

· 综述 ·

长链非编码 RNA 在宫颈癌中的研究进展

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[摘要] 宫颈癌的发生和发展是一个复杂的病理过程,除了人乳头瘤病毒(HPV)感染外,癌基因的激活和抑制基因的失活也在癌症过程中发挥了重要作用。长链非编码RNA(LncRNA)是长度大于200个核苷酸、不能编码蛋白质的长RNA转录物。一些LncRNA在肿瘤中表达异常,可作为癌基因或抑癌基因参与细胞通路调控,并与肿瘤发生、发展及转移密切相关。越来越多的证据表明,一些LncRNA在宫颈癌细胞中表达异常,可通过多种途径调控宫颈癌细胞的增殖、迁移与凋亡,并且与肿瘤的大小、血管生成、晚期FIGO分期、淋巴结转移和不良预后密切相关,是宫颈癌诊断与预后的重要指标和潜在治疗靶点。

[关键词] 宫颈癌;长链非编码RNA;作用机制

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Research progress of long non-coding RNA in cervical cancer

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[Abstract] The occurrence and development of cervical cancer is a complex pathological process. In addition to HPV infection, oncogene activation and inactivation of suppressor genes play an important role in the cancer process. LncRNAs are long RNA transcripts, which are longer than 200 nucleotides and are unable to encode proteins. Some lncRNAs are abnormally expressed in tumors and can be involved in the cellular pathways regulation as oncogenes or tumor suppressor genes, and are closely related to its development and metastasis. There are growing evidences that some lncRNAs are abnormally expressed in cervical cancer cells, and there are various ways to regulate their proliferation, migration and apoptosis. LncRNAs are closely related to tumor size, angiogenesis, FIGO late stage, lymph node metastasis and poor prognosis of cervical cancer. They are important indicators for diagnosis and prognosis, and also are potential therapeutic targets.

[Key words] cervical cancer; long non-coding RNA; mechanism

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1 宫颈癌简介

宫颈癌是女性最常见的恶性肿瘤之一,宫颈癌发病率位居全世界癌症第4位^[1]。据统计,全球每年新发病例约53万人,死亡人数高达27万人^[1-2]。

其中,宫颈癌患者主要分布在发展中国家,约占总人数的85%,低收入和中等收入国家宫颈癌的病死率是较富裕国家的19倍^[2-3]。在中国,每年约有9.89万人确诊宫颈癌,3.05万人因其死亡^[4]。宫颈癌对女性生命和健康造成极大危害。现有研究表明,95%患者因为高危型人乳头瘤病毒(high risk human papillomavirus, HR-HPV)的持续感染,从而导致宫颈癌前病变及浸润^[5-6]。HPV基因组编码的E6和E7癌基因的持续过度表达会引起遗传和表观遗传不稳定性,在宫颈癌的发展中起关键作用^[7]。然而,

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大多数 HPV 感染人群不会发展为宫颈癌,因此除了 HPV 感染外,宿主的基因组变异也是宫颈癌发生的主要促成因素^[8],所以宫颈癌的发病机制有待进一步研究。

2 长链非编码 RNA (long non-coding RNA, LncRNA) 简介

2001 年人类基因组计划 (human genome project, HGP) 发现,在含有 30 亿碱基对的人类基因组中,蛋白质编码基因仅占总转录基因的 2%,而大多数基因被转录为非蛋白质编码 RNA (noncoding RNA, ncRNA),这些大量的基因组序列被认为是非功能性的“垃圾序列”^[9-10]。随着二代测序技术和基因组分析技术的快速发展,这些 ncRNA 的作用逐渐引起人们重视。越来越多的研究证实,ncRNA 在疾病发生发展过程中发挥着不可忽视的作用。ncRNA 包括 lncRNA、微小 RNA (miRNA)、环形 RNA (circRNA) 等主要类型,这些 ncRNA 与癌症的发生、发展和治疗都密切相关^[11-12]。其中,lncRNA 定义为长度大于 200 个核苷酸,不能编码蛋白质的长 RNA 转录物^[13]。最初 lncRNA 被认为是基因组转录的“噪声”,是 RNA 聚合酶 II 转录的副产物,并不具有生物学功能^[14]。近年来,越来越多的研究表明,lncRNA 可通过转录水平、转录后水平等表观遗传学层面局部或全局调控基因表达,并在许多生命活动中发挥着重要作用,如参与 X 染色体失活、调控 mRNA 降解、参与细胞核亚结构的形成、调节染色质重塑等^[15-16]。随着生物信息学的不断发展,高通量测序、克隆、基因芯片、基因组富集分析等一系列新的实验方法的应用,越来越多的 lncRNA 逐渐被发现^[17]。虽然已发现大量 lncRNA,但只有少数分子生物学功能得到了研究,大多数 lncRNA 分子在细胞发育中的作用和机制尚不清楚^[18]。一些 lncRNA 在肿瘤中表达异常,可以作为癌基因或抑癌基因参与细胞通路调控,与肿瘤的发生、发展以及转移密切相关^[19]。肿瘤细胞中某些具有特异性的 lncRNA 的表达水平异常可作为肿瘤诊断的有效检测指标,并为肿瘤治疗提供新的研究方向^[20]。

3 LncRNA 与 HPV

多数 HPV 感染在几个月内能被清除,但未被清除的 HPV 的 DNA 能整合到宿主染色体中,增加 E6 和 E7 的表达,使 2 种重要的肿瘤抑制蛋白 p53 和视网膜母细胞瘤蛋白 (retinoblastoma protein, pRB) 失活、基因组不稳定性增加、体细胞突变,最终导致细

胞周期紊乱和恶性转化^[7-21]。将致癌 HPV DNA 整合到宿主基因组中可以改变宫颈癌细胞中 lncRNA 的表达谱;某些 lncRNA 可导致其靶蛋白差异表达,包括 HPV 阳性宫颈癌细胞系中 DNA 修复、细胞周期、增殖和凋亡的几种关键调节因子^[22]。已有研究发现,与 HPV16 E7 相互作用的 E2F6 (Polycomb 抑制复合物) 转录因子能够转录调节组蛋白-赖氨酸 N-甲基转移酶 [zeste 基因增强子同源物 2 (enhancer of zeste homolog 2, EZH2); PRC2 (Polycomb Repressive Complex 2) 复合物的关键组分],而 PRC2 复合物能与 lncRNA 相互作用;E7 可能与高表达的 PRC2 复合物成员竞争 HOTAIR 转录物上的结合位点,这可以防止 PRC2 复合物的聚集,从而促进靶基因的上调;因此,HOTAIR 可以作为宫颈癌发生过程中 HPV16 癌蛋白 E7 的靶点之一^[23]。Jiang 等^[24]发现 HPV 可能是诱导宫颈鳞状细胞癌中 MALAT-1 表达的关键因素,HPV16 E6/E7 的敲减降低了 MALAT-1 的表达:在 HPV16 阳性细胞 CaSki 中使用 HPV16 E6/E7 的短发夹 RNA (short hairpin RNA, shRNA),发现 E6/E7 下调时 MALAT-1 的表达降低,这些结果表明 HPV16 E6/E7 基因参与宫颈癌中 MALAT-1 的表达调控。

4 与宫颈癌相关的 lncRNA

随着 lncRNA 的深入研究,越来越多的 lncRNA 被发现在宫颈癌细胞中表达异常,参与基因调控,如在转录水平减弱或增强致癌过程中靶基因的表达,阻断或促进癌症发展^[25]。Gibb 等^[26]分析了由非肿瘤和上皮内瘤变 (cervical intraepithelial neoplasia, CIN) 的宫颈标本构建的长序列基因表达 (long serial analyses of gene expression, L-SAGE) 文库,首次报道了在人宫颈中表达的 1 056 个 lncRNA,并表明这些独特的 lncRNA 转录物可能有助于宫颈前体病变的发生和进展。目前 MEG3、GAS5、HOTAIR、MALAT-1、H19、lncRNA-ANRIL 等在宫颈癌中研究报道较多,这些 lncRNA 的异常表达与宫颈癌的恶性表型、FIGO 分期、侵袭转移、不良预后密切相关。

4.1 母本印记表达基因 3 (maternally expressed gene 3, MEG3)

MEG3 位于人类染色体 14q32,在多种癌症中异常表达,如在结肠癌、肺癌、乳腺癌以及宫颈癌中都能观察到 MEG3 表达下调,属于肿瘤抑制基因^[27]。在乳腺癌细胞中,MEG3 的过表达导致增殖细胞核抗原 (proliferating cell nuclear antigen, PCNA)、基质金属蛋白酶 9 (matrix metalloproteinase 9, MMP-9) 和

血管内皮生长因子A(vascular endothelial growth factor A, VEGFA)表达下调从而抑制细胞生长、侵袭和血管生成^[28]。MEG3过表达可抑制HeLa细胞的生物活性,并且通过负调控PI3K/Akt信号通路下调MMP-2和MMP-9表达,抑制肿瘤细胞的侵袭和迁移能力;同时还通过PI3K/Akt通路降低Bax、Bcl-2和P21蛋白表达,诱导细胞周期G1期停滞、抑制癌细胞增殖并加速其凋亡^[29]。Zhang等^[30]报道MEG3在宫颈癌组织中的表达与相邻正常组织相比显著下降,其表达下调与肿瘤大小、晚期FIGO分期、淋巴结转移和HR-HPV阳性都具有相关性;同时,MEG3表达上调可抑制宫颈癌细胞增殖并诱导其凋亡,这表明MEG3在宫颈癌中具有抑癌作用。宫颈癌中MEG3基因异常表达与其启动子区域中高甲基化有关;MEG3的启动子区域富含CpG二核苷酸,其上游存在2个差异甲基化区域(differentially methylated regions, DMRs):IG-DMR和MEG3-DMR,能调控MEG3的表达^[31];血浆中MEG3甲基化是诊断CIN3、HR-HPV感染和淋巴结转移的有效生物标志,在宫颈癌的临床实践中具有重要价值。

4.2 生长抑制特异性转录本-5(growth arrest-specific transcript 5, GAS5)

GAS5最初从生长停止期间高水平表达的潜在肿瘤抑制基因筛选中分离出来^[32]。该基因位于1q25,是与淋巴瘤相关的染色体位点^[33]。一些研究表明,GAS5在多种癌症如乳腺癌、胃癌和肺癌中表达下调并发挥肿瘤抑癌基因作用,参与细胞凋亡、增殖、转移、血管生成、DNA修复和肿瘤细胞代谢的控制^[34],受mTOR通路和无义介导的降解通路(non-sense-mediated mRNA decay, NMD)调控^[35]。对GAS5的进一步研究发现,尽管GAS5不能编码蛋白质,但它可通过编码位于内含子的核仁小RNA(small nucleolar RNA, snoRNA)来抑制细胞生长,并诱导细胞凋亡^[36]。Cao等^[37]发现GAS5在宫颈癌组织中的表达明显低于癌旁正常组织,其表达下降与FIGO分期、血管侵犯和淋巴结转移显著相关。此外,GAS5低表达宫颈癌患者的总体生存率明显低于GAS5高表达患者。最近有研究发现,GAS5可通过抑制miR-21,调控宫颈癌细胞程序性细胞死亡因子4(programmed cell death protein 4, PDCD4)和PTEN基因(gene of phosphate and tension homology deleted on chromosome ten, PTEN)的表达,影响蛋白激酶B(protein kinase B, PKB)的磷酸化,从而抑制细胞生长、侵袭和迁移^[38]。因此,GAS5可以作为宫

颈癌治疗中的新型生物标志和治疗靶标。

4.3 同源框转录反义RNA(HOX transcript antisense RNA, HOTAIR)

HOTAIR是位于12号染色体上的HOXC基因座的lncRNA,与HOXC基因共表达,是HOXD基因转录的抑制者^[39]。它可以与PRC2相互作用介导HOXD基因座上组蛋白H3的赖氨酸27甲基化和赖氨酸4去甲基化;还可以改变染色体状态,从而影响多种基因表达^[39-40]。HOTAIR能在多种癌症如结肠癌^[40]、肺癌^[41]及肾癌^[42]中过表达,在血管生成、肿瘤生长和转移中发挥重要调控作用。HOTAIR通过直接激活VEGFA的转录以及通过葡萄糖调节蛋白78(glucose regulated protein 78 kD, GRP78)介导的VEGFA和血管生成素2(angiogenesis 2, Ang2)表达的上调来增加肿瘤活力,促进血管生成,从而加速肿瘤生长^[43]。此外HOTAIR可通过上调VEGF、MMP-9和上皮细胞-间充质转化(epithelial mesenchymal transition, EMT)相关基因的表达,诱导细胞迁移和侵袭来促进宫颈癌进展^[44],表明HOTAIR可能通过上调这些蛋白介导肿瘤血管生成。已有研究发现,HOTAIR在宫颈癌组织和细胞系中表达显著升高,HOTAIR可通过抑制HeLa细胞中的p21诱导放射抗性;HOTAIR的敲低上调p21并因此增加C33-A细胞的放射敏感性;HOTAIR的敲低显著抑制肿瘤生长并使宫颈癌对体内放射疗法敏感,提示HOTAIR可能是宫颈癌的潜在治疗靶点^[45]。

4.4 肺腺癌转移相关转录本-1(metastasis associated in lung adenocarcinoma transcript 1, MALAT-1)

MALAT-1也被称为非编码核富集转录物2(noncoding nuclear-enriched abundant transcript 2, NEAT2),位于染色体11q13,是一种核lncRNA,长度为8.7kb,在哺乳动物物种中高度保守,参与癌症发展并在多种癌症组织和细胞系中高表达,促进癌细胞的生长、存活、迁移及转移,因此被认为是某些癌症的致癌基因,如肾癌、骨髓瘤、卵巢癌以及宫颈癌等^[46-47]。已有研究指出,MALAT-1可以促进多种辅阻遏物/共激活因子的组装,通过改变Polycomb2蛋白(Polycomb2, Pc2)的活性来改变染色质上的组蛋白修饰;此外,MALAT-1分子能与PRC2相互作用来调节靶基因的表现遗传状态:MALAT-1直接与EZH2蛋白结合发挥染色质组蛋白修饰的甲基转移酶活性,调节染色质组蛋白甲基化^[48]。MALAT-1可通过VE-钙粘蛋白/ β -连环蛋白复合物以及ERK/MMP和FAK/桩蛋白信号通路促进血管生成拟态

(vasculogenic mimicry, VM)和血管生成,从而促进胃癌的致瘤性和转移^[49]。Liu等^[50]研究发现,在HR-HPV阳性肿瘤组织和细胞系中验证了MALAT-1的高表达,敲减内源性MALAT-1表达显著降低HeLa和SiHa细胞的生长速率、侵袭能力并诱导细胞凋亡。此外,与放射治疗敏感组织相比,放射治疗耐药组织中MALAT-1水平显著升高,并且与miR-143相互作用,调节肿瘤细胞的存活、凋亡和细胞周期,从而影响放疗效率^[51]。因此,MALAT-1可能是宫颈癌进展和预后的潜在生物标志,也是抗肿瘤治疗的有效靶标。

4.5 H19

H19位于染色体11p15.5上,长度为2.3 kb,是一种母系胚胎基因,在成人组织中通常表达下调,但在癌组织中高表达^[52]。H19可调节肿瘤的癌变、血管生成和转移。在神经胶质瘤组织中,H19通过抑制microRNA-29a调节神经胶质瘤血管生成和神经胶质瘤相关内皮细胞的增殖及迁移^[53]。H19已被证实与甲基CpG结合结构域蛋白1(methyl-CpG-binding domain protein 1, MBD1)相互作用以抑制转录,还可作为miR-675的microRNA前体,促进肿瘤发生。此外,H19的致癌特性还归因于其靶向PRC2的全长转录物(通过与PRC2的组蛋白赖氨酸甲基转移酶组分EZH2结合)促进癌症转移的基因^[54]。有研究报道,H19在宫颈癌细胞系特别是HeLa和MS751细胞中表达上调,并且在细胞外囊泡(extracellular vesicles, EVs)中也存在,其可以通过转化生长因子 β (transforming growth factor beta, TGF- β)和缺氧模拟物CoCl₂处理以细胞系特异性方式调节表达;并且,H19在宫颈癌细胞中的功能主要是通过促进细胞增殖和多细胞肿瘤球体(multicellular tumor spheroid, MTS)形成,而不显著影响细胞凋亡和细胞迁移。这些发现表明H19能促进宫颈癌细胞系的特异性生长,并且可以作为癌症诊断和治疗的潜在靶标^[55]。

4.6 lncRNA-ANRIL

INK4基因座中的反义非编码RNA(antisense non-coding RNA in the INK4 locus, lncRNA-ANRIL),也称为CDKN2B-AS1,是第1个被鉴定的lncRNA,位于染色体9p21上的CDKN2A/B基因的基因簇中,含有CDK抑制剂p16、p15及p53稳定因子ARF,这些基因正向调节pRB和p53通路,在肿瘤抑制中起关键作用^[56-57]。ANRIL在多种人类癌细胞系中高表达,如非小细胞肺癌、宫颈癌和骨肉瘤,并且参与调

节多种与基因表达、细胞增殖、细胞黏附和凋亡有关的基因^[58]。Zhang等^[59]研究发现,与正常癌旁组织相比,ANRIL的表达在宫颈癌组织和细胞系中均显著增加;ANRIL的高表达与晚期FIGO分期和淋巴结转移相关;与ANRIL低表达的患者相比,ANRIL高表达患者的总体生存期较差;此外,ANRIL表达降低抑制了宫颈癌的细胞增殖、迁移和侵袭,并且抑制ANRIL的表达可导致PI3K/Akt通路的失活。这些结果表明,ANRIL可能在宫颈癌的发展中起重要作用,可作为新的宫颈癌预后生物标志和治疗靶点。

4.7 其他与宫颈癌相关的lncRNA

除了以上6种常见报道的宫颈癌相关lncRNA,还有其他的一些lncRNA也参与了宫颈癌的调控。NORAD是高度保守的lncRNA,能够通过隔离Pumilio蛋白直接调节染色体稳定性;其表达在宫颈癌组织和细胞系中显著上调,抑制NORAD能减少宫颈癌细胞的增殖、侵袭和EMT过程;此外,NORAD可通过上调smad相互作用蛋白1(smad-interacting protein 1, SIP1)表达来吸附miR-590-3p以促进宫颈癌细胞的增殖和侵袭^[60]。SRA位于染色体5q31.3,是妇科癌症的关键调节因子;宫颈癌组织中SRA表达高于癌旁组织;SRA通过调节EMT改变了宫颈癌细胞的生长、迁移和侵袭^[61]。NEAT1长为3.2 kb,从多发性内分泌肿瘤基因座转录;NEAT1通过激活PI3K/Akt信号通路促进宫颈癌细胞增殖和迁移,因此NEAT1可被认为是宫颈癌的潜在治疗靶点^[62]。DLG1-AS1在宫颈癌组织中显著上调,DLG1-AS1/miR-107/ZHX1可形成内源竞争RNA(competing endogenous RNA, ceRNA)网络;DLG1-AS1通过竞争性结合miR-107以减少miR-107对其靶基因ZHX1表达的抑制,从而促进宫颈癌细胞增殖,并导致肿瘤进展和患者预后不良^[63]。

5 结语和展望

新的研究发现,lncRNA在调节肿瘤微环境中能发挥重要作用。肿瘤细胞和基质细胞分泌的外泌体是肿瘤微环境中细胞间通讯的关键介质,外泌体衍生的lncRNA通过调节血管生成、免疫和转移在促进肿瘤的发生中起关键作用^[64]。有研究报道,与正常对照相比,HOTAIR、MALAT-1和MEG3在宫颈癌患者分离的外泌体中表达差异显著^[65]。缺氧是肿瘤微环境的经典特征,转录因子缺氧诱导因子(hypoxia-inducible factor, HIF)激活缺氧途径,与许多癌症的侵袭性表型和转移有关;缺氧反应性lncRNA

能作为间接反映 HIF 或 HIF 转录的直接调节效应物,在调控缺氧基因转录和转录后水平表达中发挥关键作用。此外,缺氧反应性 lncRNA 的异常表达与癌症患者的不良结果显著相关,可作为肿瘤标志物或治疗靶标^[66]。

LncRNA 不仅提供了对疾病机制理解的新视角,而且提供了新的治疗机会。LncRNA 相对于蛋白质编码基因具有优势,因为它们的表达更具组织特异性,因此能作为生物标记物和治疗靶标^[67]。LncRNA 可通过多种方法进行靶向治疗,包括 RNA 干扰(RNA interference, RNAi)介导的基因沉默、反义寡核苷酸、基于质粒的靶向治疗及小分子抑制剂治疗等^[67-68]。Ferreira 等^[69]发现,lncRNA PCA3 在前列腺癌中高表达,是尿液中可检测的有效生物标志物;小干扰 RNA (small interfering RNA, siRNA)介导的 PCA3 下调显著抑制前列腺癌细胞的生长和活力,并降低雄激素受体 (androgen receptor, AR) 靶基因的表达,提示它可能是潜在的治疗靶点。LncRNA 为癌症治疗提供了新的希望,预计在不久的将来,许多 lncRNA 可成为癌症诊断和治疗的有效工具。然而,lncRNA 在宫颈癌中的确切分子机制仍不清楚,需要进一步探索和验证研究来阐明这些复杂的机制以及 lncRNA 在宫颈癌中的临床应用。

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