

长链非编码RNA及其在非小细胞肺癌中的表达和作用

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Title: Characteristics, functions of lncRNAs and their expression and roles in non-small cell lung cancer

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摘要: 长链非编码RNA(long non-coding RNAs, lncRNAs)是一类转录本长度超过200个核苷酸的非编码RNA(non-coding RNAs, ncRNAs), 它们不编码蛋白质, 而是以RNA的形式通过转录, 转录后和表观遗传等多种调控机制发挥生物学功能, 包括生长发育、骨髓造血、细胞凋亡和细胞增殖等生命进程中的一系列重要过程。肺癌是全球癌症死亡的主要原因, 它是由不同病因引起的一系列疾病, 可分为小细胞肺癌(small-cell lung cancer, SCLC)和非小细胞肺癌(non-small cell lung cancer, NSCLC)两种类型。肺癌的基本特征是基因组遗传和表观遗传发生改变; 然而, 肺癌发生的具体机制目前仍不明确。近年来的研究资料表明, lncRNAs的异常表达与包括肺癌在内的多种癌症的发生发展有关。本文着重研究lncRNAs在NSCLC中的表达和作用, 并讨论其作为早期诊断, 指导预后的生物标志物以及治疗靶点的潜在临床应用。

Abstract: Long non-coding RNAs (lncRNAs) are a group of non-coding RNAs that consist of > 200 nucleotides. They do not encode proteins, but regulate the expression levels of the gene as a RNA molecular at transcription, post-transcription and epigenetic modification, which including cell growth, bone marrow hematopoiesis, cell apoptosis and cell proliferation and a series of important processes in life. Lung cancer is a common malignant tumor and the major cause of cancer death world-wide, which can be broadly classified into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Lung cancer is characterized by genomic and epigenomic alterations, however, mechanisms underlying lung tumorigenesis remain to be elucidated. Accumulating evidence indicates that abnormal expression of lncRNAs is associated with tumorigenesis of various cancers, including lung cancer. In this review, we highlight the expression and roles of lncRNAs in NSCLC and discuss their potential clinical applications as diagnostic or prognostic biomarkers, as well as therapeutic targets.

参考文献/REFERENCES

- [1] Hainer SJ, Gu W, Carone BR, et al. Suppression of pervasive noncoding transcription in embryonic stem cells by esBAF [J]. *Genes & Development*, 2015, 29(4): 362-378.
- [2] Zhang X, Sun S, Pu JK, et al. Long non-coding RNA expression profiles predict clinical phenotypes in glioma [J]. *Neurobiology of Disease*, 2012, 48(1):1-8.
- [3] Guttman M, Rinn JL. Modular regulatory principles of large non-coding RNAs [J]. *Nature*, 2012, 482(7385): 339-346.
- [4] Geisler S, Collier J. RNA in unexpected places: Long non-coding RNA functions in diverse cellular contexts [J]. *Nature Reviews Molecular Cell Biology*, 2013, 14(11): 699-712.
- [5] Zhao W, Geng D, Li S, et al. LncRNA HOTAIR influences cell growth, migration, invasion, and apoptosis via the miR-20a-5p/HMGA2 axis in breast cancer [J]. 2018, 7(3): 842-855.

- [6]Peng H, Wang J, Li J, et al.A circulating non-coding RNA panel as an early detection predictor of non-small cell lung cancer [J]. *Life Sciences*, 2016, 151: 235-242.
- [7]Zhang J, Zhu N, Chen X.A novel long noncoding RNA LINC01133 is upregulated in lung squamous cell cancer and predicts survival [J]. *Tumour Biology*, 2015, 36(10): 7465-7471.
- [8]Li Z, Guo H, Lu Y, et al.Chemotherapy with or without pemetrexed as second-line regimens for advanced non-small-cell lung cancer patients who have progressed after first-line EGFR TKIs: A systematic review and meta-analysis [J]. *Onco Targets Ther*, 2018, 11: 3697-3703.
- [9]Qiao M, Jiang T, Zhou C.Shining light on advanced NSCLC in 2017: Combining immune checkpoint inhibitors [J]. *Journal of Thoracic Disease*, 2018, 10(Suppl 13): S1534-s1546.
- [10]Vrankar M, Zwitter M, Kern I, et al.PD-L1 expression can be regarded as prognostic factor for survival of non-small cell lung cancer patients after chemoradiotherapy [J]. *Neoplasma*, 2018, 65(1): 140-146.
- [11]Fan LM, Hu ZD.Research progress of lncRNA in non-small cell lung cancer [J]. *Chinese Journal of Lung Cancer*, 2016, 19(02): 108-112.
- [12]Zhen HY, Li JZ, Bao YX, et al.lncRNA: A new strategy for diagnosis and treatment of non-small cell lung cancer [J]. *China Cancer*, 2017, 26(04): 272-278.
- [13]Novello S, Vavala T, Levra MG, et al.Early response to chemotherapy in patients with non-small-cell lung cancer assessed by [18F]-fluoro-deoxy-D-glucose positron emission tomography and computed tomography [J]. *Clinical Lung Cancer*, 2013, 14(3): 230-237.
- [14]Zhang H, Chen Z, Wang X, et al.Long non-coding RNA: A new player in cancer [J]. *Journal of Hematology & Oncology*, 2013, 6: 37.
- [15]Gibb EA, Brown CJ, Lam WL.The functional role of long non-coding RNA in human carcinomas [J]. *Molecular Cancer*, 2011, 10: 38.
- [16]Derrien T, Johnson R, Bussotti G, et al.The GENCODE v7 catalog of human long noncoding RNAs: Analysis of their gene structure, evolution, and expression [J]. *Genome Research*, 2012, 22(9): 1775-1789.
- [17]Guttman M, Amit I, Garber M, et al.Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals [J]. *Nature*, 2009, 458(7235): 223-227.
- [18]Braidotti G, Baubec T, Pauler F, et al.The Air noncoding RNA: An imprinted cis-silencing transcript [J]. *Cold Spring Harbor Symposia on Quantitative Biology*, 2004, 69: 55-66.
- [19]Pauler FM, Stricker SH, Warczuk KE, et al.Long-range DNase I hypersensitivity mapping reveals the imprinted Igf2r and Air promoters share cis-regulatory elements [J]. *Genome Research*, 2005, 15(10): 1379-1387.
- [20]Deng X, Meller VH.Non-coding RNA in fly dosage compensation [J]. *Trends in Biochemical Sciences*, 2006, 31(9): 526-532.
- [21]Yu X, Zhang Y, Li T, et al.Long non-coding RNA Linc-RAM enhances myogenic differentiation by interacting with MyoD [J]. *Nature Communications*, 2017, 8: 14016.
- [22]Wu Z, Liu X, Liu L, et al.Regulation of lncRNA expression [J]. *Cellular & Molecular Biology Letters*, 2014, 19(4):561-575.
- [23]Moretti F, Thermann R, Hentze MW.Mechanism of translational regulation by miR-2 from sites in the 5' untranslated region or the open reading frame [J]. *RNA (New York, NY)*, 2010, 16(12): 2493-2502.
- [24]Forman JJ, Legesse-Miller A, Collier HA.A search for conserved sequences in coding regions reveals that the let-7 microRNA targets Dicer within its coding sequence [J]. *Proceedings of the National Academy of Sciences of the United States of America*, 2008, 105(39): 14879-14884.
- [25]Orom UA, Nielsen FC, Lund AH.MicroRNA-10a binds the 5'UTR of ribosomal protein mRNAs and enhances their translation [J]. *Molecular Cell*, 2008, 30(4): 460-471.
- [26]Mercer TR, Dinger ME, Mattick JS.Long non-coding RNAs: Insights into functions [J]. *Nature Reviews Genetics*, 2009, 10(3): 155-159.
- [27]Ricciuti B, Mencaroni C, Paglialonga L, et al.Long noncoding RNAs: New insights into non-small cell lung cancer biology, diagnosis and therapy [J]. *Medical Oncology (Northwood, London, England)*, 2016, 33(2): 18.
- [28]Du JJ, Tan ZD, Liu CD, et al.A review of long-chain non-coding RNA [J]. *China Biotechnology*, 2016, 36(09): 59-74.
- [29]Wang KC, Chang HY.Molecular mechanisms of long noncoding RNAs [J]. *Molecular Cell*, 2011, 43(6): 904-914.
- [30]Hu X, Feng Y, Zhang D, et al.A functional genomic approach identifies FAL1 as an oncogenic long noncoding RNA that associates with BMI1 and represses p21 expression in cancer [J]. *Cancer Cell*, 2014, 26(3): 344-357.
- [31]Yin Y, Yan P, Lu J, et al.Opposing roles for the lncRNA haunt and its genomic locus in regulating HOXA gene activation during embryonic stem cell differentiation [J]. *Cell Stem Cell*, 2015, 16(5): 504-516.
- [32]He Q, Tian L, Jiang H, et al.Identification of laryngeal cancer prognostic biomarkers using an inflammatory gene-related, competitive endogenous RNA network [J]. *Oncotarget*, 2017, 8(6): 9525-9534.
- [33]Steck E, Boeuf S, Gabler J, et al.Regulation of H19 and its encoded microRNA-675 in osteoarthritis and under anabolic and catabolic in vitro conditions [J]. *Journal of Molecular Medicine (Berlin, Germany)*, 2012, 90(10): 1185-1195.
- [34]Yuan JH, Yang F, Wang F, et al.A long noncoding RNA activated by TGF-beta promotes the invasion-metastasis cascade in hepatocellular carcinoma [J]. *Cancer Cell*, 2014, 25(5): 666-681.

- [35]Tripathi V, Ellis JD, Shen Z, et al. The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation [J]. *Molecular Cell*, 2010, 39(6): 925-938.
- [36]Houseley J, Rubbi L, Grunstein M, et al. A ncRNA modulates histone modification and mRNA induction in the yeast GAL gene cluster [J]. *Molecular Cell*, 2008, 32(5): 685-695.
- [37]Berghoff EG, Clark MF, Chen S, et al. Evi2 (Dlx6as) lncRNA regulates ultraconserved enhancer methylation and the differential transcriptional control of adjacent genes [J]. *Development (Cambridge, England)*, 2013, 140(21): 4407-4416.
- [38]Xu G, Chen J, Pan Q, et al. Long noncoding RNA expression profiles of lung adenocarcinoma ascertained by microarray analysis [J]. *PLoS One*, 2014, 9(8): e104044.
- [39]Yang J, Lin J, Liu T, et al. Analysis of lncRNA expression profiles in non-small cell lung cancers (NSCLC) and their clinical subtypes [J]. *Lung Cancer (Amsterdam, Netherlands)*, 2014, 85(2): 110-115.
- [40]Gao L, Mai A, Li X, et al. LncRNA-DQ786227-mediated cell malignant transformation induced by benzo(a)pyrene [J]. *Toxicology Letters*, 2013, 223(2): 205-210.
- [41]Hu G, Yang T, Zheng J, et al. Functional role and mechanism of lncRNA LOC728228 in malignant 16HBE cells transformed by anti-benzopyrene-trans-7,8-dihydrodiol-9,10-epoxide [J]. *Molecular Carcinogenesis*, 2015, 54 (Suppl 1) : e192-204.
- [42]Thai P, Statt S, Chen CH, et al. Characterization of a novel long noncoding RNA, SCAL1, induced by cigarette smoke and elevated in lung cancer cell lines [J]. *American Journal of Respiratory Cell and Molecular Biology*, 2013, 49(2): 204-211.
- [43]Wei MM, Zhou YC, Wen ZS, et al. Long non-coding RNA stabilizes the Y-box-binding protein 1 and regulates the epidermal growth factor receptor to promote lung carcinogenesis [J]. *Oncotarget*, 2016, 7(37): 59556-59571.
- [44]Tano K, Akimitsu N. Long non-coding RNAs in cancer progression [J]. *Frontiers in Genetics*, 2012, 3: 219.
- [45]Reis EM, Verjovski-Almeida S. Perspectives of long non-coding RNAs in cancer diagnostics [J]. *Frontiers in Genetics*, 2012, 3: 32.
- [46]Xie H, Ma H, Zhou D. Plasma HULC as a promising novel biomarker for the detection of hepatocellular carcinoma [J]. *Biomed Research International*, 2013, 2013: 136106.
- [47]Leyten GH, Hessels D, Jannink SA, et al. Prospective multicentre evaluation of PCA3 and TMPRSS2-ERG gene fusions as diagnostic and prognostic urinary biomarkers for prostate cancer [J]. *European Urology*, 2014, 65(3): 534-542.
- [48]Li M, Qiu M, Xu Y, et al. Differentially expressed protein-coding genes and long noncoding RNA in early-stage lung cancer [J]. *Tumour Biology*, 2015, 36(12): 9969-9978.
- [49]Weber DG, Johnen G, Casjens S, et al. Evaluation of long noncoding RNA MALAT1 as a candidate blood-based biomarker for the diagnosis of non-small cell lung cancer [J]. *BMC Research Notes*, 2013, 6: 518.
- [50]Tantai J, Hu D, Yang Y, et al. Combined identification of long non-coding RNA XIST and HIF1A-AS1 in serum as an effective screening for non-small cell lung cancer [J]. *International Journal of Clinical and Experimental Pathology*, 2015, 8(7): 7887-7895.
- [51]Zhao W, Luo J, Jiao S. Comprehensive characterization of cancer subtype associated long non-coding RNAs and their clinical implications [J]. *Scientific Reports*, 2014, 4: 6591.
- [52]White NM, Cabanski CR, Silva-Fisher JM, et al. Transcriptome sequencing reveals altered long intergenic non-coding RNAs in lung cancer [J]. *Genome Biology*, 2014, 15(8): 429.
- [53]Zhou M, Guo M, He D, et al. A potential signature of eight long non-coding RNAs predicts survival in patients with non-small cell lung cancer [J]. *Journal of Translational Medicine*, 2015, 13: 231.
- [54]Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III [randomised controlled trial [J]. *Lancet (London, England)*, 2009, 374(9687): 379-386.
- [55]Massarelli E, Varella-Garcia M, Tang X, et al. KRAS mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer [J]. *Clinical Cancer Research*, 2007, 13(10): 2890-2896.
- [56]Ma J, Dong C, Ji C. MicroRNA and drug resistance [J]. *Cancer Gene Therapy*, 2010, 17(8): 523-531.
- [57]Tsang WP, Kwok TT. Riboregulator H19 induction of MDR1-associated drug resistance in human hepatocellular carcinoma cells [J]. *Oncogene*, 2007, 26(33): 4877-4881.
- [58]Schneider-Merck T, Pohnke Y, Kempf R, et al. Physical interaction and mutual transrepression between CCAAT/enhancer-binding protein beta and the p53 tumor suppressor [J]. *The Journal of Biological Chemistry*, 2006, 281(1): 269-278.
- [59]Yang Y, Li H, Hou S, et al. The noncoding RNA expression profile and the effect of lncRNA AK126698 on cisplatin resistance in non-small-cell lung cancer cell [J]. *PLoS One*, 2013, 8(5): e65309.
- [60]Liu Z, Sun M, Lu K, et al. The long noncoding RNA HOTAIR contributes to cisplatin resistance of human lung adenocarcinoma cells via downregulation of p21WAF1/CIP1 expression [J]. *PLoS One*, 2013, 8(10): e77293.
- [61]Liu J, Wan L, Lu K, et al. The long noncoding RNA MEG3 contributes to cisplatin resistance of human lung adenocarcinoma [J]. *PLoS One*, 2015, 10(5): e0114586.
- [62]Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer [J]. *The New England Journal of Medicine*, 2002, 346(2): 92-98.
- [63]Olaussen KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-

based adjuvant chemotherapy [J] .The New England Journal of Medicine, 2006, 355(10): 983-991.
[64]Hou Z, Xu C, Xie H, et al.Long noncoding RNAs expression patterns associated with chemo response to cisplatin based chemotherapy in lung squamous cell carcinoma patients [J] .PLoS One, 2014, 9(9): e108133.
[65]Dong S, Qu X, Li W, et al.The long non-coding RNA, GAS5, enhances gefitinib-induced cell death in innate EGFR tyrosine kinase inhibitor-resistant lung adenocarcinoma cells with wide-type EGFR via downregulation of the IGF-1R expression [J] .Journal of Hematology & Oncology, 2015, 8: 43.
[66]Torre LA, Bray F, Siegel RL, et al.Global cancer statistics, 2012 [J] .CA: A Cancer Journal for Clinicians, 2015, 65(2): 87-108.

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