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Review Article

Long non-coding RNAs as novel biomarkers and therapeutic targets in head and neck cancers

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Abstract: Long non-coding RNAs (lncRNAs) are generally defined as RNA molecules greater than 200 nt in length and without protein-coding property that different from housekeeping RNAs such as tRNAs, rRNAs, and snRNAs, and independent from small RNAs with specific molecular processing machinery such as micro- or piwi-RNAs. LncRNAs are a novel class of mRNA-like transcripts which contribute to cancer development and progression and accelerate cancer cells proliferation, invasion, metastasis, and apoptosis. These research results indicate the potential of lncRNAs as prospective novel biomarkers for diagnosis, therapeutic targets and prognosis for cancers. In this review, we synthesize present study results to highlight aberration of lncRNAs in various types of head and neck cancers, and try to clarify the molecular mechanisms of lncRNAs affecting the oncogenesis and progression of head and neck cancer, as well as pay particular attention to provide a new avenue to the diagnosis and treatment strategy.

Keywords: Long non-coding RNA, head and neck cancer, biomarker, therapeutic target

Introduction

LncRNAs were widely regarded as the "noise" of genetic transcription because they perform no biological functionsas a by-product of RNA polymerase [1]. Along with the progression of DNA sequencing technologies, study revealed that more than 98% of genes in human genome are not protein-coding genes [2]. In recent years, lncRNAs have been valued by scholars. The genome-wide transcriptional surveys have impelled the identification of large numbers of lncRNAs, which have shown that eukaryotic genomes are pervasively transcribed, with clusters of overlapping sense and antisense transcripts surrounding or intronic to known genes, as well as wide spread transcription in intergenic regions [3]. The length of lncRNAs ranges from approximately 200 nt to over 100 kb. LncRNAs are widely divided into five categories according to their association with mRNA: 1. sense; 2. antisense: the adjacent coding transcript and the transcript of lncRNAs are reversed; 3. intronic: all lncRNAs come from the introns of another transcript; 4. intergenic: lncRNAs are located between two genes; 5. bidirectional: lncRNAs are in the same reverse direction with one or more exons overlapping in the same chain [4].

Studies have demonstrated that lncRNAs contribute to the development of various diseases especially in cancers as major participants of gene regulatory network via controlling thetranscriptional, posttranscriptional, and epigenetic mechanisms. By now, although the functions of most of the lncRNAs remain unknown, several lncRNAs have been clearly illustrated that play critical roles via their molecular mechanisms in various cellular processes, which include differentiation, growth, apoptosis, development, and tumorigenesis. Following by the introduction of functions of several lncRNAs clearly clarified so far, HOTAIR has two main functional domains, a PRC2-binding domain located at the 5' end of the RNA, and a LSD1/CoREST1-binding domain located at the 3' end of the RNA [5, 6]. HOTAIR mediates epigenetic silencing of another HOX cluster on a different chromosome via binding PRC2. For instance, in breast cancer, the upregulation of HOTAIR associates with a poor prognosis and tumor metastasis [5, 7, 8] as well

as metastasis and poor outcome in hepatocellular carcinoma, colorectal cancer and pancreatic cancer [9] and also invasion ability in gastrointestinal stromal tumors. Genome-wide association studies (GWAS) have certified that there is a relationship between ANRIL and increased susceptibility to several types of cancer such as acute lymphoblastic leukemia, glioma, basal cell carcinoma, nasopharyngeal carcinoma, breast cancer and plexiform neurofibromas [10, 11]. Another strong evidence proves that MALAT1 (metastasis associated lung adenocarcinoma transcript 1) might be a screening biomarker for lung cancer, uterine endometrial stromal sarcoma, cervical cancer and hepatocellular carcinoma because of its association with metastasis. MALAT1 promotes the motility of lung cancer cells through transcriptional or posttranscriptional regulation of motility-related genes [5, 12]. Here, we review the relationship between lncRNAs and head and neck cancers and those regulatory mechanisms in different head and neck cancers.

LncRNAs in head and neck cancer

LncRNAs in nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is one of the most prevalent cancers in southern China and Southeast Asia with notable racial and geographic distribution, which manifests that the development of this cancer might be associated with genetic factors. Identification of new NPC biomarkers will contribute to the diagnosis and therapy of NPC and might provide new insight into its pathogenesis. Nie et al [13] performed real-time PCR to examine the HOTAIR expression levels in 160 paired paraffin-embedded non-cancer and NPC specimens and 20 fresh frozen non-cancer nasopharyngeal tissues. The result showed that, the expression levels of HOTAIR wereup-regulated in NPC tissues than in non-cancerous tissues. Further study demonstrated that HOTAIR was up-regulated in NPC cell lines with high invasive potential and the capacity for migration, invasion and proliferation was suppressed after knocking down HOTAIR expression. Therefore, we believe that HOTAIR mediates diverse cellular processes, including the migration, invasion and proliferation of NPC cells. These results suggest that HOTAIR has the prospect of becoming a better prognostic marker for predicting the prognosis of advanced-stage NPC patients, which differs from many previous biomarkers that are usually used for early stage NPC.

MALAT1 is a significant long non-coding RNA with many biological functions. Xie et al [14] used RT-PCR to test MALAT1 expression levels in diverse NPC cells at mRNA levels. The result found that MALAT1 was most highly expressed in 5-8F cells (high rate to be tumor and metastasis), and up-regulated in CNE-2, C666-1 and HONE-1 which is higher malignant and poorly differentiated nasopharyngeal squamous cell carcinoma, while least expressed in NP69 epithelial cells of the eternal life. The data indicated that MALAT1 might be related to the metastasis and differentiation of NPC cells. Meanwhile, CNE-1 cells, stably transfected by MALAT1 lentivirus vector in this experiment, which were high differentiated cells of nasopharyngeal squamous cell cancer and low degree of malignant cells. After stably up-regulated MALAT1 by lentivirus activating vector, they proved MALAT1 can promote the ability of migration, invasion and proliferation of CNE-1 cells via functional experiment in vitro.

In recent years, GWAS has identified ANRIL as a risk locus for NPC and other cancers [15]. ANRIL is a long noncoding RNA within the p15/CDKN2B-p16/CDKN2A-p14/ARF gene cluster as well as anantisense noncoding RNA located in the INK4 locus. Meanwhile, GWAS has found that the susceptibility to diverse diseases is distinct, slight related to SNPs in the ANRIL locus [16]. The expression level of one of the multiple ANRIL spliced transcripts might be changed by the SNPs, which possibly affect cellular proliferation pathways [17]. Moreover, very recent studies have found that ANRIL may regulate expression of protein-coding genes at the p15/CDKN2B-p16/CDKN2A-p14/ARF locus via a polycomb-mediated epigenetic silencing. Yap et al [18] have illustrated that ANRIL involves directly in epigenetic transcriptional repression of the locus as well as the Chromobox 7 (CBX7) within the polycomb repressive complex 1 (PRC1) is anchored to ANRIL [19]. Given this molecular mechanism, it may provide a novel avenue to the diagnosis, treatment, or even prognosis for NPC patients.

LncRNAs in laryngeal squamous cell carcinoma

Laryngeal squamous cell carcinoma (LSCC) is one of the most aggressive head and neck can-

cer which remains a poor prognosis despite some advance made in oncology and surgery recently. Therefore, in order to better understand the molecular mechanism of LSCC carcinogenesis, it is essential to find the accurate biomarkers for predication and development of effective therapy strategies. HOTAIR is a long intergenic noncoding RNA, which is transcribed by HOX locus, can drive PRC2 and other nuclear chromatin regulation factors to HOXD locus and many other potential gene locus. Rinn et al [20] analyzed the transcriptional expression pattern of these gene locus and found that lncRNAs which play a role on the chromosomal regions with different epigenetic modification levels. The result hints that the mechanism of these lncRNAs could be epigenetic levels but remain to be confirmed with further study. It is researched that the RNA transcribed by certain chromosome can affect the transcription of another chromosome gene. This revealed a new mechanism that lncRNAs can remotely control the silence of chromosome area, which may have significance for disease and development [21]. Li et al [22] performed quantitative real-time RT-PCR (qPCR) to examine the expression levels of HOTAIR in LSCC tissues. Inspired observed that HOTAIR was higher expressed in primary LSCC than in adjacent noncancerous tissues. It is noteworthy that over-expression of HOTAIR was related to poor differentiation, lymph node metastasis, or advanced clinical stages of LSCC. The results suggested that HOTAIR promotes the malignant progression of LSCC. And also the up-regulation of HOTAIR had statistically remarkable relationship with decreased 5-year overall survival in LSCC. It is consequently believed that HOTAIR expression level is an independent prognostic factor of overall survival rate. Besides, in vitro data showed that notably impaired invasion ability and significant increase of apoptosis of Hep-2 cells induced by siRNA-mediated knockdown of HOTAIR. These data indicated that HOTAIR suppresses PTEN expression viaepigenetic modification, thus promoting tumorigenesis and progression of LSCC.

FENG et al [23] performed real-time polymerase chain reaction to examine the expression level of MALAT1 in 72 laryngeal squamous cell cancers and the corresponding adjacent non-neoplastic tissues. The result suggested that the MALAT1 was up-regulated in primary LSCC compared with adjacent non-cancerous tissues. Further study illustrated that MALAT1 mediated the regulation of cell proliferation, growth and apoptosis, and played a vital role in metastasis and progress. Therefore, the identification of the potential oncogenic molecular mechanism will be help for provides a new avenue to effect therapy strategy.

LncRNAs in esophageal squamous cell carcinoma

Esophageal squamous cell cancer (ESCC) ranks as the ninth most prevalent malignancy and the sixth most common cause of cancer deaths worldwide. Its incidence rate has great relationship with vary greatly by geographical factors [24]. Because of the not identification of biomarkers for high-risk population screening, clinical diagnosis and prognosis, it is imperative to seek more effective biomarkers for the early diagnosis of ESCC. Lv et al [25] performed ISH and qRT-PCR to detect the HOTAIR expression levels in ESCC tissues and non-cancerous tissues. The result showed that the expression levels of HOTAIR were upregulated in samples from patients with higher tumor burdens, which were defined as those with larger tumors, advanced clinical staging, increased lymph node tumor burdens and the presence of distant metastases. The study indicates that the over-expression of HOTAIR is associated with the progression of ESCC. Similarly, the study illustrated that the silencing of HOTAIR suppressed the proliferation, migration and invasion of ESCC TE-1 cells. Thus, these in vitro experiments suggest that HOTAIR may regulate the progression of ESCC cells. Although the mechanisms remain to be unknown, HOTAIR can be served as a biomarker for prediction of diagnosis, therapy and prognosis in ESCC.

Chen et al [26] performed real-time reverse transcription-polymerase chain reaction (RT-PCR) to analyze the expression levels of HOTAIR in 78 paired primary cancerous and adjacent noncancerous tissues from ESCC patients. The results showed that, compared with non-cancerous tissues, the HOTAIR expression was upregulated in ESCC tissues. Similarly, further data indicated that up-regulated HOTAIR may decrease the ability of metastasis and invasion of cancer cells as well as increase the cell apoptosis. Multivariate analysis of overall survival rates revealed that relative HOTAIR expression level, TNM stage, and lymph node metastasis could be expected to be valuable prognostic indicators. The study indicated that dysregu-

lation of HOTAIR promotes esophageal squamous cell carcinoma metastasis and poor prognosis, and HOTAIR is a novel lncRNA molecule participating in the progression and prognosis of ESCC, with potential clinical applications. Therefore, HOTAIR might play a vital role in the metastasis and invasion of ESCC.

Ge et al [27] found that there was a great overexpression of HOTAIR in ESCC compared with the adjacent normal esophageal tissues by qPCR. Similarly, patients with high HOTAIR expression suffered a significantly poorer prognosis than those with low expression. Therefore, HOTAIR could be an independent prognosis factor for ESCC. Moreover, HOTAIR was further validated to promote migration and invasion of ESCC cells in vitro. In addition, WIF-1 was demonstrated to have an inverse correlation with HOTAIR in ESCC cells and tissues. WIF-1 was selected and further tested by immune histochemistry with a significant function in Wnt/β-catenin signaling pathway. Mechanistically, HOTAIR directly decreased WIF-1 expression via promoting its histone H3K27 methylation in promoter region and then activated the Wnt/β-catenin signaling pathway. This novel identified HOTAIR/WIF-1 axis clarified the molecular mechanism of ESCC cell metastasis and provided a novel therapeutic target in patients with ESCC.

The SOX2 gene, a master regulator of pluripotency, is embedded within the third intron of an lncRNA known as SOX2 overlapping transcript (SOX2OT). SOX2OT has been suspected to involve in regulation of SOX2 expression and/or other related processes; nevertheless, its potential involvement in tumor initiation and/or progression is unclear. Shahryari et al [28] have estimated a possible relation between expression patterns of SOX2OT and those of master regulators of pluripotency, SOX2 and OCT4, in ESCC and other cancer tissue samples. The results revealed a significant co-upregulation of SOX2OT along with SOX2 and OCT4 in tumor samples, compared to the non-tumor tissues obtained from the margin of same tumors. Therefore, the SOX2 gene might be a indicator for the early diagnosis of ESCC.

LncRNAs in papillary thyroid carcinoma

Papillary thyroid carcinoma (PTC) generally accounts for 85% of all thyroid carcinomas, with increasing incidence. PTCSC3 (papillary thyroid carcinoma susceptibility candidate 3), a unique, long, intergenic noncoding RNA gene (lincRNA), which is strictly specific expressed in thyroid. By quantitative PCR, Jendrzejewski et al [29] analyzed the expression of PTCSC3 in thyroid tumor tissues of 46 PTC patients and found that which is significantly down-regulated of PTCSC3 in papillary thyroid carcinoma tissues compared to non-cancerous tissues. The study showed that the expression of PTCSC3 in six thyroid cancer cell lines is lower and no expression was detected in any of them. The suppression of PTCSC3 in thyroid tumor tissue of PTC patients and the lack of its expression in PTC cell line cells that show features of poorly differentiated thyroid cancer [30] suggest that PTCSC3 expression is lost when the normal thyroid tissue de-differentiates into cancer. PTCSC3 affects cells growth and the expression of genes participated in DNA replication, recombination and repair. The risk allele rs944289 destroyed the binding site in silico. Both C/EBPα and C/EBPβ activated the PTCSC3 promoter in reporter assays and the risk allele rs944289 reduced the activation compared with the non-risk allele. The result showed that both C/EBPα and C/EBPβ could activate PTCSC3 promoter activity and that the risk allele significantly reduces the activity generated by p42 C/EBPα and C/EBPβ. Further study proposes that rs944289 predisposes to PTC by dysregulating the expression of PTCSC3, which acts as a tumor-suppressor.

LncRNAs in oral squamous cell carcinoma

To date, oral squamous cell carcinoma (OSCC) is a fatal disease of high incidence yet. Consequently, the exploring of the carcinogenesis and tumorigenesis of OSCC is an emergency for developing an effect method of diagnostics and therapy of OSCC. Previous study revealed that altered expression of lncRNAs documented in various human cancers has aroused an increasing desire to study their use as biomarkers for diagnosis and prognosis as well as potential therapeutic targets [31]. Tang et al [32] performed qPCR to evaluate the expression levels of 20 matched samples of OSCC and nonmalignant tissues. Subsequently, they confirmed that the expression levels of HOTAIR, NEAT-1 and UCA1 in metastasized samples was prominent higher than the non-metastatic samples. However, the lower expression of MEG-3 was distinct in cancer compared

with non-cancer tissues. In addition, MALAT1 was suggested as an insignificant gene on the expression levels between primary tumors and matched adjacent nonmalignant tissues. All of these results revealed that the expression levels of these lncRNAs are closely related to the tumor development and progression. Inspired of the observation of no association between the expression of these lncRNAs with patients' gender and age in this study, which suggests that lncRNA is a potential independent risk factor and diagnostic biomarker of OSCC. Most of these 6 lncRNAs have been identified as cancer- or metastasis-associated genes, which is in accordance with the past research and indicates that the study results are dependable and significant. Given the function of several lncRNAs on regulating transcriptional alteration, implying that the difference of lncRNAs profiling between normal and cancer cells or tissues, we believe that lncRNAs are closely linked to the cancer progression as well as the secondary effect of cancer transformation. Thus, differential expression of lncRNAs might bring much broader prospects for OSCC diagnosis, prognosis and select potential therapeutics.

lncRNAs in tongue squamous cell carcinomas

Despite the early tongue squamous cell carcinoma (TSCC) can be cured, its high risk of developing secondary or recurrent tumors in the surrounding area remains a difficult problem. Particularly, lymph node metastasis is a dominating factor to induce the TSCC patients' high mortality rate and 5-year overall survival rate under 50%, which is among the lowest for all major cancers [33]. Identification of new biomarkers is of great clinical value for the diagnosis and treatment of TSCC, which can improve the survival of patients with TSCC. Fang et al [34] performed real-time PCR to evaluate the expression of urothelial cancer-associated 1 (UCA1) in 94 samples with TSCC and matched adjacent normal mucosal tissues (ANTs). Meaningfully, the expression levels of UCA1 lncRNA were dramatically higher in TSCC tissues than those in paired ANTs. The difference is more significant when all the 94 paired samples were included. In addition, Fang et al [34] also demonstrated that there is no difference between the expression of nuclear paraspeckle assembly transcript 1 (NEAT1), HOTAIR, and highly upregulated in liver cancer long non-coding RNA (HULC) in TSCC tissues and in ANTs. Despite the up-regulation of MALAT1 and the down-regulation of maternally expressed 3 (MEG3) of TSCC compared with the non-cancer tissues, the differences were proved to be not significant. Further study implied suggested that UCA1 was up-regulated in lymph node metastases than in primary tumors. Moreover, in vitro studies confirmed that the increased expression of UCA1 tumor cells showed more strong migration ability but made a little impact on the cell proliferation. Therefore, we can draw a conclusion that enhanced expression of UCA1 lncRNA might promote cancer metastasis in TSCC. Consequently, the findings indicated that the expression level of UCA1 has the potential to be a prognostic indicator in lymph node metastasis of TSCC. Additional study implied MicroRNA miR-26a and lncRNA MEG3 gene likely play important anti-tumor effects in TSCC pathogenesis. Furthermore, they represent potential prognostic biomarkers for stratification of TSCC patients [35].

Conclusions

Differential expression of lncRNAs is increasingly recognized as a hallmark feature in cancer. However, the molecular mechanism of the vast majority of the unique genes remains unknown. In this review, we highlight lncRNAs as a regulator in head and neck cancer-associated processes, including metastasis and invasion. Aberrant lncRNA expression involved in carcinogenesis by disrupting major biological processes, such as cell proliferation, growth and apoptosis or even inactivating major tumor suppressor genes. Finally, although the roles of lncRNAs in head and neck cancer have just begun to be revealed, the potential property of lncRNAs in head and neck cancer as diagnostic and prognostic markers will bring a board prospect for the therapy of patients of head and neck cancer [31].

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Disclosure of conflict of interest

None.

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