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Mini-review

Long noncoding RNAs in cancer cells

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ABSTRACT

Long noncoding RNA (lncRNA) has recently been investigated as key modulators that regulate many biological processes in human cancers via diverse mechanisms. LncRNAs can interact with macromolecules such as DNA, RNA, or protein to exert cellular effects and to act as either tumor promoters or tumor suppressors in various malignancies. Moreover, the aberrant expression of lncRNAs may be detected in multiple cancer phenotypes by employing the rapidly developing modern gene chip technology and bioinformatics analysis. Herein, we highlight the mechanisms of action of lncRNAs, their functional cellular roles and their involvement in cancer progression. Finally, we provide an overview of recent progress in the lncRNA field and future potential for lncRNAs as cancer diagnostic markers and therapeutics.

1. Introduction

Cancer has long been considered a complex disease associated with a variety of genetic mutations, chromosomal translocations, deletions or epigenetic alterations where mutations in specific tumor suppressors and tumor promoters accumulate over the course of tumorigenesis and metastasis. More recently, emerging studies have identified long noncoding RNAs (lncRNAs) as major players in

Abbreviations: ABCB1, ATP-binding cassette; subfamily B and member 1, AFAP1-AS1; actin filament-associated protein 1 antisense RNA 1, ANRIL; antisense non-coding RNA in the ink4 locus, APOC1P1; apolipoprotein C1 pseudogene 1, AS; antisense, ASO; antisense oligonucleotide, BC; breast cancer, BCAT1; branched chain amino acid transaminase 1, Bcl-2; B-cell lymphoma 2, BRCA; breast cancer susceptibility gene, CASC2; cancer susceptibility candidate 2, Cbl; casitas b-lineage lymphoma, CCA; cholangiocarcinoma, Cdk6; cell division protein kinase 6, ceRNAs; competing endogenous RNAs, CHD4; chromodomain-helicase-DNA-binding protein 4, CRC; colorectal cancer, CUDR; long non-coding RNA UCA1a, DANCR; differentiation antagonizing non-Protein coding RNA, DLX6; distal-less homeobox 6, DNMT; DNA methyltransferase, EMT; epithelial–mesenchymal transition, EPB41L3; erythrocyte membrane protein band 4.1 like 3, EphA8; Eph receptor A8, ER; estrogen receptor, eRNA; enhancer RNA, EWSAT1; Ewing sarcoma-associated transcript 1, EZH2; enhancer of zeste homolog 2, FEZF1; FEZ family zinc finger 1, FOXM1; forkhead box M1, GAS5; growth arrest-specific 5, GBM; glioblastoma multiforme, GC; gastric cancer, GRK2; G protein-coupled receptor kinase 2, GEO; gene expression omnibus, GSCs; glioma stem cells, H3K9; histone H3 lysine 9, H3K27; histone H3 lysine 27, H19; gene comes from colon pH19, HCC; hepatocellular carcinoma, HIF-1α; hypoxia inducible factor-1α, HNF1A; HNF1 homeobox A, hnRNPL; heterogenous nuclear ribonucleoprotein L, HOTAIR; HOX transcript antisense RNA, HUVECs; human umbilical cord vein endothelial cells, IFITM3; IFN-induced transmembrane protein 3, IFN; interferon, IGFBP-4; Insulin-like growth factor binding protein-4, IL-6; interleukin-6, ISGs; interferon-stimulated genes, IQGAP1; IQ motif containing GTPase activating protein 1, KRT7; keratin 7, LAC; lung adenocarcinoma, LIT1; long QT intronic transcript 1, LNAs; locked nucleic acids, lncRNA; long noncoding RNA, LSD1; lysine (K)-specific demethylase 1A, LUSC; lung squamous cell carcinoma, LUCAT; lung cancer associated transcript, MALAT1; metastasis associated in lung adenocarcinoma transcript 1, MDR; multiple drug resistance, MEG3; maternally expressed 3, messenger RNAs; (mRNAs), miRNA; microRNA, MMP-2; matrix metalloproteinase-2, MxA; myxovirus resistance protein A, NBR2; neighbor of BRCA1 gene 2, NEAT1; nuclear enriched abundant transcript 1, NEK2; NIMA-related kinase 2, NF-κB; nuclear factor-kappa B, Notch: Notch homolog 1; translocation-associated, NRAV; negative regulator of antiviral response, NURD; nucleosome remodeling and deacetylase, OS; overall survival, OSCC; oral squamous cell carcinoma, PAMAM; poly(amidoamine), PC; pancreatic cancer, PCAT1; prostate cancer-associated transcript 1, Pdia3; protein disulfide isomerase associated 3, PFS; progression-free survival, PPAR; peroxisome proliferator-activated receptor, PRC; polycomb repressive complex, PTEN; phosphatase and tensin homolog, RBMP15; RNA-binding motif protein 15, RCC; renal cell carcinoma, ROCK1; Rho-associated, coiled-coil containing protein kinase 1; ROR, RAR-related orphan receptor; siRNAs, small inhibitory RNAs; SIRT1, NAD-dependent deacetylase sirtuin-1; SMN2, survival motor neuron 2; Snail, zinc finger protein SNAI1; SNHG20, small nucleolar RNA host gene 20; snoRNA, small nucleolar RNA; SMA, spinal muscular atrophy; SP1, specificity protein 1; SPEN, split end; STAT3, signal transducer and activator of transcription 3; TARID, TCF21 antisense RNA inducing promoter demethylation; TCF21, transcription factor 21; TDP-43, TAR DNA-binding protein-43; TERT, telomerase reverse transcriptase; TESC, tescalcin; TNFα, tumor necrosis factor alpha; TNM, tumor-node-metastasis; TRERNA1, translation regulatory long non-coding RNA 1; TSLC1, tumor suppressor in lung cancer 1; TSLNC8, long noncoding RNAs on chromosome 8p12; TUG1, taurine upregulated gene 1; TUSC7, tumor suppressor candidate 7; XIST, X-inactive specific transcript; VEGF, vascular endothelial growth factor; UCA1, urothelial cancer associated 1; Wnt, wingless-type MMTV integration site family member.

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the regulation of the epigenome that play critical roles in cancer processes and display significant regulation of fundamental protein effectors of cellular function. LncRNAs, which often lack protein coding capabilities, may act as oncogenes or tumor suppressors by regulating numerous biological processes, such as epigenetic modulation, splicing, cell development, differentiation and imprinting [1]. Interestingly, the expression of lncRNAs has been quantitatively explored in several cell types and tissues by high-throughput RNA sequencing (RNA-seq) and have commonly been found to be more cell type specific than the expression of protein-coding genes [2]. Furthermore, many studies have also indicated that the aberrant expression of lncRNAs is responsible for drug resistance, a substantial obstacle for cancer therapy [3]. With the development of therapeutic approaches based on lncRNAs, it is necessary to summarize the critical role of lncRNAs in the tumorigenic process, paying special attention to the hallmarks of cancer. In this review, we present an overview of the current knowledge regarding the critical functions of lncRNAs in cancer pathophysiology, as well as their potential clinical applications. We also suggest that lncRNAs are a novel and challenging class of potential drug targets.

2. Landscape of lncRNAs

LncRNAs are defined as a large and diverse class of transcribed RNA molecules that are more than 200 nucleotides and do not have protein-coding capacity. LncRNA sequences may resemble messenger RNAs (mRNAs) in several ways. For example, they are transcribed by RNA polymerase II, 5′-capped [4], and display the same histone modifications as protein-coding genes [5]; thus, lncRNAs were first defined as mRNA-like ncRNAs [4]. Notably, the term lncRNA is considered a broad classification which encompass various types of RNA transcripts, such as intergenic transcripts, enhancer RNAs (eRNAs), and small nucleolar RNAs (snoRNAs), in both the sense and antisense orientations [6]. Cells may modulate lncRNA expression levels independently of mRNA levels via distinct regulatory pathways [7]. LncRNAs predominantly localize to the nucleus and have lower expression levels in almost all cell types compared to mRNAs, although these details may vary across different lncRNA classes [8]. Multiple studies have shown that lncRNAs might be differentially expressed across various stages of differentiation [9–11]. Further, lncRNA expression has been quantitatively analyzed in several tissues and cell types by high-throughput RNA-seq experiments [11,12], which have been used to eliminate the possibility of protein coding potential [6]. Sequencing analysis also shows that lncRNAs are under higher selective pressures than ancestral repeat sequences, which are suggested to be under neutral selection [6]. Moreover, unlike proteins, lncRNAs, which may function both in *cis*, at the site of transcription, or in *trans*, do not need to be translated and do not require transport between the cytoplasm and the nucleus [6]. Although the definition of lncRNAs is lacking in unification, high-throughput RNA-seq and computational analyses have substantially improved lncRNA characterization. As a result, the definition of lncRNAs has become more specific and now details various features including: structure, sequence, function, interaction with protein-coding genes, metabolism and other known DNA elements [13]. Emerging evidence has implicated lncRNAs in cancer development, mainly through epigenetic modulation, stimulation of oncogenic pathways and crosstalk with other RNA subtypes [13,14]. Therefore, we can now identify critical roles of lncRNAs in various cancer phenotypes through their significant interactions with other cellular macromolecules, including DNA, RNA and protein, allowing us to further understand how widespread crosstalk among abnormal pathways may occur in human cancer. As an illustration, the lncRNA negative regulator of antiviral response (NRAV), a key modulator of antiviral innate immunity, might be related to the pathogenesis of cancers caused by viruses [15,16]. NRAV can regulate the transcription of multiple interferon (IFN)-stimulated genes (ISGs), such as IFN-induced transmembrane protein 3 (IFITM3) and myxovirus resistance protein A (human MxA), by affecting the histone modifications of these genes [15]. Many studies have also focused on identifying lncRNA-miRNA-mRNA interaction mechanisms in cancer progression, and a few reports have explored how lncRNAs and miRNAs are transcriptionally modulated [17–19]. For example, microRNA-34a (miR-34a) functions as a tumor suppressor by suppressing NAD-dependent deacetylase sirtuin-1 (SIRT1) expression, thereby triggering pathways downstream of SIRT1 in human colon cancer cells [20]. Wang et al. further found that antisense (AS) lncRNA SIRT1 could compete with miR-34a and bind to SIRT1 mRNA to modulate the efficiency of SIRT1 protein expression in myoblast differentiation [21]. RNA-binding motif protein 15 (RBM15), an RNA-binding protein, belongs to the split end (SPEN) family and has been suggested to function by modulating cell growth and apoptosis through the regulation of multiple signaling pathways such as wingless-type MMTV integration site family member (Wnt) and Notch homolog 1, translocation-associated (Notch) [22]. Tran et al. also indicated that the antisense RNA AS-RBM15 could stimulate protein translation of the sense RBM15 mRNA via an overlapping region of the sense/antisense (S/AS) pair [23]. LncRNAs may also interact with proteins to contribute to protein function and modulate protein-protein interactions. Therefore, these molecules are able to act as signals, decoys, guides, and scaffolds. Fan et al. reported that RAR-related orphan receptor (ROR), which is more highly expressed in tumor cells than in normal gastrointestinal cells and normal fibroblasts, significantly stimulates tumor progression and metastasis [24]. They further found that ROR might act as a decoy oncoRNA to block the recruitment of chromatin regulatory factors (G9 methyltransferase), abolish histone H3 lysine 9 (H3K9) modification of the tescalcin (TESC) promoter and stimulate abnormal tumor progression [24]. Liu et al. also indicated that HOX transcript antisense RNA (HOTAIR) might recruit and bind to polycomb repressive complex 2 (PRC2) to epigenetically repress miR-34a, thus modulating the targets c-Met and zinc finger protein SNAI1 (Snail) and subsequently contributing to the progression of gastric cancer (GC) cell epithelial–mesenchymal transition (EMT) and stimulating tumor metastasis [25]. Furthermore, RNA-protein affinity purification identified 11 NRON-interacting proteins, including IQ motif containing GTPase activating protein 1 (IQGAP1) [26], which regulates the cell cycle to affect progression beyond the G1/S phase [27]. Taken together, lncRNAs may be novel therapeutic targets for cancer, as summarized in Fig. 1 [21,23,24,28–31].

3. Roles of lncRNAs in cancer

3.1. Action models of lncRNAs in cancer

As expected from their diverse classifications, numerous functions have been ascribed to lncRNAs. LncRNAs may function through a variety of different mechanisms, including remodeling of and interactions with chromatin, epigenetic transcriptional modulation, translation of protein-coding genes, genome defense or RNA turnover [32]. However, most of the functions described to date involve modulation of the expression of protein-coding genes and other ncRNAs [32].

3.1.1. Epigenetic transcriptional modulation

The epigenetic alterations experienced by tumor cells are considered an influential factor in cancer growth [33]. Emerging