DOI:10.16781/j.0258-879x.2019.10.1124

·综 述·

长链非编码 RNA 在宫颈癌发生、发展中的机制

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[摘要] 宫颈癌是女性第二常见的恶性肿瘤，是发展中国家女性恶性肿瘤死亡的第三大主要原因，早期诊断和治疗是有效治疗宫颈癌、改善预后的关键。由于其复杂性，宫颈癌的发生、发展机制仍然是研究者亟需攻克的难题。近年来，大量研究表明长链非编码 RNA（lncRNA）在肿瘤发生、发展中起着重要作用。本文围绕人乳头瘤病毒（HPV）型 E6 和 E7 癌蛋白相关机制、lncRNA 性质相关机制和肿瘤发生、发展中常见信号通路相关机制，对宫颈癌机制网络中 lncRNA 的作用进行综述，为筛查宫颈癌早期诊断和治疗中可用的潜在标志物提供参考。

[关键词] 长链非编码 RNA；宫颈肿瘤；信号转导通路；微 RNA
[中图分类号] R 737.33 **[文献标志码]** A **[文章编号]** 0258-879X(2019)10-1124-06

Long non-coding RNAs in development and progression of cervical cancer: mechanism research status

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[Abstract] Cervical cancer is the second most commonly seen cancer in women and the third leading cause of cancer death in developing countries. Early diagnosis and treatment are the keys to the effective treatment of cervical cancer and the improvement of prognosis. Because of the complexity, the mechanism of development and progression of cervical cancer is still an urgent problem to solve. Recently, quantity of studies have shown that long non-coding RNAs (lncRNAs) play important roles in tumor development and progression. In this review, we sumed up the multiple effects of lncRNAs in cervical cancer, focusing on the related mechanisms of human papilloma virus (HPV) E6 and E7 oncoprotein, the nature of lncRNAs and the signaling pathway in the development and progression of cervical cancer. And we further expounded the cervical cancer mechanism network, providing reference for screening the potential markers for early diagnosis and treatment of cervical cancer.

[Key words] long non-coding RNAs; uterine cervical neoplasms; signaling pathway; microRNAs
[Acad J Sec Mil Med Univ, 2019, 40(10): 1124-1129]

宫颈癌是女性生殖系统第二常见的恶性肿瘤[1]。据美国癌症学会估计，到 2019 年将有 13 170 例新发侵袭性宫颈癌，且有 4 250 例女性患者因该病死亡[2]。宫颈癌的发生是一个循序渐进的过程，起病初表现为宫颈上皮内瘤变（cervical intraepithelial neoplasia，CIN），经 CIN1、CIN2、CIN3、早期浸润癌多个阶段最终发展成浸润癌[3]。宫颈人乳头瘤病毒（human papilloma virus，HPV）的持续感染是宫颈癌癌前病变及宫颈癌发病的必要条件[4]。高危人乳头瘤病毒（high-risk human papilloma virus，hrHPV）感染已被证实为侵袭性宫颈癌的主要病因[5]。大量研究表明长链非编码 RNA（long non-coding RNA，lncRNA）在宫颈癌的发生、发展过程中发挥着促癌或抑癌作用，其机制涉及 E6 和 E7 癌蛋白、微 RNA（microRNA，miRNA）及多条信号通路[6-9]。本文就 lncRNA 在宫颈癌发生、发展中的机制进行综述。

1 LncRNA 概述

LncRNA 是具有 200 多个核苷酸的异质性转录本，由于缺少所需长度的开放阅读框而不具备蛋白质编码能力，可以按照位置 [如长基因间 RNA（large intergenic noncoding RNA，lincRNA）]、结构 [如环状 RNA（circular

[收稿日期] 2019-05-13 **[接受日期]** 2019-06-26
[基金项目] 国家重点研发计划(2016YFC1303100). Supported by National Key Research and Development Program of China (2016YFC1303100).
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RNA，circRNA）]、功能 [如竞争性内源性 RNA（competitive endogenous RNA，ceRNA）] 和转录方向（如反义 RNA）等进行分类[10]。

研究发现，lncRNA 是一类新型的肿瘤主调控因子，在细胞增殖、细胞分化、染色质重构、基因组剪接、表观遗传调控、转录等重要生物学过程中发挥着关键作用[11]。如 lncRNA 肝细胞核因子 1 同源异型盒 A（hepatocyte nuclear factor 1 homeobox A，HNF1A）反义 RNA1 在非小细胞肺癌组织和细胞系中表达上调，其高表达与晚期临床分期和转移相关[12]。LncRNA CCAAT/增强子结合蛋白 α（CCAAT/enhancer binding protein α，*CEBPA*）反义 RNA1 是一种癌基因，其在口腔鳞状细胞癌中表达上调与临床晚期、分化不良、淋巴结转移相关[13]。

此外，lncRNA 的细胞定位与其潜在功能信息有关。细胞核 lncRNA 可通过与关键表观遗传调控因子相互作用，增强染色质环化及与剪接因子相互作用调控剪接，从而实现转录调控[14]。目前发现的细胞核 lncRNA 有 lncRNA-肺腺癌转移相关转录本 1（metastasis-associated lung adenocarcinoma transcript 1，MALAT1）[15]和 lncRNA-核富含丰富的转录本 1（nuclear-enriched abundant transcript 1, NEAT1）[16]，细胞质 lncRNA 有 lncRNA-分化拮抗非蛋白质编码 RNA（differentiation antagonizing nonprotein coding RNA，DANCR）[17]和 lncRNA-opa 相互作用蛋白 5-反义转录本 1（opa-interacting protein 5 antisense transcript 1，OIP5-AS1）[18]，双定位 lncRNA 有 lncRNA-牛磺酸上调基因 1（taurine-upregulated gene 1，TUG1）[19]、lncRNA-癌症易感性候选基因 7（cancer susceptibility candidate 7，CasC7）和 lncRNA-HOX 转录反义 RNA（HOX transcript antisense RNA，HOTAIR）[20]。研究发现，细胞质 lncRNA 在转录后作为 ceRNA 发挥作用，通过充当 miRNA 海绵并与 mRNA 结合来招募 RNA 结合蛋白，从而促进降解、抑制翻译或启动翻译，例如 lncRNA-FAM83H 反义 RNA1（FAM83H antisense RNA1，FAM83H-AS1）[14]。随着高通量测序等技术的应用，越来越多的研究表明 lncRNA 是多种生物学过程的重要调控因子，也是宫颈癌中新的生物学调控分子之一[6-8]。LncRNA 通过调节 HPV 中 E6、E7 癌蛋白、作为诱捕 lncRNA 调控 miRNA、调控 Wnt 等多条信号通路，从而参与宫颈癌的发生、发展。

2 E6、E7 癌蛋白

HPV 是一种无包膜的双链 DNA 病毒，在鳞状上皮细胞中感染和复制[21-22]。HPV 病毒基因组分为 3 个区域：（1）早期（E）区，包括 E1～E7，与病毒复制相关；（2）晚期（L）区域，包括主要（L1）和次要（L2）衣壳蛋白；（3）非编码区（non-coding region，NCR），又称长控制区（long control region，LCR）。

病毒蛋白 hrHPV E6 参与了从 HPV 感染的早期阶段到癌变的整个进程。HPV E6 癌蛋白与多种细胞蛋白相互作用而激活多种致癌途径，如导致细胞凋亡受阻、转录机制改变、细胞相互作用受到干扰和细胞永生。目前只有几个 lncRNA 被证明受到 HPV-16 E6 的特异性调控，包括 lncRNA-MALAT1 和宫颈癌增殖细胞核抗原表达调控 lncRNA（cervical carcinoma expressed PCNA regulatory lncRNA，lncRNA-CCEPR）[14]。HPV E6 可导致几种宿主 lncRNA 发生差异表达，包括 lncRNA-生长停滞特异性转录本 5（growth arrest-specific transcript 5，GAS5）、lncRNA-H19 和 lncRNA-FAM83H-AS1[14]。HPV E6 蛋白的致癌活性之一是通过靶向 p53（肿瘤抑制因子）降解使其失活，如 lncRNA-WT1 反义 RNA（WT1 antisense RNA，WT1-AS）可通过 miRNA-330-5p 上调 p53 从而抑制宫颈癌细胞生长和侵袭[23]。

病毒蛋白 hrHPV E6 和 E7 在癌细胞中可组成性表达以维持致癌表型，也可相互拮抗抑制癌基因表达，如 lncRNA-胸腺肽假基因 2（thymopoietin pseudogene 2，TMPOP2）和 HPV16/18 E6/E7 在宫颈癌细胞中相互促进表达，增强致癌活性[24]。

3 诱捕 lncRNA

根据功能可将lncRNA 分为 4 大类：信号 lncRNA、诱捕 lncRNA、向导 lncRNA、支架 lncRNA[25]。近年来，越来越多的研究报道 lncRNA 与 miRNA 结合并抑制其作用，从而发挥 ceRNA 或 miRNA 海绵的作用[26-27]。ceRNA 理论认为，lncRNA 在细胞质中高度表达，能够与 miRNA 竞争性结合调控其下游靶基因，从而抑制 miRNA 的生物学功能，参与肿瘤的发生、发展[28]。诱捕 lncRNA 可充当 ceRNA[29]，犹如一种分子海绵，能结合和吸附其他调控蛋白质和 miRNA 等，从而抑制这些分子的功能间接调控基因的表达。详见表 1。诱捕 lncRNA 可能成为改善宫颈癌患者化学治疗反应和生存的一个新靶点。

表 1　常见诱捕 lncRNA 及其在宫颈癌中的作用机制

Tab 1　Common decoy lncRNAs and its mechanisms in cervical cancer

名称	作用	具体机制
LncRNA-TOB1 AS1[30]	抑癌	低表达的 lncRNA-TOB1 AS1 通过调控 miRNA-27b 抑制宫颈癌细胞增殖、转移
LncRNA-MEG3[31]	抑癌	低表达的 lncRNA-MEG3 通过调控 miRNA-21 抑制宫颈癌细胞增殖、促进细胞凋亡
LncRNA-GAS5[32]	抑癌	高表达的 lncRNA-GAS5 通过 miRNA-106b 上调 IER3, 增强宫颈癌细胞对放射治疗的敏感性[32]; 过表达 lncRNA-GAS5 通过 miRNA-21 下调转录子 STAT3 和 E2F3 表达, 进一步降低 TIMP3 和 PDCD4 表达, 促进细胞凋亡[33]
LncRNA-SOX21-AS1[29]	致癌	高表达的 lncRNA-SOX21 AS1 通过负性调控 miRNA-7 增加 VDAC1 的表达, 促进宫颈癌细胞增殖和侵袭
LncRNA-TPT1-AS1[34]	致癌	高表达的 lncRNA-TPT1-AS1 通过 miRNA-324-5p 促进宫颈癌细胞的集落形成、增殖、转移、侵袭和上皮间质转化
LncRNA-DLG1-AS1[35]	致癌	高表达的 lncRNA-DLG1-AS1 通过与 miRNA-107 竞争性结合, 消除 miRNA-107 对其靶基因 *ZHX1* 表达的抑制作用, 调控宫颈癌细胞增殖, 导致肿瘤进展
LncRNA-NCK1-AS1[36]	致癌	高表达的 lncRNA-NCK1-AS1 与 miRNA-134-5p 竞争性结合, 调控 MSH2, 抑制宫颈癌细胞凋亡
LncRNA-PVT1[37]	致癌	高表达的 lncRNA-PVT1 通过海绵 miRNA-424 促进宫颈癌细胞增殖和迁移
LncRNA-XIST[38-40]	致癌	高表达的 lncRNA-XIST 通过抑制 miRNA-140-5p 抑制 ORC1, 促进宫颈癌细胞的恶性进展[39]; lncRNA-XIST 通过与 miRNA-200a 竞争性结合上调 Fus, 促进宫颈癌进展[40]
LncRNA-RP11-552M11.4[41]	致癌	高表达的 lncRNA-RP11-552M11.4 通过负调控 miRNA-3941 的表达调控 ATF1, 促进宫颈癌进展
LncRNA-SNHG20[42]	致癌	高表达的 lncRNA-SNHG20 通过 miRNA-140-5p-ADAM10 轴促进宫颈癌细胞增殖和侵袭
LncRNA-GIHCG[43]	致癌	高表达的 lncRNA-GIHCG 通过调控 miRNA-200b 促进宫颈癌细胞增殖, 抑制细胞凋亡, 促进细胞迁移
LncRNA-C5orf66-AS1[28]	致癌	高表达的 lncRNA-C5orf66-AS1 通过 miRNA-637 调控 RING1 对宫颈癌细胞增殖、细胞凋亡和细胞周期的影响
LncRNA-799[44]	致癌	高表达的 lncRNA-799 通过 miRNA-454-3p 调控 TBL1XR1 的表达, 促进宫颈癌细胞转移
LncRNA-DANCR[17]	致癌	高表达的 lncRNA-DANCR 通过竞争性结合 miRNA-335-5p 调控 ROCK1 的表达, 促进宫颈癌细胞增殖、转移和侵袭
LncRNA-OIP5-AS1[45]	致癌	高表达的 lncRNA-OIP5-AS1 通过介导 miRNA-143-3p 促进 SMAD3 表达, 促进宫颈癌细胞转移、侵袭
LncRNA-XLOC_006390[9]	致癌	高表达的 lncRNA-XLOC_006390 通过下调 miRNA-331-3p 和 miR-338-3p 的表达, 促进宫颈癌的发生和转移
LncRNA-NORAD[46]	致癌	高表达的 lncRNA-NORAD 通过 miRNA-590-3p 上调 SIP1 的表达, 促进宫颈癌细胞的增殖和侵袭
LncRNA-SNHG12[47]	致癌	高表达的 lncRNA-SNHG12 通过 miRNA-125b 调控 STAT3, 促进宫颈癌的发生、发展
LncRNA-HOTAIR[48-49]	致癌	LncRNA-HOTAIR 通过抑制 miRNA-206 表达调控 MKL1, 促进宫颈癌细胞迁移和侵袭[48]; 通过调控 miRNA-143-3p/BCL2 轴促进宫颈癌进展[49]

4　信号通路

目前关于宫颈癌相关 lncRNA 的研究多数仅局限于 1 个或 2 个孤立的 lncRNA，涉及的细胞信号通路也不多。由于宫颈癌调控体系复杂，涉及的细胞通路多样，有必要对宫颈癌相关的 lncRNA 进行细胞信号通路层面的归纳和总结。

4.1　Wnt/β-连环蛋白（β-catenin）信号通路　Wnt/β-Catenin 信号通路在宫颈癌的发生和转移中扮演着关键角色。LncRNA-HOTAIR 被定义为 cMyc 激活的恶性肿瘤驱动因子，在宫颈癌的进展中发挥重要作用。下调 lncRNA-HOTAIR 通过抑制 Wnt 信号通路抑制宫颈癌细胞自噬、增殖和上皮间质转化（epithelial-mesenchymal transition，EMT），从而

增强宫颈癌细胞对放射治疗的敏感性[50]。LncRNA-DiGeorge 综合征关键区域基因 5（DiGeorge syndrome critical region gene 5，DGCR5）下调可激活 Wnt 信号，从而促进宫颈癌的进展[51]。过表达 LINC00675 增强了宫颈癌细胞中的 Wnt/β-catenin 信号[52]。

4.2 磷脂酰肌醇 3 激酶（phosphatidylinositol 3-kinase，PI3K）-蛋白激酶 B（protein kinase B，Akt）-哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）信号通路 激活 PI3K/Akt/mTOR 信号通路会促进肿瘤细胞的增殖。PI3K 是一种异二聚体蛋白，由 1 个调控亚基（p85a/b）和 1 个催化亚基（p110a/b/g/d）组成。激活的 PI3K 通过调控其下游靶蛋白 Akt 进而调控细胞增殖、凋亡和肿瘤发生。下调 lncRNA-LINC01305 通过靶向 TNXB 抑制 PI3K/Akt 信号通路，最终抑制 EMT、细胞侵袭和细胞迁移[53]。肿瘤抑制因子 PTEN 是 PI3K/PTEN/Akt 信号通路的负调控因子，它以 Akt 为靶点调控细胞生长、分化、增殖和迁移。

4.3 丝裂原激活蛋白激酶（mitogen-activated protein kinase，MAPK）信号通路 MAPK 通路在细胞增殖、分化、血管生成和存活等关键过程中发挥重要作用。该通路的核心是一个三级级联的磷酸化–去磷酸化反应 MAPK 激酶激酶/MAPK 激酶/MAPK，启动后导致基因转录。MAPK 信号通路的下游是 ERK 通路，这是一个进化上保守的级联信号。ERK/MAPK 通路是肿瘤治疗的重要靶点，例如在黑素瘤和肝细胞癌中，lncRNA-RMEL3[54]和 lncRNA-URHC[55]下调可通过使 ERK/MAPK 通路失活调控肿瘤细胞增殖，诱导细胞凋亡；在子宫内膜癌中，lncRNA-BRAF 激活的非编码 RNA（BRAF-activated non-protein-coding RNA，BANCR）下调可通过降低基质金属蛋白酶（matrix metalloproteinase，MMP）-1 和 MMP-2 抑制 ERK/MAPK 通路[56]；在胶质瘤中，lncRNA-MALAT1 介导的肿瘤抑制可能通过下调 MMP-2 而降低 ERK/MAPK 信号通路活性[57]。关于宫颈癌中 lncRNA 对 MAPK 通路作用的报道较少，Liu 等[58]发现 lncRNA-MNX1 AS1 可通过激活 MAPK 通路影响宫颈癌的进展。

5 小结与展望

细胞信号通路等机制在宫颈癌的发生、发展、转归等过程中发挥着不可替代的作用，作为其中重要的组成部分，大量的 lncRNA 起着不可忽视的调控作用。LncRNA-HOTAIR 已成为宫颈癌药物治疗的分子靶标。中药有效成分青蒿琥酯可通过抑制 lncRNA-HOTAIR 表达而下调环氧合酶 2（cyclooxygenase 2，COX-2），继而抑制 MMP 和血小板源性生长因子（platelet-derived growth factor，PDGF）合成，发挥抑制宫颈癌细胞侵袭与转移的作用[59]。

由于宫颈癌调控体系的复杂性和涉及细胞通路的多样性，单一或少数的 lncRNA 并不足以产生决定性影响，应从整体层面把控 lncRNA 并进行总结归纳，分析 lncRNA 与 miRNA、癌基因 E6/E7、细胞信号通路之间的联系。基于细胞信号通路层面整体把控的宫颈癌 lncRNA 有望成为宫颈癌早期诊断和预后相关的生物标志物，从中筛选关键节点的 lncRNA 可能有助于开发新的治疗策略。

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