Review Article

Potential role of long non-coding RNA (nuclear paraspeckle assembly transcript 1 and metastasis associated lung adenocarcinoma transcript 1) in periodontitis pathogenesis: A systematic review

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Abstract: Background: Dysregulation of Long non-coding (lnc)RNAs has been linked to periodontitis, with potential importance in disease onset and progression. These lncRNAs potentially modulate inflammatory/immune responses during periodontitis. This review aimed to highlight the potential role of Nuclear Paraspeckle Assembly Transcript (NEAT)1 and Metastasis Associated Lung Adenocarcinoma Transcript (MALAT)1 lncRNAs in periodontitis pathogenesis. Methods: A literature search of three electronic databases was performed in SCOPUS, MEDLINE (PubMed) and EMBASE using search terms linking periodontitis/periodontal disease with NEAT1 and MALAT1 lncRNAs. Duplicate publications were removed from the retrieved articles which were then filtered to include the most relevant papers for evidence synthesis. Results: Nine studies (in vitro and in vivo) were included in the final analysis. The total number of studies investigating the role of NEAT1 and MALAT1 in pathogenesis of periodontitis was 4 and 5, respectively. The findings indicated gene expression changes of NEAT1 and MALAT1 in periodontitis compared with periodontal health. Conclusion: No concrete evidence could be withdrawn from this review; however, results suggested that lncRNAs, NEAT1 and MALAT1 could be involved in periodontitis pathogenesis. However, further in vivo studies are required to confirm these findings.

Keywords: Periodontitis, Long non-coding RNA, NEAT1, MALAT1, Pathogenesis

Introduction

Globally, approximately 50% of individuals over the age of 30 years are affected by periodontitis with ~11% suffering from severe form of the disease [(1)]. This results in a significant financial burden on healthcare systems amounting to billions of dollars worldwide [(2)]. The current knowledge on the pathogenesis of periodontitis gives a detailed insight into the underpinning hyper inflammatory response that is characteristic of this disease, however, many molecular and biological mechanisms remain unclear. An in-depth understanding of these mechanisms will help in disease prevention and management [(3)]. The discovery of long non-coding (lnc)RNA has offered the potential to investigate complex relationships between these molecules and different pathological events that underpin the pathogenesis of periodontitis. Approximately 93% of the human genome is involved in transcription, however only a fraction is responsible for protein encoding, the remaining constitutes the transcriptome of non-protein-coding (nc)RNA [(4)].

At the molecular level, ncRNAs are classified into two distinct groups: (i) small ncRNA and (ii) lncRNA. Micro(mi)RNAs, a subclass of ncRNAs, have been extensively studied and implicated in the pathogenesis of periodontitis [(5, 6)]. LncRNAs are another subclass of ncRNA distinguished by their nucleotide

length (over 200 nucleotides). Current data has highlighted the complex interplay between dysregulated expression of lncRNAs and the extensive range of multifactorial genetic disorders [7]. LncRNAs exert profound control over the transcriptome through various miRNA-related mechanisms. Acting as miRNA sponges, they utilize specific reaction elements to bind and sequester miRNAs, preventing their interaction with target mRNAs and subsequent degradation. Additionally, LncRNAs compete directly with miRNAs for binding sites on mRNA transcripts, further disrupting their silencing potential. Interestingly, some lncRNAs even harbor the necessary sequences to be processed into mature miRNAs. This dynamic interplay extends beyond lncRNA dominance, as miRNAs can target lncRNAs for degradation through imperfect base-pairing, influencing their abundance and regulatory capabilities [8, 9]. Beyond individual gene expression regulation, studies have revealed a powerful layer of regulation by lncRNAs in epithelial-mesenchymal transition (EMT) responsible for shifting epithelial phenotype into mesenchymal phenotype. Well-characterized lncRNAs, such as Metastasis Associated Lung Adenocarcinoma Transcript (MALAT1), function as master regulators, orchestrating the expression and activity of key EMT-associated transcription factors, particularly within the influential Snail, ZEB, and Twist families [10, 11].

Several inflammatory diseases, including periodontitis, have now been linked to the dysregulated expression of lncRNAs. According to recent literature, lncRNAs play a pivotal role in the onset and progression of periodontitis, and they are expressed differently in diseased compared to healthy tissues [12]. Interest in linking these molecules with the pathogenic mechanisms seen in periodontitis has exponentially increased since the late 1980s. Indeed, in patients with periodontitis analyses has shown dysregulation of lncRNAs, such as UCA1, ANRIL, FGD5-AS1, FAS-AS1, Linc-RAM, and NKILA, pointing to their potential involvement in disease pathogenesis [13]. Additionally, lncRNA single-nucleotide polymorphisms have been associated with increased periodontitis risk [14].

Nuclear Paraspeckle Assembly Transcript (NEAT)1 and MALAT1 are among lncRNAs proposed to be involved in periodontitis pathophysiology. NEAT1 promotes inflammation and apoptosis and has been shown to be upregulated in periodontitis tissue samples and *in vitro* periodontitis models [15, 16]. Upregulated MALAT1 is proposed to accelerate periodontitis progression through the regulation of key miRNAs [17]. Knock down of MALAT1 diminished the effect of LPS injury on periodontal ligament cells *in vitro* [18]. MALAT1 enhances inflammatory cytokine production via miRNA/Toll-like receptor (TLR)4 axis, indicating a potential regulatory role for MALAT1 in periodontal inflammation [19]. Furthermore, a recent bioinformatic study has demonstrated the complex interrelationship between MALAT1 miR-125a and miR-142 in periodontitis pathogenesis [20].

The literature demonstrates an increasing interest in the potential significance of NEAT1 and MALAT1 in the pathophysiology of periodontitis. The current review was therefore designed to systematically investigate the potential role of these lncRNAs in the pathogenesis of periodontitis.

Materials and Methods

This systematic review was conducted to answer the question whether NEAT1 and MALAT1 LncRNAs are involved in pathogenesis of periodontitis.

Search strategy and inclusion criteria

A literature search was conducted using three search engines including SCOPUS, MEDLINE (PubMed) and EMBASE by using the following keyword matrix: (periodontitis) OR (periodontal disease) OR (periodontal disease pathogenesis) AND (long noncoding RNA MALAT1) OR (long noncoding RNA NEAT1) OR (lncRNA MALAT1) OR (lncRNA NEAT1). The retrieved articles were filtered to include full-text original articles associating LncRNA (MALAT1and NEAT1), *in vitro* and *in vivo*, with periodontitis and were articles published in the English language up to the end of 2023. Only original articles were included, with reviews, case reports/series, editorials, and expert opinions excluded. In addition, studies investigating periodontitis associated with systemic diseases were also excluded.

Screening and data extraction

The filtering process was performed independently by two authors, with consistency checked after each step using kappa coefficient assay. Subsequent results were discussed to resolve inconsistencies until an agreement level ≥90% was reached. The screening process started with filtering the papers according to title, abstract, and full text reading depending on the eligibility criteria. The extracted data included study details (authors, year), aims, design, sample size, assay(s) used, and outcomes. This process was independently checked for accuracy of extracted data by two reviewers. any discrepancies were discussed and resolved.

Outcomes

The primary outcome was to detect levels of NEAT1 and MALAT1 LncRNAs in periodontitis tissues samples or experimental models and the associated pathological changes.

Results

Search results are illustrated in Fig. 1, and this shows the growth in the number of articles since 2007, when keywords linking NEAT1 and MALAT1 to periodontal disease were used. Titles and abstracts from all retrieved records were screened for potentially eligible studies.

The search process retrieved 3659 articles that were filtered to include only articles fitting the inclusion criteria and to remove duplicates. A total of 15 articles were identified after filtration (Fig. 2). The total number of studies investigating the role of NEAT1 and MALAT1 in pathogenesis of periodontitis was 4 and 5, respectively.

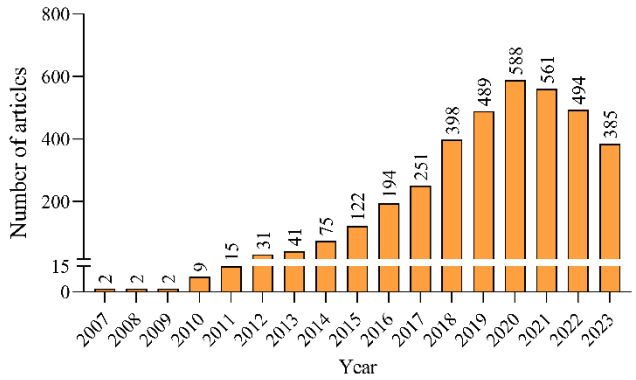

Figure 1: Number of articles retrieved using search terms linking LncRNA (NEAT1 and MALAT1) to periodontal disease.

NEAT1 expression in periodontal disease

Retrieved articles investigating expression of NEAT1 in periodontitis included one *in vitro* study [21] and three case-control studies [15, 16, 22], two of which were combined with *in vitro* analysis [15, 16] (Table 1). All studies utilized the qRT-PCR technique to detect the expression level of NEAT1. Zhang and co-authors exposed periodontal ligament stem cells (PDLSCs) to nicotine which resulted in upregulation of NEAT1 via activating the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$nAChR) [21]. Qi et al., reported in the clinical part of their study, that the expression of NEAT1 was significantly increased in the gingival crevicular fluid (GCF) of patients diagnosed with periodontitis as compared with healthy controls. NEAT1 levels in GCF showed diagnostic ability to discriminate periodontal health from disease with sensitivity and specificity of 82.4% and 88.2%, respectively [16].

While the *in vitro* component of the work demonstrated that knock down of NEAT1 may reduce LPS-mediated cell damage and production of inflammatory mediators by upregulating the level of miR-205-

5p [16]. Similar results were also reported by another study [15] which demonstrated upregulation of NEAT1 both in tissues of periodontally-diseased individuals and in *Porphyromonas gingivalis-LPS-challenged* PDLCs. While NEAT1 expression was downregulated in peripheral blood of periodontitis patients, its level was upregulated locally in diseased gingival tissue samples as compared with healthy controls [22].

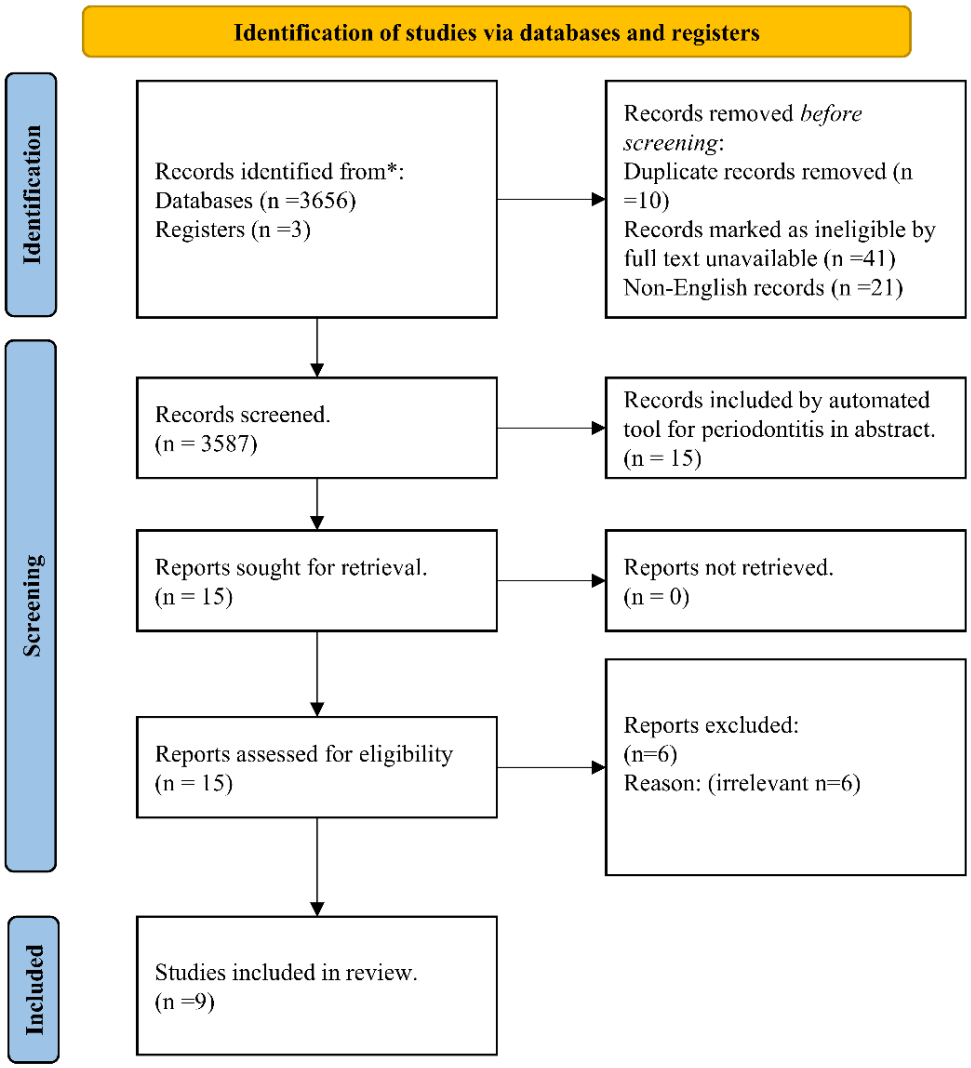

Figure 2: PRISMA flowchart applied in the study.

MALAT1 expression in periodontal disease

In the final analysis, two *in vitro* articles [17, 23] investigated the expression of MALAT1 in periodontitis and three *in vivo* studies [18, 24, 25], two of which included *in vitro* analysis [18, 25] (Table 1). Knocking down MALAT1 was associated with decreased cytokine secretion after LPS stimulation which indicated that MALAT1 may play a pro-inflammatory role [23]. In addition, silencing MALAT1 reduced antigen uptake and processing, impairs bacterial phagocytosis and macrophage (Mφ) bactericidal activity [23]. Exposure of PDLCs to LPS resulted in overexpression of MALAT1 associated with downregulation of miR-155 and over production of inflammatory cytokines [17]. Similarly, MALAT1 increased periodontal inflammation by upregulating TLR4 expression and inducing inflammatory cytokine secretion by competitively interacting with miR-20a [25]. An *in vitro* periodontitis model utilized PDLCs exposed to *P. gingivalis* LPS and demonstrated that MALAT1 and hypoxia inducible factor (HIF)-3α were upregulated, while miR-769-5p was downregulated in both gingival tissues from periodontitis patients and in a periodontitis cell model system [18]. Notably, MALAT1 knockdown increased cell viability and reduced inflammation and apoptosis in LPS-treated PDLCs [18]. Two clinical studies demonstrated upregulation of

MALAT1 expression in tissue samples collected from patients with periodontitis as compared to healthy controls. Interestingly, results reported by Gholami et al. indicated no significant difference of lncRNA MALAT1 between periodontal health and disease [24].

Table 2: Summary of evidence associating roles for NEAT1 and MALAT1 with periodontitis.

Author, year	Aims	Design	Sample, n	Assay(s)	Outcomes
NEAT1					
Zhang et al., (2023) [21]	Evaluate inflammation in nicotine treated PDLSCs	*In vitro*	• Nicotine treated vs untreated PDLSCs	qRT-PCR, TEM, immunofluorescence, the mCherry-GFP-LC3 plasmid, WB	• NEAT1 ↑ by nicotine treatment and may lead to periodontal inflammation
Qi et al., (2022) [16]	To explore the expression of NEAT1 in periodontitis and its effect on inflammatory response	*In vivo* and *in vitro*	• GCF sample from periodontitis patients (n=85) and healthy controls (n=93) • Human PDLSCs cultures	qRT-PCR, DLR	• NEAT1 ↑ in periodontitis • NEAT1 knockdown may reduce LPS-induced cell damage by increasing miR-205-5p level. • NEAT1 level could differentiate periodontal health from periodontitis
Zhang et al., (2022) [15]	To explore the role of NEAT1 in periodontitis	*In vivo* and *in vitro*	• *P. gingivalis*-LPS-induced PDLCs • Periodontitis patients (n=28), controls (n=20)	qRT-PCR, MTT, ELISA, WB, DLR assay	NEAT1 is ↑ in periodontally-diseased tissues and periodontitis *in vitro* model.
Sayad et al. (2020) [22]	Explore the role of NEAT1 in periodontitis	*In vivo*	• Gingival tissue sample: diseased and healthy periodontium (n= 30 each) • Blood sample: periodontitis patients (n=23), controls (n=18)	qRT-PCR	• NEAT1 ↓ in peripheral blood of patients compared with controls. • Expression ↑ in tissues of cases compared with controls
MALAT1					
Ahmad et al., (2023) [23]	Explore the role of MALAT1 in shaping Mφ polarization and immune functions.	*In vitro*	Gingival biopsies from periodontitis and healthy subjects (n=10 each) • ligature-induced periodontitis murine model	RT-qPCR, DLR assay	• MALAT1/miR-30b antagonistic interaction shapes Mφ polarization *in vitro* and in inflamed gingival biopsies.
Hu et al., (2022) [17]	Investigated the effects of MALAT1 on LPS-induced PDLCs	*In vitro*	Primary human PDLCs either treated with LPS or not	RT-qPCR, MTT, Flowcytometry, ELISA, and DLR test	Upregulated MALAT1 could accelerate periodontitis progression
Gholami et al., (2020) [24]	Assess expression of MALAT1 in periodontal health and disease	*In vivo*	Blood and gingival biopsies from periodontitis patients and healthy controls (n=30 each)	RT-qPCR	No significant correlation between expression levels of MALAT1 in gingival tissues and in the blood of study participants
Li et al., (2020) [25]	Explore the role of MALAT1 on inflammatory cytokine production by HGFs	*In vivo* and *in vitro*	Primary HGFs exposed to *P. gingivalis*- and *E. coli*-LPS	qRT-PCR, DLR, bioinformatics analysis, RIP, ELISA, WB	• MALAT1 upregulated in gingival tissues of periodontitis. • MALAT1 increased TLR4 level and the secretion of inflammatory cytokines.
Chen et al., (2021) [18]	Investigating the regulatory mechanism of MALAT1 in periodontitis	*In vivo* and *in vitro*	• Periodontitis patients (n=26), healthy controls (n=17). • Primary PDLCs cultures treated with *P. gingivalis*-LPS	qRT-PCR, MTT, ELISA, WB, DLR	• MALAT1 ↑ in periodontitis and LPS-treated PDLCs. • MALAT1 knockdown attenuated LPS-induced PDLC injury via regulating the miR-769-5p/HIF3A axis.

Abbreviations. PDLSCs: periodontal ligament stem cells, qRT-PCR: quantitative reverse transcription polymerase chain reaction, ELISA: enzyme-linked immunosorbent assay, WB: Western blot, TEM: transmission electron microscopy, NEAT1: nuclear paraspeckle assembly transcript 1, GCF: gingival crevicular fluid, *P. gingivalis*: *Porphyromonas gingivalis*, *E. coli*: *Escherichia coli*, LPS: lipopolysaccharide, MALAT1: metastasis-associated lung adenocarcinoma transcript 1, Mφ: macrophage, TLR4: toll like receptor 4, MTT: 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide, DLR: dual-luciferase reporter, HIF: hypoxia-inducible factor, RIP: RNA-binding protein immunoprecipitation, HGFs: human gingival fibroblasts.

Discussion

The accumulation of the dental biofilm subjacent to the gingival margin initiates an inflammatory response that may lead to dysbiosis in microbial composition, and subsequently the development of periodontitis in susceptible individuals. The molecular signalling pathways resulting from this interaction culminate in a complex inflammatory cascade, ultimately leading to hyperinflammation and enzymatic degradation of periodontal tissues and subsequent loss of alveolar bone [1, 26].

The impact of NEAT1 and MALAT1 LncRNA with up / downstream signaling that potentially modulate inflammatory/immune responses involved in periodontitis are illustrated in Fig. 3. Notably, a comprehensive microarray analysis has identified a repertoire of 8925 differentially expressed lncRNAs in periodontitis [12]. Another study identified 8632 differentially expressed lncRNAs specifically in the gingival tissues of aggressive periodontitis patients [27]. From this library of lncRNAs, NEAT1 and MALAT1 were subsequently selected for further study based on the available evidence that associated them with periodontitis and EMT. NEAT1 and MALAT1 were identified as critical regulators of Type 2 EMT responsible for tissue regeneration and organ fibrosis in different pathological conditions such as periodontitis [12, 20, 27, 28]. Indeed, a coherent epithelium which form mucosal barriers, are not passively defensive. Instead, their interactions with microbes represent a dynamic crosstalk with profound consequences for tissue integrity and cellular behavior. In this context, periodontal pathobionts have emerged as potent triggers for EMT [29], a cellular reprogramming process which fundamentally shifts epithelial organization and function towards a mesenchymal phenotype [30]. This process targets epithelial proteins such as E-cadherin/catenin complex, key components of intercellular adhesion junctions, which not only disrupts cell-cell contacts but also triggers a cascade of downstream signaling pathways. These pathways ultimately orchestrate a dramatic shift in cellular phenotype [31]. Currently, several recent studies have now demonstrated the expression of the EMT-phenotype in diseased-periodontal tissue samples [32].

Increased expression of NEAT1 in periodontally-diseased tissue was demonstrated in all *in vivo* studies included in this review [15, 16, 22]. Consistently, results from an *in vitro* component of one of these studies also demonstrated upregulation of NEAT1. While silencing this LncRNA significantly hindered inflammation and apoptosis in a periodontitis cell model via the targeting of the miR-200c/TRAF6 axis, ultimately leading to a protective role against disease progression [15]. NEAT1 knockdown also showed a stimulatory effect on cellular viability, which was effectively countered by either inhibiting miR-200c expression or via the upregulation of TRAF6 [15]. Thus, NEAT1 knockdown may prevent LPS-induced cell damage by boosting miR-200 levels [15, 16]. A previous study also indicated that NEAT1 could boost the immune response to LPS via modulating the NEAT1/miR-17/TLR4 pathway, leading to increased levels of inflammatory cytokines and molecules, including TNF-α, IL-1β, IL-6 and nitric oxide [33]. Further work has demonstrated that NEAT1 overexpression could upregulate MyD88 by sponging miR-155. Therefore, NEAT1 could aggravate LPS-induced inflammation by regulating miR-155/MyD88/NF-κB axis [34]. Notably, the induction of the EMT process has been long attributed to chronic exposure to increased levels of inflammatory cytokines [35].

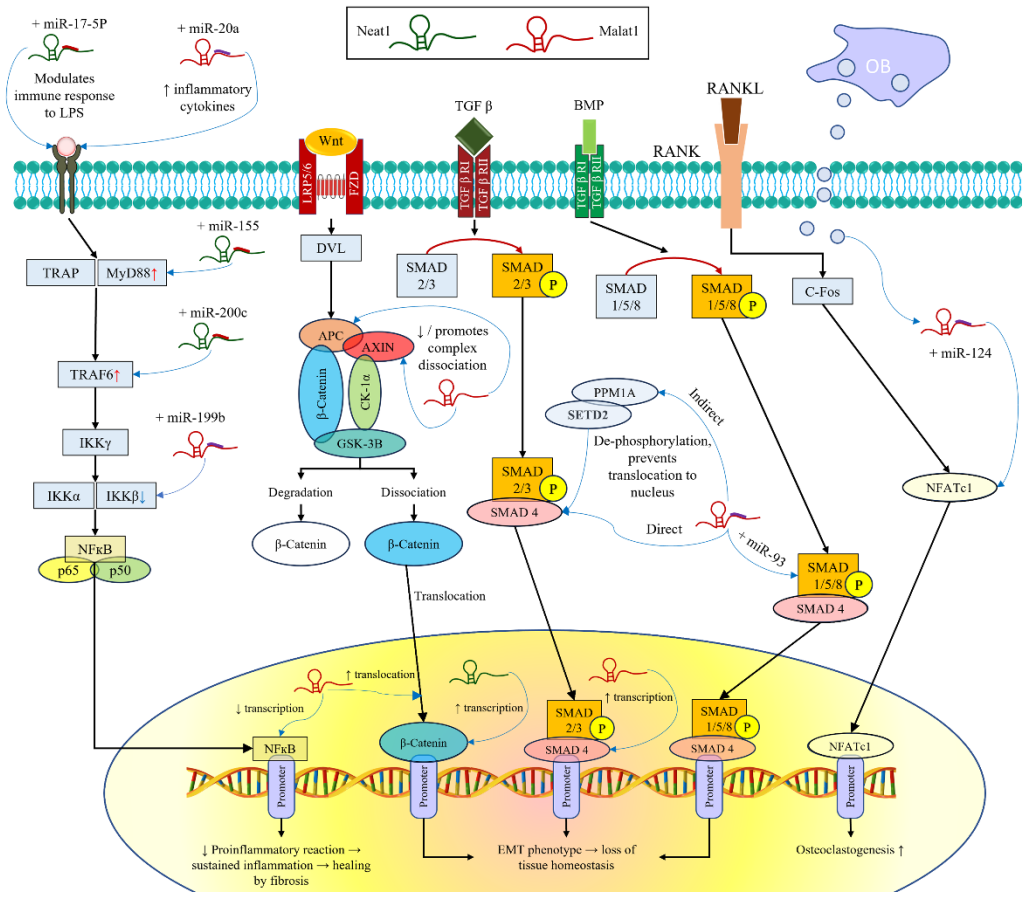

Figure 3: The potential complex modulatory effects of NEAT1 and MALAT1 on multiple signaling pathways involved in periodontitis pathogenesis. NEAT1 could potentially increase inflammatory cytokine levels by directly modulating the lipopolysaccharide (LPS)/TLR4 axis via sponging miRNA-17. Sponging of miRNA-155 and 200c by NEAT1 leads to upregulation of MyD88 and TRAF6 proteins, respectively. NEAT1 could also increase transcription of β-catenin with subsequent activation of Wnt/β-catenin signaling leading to the induction of the epithelial-mesenchymal transition (EMT) process. MALAT1 may also contribute to EMT-induction by accelerating dissociation of β-catenin and enhancing transcription of the SMAD 2,3,4 complex. Osteoclastogenesis could be accelerated by MALAT1 by sponging and downregulating miRNA-124 expression. However, MALAT1 could reduce inflammatory cytokine transcription by downregulation of IKKβ and transcription of NF-kB. Additionally, MALAT1 could prevent the expression of the EMT-phenotype by preventing nuclear translocation of the SMAD 2,3,4 and 1,5,8,4 complexes.

In a previous study involving buccal mucosa fibroblasts, it was observed that NEAT1 was upregulated in specimens associated with oral fibrosis, whereas miR-760, a potential modulator of fibrosis, was downregulated. The downregulation of NEAT1 resulted in the suppression of myofibroblast activity, and a decrease in both fibrosis and the Wnt/β-catenin pathway by targeting the miR-760/ Tropomyosin-1 (TPM1) axis. Notably, TPM1 is a key actin-binding protein crucial for the contractile system of the cytoskeleton [36]. The association between the upregulation of NEAT1 and the activation of Wnt/β-catenin pathway, the main pathways for inducing the EMT phenotype, was demonstrated by another report [37]. NEAT1 enhanced β-catenin transcription by mediating formation of a complex between this protein and DDX5; subsequently compromising its protective function against degradation of cytoplasmic β-catenin [38]. Smoking is another shared risk factor for periodontitis and EMT [2, 39]. Exposure of PDLSC cultures to nicotine led to activation of α7nAChR that in turn induced NEAT1 upregulation which compromised autophagy flux

by downregulating syntaxin 17 [21]. This latter mechanism may contribute to the development of inflammatory diseases such as periodontitis in individuals exposed to nicotine.

The other LncRNA investigated in this review was MALAT1 which also demonstrated an association with the initiation and progression of periodontitis. The expression of MALAT1 was found to be upregulated in tissue samples from periodontitis patients in comparison to healthy controls [18, 19]. The lncRNA-associated competing endogenous RNA network of periodontitis indicated that MALAT1 is one of the key regulators of the molecular mechanisms that when disrupted lead to periodontitis development [20]. These results were confirmed by several other bioinformatic studies which showed MALAT1 upregulation following surgical periodontal treatment [40] and in inflamed gingival tissues [41]. Furthermore, transcriptome and clinical data analyses from the GEO database found that MALAT1 is a necroptosis-related gene that affects immune infiltration in periodontitis [42].

Stimulation of primary PDLC cultures with LPS indicated that MALAT1 could potentially accelerate progression of periodontitis by increasing inflammatory cytokine production, altering apoptosis and macrophage function, and innate immune responses [17-19, 23]. These outcomes were attributed to the sponging of miR-20a, miR-769, and miR-30 by MALAT1 which subsequently modulated the LPS/TLR4 and HIF3A axes [18, 19, 23]. Silencing MALAT1 resulted in upregulation of the previously described miRNAs with restoration of inflammatory cytokines levels to normal. MALAT1 also modulated the TLR4 signaling pathway by sponging miR-199b which minimized NF-kB nuclear translocation and transcription by downregulating IKKβ expression [43]. The downregulatory effect of MALAT1 on this key transcription factor results in decreased production of important inflammatory cytokines, such as IL-8, a key proinflammatory cytokine in the innate immune response and in neutrophil chemotaxis [44].

Bone resorption is a hallmark of periodontitis resulting from increased osteoclast activity [45]. In an experimental periodontitis model utilizing an osteoblast-osteoclast transwell system, MALAT1 was found to be upregulated during osteoclastogenesis. Furthermore, miR-124 reduced osteoclast formation and inhibited the expression of the T cell activation factor. Notably, MALAT1 sponges miR-124, regulating the expression of the T cell activation factor, and promotes osteoclastogenesis [46].

MALAT1 could induce the EMT-phenotype by several potential mechanisms. One of these would be by increasing dissociation of β-catenin from the molecular complex engaging this protein to the E-cadherin-cytoskeletal system [30]. Consequently, nuclear translocation of β-catenin is increased, and transcriptional activity is also upregulated by MALAT1 leading to activation of Wnt/ β-catenin signaling that possibly induces the EMT process. Notably, the association of increased nuclear β-catenin levels with expression of EMT phenotype in gingival tissue samples from periodontitis patients was previously demonstrated [32]. Trafficking of other EMT-related transcriptional factors, including SMAD 2/3/4 and SMAD 1/5/8/4, to the nucleus could be compromised directly or indirectly by MALAT1. Furthermore, MALAT1 is responsible for increasing transcriptional activity of these protein complexes once translocated to the nucleus, thereby, inducing the EMT process [47]. Notably, this potential dual role of MALAT1 in periodontal health and disease remains uncertain and no definitive outcome is yet to be reached from the available literature.

Understanding the mechanisms by which lncRNAs influence immunological and inflammatory pathways, such as modulation of cell cycle, apoptosis, TLR and TNF receptor signaling, is key for understanding the complex pathways involved in periodontitis pathogenesis.

Summary

Thew reviewed studies have demonstrated that the expression of NEAT1 and MALAT1 are generally upregulated in periodontitis, modulating inflammation, cell proliferation, and migration. Exploring the role into NEAT1 and MALAT1 in the etiology of periodontitis is ongoing, however further work may identify novel therapeutic and diagnostic tools. By analysing these events, specific genes and pathways that are involved in the pathogenic mechanism of periodontitis could be clearly identified. Subsequently, it could be feasible to develop medications that target these lncRNAs to reduce periodontitis-associated inflammatory events. Indeed, knock down the NEAT1 effect on the LPS/TLR4 pathway reportedly enhance cell viability, prevents apoptosis, and decreased the production of inflammatory factors. Additionally, silencing NEAT1 could prevent the EMT that compromises epithelial barrier function by reducing β-catenin transcription. MALAT1 has demonstrated a diverse range of molecular events including increased inflammatory cytokine production, inducing the EMT-phenotype, and increased osteoclastic activity. However, MALAT1 could be responsible for stabilization, preventing nuclear translocation, and decreasing transcription of NF-kB which ultimately reduces inflammatory cytokine production and chemotaxis of immune cells. However, this dual harmful/protective effect of MALAT1 needs further characterization. The available literature investigating the role of NEAT1 and MALAT1 in periodontitis is still in its relatively early stages. Indeed, the level of evidence retrieved in this review was mostly based on *in vitro* studies; therefore, solid consensus about involvement of these lncRNAs *in vivo* in the pathophysiology of periodontitis could not be reached. Further clinical studies are therefore required for validating these data and to clarify the precise processes by which NEAT1 and MALAT1 may contribute to periodontitis pathogenesis.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

A.A.A., S.M.A., contributed to conception, design, literature search, drafted, and critically revised the manuscript; P.R.C., contributed to conception, interpretation, critically revised the manuscript; M.R.M., contributed to conception, interpretation, critically revised the manuscript. All authors have their final approval and agree to be accountable for all aspects of work.

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الدور المحتمل للحمض النووي الريبي (RNA) الطويل غير المشفر (نسخة التجميع النووي المظلي 1 والورم الخبيث المرتبط بسرطان الرئة الغدي 1) في التسبب في التهاب اللثة. مراجعة منهجية

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المستخلص:

الخلفية: تم ربط خلل تنظيم الحمض النووي الريبي الطويل غير المشفر بالتهاب اللثة، مع أهمية محتملة في ظهور المرض وتطوره. من المحتمل أن تقوم هذه الاحماض النووية الريبية الطويلة بتعديل الاستجابات الالتهابية / المناعية أثناء التهاب اللثة. تهدف هذه المراجعة إلى تسليط الضوء على الدور المحتمل للحمض النووي الريبي الطويل **NEAT1** و**MALAT1** في التسبب في التهاب اللثة. الطرق: تم إجراء بحث في الأدبيات لثلاث قواعد بيانات إلكترونية في **SCOPUS** و**MEDLINE (PubMed)** و**EMBASE** باستخدام مصطلحات البحث التي تربط التهاب اللثة/مرض اللثة مع **NEAT1** و**MALAT1**. تمت إزالة المنشورات المزدوجة من المقالات المستردة والتي تم تصفيتها بعد ذلك لتشمل الأوراق الأكثر صلة بتوليف الأدلة. النتائج: تم تضمين تسع دراسات (في المختبر وفي الجسم الحي) في التحليل النهائي. كان العدد الإجمالي للدراسات التي تبحث في دور **NEAT1** و**MALAT1** في التسبب في التهاب اللثة 4 و5 على التوالي. أشارت النتائج إلى تغيرات التعبير الجيني لـ **NEAT1** و**MALAT1** في التهاب اللثة مقارنة بصحة اللثة. الاستنتاج: لا يمكن سحب أي دليل ملموس من هذه المراجعة؛ ومع ذلك، تشير النتائج إلى أن **NEAT1** و**MALAT1** يمكن أن يشاركوا في التسبب في التهاب اللثة. ومع ذلك، هناك حاجة إلى مزيد من الدراسات في الجسم الحي لتأكيد هذه النتائج.