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Review Article

Long non-coding RNAs: The novel diagnostic biomarkers for leukemia

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ABSTRACT

Long non-coding RNAs (LncRNAs) are a category of non-coding RNAs (ncRNAs) with a length of 200 nt–100 kb lacking a significant open reading frame. The study of lncRNAs is a newly established field, due in part to their capability to act as the novel biomarkers in disease. A growing body of research shows that lncRNAs may not only useful as biomarkers for the diagnosis and clinical typing and prognosis of cancers, but also as potential targets for novel therapies. Differential expression of lncRNAs has been found in leukemia in the last two years, however, the majority of the lncRNAs described here are transcripts of unknown function and their role in leukemogenesis is still unclear. Here, we summarize the lncRNAs associated with leukemia in order to find a potential classification tool for leukemia, and a new field of research is being explored.

1. Introduction

Non-protein-coding RNAs (NcRNAs) are gradually attracting the attention of researchers in various fields, and the number of published articles is rapidly growing recently (Mattick, 2009). In the past decade, it became more and more clear that ncRNAs may be closely related to various steps in gene expression and signaling pathways (Mazidi et al., 2017). Approximately 10% RNA (mRNA) of human cells are used as templates for protein expression, while the remaining 90% RNA are collectively called the ncRNAs. Among the most famous ncRNAs, long non-coding RNAs (lncRNAs) are the transcripts which are > 200 nucleotides in length, and located within intergenic stretches or overlapping antisense transcripts of protein-coding genes (Spizzo et al., 2012; Pan et al., 2017). According to the theory of molecular biologists, lncRNAs, transcribed and capped by RNA polymerase II, contain introns and are often polyadenylated but lack of protein coding capacity (Sattari et al., 2016). Multiple studies have shown that lncRNAs were widely involved in biological processes such as DNA methylation, histone modification and chromatin remodeling. Furthermore, increased researches proved that lncRNAs played important role in interaction with transcription factors, functional RNA molecules and chromatin remodeling modifiers (Chen and Carmichael, 2010; Wierzbicki, 2012; Bai et al., 2014). In addition, lncRNAs also effectively regulated the expression of corresponding target genes at transcriptional level, post-transcriptional level and epigenetic level, respectively (Clark and Mattick, 2011). Although significant progress on lncRNAs research has been achieved, there are still many unknown territories need to further illuminated.

In recent years, the incidence of leukemia presented a rising trend, however, the specific pathogenesis of leukemia has not yet clear. Most recently, growing studies have shown that lncRNAs might be closely related to blood diseases, especially leukemia (Zhang, 2016). Leukemia, known as blood cancer, is a kind malignant disease of bone marrow abnormal clonal hematopoietic stem cells. According to the disease progression, leukemia can be roughly divided into acute leukemia (AL) and chronic leukemia (CL). The former including acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL); the latter is divided into chronic myeloid leukemia (CML) and chronic

Abbreviations: lncRNAs, long non-coding RNAs; ncRNAs, non-coding RNAs; AL, acute leukemia; CL, chronic leukemia; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphoblastic leukemia; mlncRNA, mRNA-like noncoding RNA; Ara-C, cytosine arabinoside; NEAT1, nuclear enriched abundant transcript

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lymphoblastic leukemia (CLL). Although various studies took a one-sided approach to prove the lncRNAs effects in the leukemia, their mechanisms and the functions on the leukemia are still need to systematically reviewed and discussed. This paper aims to provide a concise summary about function of lncRNAs in different types of leukemia, and a new insight in leukemia classification. The prospects applied in novel biomarkers development in leukemia diagnosis is proposed in this paper as well.

2. Overview of LncRNAs

On the basis of the most popular theory, the lncRNAs mostly originated from the following five sources (Ponting et al., 2009). 1) Incorporated from the fragments of original protein-coding genes; 2) Two transcribed and previously well-separated sequence regions of chromosomes are juxtaposed and give rise to a multi-exon noncoding RNA after its rearrangement; 3) Duplicated from a noncoding gene through retro transposition; 4) Neighboring repeats within a noncoding RNA have their origins in two tandem duplication events; 5) Transcription factor insert into a sequence to form.

In terms of the lncRNAs classification, St Laurent et al. (2015) provided a comprehensive criteria as follows: 1) According to the length of transcripts, lncRNAs can be divided into five categories: lncRNA (> 200nt); lincRNA (long integenic non-coding RNA, 2.3-17.2 kb); very long integenic non-coding RNA (50kb-1MB); macroRNA (~400 kb); promoter associated long RNA (hundreds of base pairs to more than 1 kb). 2) Based on the degree of similarity to protein-coding RNA, lncRNAs can be divided into mlncRNA (mRNA-like noncoding RNA) and lincRNA. 3) On the basis of the biological role, lncRNAs can be divided into four categories: long noncoding RNAs with enhancer-like function; the primary transcripts of miRNA and piRNA; and the competing of endogenous RNA.

The function of lncRNAs is the most complicated and the minimum understanding in lncRNAs research. However, the elucidation on lncRNAs function will promote the our cognition on pervasive transcription in terms of cell biology and evolution history (Van and Hughes, 2009). The main function of lncRNAs includes following aspects: 1) scaffold molecules for chromatin modification complexes, 2) the molecular guides to ensure the precise localization of their binding targets, 3) the regulators for DNA looping, 4) the interferer for RNA transcription, splicing, translation and stability, and 5) the co-activator for transcription factor (Sattari et al., 2016). Additionally, Li and Luo (2016) pointed out that the role of lncRNAs: Signal molecules (regulated the expression of target genes by recognizing the combined effect of transcription factors in the signaling pathway); Decoy molecules (attract the transcription factors, protein molecules or other related substances to form combination with lncRNAs directly, which block their role on their target genes, regulate transcription of target genes indirectly); Guide molecules (recruited chromatin modification related enzymes, and guided the protein complexes to *cis* or *trans* position to the regulatory site); Scaffold molecules (as a central platform to recruit a variety of protein molecules to form ribonucleoprotein complexes, which regulated target genes through affecting the histone modification at the epigenetic level).

In view of the complex multi-function of lncRNAs, we specially concentrate our attention on lncRNAs that are involved in leukemia. Perhaps we may find a new classification tool of leukemia, which contribute to the diagnosis, treatment and prognosis assessment of leukemia.

3. Leukemia related LncRNAs (Table 1/Fig. 1)

Although accumulating evidences have proved the abnormal expression (up-regulation or down-regulation) of lncRNAs in leukemia, the mechanisms on their roles in these process are still ambiguous.

Table 1
The essential information of lncRNAs associated with leukemia.

Name	Size	Genomic location	Expression level	Leukemia type
MEG3	1.6 kb	14q32.2	Down	AML, CML
RUNXOR	216 kb	21p22.12	Up	AML
NEAT1	NEAT1-1(3.7 kb) NEAT1-2(23 kb)	11q13.1	Down	APL
LLEST	ND	ND	Down	AML
IRAIN	5.4 kb	15q26.3	Down	AML
UCA1	1.4 kb	19p13.12	Up	AML
ANRIL	34.8 kb	9p21.3	Up	ALL
T-ALL-R-LncRNA1	1.5 kb	6q24.3	Up	ALL
LUNAR1	16.3 kb	15q26.3	Up	ALL
LncRNA-BGL3	994bp	11p15.4	Up	CML
H19	2.3 kb	11p15.5	Up	CML
LincRNA-p21	3.1 kb	17p13	Down	CLL
DLEU1/DLEU2	ND	13q14.2/13q14.2-13q14.3	Down	CLL
TRERNA1	1.2 kb	20q13.13	Up	CLL

Note: ND: Not determined.

3.1. AML related LncRNAs

3.1.1. MEG3

A ~1.6 kb lncRNA, which maps to chromosome 14q32.2, is related to a variety of human tumors (Miyoshi et al., 2000). AS a tumor suppressor gene, MEG3 may directly or indirectly enhance the anti-cancer effect through p53 (Wang et al., 2012). Benetatos et al. (2010) evaluated the aberrant promoter methylation of MEG3 in 42 AML patients, and interestingly, MEG3 hypermethylation occurred in 47.6% AML patients. Thus they proposed a conclusion that MEG3 hypermethylation was associated with significantly reduced overall survival rate with AML patients (Benetatos et al., 2010). However, in their research, the methylation level didn't present significant correlation with the karyotype, disease sub-type and prognostic scoring systems (Benetatos et al., 2010). Lv et al. (2015) found the expression of lncRNA MEG3 in AML patients is generally lower than that in healthy individuals. Thus they further proved that the inhibition of AML cells proliferation, promote apoptosis and regulate of cell cycle through the over-expression of MEG3 *in vitro*. In their subsequent study, they found the effect of MEG3 on the growth of AML cells may be achieved by inhibiting the activity of DNMT3A (Lv, 2015).

3.1.2. RUNXOR

The RUNXOR, in a kind of lncRNAs with the total length of 216 kb, mainly locates in the nucleus (Wang, 2015). Its promoter located in 3.8 kb upstream of RUNX1 promoter, is about, and the transcription direction is consistent with RUNX1. Compared with control group, RUNXOR is up-regulated in bone marrow samples of AML patients. Moreover, the expression of RUNXOR was increased in leukemia cells (KG-1, KG-1α, K562, Kasumi-1) which exposed under Ara-C (cytosine arabinoside) treatment *in vitro* (Wang et al., 2012). RUNXOR combined with the promoter (proximal and distal) and enhancers of RUNX1 through its 3-terminal fragment and took its part in orchestration of an intra chromosomal looping process (Wang et al., 2012). Furthermore, Wang et al. (2012) found RUNXOR utilizes its 3-terminal fragment to interact with EVI1 in chromosome 3, ETO in chromosome 8 and the fragile region of RUNX1 in chromosome 21. The above process may be involved in the occurrence of chromosome *trans*-location by changing the chromosome spatial structure.