

长链非编码RNA在消化系统肿瘤发生中的作用

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摘要 长链非编码RNA(long noncoding RNA, LncRNA)是一类长度大于200核苷酸且不具备蛋白质编码功能的一类RNA分子。近年研究表明, LncRNA与消化系统肿瘤发生的关系非常密切, 它们可在表观遗传、转录以及转录后水平广泛参与基因表达调控, 影响肿瘤的发生、发展, 并且与肿瘤侵袭、转移及患者预后密切相关。深入研究LncRNA与消化系统肿瘤发病的关系有望为消化系统肿瘤的预防和诊治提供新策略。

关键词 长链非编码RNA; 消化系统肿瘤; 发生机制

The Roles of Long Noncoding RNAs in the Occurrence of Digestive System Tumors

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Abstract Long noncoding RNAs (LncRNAs) are noncoding RNA molecules greater than 200 nt in length. Recent studies have demonstrated that the dysregulated LncRNAs are closely related with human digestive system tumors. They are widely involved in the regulation of gene expression network in the forms of epigenetic, transcriptional and post-transcriptional levels. Besides, they are associated with the tumor development, invasion, metastasis and prognosis. Further study of the relationship between LncRNAs and digestive cancers and their pathophysiological mechanisms will bring new strategies to tumor prevention and treatment.

Key words LncRNA; digestive system tumor; mechanisms

长链非编码RNA(long noncoding RNA, LncRNA)是指一类转录本长度大于200核苷酸(nucleotide, nt)且不具有蛋白质编码功能的长链RNA分子^[1]。它们的长度一般介于200~100 000 nt之间, 具有高度保守的序列元件、特定的空间二级结构, 亚细胞定位也较复杂, 可位于细胞核内或胞浆中^[2]。LncRNA曾被认为是基因转录噪音而一直未受到重视, 近年来越

来越多研究显示, LncRNA是一类重要基因表达调控元件, 能在多种水平(表观遗传、转录和转录后等)调控基因表达^[1-2]。现有研究发现, LncRNA与多种疾病(如代谢性疾病、神经退行性疾病、自身免疫疾病和肿瘤等)的发生与发展密切相关^[3-4]。正因为如此, LncRNA已成为继微小RNA(microRNA, miRNA)之后的又一个热点非编码RNA分子。

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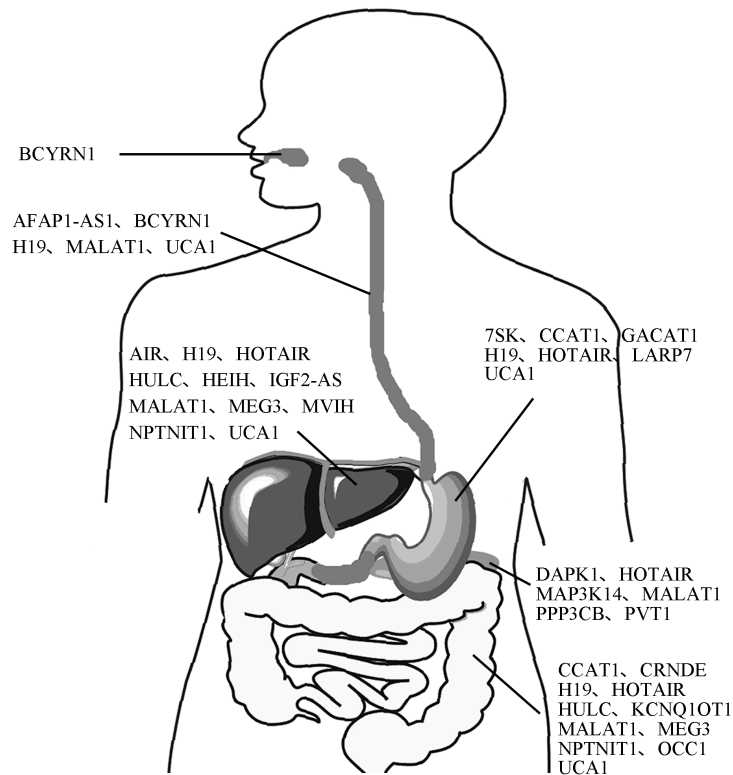


图1 LncRNAs与消化系统肿瘤

Fig.1 LncRNAs and digestive system tumors

由于环境污染、不良生活方式等诸多因素的影响,我国消化系统恶性肿瘤的发病率呈现逐年上升的趋势。在我国,该系统肿瘤占有所有肿瘤的60%~70%,位居各系统肿瘤之首;胃癌、肝癌、结直肠癌和食管癌的发病率及死亡率均已处于恶性肿瘤的前5位^[5]。消化系统肿瘤具有发病率高、起病隐匿和早期症状不明显等特点,这已成为消化系统肿瘤防治的难点。近年来研究发现,一些LncRNA异常表达于消化系统肿瘤,在消化系统肿瘤的发生、发展过程中扮演了重要角色(图1)。目前,国内外研究发现了数十种与消化系统肿瘤密切相关的LncRNA,本文将重点介绍5种作用机制较为明确的代表性LncRNA。

1 MALAT1与结直肠癌和肝癌

肺腺癌转移相关转录本1(metastasis-associated lung adenocarcinoma transcript 1, MALAT1)定位于11q13.1,全长8 708 nt,广泛表达于人体正常组织细胞,而以胰腺和肺组织中含量最高。在细胞核内转录后, MALAT1初始转录产物的3'末端通过类似tRNA转录后加工机制裂解成MALAT1相关的小胞

质RNA(MALAT1-associated small cytoplasmic RNA, mascRNA),随后被运送至胞浆中,而MALAT1则稳定地停留在胞核中^[6]。细胞内MALAT1生物学功能多样,涉及丝氨酸/精氨酸富集蛋白(serine/arginine rich protein, SR protein)的招募和磷酸化、mRNA前体加工、神经突触的形成与维持、基因表达调控等过程^[7]。

尽管MALAT1是最先在肺腺癌中发现并以此命名的,但现有许多研究证实,多种消化系统肿瘤如胰腺癌、结直肠癌、肝癌、胆囊癌和食管癌等恶性肿瘤均涉及不同程度的MALAT1异常表达^[8-9]。在研究结直肠癌(colorectal cancer, CRC)转移发生时, Xu等^[10]发现,在原发性结直肠癌组织和结直肠癌细胞株(SW620和SW480)中, MALAT1的3'末端区域存在突变;进一步实验又证明这个靠近3'末端的区域是它的一个重要功能区,对细胞的增殖、迁移和侵袭有着举足轻重的作用。在研究原发性肝细胞性肝癌(hepatocellular carcinoma, HCC)、肝母细胞瘤(hepatoblastomas, HPBL)及对应癌旁组织的基因表达类型和全基因组的改变时,人们发现MALAT1在HCC和HPBL组织中有明显的表达上调^[9],在早

期肿瘤组织中的表达水平即可比正常肝组织增加6倍^[8]; 继而有学者发现, 无论在肝癌细胞株还是HCC组织均存在MALAT1的表达上调, 并且高表达MALAT1的患者肝移植术后复发风险更大(尤其是超出米兰标准者); 多因素分析还发现, MALAT1可作为一个预测肝癌复发的独立因子; 细胞水平实验进一步证明, 下调MALAT1表达后, 肝癌细胞的生存能力、迁移及侵袭力显著下降, 而对顺铂、阿霉素等药物诱导凋亡的敏感性增强^[11]。诚然, MALAT1已经显示与多种消化系统肿瘤的密切相关性。

2 HULC与肝癌

肝癌高表达转录本(highly up-regulated in liver cancer, HULC)全长500 nt, 定位于染色体6p24.3, 在人体多数正常组织中不表达, 肝局灶性结节性增生时可轻度上调, 而发生原发性肝癌及结直肠癌肝转移后表达水平显著上调^[12-13]。迄今, HULC的生理功能及分子机制仍了解不多。

与前述MALAT1的具有较广瘤谱特点^[8-11]不同的是, HULC具有肝癌特异性。实验证明, HULC可在转录后水平对肝癌细胞内多个靶基因的表达发挥调控作用。用小干扰RNA(small interfering RNA, siRNA)下调Hep3B和HepG2等肝癌细胞中HULC的表达可改变肝癌相关基因的表达^[14], 并抑制其邻近基因——溶质载体家族35成员B3(solute carrier family 35, member B3, *SLC35B3*)的表达^[15]。这种改变并非直接基于RNA间的相互作用, 而是借助自身

miRNA应答元件与其他RNA竞争结合同种miRNA而实现转录后水平相互影响, 即通过竞争性内源RNA(competing endogenous RNA, ceRNA)作用。肝癌细胞内经蛋白激酶A(protein kinase A, PKA)途径磷酸化的cAMP应答元件结合蛋白(cAMP response element binding protein, CREB)与HULC近端启动子区域结合, 同时打开并维持局部染色质结构, 促进HULC基因转录。转录后的HULC扮演着内源性miRNA海绵样的角色, 在吸附并抑制miR-372等miRNA活性的同时, 通过ceRNA改变相关基因表达。miR-372的下调减弱了PRKACB(一种cAMP依赖的蛋白激酶的催化亚基)的靶向抑制, 进而加强PRKACB诱导CREB磷酸化作用, 而磷酸化的CREB又可以与HULC启动子区域结合, 并进一步激活HULC表达, 形成正反馈回路^[16](图2)。有意思的是, 近期报道HULC也参与乙型肝炎病毒X蛋白(hepatitis B virus X protein, HBX)介导的肝癌形成过程^[17]。其大概机制是: HBX通过与CREB相互作用调节CREB依赖启动子的转录活性, 从而间接活化HULC启动子以加强HULC基因转录, 过表达的HULC又可抑制同一染色体上邻近肿瘤抑制基因*p18*启动子活性, 造成*p18*在mRNA和蛋白质水平下调, 进而促进肝癌细胞增殖(图2)。值得关注的是, 位于HULC启动子区域的rs7763881变异基因型有助于降低HBV持续携带者发生HCC的易感性^[18], 提示HULC参与肝癌发生过程的作用亦与遗传背景有关。

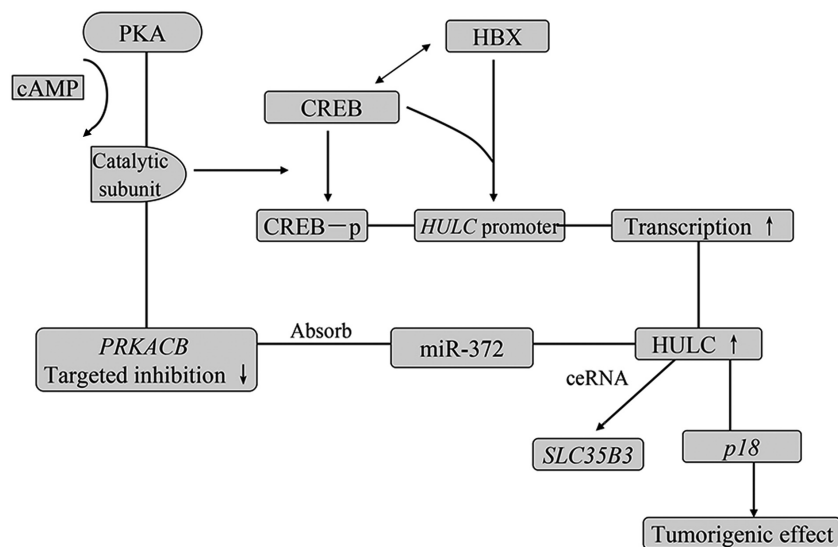


图2 HULC致癌机制

Fig.2 HULC's mechanisms in cancer promoting

3 H19与结直肠癌、肝癌和胃癌

*H19*基因定位于人染色体11p15.5区域,全长2 322 bp,包含5个外显子和4个内含子,是一母源性印记基因,主要作为印记基因网络的反式调节者控制细胞生长。它的表达受到上游4 Kb处的差异甲基化区(differentially methylated domain, DMD),即印记控制区(imprinting control region, ICR)的调控^[19]。在胚胎发育期,*H19*基因高丰度表达于源于中胚层和内胚层的组织,人出生后大多数组织的表达趋于停止,仅在骨骼肌和心肌尚有一定表达,而当机体组织再生或形成肿瘤时可被重新激活^[19]。已有报道揭示,*H19*在食道癌、胃癌、结直肠癌和肝癌等多种消化系统肿瘤中存在程度不同的异常表达^[20-24]。

*H19*可以通过多种机制发挥类似癌基因的生物学术功能。Dugimont等^[25]发现,*P53*基因能有效地抑制*H19*启动子的活性。在胃癌细胞中,Yang等^[21]研究发现,*H19*能结合*P53*并抑制*P53*的活性,并降低*P53*下游靶基因*Bax*(凋亡相关基因)的水平,从而促进胃癌细胞增殖和逃逸凋亡。在结肠癌的研究中,*H19*的促癌功能被发现与miR-675密切相关,而且两者的表达水平与抑癌基因——视网膜母细胞瘤基因(retinoblastoma, *RB*)的表达水平呈负相关。*H19*基因通过其第1外显子转录的miR-675作用于*RB* mRNA的3'端非翻译区,并抑制*RB*基因的表达进而促进肿瘤细胞的生长^[22]。因此,有理由认为,*H19*在结直肠癌中发挥了类似癌基因的生物学术作用。

值得注意的是,*H19*亦可扮演抑癌基因角色。在小鼠结肠癌、肝癌发生模型中,Yoshimizu等^[23]发现,*H19*表达的缺少能明显增加小鼠结肠息肉数量和加速肝肿瘤的形成过程。他们认为,*H19*控制着肿瘤形成的启动步骤,缺失*H19*将促进肿瘤形成。又有研究发现,如果原发性肝癌组织低表达*H19*将能显著促进肿瘤转移,患者术后无病生存期短、复发风险高,预后也较差^[24]。*H19*促癌抑癌角色的转换、功能作用的差异可能与肿瘤遗传背景、肿瘤的微环境以及致癌因素的差异有关。

关于*H19*与肿瘤转移的关系,还有研究发现,*H19*与肿瘤细胞缺氧应激相关^[26]。在缺氧应激条件下,*P53*与缺氧诱导因子1- α (hypoxia-inducible factor 1- α , HIF1- α)相互作用,并通过调节*H19*表达水平改变细胞应答状态;HIF-1上调*H19*表达、介导细胞适应低氧,而*P53*则抑制*H19*表达、加强低氧诱导细

胞凋亡作用,两者作用结果的综合效应取决于*P53*的状态。当*P53*突变或缺失时,*H19*表达上调促进肿瘤进展(包括血管生成、肿瘤转移和化疗抵抗等)。

最近研究又发现,*H19*启动子区域组蛋白异常乙酰化可引起*H19*表达下调,miR-200家族上游区域异质核糖核蛋白U(heterogeneous nuclear ribonucleoprotein U, hnRNP U)与P300/CBP相关因子(P300/CBP associated factor, PCAF)结合减少,hnRNP U/PCAF/RNA Pol II蛋白复合物组蛋白乙酰化作用减弱,miR-200家族启动子区域乙酰化异常表达水平降低,进而减弱了负调控miR-200的靶基因——锌指增强子结合蛋白1/2(zinc finger E-box binding homeobox 1/2, *ZEB1/2*)的抑制作用^[24]。*ZEB1/2*表达上调将促进肝癌细胞的上皮间充质转化(epithelial-mesenchymal transition, EMT),这又可使HCC细胞侵袭迁移能力增加。此外,*H19*也可通过与*Zeste*同源序列2的增强子(enhancer of zeste homolog 2, *EZH2*)相互作用促进EMT过程,从而增加肿瘤细胞侵袭迁移力^[27]。但有意思的是,*H19*不仅与*EZH2*相互作用,还可招募多梳蛋白抑制复合体2(polycomb repressive complex 2, PRC2)到E-钙黏蛋白(*E-cadherin*)基因启动子区域,引起组蛋白H3的第27位点赖氨酸三甲基化(H3K27me3)使E-钙黏蛋白基因的表达受到抑制;同时还可通过H3K27三甲基化使裸角质蛋白1(naked cuticle 1, *NKDI*)基因表达受阻。*NKDI*的减少将通过Wnt信号通路促进 β -链蛋白(β -catenin)核转移,并与T细胞因子/淋巴增强因子(T cell factor/lymphoid enhancer factor, TCF/LEF)结合成复合物,进一步激活*Snail*和*Slug*基因(属于锌指转录因子超家族成员)表达;而后者是重要的EMT调控因子,可通过与E-钙黏蛋白基因启动子区的增强子-盒(enhancer box, E-box)作用元件相结合下调E-钙黏蛋白表达,最终引起EMT(图3)。

*H19*在肿瘤发生中的作用确实很广泛(图3),如:最近有学者在其他系统肿瘤的研究中发现,*H19*可通过DNA结合/分化2(DNA binding/differentiation 2, ID2)促进肿瘤细胞增殖,或者由c-Myc直接诱导其表达而促进肿瘤发生^[28]。

4 HOTAIR与结直肠癌、肝癌和胃肠道间质瘤

同源异型框基因反义基因间RNA(HOX antisense intergenic RNA, HOTAIR)定位于12q13.13,

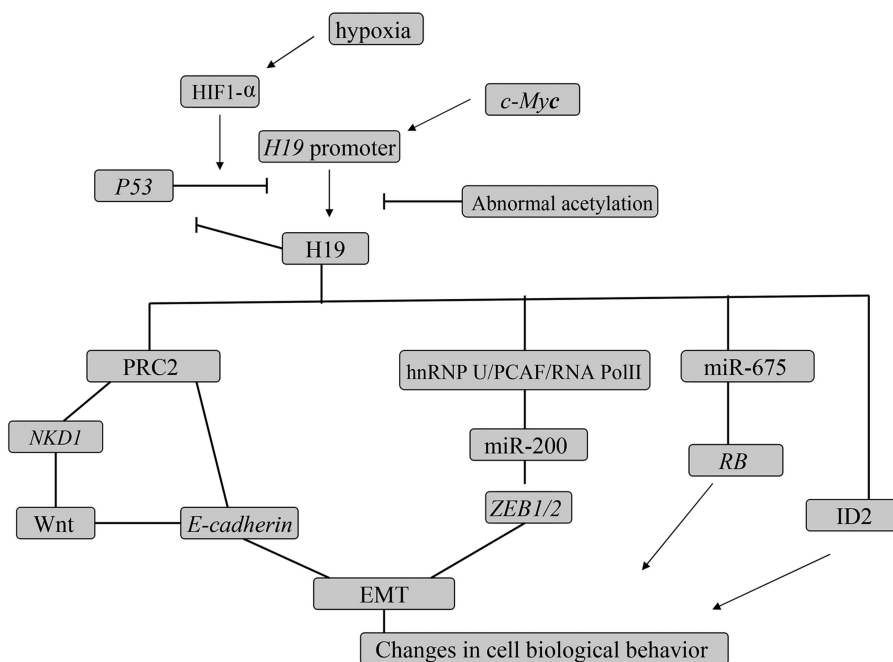


图3 H19在肿瘤发生中的作用机制

Fig.3 H19's mechanisms in tumor occurrence

全长2 337 nt, 是具有反式调控作用的LncRNA, 其功能片段位于5'端1~300 nt和3'端1 500~2 146 nt区域, 可结合染色体修饰复合物从而实现表观遗传方式调控相关基因的表达。HOTAIR的生物功能广泛, 主要涉及细胞分化、增殖、凋亡、转移及抗药等方面^[29]。

PRC2由EZH2、多梳蛋白SUZ12(suppressor of Zeste 12)及核心蛋白亚基EED(embryonic ectoderm development)组成; 而LSD1/CoREST/REST是由赖氨酸特异性脱甲基酶1(lysine-specific demethylase 1, LSD1)、阻遏元件-1沉默转录因子辅阻遏物(corepressor for repressor element-1 silencing transcription factor, CoREST)和阻遏元件-1沉默转录因子(repressor element-1 silencing transcription factor, REST)等3种蛋白质结合而成的复合体。这两类复合物都是与HOTAIR生物学功能的发挥密切相关的染色体修饰复合物。研究发现^[30-31], HOTAIR 5'端可与PRC2复合物结合, EZH2的第345位苏氨酸残基经周期蛋白依赖性激酶1(cyclin-dependent kinase 1, CDK1)磷酸化后又能增强自身与HOTAIR的结合, 然后使染色体组蛋白H3K27三甲基化, 进而沉默靶基因; 而HOTAIR 3'端则能与LSD1/CoREST/REST复合物结合, 通过介导H3K4me2去甲基化调节靶基因转录活性。所以, HOTAIR属于含有不同结合域的模块化双功能RNA, 它通过提供装配选择性组蛋

白修饰酶的结合表面来发挥类似支架的作用, 介导了染色体修饰复合物到达特定位置, 引起组蛋白三甲基化或去甲基化, 进而下调肿瘤转移抑制基因的表达(图4)。

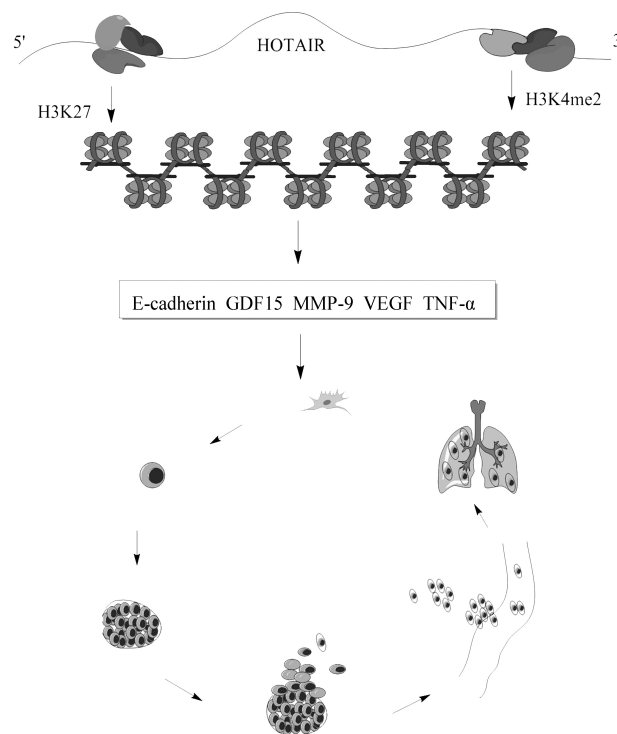


图4 HOTAIR促进肿瘤转移的机制

Fig.4 HOTAIR's mechanisms in tumor metastasis

机体发生肿瘤时, HOTAIR表达量将增加, 而上调的HOTAIR能显著促进肿瘤的发生、发展并且与患者的预后关系密切。肝癌组织中高表达的HOTAIR是患者肝切除和移植后预测肿瘤复发的独立预后因素, 高表达的患者术后HCC易复发及淋巴结转移, 无复发生存期缩短^[32]。在结直肠癌进行的类似研究中, Kogo等^[33]发现, 出现肝转移的肝癌患者的肿瘤组织中HOTAIR的表达水平较癌旁组织的显著升高; 多因素分析显示, HOTAIR水平是结直肠癌一个独立的预后指标, 相对高表达HOTAIR的患者组织分化程度相对低、肿瘤浸润较深、易发生肝转移、预后差。体外实验进一步证明, 上调HOTAIR表达将介导PRC2复合物的全基因重定位, 并显著促进结直肠癌细胞的侵袭能力^[33]。

尽管胃肠道间质瘤(gastrointestinal stromal tumors, GIST)与LncRNA关系的研究目前还较少, 但与结直肠癌相似, HOTAIR在高风险GIST组织中的表达也是上调的; 并且其表达水平与GIST的分级与转移关系密切^[34]。细胞水平实验发现, siRNA干扰*GIST-T1*表达后, *PCHD10*、*SEMA6A*、丝氨酸苏氨酸激酶17b(serine/threonine kinase 17b, *STK17B*)等HOTAIR靶基因表达增加, 细胞侵袭力减弱^[34]。

此外, 高表达HOTAIR胰腺癌患者的生存率低, 容易发生浸润和区域淋巴结转移, 患者预后差; 调整其表达水平可以在影响胰腺癌细胞侵袭的同时, 影响细胞增殖、凋亡和细胞周期进程, 这些功能也是HOTAIR通过PRC2复合物作用于生长/分化因子15(growth/differentiation factor 15, *GDF15*)基因而间接发挥的^[35]。

5 MEG3与肝癌和结直肠癌

母本印迹表达基因3(maternally expressed gene 3, *MEG3*)定位于14q32.2, 在多数正常组织表达, 而在肿瘤细胞中因MEG启动子甲基化等原因导致其表达下调甚至缺失, 从而可促进细胞增殖和血管生成, 因此MEG3被认为是一种新型的具有抑癌基因活性的LncRNA。

研究表明, MEG3具有下调E3泛素连接酶MDM2(mouse double minute 2 homolog)水平, 减少P53泛素化降解, 同时还能增加P53与*GDF15*启动子的结合促进细胞增殖抑制剂GDF15转录从而抑制肿瘤发生等功能^[36]。此外, 也有研究表明, 除P53

外, MEG3还可经其他途径抑制细胞恶性增殖, 从而发挥抑癌功能^[37]。人们观察到, 肝癌细胞MEG3的低表达与miR-29的负性调控有关。miR-29的靶蛋白为DNA甲基转移酶1(DNA-methyltransferase 1, DNMT1)和DNMT3b, 而肝癌细胞中miR-29往往是低表达的, 这样将减少其对这些酶表达的抑制作用, 从而使MEG3基因启动子区域高度甲基化, 造成MEG3的表达下降, 最终促进细胞的增殖^[38]。Anwar等^[39]对肝癌组织中223个印记基因位点的系统荟萃分析发现, MEG3区域频繁异常伴随广泛的DNA甲基化畸变, 同时确认印记的不稳定性与细胞的恶变过程有关。

早年在结直肠癌研究方面也有MEG3表达缺失的报道^[40]。作为LncRNA家族中具有抑癌功能的MEG3展现了表观遗传、LncRNA与miRNA间复杂的调控关系, 这些现象正体现了LncRNA作用机制的复杂性。

6 其它LncRNA与消化系统肿瘤

Barrett食管和食管腺癌非编码区域的异常低甲基化能改变AFAP1反义RNA1(AFAP1 antisense RNA 1, AFAP1-AS1)在组织细胞中的表达量, 人为沉默食管癌细胞AFAP1-AS1的表达后, 癌细胞集落形成、侵袭迁移、抵抗凋亡等生物学行为随之改变^[41], 提示AFAP1-AS1可能参与食管癌的形成。Yang等^[42]在研究结肠癌相关的转录物1(colon cancer associated transcript 1, CCAT1)与胃癌关系时发现, CCAT1的表达量与胃癌分期和转移相关, 而体外提高CCAT1表达能促进胃癌细胞增殖和迁移; 机制研究发现, 这是由于上调的c-Myc能直接与CCAT1基因启动子区域的顺式调控元件E-box结合, 通过增强启动子活性促进CCAT1转录。

肿瘤生长与转移很大程度上依赖于血管形成。Yuan等^[43]发现, 过度表达的肝癌微血管侵犯相关LncRNA(long noncoding RNA associated with microvascular invasion in HCC, LncRNA-MVIH)的肝癌组织常伴有频繁微血管侵犯。造成这种现象的原因是, MVIH抑制肝癌细胞磷酸甘油酸激酶1(phosphoglycerate kinase 1, PGK1)的分泌, 削弱了PGK1抑制血管生成作用。该研究的发现丰富了肿瘤诱导血管生成的分子机制, 体现了LncRNA促进肿瘤转移模式的多样性。

细胞周期网络调控失衡是肿瘤细胞恶性增殖的重要机制之一。Yang等^[44]发现, 长链基因间非蛋白质编码RNA-高表达于肝细胞肝癌(long intergenic non-protein coding RNA, highly expressed in hepatocellular carcinoma, LINC-HEIH; 又名LncRNA-HEIH) 5'端区域通过与EZH2相互作用介导PRC2复合物定

位于P16、P27等细胞周期相关基因启动子区域, 催化组蛋白过度甲基化进而抑制P16、P27等表达, 解除肝癌细胞G₀/G₁期阻滞, 参与肝癌细胞增殖调控。该项研究成果展示了典型的LncRNA在表观遗传层面的调控模式, 同时提示LncRNA亦可参与细胞周期调控网络的构成。

表1 消化系统肿瘤中常见异常表达的LncRNAs
Table 1 The dysregulated LncRNAs in digestive system neoplasms

简称 Abbreviation	全称 Full name	长度(nt) Size(nt)	基因定位 Location	表达情况 Expression	肿瘤类型 Tumor types	参考文献 References
AFAP1-AS1	AFAP1 antisense RNA 1	6 810	4p16.1	↓	Barrett's esophagus, esophageal adenocarcinoma	[41]
AIRN	Antisense of IGF2R non-protein coding RNA	1 489	6q26	↑	Liver cancer	[57]
BCYRN1 (BC200)	Brain cytoplasmic RNA 1	200	2p21	↑	Tongue cancer, oesophagus cancer	[47]
CCAT1	Colon cancer associated transcript-1	2 407	8q24.21	↑	Colon cancer, gastric cancer	[42,49]
CRNDE	Colorectal neoplasia differentially expressed	1 070	16q12.2	↑	Colorectal neoplasia	[51]
DAPK1	Death-associated protein kinase 1	5 942	9q21.33	↑	Pancreatic ductal adenocarcinoma	[56]
GACAT1	Gastric cancer associated transcript 1	84 591	2q12.3	↓	Gastric cancer	[46]
H19	The reciprocally imprinted partner of Igf2	2 322	11p15.5	Loss of imprinting, ↓ or ↑	Colon cancer, liver cancer, gastric cancer, oesophagus cancer	[19-22]
HEIH	Highly expressed in HCC	1 781	5q35.3	↑	Liver cancer	[44]
HOTAIR	Hox transcript antisense RNA	2 337	12q13.13	↑	Colon cancer, liver cancer, gastrointestinal stromal tumors	[32-35]
HULC	Highly up-regulated in liver cancer	500	6p24.3	↑	Liver cancer, hepatic colorectal metastasis	[12-13]
IGF2-AS	Insulin-like growth factor 2 antisense	2 881	11p15.5	↑	Liver cancer	[58]
KCNQ1OT1	KCNQ1 opposite strand/antisense transcript 1	9 1671	11p15	Loss of imprinting	Colorectal cancer	[52]
MALAT1	Metastasis-associated lung adenocarcinoma transcript-1	8 708	11q13.1	↑	Colon cancer, liver cancer, pancreas cancer	[6,8-9]
MEG3	Maternally expressed gene 3	1 506-9 701	14q32.2	Loss of imprinting	Colon cancer, liver cancer,	[38,40]
MAP3K14	Mitogen-activated protein kinase kinase 14	906-1 260	17q21.31	↑	Pancreatic ductal adenocarcinoma	[56]
lncRNA MVIH	Long noncoding RNA associated with microvascular invasion in HCC	2 146	10q22	↑	Liver cancer	[43]
NPTN-IT1	NPTN intronic transcript 1	2 271	15q24.1	↓	Colorectal cancers, liver cancer	[55]
OCC-1	Overexpressed in colon carcinoma-1	1 383	12q23.3	↑	Colorectal cancer	[53]
PPP3CB	Protein phosphatase 3, catalytic subunit, beta isozyme	3 165	10q22.2	↑	Pancreatic ductal adenocarcinoma	[56]
PVT1	Plasmacytoma variant translocation 1	1 716	8q24	↑	Pancreatic cancer,	[54]
UCA1 (CUDR)	Urothelial cancer associated 1	2 314	19p13.12	↑	Colon cancer, liver cancer, gastric cancer, oesophagus cancer	[50]
7SK(LARP7)	7SK small nuclear RNA	332	6p12.2	↓	Gastric cancer	[48]

“↑”: 上调表达; “↓”: 下调表达。

“↑” represents up-expression; “↓” represents down-regulation.

在肝癌、结直肠癌等恶性肿瘤组织中常常出现一种名为“肿瘤低表达LncRNA(lncRNA low expression in tumor, LncRNA-LET)”的LncRNA。研究证实,低氧微环境可导致组蛋白去乙酰化酶3(histone deacetylase 3, HDAC3)活性下降,而使LncRNA-LET启动子区域乙酰化水平减少,结果导致LncRNA-LET表达减少^[45];有意思的是,LncRNA-LET的下调又能减少核因子90(nuclear factor 90, NF90)的降解,而后者在由低氧诱导的癌细胞侵袭过程中发挥关键作用^[45]。最近,本课题组研究发现,胃癌相关转录本1(gastric cancer associated transcript 1, GACAT1; 即AC096655.1-002)的表达水平与胃癌患者的淋巴结转移、远处转移和TNM分期等负相关^[46]。由此可见,LncRNA与肿瘤转移关系的密切性。

总之,现有发现充分证明,许多LncRNA可在表观遗传、转录、转录后等多个层次参与基因表达的调控,在消化系统肿瘤的发生、发展中扮演着重要角色(表1)。

7 结语与展望

随着人们对LncRNA与肿瘤关系的日益关注,越来越多的与消化系统肿瘤相关LncRNA相继被发现,与此同时它们在肿瘤发生、发展中的作用机制也不断被丰富。基于LncRNA在肿瘤发生中作用的认识,人们可针对肿瘤形成中起关键作用的LncRNA设计靶向药物,为肿瘤的分子靶向治疗提供新途径;有些LncRNA表达的组织特异性提示其可作为肿瘤标志物用于消化系统肿瘤的辅助诊断;有些LncRNA由于其与肿瘤分期、分级及患者无病生存期密切相关,则说明它们可用于肿瘤患者术后的预后判断;而另一些LncRNA的分布具有肿瘤亚型差异,所以它们有希望用于肿瘤亚型的鉴别。总而言之,LncRNA在肿瘤发生、发展过程中扮演着重要的角色;开展LncRNA与消化系统肿瘤相关性的研究有望给肿瘤诊疗带来新思路、开辟新路径。

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