Original Article

Linc00467 promotes invasion and inhibits apoptosis of head and neck squamous cell carcinoma by regulating miR-1285-3p/TFAP2A

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Received February 9, 2021; Accepted March 20, 2021; Epub June 15, 2021; Published June 30, 2021

Abstract: Objective: To explore the invasion and apoptosis of head and neck squamous cell carcinoma (HNSCC) regulated by Linc00467 through the miR-1285-3p/TFAP2A axis. Methods: qRT-PCR was used to detect the expressions of Linc00467, miR-1285-3p, and TFAP2A in tissues and cells of HNSCC patients. The targeting relationships between Linc00467 and miR-1285-3p, miR-1285-3p, and TFAP2A were verified by dual-luciferase reporter assay. Transfection and grouping were carried out, after HNSCC cell lines were screened. Transwell assay and flow cytometry were used to test cell invasion and apoptosis, respectively. Results: Compared with normal tissues adjacent to the tumor, the expressions of Linc00467 and TFAP2A increased significantly in cancer tissues, while the expression of miR-1285-3p decreased (all P<0.05). Compared with the si-NC group, the invasion of the si-Linc00467 group decreased and the apoptosis rate increased (both P<0.05). In HNSCC cells, over-expression of Linc00467 promoted increased cell invasion and decreased apoptosis rate, which could be partially rescued by over-expression of miR-1285-3p (all P<0.05). Over-expression of miR-1285-3p caused decreased cell invasion and increased apoptosis rate, which was partially reversed by over-expression of TFAP2A (all P<0.05). Conclusion: Linc00467 can be used as ceRNA to adsorb miR-1285-3p to regulate the expression of TFAP2A, promote invasion and inhibit apoptosis of HNSCC cells. Linc00467 inhibitors may become one of the targeted therapeutic drugs for HNSCC.

Keywords: Linc00467, miR-1285-3p, head and neck squamous cell carcinoma, invasion, apoptosis

Introduction

Head and neck squamous cell carcinoma (HNSCC), one of the top ten malignant tumors, is the most common epidermal malignant tumor of the head and neck, with at least 600,000 new cases worldwide each year [1, 2]. In China, about 135.1 people per 100,000 population suffer from the disease. At present, due to few methods and poor prognosis, more than 50% of patients will experience recurrence and metastasis within 3 years, which means a high mortality [3]. Therefore, exploring the key factors and regulatory factors in the occurrence and development of HNSCC is the key to improving the diagnosis, treatment and prognosis of the disease.

Non-coding RNA (ncRNA) is a functional RNA molecule that cannot be translated into protein. In recent years, ncRNAs, as a group of important epigenetic regulation genes, have been widely used in clinical diagnosis and treatment, and they play an important role in the occurrence and development of tumors [4, 5]. ncRNA is divided into long non-coding RNA, (LncRNA) and short non-coding RNA (piRNA, siRNA, miRNA) according to its length. ncRNAs can regulate gene expression at the levels of transcription, post-transcription and chromosomes, and participate in the biologic processes of different cells as well [6, 7]. Some abnormally expressed LncRNAs in the development of tumors are involved in the proliferation, invasion, and apoptosis of cancer cells. Liang et al. found that LncRNA-SOX2O promoted the invasion and metastasis of liver cancer cells through miR-122-5p-mediated PKM2 activation [8, 9]. It was also reported that LncRNA-TTN-AS1 improved the proliferation and migration of oral
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squamous cell carcinoma cells through miR-411-3p/NFAT5, which caused progression of cancer cells [10]. Current research results show that Linc00467 mainly functions as a cancer promoter in HNSCC [11].

As an endogenous single-stranded RNA with a length of about 22nt, miRNA affects the pathogenesis of tumors by binding to LncRNA after transcription [12, 13]. miR-1285-3p has anti-neoplastic effects in a variety of cancers, but its role in HNSCC remains unclear [14, 15]. TFAP2A is also known as AP-2alpha. It has been confirmed that the loss of TFAP2A expression is closely related to HNSCC growth inhibition. However, it is overexpressed in about 70% of HNSCC patients, suggesting that TFAP2A acts in as a cancer-promoting factor in HNSCC [16, 17]. However, whether it has a targeting relationship with miR-1285-3p has not been confirmed.

In this study, we explored the role of Linc00467 in the development of HNSCC, as well as the specific mechanism of action of Linc00467 in HNSCC through miR-1285-3p and TFAP2A, so as to provide a theoretical basis and data support for the treatment of HNSCC.

Materials and methods

Bioinformatics

http://cm.jefferson.edu/rna22/ was used to predict possible miRNA-LncRNA interaction relationships. miRDB (http://www.mirdb.org/) was used to find the target gene of miR-1285-3p. The risk genes for HNSCC disease were predicted through DisGeNET database (http://disgenet.org/search). The protein interaction relationship between disease risk genes and candidate genes was found by String database (https://string-db.org/), and visualized with Cytoscape software.

Subjects

Thirty-five HNSCC patients treated in our hospital from March 2019 to July 2020 were selected for the study [18]. The protocol was approved by the Ethics Committee of our hospital with written informed consent taken from all subjects.

Inclusion criteria: Patients were diagnosed with primary HNSCC confirmed by pathological examination; patients did not receive chemotherapy or any other form of treatment before entering the group.

Exclusion criteria: Patients also had primary hypertension, heart disease, etc.; patients received chemotherapy or other treatment; patients participated in other projects.

The selected patients were aged from 25 to 55 years old, with an average age of 40.4±7.3 years. There were 23 male cases and 12 female cases. All patients included 9 cases of throat cancer, 12 cases of pharynx cancer, 10 cases of tongue cancer, and 4 cases of cheek cancer. There were 15 cases with lymph node metastasis and 20 with no lymph node metastasis. According to WHO pathology classification, there were 10 cases, 17 cases and 8 cases of grade I (high differentiation), grade II (middle differentiation), and grade III (low differentiation), respectively [13]. Twenty cases of normal tissues adjacent to the tumor were taken as a control.

Cell strain culture

The HNSCC cell lines (HN4, HN6, SCC-4, SCC-9) and normal endocystal cell line HOK (ATCC cell bank, USA) were placed into the DMEM medium (including 10% fetal bovine serum) (PM-150210, Shanghai Pure Biotech Co., Ltd., China). The medium was placed in an incubator at 37°C, 5% CO₂ for growth. Cell strains passed down to 3 generations were tested by qRT-PCR, and the cell strains with the highest expression of Linc00467 were selected for the follow-up experiment.

Fluorescence in situ hybridization (FISH)

LncATLAS (http://lncatlas.crg.eu) was used to predict whether Linc00467 existed in the cytoplasm. Localization of Linc00467 was detected by fluorescence in situ hybridization kit (C10920, Guangzhou Ruibo Biotechnology Co., Ltd., China). According to the instructions, the cells were cultured on a glass slide in a 24-well plate for 24 hours. After fixation and permeabilization, the Linc00467 probe was hybridized overnight at 37°C. DAPI (C00060, Beijing Soleichao Technology Co., Ltd., China) was used to
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Table 1. Primer sequences

<table>
<thead>
<tr>
<th>Gene</th>
<th>Sequence (5'-3')</th>
</tr>
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<tbody>
<tr>
<td>Linc00467</td>
<td>F: TAGACATGGAAGAAGTCCACTCCAG</td>
</tr>
<tr>
<td></td>
<td>R: CTGAAGAGATGATAGGAGGAGGAAGGG</td>
</tr>
<tr>
<td>miR-1285-3p</td>
<td>F: TCTGGGCAACAAAAGTGAG</td>
</tr>
<tr>
<td></td>
<td>R: CTCAACAGGTGTCGAGGGAAGG</td>
</tr>
<tr>
<td>TFAP2A</td>
<td>F: TGCTACACTGACTCCGGCT</td>
</tr>
<tr>
<td></td>
<td>R: GAATGCCTGAAATCGAGGG</td>
</tr>
<tr>
<td>U6</td>
<td>F: CTGGCTTCGGCAGCTCACCA</td>
</tr>
<tr>
<td></td>
<td>R: AACGCTTCAAGATTTGCGT</td>
</tr>
<tr>
<td>GAPDH</td>
<td>F: GGAGCGAGATCCCTCCAAATT</td>
</tr>
<tr>
<td></td>
<td>R: GGCTGTTGTCATACTTCTCAATG</td>
</tr>
</tbody>
</table>

stain fixed cells, and finally a fluorescence microscope (FM-200, Shanghai Pudan Optical Instruments, China) was used to observe cells.

**Dual-luciferase reporter assay**

The wild-type and the mutant 3'-UTR sequences of Linc00467 and TFAP2A were constructed respectively. Then these sequences were cloned into pmiR-GLO vector. The above plasmids were co-transfected into HNSCC cells with miR-NC and miR-1285-3p mimic using LipofectamineTM 3000 reagent (L3000001, Thermo Fisher, USA). Cell luciferase activity was determined by dual-luciferase reporter assay kit (D0010-100T, Beijing Soleibao Technology Co., Ltd., China).

**Cell grouping and transfection**

The selected HNSCC cells were grouped as NC group (HNSCC cells + Linc00467 negative control sequence), si-NC group (HNSCC cells + si-Linc00467 negative control sequence), Linc00467 group (HNSCC cells + Linc00467), si-Linc00467 group (HNSCC cells + si-Linc00467), miR-NC group (HNSCC cells + miR-1285-3p negative control sequence), Linc00467 group (HNSCC cells + Linc00467 + miR-NC), miR-1285-3p mimic group (HNSCC cells + Linc00467 + miR-1285-3p mimic), miR-1285-3p mimic group (HNSCC cells + miR-1285-3p mimic + vector group (HNSCC cells + miR-1285-3p mimic + blank carrier), miR-1285-3p mimic + TFAP2A group (HNSCC cells + miR-1285-3p mimic + TFAP2A). According to the instructions of LipofectamineTM 3000 kit (L3000001, Thermo Fisher, USA), each group of cells was transfected. The sequences and transfection vectors used were provided by Shanghai Jima Pharmaceutical Technology Co., Ltd.

**qRT-PCR**

Total RNA from HNSCC cells was extracted with Trizol reagent (R1100, Beijing Solebold Technology Co., Ltd., China), whose concentration and quality were determined. cDNA was synthesized by reverse transcription kit (T2240, Beijing Solebold Technology Co., Ltd., China), which was inactivated in a warm bath at 80°C. The PCR reaction system and reaction conditions were detailed in the kit instructions. U6 was used as the internal control for the relative expression level of miR-1285-3p, and GAPDH was used as the internal control for Linc00467 and TFAP2A. The 2-ΔΔCt method represented the relative expression of each target gene. This experimental method was also applicable to tissue experiments. See Table 1.

**Transwell assay**

Cells were resuspended at 1×10^6 cells/mL. Cell suspension (150 μL) was added to the upper chamber of the transwell chambers. DMEM medium (550 μL containing 10% fetal bovine serum) (PM150210, Shanghai Yuchun Biotechnology Co., Ltd., China) was added to the lower chamber. The transwell chamber was placed at 37°C and 5% CO₂ for 24 hours. Then the Transwell chambers were taken out. The remaining cells in the upper chamber were wiped with a cotton swab. Cells were stained with 0.1% crystal violet (C8470, Beijing Soleibao Technology Co., Ltd., China) for 10 minutes, and fixed with 4% paraformaldehyde (P0099, Shanghai Biyuntian Biotechnology Co., Ltd., China). After 15 minutes, an inverted microscope (CX43, OLYMPUS, Japan) was used to observe the cells and take pictures.

**Flow cytometry**

Cells after 48 h transfection were collected, digested with trypsin (C202, Shanghai Biyuntian Biotechnology Co., Ltd., China), and washed with PBS (C0221A, Shanghai Biyuntian Biotechnology Co., Ltd., China). Cells were resuspended at 1×10^5 cells/mL. Annexin-V-FITC/PI
staining solution was prepared according to the Annexin-V-FITC/PI kit (BB-4101, Shanghai Beibo Biological Technology Co., Ltd., China). Cells were stained for 20 minutes in the dark, and the apoptosis situation was analyzed by the flow cytometer (Attune Nxt, Thermo Fisher, USA).

Statistical analysis

GraphPad prism 8.0 software was adopted for graph. SPSS 21.0 was used for statistical analysis. Shapiro and Levene tests were adopted to determine the normal distribution and the homogeneity of variance of data. The measurement data conforming to the homogeneity of variance were expressed as mean ± standard deviation. T-test was used for analysis between two groups, single-factor variance for comparison between multiple groups, and LSD or SNK method for post-hoc test. For non-normal distribution, the Mann-Whitney U test was used between the two groups, and the Bonferroni test was used between multiple groups. P<0.05 indicated that the difference was significant.

Results

Linc00467 was up-regulated in HNSCC while miR-1285-3p was down-regulated

Compared with normal tissues adjacent to the tumor, the expression of Linc00467 increased significantly while the expression of miR-1285-3p decreased significantly (both P<0.05, Figure 1A, 1B). In the HNSCC cell lines (HN4, HN6, SCC-4 and SCC-9) and the normal epithelial cell line HOK, SCC-9 had the highest expression of Linc00467 and the lowest expression of miR-
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1285-3p, so it was chosen for follow-up experiments (all P<0.05, Figure 1C, 1D).

Knockdown of Linc00467 inhibited HNSCC cell invasion and promoted apoptosis

si-NC and si-Linc00467 plasmids were transfected into SCC-9 cells. Compared with si-NC group, the number of invaded cells in the si-Linc00467 group decreased by Transwell (P<0.05, Figure 2A). Compared with si-NC group, the number of apoptotic cells in the si-Linc00467 group increased by flow cytometry (P<0.05, Figure 2B).

Linc00467 worked as a ceRNA of miR-1285-3p

LncATLAS website revealed that Linc00467 mainly existed in the cytoplasm (Figure 3A). FISH experiments confirmed that Linc00467 was expressed in the cytoplasm and worked as a ceRNA (Figure 3B). RNA22 found binding sites between Linc00467 and miR-1285-3p (Figure 3C). Dual-luciferase reporter assay showed miR-1285-3p mimic significantly inhibited the luciferase activity of Linc00467-3’UTR-WT (P<0.05), but had no significant effect on the luciferase activity of Linc00467-3’UTR-MUT (P>0.05, Figure 3D).

Up-regulation of miR-1285-3p partially rescued the effect of Linc00467 overexpression on cancer cells

Previous experiments confirmed that Linc00467 had a targeting relationship with miR-1285-3p. Their role in cells was explored by regulating their expression in HNSCC cells. Transwell assay demonstrated stronger invasion ability of the cells in the Linc00467 group than in the NC group. Compared with Linc00467 + miR-NC group, Linc00467 + miR-1285-3p mimic group had lower invasion ability. The enhanced cell invasion ability caused by Linc00467 overexpression was partially rescued by miR-1285-3p overexpression (all P<0.05, Figure 4A). Flow cytometry revealed that, the number of apoptotic cells decreased after up-regulating Linc00467, but increased after overexpression of miR-1285-3p (P<0.05, Figure 4B). That is, Linc00467 promoted the malignant biologic behavior of HNSCC cells, but up-regulating miR-1285-3p partially reversed the effect of Linc00467 in HNSCC cells.
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TFAP2A is the downstream target of miR-1285-3p, whose expression was regulated by Linc00467 and miR-1285-3p

miRDB was used to find the target genes of miR-1285-3p, and 167 target genes with a target score of 80 or more were used for GO and KEGG analysis. There was no interesting pathway in KEGG, but the negative regulation pathway of apoptosis was found in GO analysis (Figure 5A). Cancer progression was related to the inhibition of cancer cell apoptosis, and the negative regulatory pathway of apoptosis became a focus. This pathway included TFAP2A, AHI1, EGR3, PTEN, RARB, APBB2, and SMAD6. The expression of TFAP2A was dysregulated in a variety of squamous cell carcinomas and had been proven to be closely related to the progression of HNSCC, so it was speculated that Linc00467/miR-1285-3p may achieve regulation of HNSCC by targeting TFAP2A. DisGeNET database (http://disgenet.org/search) was adopted to predict the disease risk genes of HNSCC (C1168401), and the top 10 were selected to analyze the protein interaction relationship between HNSCC risk genes and TFAP2A with String database. It was found that there was an association between them with potential biologic significance, though the tightness was small (Figure 5B). After that, we found that the expression of TFAP2A in cancer tissues was significantly higher than that of adjacent tissues (P<0.05; Figure 5C). The expression of TFAP2A in the selected HNSCC cell lines was higher than that of normal epithelial cell line HOK (all P<0.05), and the SCC-9 cell line had the highest expression of TFAP2A (Figure 5D). The targeting relationship prediction website confirmed that there were binding sites between miR-1285-3p and TFAP2A (Figure 5E),
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Figure 4. Up-regulation of miR-1285-3p partially reversed the effect of Linc00467 overexpression on cancer cells. A: Results from Transwell (200×); B: Results from flow cytometry. Compared with NC group, *$P<0.05$; compared with Linc00467 + miR-NC group, ^$P<0.05$. 
TFAP2A is a downstream target of miR-1285-3p. A: Results from GO analysis; B: Results from String database; C: Expressions of TFAP2A in the normal tissues adjacent to the tumor and cancer tissues; D: Expressions of TFAP2A in cell lines; E: Results from prediction of target relationship; F: Results from dual-luciferase report assay; G: Effects of knockdown of Linc00467 on the expression of TFAP2A; H: Effects of overexpression of miR-1285-3p on the expression of TFAP2A; I: The effect of simultaneous overexpression of Linc00467 and miR-98-5p on the expression of TFAP2A. Compared with the Normal group, △P<0.05; compared with HOK, #P<0.05; compared with SCC-9, @P<0.05; compared with co-transfected miR-NC and Linc00467-3’UTR-WT group, &P<0.05; compared with the si-NC group, ▲P<0.05; compared with the miR-NC group, ○P<0.05; compared with the miR-1285-3p mimic group, ●P<0.05.

The above results indicated that TFAP2A was a target gene of miR-1285-3p by regulating the expression of Linc00467 or miR-1285-3p in HNSCC cells. qRT-PCR was used to detect the expression of TFAP2A in cancer cells. It was found that knockdown of Linc00467 decreased the expression of TFAP2A, which was consistent with the trend after overexpression of miR-1285-3p (all P<0.05, Figure 5G, 5H). The expression of TFAP2A was decreased after overexpression of miR-1285-3p, but the effect was inhibited by overexpression of Linc00467 (P<0.05, Figure 5I).

Effects of overexpression of miR-1285-3p in cancer cells were partially reversed by upregulation of TFAP2A

The regulation of miR-1285-3p and TFAP2A demonstrated that the invasion and colony-forming ability of HNSCC cells in the miR-1285-3p mimic group were significantly lower than that in the miR-NC group, and the number of apoptotic cells increased. Compared with miR-
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Figure 6. Effects of overexpression of miR-1285-3p in cancer cells were partially reversed by upregulation of TFAP2A. A: Results from Transwell assay (200×); B: Results from flow cytometry. Compared with miR-NC group, *P<0.05; compared with miR-1285-3p mimic + vector, ^P<0.05.
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1285-3p mimic + vector group, miR-1285-3p mimic + TFAP2A group had enhanced invasion activity of HNSCC cells, and reduced number of apoptotic cells (all P<0.05), but not like the miR-NC group (Figure 6).

Discussion

In this study, in vitro experiments confirmed that Linc00467 up-regulated the expression of TFAP2A by competitively binding with miR-1285-3p, played a role in HNSCC, promoted the progress of HNSCC, and provided a new molecular target for the diagnosis and treatment of HNSCC.

The expression of Linc00467 was increased in HNSCC tissues and cells. Knockdown of Linc00467 inhibited cancer cell invasion and promoted cell apoptosis, suggesting that Linc00467 may play a role in promoting cancer in HNSCC.

The lncRNA-miRNA-mRNA interaction plays an important role in cancer. Construction of a disease-specific lncRNA-miRNA-mRNA regulatory network can reveal potential regulatory axes in cancer and predict prognosis biomarkers, which is of great significance in the treatment of cancer [19-21]. LncRNA is involved in the invasion of colorectal cancer, cervical cancer, and bladder cancer [22-24]. As one of the members of LncRNAs, the role of Linc00467 in tumors is constantly being revealed. Zhang et al. found that Linc00467 inhibited the expression of p53 by binding to DNMT1, thereby promoting the proliferation and invasion of glioma cells [25]. Recent studies have shown that Linc00467 is significantly up-regulated in HNSCC; knockdown of Linc00467 inhibits the proliferation, migration, and epithelial-mesenchymal transition of SCC-9 [11].

In order to explore the molecular network of Linc00467 in HNSCC, miR-1285-3p was verified as an effective regulatory target with the target relationship website and dual-luciferase reporter assay in this study. Previous studies confirmed that down-regulation of miR-1285-5p in breast cancer promoted the apoptosis of breast cancer cells by inhibiting the expression of TMEM194A [26]. In addition, Hu et al. reported that as a prognostic marker of ovarian cancer, miR-1285-3p exerts a tumor suppressor effect in ovarian cancer [27]. The role of miR-1285-3p in HNSCC has not yet been elucidated. In this study, the expression of miR-1285-3p was decreased in cancer tissues and cells. After regulating Linc00467 and miR-1285-3p, it was found that overexpression of Linc00467 promoted the invasion of HNSCC cells and reduced the number of apoptotic cells. This further confirmed the functional mechanism of miR-1285-3p as a tumor suppressor in HNSCC and the interaction network with Linc00467.

Generally, LncRNA regulates the post-transcriptional level of target genes by competitively binding with targeted miRNAs, thereby affecting biologic functions [28]. Therefore, in this study, miRDB was used to predict the downstream target genes of miR-1285-3p, and GO analysis and KEGG analysis were performed on the found target genes. From GO analysis, it was found that miR-1285-3p was closely related to the negative regulation of apoptosis; meanwhile, the occurrence and development of cancer were closely related to the inhibition of apoptosis of cancer cells. Thus, as a negative regulator of apoptosis, the gene TFAP2A was found. TFAP2A is one of the important transcription factors in the TFAP2 family. Previous studies demonstrated that it was involved in the proliferation, invasion and migration of cancer cells, and had potential in the diagnosis of specific tumors [29-31]. TFAP2A is highly expressed in HNSCC, and promotes the proliferation of cancer cells and inhibits cell apoptosis [16, 17]. After analysis of HNSCC disease risk genes with DisGeNET database, an association between TFAP2A and HNSCC risk genes was found. The detection of expression of TFAP2A in HNSCC revealed a high expression in cancer tissues and cells. Moreover, TFAP2A is a downstream target gene of miR-1285-3p. The regulation of the expression of miR-1285-3p and TFAP2A manifested that overexpression of miR-1285-3p promoted the apoptosis of cancer cells and inhibited cell invasion, which can be partially rescued by upregulating TFAP2A. In this study, knockdown of Linc00467 or overexpression of miR-1285-3p down-regulated the expression of TFAP2A. The expression of TFAP2A also increased after overexpression of Linc00467, but the up-regulation of miR-1285-3p partially inhibited the expression of TFAP2A, which further indicated that Linc00467 regulated TFAP2A by miR-1285-3p.

However, this study also needs further improvement, since it had no relevant in vivo experiments, and limited research samples.
In summary, Linc00467 can regulate the expression of miR-1285-3p/TFAP2A, thereby promoting the invasion of HNSCC cells and inhibiting cell apoptosis, which may provide a treatment plan for the study of HNSCC.

Acknowledgements

This work was supported by Hainan Provincial Natural Science Foundation of China for Study on the mechanism of mesenchymal stem cells in the treatment of radiation-induced salivary gland injury (20168315).

Disclosure of conflict of interest

None.

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