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Role of long noncoding RNAs in malignant disease (Review)

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Abstract. Long noncoding RNAs (lncRNAs) are endogenous transcribed RNA molecules without protein-coding potential, ranging between 200 and 100,000 nt in length. LncRNAs regulate the expression of specific genes in several ways, including guiding chromatin-remodeling, and affecting splicing, transcription or translation. The mutations and dysregulation of lncRNAs have been found to be important in various human diseases, but particularly in human cancer. Previous studies have demonstrated that changes to lncRNAs are closely associated with tumorigenesis, metastasis, prognosis and diagnosis. The current review aims to present a brief overview of the associated reports of lncRNAs in malignant neoplasms, including breast cancer, prostate cancer and hematological malignancies. LncRNAs may be evaluated as novel markers in disease diagnosis, and as prospective therapeutic targets for the prevention and treatment of human diseases.

Contents

1. Introduction

The regulation of protein-coding genes follows the central dogma: DNA→RNA→protein. Results of human genome projects indicate that >90% of the genome is transcribed into RNA, only 1.5-2.0% of the genome encodes protein-coding genes, and the remainder are noncoding RNAs (ncRNAs), which were once considered to be transcriptional noise (1).

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The ncRNAs are divided into two major groups based on their length: Small ncRNAs and long ncRNAs (lncRNAs) (2,3). Small ncRNAs (length, <200 nt), including microRNAs (miRs), are important in various cancer processes (4-6). LncRNAs are commonly defined as independent transcriptional units with no significant protein-coding capacity, and are between 200 and 100,000 nt in length. Previous mass-scale transcriptome sequencing has revealed that thousands of lncRNAs are transcribed in large quantities in human and other mammalian genomes (7).

2. Definition and classification of lncRNAs

LncRNAs are commonly defined as non-protein-coding RNA molecules of >200 nt. Despite poor conservation of their nucleotide sequences, compared with protein-coding genes, lncRNAs have tissue-specific expression patterns (8). LncRNAs are divided into several subtypes, according to their location with respect to protein-coding genes: i) Sense lncRNAs intersect one or more exons of another transcript on the same strand; ii) antisense lncRNAs have transcripts, which overlap with one or more exons of a protein-coding locus on the opposite strand, and show evidence of antisense regulation of a protein-coding gene (9); iii) intergenic lncRNAs, also designated lincRNAs, do not intersect with any protein-coding loci, and are located between two other genes; iv) intronic lncRNAs are contained completely within protein-coding introns and do not intersect any exons; v) bidirectional lncRNAs share a promoter with another transcript in the opposite strand and are, thus coregulated (9,10).

3. Biological function of lncRNAs

With the development of whole genome and mass-scale transcriptome sequencing technologies, the functions of lncRNAs have been investigated in various fields (11-13). Although only a small fraction of lncRNAs identified have been investigated experimentally, an emerging paradigm suggests that lncRNAs function in multiple biological contexts. For example, lncRNAs can also act as scaffolds during the formation of cellular substructures or protein complexes (14-16), and evidence indicates that lncRNAs are involved in regulating gene expression at transcriptional, post-transcriptional and epigenetic levels (17,18), which affect cell differentiation and cycle control (19,20), as well as controling apoptosis and cell death (21,22).

Transcriptional control is important in the regulation of gene expression in prokaryotes and eukaryotes. It has been demonstrated that lncRNAs modulate large-scale gene expression via interacting with chromatin at numerous different locations across multiple chromosomes (23). It has been determined that lncRNAs can affect transcription via various mechanisms, including altering the activity of specific transcription factors and polymerases, acting as coactivators of transcription factors, binding to DNA or proteins, interacting with RNA binding proteins and inhibiting the promoter of their target gene (24-26).

LncRNAs modulate the expression of mRNA at the post-transcriptional level by affecting mRNA stability and modulating cell cycle distribution and cell differentiation. For example, growth-arrested DNA damage-inducible gene 7 (gadd7), a DNA damage-inducible lncRNA, controls cell-cycle progression (27,28). It is key in the regulation of the G_1/S checkpoint following DNA damage (28). UV-induced gadd7 specifically binds to TAR DNA-binding protein (TDP-43), disrupting the interaction between TDP-43 and cyclin-dependent kinase 6 (Cdk6) mRNA, and decreasing the expression of Cdk6 (28). The antisense transcript for β-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1-AS) has been observed to stabilize mRNA, thus, maintaining mRNA expression levels at the post-transcriptional level (29-31). BACE1, also termed β-secretase-1, is a crucial enzyme in the pathophysiology of Alzheimer's disease. Increased expression levels of BACE1 and APP in plaque-associated presynaptic dystrophies increase the generation of local peri-plaque amyloid β (Aβ) and accelerate the growth of amyloid plaque in Alzheimer's disease (32,33). BACE1-AS can regulate BACE1 mRNA and subsequent BACE1 protein expression *in vitro* and *in vivo,* and in Alzheimer's disease, the upregulated expression of BACE1-AS increases the stability of BACE1 mRNA and generates additional Aβ1-42 via a post-transcriptional feed-forward mechanism (29).

The term epigenetics refers to reversible modifications of DNA molecules of one cell or histones, which change the DNA conformation and result in changes to the expression of genes without altering the sequence of bases in the DNA (30). Epigenetic changes, including DNA methylation, histone modification, chromatin remodeling, genome imprinting and the regulatory mechanisms of RNA editing, can affect gene expression (35,36). Aberrations in epigenetic modifications are common in several human diseases, including cancer (35,37,38). DNA methylation, the best-known epigenetic marker, is important in the regulation of a wide variety of molecular processes, including maintaining the stability of the genome and regulating gene expression and inactivation (36). Previous studies have demonstrated that lncRNAs are critical in epigenetic regulation (39,40), and have also indicated that DNA methylation and histone modifications are common epigenetic mechanisms, resulting in the deregulation of lncRNA expression levels in tumors (41,42).

Brannan *et al* (43) identified H19, a 2.3 kb lncRNA, which can interact with methyl-CpG-binding domain protein 1 (MBD1) that is involved in the maintenance of repressive H3K9me3 histone marks, forming the H19 lncRNA-MBD1 complex and controlling gene expression of the imprinted gene network (IGN) (15). H19 associated with chromatin-modifying complexes provides a method for regulating embryonic growth (15).

4. LncRNAs in tumors

Numerous experimental studies and clinical observations have suggested that aberrant lncRNA expression is associated with various human diseases and disorders, particularly in tumors (44-46). Although the precise mechanism underlying how lncRNAs result in the development and progression of cancer remains to be elucidated, previous studies (15,22,47) have linked distinct types of mutations in lncRNA genes with diverse diseases, and have demonstrated that certain lncRNAs serve as tumor suppressors or carcinogenic factors in the development of cancer.

4.1 LncRNAs in lung cancer. Lung cancer is a leading cause of mortality worldwide (48). Non-small cell lung cancer (NSCLC), including adenocarcinoma, squamous cell carcinoma and large cell carcinoma accounts for 80-85% of new cases of lung cancer (49-52). Evidence indicates that lung cancer metastasis is significantly associated with the noncoding metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) located on chromosome 11q13, which is a highly expressed lncRNA with a length of >6,500 bp (53,54). The overexpression of MALAT1 results in an increase in cell proliferation and migration in lung cancer, and MALAT1 serves as a novel prognostic marker for survival in NSCLC (54,55).

4.2 LncRNAs in breast cancer. Breast cancer is a common malignancy in females, and its incidence in younger women is increasing. Previous studies have suggest that lncRNAs have a significant correlation with the onset and development of breast cancer (56,57).

HOX antisense intergenic RNA (lincRNA-HOTAIR) is a 2.2 kb carcinogenic lncRNA, which is located in the mammalian homeobox C (HOXC) locus on chromosome 12q13.13 (58). HOTAIR acts as a scaffold by combining its 3' region with the lysine-specific demethylase 1 (LSD1)/corepressor for element-1-silencing transcription factor/repressor element RE-1 silencing transcription factor complex, and its 5' region with polycomb repressive complex 2 (PRC2) (58-60). This acts to regulate histone H3 methylation at lysine 27 and demethylation at lysine 4, and silence the HOXD loci *in trans* (58). PRC2 is a protein responsible for H3K27 methyltransferase, and is associated with developmental gene silencing and cancer progression (58-61). LSD1 is a histone methyltransferase, which mediates the enzymatic demethylation of H3K4Me2 (62). The increased expression levels of HOTAIR have been associated with poor prognosis and tumor metastasis in breast cancer (58,63), and Gupta *et al* (63) demonstrated that the expression levels of HOTAIR in the primary tumor and metastases were significantly increased, compared with non-cancerous tissues. The systematically dysregulated HOTAIR results in increased *in vitro* cell invasion and *in vivo* metastasis in breast cancer cells (63-65). The genome-wide reorientation of PRC2, caused by enforced HOTAIR expression in epithelial cancer, leads to altered histone H3 lysine 27 methylation and gene expression, which can increase the cancer invasiveness and metastasis, in a PRC2-dependent

manner (63). Decreased levels of HOTAIR markedly reduce cancer invasiveness, particularly in cells with increased PRC2 activity (63).

LncRNA-LOC554202 is another lncRNA, which is important in the development and progression of breast cancer (66,67). Compared with normal breast tissue, the expression level of lncRNA-LOC554202 in breast cancer tissues is significantly upregulated, and is correlated with tumor size and advanced pathological stage (66). Small interfering (si)RNA-mediated knockdown of LOC554202 results in a significant accumulation of cells at the G_0/G_1-phase ($P<0.05$) and a marked decrease in cells in S-phase. This indicates that siRNA-mediated knockdown of lncRNAs-LOC554202 inhibited breast cancer proliferation, invasion and migration, and increased apoptosis *in vitro* and prevent tumorigenesis (66).

LncRNAs are important in modulating the occurrence and development of cancer, reinforcing the potential of identifying a novel type of targeted therapy to diagnose, treat and prevent breast cancer effectively. Further investigations to identify lncRNA markers with higher sensitivity and specificity in breast cancer-associated lncRNAs is required, as are investigations aimed at reducing the occurrence of breast cancer by regulating the expression of specific lncRNAs that affect transcription of tumor suppressor genes.

4.3 LncRNAs in prostate cancer (PCa). Previous studies (68,69) have demonstrated that the abnormal expression of genes regulated by lncRNAs are associated with PCa. Studies have indicated that lncRNAs are involved in cell proliferation, cell invasion and metastasis by functioning as oncogenes or as tumor suppressor genes, and lncRNAs associated with PCa have been identified, including PCA3 and PCAT1 (70,71).

PCA3 is a well-investigated lncRNA in PCa (72,73). Compared with normal prostate tissue, the expression levels of PCA3 have been found to be upregulated 66-fold in PCa tissue, and this overexpression was observed in >95% of primary and metastatic PCa specimens (73). PCA3 has been used as a biomarker for molecular diagnostics in clinical urological practice (72,73). PCa associated ncRNA transcript-1 (PCAT-1) is a highly prostate-specific lncRNA, which is markedly overexpressed in a subset of PCa and promotes cell proliferation (69). Crea *et al* (74) observed that a novel lncRNA, PCAT18, was specifically expressed in the prostate. PCAT18 silencing can markedly inhibit PCa cell proliferation, and inhibit tumor cell migration and invasion (74). Together, this suggests that lncRNAs may act as novel therapeutic targets in PCa and as biomarkers for metastatic PCa.

4.4 LncRNAs in hematological malignancies

4.4.1 LncRNAs in acute leukemia. Leukemia is one of the most common types of malignant tumor. In previous years, miRs have been well described in hematological malignancies, while lncRNAs are expected to be increasingly investigated.

Maternally expressed gene 3 (MEG3) is an imprinted gene located at 14q32, which encodes an lncRNA correlated with several types of human cancer (75,76). MEG3 is also expressed in various normal tissues and functions as an lncRNA tumor suppressor. The loss of MEG3 expression in tumors occurs as a result of gene deletion, promoter hypermethylation and hypermethylation of the intergenic differentially methylated region (76). It was shown to activate p53 and facilitate p53-dependent or independent pathways, functioning as a tumor suppressor (77). Benetatos *et al* (78) observed that MEG3 was abnormally methylated in patients with acute myelogenous leukemia (AML) and myelodyplastic syndrome, and MEG3 hypermethylation was associated with significantly reduced overall survival rates in individuals with AML. The MEG3 methylation status may serve as a useful biomarker in leukemia.

T-cell acute lymphoblastic leukemia (T-ALL) is an agressive hematological malignancy (79,80). T-ALL-R-LncR1, is a novel long non-coding RNA associated with apoptosis regulation in T-ALL cells, and is prominently expressed in certain tumor tissues, but not detected in normal human tissues (80). T-ALL-R-LncR1 knockdown induced the formation of a prostate apoptosis response-4/THAP protein complex, enhance the activation of caspase-3, and accelerated apoptosis in Jurkat cells (80,81). Therefore, suppressing RNA T-ALL-R-LncR1 may be a potential therapeutic strategy in human T-ALL.

Two novel lncRNAs have been identified in acute promyelocytic leukemia cells, HOX antisense intergenic RNA myeloid 1 (HOTAIRM1) and HOXA cluster antisense RNA 2 (HOXA-AS2) (82-84). HOTAIRM1 and HOXA-AS2 are upregulated in NB4 promyelocytic leukemia cells (82,83). HOTAIRM1 is a small intergenic transcript from the plus (opposite) strand between the HOXA1 and HOXA2 genes, and shows myeloid-specific expression (84). It is involved in myelopoiesis through modulation of gene expression in the HOXA cluster (84). Knockdown of HOTAIRM1 quantitatively decreases RA-induced expression of HOXA1 and HOXA4 during the myeloid differentiation of NB4 cells, and selectively attenuates the expression of myeloid differentiation genes, cluster of differentiation (CD)11b, CD11c and CD18 (82,84), but does not affect the more distal HOXA genes (83). HOXA-AS2 is located between HOXA3 and HOXA4 within the HOXA cluster in the human genome, and is transcribed in the opposite direction. It functions as an apoptosis repressor in all trans RA (ATRA)-treated NB4 cells via mechanisms mediated, in part, by tumor necrosis factor-related apoptosis-inducing ligand, which is a prominent biologically-targeted anti-tumor protein due to its induction of apoptosis in a variety of human cancer cell lines, avoiding normal cells (85). Knockdown of HOXA-AS2 decreases the number of viable cells and increases the proportion of apoptotic cells, and HOXA-AS2-mediated negative regulation contributes to the fine-tuning of apoptosis in the myeloid differentiation induced by ATRA in NB4 cells (83).

LncRNA-IRAIN is another novel antisense ncRNA, 5.4 kb in length, with no large open reading frames (86). It is located in the insulin-like growth factor type I receptor (IGF1R) locus (86). IRAIN is expressed exclusively from the paternal allele, while the maternal counterpart is silenced as demonstrated by Sun *et al* (86) on investigating the underlying mechanism of IGF1R dysregulation in tumors. IGF1R is an abundantly phosphorylated receptor tyrosine kinase, which promotes cell growth via the phosphatidylinositol-4,5-bisphosphate 3-kinase/Akt signaling pathway (86-88). IGF1R regulates multiple cellular functions in tumors, including cellular survival, growth, tumor neovascularization and metastasis (89,90). IRAIN is transcribed in an antisense direction from an intronic promoter, and is downregulated in leukemia cell lines and in patients with high-risk AML (86). Knockdown of IRAIN lncRNA with small hairpin

Table I. Types of cancer associated with lncRNAs.

LncRNA	Cancer	Cytoband	References
ANRIL	Prostate, leukemia, gastric	9p21.3	(102-104)
Anti-NOS2A	Brain	17q23.2	(105)
BC200	Breast, cervical, esophageal, lung, ovarian, parotid, tongue	2p21	(106-108)
GAS5	Prostate, colorectal, renal cell, breast, pancreatic, lymphoma	1q25.1	(109-113)
HOTAIR	Prostate, bladder, kidney, breast, lung, gastric adenocarcinoma, colon	12q13.13	(114-118)
PlncRNA-1	Esophageal squamous, prostate carcinoma	21	(119-120)
H19	Bladder, lung, liver, breast, esophagus, gastric	11p15.5	(121-124)
MEG3	Gastric, meningiomas, bladder, leukemia	14q32	(76,78,125)
PCA3	Prostate	9q21.2	(73)
FAS-AS1	Lymphoma	10q24.1	(42)

LncRNA, long noncoding RNA; ANRIL, antisense noncoding RNA in the INK4 locus; NOS2A, nitric oxide synthase, inducible; BC200, brain cytoplasmic RNA 1; GAS5, growth arrest-specific 5; HOTAIR, HOX antisense intergenic RNA; PlncRNA-1, CBR3 antisense RNA 1; H19, H19, imprinted maternally expressed transcript; MEG3, maternally expressed 3; PCA3, prostate cancer associated 3; FAS-AS1, FAS antisense RNA 1.

RNA eliminates the intrachromosomal interaction between chromatin DNA and lncRNA (86).

4.4.2 LncRNAs in chronic myeloid leukemia. Chronic myeloid leukemia (CML) is a malignant disease occurring in clonal hematopoietic stem cells, which accounts for ~20% of all adult leukemia cases (91) and is characterized by the clonal hyperproliferation of immature white blood cells. The Philadelphia (Ph) chromosome and/or breakpoint cluster region (Bcr)/ABL proto-oncogene 1 (Abl) gene rearrangement is a specific marker of CML (91,92). The BCR-ABL gene is a fusion gene generated by the t(9;22)(q34.1;q11.21) translocation, which produces the Ph chromosome (93). Bcr-Abl-induced tumorigenesis involves the alteration of numerous signaling pathways that regulate cell survival and proliferation, including the PI3K/phosphatase and tensin homolog (PTEN)/AKT, RAS and Janus kinases/signal transducer and activator of transcription signaling pathways (94-97). Altering the expression of the BCR-ABL gene regulates the induction of cellular proliferation, and the inhibition of cellular differentiation and programmed cell death (98,99). Guo *et al* (97) identified a novel lncRNA, lncRNA-BGL3, which is a key regulator of Bcr-Abl-mediated cellular transformation. LncRNA-BGL3 was found to function as a competitive endogenous RNA for binding the miRs that repress PTEN mRNA, including miR-17, miR-93, miR-20a, miR-20b, miR-106a and miR-106b, to cross-regulate PTEN expression. LncRNA-BGL3 was induced following inhibition of Bcr-Abl kinase activity or disruption of Bcr-Abl expression in K562 cells and leukemic cells derived from patients with CML (97). It has been demonstrated that Bcr-Abl represses the expression of lncRNA-BGL3 via c-Myc-dependent DNA methylation (97), which suggests that regulating the expression of lncRNA-BGL3 may be a potential therapeutic strategy for Bcr-Abl-positive leukemia.

4.4.3 LncRNAs in lymphoma. FAS-AS1 is an lncRNA corresponding to an antisense transcript of Fas, which can tightly regulate the alternative splicing of Fas in lymphomas. Sehgal *et al* (42) found that expression levels of FAS-AS1 have a negative correlation with the production of soluble Fas (sFas), and that increased levels of FAS-AS1 decrease the expression of sFas, and eliminate the inhibition of apoptosis by the sFas ligand, enhancing Fas-mediated apoptosis. Studies have demonstrated that impaired Fas-mediated apoptosis is associated with poor clinical outcomes and cancer chemoresistance (100,101). Therefore, FAS-AS1 may be an important target for lymphoma diagnosis and therapy.

Changes in specific lncRNAs have been demonstrated to correlate with a wide variety of types of cancer (Table I). These findings suggest that lncRNAs are important in tumor cell activation and progression, however, the mechanism of action requires further investigation.

5. Conclusions and future perspectives

LncRNAs are significant in a series of biological processes, including epigenetics, the regulation of translation and post-transcriptional processing. Aberrant lncRNA expression is associated with various human diseases. Unlike protein coding genes and miRNA, the specific roles of lncRNAs remain to be fully elucidated. Aberrant lncRNA expression is involved in carcinogenesis by disrupting major biological processes, including DNA methylation in epigenetic modifications and gene silencing. However, only a small number of lncRNAs have been identified and, thus, the impact of lncRNAs in tumor development remains to be fully elucidated. Technological developments in investigating the function and mechanism of lncRNAs require further exploitation. The differential expression of lncRNAs may be a significant marker in cancer diagnosis and prognosis, and may offer potential in lncRNA-mediated targeted therapy in the future.

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