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Review

Targeting long non-coding RNAs in cancers: Progress and prospects

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ABSTRACT

Pervasive transcription occurs in the human genome to generate thousands of RNA transcripts, and accumulating evidence suggested that the RNA molecules, without protein coding ability, have important roles in diverse biological functions. Long non-coding RNA (lncRNA), with size larger than 200 nt, is a new class of the non-coding RNA that contributes to cancer development and progression. Roles for several lncRNAs in cancers have been characterized and strategies targeting them have inhibitory effects to malignant cells in vitro and in vivo. These findings point to the potential of lncRNAs as prospective novel therapeutic targets in cancers. Recent advance in biological drugs, led by nucleic acid drugs (i.e. siRNAs, antisense oligonucleotides), suggest directions for the development of cancer therapies targeting lncRNAs. Here, we discuss the characteristics of lncRNAs regarding their synthesis, stability and functional role in cells, and emphasize their unique properties that determine their molecular functions. We then discuss the association of lncRNAs with cancers, and illustrate the anticancer effects induced upon modulating the level and function of lncRNAs. We also revisit established methods for targeting RNA molecules and discuss new agents and strategies to attenuate lncRNAs in cancer.

Contents

Abbreviations: ANRIL, antisense non-coding RNA in the INK4 locus; ATRA, all-trans retinoic acid; ASO, antisense oligonucleotide; CRC, colorectal carcinoma; CREB, cAMP-responsive element binding protein; DM1, myotonic dystrophy type 1; DsRNA, double-stranded RNA; EMT, epithelial–mesenchymal transition; HamRz, hammerhead ribozyme; HCC, hepatocellular carcinoma; HOTAIR, HOX transcript antisense intergenic RNA; HULC, highly up-regulated in liver cancer; IRES, internal ribosomal entry site; LincRNA, long intergenic non-coding RNA; LncRNA, long non-coding RNA; LSCC, laryngeal squamous cell carcinoma; MALAT1, metastasis associated lung adenocarcinoma transcript 1; NAT, natural antisense transcript; NSCLC, non-small cell lung carcinoma; ORF, open reading frame; PCa, prostate cancer; PCGEM1, prostate cancer gene expression marker 1; RNAi, RNA interference; RISC, RNAi silencing complex; SELEX, systematic evolution of ligands by exponential enrichment; shRNA, small hairpin RNA; siRNA, small interfering RNA; TAR, transactivation response element; T-UCR, transcribed ultraconserved region; UTR, untranslated region.

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1. Introduction

With the advance of high-resolution microarray and genome-wide sequencing technology, massive amount of novel transcripts are revealed (Carninci et al., 2005; Trapnell et al., 2010). The ENCODE consortium has shown that around 70% of the genome is actively transcribed (Djebali et al., 2012), and several lines of evidence suggested that most transcribed products are functional rather than mere transcriptional noise. A new class of non-coding RNA, with length ranged from 200 bp to 100 kbp, is named long non-coding RNA (lncRNA) and has recently caught increasing attention. The latest GENCODE project has annotated 14,880 lncRNAs from 9277 loci (Derrien et al., 2012), but only a few of them are characterized. Studies demonstrated that lncRNAs play major biological roles in embryogenesis (Pauli et al., 2011), stem cell biology and cellular development (Guttman et al., 2011), and show developmental and tissue specific expression patterns (Mercer et al., 2009; Ponting et al., 2009). Studies also suggest that misexpression of lncRNAs is associated with numerous diseases including cancer (Wapinski and Chang, 2011). Currently, dozens of lncRNAs are identified to play critical roles in the development and progression of cancer (Gibb et al., 2011; Huarte and Rinn, 2010), hence they may open a new avenue for identification of cancer therapeutic targets.

The association of lncRNAs with cancer has been well-summarized (Gutschner and Diederichs, 2012) and the potential of lncRNA-based cancer therapy has been pointed out (Tsai et al., 2011). Extensive studies have conducted to interrogate the molecular functions of lncRNAs (Lee, 2012), which allows the development of targeting approach specific to individual lncRNA. Advance RNA sequencing technology also accelerates the progress of developing lncRNA-based cancer management. Data are robustly generated to identify new and critical cancer-associated lncRNAs (Prensner et al., 2011; Sinicropi et al., 2012). The single-nucleotide resolution of the sequencing results allows characterization of the structure, potential function and disease-associated polymorphisms of the lncRNAs (Wang et al., 2011a; Chu et al., 2011; Jin et al., 2011; Zhao et al., 2010). Importantly, discoveries are not confined to known lncRNAs as RNA sequencing can survey whole transcriptome without preceding annotation. Besides, recent improvement of biological drugs has broadened the types of therapeutic targets, which enables strategies targeting RNA molecules (Castanotto and Rossi, 2009; Davis et al., 2010). These strategies show promising results for the inhibition of cancers as exemplified by the advancement of several RNA targeting therapies in clinical trials. Taken together, maturity has been reached to kick-off the development of lncRNA-based cancer therapy. In this review, we will firstly discuss the current understanding of the lncRNAs in regard to their structural and functional characteristics as well as their roles in cancer development and progression. Subsequently, we focus on four defined categories of lncRNAs: (1) long intergenic non-coding RNA (lincRNA), (2) natural antisense transcripts (NAT), (3) transcribed ultraconserved regions (T-UCR) and (4) non-coding pseudogenes, as currently there are substantial amount of data showing their association with cancers. We will discuss the role for important members regarding their functions in cancer and evaluate their potential as novel therapeutic targets. Lastly, we will review various methods that are promising in targeting lncRNAs (i.e. nucleic acid drugs and small molecules), and discuss their prospects as the drugs administrated in lncRNA targeting cancer therapies. We will also discuss potential strategies to attenuate or modulate the functions of lncRNAs.

2. Characteristics of LncRNA

LncRNAs are involved in numerous biological roles such as imprinting (Jeon et al., 2012), epigenetic regulation (Mattick et al., 2009), apoptosis and cell cycle control (Wapinski and Chang, 2011), transcriptional (Ørom et al., 2010) and translational regulation, splicing, cell development and differentiation, (Clark and Mattick, 2011) and aging (Rando and Chang, 2012). Understanding the molecular pathways that determine the production, structure, and turnover of lncRNAs is critical to characterize the function of lncRNAs. LncRNAs are mostly transcribed by RNA polymerase II, and subsequently undergo co-transcriptional modifications such as polyadenylation and pre-RNA splicing (Mercer et al., 2009). Although lncRNAs generally are less stable than mRNAs, a study using mouse cells as model suggested a large portion of lncRNAs have high stability (Clark and Mattick, 2011). LncRNAs harbor standard canonical splice site signals, but have fewer exons than mRNAs. As such, lncRNAs are generally shorter than mRNAs, with median of 592 nt compared to 2453 nt for mRNA (Derrien et al., 2012). The predicted open reading frames (ORFs) in lncRNAs have poor start codon and ORF contexts, hence translation of lncRNAs is less likely to happen as it would activate nonsense-mediated decay pathways. Hence, the biological functions of lncRNAs are primarily attributed to the basic structural and biochemical properties of RNA molecules. The upstream regulatory elements/promoters of lncRNA genes are marked by active histone marks (H3K4me2/3, H3K9ac, H3K27ac) and the gene bodies are marked by H3K36me3, which are the hallmarks of genomic region that are actively transcribed (Guttman et al., 2009; Derrien et al., 2012). This implies that lncRNAs are subjected to common epigenetic regulatory machineries. Analysis of GENCODE consortium showed that most lncRNA are independent transcriptional units, which further supports specific regulating mechanism of lncRNA transcription (Derrien et al., 2012).

Majority of lncRNAs are located in nucleus (Derrien et al., 2012), which is consistent with the major functions of lncRNA for epigenetic regulation of gene expression. To target these nuclear bound lncRNAs, efficient nuclei delivery of the drug is necessary. There is still a population of lncRNAs that are enriched in cytoplasm and have important functions including translational regulation. Interestingly, some lncRNAs are cleaved to generate different fragments that function in nucleus and cytoplasm. For example, lncRNA MALAT1 is cleaved by RNase P to yield a nuclear-retained RNA and a small tRNA-like RNA that are shuttled to the cytoplasm as an output signal (Wilusz et al., 2008). Knowledge of the geographical information of lncRNAs is essential for efficient targeting. Role for lncRNAs in any cellular compartments