LncRNAs in ALL Classification, Pathogenesis and Treatment

Subjects: Hematology
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The coding regions account for only a small part of the human genome, and the remaining vast majority of the regions generate large amounts of non-coding RNAs. Although non-coding RNAs do not code for any protein, they are suggested to work as either tumor suppressers or oncogenes through modulating the expression of genes and functions of proteins at transcriptional, posttranscriptional and post-translational levels. Acute Lymphoblastic Leukemia (ALL) originates from malignant transformed B/T-precursor-stage lymphoid progenitors in the bone marrow (BM). The pathogenesis of ALL is closely associated with aberrant genetic alterations that block lymphoid differentiation and drive abnormal cell proliferation as well as survival. While treatment of pediatric ALL represents a major success story in chemotherapy-based elimination of a malignancy, adult ALL remains a devastating disease with relatively poor prognosis. Thus, novel aspects in the pathogenesis and progression of ALL, especially in the adult population, need to be further explored. Accumulating evidence indicated that genetic changes alone are rarely sufficient for development of ALL. Recent advances in cytogenic and sequencing technologies revealed epigenetic alterations including that of non-coding RNAs as cooperating events in ALL etiology and progression, which might provide new options for managing the disease in the future.

acute lymphoblastic leukemia ALL long non-coding RNA lncRNA circular RNA

1. LncRNAs in ALL Classification and Diagnosis

According to a study by Melo et al., the lncRNA expression profile showed significant alterations between different leukemia types and different subtypes of the same leukemia including ALL[1]. Another study found T-ALL subtype-specific lncRNA expression profiles, suggesting the involvement of lncRNAs as cooperators or downstream effectors during the corresponding oncogene-mediated leukemogenesis[2]. Alterations in chromatin and DNA modification also affect lncRNA expression profiles. It is reported that lncRNAs methylation per base pair shows a distinct profile between ALL and normal B-cell lymphoid precursors as well as among three sub clusters of ALL cases[3]. In human B-ALL samples, it was found that the lncRNA expression profile also correlates with cytogenetic abnormalities[4]. Likewise, many other studies also revealed subtype-specific and/or relapse-specific lncRNA signatures in ALL patent samples[5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20]. These studies suggest that lncRNAs are associated with the pathogenesis of ALL and might be used as molecular markers for disease classification and diagnosis.

2. LncRNAs as Cooperating Events of Genetic Abnormalities in T-ALL Pathogenesis

T-ALL patients have a worse prognosis than those with B-ALL probably due to the less-known and more complex mechanism on its etiology, maintenance, and progression[21][22], suggesting the importance of exploring novel aspects in the pathogenesis and progression of T-ALL. Zhang et al. found that a lncRNA named T-ALL-related long non-coding RNA (T-ALL-R-LncR1) is markedly expressed in T-ALL Jurkat cells and 50% of T-ALL patient primary cells[23]. Importantly, knockdown of T-ALL-R-LncR1 led to apoptosis in Jurkat cells[23]. This finding suggests that the lncRNA T-ALL-R-LncR1 confers resistance to apoptosis, playing an oncogenic role in T-ALL development. It is well demonstrated that T cell acute lymphocytic leukemia protein 1 (TAL1, also known as SCL) is one of the most prevalent oncogenic transcription factors in T-ALL[24][25]. Generally, TAL1 coordinates with other transcription factors including GATA3, RUNX1, and MYB to regulate the expression of their downstream target genes in T-ALL cells[26]. Interestingly, TAL1 reportedly activated a subset of lncRNAs, some of which are regulated by GATA3,RUNX1, and MYB in a coordinated manner[19]; another subset of lncRNAs negatively regulated by TAL1 were also identified. Notably, the transcription factors T-cell leukemia homeobox 1 (TLX1) and TLX3 are key drivers of the TLX1/NKX2.1 and TLX subgroups of T-ALL, respectively[24][27]. A study showed that TLX1 directly regulates a set of lncRNAs, some of which are marked by super-enhancers[20], indicating the involvement of lncRNAs in TLX1-induced gene expression regulation. Intriguingly, some lncRNAs give rise to other ncRNA types following further processing. It was reported that TLX3 binds and transactivates lncRNA LINC00478, which is the host of miR125-b, to regulate miR-125b production, through which supports growth and invasiveness of T-ALL cells[28]. Collectively, these findings suggest that lncRNAs are crucial downstream effectors of major genetic abnormalities in the pathogenesis of T-ALL.

T-ALL is driven by oncogenic transcription factors (e.g., LTX1, LTX3 or HOXA, and TAL/LMO) that act along with secondary acquired mutations[24][25]. For instance, NOTCH1 activating mutations are identified in more than 50% of T-ALL cases, suggesting a key role in driving the disease[29]. A study by Durinck et al. established a novel lncRNA network that acts downstream of NOTCH1 during normal and malignant thymocyte development[30], specifically, they identified 40 lncRNAs that are positively regulated by NOTCH1 in both normal and malignant T lymphocytes, supporting an important role for these lncRNAs as downstream effectors in NOTCH1-regulated T-cell biology. Another study also uncovered a set of T-ALL-specific lncRNAs, many of which are directly regulated by the NOTCH1/RPBJκ activator complex[5]; the authors showed that one specific NOTCH-regulated lncRNA, LUNAR1, is required for efficient T-ALL growth in vitro and in vivo due to its ability to enhance insulin-like growth factor 1 (IGF1) receptor (IGF1R) mRNA level and sustain IGF1 signaling. Likewise, a lncRNA named NALT, which is located only 100 bp away from NOTCH1 gene, was upregulated in human NOTCH1-activated T-ALL samples[31]; increased expression of NALT dramatically promoted cell proliferation, while knockdown of NALT caused the opposite effect; mechanistically, nuclear located NALT functioned as a transcription activator causing activation of the NOTCH1 signaling pathway.

3. LncRNAs as Cooperating Events of Genetic Abnormalities in B-ALL Pathogenesis

Fusion genes produced by chromosomal translocations are often strong oncogenic drivers and cytogenetic abnormalities in hematological malignancies such as acute myeloid leukemia (AML) or lymphoma[32][33]. Similarly, fusion oncogenes represent a prominent class of oncogenic drivers in ALL as well[21][34][35]. ETV6-RUNX1 generated by t(12;21) is the most common oncogenic fusion gene in childhood B-ALL[36]. A comprehensive analysis of the lncRNA transcriptome in ETV6-RUNX1$^+$ B-ALL revealed the fusion protein-specific lncRNA expression signature[37]. Further analysis showed that expression of lncRNAs NKX2-3-1, TIMM21-5, ASTN1-1, and RTN4R-1 are linked to the oncogenic fusion protein. Knockdown of NKX2-3-1 and RTN4R-1 in ETV6-RUNX1$^+$ cells reversed the expression of genes deregulated by the ETV6-RUNX1 fusion protein[37]. Likewise, lncRNA CASC15 is overexpressed in ETV6-RUNX1$^+$ B-ALL, and shows increased expression of its chromosomally adjacent gene, SOX4, which encodes a transcriptional activator in lymphocytes, thereby upregulating cell survival, and proliferation[38]. An oncogenic lncRNA TCL6 was also upregulated in the ETV6-RUNX1$^+$ B-ALL and probably associates with poor disease-free survival[9]. Collectively, these findings suggest the involvement of lncRNAs in fusion oncogene-mediated pathogenesis and progression of ALL.

Fusion of the mixed lineage leukemia (MLL) gene with other partner genes are common in pediatric leukemias, and MLL-rearranged B-ALL has long been considered a refractory disease due to the poor prognosis of associated patients[39]. A genome-wide lncRNA expression study found 52 upregulated and 59 downregulated lncRNAs between MLL-rearranged and MLL-unarranged ALL patient samples[40]; bioinformatics analysis showed that several lncRNAs correspond to the expression of the MLL fusion protein partner genes, such as HOXA and MEIS1 among others, and some other lncRNAs are associated with histone-related functions or membrane proteins; further, three subtypes of MLL rearranged ALL (MLL-AF4$^+$, MLL-AF9$^+$, and MLL-ENL$^+$) showed a translocation specific lncNRA expression signature[40]. Another study reported that lncRNA BALR-6 is highly expressed in MLL-rearranged patient samples[41]; knockdown of BALR-6 reduced cell proliferation and induced apoptosis, while overexpression of BALR-6 caused a significant increase in early hematopoietic progenitor populations in murine BM transplantation experiments, suggesting that its dysregulation may cause developmental changes.

4. LncRNAs and Immune Response Modulation in ALL Pathogenesis and Treatment

The immune suppressive tumor microenvironment is proven essential in the pathogenesis of many cancer types[42][43][44]. LncRNAs NONHSAT027612.2 and NONHSAT134556.2 were significantly elevated in the blood and bone marrow (BM) of pediatric ALL patients, and may serve important roles in the pathogenesis of childhood ALL via suppressing immune response-associated pathways[11]. Besides, in the BM of patients with childhood T-ALL, membrane-localized and cytoplasm-localized lncRNA insulin receptor precursor (INSR) promoted CD4$^+$ regulatory T-cell distribution and decreased the percentage of CD8$^+$ cytotoxic T-cells in the BM of pediatric T-ALL patients, facilitating leukemic cell growth via immune suppression[45]. Mechanistically, through direct binding with INSR protein, lncRNA-INSR blocked the INSR ubiquitination site, causing abnormal accumulation and activation of INSR

and the PI3K/AKT-signaling pathway. LncRNAs are also implicated in CART therapy of B-ALL[46]; specifically, a set of lncRNAs showed high degree of co-expression with transcription factors or histones (i.e., FOS and HIST1H4B) and were associated with immune processes during CAR-T therapy of B-ALL. These findings suggest that lncRNAs are important players in the immune response regulation in ALL pathogenesis and treatment.

5. LncRNAs in Susceptibility, Treatment Response and Prognosis of ALL

Single nucleotide polymorphism (SNP) is common in the human genome, and has profound implications in the pathogenesis/susceptibility of varying diseases. It was reported that the rs2147578 polymorphism of lncRNA LAMC2-1 may be a risk factor for developing childhood ALL, suggesting that SNPs might confer oncogenic properties on lncRNAs[47]. LncRNA PAX8-AS1 is located in the upstream region of PAX8, a gene encodes the transcription factor PAX8 required for cell growth and differentiation during embryonic development, and potentially regulates PAX8 expression[48]. Similarly, Bahari et al. reported that polymorphisms rs4848320 and rs6726151 of PAX8-AS1 might be risk factors for the development of childhood ALL[49]. Also, rs7158663 AG/AA genotypes of lncRNA MEG3 were associated with higher susceptibility to childhood ALL[50]. These findings indicate that some SNPs on lncRNAs are indicative of higher susceptibility for developing ALL.

Fernando et al. reported a correlation of high lncRNA BALR-2 expression with the diminished response to prednisone treatment and poor survival in patients[4]. BALR-2 knockdown led to reduced proliferation, increased apoptosis, as well as augmented sensitivity to prednisone treatment via activation of the glucocorticoid (GC) response pathway in both human and mouse B cells[4]. Another study reported that five lncRNAs are specifically upregulated in childhood B-ALL, and these lncRNAs had significant impacts on cell proliferation, migration, apoptosis, and treatment response[51]. In particular, expression of lncRNA RP11-137H2.4 was negatively associated with GC response[51]. Similarly, lncRNA GAS5 was also found to be a potential marker of GC response in remission induction therapy of childhood ALL[52]. A high expression of the lncRNA CDKN2B-AS1 level was associated with Adriamycin resistance[53]. Gioia et al. reported that LncRNAs RP11-624C23.1 and RP11-203E8 were downregulated in ALL, and restoring their expression in ALL cells' increased sensitivity to genotoxic stress (e.g., chemotherapy agents), possibly by modulating the DNA damage response pathway[54]. These studies suggest that lncRNAs are important indicators of treatment response in ALL therapy.

Due to the strong oncogenic roles, some lncRNAs might predict prognosis in ALL patients. For example, lncRNA ZEB1-AS1 promoted the activation of IL-11/STAT3 signaling pathway by interacting with IL-11 in B-ALL cells, and a high expression of lncRNA ZEB1-AS1 predicted a poor prognosis for B-ALL patients[38]. A bioinformatics analysis presented a lncRNA-mRNA-based classifier that might be clinically useful to predict the recurrence and prognosis for childhood ALL[55]. It is also reported that the lncRNAs NEAT1 and MALAT1 sponges miR-335-3p, increasing the multidrug-resistance gene ATP-binding cassette sub-family A member 3 (ABCA3) expression and leading to poor prognosis in childhood ALL[56]. Many other studies also found similar roles of lncRNAs in prediction of the prognosis in ALL patients[36][49][57][58][59][60][61][62].

In conclusion, alterations in the expression of lncRNAs are important cooperating events in ALL pathogenesis, maintenance, and progression. Therefore, lncRNAs could be applied in diagnosis, classification, risk stratification, prognosis, as well as treatment of ALL.

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