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REVIEW ARTICLE

The stem cell-specific long non-coding RNAs in leukemia

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Abstract

Leukemia is defined as a heterogeneous group of hematological cancers whose prevalence is on the rise worldwide. Despite the large body of studies, the etiology of leukemia has not been fully elucidated. Leukemia stem cells (LSCs) are a subpopulation of cancer cells that sustain the growth of the leukemic clone and are the main culprit for the maintenance of the neoplasm. In contrast to most leukemia cells, LSCs are resistant to chemo- and radiotherapy. Several recent studies demonstrated the altered expression profile of long non-coding RNAs (lncRNAs) in LSCs and shed light on the role of lncRNAs in the survival, proliferation, and differentiation of LSCs. LncRNAs are transcripts longer than 200 nucleotides that are implicated in several cellular and molecular processes such as gene expression, apoptosis, and carcinogenesis. Likewise, lncRNAs have shown a prognostic marker in leukemia patients and represent novel treatment options. Herein, we review the current knowledge concerning lncRNAs' implication in the pathogenesis of LSCs and discuss their prognostic, diagnostic, and therapeutic potential.

Keywords Long non-coding RNAs · Leukemia · Cancer · Biomarker

Introduction

Leukemia is a common malignancy caused by the neoplastic transformation in the hematopoietic stem cells (HSCs) and precursors cells in the bone marrow [1, 2]. In 2018, the incidence rate of leukemia has been estimated at about 437,000 and a total of 309,000 cases died due to this life-threatening disorder worldwide [3]. Based on the clinical course of the disease (acute or chronic), and the originator cell (myeloid or lymphoid), leukemia is classified into acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and a set of atypical leukemia types [4]. ALL is a leukemia type mostly diagnosed in children and young adults, while AML is frequently detected in adults [3]. However, the etiology of leukemia is not fully understood, studies confirm the role of environmental and genetic risk factors in the pathology of this malignancy [5]. There were various treatment options for different types of leukemia such as chemotherapy [6], radiation [7], monoclonal antibodies [8], or HSCs transplantation [9]. However, the appropriate treatment option for leukemia depends on the type of leukemia, the age of the patient, and the molecular and cytogenetic findings [10, 11]. Therefore, understanding the molecular

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pathways involved in the development and progression of leukemia leads to the appropriate approach for the effective treatment of leukemia [12–14]. One of the key players in the therapeutic failure and dysfunctional expression of the hematopoietic specific genes are leukemia stem cells (LSCs) [15]. Cancer stem cells were first identified in AML patients in 1997 and then extended to a wide range of tumors [16]. They possess stem cell properties including self-renewal, proliferation, and differentiation [17]. LSCs may originate from the malignant transformations of normal HSCs or their progenitor cells undergo mutations [18, 19]. LSCs can often be hidden from bone marrow treatments and interfere with chemotherapy or radiotherapy [20]. LSCs by targeting several signaling pathways, including Notch, Wnt, Hedgehog, and STAT3 play essential roles in the pathogenesis of leukemia [15, 21]. Several factors have been reported to contribute to the regulation of LSCs including their microenvironment, critical surface antigens, signaling pathways, and some molecules such as long non-coding RNAs (lncRNAs) [17, 22]. LncRNAs are a class of non-coding RNAs with lengths > 200 nucleotides that are suggested as key regulators of biological processes and are particularly involved in tumorigenesis [23–25]. Due to the contribution of some lncRNAs in leukemogenesis, researchers have suggested them as the diagnostic, prognostic, and therapeutic response biomarkers in leukemia patients. Therefore, the focus of this review is to summarize the current advanced related to the role of lncRNAs in leukemogenesis and describe how these lncRNAs influence the pathogenesis of LSCs and convey their clinical applications.

The potential roles of lncRNAs in LSCs development

Several lncRNAs have been shown with dysregulated expression levels, which functionally regulate the self-renewal, proliferation, and leukemogenesis of LSCs. Altered expression levels of lncRNAs are associated with the transformation of HSCs and progenitor cells into LSCs. Accordingly, targeting these lncRNAs has been suggested as a therapeutic approach for the treatment of hematological malignancies [26] (Fig. 1). These include HOTAIR, HOTTIP, LAMP5-AS1, LINC00152, MAGI2-AS3, HOXA10-AS, KIAA0125, Morrbid, and DANCR (Table 1).

HOTAIR

Gao et al. [27] found that the expression of the lncRNA HOTAIR is increased in LSCs compared to normal hematological stem and progenitor cells (HSPCs). Experimental investigations revealed that HOTAIR knockdown using specific short hairpin RNAs (shRNAs) suppressed self-renewal, proliferation, and colony formation in human leukemia U937 and Kasumi-1 cell lines and AML blasts, while HOTAIR overexpression showed inverse effects. Also, in vivo experiment using U937-transplanted NSG mice demonstrated that HOTAIR silencing inhibited the self-renewal of LSCs, delayed MLL-AF9-induced development of leukemia, and prolonged the overall survival in animal models. Besides, Wright's staining of peripheral blood showed decreased expansion of engrafted leukemic blasts. Mechanistically,

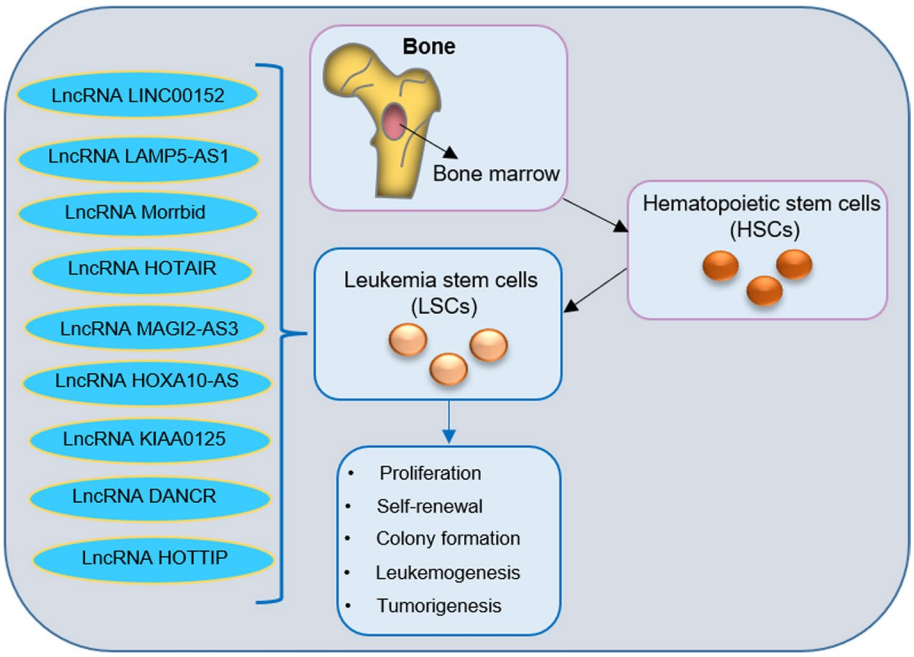

Fig. 1 Several lncRNAs, including HOTAIR, HOTTIP, LAMP5-AS1, LINC00152, MAGI2-AS3, HOXA10-AS, KIAA0125, Morrbid, and DANCR have critical roles in LSCs self-renewal, proliferation and tumorigenesis

Table 1 Functional roles of lncRNAs in leukemic stem cells

LncRNA	Cell line (in vitro)	Animal model (in vivo)	Patients-derived tissue	Si-lncRNA- targeted therapy	Cancer initiation (cell proliferation)	Cancer cell progression	Cancer cell metastasis	Cancer cell apoptosis	Chemoresistance	References
HOTAIR	Increase cell proliferation and colony formation	Lower survival	–	Improve survival in vivo	↑	–	–	–	–	[27]
HOTTIP	Increase AML cell proliferation, the self-renewal capacity, differentiation of HSCs, and development of AML-like disease	Lower survival	–	Improve survival in vivo	↑	–	–	–	–	[37]
LAMP5-AS1	Enhance colony formation, and self-renewal potential, and inhibit differentiation	Enhance leukemia cell infiltration, inhibit cell differentiation, and shorter survival	LAMP5-AS1 can act as a predictor of poor outcome in MLL leukemia	Suppress self-renewal potential of MLL leukemia cells, improve survival in vivo	↑	↑	↑	–	–	[29]
LINC00152	Enhance colony formation	–	High expression of LINC00152 was associated with worse prognosis in AML patients	Repress colony formation and chemoresistance of AML cells	↑	–	–	–	↑	[30]
DANCR	Enhance self-renewal potential	Decrease survival	Upregulation	Decrease LSCs frequency and self-renewal in vitro, and improve survival in vivo	–	–	–	–	–	[34]
MAGI2-AS3	Decrease self-renewal potential	Prolong survival	–	MAGI2-AS3 overexpression improve survival in vivo	–	–	–	–	–	[28]
HOXA10-AS	Promote leukemogenesis, perturbed monocytic differentiation	Enhance leukemic growth	Upregulation predictor of poor prognosis	Impair leukemic growth	↑	–	–	–	–	[35]
KIAA0125	Progression of HSCs and LSCs	–	A potential prognostic biomarker in AML patients	–	–	–	–	–	–	[38]
Morrbid	Progression of pre-LHSPCs	Enhance leukemic progression	A potential prognostic biomarker in AML patients	–	–	↑	–	–	–	[39]

HOTAIR was shown to exert its role in enhancing the self-renewal of LSCs via epigenetic silencing of tumor suppressor gene p15 through enrolling EZH2-mediated H3K27me3.

MAGI2-AS3

The role of lncRNA MAGI2 antisense RNA 3 (MAGI2-AS3) in regulating the oncogenic behaviors of LSCs was studied by Chen et al. [28]. This group isolated and identified LSCs from the bone marrow of AML patients using the $CD34^+$/$CD123^+$ immune profiling. Expression analysis using qRT-PCR demonstrated lower expression of MAGI2-AS3 in LSCs compared to normal human HSCs. Overexpression of MAGI2-AS3 inhibited the self-renewal capacity of LSCs. MAGI2-AS3 was shown to perform its role in restricting the self-renewal of LSCs through recruiting the Translocation-2 (TET2) to the promotor region of the leucine-rich repeats and Ig-like domains 1 (LRIG1) and upregulating its expression. In vivo study revealed that MAGI2-AS3 overexpression extended survival of NOD/SCID mice with AML.

LAMP5-AS1

To explore the functional relevance of LAMP5-AS1 in the progression of mixed-lineage leukemia (MLL) gene-originated leukemia (MLL leukemia) and leukemia cell stemness, Wang et al. conducted a series of cell and animal studies [29]. Their results revealed that LAMP5-AS1 knockdown caused a significant decrease in colony formation and self-renewal potential while enhancing differentiation of MOLM13, THP1, MV4-11, and RS4-11 MLL leukemia cells. Further investigations in MOLM13 cells-injected NOD/SCID mice to develop xenograft models illustrated that LAMP5-AS1 knockdown suppressed leukemia cell infiltration in several organs in addition to increased differentiation of leukemia cells. Besides, LAMP5-AS1-silenced mice had longer survival compared to the control group. LAMP5-AS1 was found to affect the self-renewal of MLL leukemia cells by binding and regulating the methyltransferase activity of the H3K79 methyltransferase DOT1L. This lncRNA can act as a predictor of poor outcomes in MLL leukemia. Overall, this study suggested that LAMP5-AS1 triggered the stemness and leukemogenesis of MLL leukemia [29].

LINC00152

Identifying high expression of LINC00152 in $CD34^+CD38^-$ cells, Cui et al. reported a substantial role of LINC00152 in leukemogenesis and self-renewal of LSCs derived from patients with AML [30]. LINC00152 upregulation was found in association with the expression of 16 genes of a total of 17 genes used in a LSC biomarker panel. LINC00152 knockdown significantly decreased colony formation and enhanced chemosensitivity of $CD34^+$ AML cells. Moreover, expression levels of LINC00152 were significantly associated with the poly ADP-ribose polymerase 1 (PARP1). PARP1 is already known to play an important role in DNA damage repair with high expression in cancer cells. PARP1 was found to enhance the effects of LINC00152 on doxorubicin-chemoresistance of K562 cells. Notably, overexpression of LINC00152 or PARP1 was correlated with poor prognosis in AML patients according to the data retrieved from the GEPIA database. Therefore, LINC00152 could accelerate LSCs chemoresistance [30].

DANCR

LncRNA differentiation antagonizing nonprotein coding RNA (DANCR) has been frequently reported with high expression in a variety of cancer tissues [31, 32]. DANCR was shown to promote the malignant features of cancer stem cells such as those in osteosarcoma and collectively suggested as an oncogenic lncRNA with therapeutic significance in human malignancies [32, 33]. Investigating the expression of lncRNAs in LSCs, Bill et al. evaluated the expression profile of lncRNAs in 375 patients younger than 60 years and 76 patinates older than 60. They found an association between the expression levels of a set of lncRNAs retrieved from two RNA-seq datasets among 451 AML patients and the LSCs-associated gene expression signature (GES) [34]. Their results demonstrated 111 lncRNAs with specific expression in LSCs. Among the highly expressed lncRNAs, DANCR was identified. Experimental analyses confirmed the upregulation of DANCR in cell populations enriched with LSCs. Besides, DANCR knockdown resulted in low expression of MYC oncogene, the frequency and self-renewal of LSCs. Furthermore, in vivo experiment using AML mouse models showed that mice with serial transplantation had improved survival compared to the control group. This study suggested that DANCR with a specific expression pattern in LSCs may have a prognostic and therapeutic significance in patients with leukemia [34].

HOXA10-AS

Al-Kershi et al. explored the oncogenic role of HOXA10-AS in KMT2A-rearranged AML [35]. HOXA10-AS showed highly and specific expression in HSCs, which was functionally essential for the survival of KMT2A-rearranged AMLs. HOXA10-AS overexpression promoted leukemogenesis, perturbed monocytic differentiation, and notably blocked differentiation of normal HSPCs with the NF-κB pathway, while its knockdown impaired leukemic growth in vivo. Therefore, this lncRNA as a prognostic factor can be a potent biomarker for the treatment of AML [36].

HOTTIP

Luo et al. displayed that overexpression of HOTTIP in AML was associated with leukemogenesis [37]. Upregulation of HOTTIP altered HOXA-driven topologically associated domain (TAD) and hematopoietic gene expression. Interestingly, HOTTIP knockdown suppressed leukemogenesis in AML xenograft mice models. Whereas, its expression restored oncogenic function in CTCF-boundary-attenuated AML cells and promoted self-renewal of HSCs. Therefore, HOTTIP enhanced the development of AML-like disease by altering the gene-associated chromatin signature in hematopoietic cells [37].

KIAA0125

Wang et al. demonstrated that the expression of KIAA0125 in AML-derived bone marrow cells patients was higher than in normal hematopoietic cells [38]. KIAA0125 expression was associated with clinicopathological features of AML patients. In situ analyses demonstrated that high expression of KIAA0125 was associated with HSCs and LSCs signatures, and ATP-binding cassette transporters [38].

Morrbid

Hypothesizing the high glucose exposure-driven chronic inflammation can improve the development of the $Tet2^{+/-}$ pre-leukemic hematopoietic stem and progenitor cells (pre-LHSPCs) phenotype and eventually AML/MPN, Cai et al. used $Tet2^{+/-}$ mice models to demonstrate development of the lethal form of MPN/AML in compound mutant mice [39]. It was shown that the proinflammatory pathways and high expression of Morrbid may play a pivotal role in the progression of pre-leukemic hematopoietic stem and progenitor cells (pre-LHSPCs) [39].

Clinical application of lncRNAs in leukemia

Since the discovery of high-tissue as well as disease-specificity characteristics of lncRNAs, such lncRNA can be regarded as the best possible candidates for the diagnosis and prognosis of cancer cells. Currently, identification of lncRNAs as biomarkers in body fluids including blood, plasma/serum or urine has gained much attention [40]. LncRNA can be obtained from apoptotic/necrotic cells or from living cells-derived exosomes [41, 42]. Exosomes are known as released membrane vesicles which is required for trafficking different molecules all through biological fluids, thereby being supposed to be screening markers and possible curative targets in leukemia [43, 44]. RNA sequencing, microarray, and qRT-PCR are current technologies which are applied to recognize and measure lncRNAs as biomarkers in biopsies. However, such insights need numerous fine-tuning to be utilized commonly in the clinic. Therefore, it is necessity for expansion of a rapid, standardized, and clinically appropriate tool which can translate the lncRNAs profiling from bench to bedsides [40, 45]. Microarray analysis showed that the expression profiles of lncRNAs in aged patients with normal cytogenetic-AML was correlated to the traditional mutations and phenotypes. It was found that deregulated lncRNAs were correlated with gene mutations and clinical outcomes [46]. Due to the heterogeneity in leukemia, it is so challenging to discover a strong biomarker in diverse leukemia subtype [47]. Currently, three-lncRNA expression-based risk score was expanded according to the RNA-seq data for patients suffering from AML using two leading data repositories, including Therapeutically Available Research to Generate Effective Treatments (TARGET) and The Cancer Genome Atlas (TCGA). Based on prognosis modelling that was expanded according to survival data, the lncRNA risk score in combination with cytogenetics risk group exerted a preferable prognostic value in comparison to any of the individual prognostic factor [47, 48]. The progression of novel molecular approaches such as CRISPR/Cas9 to correct the mutated genome predicted lncRNA applicability as a target to manage leukemia [49]. It is suggested that prior to their clinical applications of lncRNA as leukemia biomarkers, comprehensive prospective experiments should be done to investigate robustness of such technologies to test whether lncRNA score justified their accuracy and sensitivity as prognostic and diagnostic biomarkers.

Conclusion

LSCs possess the capacities for proliferation, differentiation, and self-renewal. Increasing evidence has confirmed that LSCs-targeted therapies could improve survival outcomes of leukemia patients. Among several regulators of LSCs function and properties, lncRNAs are potential agents that have attracted attention toward the development of LSCs-targeted therapies. Conventional anticancer strategies are not applicable to all patients for instance elderly subjects. Moreover, these patients are generally at risk of tumor metastasis, recurrence, and drug resistance. One reason is that these therapeutic strategies mainly target all tumor cell populations but leave LSCs behind. Notably, cancer stem cells by high expression of ATP-binding cassette (ABC) transporters are resistant to the attacks of chemotherapeutic agents. Since, the failure to eliminate LSCs leads to inefficient therapies, the development of LSC-selective treatment is critical for combating leukemia. Understanding the precise mechanisms by which lncRNAs and their signaling

pathways regulate LSCs may help to develop effective LSCs-based therapies for leukemia.

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Declarations

Conflict of interests The authors declare that there is no conflict of interests.

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