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述评 EDITORIAL

长链非编码RNA在结直肠癌中的研究进展

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Long noncoding RNAs in colorectal cancer

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Abstract
Long noncoding RNAs (lncRNAs) are broadly defined as RNA molecules greater than 200 bp in length and lacking an open reading frame. Recent studies have demonstrated that lncRNAs are widely involved in the regulation of gene expression network at epigenetic, transcriptional and post-transcriptional levels, which may affect cell growth, proliferation, differentiation, metabolism, apoptosis and other important physiological processes. Abnormal expression of lncRNAs is closely associated with the tumor development, invasion, metastasis and prognosis. The development of colorectal cancer is a multi-factor, multi-step process, and abnormal gene expression may play an important role in this process. This review focuses on the current advances in research of lncRNAs in colorectal cancer, with an aim to provide new clues to clinical prevention, diagnosis and treatment of this malignancy.

Key Words: LncRNAs; Colorectal cancer

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摘要
长链非编码RNA(long non-coding RNA, lncRNA)是一类长度超过200个核苷酸但无蛋白质编码功能的RNA分子. 近年来许多研究表明其可在表观遗传学、转录及转录后等多个水平参与基因的表达调控, 影响细胞的生长发育、增殖、分化、代谢和凋亡等重要生理过程. lncRNA的异常表达与肿瘤的发生、发展、侵袭、转移及预后有着密切的关系. 结直肠癌的发病是一个多因素、多步骤的复杂过程, 而基因表达的异常在其中发挥着重要的作用. 本文就lncRNA在结直肠癌中的作用及研究进展进行综述, 为临床预防、诊断和治疗结直肠癌提供新策略.

关键词: LncRNA; 结直肠癌

核心提示: lncRNA可在表观遗传等多个水平参与基因的表达调控, 影响细胞的增殖和分化, 其异常表达与肿瘤的发生、发展及预后有密切的关系. 结直肠癌的发病是一个多因素、多步骤的复杂过程, 而基因表达的异常在其中发挥着重要的作用.

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0 引言
长链非编码RNA(long non-coding RNA, lncRNA)

■背景资料
lncRNA是一类长度超过200个核苷酸、具有调控基因表达的作用, 但无蛋白质编码功能的RNA分子. lncRNA通过多种调控方式在表观遗传、转录和转录后等多种水平影响细胞的生长发育, 参与肿瘤的发生、发展、转移和预后等过程. 结直肠癌是常见的消化系恶性肿瘤之一, 近年来随着国人生活水平的提高、饮食习惯的改变、人口的老龄化以及结直肠癌普查的开展, 我国结直肠癌的发病率呈明显上升趋势, 严重影响人们的健康和生活质量.

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■研发前沿
结直肠癌的发病是一个多因素、多步骤的复杂过程，基因表达的异常在其中发挥着重要的作用. 随着对结直肠癌发病机制研究的不断深入，有望发现对其早期诊断、临床分期、个体化治疗、靶向治疗和预后评估起关键作用的新型分子标志物，而lncRNA在此方面具有非常广阔研究和应用前景.

是一类长度超过200个核苷酸、具有调控基因表达的作用, 但无蛋白质编码功能的RNA分子. lncRNA通过多种调控方式在表观遗传、转录和转录后等多种水平影响细胞的生长发育, 参与肿瘤的发生、发展、转移和预后等过程[1,2]. 结直肠癌是常见的消化系恶性肿瘤之一, 近年来随着国人生活水平的提高、饮食习惯的改变、人口的老龄化以及结直肠癌普查的开展, 我国结直肠癌的发病率呈明显上升趋势, 严重影响人们的健康和生活质量. 结直肠癌的发病是一个多因素、多步骤的复杂过程, 基因表达的异常在其中发挥着重要的作用[3]. 随着对结直肠癌发病机制研究的不断深入, 有望发现对其早期诊断、临床分期、个体化治疗、靶向治疗和预后评估起关键作用的新型分子标志物, 而lncRNA在此方面具有非常广阔的研究和应用前景.

1 lncRNA概述

lncRNA是一类长度超过200个核苷酸但无蛋白质编码功能的RNA分子, 具有高度保守的空间二级结构, 复杂的亚细胞定位, 可位于细胞核内, 也可位于细胞浆内[4]; 而且某些lncRNA的表达还具有组织和时空特异性. lncRNA的产生方式有多种, 目前认为可能有以下几种方式[5,6]: (1)染色体重排; (2)编码蛋白基因结构变化而转变为lncRNA; (3)非编码RNA内部发生串联重复产生相邻的重复序列, 即lncRNA; (4)由非编码基因在复制过程中的反移位产生; (5)基因中插入转座子而产生有功能的lncRNA. 近年来, 越来越多的研究表明lncRNA可通过多种途径调节DNA甲基化、组蛋白修饰、染色质重构和作为miRNA的前体, 参与表观遗传沉默、基因的转录和翻译、细胞周期和细胞凋亡等调控过程.

2 lncRNA与结直肠癌

越来越多的研究表明lncRNA与结直肠癌的发生发展有着密切的关系, 其异常表达可能在肿瘤的发生发展过程中发挥着抑癌基因或促癌基因的作用[7]. Pibouin等[8]在结肠癌细胞系TC7中发现了lncRNA-OCC-1(overexpressed in colon carcinoma-1)的过表达, 通过体外实验证明OCC-1 cDNA可编码数种多肽. lncRNA表达水平上的差异以及某些肿瘤中特异型lncRNA的表达, 预示着lncRNA可作为一些肿瘤临床诊断和治疗的新型分子标志物, 如lncRNA DD3(PCA3)已被证实可作为前列腺癌高度特异的核算分子标志物, 其特异性高于血清前列腺特异性抗原(prostate specific antigen, PSA). Gibb等[9]研究发现了人类正常组织及癌组织的lncRNA转录谱, 认为在肿瘤中普遍存在lncRNA的异常表达. lncRNA的种类繁多、数量庞大、功能广泛, 目前在结直肠癌的发病机制中研究较多的种类不多(表1), 下面将重点阐述几种常见的lncRNA在结直肠癌中的研究现状.

2.1 MALAT1与结直肠癌 肺腺癌转移相关转录子1(metastasis-associated lung adenocarcinoma transcript 1, *MALAT1*)基因定位于11q13.1, 全长8.7 kb, 在正常人组织中广泛表达, 神经组织中表达量最高. 其最早是在早期非小细胞肺癌组织中发现的, 故因此而得名[47]. *MALAT1*基因转录产物的亚细胞定位比较特殊, 主要存在于细胞核内, 细胞质中分布很少. Wilusz等[48]发现MALAT1在转录的过程中可产生一种仅含61个核苷酸的非编码MALAT1相关胞浆小RNA(MALAT1-associated small cytoplasmic RNA, mascRNA), mascRNA可被转运到细胞质中, MALAT1的初级转录产物经过RNA酶剪切可形成mascRNA. 由此可见, MALAT1特殊的亚细胞结构定位决定了其在细胞内功能的多样性, 主要涉及SR蛋白(serine/arginine rich protein, SR protein)的招募和磷酸化、基因的表达调控、mRNA前体的剪切和修饰以及神经突触的形成等重要生理过程.

近年来诸多研究表明, 在结直肠癌、胰腺癌、肝癌和食管癌等多种消化系统肿瘤中均有不同程度的MALAT1异常表达. Xu等[49]发现, 在*MALAT1*基因的3'端存在一段长约1524个核苷酸的特殊序列, 其与结直肠癌细胞SW480、SW620的转移行为直接相关, 通过实验证实下调*MALAT1*基因可有效抑制肿瘤细胞的转移. AKAP9蛋白是γ微管蛋白复合体(γTuRCs)的重要成员, 在纺锤体的极化过程中起着至关重要的作用, 其功能丧失会导致成核失败、中心体与高尔基体复合异常, 进而导致肿瘤发生[50]. 有研究表明*AKAP9*作为*MALAT1*调控基因表达的一种靶基因, 参与了结直肠癌的发生、发展和转移等过程, 有望成为临床检测诊断结直肠癌的新型生物标志物和治疗的新靶点.

2.2 HOTAIR与结直肠癌 HOX转录反义RNA(HOX transcript antisense RNA, HOTAIR)定位于12q13.13, 全长2.3 kb, 是第一个被发现的具有反式转录调控作用的lncRNA. 研究表明, HOTAIR可同时结合在多梳抑制复合体2(polycomb

表 1 结直肠癌组织中常见异常表达的lncRNA

lncRNA	基因位点	长度(kb)	生物学功能	参考文献
CCAT1	8q24.21	2.4	上调c-Myc, 促进肿瘤细胞增殖和迁移	[10-12]
H19	11q15.5	2.3	促癌和抑癌双重功能	[13-20]
HOTAIR	12q13.13	2.3	招募PCR2和LSD1复合体到HOXD,沉默HOXD, 促癌	[21-27]
MALAT1	11q13.1	8.7	调节内源性靶基因的可变剪接, 表观遗传水平调控基因表达, 促癌	[28-32]
MEG3	14q32.2	1.6-1.8	促进*P53*基因表达, 抑制肿瘤增值	[33-37]
OCC-1	12q23.3	1.4	促进细胞增殖, 促癌	[38-40]
PTENP1	9p21	3.9	与miRNA竞争性结合调控细胞的生长发育, 缺失可导致肿瘤发生	[41-43]
UCA1	19p13.12	1.4	影响细胞生长发育, 促进肿瘤侵袭	[44-46]

repressive complex 2, PRC2)和组蛋白去甲基化酶复合体上, 并介导这2种复合体结合到相应特异性的基因组位点, 分别使染色体组蛋白H3第27位赖氨酸三甲基化(histone H3 tri-methylated at lysine 27, H3K27me3)和组蛋白H3第4位赖氨酸二甲基化(histone H3 dimethyl Lys4, H3K4me2), 继而导致基因沉默[51]. 临床研究表明, 乳腺癌、结肠癌和肝癌等肿瘤组织中HOTAIR的表达水平与肿瘤的转移、复发以及预后紧密相关[52]. 高表达HOTAIR能够抑制相关肿瘤转移抑制基因的表达, 促进肿瘤的转移和恶变; 而下调HOTAIR的表达则可以降低肿瘤细胞的转移侵袭能力[53].

Kogo等[54]对结直肠肿瘤与HOTAIR之间的关系进行了研究, 发现在结直肠癌组织中HOTAIR的表达水平与结直肠癌术后的预后呈正相关. 体外实验证实上调HOTAIR的表达量能显著增加结直肠肿瘤细胞的侵袭能力; 此外, 通过基因探针富集分析(gene set enrichment analysis, GSEA)发现, HOTAIR可结合并介导PRC2结合于特定的基因位点而使相关的基因沉默, 加速肿瘤细胞的生长、侵袭和转移. Niinuma等[55]研究发现HOTAIR的过表达与胃肠间质瘤的转移有密切关系, 高表达HOTAIR能抑制GIST细胞的侵袭能力, 从而抑制胃肠间质瘤的恶化和转移. 以上现象说明*HOTAIR*基因不仅与上皮细胞来源肿瘤的转移和侵袭能力相关, 而且与间质瘤的侵袭和转移也有密切关系. 通过多因素综合分析表明HOTAIR还可作为预测肿瘤患者生存期的独立危险因素, 拓宽了HOTAIR与肿瘤之间的关系.

2.3 H19与结直肠癌 *H19*基因定位于人类染色体11p15.5, 全长约2.3 kb, 包含5个外显子和4个内含子, 是一种母源性印迹基因. 在*H19*基因的上游4 kb处有一段区域被称为差异甲基化区(differentially methylated domain, DMD), 即印迹控制区(imprinting control region, ICR)[56], 其可参与调控*H19*基因的表达, H19作为印记基因网络的反式调控者参与调节细胞的生长、发育、增殖、分化和凋亡. 近年来, 许多研究表明H19基因的表达异常与食道癌、胃癌、结直肠癌和肝癌等多种消化系肿瘤有关, 其通过多种作用机制在机体内发挥着癌基因和抑癌基因的双重功能[57].

Tsang等[58]在结直肠癌的研究中发现, *H19*基因的促癌作用是通过抑制抑癌基因-视网膜母细胞瘤基因(retinoblastoma, *RB*)的表达来实现的, 而此过程又与miR-675有着密切的关系, 分析发现H19其实是miR-675的前体, H19通过结合于RB mRNA的3'端非翻译区, 抑制mRNA的翻译, 从而抑制*RB*基因的表达, 促进肿瘤细胞的生长. 由此可见, H19在结直肠癌中发挥了类似癌基因的生物学作用. 相反, Yoshimizu等[59]在研究小鼠结肠癌、畸胎瘤和肝癌模型时发现, 敲除*H19*基因后, 肿瘤的生长速度加快, 侵袭转移能力增强, 这表明H19在肿瘤的发生过程中起抑癌基因的作用. 最新的研究显示, P53、HIF1-α和H19之间也存在着一定的相关性, 通过体外实验证实, 在过表达HIF1-α的同时抑制*P53*基因的表达可协同提高肿瘤细胞中H19的表达水平[57].

2.4 MEG3与结直肠癌 母系印记表达基因3(maternally expressed gene 3, *MEG3*)定位于14q32.2, 是第一个被发现具有肿瘤抑制功能的lncRNA. MEG3仅含有10个外显子, 由于剪接方式的不同, 到目前为止共发现12个MEG3表型, 每个表型包含共同的外显子1-3和8-10, 而外显子4-7则有不同的链接方式. 在结构上, 12个不同表型的MEG3均具有3个明显的二级结构域; 功能上, MEG3能与cAMP、P53、鼠双微基因2(murine double mimute 2, *MDM2*)和生长分化因子

■相关报道

Pibouin等在结肠癌细胞系TC7中发现了lncRNA-OCC-1的过表达, 通过体外实验证明OCC-1 cDNA可编码数种多肽. lncRNA表达水平上的差异以及某些肿瘤中特异型lncRNA的表达, 预示着lncRNA可作为一些肿瘤临床诊断和治疗的新型分子标志物, 如lncRNA DD3(PCA3)已被证实可作为前列腺癌高度特异的核算分子标志物, 其特异性高于血清前列腺特异性抗原. Gibb等研究发现了人类正常组织及癌组织的lncRNA转录谱, 认为在肿瘤中普遍存在lncRNA的异常表达.

■创新盘点
本文就lncRNA在结直肠癌中的作用及研究进展进行综述, 为临床预防、诊断和治疗结直肠癌提供新策略. 较为全面的描述了lncRNA在结直肠癌发生过程中的病理生理作用. 有较好的创新性.

15(growth differentiation factor 15, GDF15)相互作用, 下调MDM2的水平, 减少P53降解, 同时增加P53与GDF15启动子的结合, 促进细胞增殖抑制剂GDF15的转录和翻译, 从而抑制肿瘤的发生和发展[60].

已有研究报道, 在结直肠癌、肝癌和神经胶质瘤等多种癌症类型中MEG3存在异常CpG甲基化, 导致其表达下调甚至缺失, 进而导致细胞和血管异常增生, 加速肿瘤的转移和恶变[61]. 此外, MEG3本身的表达也受到表观遗传学的调控, 其表达的下调或缺失与肿瘤的分级和预后也存在强烈的相关性[62]. 由此可见, MEG3与表观遗传、miRNA之间存在复杂的网络调控关系, 而其中的具体调控机制还有待进一步的研究.

3 结论

目前对lncRNA在结直肠癌中的研究还比较少, 主要集中在lncRNA的表达及功能方面的研究, lncRNA影响肿瘤的发生、发展、转移和凋亡等机制仍不清楚. 随着人们对lncRNA与结直肠癌关系研究的不断深入, 越来越多的lncRNA会相继被发现, 其异常表达对结直肠癌的影响机制也将被一步步揭示, 而这些异常表达的lncRNA则可能成为结直肠癌早期诊断的重要检测指标. 此外, lncRNA具有天然、无毒性、内源性和多水平调控基因表达等特点, 在结直肠癌的分子靶向治疗和药物研发等方面有着巨大的发展空间, 有望为恶性肿瘤的预防、诊断、治疗和预后提供新思路, 开辟新途径.

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■应用要点

随着人们对lncRNA与结直肠癌关系研究的不断深入, 越来越多的lncRNA会相继被发现, 其异常表达对结直肠癌的影响机制也将被一步步揭示, 而这些异常表达的lncRNA则可能成为结直肠癌早期诊断的重要检测指标. 此外, lncRNA具有天然、无毒性、内源性和多水平调控基因表达等特点, 在结直肠癌的分子靶向治疗和药物研发等方面有着巨大的发展空间, 有望为恶性肿瘤的预防、诊断、治疗和预后提供新思路, 开辟新途径.

■同行评价
本综述较为全面的描述了lncRNA在结直肠癌发生过程中的病理生理作用. 有较好的创新性.

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