Introduction

Esophageal cancer is the eighth most common malignant tumors worldwide and the sixth most common cause of death from cancer with geographic differences in incidence rate (1). Histologically, esophageal cancer mainly consists of squamous cell carcinoma and adenocarcinoma. In high-incidence areas, such as in China, more than 90% of the esophageal cancers are esophageal squamous cell carcinoma (ESCC) (2). Despite the advancement in treating ESCC, the overall survival still remains poor, with a five-year survival rate of 15–34% (1,3,4). To date, the factors that influence the development and prognosis of ESCC are still not clearly known (5). Therefore, identification of the biomarkers which could predict the prognosis of ESCC remains meaningful and urgently necessary, which can be not only helpful with clinical monitoring but also suggestive of therapeutic decision-making (6).

Recently, long noncoding RNAs (lncRNAs), which are commonly defined as non-protein-coding RNA molecule longer than 200 nucleotides, have been intensively researched all around the world. lncRNAs are a new group of noncoding RNAs locating within nuclear or cytosolic fractions (7), which were found to be important regulators of tissue physiology and diseases processes, especially in cancer (8). More and more studies have found that lncRNAs were significantly correlated with the prognosis and diagnosis of patients with ESCC. Therefore, all those accumulating evidence indicated that lncRNAs could serve as a prognostic biomarker of ESCC. In this, we summarized the relation between lncRNAs and ESCC as well as the potential biomarker role of lncRNAs in ESCC, especially the prognostic value of lncRNAs. Our current review highlighted the need of further studies to explore the biomarker functions as well as therapeutic values of lncRNAs in ESCC.

Keywords: Long noncoding RNAs (lncRNAs); esophageal squamous cell carcinoma (ESCC); prognosis; review

Abstract: Esophageal squamous cell carcinoma (ESCC) still has a poor prognosis. The prognostic biomarkers of ESCC are not yet well established. Long noncoding RNAs (lncRNAs) have recently been intensively investigated in various cancers including ESCC, and are found to be closely correlated to ESCC. Dysregulated expression of lncRNAs was widely observed in ESCC tumor tissue and was closely related to the tumorigenesis and progression of ESCC. More and more studies have found that lncRNAs were significantly correlated with the prognosis and diagnosis of patients with ESCC. Therefore, all those accumulating evidence indicated that lncRNAs could serve as a prognostic biomarker of ESCC. In this, we summarized the relation between lncRNAs and ESCC as well as the potential biomarker role of lncRNAs in ESCC, especially the prognostic value of lncRNAs. Our current review highlighted the need of further studies to explore the biomarker functions as well as therapeutic values of lncRNAs in ESCC.

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LncRNAs and cancer: an emerging noncoding RNA closely related to cancer

Cancer has been known to have the ability to sustain proliferate signaling and evade growth suppressors, and consequently resist cell death (15). It is well known that tumorigenesis is related with various deregulations of different biomolecules and signal pathways. However, the detailed mechanism of initiation and progression of cancer still needs to be uncovered and clearly understood. Recently, aberrant expression of the lncRNAs was found to be closely related to human diseases, especially cancer. Therefore, more and more studies have focused on lncRNAs, which were found to lead to cancer development and progression through multiple mechanisms (16). Recent evidence has begun to accumulate describing the mechanisms of the lncRNAs related to cancer, and these mechanisms mainly involved in epigenetics, transcription regulation, and post-transcription processing (9,12,16,17). Generally, some lncRNAs (oncogenic lncRNAs) play an oncogenic role in cancer, while others (tumor suppressor lncRNAs) have oncosuppressive functions (9,15). With the development of various techniques including expression microarrays, tiling arrays, next generation sequencing, and methylation analysis (18), recent studies have found that dysregulation of lncRNAs could promote ESCC cell proliferation and metastasis, indicating that abnormal expression of lncRNAs is significantly related to the poor prognosis of patients with ESCC (6,23-26). Therefore, lncRNAs may be a group of prognostic markers for ESCC. Herein, our current review specifically focused on the relationship of lncRNAs and ESCC.

LncRNAs and ESCC: the roles of lncRNAs in ESCC and their prognostic value

Even though there are a lot of researches demonstrating the mechanisms of the development and progression of ESCC (27), there are still much more to uncover and understand, and the prognosis of ESCC remains dismal. Therefore, it urgently requires the identification of biomarkers which may explain the mechanisms of tumorigenesis and predict the prognosis for clinical monitoring as well as therapeutic strategies of ESCC. With the development of biomolecular and genetic techniques, many researches have been carried out to explore the relationship and potential mechanisms between various lncRNAs and ESCC, as well as the prognostic value of lncRNAs in ESCC (5,6,23-26,28-33). These major lncRNAs with aberrant expression in ESCC were summarized in Table 1.

HOTAIR, as a predominantly focused oncogenic lncRNA (36), was initially found to be involved with primary breast tumor and its metastasis (23,37). It is widely known that overexpression of HOTAIR induced genome-wide re-targeting of polycomb repressive complex 2 (PRC2), which led to an altered methylation of histone H3 lysine 27 (H3K27) and gene expression (especially metastasis-suppressing genes), and thus the aberrant expression of HOTAIR promoted tumor invasiveness and metastasis (23,24,28,37). Recently, accumulating evidence showed that HOTAIR was related closely to the development and progression of ESCC (38). Studies have found that HOTAIR was notably highly expressed in ESCC tumor tissues and the overexpression of HOTAIR was significantly related to poor prognosis of the patients (23,24,28,29). Studies have showed that elevated HOTAIR expression was correlated with increased occurrence of lymph node metastasis and shorter overall survival (23,24,28,29). HOTAIR was believed to act its role in promoting the invasiveness and progression of ESCC in a manner dependent on PRC2 (38), and lncRNAs may become potential biomarkers in various types of cancer including ESCC (22). Accumulating evidence showed that dysregulation of lncRNAs could promote ESCC cell proliferation and metastasis, indicating that abnormal expression of lncRNAs is significantly related to the poor prognosis of patients with ESCC (6,23-26). Therefore, lncRNAs may be a group of prognostic markers for ESCC.
which was also showed to inhibit WIF-1 expression and activate Wnt pathway (24). In vitro, knockdown or suppression of the HOTAIR reduced the invasiveness and metastasis of ESCC cells (23,28). The detailed mechanisms, however, still need further investigations to elucidate. Based on above evidence, it is believed that HOTAIR remained to be an independent prognostic factor of ESCC as well as potential biomarker for the existence of lymph node metastasis in ESCC. A recent meta-analysis also found that elevated level of HOTAIR was a powerful prognostic biomarker for patients with ESCC and may serve as a potential therapeutic target for ESCC (39), which may lead the direction of the researches on novel therapeutic strategy for ESCC.

MALAT1, as one of the most studied oncogenic lncRNAs, was originally showed to be overexpressed in non-small cell lung cancer patients with lymph node metastasis (40). However, apart from lung cancer, MALAT1 was found to be closely related to various cancers (bladder cancer, gallbladder carcinoma, prostate cancer), and significantly correlated with relapse and progression of these cancers (15). Recent evidence showed that MALAT1 promoted tumor growth by regulating cell cycle and epithelial-to-mesenchymal transition as well as angiogenesis (10), which may lead to uncontrollable tumor growth. MALAT1 was also found to be overexpressed in ESCC cells (30,41), and its aberrant expression was positively correlated with clinical stage and lymph node metastasis (41), as well as poor prognosis (30) of ESCC patients. Hu et al. (41) have showed that up-regulation of MALAT1 may promote ESCC growth by dephosphorylation of the ATM-CHK2 pathway, which may lead to the loss of cell cycle arrest and ultimately proliferation and metastasis of ESCC cells. Recent studies have showed that knockdown or silencing of MALAT1 can lead to G2/M phase arrest and an increased apoptosis ratio (41,42), and thus inhibit proliferation, migration, and invasion of ESCC cells (43). Moreover, Wang et al. (44) found that knockdown of MALAT1 decreased tumor formation and improved survival in animal experiments, suggesting that inhibition of MALAT1 may be a potential target for treating ESCC. However, how the amplification of MALAT1 in ESCC cells occurs still remains unclear. Therefore, further studies are warranted to explore the prognostic biomarker role of MALAT1 in ESCC as well as its potentiality of therapeutic target for treating ESCC.

Colon cancer-associated transcript 2 (CCAT2) is a novel lncRNA, which was found to be related with colon cancer (45), breast cancer (46), lung cancer (47), gastric cancer (48), as well as ESCC (5). In ESCC, the level of CCAT2 expression was positively related with TNM stage and lymph node metastasis, and high expression of CCAT2 correlated with poor survival of ESCC patients (5). Similarly, Wang et al. found that CCAT2 was significantly overexpressed in ESCC tumor tissue and that CCAT2 might have the potential as a diagnostic biomarker (49). Based on above evidence, CCAT2 could also serve as a

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<th>Function</th>
<th>Potential values</th>
<th>Expression</th>
<th>IncRNAs</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Oncogenic</td>
<td>Prognostic factor</td>
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<td>Cao et al. [2015] (30)</td>
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<td>CCAT2</td>
<td>Zhang et al. [2015] (5)</td>
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<td>SPRY4-IT1</td>
<td>Xie et al. [2014] (26)</td>
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<td>Shi et al. [2015] (32)</td>
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<td>NEAT1</td>
<td>Chen et al. [2015] (6)</td>
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<td>Tong et al. [2015] (34)</td>
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<td>AFAP1-AS1</td>
<td>Zhou et al. [2016] (35)</td>
</tr>
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<td>Oncosuppressive</td>
<td>Prognostic factor/chemoradiotherapy resistance</td>
<td>Down-regulated</td>
<td>LOC258194</td>
<td>Tong et al. [2014] (33)</td>
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prognostic as well as diagnostic biomarker and a therapeutic target of ESCC, and it is worthy of further study.

With more and more researches exploring the relationship between lncRNAs and ESCC accomplished, many other lncRNAs were continuously found out to be significantly related to ESCC. Other overexpressed lncRNAs included lncRNA SPRY4 intronic transcript 1 (SPRY4-IT1) (26,50), urothelial carcinoma associated 1 (UCA1) (25), lncRNA ZEB1 anti-sense1 (ZEB1-AS1) (31), prostate cancer-associated ncRNA transcript 1 (PCAT-1) (32), nuclear paraspeckle assembly transcript 1 (NEAT1) (6), and lncRNA AFAP1-AS1 (35). The upregulation of above lncRNAs was significantly related to poor prognosis of patients with ESCC, and those lncRNAs could be potential therapeutic target of ESCC (summarized in Table 1).

LncRNAs have not only oncogenic functions but also oncosuppressive roles. LncRNA LOC258194, also called LSAMP antisense RNA 3, was showed to be within a tumor suppressor unit in osteosarcoma and to suppress tumor cell growth (51), and was found to be a p53-regulated oncosuppressive lncRNA (52). Recently, Tong et al. (33) found that the expression of lncRNA LOC285194 was significantly down-regulated in ESCC tumor tissue as compared with normal esophageal tissue, and low expression of lncRNA LOC285194 was significantly related to advanced TNM stage and metastasis of ESCC as well as poor prognosis of patients with ESCC. Moreover, low expression of lncRNA LOC285194 was also associated with chemoradiotherapy resistance. Therefore, decreased expression of lncRNA LOC285194 may serve as a biomarker of prognosis as well as selection criteria for patients who could benefit from chemoradiotherapy (33). Recently, Wang et al. (53) have introduced another oncosuppressive lncRNA in ESCC, LncRNA-Low Expression in Tumor (lncRNA-LET). They found that the expression level of lncRNA-LET was decreased in ESCC tissue and overexpression of lncRNA-LET could inhibit the migration and invasion of ESCC cells in vitro, suggesting that lncRNA-LET may serve as a tumor suppressor in ESCC (53). However, to date, oncosuppressive lncRNAs were hardly explored and figured out in ESCC. Further studies are needed to figure out the oncosuppressive functions of lncRNAs in ESCC, which may help with better understanding of development and progression of ESCC.

Future prospective

As accumulating evidence has showed that lncRNAs played an important role in the tumorigenesis and progression of ESCC and that lncRNAs may serve as a prognostic biomarker as well as a therapeutic target for ESCC, more researches are warranted to unveil the detailed relationship between lncRNAs and ESCC. However, as a novel field for further studies, there are some future prospective needed to be addressed. First, although more and more lncRNAs were figured out to be related to ESCC, the underlying mechanisms of how those lncRNAs correlated to ESCC are still unknown, and therefore, the therapeutic value of lncRNAs is still theoretical. As a result, the bench research testified therapeutic benefits of lncRNAs in ESCC are still at its very beginning, and how to transfer bench research benefits into clinical benefits is another important aspect for future researches. Second, most of the lncRNAs mentioned above were evaluated in ESCC tumor tissue, and those lncRNAs showed the prognostic value for patients with ESCC. However, similar to miRNAs, lncRNAs could also serve as a diagnostic biomarker for ESCC (22). So far, only Wang et al. (49) and Tong et al. (34) have explored the diagnostic value of lncRNAs in ESCC. Tong et al. (34) found that lncRNA POU3F3 in plasma could serve as a potential noninvasive biomarker for diagnosis of ESCC, which may help with early tumor screening. Therefore, the noninvasive diagnostic value of lncRNAs in ESCC is still needed for further researches to elucidate. Third, as there are more and more new lncRNAs being found out to significantly correlate with ESCC, how to improve the prognostic and diagnostic power of lncRNAs for ESCC still remains to be solved. In order to robustly predict the survival of patients with ESCC, Li et al. (54) have firstly found out that a three-lncRNA signature (including the lncRNAs ENST00000433856.1, XLOC_012014 and ENST0000047963.1) could serve as a new biomarker for the prognosis of patients with ESCC. Similar to miRNAs, a three-lncRNA signature enabled more accurate prediction of survival for those patients. Similarly, Pan et al. (55) used “lncRNA-mRNA gene pair” (lncRNA FOXCUT and mRNA FOXC1 pair) to predict the prognosis of patients with ESCC, and they found that this novel lncRNA-mRNA pair could represent a potential prognostic biomarker and therapeutic target for ESCC patients. Therefore, a combination of lncRNAs or lncRNAs and other genes could be used as a more accurate prognostic biomarker for patients with ESCC. Future studies are needed, however, to explore the prognostic and diagnostic value of such combination in ESCC before their biomarker functions can be applied in clinical practice. Finally, most of those
researches concerned predominantly the roles of lncRNAs in ESCC, while only a small number of studies focused on esophageal adenocarcinoma (56) which is the main pathologic type of esophageal cancer in western countries. As lncRNAs have showed more and more promising results in ESCC, more efforts are needed to explore the role of lncRNAs in esophageal adenocarcinoma.

Conclusions

Patients with ESCC still have a poor prognosis, and identification of prognostic and diagnostic biomarkers for ESCC is still badly needed. With the development of genome and transcriptome sequencing technologies, more and more dysregulated oncogenic and oncosuppressive lncRNAs were found out to be closely related to various cancers. There are also a myriad of published studies about aberrant expression of lncRNAs in ESCC. Even though current knowledge has revealed the possible mechanisms between lncRNAs and cancers (including epigenetics, transcription regulation, and posttranscription processing), the detailed mechanisms of lncRNAs in the tumorigenesis and progression of ESCC are still unclear. In our current review, we summarized the prognostic value of lncRNAs in ESCC, and pointed out that lncRNAs may serve as novel prognostic and diagnostic biomarkers as well as therapeutic targets for ESCC. Our study highlighted the promising biomarker functions of lncRNAs in ESCC and pointed out some perspectives needed to be addressed for future researches. Even though there is still a long way from bench research-testified benefits to clinical benefits, with more and more researches digging into the aberrant expression of lncRNAs in ESCC, we believe that lncRNAs will exert more important roles in the treatment of ESCC in the near future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References