

- [28] Zhao Y, Xu L, Tian D, et al. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: A meta-analysis of randomized controlled trials[J]. *Diabetes Obes Metab*, 2018, 20(2): 458-462.
- [29] Tanaka M, Yamakage H, Inoue T, et al. Beneficial Effects of Ipragliflozin on the Renal Function and Serum Uric Acid Levels in Japanese Patients with Type 2 Diabetes: A Randomized, 12-week, Open-label, Active-controlled Trial[J]. *Intern Med*, 2020, 59(5): 601-609.
- [30] Xu J, Kitada M, Ogura Y, et al. Dapagliflozin Restores Impaired Autophagy and Suppresses Inflammation in High Glucose-Treated HK-2 Cells[J]. *Cells*, 2021, 10(6): 1457.
- [31] Bimbaum Y, Chen H, Tran D, et al. Ticagrelor and Dapagliflozin Have Additive Effects in Ameliorating Diabetic Nephropathy in Mice with Type-2 Diabetes Mellitus[J]. *Cardiovasc Drugs Ther*, 2022, 36(5): 829-840.
- [32] Das NA, Carpenter AJ, Belenchia A, et al. Empagliflozin reduces high glucose-induced oxidative stress and miR-21-dependent TRAF3IP2 induction and RECK suppression, and inhibits human renal proximal tubular epithelial cell migration and epithelial-to-mesenchymal transition[J]. *Cell Signal*, 2020, 68: 109506.
- [33] Lega IC, Bronskill SE, Campitelli MA, et al. Sodium glucose cotransporter 2 inhibitors and risk of genital mycotic and urinary tract infection: A population-based study of older women and men with diabetes[J]. *Diabetes Obes Metab*, 2019, 21(11): 2394-2404.
- [34] Toyama T, Neuen BL, Jun M, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis[J]. *Diabetes Obes Metab*, 2019, 21(5): 1237-1250.
- [35] Herring RA, Shojaee-moradie F, Garesse R, et al. Metabolic Effects of an SGLT2 Inhibitor (Dapagliflozin) During a Period of Acute Insulin Withdrawal and Development of Ketoacidosis in People With Type 1 Diabetes[J]. *Diabetes Care*, 2020, 43(9): 2128-2136.
- [36] Tomita I, Kume S, Sugahara S, et al. SGLT2 Inhibition Mediates Protection from Diabetic Kidney Disease by Promoting Ketone Body-Induced mTORC1 Inhibition[J]. *Cell Metab*, 2020, 32(3): 404-419.e6.
- [37] Blau JE, Tella SH, Taylor SI, et al. Ketoacidosis associated with SGLT2 inhibitor treatment: Analysis of FAERS data[J]. *Diabetes Metab Res Rev*, 2017, 33(8): 10.
- [38] Horii T, Oikawa Y, Atsuda K, et al. On-label use of sodium-glucose cotransporter 2 inhibitors might increase the risk of diabetic ketoacidosis in patients with type 1 diabetes[J]. *J Diabetes Investig*, 2021, 12(9): 1586-1593.
- [39] Aloe S, Filliter C, Salmasi S, et al. Sodium-glucose cotransporter 2 inhibitors and the risk of venous thromboembolism: A population-based cohort study[J]. *Br J Clin Pharmacol*, 2023, 89(9): 2902-2914.
- [40] Menne J, Dumann E, Haller H, et al. Acute kidney injury and adverse renal events in patients receiving SGLT2-inhibitors: A systematic review and meta-analysis[J]. *PLoS Med*, 2019, 16(12): e1002983.

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长链非编码RNA00649的研究进展

王锦玉¹, 贾依晗¹, 张 芳², 王 卯³, 陈 健^{1*}

(1.承德医学院附属医院消化内科, 河北承德 067000; 2.承德医学院附属医院康复科; 3.承德医学院附属医院放射科)

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在全球范围内,2020年约有1930万新增癌症病例和近1000万因癌症死亡的病例,其中肺癌仍然占癌症死亡病例的死亡原因的首位,其次是结直肠癌、肝癌、胃癌和女性乳

腺癌。研究证明,癌症的发生率和死亡率与性别、地区及癌症种类相关^[1]。在中国,癌症发病率和死亡率攀升,截止2015年,癌症成为疾病中的主要死亡原因^[2]。随着科技

* 通讯作者

的不断发展,许多生物分子被用来提示癌症的发生发展,如蛋白质、糖蛋白、核酸(包括信使RNA、环状RNA及长链非编码RNA等)。在分子生物学方面,核苷酸被分为具有编码蛋白质能力的信使RNA(mRNA)和不编码蛋白质的非编码RNA(ncRNA)^[3]。人类基因组包含大约6万个基因,其中大部分为主要由长链非编码RNA(LncRNA)组成的非编码基因^[4]。非编码序列一般至少大于编码序列的4倍,LncRNA是长度至少200个核苷酸的非编码RNA^[5],它被认为呈现高度保守性,且缺乏明显的开放阅读框^[6]。LncRNA的功能多种多样,参与生物作用的很多方面,包括细胞增殖、分化、发育、凋亡和转移,从而参与良恶性疾病的发生发展。

1 LINC00649概念

长链非编码RNA00649(LINC00649)是21号染色体上的基因,包含20个转录本^[7],这种LncRNA在免疫细胞类型中表达情况为:CD4+的单核细胞,CD4+和CD8+的T细胞以及NK细胞。LINC00649可能与胎盘功能及昼夜节律相关^[8,9]。此外,LINC00649中含有一CpG位点cg08309687^[10],同样具有一定的生物学意义。通过GEPIA及NCBI可以了解到,LINC00649也被称为长链非编码RNA intersectin 1-2(Lnc-ITSN1-2)^[11],人们同样对其在疾病中的表达进行了一定的研究,但研究的内容还很稀少,因此,我们对其生物功能的了解仍不够全面和详尽。

2 LINC00649与癌症及其他疾病

2.1 胃癌

研究表明^[12],LINC00649在体外可促进胃癌细胞的增殖、迁移和上皮-间充质转化(EMT),且在胃癌中LINC00649表达上调,从而进一步促进胃癌细胞在体内的生长。LINC00649和YAP1mRNA在胃癌组织中成正相关高表达,而miR-16-5p则呈下调趋势,故LINC00649通过下调miR-16-5p上调YAP1,呈现miR-16-5p依赖性。LINC00649可以通过调节miR-16-5p/YAP1轴来降低YAP1/Hippo通路下游靶点EGFR、SOX2和OCT4的表达水平,从而促进胃癌的进展。

2.2 结直肠癌

何等^[13]通过建立LncRNA介导的竞争性内源RNA(ceRNA)网络(LMCN)得出LINC00649是结直肠癌核心LncRNA,提示其可能是结直肠癌的预后标志物。LINC00649在结直肠癌中呈现高表达,高表达LINC00649

与结直肠癌患者的预后呈现负性相关。在功能上,下调LINC00649可以减少细胞的增殖、迁移、侵袭,并且可以诱导细胞凋亡,从而起到拮抗结直肠癌的作用。因此,当抑制LINC00649基因的表达时,结直肠癌细胞的生长同样受到抑制。LINC00649在结直肠癌细胞中通过与miR-432-5p竞争性结合,诱导HEPA-Toma衍生生长因子(HDGF)增加,进而促进结直肠癌的发生发展^[14]。

2.3 膀胱癌

通过冯等^[15]的研究可以了解到,LINC00649在膀胱癌细胞、膀胱癌组织中表达量均升高,并主要表达于细胞质。同样,陈等^[16]研究发现,LINC00649在膀胱癌细胞中过表达可抑制miR-15a-5p的表达,并通过部分逆转miR-15a-5p对HMGA1的抑制作用,增强HMGA1的表达,进而显著增强癌细胞的增殖、迁移和侵袭能力,因此与肿瘤细胞的肌层浸润十分相关,提示膀胱癌患者预后不良。此外,有研究表明^[17],LINC00649在膀胱癌中可以通过与miR-16-5p结合,降低miR-16-5p在膀胱癌中的表达。下调膀胱癌中的LINC00649或上调miR-16-5p后,JARID2mRNA的表达受到抑制,故得出LINC00649是通过膀胱癌中的miR-16-5p/JARID2轴实现其致癌功能,来促进癌细胞的增殖、迁移和侵袭。

2.4 急性髓系白血病

在郭等^[18]的研究中,LINC00649在急性髓系白血病(AML)细胞中的表达明显低于正常造血细胞,其中154个蛋白编码基因、28个LncRNA和31个miRNA与其表达相关,而有9个HOXA家族成员的表达情况与LINC00649呈显著负相关,故其同样参与了HOXA基因的下调。LINC00649在AML中低表达激活了PI3K-Akt-mTOR通路,进而影响AML的病理过程。

2.5 肺癌

转录因子E2F7激活并诱导LINC00649在肺鳞状细胞癌中表达上调,而且LINC00649通过激活TAF15稳定丝裂原活化蛋白激酶6(MAPK6)的表达,进一步使MAPK6的转录活跃,因此,LINC00649在肺鳞状细胞癌中呈现高表达状态^[19]。

2.6 乳腺癌

LINC00649与核因子90/核因子45(NF90/NF45)复合物相互作用,但不影响NF90/NF45的表达,其通过该复合物增

加缺氧诱导因子1 α (HIF-1 α)mRNA的稳定性和上调HIF-1 α 的表达,从而诱导三阴性乳腺癌细胞的增殖、侵袭和转移,以及肿瘤的生长和转移^[20]。

2.7 宫颈癌

LINC00649在宫颈癌组织中表达增加。通过Si等^[21]的研究可以了解到,LINC00649可以直接与miR-216a-3p结合,使其在癌细胞中的表达降低,进一步沉默LINC00649可以增强miR-216a-3p的表达,抑制宫颈癌细胞的增殖能力、迁移能力和侵袭力。旦等^[22]的研究中发现,LINC00649与miR-424-5p呈负相关,可以通过LINC00649/miR-424-5p/IGF1R轴来影响宫颈癌的发生发展。因此,LINC00649在宫颈癌中起到促进作用。

2.8 多发性硬化症

通过差异表达基因和ceRNA网络的综合分析发现^[23],LINC00649是重要的调节因子,可以在多发性硬化症(multiple sclerosis,MS)的免疫和炎症发病机制期间影响ceRNA机制。上调的LINC0064通过介导不同ceRNA(如MS4A1、DOX17、hsp-miR-275等)来影响MS的疾病进程。LINC00649的表达量可能与MS风险程度有关,从而在MS中发挥特定作用。

3 CpG位点的生物学作用

LINC00649中存在的CpG位点cg08309687,在全基因组关联研究中,cg08309687(LINC00649)的rs2834288与肠道微生物区丰富度相关^[10]。马等^[24]的IVW分析中显示,对生活方式因素、甘油三酯以及血清丙氨酸转氨酶、血清天冬氨酸氨基转移酶和非酒精性脂肪肝的遗传风险评分进行额外调整后,仍可得出cg08309687(LINC00649)上的低甲基化与非酒精性脂肪性肝病显著相关。在墨西哥等地区,cg08309687位点与2型糖尿病相关的三个特征—2型糖尿病易感性、空腹血糖水平和胰岛素抵抗指数(HOMA-IR)显著相关,同时观察到基因间隔点cg08309687与附近的单核苷酸多态性SNPs(CpG $\pm$ 50kb)相关联^[25]。同时,在英国人群中的欧洲诺福克癌症前瞻性研究中^[26],LINC00649的甲基化位点cg08309687与2型糖尿病的发病和流行存在方向的一致性,并且与空腹血糖、空腹胰岛素水平和身体质量指数(BMI)呈方向性一致;在1型糖尿病里,该位点与血糖对DNA甲基化强度的影响也存在一致性。王等^[27]也通过研究推测LINC00649甲基化位点cg0830968与空腹血糖和糖

化血红蛋白相关,参与糖尿病的病理生理机制。代谢综合征作为2型糖尿病和心血管疾病的先天代谢状态,通过研究相关的CpG位点发现cg08309687与腰围相关。尽管cg08309687与蛋氨酸的脂类成分有普遍的相关性,但与高密度脂蛋白无关,进一步提示了该位点与甘油三酯相关而参与脂质代谢^[28]。

4 Lnc-ITSN1-2的表达与临床疾病的关系

聂等^[29]对Lnc-ITSN1-2在炎症性肠病中的作用进行了研究,并得出其在肠黏膜中的表达与炎症性肠病的活动性、炎症因子表达呈正相关,且在英夫利昔单抗治疗后表达下调。有研究表明^[30],血浆Lnc-ITSN1-2的表达与类风湿关节炎相关,在类风湿关节炎中,Lnc-ITSN1-2表达水平显著升高。通过ROC曲线分析表明,Lnc-ITSN1-2对类风湿关节炎的诊断具有较高意义。同时发现,Lnc-ITSN1-2在类风湿关节炎的成纤维细胞样滑膜细胞中呈现高表达,并且下调Lnc-ITSN1-2还可减少炎症反应,降低类风湿关节炎的发病风险和活动度^[31]。在李等^[32]的研究中发现,Lnc-ITSN1-2在强直性脊柱炎中存在高表达,且在肿瘤坏死因子 α 抑制剂治疗后表达下降。Lnc-ITSN1-2同样在急性重症胰腺炎中存在高表达,并且可以很好地区分重症急性胰腺炎(severe acute pancreatitis, SAP)和中重度急性胰腺炎(moderately severe acute pancreatitis, MSAP),其在血清中的表达可以提示病情,但在SAP患者血清中的表达强度与病情严重程度的相关性明显强于MSAP和轻症急性胰腺炎(mild acute pancreatitis, MAP)患者,其表达强度可以一定程度上提示SAP、MSAP患者的死亡率和预后^[33]。张等^[34]研究了Lnc-ITSN1-2在急性缺血性卒中的表达,提示Lnc-ITSN1-2可以预测急性缺血性脑卒中的危险性,其表达增强与急性缺血性卒中患者病情及炎症加重相关。

5 小结与展望

综上所述,随着癌症越来越成为威胁人类健康的焦点,早期发现、早期诊疗就显得愈发重要。近些年,在基因表达方面的研究中,LncRNA逐渐被人们发现并重视。LINC00649作为一种LncRNA,在结直肠癌、胃癌、膀胱癌、急性髓系白血病、肺鳞状细胞癌、三阴性乳腺癌、宫颈癌多种肿瘤中出现表达量升高,并分别通过不同的信号通路影响肿瘤细胞的生理过程,从而达到促进肿瘤细胞生长、迁移等作用。此外,其表达量升高的情况同样出现在炎

症性肠病、类风湿关节炎、强直性脊柱炎等以免疫异常为主要发病机制的良性疾病中,并且在急性胰腺炎、急性缺血性脑卒中里也发现了LINC00649表达量上调,但其在良性疾病致病的生理病理的作用机制仍待深入研究。我们需要进一步关注以下两个方面:(1)LINC00649在肿瘤的发生机制是否存在统一性,是否在其他恶性肿瘤也存在表达量异常。(2)在免疫机制方面,LINC00649是否也参与其他免疫疾病的发生发展。LINC00649是丰富的LncRNA中的一种,但多数LncRNA的机制仍不明了。因此,进一步研究LncRNA,在正常生理过程及肿瘤的诊断和治疗等方面具有无限的发展前景。

参考文献

- [1] Sung H, Ferlay J, Laversanne M, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries[J]. CA Cancer J Clin, 2021, 71(3): 209-249.
- [2] Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015[J]. CA Cancer J Clin, 2016, 66(2): 115-132.
- [3] Boon RA, Jaé N, Holdt L, et al. Long Noncoding RNAs: From Clinical Genetics to Therapeutic Targets? [J]. J Am Coll Cardiol, 2016, 67(10): 1214-1226.
- [4] Kleinbrink EL, Gomez-Lopez N, Ju D, et al. Gestational Age Dependence of the Maternal Circulating Long Non-Coding RNA Transcriptome During Normal Pregnancy Highlights Antisense and Pseudogene Transcripts[J]. Front Genet, 2021, 12: 760849.
- [5] Mercer TR, Dinger ME, Mattick JS, et al. Long non-coding RNAs: insights into functions[J]. Nat Rev Genet, 2009, 10(3): 155-159.
- [6] Holdt LM, Hoffmann S, Sass K, et al. Alu elements in ANRIL non-coding RNA at chromosome 9p21 modulate atherogenic cell functions through trans-regulation of gene networks[J]. PLoS Genet, 2013, 9(7): e1003588.
- [7] Wang H, Di X, Bi Y, et al. Long non-coding RNA LINC00649 regulates YES-associated protein 1 (YAP1)/Hippo pathway to accelerate gastric cancer (GC) progression via sequestering miR-16-5p[J]. Bioengineered, 2021, 12(1): 1791-1802.
- [8] Kleinbrink EL, Gomez-Lopez N, Ju D, et al. Gestational Age Dependence of the Maternal Circulating Long Non-Coding RNA Transcriptome During Normal Pregnancy Highlights Antisense and Pseudogene Transcripts[J]. Front Genet, 2021, 12: 760849.
- [9] Zhou G, Fichorova RN, Holzman C, et al. Placental circadian lincRNAs and spontaneous preterm birth[J]. Front Genet, 2023, 13: 1051396.
- [10] Bonder MJ, Kurilshikov A, Tigchelaar EF, et al. The effect of host genetics on the gut microbiome[J]. Nat Genet, 2016, 48(11): 1407-1412.
- [11] Tang Z, Li C, Kang B, et al. GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses[J]. Nucleic Acids Res, 2017, 45(W1): W98-W102.
- [12] Wang H, Di X, Bi Y, et al. Long non-coding RNA LINC00649 regulates YES-associated protein 1 (YAP1)/Hippo pathway to accelerate gastric cancer (GC) progression via sequestering miR-16-5p[J]. Bioengineered, 2021, 12(1): 1791-1802.
- [13] He M, Lin Y, Xu Y, et al. Identification of prognostic biomarkers in colorectal cancer using a long non-coding RNA-mediated competitive endogenous RNA network[J]. Oncol Lett, 2019, 17(3): 2687-2694.
- [14] Bao J, Bi X, Wang J, et al. Long noncoding RNA LINC00649 functions as a microRNA-432-5p sponge to facilitate tumorigenesis in colorectal cancer by upregulating HDGF[J]. Mol Med Rep, 2022, 25(3): 104.
- [15] Feng L, Yang J, Zhang W, et al. Prognostic significance and identification of basement membrane-associated lncRNA in bladder cancer[J]. Front Oncol, 2022, 12: 994703.
- [16] Chen X, Chen S. LINC00649 promotes bladder cancer malignant progression by regulating the miR-15a-5p/HMGA1 axis[J]. Oncol Rep, 2021, 45(4): 8.
- [17] Liu Y, Huang X, Guo L, et al. LINC00649 Facilitates the Cellular Process of Bladder Cancer Cells via Signaling Axis miR-16-5p/JARID2[J]. Urol Int, 2022, 106(3): 304-312.
- [18] Guo C, Gao YY, Ju QQ, et al. LINC00649 underexpression is an adverse prognostic marker in acute myeloid leukemia[J]. BMC Cancer, 2020, 20(1): 841.
- [19] Zhu H, Liu Q, Yang X, et al. LncRNA LINC00649 recruits TAF15 and enhances MAPK6 expression to promote the development of lung squamous cell carcinoma via activating MAPK signaling pathway[J]. Cancer Gene Ther, 2022, 29(8-9): 1285-1295.
- [20] Zhang J, Du C, Zhang L, et al. LncRNA LINC00649 promotes the growth and metastasis of triple-negative breast cancer by maintaining the stability of HIF-1 α through the NF90/NF45 complex[J]. Cell Cycle, 2022, 21(10): 1034-1047.
- [21] Si C, Yang L, Cai X, et al. LncRNA LINC00649 aggravates the progression of cervical cancer through sponging miR-216a-3p[J]. J Obstet Gynaecol Res, 2022, 48(11): 2853-2862.

- [22] 旦慧文,张焕敏,王婷婷. LINC00649通过miR-424-5p/IGF1R轴调控内质网应激介导的宫颈癌细胞凋亡[J]. 肿瘤防治研究, 2022, 49(2): 101-109.
 - [23] Wang T, Xu S, Liu L, et al. Integrated analysis of differentially expressed genes and a ceRNA network to identify hub lncRNAs and potential drugs for multiple sclerosis[J]. Am J Transl Res, 2022, 14(2): 772-787.
 - [24] Ma J, Nano J, Ding J, et al. A Peripheral Blood DNA Methylation Signature of Hepatic Fat Reveals a Potential Causal Pathway for Nonalcoholic Fatty Liver Disease[J]. Diabetes, 2019, 68(5): 1073-1083.
 - [25] Kulkarni H, Kos MZ, Neary J, et al. Novel epigenetic determinants of type 2 diabetes in Mexican-American families[J]. Hum Mol Genet, 2015, 24(18): 5330-5344.
 - [26] Cardona A, Day FR, Perry JRB, et al. Epigenome-Wide Association Study of Incident Type 2 Diabetes in a British Population: EPIC-Norfolk Study[J]. Diabetes, 2019, 68(12): 2315-2326.
 - [27] Wang Z, Peng H, Gao W, et al. Blood DNA methylation markers associated with type 2 diabetes, fasting glucose, and HbA1c levels: An epigenome-wide association study in 316 adult twin pairs[J]. Genomics, 2021, 113(6): 4206-4213.
 - [28] Nuotio ML, Pervjakova N, Joensuu A, et al. An epigenome-wide association study of metabolic syndrome and its components[J]. Sci Rep, 2020, 10(1): 20567.
 - [29] Nie J, Zhao Q. Lnc-ITSN1-2, Derived From RNA Sequencing, Correlates With Increased Disease Risk, Activity and Promotes CD4+ T Cell Activation, Proliferation and Th1/Th17 Cell Differentiation by Serving as a ceRNA for IL-23R via Sponging miR-125a in Inflammatory Bowel Disease[J]. Front Immunol, 2020, 11: 852.
 - [30] Gong X, Fan X, Zhang Z, et al. Circulating Lnc-ITSN1-2 expression presents a high value in diagnosis of rheumatoid arthritis and correlates with disease activity[J]. Int J Clin Exp Pathol, 2017, 10(10): 10451-10458.
 - [31] Yue T, Fan X, Zhang Z, et al. Downregulation of lncRNA ITSN1-2 correlates with decreased disease risk and activity of rheumatoid arthritis (RA), and reduces RA fibroblast-like synoviocytes proliferation and inflammation via inhibiting NOD2/RIP2 signaling pathway[J]. Am J Transl Res, 2019, 11(8): 4650-4666.
 - [32] Li M, Zhou X. Long noncoding RNA intersectin 1-2 gradually declines during adalimumab treatment, and its reduction correlates with treatment efficacy in patients with ankylosing spondylitis[J]. Inflammopharmacology, 2021, 29(5): 1371-1378.
 - [33] Li J, Bu X, Chen X, et al. Predictive value of long non-coding RNA intersectin 1-2 for occurrence and in-hospital mortality of severe acute pancreatitis[J]. J Clin Lab Anal, 2020, 34(5): e23170.
 - [34] Zhang Y, Niu C. The correlation of long non-coding RNA intersectin 1-2 with disease risk, disease severity, inflammation, and prognosis of acute ischemic stroke[J]. J Clin Lab Anal, 2020, 34(2): e23053.
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成人隐匿性自身免疫性糖尿病合并肛周脓肿误诊1例

陈海兰¹, 卢黎明^{2*}, 任 柳³

(1.联勤保障部队第九八一医院内分泌科,河北承德 067000;

2.联勤保障部队第九八一医院质控科;3.联勤保障部队第九八一医院体检科

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* 通讯作者