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Short Communication

Long non-coding RNAs in acute lymphoblastic leukemia

Araceli Diez-Fraile[1], Eva Terras[2], Yves Benoit[2], Tim Lammens[*2]

[1]*Belgian Cancer Registry, Belgium*

[2]*Department of Pediatric Hematology-Oncology and Stem Cell Transplantation, Belgium*

**Corresponding author:* *Dr. Tim Lammens, Department of Pediatric Hematology-Oncology and Stem Cell Transplantation,3K12D, De Pintelaan 185,9000 Ghent,Belgium, Tel:+3293322480; Email:tim.lammens@ugent.be.*

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Recently, it has become apparent that in addition to gene transcription, much of the genome is transcribed into non-coding RNAs (ncRNAs). These ncRNAs have been organized into classes based on length and/or function [1,2]. The most recently established class includes ncRNAs that are more than 200 nucleotides in length (lncRNAs), and deep-sequencing studies have revealed that the human genome encodes similar numbers of lncRNAs and coding RNAs. Furthermore, some of these lncRNAs have proven vital for a variety of biological processes, including the epigenetic control of chromatin, promoter-specific gene regulation, X-chromosome inactivation, imprinting, nuclear import, and the structural maintenance of nuclear bodies [3-8].

Several lncRNAs have also been functionally implicated in non-hematological cancers. For example, overexpression of UCA1 has been detected in bladder cancer, expression of MALAT1 has been associated with metastasis in lung cancer, and overexpression of HOTAIR is linked to poor prognosis in colon and pancreatic cancers [9-11]. Fewer advances have been made in elucidating the function and dysregulation of lncRNA(s) in acute lymphoblastic leukemia (ALL) [12,13]. However, advances in high-throughput sequencing and transcriptome profiling have identified lncRNAs that are expressed in ALL samples [14-22].

In 2013, Zhang and colleagues performed a deep sequencing of the transcriptome of human Jurkat cells, a T-cell ALL (T-ALL) cell line [14]. Of the more than 200 novel lncRNAs discovered, T-ALL-R-lncR1 was found to be markedly overexpressed in T-ALL samples, and only barely detectable in most healthy tissues [14]. They further demonstrated that expression of this lncRNA blocks the formation of the Par-4/THAP1 protein complex, which eventually resulted in the negative regulation of TNF-α-induced apoptosis [14,15]. Thus, T-ALL-R-LncR1 appears to be a valid therapeutic target for ALL.

MLL-rearranged (MLL-r) ALL is one of the most aggressive subtypes of ALL, and its incidence is as high as 80% in infants with ALL [16-18]. Recently, Fang and colleagues performed lncRNA expression studies for a series of MLL-r cases, and also for non-MLL-r ALL cases and healthy subjects [19]. In addition to finding MLL-r-specific lncRNAs, the authors also demonstrated that each MLL-r form can be distinguished by a unique expression profile. To examine the possible functions of these lncRNAs, a lncRNA/mRNA co-expression analysis (also termed a guilt-by-association analysis) was performed and the following functions and protein classes were identified: apoptosis, chromatin assembly, transcription, cell secretion, zinc finger proteins, and cytoplasmic vesicle or plasma membrane components. Co-expression of lncRNAs with mRNAs coding for plasma membrane components allowed for the development of flow cytometry panels for diagnosis and follow-up. Another intriguing finding of their study was the association between lncRNAs and expression of the corresponding MLL target genes. In particular, a set of lncRNAs were found to be epigenetically regulated by H3K79 methylation, which is a well-established hallmark of activated oncogene expression in MLL-r [16].

Recently, two research teams have undertaken an effort to fully characterize the Notch-driven lncRNA-ome of pediatric T-ALL patients using ultra-deep RNA sequencing of prima-

ry T-ALL samples, normal T-cell counterparts, T-ALL cell lines, and Notch-inhibitor treated lines [20,21]. The latter included the use of gamma secretase inhibitors (GSIs) that block the cleavage of Notch, which is necessary for release of the intracellular domain. Both publications clearly illustrate that Notch positively regulates a limited set of lncRNAs in both T-ALL and normal T-cell development, although not all of them are directly bound by the intracellular domain of Notch (ICN1), which upon activation of Notch acts as a transcriptional activator. Trimarchi and colleagues further determined which lncRNAs significantly enhance the expression of nearby genes through cis-regulation in an attempt to functionally annotate some of these lncRNAs [21]. To their surprise, only one lncRNA, which they termed, leukemia-induced noncoding activator RNA (LUNAR1), showed a strong correlation with its neighboring coding gene, insulin-like growth factor receptor 1 (IGF1R), which has been suggested to play a role in T-ALL [22].

In conclusion, research on the role of lncRNAs in ALL is in its early stages, and a fundamental understanding of the involvement and function of lncRNAs in ALL, and in hematological malignancies in general, remains to be elucidated. It is anticipated that these insights will also be applicable to the general field of cancer biology, and will provide opportunities for the identification of novel diagnostic/prognostic markers and drug targets.

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References

1. Stadler PF. Class-specific prediction of ncRNAs. Methods Mol Biol. 2014, 1097:199–213.

2. Sana J, Faltejskova P, Svoboda M, Slaby O. Novel classes of non-coding RNAs and cancer. J Transl Med. 2012, 10:103.

3. Lyle R, Watanabe D, te Vruchte D, Lerchner W, Smrzka OW et al. The imprinted antisense RNA at the Igf2r locus overlaps but does not imprint Mas1. Nat Genet. 2000, 25(1):19–21.

4. Willingham AT, Orth AP, Batalov S, Peters EC, Wen BG et al. A strategy for probing the function of noncoding RNAs finds a repressor of NFAT. Science. 2005, 309(5740):1570–1573.

5. Martianov I, Ramadass A, Serra Barros A, Chow N, Akoulitchev A. Repression of the human dihydrofolatereductase gene by a noncoding interfering transcript. Nature. 2007, 445(7128): 666–670.

6. Tian D, Sun S, Lee JT. The long noncoding RNA, Jpx, is a molecular switch for X chromosome inactivation. Cell. 2010, 143(3): 390–403.

7. Mao YS, Sunwoo H, Zhang B, Spector DL. Direct visualization of the co-transcriptional assembly of a nuclear body by noncoding RNAs. Nat Cell Biol. 2011, 13(1):95–101.

8. Wang Y, Xu Z, Jiang J, Xu C, Kang J et al. Endogenous miRNA sponge lincRNA-RoR regulates Oct4, Nanog, and Sox2 in human embryonic stem cell self-renewal. Dev Cell. 2013, 25(1):69–80.

9. Geng YJ, Xie SL, Li Q, Ma J, Wang GY. Large intervening non-coding RNA HOTAIR is associated with hepatocellular carcinoma progression. J Int Med Res. 2011, 39(6):2119–2128.

10. Wang Y, Chen W, Yang C, Wu W, Wu S et al. Long non-coding RNA UCA1a (CUDR) promotes proliferation and tumorigenesis of bladder cancer. Int J Oncol. 2012, 41(1):276–284.

11. Gutschner T, Hämmerle M, Eißmann M, HSU J, Kim Y et al. The non-coding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Res. 2013, 73(3): 1180–1189.

12. Faderl S, O'Brien S, Pui CH, Stock W, Wetzler M et al. Adult acute lymphoblastic leukemia: concepts and strategies. Cancer. 2010, 116(5): 1165–1176.

13. Pui CH, Mullighan CG, Evans WE, Relling MV. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood. 2012, 120(6): 1165–1174.

14. Zhang L, Xu HG, Lu C. A novel long non-coding RNA T-ALL-R-LncR1 knockdown and Par-4 cooperate to induce cellular apoptosis in T-cell acute lymphoblastic leukemia cells. Leuk Lymphoma. 2014, 55(6): 1373–1382.

15. Roussigne M, Cayrol C, Clouaire T, Amalric F, Girard JP. THAP1 is a nuclear proapoptotic factor that links prostate-apoptosis-response-4 (Par-4) to PML nuclear bodies. Oncogene. 2003, 22(16): 2432–2442.

16. Slany RK. The molecular biology of mixed lineage leukemia. Haematologica. 2009, 94(7): 984–993.

17. Tamai H, Inokuchi K. 11q23/MLL acute leukemia: update of clinical aspects. J Clin Exp Hematop. 2010, 50(2): 91–98.

18. Muntean AG, Hess JL. The pathogenesis of mixed-lineage leukemia. Annu Rev Pathol. 2012, 7: 283–301.

19. Fang K, Han BW, Chen ZH, Lin KY, Zeng CW et al. A distinct

set of long non-coding RNAs in childhood MLL-rearranged acute lymphoblastic leukemia: biology and epigenetic target. Hum Mol Genet. 2014, 23(12): 3278–3288.

20. Durinck K, Wallaert A, Van de Walle I, Van Loocke W, Volders PJ et al. The Notch driven long non-coding RNA repertoire in T-cell acute lymphoblastic leukemia. Haemtologica. 2014, 99(12): 1808–1816.

21. Trimarchi T, Bilal E, Ntziachristos P, Fabbri G, Dalla-Favera R et al. Genome-wide mapping and characterization of Notch-regulated long noncoding RNAs in acute leukemia. Cell. 2014, 158(3): 593–606.

22. Medyouf H, Gusscott S, Wang H, Tseng JC, Wai C et al. High-level IGF1R expression is required for leukemia-initiating cell activity in T-ALL and is supported by Notch signaling. J Exp Med. 2011, 208(9): 1809–1822.