Abstract: Acute leukemia (AL) is the main type of cancer in children worldwide. Mortality by this disease is high in developing countries and its etiology remains unanswered. Evidences showing the role of the long non-coding RNAs (lncRNAs) in the pathophysiology of hematological malignancies have increased drastically in the last decade. In addition to the contribution of these lncRNAs in leukemogenesis, recent studies have suggested that lncRNAs could be used as biomarkers in the diagnosis, prognosis, and therapeutic response in leukemia patients. The focus of this review is to describe the functional classification, biogenesis, and the role of lncRNAs in leukemogenesis, to summarize the evidence about the lncRNAs which are playing a role in AL, and how these genes could be useful as potential therapeutic targets.

Keywords: long non-coding RNAs; cancer; acute leukemia; therapeutic targets

1. Introduction

Leukemia is a group of hematological malignancies characterized by an oligoclonal expansion of abnormally differentiated, and sometimes poorly differentiated hematopoietic cells which infiltrate the bone marrow, and could also invade the blood and other extramedullary tissues. In general, AL can be divided into acute or chronic, and lymphoid or myeloid, according to their progression and affected lineage, respectively. Thus, we can identify the following subtypes: acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML). AL is the main type of cancer in children worldwide [1,2]. In recent years, it has reported a trend of increase in the incidence AL; notwithstanding, the causes are still unclear. Studies conducted to identify the etiology of this disease have reported that a genetic background interacting with environmental factors (i.e., high doses of ionizing radiation, infections, parental occupational exposures, etc.) could explain this phenomenon [3]; however, the molecular mechanisms involved are not fully understood. To date, growing data have shown that different non-coding RNAs (ncRNAs) might be the link between the genome and the environment because they are closely related to normal physiological and pathological processes [4,5]. ncRNAs, also known
as non-protein-coding RNAs (npcRNAs), non-messenger RNAs (nmRNAs) or functional RNAs (fRNAs), are functional RNA molecules which are not translated into proteins [6]. These RNAs consist of several distinct families which include microRNAs (miRNAs), small nuclear RNAs (snRNAs), PIWI-interacting RNAs (piRNAs), and long non-coding RNAs (lncRNAs), among others. LncRNAs are one of the most studied ncRNA types, and play an important role as gene expression modulators at the epigenetic, transcriptional, and post-transcriptional level. In fact, it has been suggested that various miRNAs and lncRNAs could act as tumor suppressors genes or oncogenes, because they regulate directly or indirectly the expression of genes involved in molecular mechanisms as cell proliferation/differentiation, apoptosis, and metastasis [4,5]. In comparison with miRNAs, the lncRNAs are more numerous and represents the 41% of the overall ncRNAs. Over the last years, massive technological tools have been useful to increase the knowledge about lncRNAs that are abnormally expressed or mutated in AL and the list of relevant lncRNAs in leukemogenesis is growing rapidly. Moreover, it has reported a distinctive lncRNAs expression signature associated with AL prognosis, suggesting the potential application of these genes to make treatment decisions. Here, we review the most recent findings about lncRNAs in AL pathogenesis and their role as potential biomarkers. We also are pointing out the lncRNAs as promising druggable molecules in the development of new treatments for leukemia [7].

2. Genetic Features of Acute Leukemia

AL has been recognized as a highly genetically heterogeneous disease, where chromosomal abnormalities, either numerical (hyperdiploidy and hypodiploidy) or structural alterations (translocations, amplifications, DNA copy number alterations, insertions/deletions, and punctual mutations) are usually observed; thus, these alterations are the hallmarks of the leukemic cells and represent the major class of oncogenic drivers to the disease. Indeed, due to the fact many childhood ALL cases carry specific fusion genes (MLL gene fusions, ETV6/RUNX1, E2A/PBX1, etc.) and AML (AML1/ETO, PML/RARa, CBFβ/MYH11, etc.), this gives more evidence that childhood AL is initiated in utero during fetal hematopoiesis [8]. In addition to the numerical alterations and common targets of translocations in ALL, this disease is characterized by mutations in transcriptional factors (AML1, ETS, PAX5, IKZF1, EBF1, ETV6, and STAT), suppressor genes (TP53, RB1, CDKN2A/CDKN2B, etc.), oncogenes (ABL1, ABL2, CSF1R, JAK2, PDGFRB, and CRLF2), B lymphoid cell differentiators (IKZF1, TCF3, EBF1, PAX5, and VPREB1), chromatin remodelers, or epigenetic modifiers (DNMT3A, CREBBP, MLL2, NSD2, EP300, ARID1A, TET2, and CHD6) [9–12]. Data from the St. Jude/Washington Pediatric Cancer Genome Project (PCGP), that has characterized pediatric cancer genomes by whole-genome or whole-exome sequencing, revealed that the somatic mutation rate in childhood ALL ranges from $7.30 \times 10^{-8}$ per base [13]. In spite of the fact that chromosomal changes detectable by cytogenetic techniques are present in nearly 75% of the precursor B (pre-B) cell ALL cases, the gene expression profiling and genome-wide sequencing analyses have showed that B cell leukemogenesis is more complex [14]. Meanwhile, mutations in nRAS, RUNX1, FLT3, KIT, etc., abnormalities of DNA methylation, biogenesis of ribosomes, activated signaling pathways, myeloid transcription factors, chromatin remodeling, and cohesion complex processes are very common in AML [15].

The discovery of frequent mutations in epigenetic modifiers genes in AL show that epigenetic alterations also play a critical role in leukemogenesis. In this regard, it is known that most of the genes involved in epigenetic process do not code for proteins, and many of them are classified as lncRNAs, which regulate gene expression through different mechanisms.
3. LncRNAs Characteristics

LncRNAs comprise a highly functionally heterogeneous group of RNA molecules with sizes are greater than 200 nucleotides, and, as all the mRNAs usually have more than one exon, most of them are transcribed by RNA polymerase II (RNA pol II), are capped, may be polyadenylate, and can be located within the nucleus or cytoplasm. LncRNAs genes differ from mRNAs because lncRNAs lack protein-coding potential, are mostly expressed in low levels, and show poor species conservation compared to protein-coding genes (mRNAs). Additionally, lncRNAs display tissue-specific and development stage-specific expression showing their important role in cell differentiation mechanisms [16].

The number of lncRNAs is larger than the number of protein-coding RNAs. To date, the GENCODE project lncRNAs catalog consists of 15,779 transcripts (there are potentially more than 28,000 distinct transcripts) in the human genome (https://www.gencodegenes.org); nevertheless, this number could increase, since many primary long non-coding transcripts are often processed into smaller ncRNAs [17]. ncRNA detection led to a solution for the G-value paradox that states that there is no correlation between the amount of coding genes and the complexity of the organism, while we observe a correlation between the complexity of the organism and the ratio of the number of non-coding genes to total genomic DNA. Nowadays, cumulative evidence exhibits that lncRNAs are relevant players in many cellular processes either in physiological as well as pathological conditions. In cancer, the lncRNAs could have oncogenic function and tumor suppressive function since they have been found as upregulated or downregulated in several types of tumors in comparison to healthy tissues [18].

4. Biogenesis and Classification

It has hypothesized that most of lncRNAs are originated from (1) the incorporation of the fragments of original protein-coding genes; (2) juxtaposition of two transcribed and previously well-separated sequence regions of chromosomes giving rise a multi-exon ncRNA; (3) duplication of non-coding genes through retrotransposition; (4) tandem duplication events of neighboring repeats within a ncRNA; and (5) insertion of transcription factor, which is inserted into a sequence.

LncRNAs are transcribed and processed by the RNA pol II transcriptional machinery, thus many of them undergo post-transcriptional modifications such as 5’ capping, splicing, and polyadenylation. Nevertheless, there are also nonpolyadenylated lncRNAs that derive from RNA pol III promoters and snoRNA-related lncRNAs (sno-lncRNAs) expressed from introns via the snoRNP machinery (with the supplementary production of two snoRNAs). LncRNAs have been mapped into a wide range of regions, including coding and non-coding regions (intergenic regions, promoters, enhancers, and introns) [19–27].

To date, there is not a unique system to classify lncRNAs; however, different classifications have been proposed based on their size, genome localization, RNA mechanism of action, and function [28]. According to their location (Figure 1a), orientation (Figure 1b), and transcription direction (Figure 1c) relative to protein-coding genes, an lncRNA can be placed into one or more broad categories. Thus, lncRNAs can be intronic, when they lie into a intron of a second transcript (COLDAIR, located in the first intron of the flowering repressor locus C or FLC), intergenic (lincRNA) if it is located between two genes without any overlap at least 5 kb from both sides (exemplified by H19, XIST, and lincRNA-p21), exonic if lncRNA is encoded within a exon, or overlapping, which includes those lncRNA located within one or two genes [4,13,29,30]. Based on the orientation, lncRNAs can be transcribed from either the same strand or antisense in a divergent or convergent manner. LncRNAs can be also classified as enhancer-associated RNAs (eRNAs) and promoter-associated long RNAs (or PROMPTs) if they are produced from enhancer or promoter regions, respectively [31].
Figure 1. Positional classification of the long non-coding RNAs (lncRNA). Cartoon displays the lncRNA (red) classification base on (a) the location between two coding genes (intronic, exonic, intergenic, or overlapping), (b) the template strand (sense, antisense), and (c) transcription direction when coding genes and lncRNA are transcribed in the same strand (divergent, convergent). Gray arrow indicates in which direction transcription is proceed. Green and blue boxes represent exons of two different genes.

Although lncRNAs show a spatiotemporal expression pattern during proliferation, differentiation, and cell death; these genes are classified based on their function as guide, decoy, signaling, scaffold, or enhancer lncRNAs [32]. Guide lncRNAs interact with transcription factors or proteins and recruit them to their gene target or their genomic loci regulating downstream signaling events and gene expression. Decoy lncRNAs mimic and compete with their consensus DNA-binding motifs for binding nuclear receptors or transcriptional factors in the nucleus, facilitating gene activation or silencing. These genes can also “sponge” proteins such as chromatin modifiers, adding an extra level transcriptome regulation. Signaling lncRNAs are associated with signaling pathways to regulate transcription in response to various stimuli. Scaffold lncRNAs act as a central platform where many protein complexes tying and get directed to specific genomic loci or target gene promoter [17]. Enhancer lncRNAs are cis-encoded DNA elements that bind with mediator complex to regulate transcription genes located within their own chromosome (Table 1) [33]. However, this classification is too simple to cover the whole lncRNAome, cases such as pseudogenes and telomerase RNA (TERC) still lie outside the list [20,32].

Table 1. Classification of lncRNAs according to their function.

| Functional Type | Cellular Location                        | Mechanism of Action                                                                 | Examples       | Reference |
|-----------------|-----------------------------------------|--------------------------------------------------------------------------------------|----------------|-----------|
| Guide           | Nucleus                                 | Essential for the proper localization of proteins to their site-specific reaction.    | XIST, ANRIL    | [34]      |
| Decoys          | Plasma membrane, nucleus and cytosol     | Sequestering regulatory factors (transcription factors, catalytic proteins subunits, chromatin modifiers, etc.) to modulate transcription | GASS, MALAT1   | [35–37]   |
| Scaffold         | Nucleus                                 | Providing platforms for assembly of multiple-component complexes such as the polycomb repressive complexes and ribonucleoprotein complex. | CDKN2B-AS1, HOTAIR | [35,36]   |
| Signaling       | Nucleus                                 | Serving as a molecular signal to regulate transcription in response to various stimuli | TP53CORG1, PANDAR | [35,36]   |
| Enhancer        | Nucleus                                 | Binding with mediator complex to enhance transcription                              | HOTTIP, CCAT1-L, LUNAR1 | [25,33]   |
In terms of size, lincRNAs often range from hundreds of nucleotides to several kilobases [20]. Nevertheless, there are exceptionally long lncRNAs (macroRNAs) and very long intergenic non-coding RNAs (vlincRNAs), stretching 10 kb and 1 Mb, respectively [30].

In addition, lncRNAs have regulatory roles in gene expression at both, the transcriptional, and post-transcriptional levels in mostly biological mechanisms and pathophysiological processes. These molecules can regulate the expression of neighboring genes (cis) or affect genes located at different chromosomes (trans) [38]. In this way, lncRNAs can regulate gene expression via transcription factor and chromatin-modifiers complex recruitment to their DNA targets, acting as enhancers to activate genes, as part of the heterogeneous nuclear ribonucleoprotein (hnRNP) complex, interacting with RNA and DNA by base paring, etc. [38].

5. LncRNAs in Normal Hematopoiesis

Hematopoietic cell lineage differentiation involves the regulation of gene expression at different levels that can occur to activate lineage specific genes and repress those genes that are not specific to that lineage. This activation/suppression is mediated by transcription factors and chromatin remodeling that act as determinants of the intrinsic cell lineage. However, these factors are reactivated in different lines and stages of differentiation, so that the choice of the final lineage reflects the particular combination of elements interacting in a certain stage of cell differentiation [39]. LncRNAs are involved in regulating different steps in hematopoiesis, immune system development, and activation. In fact, several lncRNAs have been identified in the blood cells either in animal models or human samples. For example, over 1109 poliA+ lncRNAs were detected in murine megakaryocytes, erythroblast, and megakaryocyte-erythroid precursors, of which 15% are expressed in humans [40]. The Eosinophil Granule Ontogeny (EGO) was one of the first lncRNAs related with the human normal hematopoiesis process. EGO is nested within an intron of inositol triphosphate receptor type 1 (ITPR1) and was found to be highly expressed in human bone marrow and in mature eosinophils. Despite that the molecular mechanism of their actions is not well known, experimental evidences show that EGO is involved in the eosinophil differentiation of CD34+ hematopoietic progenitor cells by regulating eosinophil granule protein expression at the transcription level [41].

PU.1-As, which is antisense to the master hematopoietic transcriptional factor PU.1, negatively regulates the expression of PU.1, repressing myeloid cells and B cells differentiation [42]. Other examples include dendritic cell-specific lncRNA (Inc-DC), non-coding RNA repressor of NFAT (NRON), and lincRNA-Cox2. Inc-DC was identified from extensive profiling of lncRNAs expression during differentiation of monocytes into dendritic cells (DCs). Mechanistic studies suggest that Inc-DC contributes to prevent STAT3 (signal transducer and activator of transcription 3) dephosphorylation by Src homology region 2 domain-containing phosphatase-1 (SHP1) by directly binding to STAT in the cytoplasm [43]. NRON plays a relevant role in the adaptive immune response through sequestering transcription factors in the cytoplasm, such as the nuclear factor of activated T cells (NFAT). LincRNA-Cox2 contributes with the regulation of the innate immune response by repressing the expression of critical immune-response regulators and by the coordinating the assembly, location and orientation of the complexes that specify the cellular fate [39].

Studying twelve distinct blood cell population purified by multicolor flow cytometry, Schwarzer et al. [44] established a human ncRNA hematopoietic expression atlas per blood cell population, finding LINC00173, LINC000524, RP11-1029J19, and HOTAIR1M1 among the lncRNAs that characterize cells of the different human blood lineages. LINC00173 exhibited the most specific expression, with critical regulatory circuits involved in blood homeostasis and myeloid differentiation. In vitro models showed that suppression of LINC00173 in human CD34+ hematopoietic stem and progenitor cells (HSPCs) specifically affects granulocyte differentiation and decreases its phagocytic capacity (which is associated with perturbed maturation). Additional studies reported that LINC00173 is highly expressed in granulocytes [45]. H19, XIST, IncHSC-1, and IncHSC-2, which maintain long-term
hematopoietic stem cell (HSC) quiescence and self-renewal, have also been involved in normal hematopoiesis [46].

6. LncRNAs in Acute Leukemia

Although many studies have implicated lncRNAs in many cancer types, little is known about the functional impact of lncRNAs in AL etiology, progression, and treatment response [44]. Several lncRNAs have been reported to be exclusively involved in specific ALL lineages but few of these are abnormally expressed in ALL and AML [47,48]. For instance, CASC15, involved in cellular survival proliferation and the expression of SOX4 (cis regulation), was detected to be upregulated in t(12;21) (p13;q22) (ETV6/RUNX1) B cell ALL and in AML patients with the (8;21) translocation. In both cases, upregulation of CASC15 was associated with a good prognosis [48]. To date, a large number of lncRNAs have been identified in AL; however, their molecular mechanisms remains elusive. Table 2 includes some examples of lncRNAs which have been reported as implicated in acute leukemia in children [49–77].

Table 2. Examples of lncRNAs described in acute leukemia.

| LncRNAs | Classification | Function | Target Genes | Expression Level in Leukemia | Reference |
|---------|----------------|----------|--------------|-----------------------------|-----------|
| IRAIN   | Intronic       | Intrachromosomal interactions | IGF1R | Downregulated in leukemia cell lines and in patients with high risk AML | [49] |
| UCA1    | Intergenic     | Proliferation of AML cells, Oncofetal gene | CDKN1B | Upregulated | [50–52] |
| MEG3    | Intergenic     | Tumor suppressor gene | P53 | Downregulated | [52,53] |
| RINXOR  | Sense          | Chromosomal translocations | RUNX1 | Upregulated | [54] |
| NEAT1   | Intergenic     | Myeloid differentiation cells | Unknown in AML | Downregulated | [50,52,55] |
| LLEST   | Intergenic     | Tumor suppressor | BCL-2 | Downregulated or even not expressed. | |
| HOTAIRM1| Antisense      | Myeloid differentiation cells, autophagy mechanisms, chromatin remodeling and architecture | HOXA1, HOXA4, CD11b and CD18 | Upregulated | [52,56–60] |
| HOXA-AS2| Antisense      | Apoptotic repressor in NB4 promyelocytic leukemia cells | Unknown | Upregulated | [61] |
| PLU1-AS | Antisense      | Involved in the translation of PU.1 | PU.1 | Downregulated | [62] |
| WT1-AS  | Antisense      | WT1 expression | WT1 | | [63] |
| EGO     | Intronic       | MBP and EDN expression | | | [41] |
| BGL3    | Intergenic     | Apoptosis and DNA methylation | miR-17, miR-93, miR-20a, miR-20b, miR-106a and miR-106b | Upregulated | [50,52,64] |
| CCAT1   | Intergenic     | Monocytic cell differentiation | miR-155 | | [9,52,65] |
| CCDC26  | Intergenic     | AML cell proliferation | c-Kit | | [66] |
| HOTAIR  | Intergenic     | Apoptosis inhibitor | miR-193a and c-Kit | Upregulated | [67] |
Table 2. Cont.

| LncRNAs        | Classification | Function                                      | Target Genes | Expression Level in Leukemia | Reference |
|----------------|----------------|-----------------------------------------------|--------------|------------------------------|-----------|
| PVT1           | Intergenic     | Proliferation of promyelocytes                | MYC          | Upregulated                  | [52,68]   |
| ZNF571-AS1     | Antisense      | Regulator of JAK/STAT signaling pathway       | KIT and STAT5|                              | [69]      |
|                | Lymphoblastic Leukemia |                                      |              |                              |           |
| BALR-2         | Uncharacterized| Unknown                                       | Unknown      | Overexpressed in prednisone-resistant B-ALL patients | [70]      |
| BALR-1         | Unknown        | Unknown                                       | Unknown      | Upregulated                  | [70]      |
| BART-6         | Unknown        | Promotes cell survival and inhibits apoptosis | Unknown      | Upregulated                  | [70]      |
| LINC00958      | Intergenic     | Unknown                                       | Unknown      | Upregulated in t(12;21) preB cALL | [70,71]  |
| DBH-AS1        | Antisense      | Cell proliferation and cell survival          | Unknown      | Upregulated                  |           |
| RP11-137H2.4   | Uncharacterized| Apoptosis, proliferation, cell migration      | Unknown      | Upregulated. Glucocorticoids resistance | [72]      |
| ANRIL          | Antisense      | Cellular proliferation and apoptosis          | CDKN2A/B, CBX7, SUZ12 |                      | [52]      |
| T-ALL-R-LncR1  | Unknown        | Promotor of the formation of Par-4/THAP1 protein complex, and the activity of caspase-3 | Unknown      | Upregulated in children with T-ALL | [73]      |
| LUNAR1         | Enhancer-like  | Promotor of T-ALL proliferation by inducing IGF1R expression. | IGF1R        | Downregulated                | [50,52,74]|
| MALAT1         | Intergenic     | Alternative splicing and epigenetic modification | Unknown      | Upregulated Downregulated in vincristine-resistant ALL | [50,52,75-77]|
| CASC15         | Intergenic     | Cellular survival and proliferation           | SOX4         | Upregulated                  | [48]      |

7. LncRNAs in Acute Myeloid Leukemia

Regarding the association between lncRNA and hematopoietic cancer, AML has been the most investigated, and has been reported to be an important lncRNA in the biological and pathological processes of the disease. For example, insulin-like growth factor I receptor antisense imprinted non-protein RNA (IRAIN), which is transcribed antisense to insulin-like growth factor type I receptor (IGF1R) gene, is downregulated in leukemia cell lines and in patients with high-risk AML. IRAIN is involved in the formation of a long-range intrachromosomal interaction between the IGF1R promoter and a distant intragenic enhancer [49]. ZNF571-AS1 is another lncRNA that has been suggested as a relevant player in AML. Based on co-expression correlation analysis across all AML samples with lncRNA–lncRNA pairs, this lncRNA was identified as potential regulator of the Janus Kinase (JAK)/signal transducer and activator of transcription (STAT) 5A and tyrosine-protein kinase Kit (KIT) expression. Thus their participation in AML was suggested via the JAK/STAT signaling pathway [69]. As well, Urothelial carcinoma-associated 1 (UCA1), an oncofetal gene that has been involved in embryonic development and carcinogenesis, was found to be upregulated in myeloid cell lines promoting cell viability, migration, invasion, and apoptosis processes [78–80]. A significant upregulation of UCA1 expression in AML with CEBPA (a crucial component during myeloid differentiation) mutations and its relation with chemoresistance in pediatric AML was documented [51,81]. The maternally expressed 3 non-protein-coding gene (MEG3), a tumor suppressor,
has also been associated with significantly reduced overall survival rate in AML patients. This gene is related to a variety of human tumors and data point out that directly enhance the anticancer effect through p53 [82,83]. Benetatos et al. [53] evaluated the aberrant promoter methylation of \( \text{MEG3} \) in 42 AML patients, and found that \( \text{MEG3} \) hypermethylation was present in 47.6% AML cases and might be associated with significantly reduced overall survival rate in these patients [53]. LncRNAs have also been profiled from AML patients cytogenetically normal (CN) and with specific translocation. For example, AML patients carrying \( \text{NPM1}, \text{CEBP A}, \text{IDH2}, \text{ASXL1}, \) and \( \text{RUNX1} \) mutations and internal tandem duplication mutations in \( \text{FLT3} \) (FLT3/ITD) gene exhibited specific lncRNA expression signature. As well, Diaz-Beya et al. [84], studying AML cases with t(15;17), t(8;21), inv(16), t(6;9), t(3;3), t(9;11), t(8;16), FLT3/ITD, and monosomal karyotype, found a specific lncRNA profile in t(15;17), t(6,9), and t(8;16) positive cases. That study also revealed a correlation between t(8;16) and \text{linc-HOXA11, HOXA11-AS, HOTTIP,} and NR_038120 expression, and suggested that GAT2 is an important transcription factor to these lncRNAs. Otherwise, lncRNAs expression correlated with treatment response and survival. One of the lncRNAs that is specifically upregulated in CN-AML cases with \( \text{CEBP A} \) mutation is the lncRNA \( \text{UCA1} \) [85]. Taurine-upregulated gene 1 (\( \text{TUG1} \)) expression was reported to be associated with higher white blood cell counts, monosomal karyotype, FLT3/ITD mutation, and worse prognosis in AML adults. In vitro studies in AML cells indicates that \( \text{TUG1} \) induces cell proliferation but suppressing cell apoptosis via targeting \( \text{AURKA} \) [86].

Schwarzer et al. [44] made a high-density reconstruction of the human coding and non-coding hematopoietic landscape to identify an ncRNA fingerprint associated with lineage specification, HSPC maintenance, and cellular differentiation. They define a core ncRNA stem cell signature in normal HSCs and AML blast, which can serve as a prognostic marker in a different cohort of AML patients and may pave the way for novel therapeutic interventions targeting the non-coding transcriptome [44].

8. LncRNAs in Acute Lymphoblastic Leukemia

Data regarding lncRNA playing a role in ALL are still scarce. One of the first clinicopathological correlations with lncRNA expression data in ALL was performed by Fernando et al. [70] who studied 160 children with B-ALL observing that \( \text{BALR-2} \) correlates with overall survival and with response to prednisone. These authors also demonstrated a putative mechanism in regulating cell survival in B-ALL that it is downregulated by glucocorticoid receptor engagement, and that its downregulation results in the activation of the glucocorticoid receptor signaling pathway [70]. Loie et al. [71] also reports that lncRNA expression patterns can classify ALL disease by subtypes as well as protein-coding genes. In addition to lncRNA, \( \text{BARL-2} \), which is also correlated with resistance to prednisone treatment, these authors found that lncRNAs \( \text{BALR-1, BRL-6, and LINC0098} \) were overexpressed in pre-B ALL cases and that all of these genes correlated with cytogenetic abnormalities, disease subtypes, and survivals of B-ALL patients [71]. In that study, they also observed that diverse coding genes adjacent to several of those lncRNAs showed unique overexpression profile in \( \text{ETV6/RUNX1} \) positive BCP-ALLS suggesting a possible \textit{cis} regulatory relationship. Furthermore, Ghazavi et al. [47] identified an \( \text{ETV6/RUNX1} \)-specific lncRNA signature in a 64 children cohort and in 13 BCP-ALL cell lines. Five-hundred-and-ninety-six lncRNA transcripts (434 up- and 162 downregulated) showed significant differential expression between \( \text{ETV6/RUNX1}-\text{positive BCP-ALL} \) and other genetic BCP-ALL subclasses. However, 16 lncRNAs, of which 14 were upregulated and two were found downregulated, overlapped with the \( \text{ETV6/RUNX1} \)-specific lncRNA signature, including \( \text{NKX2-3-1, lncRTN4R-1, lncGIP-1, lnc-LRP8-3, lnc-TCF12-2, lncC8orf4-1, lnc-C8orf4-2, lnc-TINAGL1-1, lnc-LSM11-4, and lnc-SARDH-1} \) (also known as \( \text{DBH-AS1} \)). \( \text{Lnc-SARDH-1} \) is known to possess an oncogenic role promoting cell proliferation and cell survival through activation of MAPK signaling in the context of hepatocellular carcinoma [87]. Furthermore, the H3K27ac epigenetic mark (associated to enhancers) was found in nine loci of the rest of the lncRNAs and their adjacent coding genes, which, in addition to the finding of a unique expression signature of these coding genes in \( \text{ETV6/RUNX1} \) pre-B ALL, suggests a \textit{cis} interaction between the lncRNAs and their neighboring coding genes [47]. In another
study, Ouimet et al. performed a whole transcriptome analysis in a 56 pre-B ALL children cohort finding five lncRNAs specifically overexpressed in pre-B ALL. These genes may have impact in cancer traits such as cell proliferation, migration, apoptosis and treatment response. Specifically, lncRNA RP11-137H2.4 had a considerable impact on apoptosis, proliferation, and cell migration and its silencing is sufficient to restore a NR3C1-independent cellular response to glucocorticoid (GC) in GC-resistant pre-B ALL cells, leading to GC-induced apoptosis [72]. Further to this study, Gioia et al. functionally characterized three lncRNAs—RP-11-624C23.1, RP11-203E8, and RP11-446E9—specifically repressed in pre-B ALL, restoring their expression in a pre-B ALL cell line. All the lncRNAs promoted tumor suppressor-like phenotypes: apoptosis induction in response to DNA damaging agents and a reduction in cell proliferation and migration [88]. Additionally, Garitano-Trojaola et al., while analyzing ALL samples and peripheral blood samples obtained from healthy donors, found 43 lncRNAs abnormally expressed in ALL. Linc-PINT was downregulated both in T- and B-ALL cases [89]. Studies in T-ALL cells found a significant difference in expression of LUNAR1 and lnc-FAM120AOS-1 between NOTCH1 wild type and mutant cases [68]. The use of bioinformatics tools identified that lnc-OAZ3-2:7—located near the RORC gene—was repressed in this leukemia subtype [90]. These studies suggest that lncRNAs might be utilized as diagnostic and prognostic markers in leukemia, but additional analyses are needed.

9. Future Outlooks: Potential Clinical Implications on LncRNAs in Acute Leukemia

It is suggested that more than 97% of the transcribed genome does not encode for proteins. The discovery of the biological role of these non-coding genes took place in 1990, when XIST was reported to be involved in X chromosome inactivation (XCI) and gene dosage compensation. Subsequently, HOTAIR was identified as a repressor of HOX family gene transcription [91]. Most recently, high-throughput expression analyses have been conducted to identify thousands of expressed lncRNA genes either in normal or tumor tissues, showing the potential of lncRNAs as biomarkers for different types of cancer [37,44,52].

Deciphering the molecular mechanisms involved in hematological malignancies addresses new routes to improve diagnosis, prognosis, and treatment of patients with leukemia. In fact, abnormal expression of specific lncRNAs have been reported to be associated with some clinicopathological parameters and molecular subtypes in AL. As example, BALR-1 and LINC0098 have been identified as correlating with poor overall survival and diminished response to prednisone treatment in B cell ALL cases [70,71]. Regarding AML, HOTAIR, IRAIN, and SNHG5 have been suggested as biomarkers for diagnosis [92]; meanwhile, UCA1 overexpression was associated with chemoresistance of pediatric cases [81]. SNHG5 upregulation, which was detected in bone marrow and plasma, was correlated with unfavorable cytogenetics and shorter overall patient survival and was suggested as an independent factor to predict prognosis in AML [93].

Notwithstanding, few of these genes have been replicated across cohorts, probably evidencing biases due to different sample collection and processing techniques, but also as a consequence of AL biological complexity, which is characterized by a wide range of interactions among coding and non-coding genome and spatiotemporal relationships. HOTAIR, a proliferation promotor of leukemic blast and leukemia stem cells [94], is one of the most consistently found in AL. A high-expression level defines a subgroup of AL patients with high white blood cell counts at the time of diagnosis and low survival rates [95,96]. Recently, HOTAIR high-expression was associated with acquired resistance to antileukemic drugs such as doxorubicin and imatinib [97,98], making this gene as a potential therapeutic target molecule that could contribute to solve a tremendous problem in leukemia chemotherapy, the drug-resistance. On the other hand, experimental data suggest that HOTAIR low-expression could be mediated by small interference RNA (siRNA), but still no evidences exist regarding its potential benefit in humans [98]. The development of new molecular strategies as CRISPR/Cas9 to edit the mutated genome or nanotechnology approaches to deliver drugs specifically to leukemia cells prognosticate high applicability of lncRNA as a target to develop new treatments to leukemia [99,100]. Additionally, the high specificity and feasible detection in tissues, serum, plasma,
urine, and saliva of the lncRNAs led us to think that lncRNAs could be useful as signals of specific cellular states or read-outs of active cellular pathologies such as leukemia, being promising as predictive biomarkers and potential therapeutic targets in cancer [19].

There is no doubt of the role of lncRNAs in hematopoietic cell transformation, disease evolution, or drug resistance; nevertheless, due to the limited number of studies in hematological entities, these applications are still inconclusive. In fact, before their use as biomarkers in childhood AL, prospective and well-designed cohort studies with adequate sample sizes and further validation of the results in independent cohorts are needed to confirm their clinical usefulness. Therefore, translating this knowledge into the clinical practice still represents a big challenge.

10. Conclusions

At this time, we know that lncRNAs are playing a relevant role in cancer development, including leukemia. However, regarding molecular mechanisms underlying the pathogenesis of these diseases remains limited. Massive parallel analysis techniques and, likewise, transcriptome expression analysis and RNA sequencing technologies are increasing the possibility to identify those lncRNAs potentially involved in the pathogenesis of AL and other hematopoietic malignancies. To date, large improvements of the surveillance of AL cases have been achieved; nevertheless, cases still die during the AL treatment. Thus, it is necessary to find suitable biomarkers for early diagnosis and accurate risk stratification in AL patients. The association of lncRNAs with several subtypes of leukemia, such as MEG3, IRAIN, and UCA1 related to AML and ANRIL, LUNAR1, in ALL, increase the possibility to use them as biomarkers for the diagnosis, prognosis, and treatment (to provide a target) for the different subtypes of this disease. In addition, further investigation of the function of aberrant expressed lncRNAs may help to understand the pathogenesis of hematological malignancies and provide an important insight in childhood leukemia therapy.

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Abbreviations

1. ABL1 2. ABL protooncogene 1
3. ABL2 4. ABL protooncogene 2
5. AL 6. Acute leukemia
7. ALL 8. Acute lymphoblastic leukemia
9. AML 10. Acute myeloblastic leukemia
11. ANRIL 12. Antisense non-coding RNA in the INK4-ARF locus B-ALL B cell Acute lymphoblastic leukemia
13. ARID1A 14. AT-rich interaction domain 1A
15. AURKA 16. Aurora kinase A gene
17. BALR 18. B-ALL-associated long non-coding RNAs BL Burkitt Lymphoma
19. CAS9 20. CRISPR associated protein 9
21. CBF 22. Core-binding factor subunit beta
23. CCAT1 24. Colon cancer associated transcript 1 ceRNA Competing endogenous RNA
25. CDKN2A 26. Cyclin dependent kinase inhibitor 2A
|   |   |   |
|---|---|---|
| 27. | CDKN2B | Cyclin dependent kinase inhibitor 2B |
| 28. | CDKN2B-AS1 | CDKN2B antisense RNA 1 |
| 29. | CEBPA | CCAAT enhancer binding protein alpha |
| 30. | CHD6 | Chromodomain helicase DNA binding protein 6 |
| 31. | circRNA | Circular RNA |
| 32. | CLL | Chronic lymphocytic leukemia |
| 33. | CML | Chronic myeloblastic leukemia |
| 34. | CN | Cytogenetically normal |
| 35. | COLDAIR | COLD assisted intronic non-coding RNA |
| 36. | CREBBP | CREB binding protein |
| 37. | CRISPR | Clustered regularly interspaced short palindromic repeats |
| 38. | CRLF2 | Cytokine receptor like factor 2 |
| 39. | CSF1R | Colony stimulating factor 1 receptor |
| 40. | DCs | Dendritic Cells |
| 41. | DNMT3A | DNA methyltransferase 3α |
| 42. | EBF1 | Early B cell factor 1 |
| 43. | EGO | Eosinophil granule ontology |
| 44. | EP300 | E1A binding protein P300 |
| 45. | eRNAs | Enhancer RNAs |
| 46. | ETS1 | ETS proto-oncogene 1 transcription factor |
| 47. | ETV6 | ETS Variant6 |
| 48. | FLC | Flowering repressor locus |
| 49. | FLT3 | Fms related tyrosine kinase 3 |
| 50. | fRNAs | Functional RNAs |
| 51. | GAS5 | Growth specific 5 |
| 52. | GEO | Gene expression omnibus |
| 53. | H19 | Imprinted maternally expressed transcript |
| 54. | hnRNP | Heterogenous nuclear ribonucleoprotein |
| 55. | HOTAIR | The HOX transcript antisense intergenic RNA |
| 56. | HOTTIP | HOXA distal transcript antisense RNA |
| 57. | IKZF1 | IKAROS family zinc finger 1 |
| 58. | IKN1 | IGFR1 antisense non-coding RNA |
| 59. | ITPR1 | Inositol-1,4,5-trisphosphate receptor type 1 |
| 60. | JAK2 | Janus kinase 2 |
| 61. | KIT | Tyrosine protein kinase |
| 62. | LincRNA | Long intergenic non-coding RNA |
| 63. | LCNRNA | Long non-coding RNA |
| 64. | Inc-DC | Dendritic cell-specific IncRNA |
| 65. | linRNA-p21 | Large intergenic non-coding RNA p21 |
| 66. | IncRNA | Long non-coding RNA |
| 67. | LUNAR1 | Leukemia-associated non-coding IGF1R |
| 68. | MALAT1 | Metastasis associated lung adenocarcinoma transcript 1 MCL Mantle cell lymphoma |
| 69. | MEG3 | Maternally expressed 3 |
| 70. | miRNA | MicroRNA |
| 71. | mRNA | Messenger RNA |
| 72. | NCBI | National center of biotechnology information |
| 73. | ncRNA | Non-coding RNA |
| 74. | NFAT | Nuclear factor activated T cells |
| 75. | Non mRNA | Non messengers RNA |
| 76. | NPCRNA | Non protein-coding RNA |
| 77. | NRAS | NRAS proto-oncogene |
| 78. | NRON | Non-protein-coding RNA Repressor of NFAT |
133. NSD2 134. Nuclear receptor binding SET domain protein 2
135. PANDAR 136. Promoter of CDKN1A antisense DNA damage activated RNA
137. PAX5 138. Paired box 5
139. PBX1 140. PBX Homeobox 1
141. PCGP 142. Pediatric cancer genome project
143. PDGFRB 144. Platelet derived growth factor receptor beta
145. piRNAs 146. PIWI-interacting RNAs
147. PML 148. Promyelocytic Leukemia gene
149. PROMPTs 150. Promoter-associated long RNAs
151. RB1 152. RB transcriptional corepressor 1
153. RBPs 154. RNA-binding proteins
155. RUNX1 156. Runt related transcription factor 1
156. siRNA 157. Small interference RNA
157. STAT3 158. Signal transducer and activator of transcription 3
158. SHP1 159. Scr homology region 2 domain containing phosphatase-1
160. snRNAs 161. Small nuclear RNA
161. snRNAs 162. Small nuclear RNA
162. snoRNAs 163. Small nucleolar RNA
163. STAT3 164. Signal transducer and activator of transcription 3
164. TCF3 165. Transcription Factor 3C
165. TERC 166. Telomerase RNA component
166. TET2 167. Tet methylcytosine dioxygenase 2
167. TLR 168. Tool-like receptor
168. TP53 169. Tumor protein P53
169. TP53COR1 170. Tumor protein P53 pathway corepressor 1
170. TUG1 171. Taurine-up regulated gene 1
171. UCA1 172. Urothelial carcinoma associated 1
172. vlincRNA 173. Very long intergenic RNA
173. XIST 174. X inactive specific transcript

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