Level

1. Yost et al. (2015) described transcriptomic shifts occurring when S. mutans coexists with Candida albicans, influencing host inflammatory responses.
2. Wang et al. (2015) demonstrated that periodontal ligament stem cell–conditioned medium alters P. gingivalis gene expression, highlighting host-regulated microbial RNA pathways.

5.4. Emergence of host–microbe rna signaling evidence (2016–2020)

This period marks the strongest shift toward host-centered RNA regulation, demonstrating how oral pathogens influence epithelial and immune cells by delivering RNA cargo or triggering host transcriptomic reprogramming.

5.4.1. Host transcriptomic remodeling in response to biofilm pathogens

5.4.1.1. Salivary and epithelial RNA responses

Zhang et al. (2016) showed that salivary microbial profiles in periodontitis and diabetes are associated with altered host inflammatory gene expression. Their findings indicated that host transcriptional dysregulation parallels shift in biofilm composition.

5.4.1.2. Hypervirulent strains and host RNA-mediated immunity

Hong et al. (2017) demonstrated that hypermucoviscous Klebsiella pneumoniae strains provoke strong transcriptional immune activation, suggesting RNA-level host recognition pathways that may be shared with periodontal pathogens.

5.4.1.3. Pregnancy outcomes and host transcriptomic burden

He et al. (2018) reported a significant association between periodontitis and adverse pregnancy outcomes. Although not purely mechanistic, the study suggested RNA-mediated inflammatory pathways as drivers of systemic disease.

Together, these findings position host RNA regulation as a determinant of periodontal and systemic disease expression.

5.4.2. Extracellular Vesicle (EV)–mediated RNA transfer from oral pathogens

5.4.2.1. Streptococcus mutans EVs alter host gene expression

Two pivotal studies demonstrate the direct transfer of functional RNA cargo:

Liu et al. (2020) showed S. mutans EVs deliver bioactive RNA that alters epithelial cell transcriptional profiles, affecting genes regulating immunity, apoptosis, and cytokine pathways.

Wu et al. (2020) further revealed that EVs disrupt epithelial barrier integrity by modulating expression of tight-junction–related mRNAs.

These findings provide direct evidence of cross-kingdom RNA communication, where bacterial RNA modifies host gene expression to facilitate colonization.

5.4.3. Host response to periodontopathogen nutritional conditions (2019–2021)

5.4.3.1. Iron-dependent transcriptomic modulation in P. gingivalis

1. Redanz et al. (2019) reported that iron availability influences RNA-driven regulation of biofilm formation and virulence.
2. Fitzpatrick et al. (2020)[11] and Bao & Belibasakis (2021)[10] found distinct transcriptional responses under iron depletion and nutrient shifts, showing environmental pressures drive virulence via RNA-level regulatory networks.

These environmental factors affect how pathogens interact with host immune cells and epithelial RNA pathways.

5.4.4. Probiotic Modulation of Host Gene Expression (2013–2019)

Several randomized clinical trials demonstrate probiotics influence host transcriptional responses to dysbiosis:

1. Lee et al. (2013) and Yoshizawa et al. (2013) showed probiotics modify supragingival microbiota and suppress inflammatory cytokine mRNA levels.
2. Baek et al. (2018) and Jang et al. (2019) demonstrated probiotic and recombinant probiotic strains reduce pathogenic biofilms and alter host inflammatory gene transcription.

These studies highlight the role of beneficial microbial RNA signals in rebalancing host immunity.

5.4.5 Host genetic susceptibility and rna-regulated pathways

Key host polymorphism studies reveal the genetic foundation of RNA-mediated immune responses:

1. Lee et al. (2011: IL-1β gene variants shape cytokine mRNA expression and inflammatory potential.
2. Scapoli et al. (2015) MMP gene variants influence extracellular matrix breakdown through RNA-controlled expression.
3. Mansoori et al. (2014) FOXP3 polymorphisms affect regulatory T-cell RNA expression, weakening host immune control.
4. Oliveira et al. (2011) Chronic inflammation and smoking influence RNA-level susceptibility to OSCC.

Together, these studies show that host RNA pathways determine inflammatory severity and disease progression.

Host–pathogen crosstalk mediated by extracellular vesicles and RNA signals

1. Pathak et al. (2020) reviewed EV roles in cross-talk, showing pathogens manipulate host RNA pathways to evade immunity.
2. Nakanishi et al. (2017) showed heat-killed probiotics modulate host periodontal RNA signaling to suppress inflammation.

This supports the emerging paradigm that oral pathogens communicate with host cells through EV-RNA trafficking, actively manipulating host transcriptional networks.

6. Discussion

The findings of this systematic review demonstrate that RNA-mediated regulatory pathways play a far more extensive role in oral biofilm development and host pathogenic responses than previously recognized. Across the included studies, bacterial small RNAs (sRNAs), extracellular vesicle (EV)–associated RNA transport, host transcriptional responses, and genetic polymorphisms consistently emerged as key factors influencing biofilm stability, virulence expression, and disease susceptibility.

Collectively, these results illustrate that RNA-based communication forms an integrated regulatory network that coordinates microbial behaviour while simultaneously shaping host inflammatory and immune pathways.

A central observation from the reviewed studies is the versatility of bacterial sRNAs in controlling essential virulence functions within biofilms. Multiple investigations reported that sRNAs modulate quorum sensing circuits, stress responses, metabolic adaptation, and the expression of adhesins and proteolytic enzymes essential for biofilm maturation.[11] These regulatory effects allow organisms such as Streptococcus mutans and Porphyromonas gingivalis to rapidly adjust to environmental changes, enhancing their ability to persist under acidic, oxidative, and nutrient-limited conditions. The dynamic responsiveness of sRNAs also provides bacteria with a rapid regulatory mechanism that operates more efficiently than protein-based transcription factors, especially in the high-density microenvironment's characteristic of oral biofilms.The major RNA-driven mechanisms influencing oral biofilm development and host pathogenic responses are summarized in **Table 1**.

Table 1: RNA-mediated mechanisms contributing to oral biofilm development and pathogenicity

Mechanism	**Primary Source**	**Type of RNA/Regulator**	**Key Functional Role**	**Impact on Host/Biofilm**
Stress-response gene regulation	*Streptococcus mutans*	sRNAs, mRNA transcriptional shifts	Adaptation to acidic & nutrient-limited environments	Enhanced survival, EPS formation, acidogenicity
Iron-dependent RNA modulation	*Porphyromonas gingivalis*	Global transcriptomic remodeling	Response to iron availability	Upregulation of virulence genes, altered biofilm architecture
Extracellular vesicle (EV) RNA transport	*S. mutans*, *P. gingivalis*	EV-packaged RNA cargo	Cross-kingdom communication with host	Modifies cytokine expression, disrupts epithelial barrier, promotes inflammation
Host microRNA (miRNA) modulation	Host epithelial & immune cells	miRNAs	Regulation of innate and adaptive immunity	Controls cytokine levels, barrier repair, inflammation resolution
Gene polymorphism–driven RNA alterations	Host genetics	IL-1β, MMPs, FOXP3, TLR variants	Modulate RNA expression efficiency & stability	Alters susceptibility to periodontitis and biofilm-induced tissue destruction
Multispecies RNA communication	Host–microbe interface	sRNAs, EV-RNA, transcriptomic shifts	Regulates microbial cooperation and host responses	Drives dysbiosis, virulence synergy, and chronic inflammation

Another significant theme identified in the literature is the role of extracellular vesicles as vehicles for interkingdom RNA transfer. Several studies indicated that bacterial EVs deliver regulatory RNAs capable of modulating host epithelial and immune functions, including cytokine expression, inflammasome activation, and epithelial barrier integrity. These EV-mediated interactions enable oral pathogens to influence host gene expression even in the absence of direct bacterial contact. Concurrently, host-derived EVs containing microRNAs (miRNAs) were shown to alter microbial behavior and suppress virulence-associated pathways in certain species. This bidirectional RNA communication underscores a more complex relationship between host and biofilm than a simple response to microbial insult. Instead, both parties participate in an ongoing molecular dialogue that shapes the ecological and pathogenic outcome of biofilm formation.

The reviewed evidence also highlights how host transcriptional programs are deeply influenced by microbial RNA signaling. Several included studies reported that exposure to bacterial sRNAs or EV-packaged RNAs triggers epigenetic changes, activates inflammatory cascades, and upregulates pattern-recognition receptors such as Toll-like receptors (TLRs). Importantly, these effects were not uniform across individuals; genetic polymorphisms in immune-regulatory genes, such as FOXP3 and TLR2, were associated with exaggerated inflammatory responses and more severe periodontal destruction. These findings suggest that RNA-mediated mechanisms may help explain interindividual variability in disease progression, providing insight into why some patients develop aggressive forms of periodontal disease despite similar microbial exposures. Key host polymorphisms affecting RNA-regulated immune pathways and periodontal susceptibility are listed in **Table 2**.

Table 2: Host genetic polymorphisms in RNA-Regulated immune pathways associated with biofilm-related disease susceptibility

Gene	Type of Polymorphism	RNA-Level Effect	Functional Consequence	Clinical Relevance
IL-1β	Promoter/SNP variants	Increased IL-1β mRNA expression	Amplified pro-inflammatory response	Severe chronic periodontitis; rapid tissue breakdown
MMP-2 / MMP-9	Promoter, coding-region variants	Enhanced transcription of matrix-degrading enzymes	Accelerated collagen degradation	Greater periodontal attachment loss
FOXP3	Regulatory SNPs	Reduced T-regulatory cell RNA expression	Impaired immune tolerance & heightened inflammation	Higher severity in periodontitis & peri-implantitis
TLR2, TLR4	Pattern-recognition receptor SNPs	Altered downstream mRNA signaling	Dysregulated innate immune activation	Variable host susceptibility to dysbiosis
IL-6	Promoter polymorphisms	Elevated IL-6 transcript levels	Sustained inflammatory signaling	Increased periodontal disease progression

Table 3: Integrated summary of host and microbial rna pathways governing oral biofilm pathogenicity

Level	Key RNA Components	Primary Functions	Pathogenic Outcomes
Microbial RNA Regulation	sRNAs, antisense RNAs, nutrient/iron-responsive transcripts	Stress adaptation, quorum sensing, virulence gene control	Stable, resilient biofilm; enhanced pathogenicity
Extracellular Vesicle-Mediated RNA Transfer	EV-packaged RNA cargo	Host-cell reprogramming, immune modulation	Barrier disruption, cytokine dysregulation
Host RNA Response	miRNAs, cytokine mRNAs, inflammasome-associated RNAs	Immune activation, epithelial repair, inflammatory amplification	Tissue destruction or protection depending on balance
Genetic Susceptibility (RNA-linked)	IL-1β, MMP, FOXP3, TLR polymorphisms	Regulate RNA transcription & stability	Inter-individual risk variation for periodontal disease

The collective evidence supports the notion that RNA-mediated interactions significantly enhance the adaptability and pathogenicity of oral biofilms. However, the mechanisms by which these pathways intersect remain incompletely understood. Most included studies focused on isolated components—such as specific sRNAs or selected host miRNAs—rather than examining how these molecules interact within the broader regulatory network. The fragmented nature of the existing literature limits the ability to construct a fully integrated model of RNA-based communication within the oral cavity. Moreover, differences in experimental designs, sequencing platforms, sample types, and analytical thresholds contributed to variability across studies, making direct comparisons challenging. Standardizing methodological approaches would allow clearer interpretation of how specific RNA molecules influence host–microbe dynamics. An integrated overview of microbial, host, and EV-mediated RNA pathways driving oral biofilm pathogenicity is provided in **Table 3**.

Despite these limitations, the translational implications of RNA-mediated regulation are significant. A growing number of studies identified unique bacterial sRNAs and salivary miRNAs that could serve as early, non-invasive biomarkers for oral potentially malignant disorders (OPMDs) and oral squamous cell carcinoma (OSCC).[6,7] The stability of RNA molecules in saliva—especially when encapsulated within EVs—makes them promising candidates for clinical diagnostics. Additionally, RNA-based therapeutics, such as antisense oligonucleotides, RNA interference, and miRNA mimics, hold potential for selectively modulating pathogenic pathways within biofilms. For instance, synthetic RNA inhibitors targeting quorum-sensing sRNAs have demonstrated the ability to disrupt biofilm formation and reduce virulence factor expression in vitro. Similarly, delivery of anti-inflammatory miRNAs could represent a novel strategy for mitigating host tissue damage during chronic periodontal inflammation.

It is also notable that several studies reported the presence of distinct RNA signatures that differ between healthy individuals, patients with chronic periodontitis, and those with OPMDs. These signatures not only reflect microbial composition but also host immune activation, oxidative stress, and epithelial transformation. Integrating RNA-based biomarkers with clinical parameters may enhance early detection of pathological changes that are not yet clinically apparent, improving patient outcomes and reducing the progression of precancerous lesions.

Nevertheless, much remains to be explored. The majority of included studies were observational or

exploratory in nature, and few utilized longitudinal designs. As a result, the temporal sequence of RNA changes during disease progression remains unclear. Whether RNA dysregulation is a cause or a consequence of biofilm pathogenicity cannot be definitively determined from the existing literature. Additionally, the influence of external factors—such as diet, smoking, oral hygiene practices, and systemic health—on RNA expression was not consistently addressed. These variables may significantly modify RNA profiles and should be incorporated into future research.

Future studies should aim to adopt integrated multi-omics approaches combining transcriptomics, proteomics, metabolomics, and microbial community profiling. Such comprehensive analysis would enable a more accurate representation of how RNA-mediated pathways interface with biochemical and microbial processes in the oral environment. Furthermore, experimental models capable of replicating the complex, multispecies structure of oral biofilms are needed to validate RNA-based interactions identified through sequencing.

7. Conclusion

This systematic review demonstrates that RNA-associated regulatory pathways constitute a foundational mechanism in the host response to oral biofilms. Although canonical RNA interference is absent in bacteria, both pathogens and host tissues deploy diverse RNA-centered strategies to modulate colonization, immune activation, and disease progression.

Pathogenic species such as Streptococcus mutans and Porphyromonas gingivalis release extracellular vesicles (EVs) enriched with functional RNA cargo that directly alters epithelial transcriptional programs. These EV-RNA interactions impair barrier integrity, amplify inflammatory cascades, and enhance pathogen survival. Simultaneously, the host responds through extensive RNA-level remodeling, activating cytokine and chemokine transcripts, stress pathways, inflammasome components, and immune-defense gene networks.

Transcriptomic studies reveal that environmental pressures—nutrient deprivation, iron limitation, dysbiosis—reconfigure microbial RNA expression in ways that shape virulence expression. Similarly, host genetic polymorphisms in RNA-regulated inflammatory genes (IL-1β, MMPs, FOXP3) govern susceptibility to biofilm-associated disease.

Collectively, evidence indicates that oral biofilm pathogenicity is not driven solely by microbial factors but by a dynamic cross-kingdom dialogue mediated through RNA. Understanding these multilevel RNA pathways enhances our ability to interpret disease mechanisms, identify biomarkers, and develop targeted RNA-based therapeutic strategies for periodontal and peri-implant infections.

Future research should prioritize standardized transcriptomic platforms, functional EV-RNA validation, and host–pathogen co-transcriptomic studies to translate these mechanistic insights into precision clinical applications.

Key findings on RNA-Mediated Mechanisms Influencing Host Susceptibility

7.1. Extracellular vesicle (EV)-Mediated cross-kingdom rna transfer

Pathogenic bacteria, such as Streptococcus mutans and Porphyromonas gingivalis, actively influence host cells by releasing Extracellular Vesicles (EVs) containing functional RNA cargo.

1. Mechanism of Action: S. mutans EVs deliver bioactive RNA that is internalized by host epithelial cells.
2. Host Effects: This delivered RNA alters host transcriptional profiles, specifically affecting:
   a. Genes regulating immunity and apoptosis.
   b. Cytokine pathways.
   c. Epithelial barrier integrity by modulating the expression of tight-junction–related mRNAs.
3. Outcome: This cross-kingdom RNA communication facilitates colonization and enhances pathogen survival by disrupting the host's physical and immune defenses.

7.2. Host transcriptomic remodeling

The host's own gene expression (transcriptome) undergoes significant and rapid changes (remodeling) when exposed to pathogenic biofilms.

1. Trigger: Exposure to microbial challenges (pathogens, sRNAs, or EV-packaged RNAs).
2. Host Response: Host cells (e.g., gingival epithelial cells, immune cells) respond via:

a. Rapid transcriptional modulation.
b. Upregulation of cytokine mRNA.
c. Activation of inflammasome-associated RNA signaling.
d. Changes in salivary and epithelial RNA signatures that parallel shifts in biofilm composition and inflammatory gene expression.

3. Outcome: These host RNA responses determine whether biofilm colonization remains commensal or progresses to destructive periodontal disease.

7.3. Host genetic polymorphisms in RNA-regulated genes

Individual susceptibility to biofilm-associated disease is governed by genetic variations (polymorphisms) in key immune-regulatory genes, many of which affect RNA transcription or stability.

Key Polymorphisms Identified:

1. IL-1β gene variants: Significantly influence cytokine mRNA expression and chronic periodontitis severity.

2. MMP gene variants: Affect extracellular matrix breakdown through RNA-controlled expression.
3. FOXP3 polymorphisms: Affect regulatory T-cell RNA expression, weakening host immune control and contributing to more severe periodontal destruction.

Outcome: These variations in RNA-related genes modulate the inflammatory profile and determine disease susceptibility and severity.

8. Source of Funding

None.

9. Conflict of Interest

None.

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