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Evaluation of exo-long noncoding RNA MALAT1 in OSCC in comparison to dysplastic and normal: A cross-sectional study

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ABSTRACT

Objective: This study explores the role of MALAT1 as a valuable target for creating minimally-invasive diagnostic methods and personalized treatments in the management of OSCC. It focuses on evaluating the role of exosomal MALAT1 in the progression of dysplasia to OSCC by influencing the PI3K/AKT pathway.
Method: This cross-sectional study evaluated MALAT1 expression and PI3K/AKT pathway components in exosomes derived from plasma samples of patients with various stages of oral dysplasia, OSCC and compared with normal. RNA concentration was estimated, real-time polymerase chain reaction (qPCR) was used for quantitative analysis. Gene expression levels of MALAT1, PI3K, AKT1, and PTEN were analysed and compared across groups using one way ANOVA and Post-hoc Tukey analysis was performed for pairwise comparisons to assess correlations between MALAT1 expression and PI3K/AKT pathway components.
Result: MALAT1 was found to be overexpressed in OSCC in comparison to normal, significantly ($p < 0.001$*). There was no significant change in expression pattern of MALAT1 between dysplastic patients and normal, yet, significant association was found on corelation analysis between expression pattern of MALAT1 and PI3K/AKT/PTEN (p 0.001*) among individuals of dysplasia and OSCC. As well pairwise comparisons of MALAT1 expression levels between all three stages of dysplasia showed significant association ($p < 0.001$*).
Conclusion: MALAT1 stands out as a key player in the complex landscape of OSCC pathogenesis, impacting tumorigenesis, metastasis, and treatment outcomes through multifaceted molecular mechanisms. Continued research into MALAT1's regulatory roles and its interactions within the tumor microenvironment holds promise for uncovering novel therapeutic targets and biomarkers that could redefine the management of OSCC in the future.

1. Introduction

Oral Squamous Cell Carcinoma (OSCC) represents a significant burden on global health, accounting for a majority of oral malignancies worldwide.[1] The prognosis for OSCC patients remains poor despite developments in diagnostic methods and treatment strategies, underscoring the urgent need for greater understanding of the disease's underlying molecular mechanisms in order to enhance therapeutic results.[2] Long non-coding RNAs (lncRNAs) are important regulators of gene expression and cellular activities in the past few decades, and they have intricate role in the initiation and progression of cancer.[3] MALAT1 (Metastasis-Associated Lung Adenocarcinoma Transcript 1), the most extensively studied lncRNAs which has been implicated in various cancers including OSCC where its dysregulation influences tumor biology and clinical outcomes. MALAT1, formerly reported as a predictive marker in lung cancer metastasis, has now been explored in several facets of OSCC pathophysiology. In cancer cells, MALAT1 acts as a regulator of gene expression at transcriptional and post-transcriptional

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levels, impacting cellular proliferation, apoptosis, migration, and invasion, critical processes that drive tumor progression.[4] A significant mechanism through which MALAT1 exerts its oncogenic effects in OSCC is by modulating key signalling pathways, notably the PI3K/AKT pathway. Activation of PI3K/AKT signalling is known to promote cell survival, growth, and resistance to apoptosis, thereby conferring a growth advantage to cancer cells. MALAT1 has been shown to enhance PI3K/AKT pathway activity in OSCC cells, promoting aggressive tumor phenotypes and contributing to therapy resistance. Beyond its role in signalling pathways, MALAT1 participates in epigenetic modifications that contribute to OSCC metastasis.[5] MALAT1 may regulate the gene expression profiles linked to the epithelial-mesenchymal transition (EMT) by interacting with chromatin-modifying proteins and microRNAs. EMT induction facilitated by MALAT1 enhances cell motility and invasiveness, crucial steps in the metastatic cascade.[6] MALAT1 has been widely recognized as a pivotal regulator of cancer progression through multiple mechanisms, including EMT induction, modulation of cell cycle regulators, and enhancing metastatic potential. Its role in dysplasia could lie in promoting early oncogenic changes through pathways such as Wnt/β-catenin and PI3K/AKT signalling, both of which are critical in the transformation of dysplastic tissues to malignant phenotypes. One of the hallmark features of cancer progression is the epithelial-mesenchymal transition (EMT), where epithelial cells lose adhesion properties and gain mesenchymal, invasive traits. MALAT1 is known to promote EMT by regulating transcription factors such as ZEB1, ZEB2, and Snail, which are directly involved in OSCC progression. This mechanistic insight could bridge the gap between dysplastic changes and the invasive phenotype seen in oral cancer. The dysregulated expression of MALAT1 in OSCC tissues and its presence in circulating blood and saliva samples underscore its potential as a diagnostic and prognostic biomarker. Studies have correlated elevated MALAT1 levels with advanced tumor stages, lymph node metastasis, and poorer overall survival rates in OSCC patients.[7] This study potentially highlights MALAT1 as a promising target for developing non-invasive diagnostic tools and personalized therapeutic strategies in OSCC management. The study aims at assessing the role of exosomal MALAT 1 in progression of dysplasia to OSCC by modulating PI3K/AKT pathway.

2. Methodology

2.1. Ethical considerations

The study was approved ethically after it had been submitted to the institutional ethical committee (IHEC/SDC/PHD/BIOCHEM-2108/21/TH-035(A)). All the participants were explained the study in detail and informed consent was obtained. The details of all the participants were maintained confidentially and all data was anonymized.

2.2. Study design

This cross-sectional study assessed the expression levels of MALAT1 and components of the PI3/AKT pathway in exosome derived from blood-plasma samples of patients with varying stages of oral dysplasia, OSCC in comparison to normal. Real-time PCR (qPCR) was utilized for quantitative analysis.

2.3. Participants

The study included a total of 75 participants with 25 participants in each group Group I- Normal; Group II- Dysplasia; Group III- OSCC. The study included patients above 18 years of age, patients who did not receive any prior treatment like chemotherapy/radiotherapy or surgical intervention. Patients who provided informed consent for participation. Those patients with other systemic diseases or malignancies, those had recurrent lesions are excluded from the study.

2.4. Sample collection

About 5 ml of peripheral blood from each participant were collected using EDTA coated tubes. The blood samples were stored at 4 °C and processing was done within 2 h of collection to maintain RNA integrity.

2.5. Total exosome RNA isolation and gene expression analysis

Blood samples were collected, and plasma was separated for the exosome isolation process. To facilitate this, the Invitrogen exosome isolation kit (catalogue no: 4484450) was employed. Initially, the obtained plasma was centrifuged at 2000×*g* for 20 min at room temperature. The supernatant was then subjected to proteinase treatment to ensure the purification of the exosome content. Following the isolation of the exosomes, RNA was extracted using the Invitrogen RNA isolation kit (catalogue no: 4478545). The quantity of RNA in the sample was measured using a nanodrop lite UV–visible spectrophotometer (THERMO, AMP10) and expressed in μg. The RNA pellet was measured at 260/280 nm and has a purity range of 1.8–2.0 μg. A reverse transcriptase enzyme was utilized to produce cDNA via reverse transcription. The genes were amplified using Bio-Rad Real Time (C1000 Touch, thermal cycle-20 μl reaction) under the following thermal conditions: a 5-min initial denaturation step at 95 °C, followed by 40 cycles of 30 s at 95 °C, 1 min at 59 °C, and 30 s at 72 °C. To analyze the relative quantification, amplification plot, and melt curve analyses were utilized. Specific primers targeting genes such as MALAT1, PI3K, AKT, and PTEN were utilized in the amplification process, and GAPDH was used as an internal control. Primers[8] used in this study were MALAT1 forward: 5′-AAA GCA AGG TCT CCC CAC AAG-3′; MALAT1 reverse: 5′-GGT CTG TGC TAG ATC AAA AGG C-3′; PI3K forward: 5′-AAC ACA GAA GAC CAA TAC TC-3′ and PI3K reverse: 5′-TTC GCC ATC TAC CAC TAC-3′; GAPDH forward: 5′-GGT GGT CTC CTC TGA CTT CAA CA-3′; GAPDH reverse: 5′-GTG GTC GTT GAG GGC AAT G-3′; AKT forward 5′-ATC GTC GCC AAG GAT GAG GT-3′ and AKT reverse 5′-TCT CGT GGT CCT GGT TGT AG-3′; PTEN forward 5′- TGG AAA GGG ACG AAC TGG TG-3′, and PTEN reverse 5′-CAT AGC GCC TCT GAC TGG GA-3′. The resultant amplified products were analysed, and the melt curve data were examined to ensure the accuracy of relative quantification of the target genes.

2.6. SDS PAGE of isolated exosome

The Bio-Rad Mini-PROTEAN Tetra Cell (catalog number 1658004) was used for SDS-PAGE analysis. Exosome samples were lysed using lysis buffer and the lysed samples and a ladder were loaded onto a polyacrylamide gel, and the gel was run in SDS-PAGE running buffer. After electrophoresis, the protein bands were visualized by staining them with Coomassie Brilliant Blue, followed by destaining using a solution of methanol and acetic acid. (supplementary).

2.7. Real-time PCR (qPCR)

The reaction was setup with the qPCR master mix for each reaction, the composition includes 10 μL SYBR Green Master Mix; 1 μL forward primer; 1 μL reverse primer; 2 μL cDNA template and 6 μL Nuclease-free water. The program for the thermocycler was set up with Initial denaturation at 95 °C for 10 min, denaturation: 95 °C for 15 s, annealing: 60 °C for 30 s, extension: 72 °C for 30 s and the reaction was set up for 40 cycles. The expression levels of target genes MALAT1, PI3K, AKT1, PTEN are normalized to the housekeeping gene GAPDH using $2_{\bar{T}}^{-\Delta\Delta C}$ method.

2.8. Statistical analyses

The data was entered in Microsoft Excel and was analysed using SPSS (Statistical Package for Social Sciences) software version 26.0. Continuous variables were expressed as mean ± standard deviation (M±S.D) and categorical variables were expressed as n and %. The data was

checked for normal distribution by Shapiro Wilk Test. Levene's test was used to check the homogeneity of variance of the data. The results showed that homogeneity of variance was violated and hence, non-parametric test of ANOVA was used. A p-value of less than 0.05 was considered as statistically significant.

Kruskal Walli's One-Way ANOVA was used for intergroup comparisons of continuous variables (MALATI Expression levels, PI3 expression levels, AKT expression levels, PTEN expression levels and GAPDH) between three study groups' namely normal children, children with OSCC and children with dysplasia. Post-hoc Bonferroni test was used for multiple pair wise comparisons of the continuous variables between the groups.

3. Results

3.1. Demographic data

Among the participants who were normal, about 10 (40 %) of them was 18–30 years, 1 (4 %) of them was 31–40 years of age, 4 (16 %) of them were 41–50 years of age, about 8 (32 %) of them were 51–60 years of age, 2 (8 %) of them were 61–70 years of age. Among the participants who had dysplasia, about 9 (36 %) of them were in 18–30 years of age, 3 (12 %) of them was 31–40 years of age, 4 (16 %) of them were 41–50 years of age, about 7 (28 %) of them were 51–60 years of age, 2 (8 %) of them were 61–70 years of age. Among the individuals who had OSCC, about 1 (4 %) of them was 31–40 years of age, 3 (12 %) of them were 41–50 years of age, about 14 (56 %) of them were 51–60 years of age, 7 (28 %) of them were 61–70 years of age. There were about 21 (84 %) males and 4 (16 %) females in normal and dysplasia group. In OSCC, there were about 20 (80 %) males and 5 (20 %) females (Table 1).

3.2. Clinical expression levels of MALAT1 associated with PI3K/AKT pathway

MALAT1, PI3K, AKT, and PTEN expression levels were compared between Group I,II,III (Table 2). The MALAT1 expression levels in normal, dysplasia, and OSCC were found to be, respectively, 0.92 ± 0.27, 1.63 ± 0.80, and 4.73 ± 1.58, with a p-value<0.001. This difference was statistically significant. In normal, dysplasia, and OSCC, the corresponding PI3K Expression levels were found to be 0.96 ± 0.2, 1.13 ± 0.39, and 1.45 ± 0.45, respectively. This difference was shown to be statistically significant (p-value<0.001). AKT expression levels were shown to differ statistically significantly (p-value<0.001) between normal, dysplasia, and OSCC, correspondingly, at 0.96 ± 0.20, 1.01 ± 0.04, and 1.82 ± 0.73. PTEN expression levels were shown to differ statistically significantly (p-value<0.001) between normal, dysplasia, and OSCC, correspondingly, at 1.00 ± 0.0, 1.00 ± 0.0, and 0.71 ± 0.21. From the results, it was evident that MALAT1, PI3K, AKT and PTEN expression levels differed significantly between the study Groups (Fig. 1).

Table 1
Age and gender distribution of study participants.

Socio-demographic variable	Stages	Normal n (%)	Dysplasia n (%)	OSCC n (%)
Age	*18-30 years*	10 (40)	9 (36)	0 (0)
	31-40 years	1 (4)	3 (12)	1 (4)
	41-50 years	4 (16)	4 (16)	3 (12)
	51-60 years	8 (32)	7 (28)	14 (56)
	61-70 years	2 (8)	2 (8)	7 (28)
Gender	*Males*	21 (84)	21 (84)	20 (80)
	Females	4 (16)	4 (16)	5 (20)

Table 2
Intergroup comparisons of MALAT1, PI3, AKT, PTEN, GAPDH expression levels between all three groups.

Expression level	Groups	Mean ± S.D	*p*-value
MALAT1 Expression level	*Normal*	0.92 ± 0.27	<0.001[a]
	Dysplasia	1.63 ± 0.80	
	OSCC	4.73 ± 1.58	
PI3K Expression level	*Normal*	0.96 ± 0.2	<0.001[a]
	Dysplasia	1.13 ± 0.39	
	OSCC	1.45 ± 0.45	
AKT Expression level	*Normal*	0.96 ± 0.20	<0.001[a]
	Dysplasia	1.01 ± 0.04	
	OSCC	1.82 ± 0.73	
PTEN Expression level	*Normal*	1.00 ± 0.0	<0.001[a]
	Dysplasia	1.00 ± 0.0	
	OSCC	0.71 ± 0.21	
	OSCC	1.0 ± 0.0	
	Dysplasia	0.95 ± 0.20	

-Kruskal Wallis One way ANOVA.
[a] p-value<0.05- statistically significant.

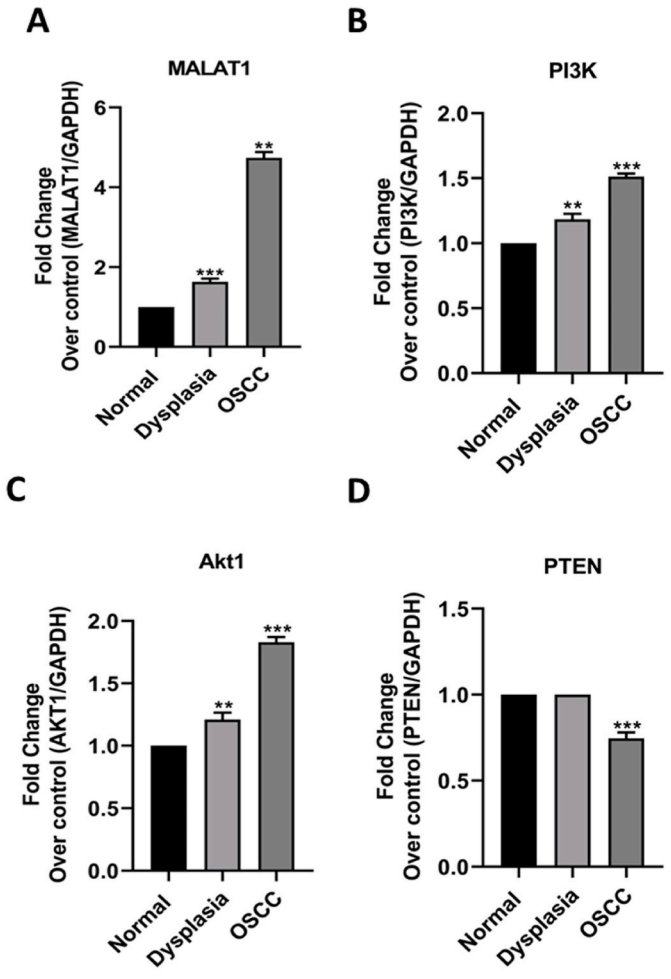

Fig. 1. Differential expression of MALAT1, PI3K, AKT1, and PTEN in normal, dysplasia and OSCC tissues. Quantitative real-time PCR (qRT-PCR) analysis was performed to measure the relative gene expression levels of (A) MALAT1, (B) PI3K, (C) AKT1, and (D) PTEN in normal, dysplasia, and oscc groups. Gene expression was normalized to GAPDH as the reference gene, and the fold change over the control group is shown. Statistical significance was determined using ANOVA, with $p < 0.05$ considered statistically significant. (fold change over control was indicated as * for the normal group and ** for the dysplasia group).

3.3. Pairwise comparison of MALAT1, PI3K, AKT, PTEN between three groups

Table 3 shows pairwise comparisons of MALAT1, PI3K, AKT, PTEN expression levels between all three groups. Individuals with OSCC had higher levels of MALAT1 expression than normal and dysplasia and this was found to be statistically significant (p-value<0.001 respectively). MALAT1 levels were slightly lower in normal than in dysplasia and this difference was also statistically significant (p-value = 0.04). Individuals with OSCC had higher levels of PI3K expression than normal and dysplasia and this was found to be statistically significant (p-value<0.001 respectively). PI3K levels were slightly lower in normal than in dysplasia and this difference was statistically non-significant. OSCC had higher levels of AKT expression than normal and dysplasia and this was also found to be statistically significant (p-value<0.001 respectively). AKT levels were slightly lower in normal than dysplasia and this difference was statistically non-significant.

3.4. Intergroup comparison expression pattern of MALAT1, PI3K, AKT, PTEN

Table 4 shows intergroup comparisons of MALAT1, PI3K, AKT, PTEN, expression levels between three stages of dysplasia. MALAT1 expression levels among children with mild, moderate and severe dysplasia were 1.04 ± 0.19, 1.66 ± 0.14 and 2.54 ± 0.56 respectively and this difference was found to be statistically significant (p-value<0.001). PI3K Expression levels among children with mild, moderate and severe dysplasia were 0.92 ± 0.26, 1.04 ± 0.06 and 1.48 ± 0.36 respectively and this difference was found to be statistically significant (p-value = 0.001). From the results, it is evident that MALAT1 and PI3K expression levels differed significantly between the stages of dysplasia. On the other hand, AKT and PTEN didn't differ much between the three stages of dysplasia and was statistically non-significant.

3.5. Comparative correlation of expression pattern of MALAT1 vs PI3K/AKT/PTEN

Fig. 2 shows Correlation between MALAT-1 Expression and PI3K, AKT, PTEN expression based on study groups. MALAT1 and PI3K expression were strongly correlated in OSCC (correlation coefficient = 0.65) and dysplasia (correlation coefficient = 0.69) and this was found to be statistically significant as well (p-value<0.05 respectively). MALAT1 and AKT expression levels were strongly correlated in OSCC (correlation coefficient = 0.77) and moderately correlated with dysplasia (correlation coefficient = 0.42) and this was also found to be statistically significant as well (p-value<0.05 respectively).

Effect size was found out by calculating Cohen's D. An effect size of more than 0.8 can be considered as large. Since the parameters MALAT 1 Expression, PI3 Expression level, AKT Expression level and PTEN Expression levels had an effect size value of more than 1.0, all these expressions can be considered as clinically relevant in identifying OSCC (Table 5).

Table 3
Pairwise comparisons of MALAT1, PI3K, AKT, PTEN expression levels between all three groups.

Expression level	Comparisons	Median difference	p-value
MALAT1 Expression level	***Normal vs OSCC***	−3.3	**<0.001**[a]
	Normal vs Dysplasia	0	**0.04**[a]
	OSCC vs Dysplasia	3.3	**<0.001**[a]
PI3 Expression level	***Normal vs OSCC***	−0.4	**<0.001**[a]
	Normal vs Dysplasia	0	0.12
	OSCC vs Dysplasia	0.4	**<0.001**[a]
AKT Expression level	***Normal vs OSCC***	−0.8	**<0.001**[a]
	Normal vs Dysplasia	0	1.0
	OSCC vs Dysplasia	0.8	**<0.001**[a]
PTEN Expression level	***Normal vs OSCC***	0.2	**<0.001**[a]
	Normal vs Dysplasia	0	1.0
	OSCC vs Dysplasia	−0.2	**<0.001**[a]

Post hoc Bonferroni test.
[a] p-value<0.05- statistically significant.

Table 4
Comparisons of MALAT1, PI3K, AKT, PTEN expression levels between three stages of dysplasia.

Expression level	Stages of dysplasia	Mean ± S.D	Median (IQR)	P-value
MALAT1 Expression level	***Mild dysplasia***	1.04 ± 0.19	1 (1,1)	**<0.001**[a]
	Moderate dysplasia	1.66 ± 0.14	1.6 (1.56)	
	Severe dysplasia	2.54 ± 0.56	2.67 (1.94, 3.09)	
PI3 Expression level	***Mild dysplasia***	0.92 ± 0.26	1 (1,1)	**<0.001**[a]
	Moderate dysplasia	1.04 ± 0.06	1.04 (1)	
	Severe dysplasia	1.48 ± 0.36	1.54 (1.10, 1,78)	
AKT Expression level	***Mild dysplasia***	1.0 ± 0.0	1 (1,1)	0.15
	Moderate dysplasia	1.0 ± 0.0	1 (1,1)	
	Severe dysplasia	1.03 ± 0.06	1 (1, 1.04)	
PTEN Expression level	***Mild dysplasia***	1.0 ± 0.0	1 (1,1)	1.0
	Moderate dysplasia	1.0 ± 0.0	1 (1)	
	Severe dysplasia	1.0 ± 0.0	1 (1,1)	
	Moderate dysplasia	0.96 ± 0.04	0.96 (0.93)	
	Severe dysplasia	1.0 ± 0.0	1 (1,1)	

-Kruskal Wallis One Way ANOVA.
[a] p-value<0.05 – statistically significant.

4. Discussion

MALAT1 (Metastasis-Associated Lung Adenocarcinoma Transcript 1) is a long non-coding RNA (lncRNA) that has been extensively studied for its role in various cancers, including Oral Squamous Cell Carcinoma (OSCC).[9] The study findings underscore the role of MALAT1 as a key molecular driver in oral cancer progression. The differential expression of MALAT1 observed across normal tissues, dysplasia, and OSCC highlights its progressive upregulation as a hallmark of tumorigenesis. MALAT1 drives tumor cell proliferation through its interaction with the PI3K/AKT/mTOR signalling pathway, which regulates cellular growth, metabolism, and resistance to apoptosis. Its elevated expression in dysplasia could indicate an early activation of this pathway, potentially predisposing tissues to malignant transformation.

The PI3/AKT pathway is crucial for cell survival, proliferation, apoptosis and autophagy. In OSCC, components of the PI3/AKT pathway, including PI3K and AKT1, are often upregulated, leading to enhanced tumor growth and resistance to apoptosis. MALAT1 modulates the PI3K/AKT pathway through various mechanisms. One significant mechanism involves the regulation of PTEN, a tumor suppressor that negatively regulates the PI3K/AKT pathway. MALAT1 has been shown to downregulate PTEN expression, leading to the activation of the PI3K/AKT pathway. This activation promotes cell survival and proliferation, contributing to OSCC progression.

The primary results of our study show that MALAT1 is about four times hyperexpressed in OSCC in comparison to normal. Similarly, the

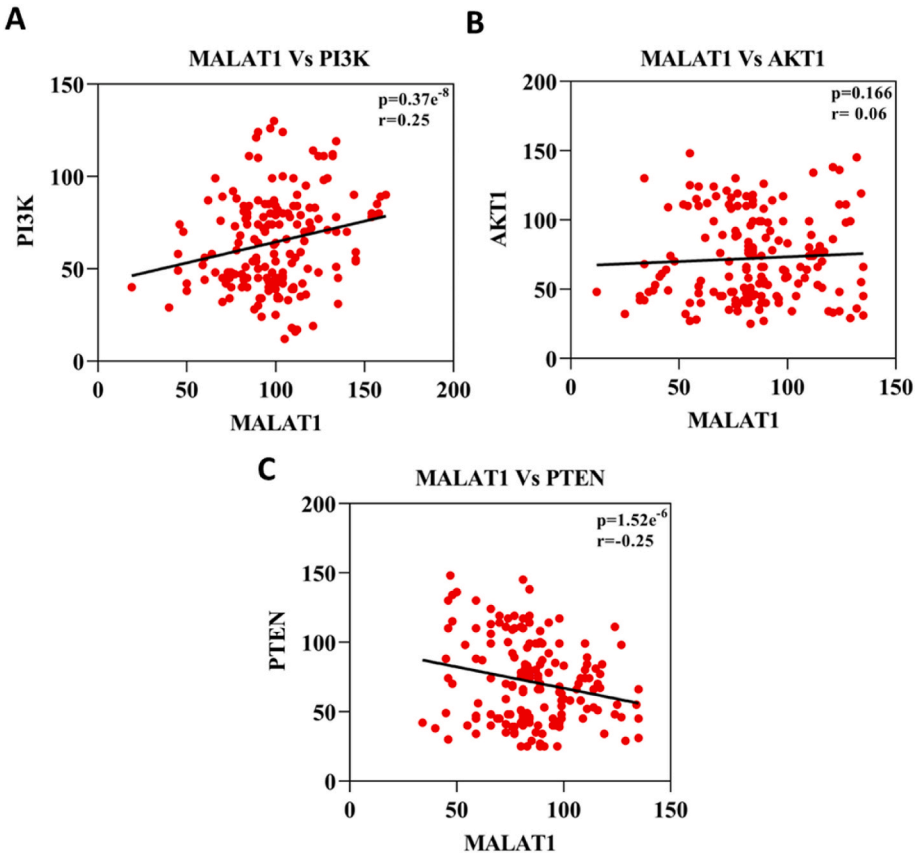

Fig. 2. Corelation plots of MALAT1 associated with PI3K/AKT pathway in OSCC samples. (A) PI3K (r = 0.25), (B) AKT (r = 0.06), and (C) PTEN (r = −0.25) targets corelated with MALAT1 in OSCC samples. Red colour denotes the samples and black line denotes the regression curve. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 5
Clinical significance of various parameters.

	Effect size
MALAT Expression	3.36
PI3 Expression level	1.40
AKT Expression level	1.60
PTEN Expression level	1.76
GAPDH	0.25

expression pattern of PI3K/AKT was also increased in OSCC in comparison to normal, whereas, the expression of PTEN was downregulated in OSCC in comparison to normal. The results of this study indicate that MALAT1 is differentially expressed in OSCC individuals that has modulating effect on PI3K/AKT pathway.

Numerous studies have been conducted to assess MALAT1's function in the development of oral cancer. MALAT1 has been demonstrated by Zhou et al. (2015)[10] to play an important part in the progression of OSCC by initiating EMT, which in turn promotes tumor growth and metastasis. These results emphasize the significance of MALAT1 in the pathophysiology of OSCC and imply that MALAT1 may function as a therapeutic target as well as a biomarker in the treatment of OSCC. Through its control of the PI3K-AKT pathway, MALAT1 has been shown by Feng et al. (2017)[11] to be a significant promoter of the formation and progression of tongue squamous cell carcinoma (TSCC). These discoveries shed light on possible targets for therapeutic intervention and advance our knowledge of the molecular mechanisms driving TSCC. Similarly, in our study MALAT1 has been shown to promote progression of disease by their increased expression across normal, dysplasia, OSCC.

Xu et al. (2017)[12] showed that MALAT1 upregulates C-C chemokine receptor type 7 (CCR7) and related genes, which in turn enhances OSCC development and metastasis. The molecular frameworks of OSCC metastasis are clarified by this work, which also suggests MALAT-1 and CCR7 could be potential targets for therapeutic intervention. The results highlight how crucial it is to treat OSCC by focusing on the MALAT-1/CCR7 axis. According to Liang et al. (2017),[13] MALAT1 activates the wnt/β-catenin signalling pathway in tongue cancer cells, which promotes EMT and suppresses apoptosis. These results provide light on MALAT1 as a putative biomarker and therapeutic target and provide light on the molecular pathways underlying the development of tongue cancer.

Chang et al. (2018)[14] observed that MALAT1 utilises the miR-125 b/STAT3 axis to promote the growth of OSCC. MALAT1 increases STAT3 expression and activity by downregulating miR-125 b, which increases the proliferation, invasion, and survival of tumor cells. These results indicate possible targets for therapeutic intervention and shed information on the molecular mechanisms underlying the evolution of OSCC. According to Han et al. (2019),[15] MALAT-1 inhibition inhibits TSCC cell proliferation and migration, triggers apoptosis, and lowers the expression of important carcinogenic genes. These results highlight MALAT-1's potential as a biomarker and therapeutic target in the treatment of tongue squamous cell carcinoma.

By controlling the miR-140-5p-PAK1 pathway, Zhu et al. (2019)[16] clarified the function of lncRNA MALAT1 in the development of tongue squamous cell carcinoma. Their results highlight MALAT1 as a crucial modulator of tumor growth and metastasis in TSCC and point to its potential as a biomarker for diagnosis as well as a target for treatment.

Wang et al. (2020)[17] report that MALAT1 contributes to OSCC cisplatin resistance. The results of the study showed that MALAT1 stimulates cisplatin resistance and EMT through the PI3K/AKT/m-TOR signalling pathway. Because of the function that MALAT1 plays in therapeutic resistance, this study suggests that targeting it could improve the outcomes of OSCC treatment. According to Xiao et al. (2020),[18] lncRNA MALAT1 controls the miR-101/EZH2 axis to stimulate cell invasion and proliferation in OSCC. These findings provide insights into the molecular mechanisms of OSCC progression and highlight MALAT1 as a potential biomarker and therapeutic target.

The effects of genetic variations in MALAT1 and exposure to environmental carcinogens together have been shown by Ding et al. (2021)[19] to have a significant impact on the susceptibility to and progression of OSCC. The significance of a multifaceted approach in comprehending the pathophysiology of OSCC and formulating focused preventive and therapeutic measures is highlighted by these results. MALAT1's association with miRNA-124 demonstrated its potential as a salivary biomarker for OSCC, as reported by Shalaby et al. (2024).[20] The results imply that MALAT1 may help with non-invasive diagnostics and be a target for cutting-edge treatment strategies in the treatment of OSCC.

Role of exosomal MALAT1 in promoting angiogenesis and associated poor prognosis in epithelial ovarian cancer (EOC) was studied by Qiu et al. (2018).[21] The study sheds light on the significance of MALAT1 as a potential biomarker and therapeutic target in EOC. Similarly in our study, exosomal MALAT1 has been identified with profound role in tumor progression. Differential expression of MALAT1 across stages of oral dysplasia and OSCC suggests that their activation may be a key event in OSCC progression. Our study indicates that MALAT1 expression levels are significantly elevated in OSCC compared to dysplasia and normal individuals. The elevation also correlates with the severity of the disease, indicating a potential role in the transition from dysplasia to malignancy. In our study it is evident that MALAT1 could act as a potential marker in identifying the prognosis of the disease.

5. Conclusion

Despite the promising insights into MALAT1's role in OSCC progression, several challenges remain. Variability in MALAT1 expression across different OSCC subtypes and patient populations necessitates larger-scale studies to validate its clinical utility. Furthermore, elucidating the precise mechanisms by which MALAT1 influences PI3/AKT oncogenic pathways and therapeutic responses will be crucial for translating research findings into clinical applications. In conclusion, MALAT1 stands out as a key player in the complex landscape of OSCC pathogenesis, impacting tumorigenesis through multifaceted molecular mechanisms. Continued research into MALAT1's regulatory roles and its interactions within the tumor microenvironment holds promise for uncovering novel therapeutic targets and biomarkers that could redefine the management of OSCC in the future.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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