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Multifaceted Roles of Long Non-coding RNAs in Head and Neck Cancer

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Abstract

The majority of RNA transcripts are non-coding RNA (ncRNA) transcripts with lengths exceeding 200 nucleotides that are not translated into protein. Unlike microRNAs (miRNAs), long ncRNAs (lncRNAs) are not confined to a single mechanism of action but have a large and diverse role in biological processes as they can function as transcription regulators, decoys, scaffolds, and enhancer RNAs. Currently, many lncRNA molecules are under investigation for their role in tumorigenesis, metastasis, and prognosis in different types of cancer. This review not only summarizes the characteristics and functions of lncRNAs but also discusses the therapeutic implications and applications of lncRNAs with roles associated with head and neck cancer. Our aim is to pinpoint the potential way to perturb specific lncRNAs for future therapeutic use.

Keywords

lncRNA; Roles and functions; Head and neck cancer

7.1 Introduction

The human body is a large and complex system that needs a precise set of directions to function properly. The genetic code that manages the body comes from DNA, and the process to make and replicate DNA is intense and complicated, and made up of many molecular stages. A key molecule used in this process is RNA, of which there are many different types. The three main types of RNA are messenger (mRNA), transfer (tRNA), and ribosomal RNA (rRNA). In a process known as transcription, DNA is transcribed into

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mRNA. The mRNA is then translated using tRNAs to make amino acid sequences known as peptide chains. Some genes, however, do not code for proteins. These genes result in a transcript known as a non-coding RNA (ncRNA). The ncRNAs are broken into two classes known as small ncRNAs (sncRNAs) and long ncRNAs (lncRNAs). Further subdivision of sncRNAs results in more classes of ncRNAs with one of the main types being the microRNAs (miRNAs). If the RNA is made up of 20–25 nucleotides, it is considered as miRNA. If the RNA is made up of 200 nucleotides or more, it is considered as a lncRNA [1-5]. In research, miRNAs are currently under intensive study as they are important regulators of the stability and expression of intracellular mRNAs. With many researchers examining miRNAs for possible therapeutic treatments for cancer, this has sparked research on lncRNAs. The function of lncRNAs is not fully understood, but these molecules are known to play a major role in inhibition and activation of many genes. Because previous research has exemplified the importance of ncRNAs, the lncRNA class is currently being studied in connection with human diseases, especially cancer.

7.2 Structure and Characteristics of lncRNAs

Generally, lncRNA is made up of 200 nucleotides or more and does not encode proteins. More than 98% of the genes transcribed are non-coding [1, 6-11]. While the exact function is unknown, evidence has shown the importance of lncRNA in splicing, imprinting, transcription, translation, cell cycle regulation, and apoptosis. These lncRNA are also suggested to play a part in cancer and other human diseases [12-14]. Structurally, an lncRNA molecule consists of a 3' polyadenylated tail and a 5' cap [1, 7]. Due to the abundance of lncRNA transcripts, a classification system has been created. Based on the location and context of the genome, the effect on DNA sequences, the mechanism of functioning, and the target mechanism, lncRNAs can be categorized [1-4, 15]. There are two classifications for the location of the gene called intergenic and intronic. Intergenic refers to an lncRNA that is between two coding regions. Intronic refers to an lncRNA that is transcribed from introns only. Similar to the location, the context also subdivides lncRNA into two categories known as sense and antisense. Sense lncRNAs are transcribed from the sense strand of protein encoding genes and contain exons. These may overlap with part or all of the protein encoding genes. Conversely, antisense lncRNA is transcribed from the antisense strand of protein encoding genes. It has been discovered that lncRNAs are involved in transcriptional regulation, and therefore they are also classified based on how they interact with DNA, known as *cis*- and *trans*-lncRNAs. The *cis*-lncRNAs help regulate expression of genes that are close by. The *trans*-lncRNAs help regulate expression of genes that are further away. The mechanism of functioning for the lncRNA transcripts falls into three groups including transcriptional regulation, post-transcriptional regulation, and other forms of regulation [1, 16]. Both transcriptional and post-transcriptional regulation can be further subdivided based on how the regulation is occurring. The third classification for the mechanism of functioning is made up of unknowns. There are no subgroups, because there is not enough available information to classify these lncRNAs other than via the mechanisms of functioning. The last group of classification is target mechanisms, and there are four types known as signal, decoy, guide, and scaffold. Signal targeting mechanisms refer to specific expression based on cell type. Decoy mechanisms bind and move different protein

targets as their only function. Proteins that are bound and directed to specific target regions are under control of guided target mechanisms. Lastly, proteins that are gathered are done so through scaffold target mechanisms which serve as a central platform. Further details regarding these classifications discussed above are given in Table 7.1. It is important to note that these classifications exist only through current knowledge of the subject and are expected to change as more information is gathered [17].

7.3 lncRNAs Associated with Tumorigenesis and Development of Head and Neck Cancer (HNC)

With 98.5% of the human genome consisting of ncRNA, of which tens of thousands are of the lncRNA subtype, there are a multitude of studies being conducted on their potential roles. The new found discovery of lncRNA in the initiation and progression [18-22] of HNC has led to the idea of using them as a new treatment that may provide a better prognosis for patients. Due to the abundance of lncRNAs, there are numerous lncRNAs that are known to function in head and neck tumorigenesis, with more being discovered. There are many types of cancers that fall into the HNC category [23, 24]. The most prevalent subset of these is head and neck squamous cell carcinoma (HNSCC). This includes cancers found in the lining of the upper digestive tract including the throat, nose, and mouth regions. These cancers have been found to have a correlation with multiple lncRNAs including HOX transcript antisense RNA (HOTAIR), H19 imprinted maternally expressed transcript (H19), and HNSCC glycolysis-associated 1 (HNGA1) [25, 26]. HOTAIR was seen to be expressed at very high levels in HNSCC when compared to normal tissues [27-29]. It was discovered that a reduction in the HOTAIR levels leads to cell death and slow tumor development. H19 is also seen to be expressed highly in HNSCC and leads to a higher invasive capacity as well as a higher rate of tumor recurrence. HNGA1 is involved in the process of glycolysis and increases cancer cell proliferation. Regulation of these three lncRNAs may offer a treatment for HNSCC via knockdown of the genes. It has been shown that knockdown of all three of these lncRNAs resulted in poor proliferation, migration, and invasion of HNSCC cells [18, 30-32]. Thyroid cancer has associated lncRNAs as well, partially overlapping with those of HNSCC. For example, HOTAIR has also been seen to function in thyroid cancer along with BRAF-activated ncRNA (BANCR) and non-protein coding RNA, associated with MAP kinase pathway and growth arrest (NAMA). BANCR has been shown to be upregulated in thyroid cancer cells in comparison with healthy tissue, and apoptosis was found to be induced by the reduction of BANCR expression, although there was no effect of this on cell migration [18]. Other evidence shows conflicting data suggesting unknown factors may be involved in the regulation of BANCR expression in thyroid cancer. NAMA, closely related to BANCR, has been found to be downregulated in thyroid cancer. In addition, NAMA expression was found to be stimulated by reduced BRAF expression, inactivation of the MAP pathway, or DNA damage. These changes lead to activation of the proto-oncogene serine/threonine-protein kinase/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling pathway known to regulate cell growth and differentiation [18]. Therefore, the activation of this pathway is a potential target for future treatment of thyroid cancer, and further research in this area should help to confirm this.

7.4 lncRNAs Associated with Invasion and Metastasis of HNC

Metastasis is partially responsible for the relapse and poor prognosis [1] of HNC. Recently the discovery of the role of lncRNAs in mediating metastasis has led to possible future advances for treatment of HNC. Multiple lncRNAs have been studied specifically for their effects on metastasis in HNC including metastasis associated lung adenocarcinoma transcript 1 (MALAT1), HOTAIR, and NF- κ B interacting lncRNA (NKILA) [33-36]. It has also been suggested that the lncRNAs could function by working in tandem with their corresponding mRNAs [1]. To understand how lncRNAs aid in the process of metastasis, the mechanisms underlying metastasis must first be understood. Epithelial mesenchymal transitions (EMT) are important for cancer cells to metastasize [37-43]. In this process, epithelial cells transition to resemble the mesenchymal phenotype. This allows the cancer cells to migrate, proliferate, and differentiate into specific tissues and organs since mesenchymal cells do not have a specialized function [41-48]. By traveling through the lymph nodes and bloodstream, these cells choose the best environment for proliferation based on the ability to obtain the best nutrition. MALAT1 has been studied for its role in metastasis based on its ability to aid HNC cells to undergo EMT and invade other tissues [1, 49]. It was seen that when MALAT1 was inhibited, the EMT of HNC cells was altered. One possibility for this change is thought to be the inactivation of P-catenin and NF- κ B pathways. These pathways are regulators of EMT, so as they are inhibited, a chain reaction effect is seen in the modification of EMT [1, 33, 36, 49]. In this case, it was also seen that two EMT markers, N-cadherin and vimentin, in MALAT1 were knocked down in HNC cells [1, 33, 36, 49]. Several studies have provided evidence that the knockdown of MALAT1 in HNC could impair migration of the cancer. HOTAIR is another lncRNA that is being studied in its effects of cancer metastasis [1, 35, 50, 51]. Studies have shown several ways by which HOTAIR influences HNC metastasis. Recently it has been indicated that HOTAIR functions in EMT by decreasing E-cadherin levels. Other studies have shown that a knockdown in HOTAIR decreased the invasiveness of HNC significantly. Aside from other regulation responsibilities, HOTAIR has also been suggested to work in a regulatory loop progressing metastasis in correspondence with the RNA-binding protein Hu antigen R (HuR) [52]. HuR is an RNA binding protein that works to stabilize mRNA to better regulate gene expression. Unlike MALAT1 and HOTAIR, NKILA suppresses metastasis. In addition, NKILA is being studied for its negative regulation of HNC and its function as a poor prognosis indicator [1]. It has been seen that the levels of NKILA are lower in HNC than in unaffected cells and normal tissue. The knockdown of NKILA actually resulted in the increased metastasis of HNC, confirming the negative correlation. These three lncRNAs are not alone in their regulation of metastasis. They are aided by multiple other lncRNAs shown in Table 7.2.

7.5 lncRNAs Associated with Treatment Resistance in HNC

While new therapies are being discovered as possible targets for HNC patients, there is also the concern of maintaining oral function [53]. In order to protect the functionality of patients, numerous therapies have been used in combination including chemotherapy and radiotherapy. The drugs frequently used in both chemotherapy and radiotherapy are known as antineoplastic drugs, which act to inhibit or stop the development of tumors. Combination therapies can lead to what is known as multiple drug resistance (MDR) leading

to the resistance to non-structurally related drugs as well. Factors that have been linked to resistance include the ATP-binding cassette transporter (ABC) and cancer stem cells (CSCs). A gene known as *ABCB1*, or *MDR1*, produces P-glycoprotein (P-gp) which is known to be an ABC transporter associated with MDR. P-gp has been known to provide resistance in HNC. In one experiment, cell lines were treated with a drug known as doxorubicin. After treatment with this drug for 3 months, the cells were seen to be resistant. The overexpression of P-gp has been suggested to increase resistance more than 100 times greater than in normal cells [53-56]. While the process causing the expression of P-gp is unknown, recently it was demonstrated that P-gp is transferred between cells via micro-vesicles. However, this occurrence has yet to be seen specifically in HNC. Cancer stem cells aid tumors to maintain growth and recur in patients through renewing and preserving themselves. CSCs are recognized in HNSCC by the increased expression of the cell surface adhesion receptor, CD44. The ability of the cancer stem cells to alter their phenotype shows the relationship to EMT. It is seen that molecules important in the process of EMT are associated with poor prognosis. It has been theorized that the relationship between EMT and CSCs are a critical cause for the resistance to antineoplastic treatments.

7.6 Prognostic Role of lncRNAs in HNC

Some lncRNAs have been found to be associated with the prognosis of HNC. By analyzing a group of HNC patients and creating a model to identify specific lncRNAs, it has been suggested that five individual lncRNAs can be used to predict prognosis of HNSCC patients postoperatively [54]. This model also accounted for the co-expression of genes and lncRNAs, to serve as a final confirmation of prognosis. A risk score was calculated and this showed that as the mortality risk increased so did the risk score. Conversely, as the risk score increased the expression of the five lncRNAs being studied decreased. The lncRNAs identified to be an indicator of prognosis are RP11-180M15.7, RP11-197N18.2, AC021188.4, RP11-474D1.3, and RP11-347C18.5. Not only are these lncRNAs closely associated with HNSCC but they are also involved in many cellular pathways associated with cancer proliferation.

Other studies showed similar results with more lncRNAs having prognostic value. For example, poor survival was seen in patients with over-expression of RP11-366H4.1, HOTTIP, RP11-865I6.2, and RP11-275N1.1 [55]. These lncRNAs differ from those previously mentioned, in that their over-expression correlates with a poor prognosis. While miRNAs have been studied in the past, they have not been studied in combination with lncRNAs. A risk score was developed for the performance of lncRNA, miRNA, and mRNA. Patients with a high risk score were also seen to have a worse survival than those with a low risk score. Success in predicting lncRNA, miRNA, and mRNA interactions may reveal much needed new information on HNSCC [55].

7.7 Conclusions

HNC is characterized by a poor prognosis due to the late-stage diagnosis and the aggressive nature of this form of cancer [57]. Improvements have been made in medical techniques, although about 50% of HNC diagnoses are still advanced cases. The treatments including

surgical procedures, chemotherapy, and radiotherapy have all significantly improved as well. However, the 5-year survival rate of patients with advanced HNC does not reflect the most recent advances in detection and treatment. Increasing studies have demonstrated that lncRNAs play key roles in tumorigenesis and tumor progression, leading to abnormal signaling transduction, immune escape, and cellular metabolic rewiring. By better understanding lncRNAs and applying novel technologies (e.g., a new generation of gene-editing tools and effective tumor-seeking drug delivery systems) to target cancer-associated lncRNAs, there may be more hope for treatment of HNC patients. Currently, the research is still in its early stages and has large barriers to overcome, although great promise has been shown in using lncRNAs as both compelling indicators and targets for HNC.

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Abbreviations

BANCR	BRAF-activated non-coding ribonucleic acid
EMT	Epithelial-mesenchymal transitions
ERK	Extracellular signal-regulated kinase
H19	H19 imprinted maternally expressed transcript
HNC	Head and neck cancer
HNGA1	Head and neck squamous cell carcinoma glycolysis-associated 1
HNSCC	Head and neck squamous cell carcinoma
HOTAIR	HOX transcript antisense ribonucleic acid
HuR	Human antigen R
lncRNA	Long non-coding RNA
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
MAP	Mitogen-activated protein
MEK	Mitogen-activated protein kinase
miRNA	MicroRNA
mRNA	Messenger RNA
NAMA	Mitogen-activated protein kinase pathway and growth arrest
ncRNA	Non-coding RNA
NKILA	NF- κ B interacting lncRNA

Raf	Rapidly accelerated fibrosarcoma
rRNA	Ribosomal RNA
sncRNA	Small non-coding RNA
tRNA	Transfer RNA

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Table 7.1

Categorization and functions of lncRNAs

Category	Sub-category	Functions
Location and context of the genome	Intergenic lncRNA	Transcribed between coding regions
	Intronic lncRNA	Transcribed from introns
	Sense lncRNA Antisense lncRNA	Transcribed from sense strand Transcribed from antisense strand
The effect on DNA sequences	Cis lncRNA	Regulates genes close
	Trans lncRNA	Regulates genes far
The mechanism of functioning	Transcriptional lncRNA	
	Post-transcriptional lncRNA	
	Other lncRNA	
The target mechanism	Signal lncRNA Decoy lncRNA Guide lncRNA Scaffold lncRNA	Regulates transcription in response to stimuli Binds and moves targets Directs proteins to targets Serves as central platform

Table 7.2

Known lncRNAs involved in HNC metastasis

lncRNA	HNC subtypes
HOTAIR	NPC, OSCC, LSCC
H19	NPC, LSCC
MALAT1	NPC
ANRIL	NPC
ROR	NPC
AFAP1-AS1	NPC
LET	NPC
LINC0086	NPC
LOC401317	NPC
PTENP1	OSCC
UCA1	OSCC
FOXCUT	OSCC
FTH1P3	OSCC
TUG1	OSCC
NEAT1	LSCC
PVT1	LSCC
LOC157273	LSCC

HNC head and neck cancer, *NPC* nasopharyngeal carcinoma, *OSCC* oral squamous cell carcinoma, *LSCC* laryngeal squamous cell carcinoma