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·综 述·

lncRNA与白血病

lncRNA and leukemia

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[摘 要] 在基础研究方面,业已证实lncRNA主要以癌基因或抑癌基因两种形式参与白血病细胞的增殖、分化或凋亡过程,是白血病发生和发展的重要因素。临床研究表明,lncRNA与白血病的诊断、分型、风险分级和预后判断有关,具有成为临床病情监测的生物标志物潜力。以lncRNA siRNA为代表的白血病治疗性分子产品也表现出了良好的应用前景。但是,lncRNA在AML领域的研究依然面临着许多问题和挑战,需要进一步筛选特异性较高的关键标志性和功能性lncRNA,通过大型队列非干预性临床试验验证其作为生物标志物或治疗靶点的可行性。

[关键词] lncRNA;白血病;诊断;预后
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在人类基因组中,lncRNA在表观遗传水平、转录和转录后水平、翻译和翻译后水平等多种层面调控病理生理过程[1-2],可以癌基因或抑癌基因形式参与白血病的发生、发展、耐药或转移[3-4]。越来越多的研究[3,5]发现,lncRNA与白血病的诊断、分型、预后或风险分层密切相关,并且具有成为监测白血病病情演化的生物标志物的潜力。针对白血病特异性和功能性lncRNA的siRNA等干预技术或分子产品有望给白血病患者提供新的治疗方法[5-6]。本文依据文献报道和数据库分析的结果,对lncRNA和白血病之间的关系进行分析和总结,同时对该研究领域的发展趋势进行展望。

1 lncRNA与白血病细胞的生物学活性

lncRNA在多种类型的白血病中表达异常或紊乱,并以癌基因或抑癌基因的形式发挥着促进或抑制白血病细胞增殖、分化或凋亡的不同作用。

以促进白血病细胞增殖为主的lncRNA包括:lncRNA IRAIN[7-10]、lncRNA CCAT1[11]、lncRNA RUNXOR[12]、lncRNA ANRIL[13],与T-ALL[14-15]或CLL[5,16-17]相关的lncRNA NALT1,以及lncRNA KCNQ1OT1(KCNQ1 opposite strand/antisense transcript 1,KCNQ1OT1)[18-19]。而lncRNA Xist则是发挥抑癌基因作用的典型代表[20-21]。

对lncRNA与白血病细胞分化的研究结果发现,lncRNA NEAT1与急性早幼粒细胞白血病(acute promyelocytic leukemia,APL)NB4细胞株的粒系分化程度正相关,干扰NEAT1表达可以阻滞其分化水平[22-23]。在慢性髓系白血病(chronic myeloid leukemia, CML)细胞中,下调lncRNA SNHG5的表达可以显著增加CML细胞的分化水平[24-25]。lncRNA HOTAIRM1在ATRA诱导的NB4细胞粒细胞成熟分化过程中表达水平升高,敲除HOTAIRM1基因会阻滞粒细胞的分化成熟[26-27]。与急性髓系白血病分化有关的lncRNA NR-104098[28-29],lncRNA PVT1[30-31]和lncRNA UCA1[32-33]等也相继被发现和公开报道。

除了上述增殖和分化两个角度的报道外,lncRNA对白血病细胞凋亡也有重要的调控作用。例如,lncRNA UCA1以UCA1/miR-296-3p/Myc信号轴的形式发挥抑制AML细胞凋亡的作用[34-35];lncRNA HOXA-AS2通过抑制TRAIL的表达而抑制白血病细胞的凋亡水平[36];lncRNA HULC通过PI3K/Akt途径或miRNA-150-5p阻止CML细胞的凋亡[37-39]。

有研究[40-41]利用数据库对众多与白血病有关的lncRNA进行了系统性的分析和总结,结果发现,癌基因lncRNA包括H19、HOTAIR、TUG1、UCA1、PANDAR、RUNXOR、SNHG5、ANRIL、PVT-1、CCAT1、HOTAIRM1、CCDC26、XLOC_109948、DANCR、MALAT1、PACT-1和TUC338等;抑癌基因lncRNA主要包括IRAIN、NEAT1、MEG3、CASC15、

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GAS5、lincRNA-p21 和 PTENP1 等。其中，以 MEG3 为代表的部分 lncRNA 同时具有致癌性和抑癌性双重作用。总之，随着研究的不断深入，高通量筛选平台和技术的提高，将会有更多的增殖、分化或凋亡关联 lncRNA 被逐渐发现，而如何发现和筛选关键的白血病关联性和相对特异性 lncRNA，对于其作为生物标志物或治疗靶点的价值至关重要。

2　lncRNA 与白血病的诊断

lncRNA 的表达水平或其差异表达谱可以用作白血病诊断、分型、风险分级和预后判断的生物标志物[3-5]。例如，Lnc-SOX6-1[42]和 lncRNA HOTAIR 的表达上调是 AML 患者诊断的辅助指标[20,43-44]，lncRNA PVT1 是 APL 患者的特异诊断指标[45-46]，T-ALL-R-lncR1 是 T-ALL 临床诊断辅助指标[46]，而 NONHSAT027612.2 和 NONHSAT134556.2 两个新发现的 lncRNA 是 C-ALL 患者的相对特异性诊断指标[47]。目前，被认为可用于白血病患者辅助诊断的高表达 lncRNA 包括 CCAT1、CCDC26、CRNDE、HOTAIR、KCNQ5IT1、LINC00265、MALAT1、PVT1、SNHG5 和 TUG1，而低表达 lncRNA 包括 MEG3 和 NEAT1[48]。

lncRNA 对于白血病的分型也有一定的参考价值。研究[3-5,20]发现了部分白血病亚型特征性 lncRNA，例如，lncRNA H19 在 M1-2 型 AML 患者中表达上调，LINC00877、lncRNA RP11-84C10.2、lncRNA RP11-848P1.3 和 lncRNA ZNF667-AS1 在 M3 型 AML 中表达下调，LINC02082-201 和 lncRNA AC009495.2 在 M3 AML 中则表达上调，lncRNA HOTTIP、lncRNA SNHG5 和 lncRNA CCAT1 在 M4-5 型 AML 中表达上调，CCAT1、PVT1 和 XLOC_109948 则是在携带风险突变基因的 AML 患者中过度表达。PAPAIOANNOU 等[49]检测了 148 名细胞遗传学正常 AML（CN-AML）老年患者的 lncRNA 表达，发现与 FLT3-ITD、NPM1、CEBPA、IDH2、ASLX1 或 RUNX1 等突变相关的独特 lncRNA 表达谱可以区别不同突变类型的白血病。GOURVEST 等[50]通过 RNA 测序破译了与复发性 AML 突变相关的 lncRNA 转录组，发现 12 种 lncRNA 的不同表达谱能够区分 NPM1 突变和 NPM1 野生型患者。此外，DIAZ-BEYA 等[51]通过微阵列研究了与染色体异常相关的 AML 患者的 lncRNA 表达，发现在 t（8; 16）阳性病例 linc-HOXA11、HOXA11-AS、HOTTIP 和 NR_038120 表达上调。当然，上述 lncRNA 在临床诊断或亚型鉴别中的作用价值，还需要进一步的多中心大样本研究结果来证实。

3　lncRNA 与白血病的治疗

lncRNA 在白血病的发生发展中有重要作用，因此其发挥作用的各个环节均具有成为白血病靶向干预治疗靶点的潜力。虽然尚无成功用于临床或上市的 lncRNA 干扰药物，但是针对 lncRNA 靶向治疗的研究依然是目前国内外学者关注的重点方向之一。但是，研究人员逐渐认识到，与蛋白质编码转录本相比，靶向 lncRNA 具有一定的挑战性。因为缺乏蛋白质产物就意味着只能使用基于 RNA 的干预治疗工具。此外，与具有小分子药物靶向结合的特定结构域的蛋白质不同，研究者对 lncRNA 的构象知之甚少，使得基于结构的策略也难以实施。即使如此，国内外学者依然尝试了几种比较可行的方法：其一是基于传统的 siRNA 技术的策略[40]，在这方面，lncRNA DANCR siRNA 纳米颗粒[52]和 UCA1 siRNA 都在白血病细胞体外实验中获得明显效果[53]；另一种方法是使用反义寡核苷酸抑制 lncRNA 表达[54-56]。目前，研究人员正在积极开发基于寡核苷酸的白血病治疗策略，但面临着如何提高药物递送效率和延长体内半衰期的问题。另外，也有学者[57]尝试使用基于破坏 lncRNA-蛋白质相互作用的小分子抑制剂的创新治疗策略。

针对抑癌基因类 lncRNA，可以通过病毒或非病毒载体转染而诱导特定的抑癌 lncRNA 过表达，从而抑制白血病细胞的生长。例如，增强 HOTAIRM1 表达可以诱导 APL 细胞中 PML/RARα 癌蛋白的降解，恢复白血病细胞的正常分化过程[26]。另外，新的基因组编辑策略，如 CRISPR/Cas9，也可用于插入抑癌基因或敲除癌基因 lncRNA。甚至改进后的 CRISPR 系统还可以纠正致癌 lncRNA 的 SNP，如 ANRIL、MALAT1、HULC 中的 SNP [40,58]。

耐药性是白血病治疗失败的主要原因之一，lncRNA 干预可在一定程度上逆转白血病细胞的耐药。lncRNA FENDRR 在多柔比星耐药的 CML 细胞中表达明显下调，诱导 FENDRR 表达有望成为 CML 耐药性逆转的重要手段[59]。YANG 等[60]证明，linc00239 主要通过调控 PI3K/Akt/mTOR 轴而促进 AML 细胞增殖，降低其对多柔比星的敏感性，表明干预 linc00239 表达是治疗 AML 的潜在途径。与癌症化疗耐药性相关的 lncRNA TUG1[61]在多柔比星耐药的 AML 细胞中也表达上调，下调 TUG1 的表达则提高耐药 AML 细胞的凋亡水平[23,62]。但尚未见有关靶向干预 lncRNA 用于临床治疗的成功案例的报道。

4　lncRNA 与白血病的预后

部分 lncRNA 在监测白血病患者预后中均表现

出了较好的应用潜力。如lncRNA CASC15高表达是儿童B-ALL和AML患者良好预后指标[63]；lncRNA MEG3甲基化水平较高的AML患者具有更长的总体生存期（overall survival，OS）和较高的5年无病生存率（disease free survival，DFS）[64-65]。然而，更多的研究结果显示lncRNA高表达与预后不良有关，如较低的完全缓解（complete remission，CR）率、较短的OS、较低的DFS或者无事件生存率（event-free survival，EFS）。例如，各个亚型的非M3型AML患者中的lncRNA PANDAR [66-67]、细胞遗传学异常的AML患者中的lncRNA SNHG5[68]、NPM1突变的中风险亚组AML)患者的lncRNA HOTAIRM1[69]、AML患者的lncRNA LOC285758[70]、t（8;21）阳性AML患者的lncRNA CCAT1和lncRNA PVT1[71]，以及AML患者的lncRNA H19[72-73]的高表达等。

一些较大规模或多中心的研究结果进一步证实了lncRNA在白血病预后中的作用。例如，分析148例未经治疗的正常核型AML老年患者lncRNA的丰度和表达谱，筛选出与预后相关程度最高的48个lncRNA并确定了评分标准，证明lncRNA表达谱与AML的复发和预后有关，有助于制定白血病精准治疗方案[49]。在另一项涉及AML患者lncRNA表达谱的临床研究中发现，P11-222K16.2、AC092580.4和RP11-305O.6三种lncRNA的表达与AML复发或OS有关[74]。PAPAIOANNOU等[75]确定了24个lncRNA的评分体系，并证实它们是无病生存和无事件生存的独立预后指标。TANG等[76]在一组细胞遗传学正常的AML患者中选择了DIRC3-AS1等10个lncRNA，基于Cox系数生成了10-lncRNA风险评分系统，发现DIRC3-AS1的功能失常与AML患者预后相关。尽管发现了某些个体lncRNA或lncRNA组可能具有独立或辅助评估白血病预后的生物标志物作用，但是其预后判断价值仍然需要多中心和大规模的临床验证来佐证。

5 小 结

目前，lncRNA是白血病RNA基因组研究领域的热点，其不仅可以通过癌基因或抑癌基因等形式参与白血病的发生和发展过程，也是白血病诊断、分型、风险分层和预后判断的生物标志物。随着研究的不断深入和高通量测序技术的不断发展，越来越多的与白血病相关的lncRNA被发现，以lncRNA siRNA为代表的靶向干预治疗技术或分子产品也将会给白血病患者带来新的希望。但要实现从基础研究过渡到临床应用的真正转化，依然面临着许多问题和挑战。首先是需要进一步明确白血病亚型或分子遗传背景不同的患者中，特异性或相对特异性的癌基因或抑癌基因lncRNA；其次，lncRNA在用作诊断生物标志物或治疗靶标方面的研究更是处于起步阶段，需要精心设计的队列研究，特别是大型队列非干预性临床试验数据的支持；第三，siRNA等干预技术或分子产品的载体或递送技术仍仍需优化；最后，抑癌基因lncRNA的表达恢复、其下游信号的抑制剂和耐药逆转等策略均尚不成熟，有待进一步研究。

[参 考 文 献]

[1] KOPP F, MENDELL J T. Functional classification and experimental dissection of long noncoding RNAs[J]. Cell, 2018, 172(3): 393-407. DOI:10.1016/j.cell.2018.01.011.

[2] JARROUX J, MORILLON A, PINSKAYA M. History, discovery, and classification of lncRNAs[J]. Adv Exp Med Biol, 2017, 1008: 1-46. DOI:10.1007/978-981-10-5203-3_1.

[3] LI M, MENG F, LU Q. Expression profile screening and bioinformatics analysis of circRNA, LncRNA, and mRNA in acute myeloid leukemia drug-resistant cells[J]. Turk J Haematol, 2020, 37 (2): 104-110. DOI:10.4274/tjh.galenos.2019.2019.0312.

[4] CRUZ-MIRANDA G, HIDALGO-MIRANDA A, BÁRCENAS-LÓPEZ D, et al. Long non-coding RNA and acute leukemia[J/OL]. Int J Mol Sci, 2019, 20(3): 735 [2021-04-30]. https://doi. org/10.3390/ijms20030735. DOI:10.3390/ijms20030735.

[5] BHAT A A, YOUNES S N, RAZA S S, et al. Role of non-coding RNA networks in leukemia progression, metastasis and drug resistance[J]. Mol Cancer, 2020, 19(1): 1-21. DOI:10.1186/s12943-020-01175-9.

[6] LIU Y, CHENG Z, PANG Y, et al. Role of microRNAs, circRNAs and long noncoding RNAs in acute myeloid leukemia[J/OL]. J Hematol Oncol, 2019, 12(1): 51[2021-04-30]. https://www. ncbi.nlm.nih.gov/pubmed/31126316/. DOI:10.1186/s13045-019-0734-5.

[7] BLEIN T, BALZERGUE C, ROULÉ T, et al. Landscape of the non-coding transcriptome response of two Arabidopsis ecotypes to phosphate starvation[J]. Plant Physiol, 2020, 183(3): 1058-1072. DOI:10.1104/pp.20.00446.

[8] LIU Y, SUN P, ZHAO Y, et al. The role of long non-coding RNAs and downstream signaling pathways in leukemia progression[J]. Hematol Oncol, 2021, 39(1): 27-40. DOI:10.1002/hon.2776.

[9] JIANG Y, CHEN J, CHEN G. Long noncoding RNA IRAIN acts as tumor suppressor via miR-125b in multiple myeloma[J]. Oncol Lett, 2019, 18(6): 6787-6794. DOI:10.3892/ol.2019.11012.

[10] PASHAIEFAR H, IZADIFARD M, YAGHMAIE M, et al. Low expression of long noncoding RNA IRAIN is associated with poor prognosis in non-M3 acute myeloid leukemia patients[J]. Genet Test Mol Biomarkers, 2018, 22(5): 288-294. DOI: 10.1089/gtmb.2017.0281.

[11] WANG C H, CHEN F P, FAN Z L, et al. lncRNA CCAT1/miR-490-3p/MAPK1/c-Myc positive feedback loop drives progression of acute myeloid leukaemia[J]. J Biochem, 2020, 167(4): 379-388. DOI:10.1093/jb/mvz107.

[12] ENGREITZ J M, HAINES J E, PEREZ E M, et al. Local regulation of gene expression by lncRNA promoters, transcription and splicing

[J]. Nature, 2016, 539(7629): 452-455. DOI:10.1038/nature20149.

[13] LI G, GAO L, ZHAO J, et al. LncRNA ANRIL/miR-7-5p/TCF4 axis contributes to the progression of T cell acute lymphoblastic leukemia[J/OL]. Cancer Cell Int, 2020, 20: 335[2021-04-30]. https://www.ncbi.nlm.nih.gov/pubmed/32714094/. DOI:10.1186/s12935-020-01376-8.

[14] KHOSHAMOOZ H, KAVIANI S, ATASHI A, et al. Combination effect of Notch1 and PI3K/AKT/mTOR signaling pathways inhibitors on T-ALL cell lines[J]. Int J Hematol - Oncol Stem Cell Res, 2020, 14(2): 99-109.

[15] SHIM S, SOH S H, IM Y B, et al. Induction of systemic immunity through nasal-associated lymphoid tissue (NALT) of mice intranasally immunized with Brucella abortus malate dehydrogenase-loaded chitosan nanoparticles[J/OL]. PLoS One, 2020, 15(2): e0228463 [2021-04-30]. https://www.ncbi.nlm.nih.gov/pubmed/32027689/. DOI:10.1371/journal.pone.0228463.

[16] MADONNA R, PIERAGOSTINO D, CUFARO M, et al. Ponatinib induces vascular toxicity through the Notch-1 signaling pathway[J/OL]. J Clin Med. 2020, 9(3): 820 [2021-04-30]. https://www.mdpi.com/resolver?pii=jcm9030820. DOI: 10.3390/jcm9030820.

[17] SPINA V, ROSSI D. Overview of non-coding mutations in chronic lymphocytic leukemia[J]. Mol Oncol, 2019, 13(1): 99-106. DOI: 10.1002/1878-0261.12416.

[18] LIU C Z, GAO J M, SU G Y, et al. MicroRNA-1202 plays a vital role in osteoarthritis via KCNQ1OT1 has-miR-1202-ETS1 regulatory pathway[J/OL]. J Orthop Surg Res, 2020, 15(1): 130 [2021-04-30]. https://www. ncbi. nlm. nih. gov/pubmed/32252801/. DOI:10.1186/s13018-020-01655-0.

[19] CHENG P, LU P, GUAN J, et al. LncRNA KCNQ1OT1 controls cell proliferation, differentiation and apoptosis by sponging miR-326 to regulate c-Myc expression in acute myeloid leukemia[J]. Neoplasma, 2020, 67(2): 238-248. DOI: 10.4149/neo_2018_181215N972.

[20] WURM A A, PINA C. Long non-coding RNAs as functional and structural chromatin modulators in acute myeloid leukemia[J/OL]. Front Oncol, 2019, 9: 899 [2021-04-30]. https://www.ncbi.nlm.nih.gov/pubmed/31572684/. DOI:10.3389/fonc.2019.00899.

[21] WANG C, LI L, LI M, et al. Silencing long non-coding RNA XIST suppresses drug resistance in acute myeloid leukemia through down-regulation of MYC by elevating microRNA-29a expression[J/OL]. Mol Med, 2020, 26(1): 114. https://www.ncbi.nlm.nih.gov/pubmed/33228517/. DOI:10.1186/s10020-020-00229-4.

[22] WANG Y W, FU L, SUN A L, et al. C/EBPβ contributes to transcriptional activation of long non-coding RNA NEAT1 during APL cell differentiation[J]. Biochem Biophys Res Commun, 2018, 499(2): 99-104. DOI:10.1016/j.bbrc.2017.10.137.

[23] ZIMTA A A, TOMULEASA C, SAHNOUNE I, et al. Long non-coding RNAs in myeloid malignancies[J/OL]. Front Oncol, 2019, 9: 1048 [2021-04-30]. https://www. ncbi. nlm. nih. gov/pubmed/31681586/. DOI:10.3389/fonc.2019.01048.

[24] GAO B, LI S, LI G. Long noncoding RNA (lncRNA) small nucleolar RNA host gene 5 (SNHG5) regulates proliferation, differentiation, and apoptosis of K562 cells in chronic myeliod leukemia[J]. Med Sci Monit, 2019, 25: 6812-6819. DOI:10.12659/msm.916661.

[25] WANG D, ZENG T, LIN Z, et al. Long non-coding RNA SNHG5 regulates chemotherapy resistance through the miR-32/DNAJB9 axis in acute myeloid leukemia[J/OL]. Biomed Pharmacother, 2020, 123: 109802 [2021-04-30]. https://www.ncbi.nlm.nih.gov/pubmed/31884339/. DOI:10.1016/j.biopha.2019.109802.

[26] CHEN Z H, WANG W T, HUANG W, et al. The lncRNA HOTAIRM1 regulates the degradation of PML-RARA oncoprotein and myeloid cell differentiation by enhancing the autophagy pathway[J]. Cell Death Differ, 2017, 24(2): 212-224. DOI:10.1038/cdd.2016.111.

[27] WEI S, ZHAO M, WANG X, et al. PU.1 controls the expression of long noncoding RNA HOTAIRM1 during granulocytic differentiation[J/OL]. J Hematol Oncol, 2016, 9(1): 44 [2021-04-30]. https://www. ncbi. nlm. nih. gov/pubmed/27146823/. DOI: 10.1186/s13045-016-0274-1.

[28] FENG Y, HU S, LI L, et al. LncRNA NR-104098 inhibits AML proliferation and induces differentiation through repressing EZH2 transcription by interacting with E2F1[J/OL]. Front Cell Dev Biol, 2020, 8: 142 [2021-04-30]. https://www.ncbi.nlm.nih.gov/pubmed/32296698/. DOI:10.3389/fcell.2020.00142.

[29] FENG Y B, NIU R W, CHENG X, et al. ATPR-induced differentiation and G0/G1 phase arrest in acute promyelocytic leukemia by repressing EBP50/NCF_1 complex to promote the production of ROS[J/OL]. Toxicol Appl Pharmacol, 2019, 379: 114638 [2021-04-30]. http://dx.doi.org/10.1016/j.taap.2019.114638. DOI:10.1016/j.taap.2019.114638.

[30] YAZDI N, HOUSHMAND M, ATASHI A, et al. Long noncoding RNA PVT1: potential oncogene in the development of acute lymphoblastic leukemia[J]. Turkish J Biol, 2018, 42(5): 405-413. DOI:10.3906/biy-1801-46.

[31] GHADIRI A, SHARIFI M, MEHRZAD V, et al. Reduce proliferation of human bone marrow cells from acute myeloblastic leukemia with minimally differentiation by blocking lncRNA PVT1 [J]. Clin Transl Oncol, 2020, 22(11): 2103-2110. DOI: 10.1007/s12094-020-02360-4.

[32] HUGHES J M, LEGNINI I, SALVATORI B, et al. C/EBPα -p30 protein induces expression of the oncogenic long non-coding RNA UCA1 in acute myeloid leukemia[J]. Oncotarget, 2015, 6(21): 18534-18544. DOI:10.18632/oncotarget.4069.

[33] HOSSEINI N F, MANOOCHEHRI H, KHOEI S G, et al. The functional role of long non-coding RNA UCA1 in human multiple cancers: a review study[J]. Curr Mol Med, 2021, 21(2): 96-110. DOI:10.2174/1566524020666200619124543.

[34] LI J, WANG M, CHEN X. Long non-coding RNA UCA1 modulates cell proliferation and apoptosis by regulating miR-296-3p/Myc axis in acute myeloid leukemia[J]. Cell Cycle, 2020, 19(12): 1454-1465. DOI:10.1080/15384101.2020.1750814.

[35] LIANG Y, LI E, ZHANG H, et al. Silencing of lncRNA UCA1 curbs proliferation and accelerates apoptosis by repressing SIRT1 signals by targeting miR-204 in pediatric AML[J/OL]. J Biochem Mol Toxicol, 2020, 34(3): e22435 [2021-04-31]. https://www.ncbi.nlm.nih.gov/pubmed/31916649/. DOI:10.1002/jbt.22435.

[36] DONG X, FANG Z, YU M, et al. Knockdown of long noncoding RNA HOXA-AS2 suppresses chemoresistance of acute myeloid leukemia via the miR-520c-3p/S100A4 axis[J]. Cell Physiol

Biochem, 2018, 51(2): 886-896. DOI:10.1159/000495387.

[37] LU Y H, LI Y, CHAI X, et al. Long noncoding RNA HULC promotes cell proliferation by regulating PI3K/AKT signaling pathway in chronic myeloid leukemia[J]. Gene, 2017, 607: 41-46. DOI:10.1016/j.gene.2017.01.004.

[38] HAN Y, MA Z. LncRNA highly upregulated in liver cancer regulates imatinib resistance in chronic myeloid leukemia via the miR-150-5p/MCL1 axis[J]. Anticancer Drugs, 2021, 32(4): 427-436. DOI:10.1097/cad.0000000000001019.

[39] LIU T, LIU Y, WEI C, et al. LncRNA HULC promotes the progression of gastric cancer by regulating miR-9-5p/MYH9 axis[J/OL]. Biomed Pharmacother, 2020, 121: 109607 [2021-04-30]. https: //www. ncbi. nlm. nih. gov/pubmed/31726371/. DOI: 10.1016/j. biopha.2019.109607.

[40] GOURVEST M, BROUSSET P, BOUSQUET M. Long noncoding RNAs in acute myeloid leukemia: functional characterization and clinical relevance[J/OL]. Cancers, 2019, 11(11): 1638 [2021-04-30]. https://doi. org/10.3390/cancers11111638. DOI: 10.3390/cancers11111638.

[41] MORLANDO M, BALLARINO M, FATICA A. Long non-coding RNAs: new players in hematopoiesis and leukemia[J/OL]. Front Med, 2015, 2: 23 [2021-04-30]. https://www. ncbi. nlm. nih. gov/pubmed/25927065/. DOI:10.3389/fmed.2015.00023.

[42] GUAN X, WEN X, XIAO J, et al. Lnc-SOX6-1 upregulation correlates with poor risk stratification and worse treatment outcomes, and promotes cell proliferation while inhibits apoptosis in pediatric acute myeloid leukemia[J]. Int J Lab Hematol, 2019, 41 (2): 234-241. DOI:10.1111/ijlh.12952.

[43] ZHANG Y Y, HUANG S H, ZHOU H R, et al. Role of HOTAIR in the diagnosis and prognosis of acute leukemia[J]. Oncol Rep, 2016, 36(6): 3113-3122. DOI:10.3892/or.2016.5147.

[44] RAJAGOPAL T, TALLURI S, AKSHAYA R L, et al. HOTAIR LncRNA: a novel oncogenic propellant in human cancer[J]. Clin Chim Acta, 2020, 503: 1-18. DOI:10.1016/j.cca.2019.12.028.

[45] IZADIFARD M, PASHAIEFAR H, YAGHMAIE M, et al. Expression analysis of PVT1, CCDC26, and CCAT1 long noncoding RNAs in acute myeloid leukemia patients[J]. Genet Test Mol Biomarkers, 2018, 22(10): 593-598. DOI:10.1089/gtmb.2018.0143.

[46] ZHANG L, XU H G, 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[J]. Leuk Lymphoma, 2014, 55(6): 1373-1382. DOI: 10.3109/10428194.2013.829574.

[47] LI S, BIAN H, CAO Y, et al. Identification of novel lncRNAs involved in the pathogenesis of childhood acute lymphoblastic leukemia[J]. Oncol Lett, 2019, 17(2): 2081-2090. DOI: 10.3892/ol.2018.9832.

[48] DIETER C, LOURENCO E D, LEMOS N E. Association of long non-coding RNA and leukemia: a systematic review[J/OL]. Gene, 2020, 735: 144405 [2021-04-30]. https://www. ncbi. nlm. nih. gov/pubmed/32014562/. DOI:10.1016/j.gene.2020.144405.

[49] PAPAIOANNOU D, NICOLET D, OZER H G, et al. Prognostic and biologic relevance of clinically applicable long noncoding RNA profiling in older patients with cytogenetically normal acute myeloid leukemia[J]. Mol Cancer Ther, 2019, 18(8): 1451-1459. DOI:10.1158/1535-7163.mct-18-1125.

[50] GOURVEST M, DE CLARA E, WU H C, et al. A novel leukemic route of mutant NPM1 through nuclear import of the overexpressed long noncoding RNA LONA[J]. Leukemia, 2021, 35(10): 2784-2798. DOI:10.1038/s41375-021-01307-0.

[51] DIAZ-BEYA M, NAVARRO A, CORDEIRO A, et al. Exploring the expression profile of long non-coding RNA (lncRNA) in different acute myeloid leukemia (AML) subtypes: t(8;16)(p11;p13)/MYST3-crebbp AML harbors a distinctive lncrna signature[J/OL]. Blood, 2015, 126(23): 1397 [2021-04-30]. https://doi. org/10.1182/blood.v126.23.1397.1397. DOI:10.1182/blood.v126.23.1397.1397.

[52] BILL M, PAPAIOANNOU D, KARUNASIRI M, et al. Expression and functional relevance of long non-coding RNAs in acute myeloid leukemia stem cells[J]. Leukemia, 2019, 33(9): 2169-2182. DOI:10.1038/s41375-019-0429-5.

[53] ZHANG Y, LIU Y, XU X. Knockdown of LncRNA-UCA1 suppresses chemoresistance of pediatric AML by inhibiting glycolysis through the microRNA-125a/hexokinase 2 pathway[J]. J Cell Biochem, 2018, 119(7): 6296-6308. DOI:10.1002/jcb.26899.

[54] WU X, TUDORAN O M, CALIN G A, et al. The many faces of long noncoding RNAs in cancer[J]. Antioxid Redox Signal, 2018, 29(9): 922-935. DOI:10.1089/ars.2017.7293.

[55] DE CLARA E, GOURVEST M, MA H, et al. Long non-coding RNA expression profile in cytogenetically normal acute myeloid leukemia identifies a distinct signature and a new biomarker in NPM1-mutated patients[J]. Haematologica, 2017, 102(10): 1718-1726. DOI:10.3324/haematol.2017.171645.

[56] AMODIO N, STAMATO M A, JULI G, et al. Drugging the lncRNA MALAT1 via LNA gapmeR ASO inhibits gene expression of proteasome subunits and triggers anti-multiple myeloma activity[J]. Leukemia, 2018, 32(9): 1948-1957. DOI:10.1038/s41375-018-0067-3.

[57] CONNELLY C M, MOON M H, SCHNEEKLOTH J S Jr. The emerging role of RNA as a therapeutic target for small molecules [J]. Cell Chem Biol, 2016, 23(9): 1077-1090. DOI: 10.1016/j.chembiol.2016.05.021.

[58] SAKUMA T, YAMAMOTO T. Acceleration of cancer science with genome editing and related technologies[J]. Cancer Sci, 2018, 109 (12): 3679-3685. DOI:10.1111/cas.13832.

[59] ZHANG F, NI H, LI X, et al. LncRNA FENDRR attenuates adriamycin resistance via suppressing MDR1 expression through sponging HuR and miR-184 in chronic myelogenous leukaemia cells[J]. FEBS Lett, 2019, 593(15): 1993-2007. DOI:10.1002/1873-3468.13480.

[60] YANG Y, DAI W, SUN Y, et al. Long non-coding RNA linc00239 promotes malignant behaviors and chemoresistance against doxorubicin partially via activation of the PI3K/Akt/mTOR pathway in acute myeloid leukaemia cells[J]. Oncol Rep, 2019, 41 (4): 2311-2320. DOI:10.3892/or.2019.6991.

[61] TANG T, CHENG Y, SHE Q, et al. Long non-coding RNA TUG1 sponges miR-197 to enhance cisplatin sensitivity in triple negative breast cancer[J]. Biomed Pharmacother, 2018, 107: 338-346. DOI: 10.1016/j.biopha.2018.07.076.

[62] ZHANG B, SUN Y F, ZHANG X M, et al. TUG1 weakens the sensitivity of acute myeloid leukemia cells to cytarabine by regulating miR-655-3p/CCND1 axis[J]. Eur Rev Med Pharmacol

Sci, 2020, 24(9): 4940-4953. DOI:10.26355/eurrev_202005_21185.

[63] FERNANDO T R, CONTRERAS J R, ZAMPINI M, et al. The lncRNA CASC15 regulates SOX4 expression in RUNX1-rearranged acute leukemia[J]. Mol Cancer, 2017, 16(1): 126. DOI: 10.1186/s12943-017-0692-x.

[64] GAO W. Long non-coding RNA MEG3 as a candidate prognostic factor for induction therapy response and survival profile in childhood acute lymphoblastic leukemia patients[J]. Scand J Clin Lab Invest, 2021, 81 (3): 194-200. DOI:10.1080/00365513.2021.1881998.

[65] XUE H J, GAO H L, XIA H, et al. Prognostic significance of long non coding maternally expressed gene 3 in pediatric acute myeloid leukemia[J/OL]. Medicine, 2021, 100(35): e26959[2021-04-30]. https://www. ncbi. nlm. nih. gov/pubmed/34477125/. DOI: 10.1097/MD.0000000000026959.

[66] TIAN L Y, CHEN X, LUN L M, et al. LncRNA PANDAR is a novel prognostic biomarker in patients with cancer: a meta-analysis[J]. Clin Lab, 2019, 65(1). DOI:10.7754/clin.lab.2018.180622.

[67] YANG L, ZHOU J D, ZHANG T J, et al. Overexpression of lncRNA PANDAR predicts adverse prognosis in acute myeloid leukemia[J]. Cancer Manag Res, 2018, 10: 4999-5007. DOI: 10.2147/cmar.s180150.

[68] LI J, SUN C K. Long noncoding RNA SNHG5 is up-regulated and serves as a potential prognostic biomarker in acute myeloid leukemia[J]. Eur Rev Med Pharmacol Sci, 2018, 22(11): 3342-3347. DOI:10.26355/eurrev_201806_15154.

[69] ZHAO Y, WANG W, GUAN C, et al. Long noncoding RNA HOTAIRM1 in human cancers[J]. Clin Chim Acta, 2020, 511: 255-259. DOI:10.1016/j.cca.2020.10.011.

[70] LEI L J, XIA S Y, LIU D, et al. Genome-wide characterization of lncRNAs in acute myeloid leukemia[J]. Briefings Bioinform, 2018, 19(4): 627-635. DOI:10.1093/bib/bbx007.

[71] EL-KHAZRAGY N, ELAYAT W, MATBOULY S, et al. The prognostic significance of the long non-coding RNAs "CCAT1, PVT1" in t(8; 21) associated Acute Myeloid Leukemia[J]. Gene, 2019, 707: 172-177. DOI:10.1016/j.gene.2019.03.055.

[72] ZHANG T J, ZHOU J D, ZHANG W, et al. H19 overexpression promotes leukemogenesis and predicts unfavorable prognosis in acute myeloid leukemia[J/OL]. Clin Epigenetics, 2018, 10: 47 [2021-04-30]. https://www. ncbi. nlm. nih. gov/pubmed/29643943/. DOI:10.1186/s13148-018-0486-z.

[73] CHENG Y Q, SU Y R, WANG S B, et al. Identification of circRNA-lncRNA-miRNA-mRNA competitive endogenous RNA network as novel prognostic markers for acute myeloid leukemia[J/OL]. Genes, 2020, 11(8): 868[2021-04-30]. https://doi.org/10.3390/genes11080868. DOI:10.3390/genes11080868.

[74] WANG R Q, CHEN C J, JING Y, et al. Characteristics and prognostic significance of genetic mutations in acute myeloid leukemia based on a targeted next-generation sequencing technique [J]. Cancer Med, 2020, 9(22): 8457-8467. DOI:10.1002/cam4.3467.

[75] PAPAIOANNOU D, NICOLET D, VOLINIA S, et al. Prognostic and biologic significance of long non-coding RNA profiling in younger adults with cytogenetically normal acute myeloid leukemia [J]. Haematologica, 2017, 102(8): 1391-1400. DOI: 10.3324/haematol.2017.166215.

[76] TANG P, XIE M, WEI Y, et al. A 10-long non-coding RNA-based expression signature as a potential biomarker for prognosis of acute myeloid leukemia[J]. Med Sci Monit, 2019, 25: 4999-5004. DOI: 10.12659/msm.917182.

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