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文献综述 REVIEW

microRNA与大肠癌关系的研究进展

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■背景资料
大肠癌的发病是一个多因素、多步骤的演进过程, 基因表达异常在其中起重要作用. 近年来研究证实miRNA广泛存在于真核生物体内, 与大肠癌相关基因表达调控密切相关.

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Advances in understanding the relationship between microRNAs and colorectal cancer

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Abstract
The development of colorectal cancer is a multifactorial, multi-step process in which abnormal gene expression may play an important role. In recent years, it has been reported that microRNAs (miRNAs), which widely exist in eukaryotes, are closely related to gene expression regulation in colorectal cancer. These findings have greatly expanded our understanding of the pathogenesis of colorectal cancer and provide new ideas and methods for the diagnosis and treatment of this malignancy.

Key Words: Colorectal cancer; MicroRNAs; Mechanism; Expression

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摘要
大肠癌的发病是一个多因素、多步骤的演进过程, 基因表达异常在其中起重要作用. 近年来研究证实microRNA(miRNA, 微小核糖核酸)广泛存在于真核生物体内, 与大肠癌相关基因表达调控密切相关. 这些发现极大地扩展了大肠癌的发病机制, 为大肠癌的诊断和分子靶向治疗提供了新的思路和手段.

关键词: 大肠癌; microRNAs; 机制; 表达

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0 引言
miRNA是一类广泛存在于多种生物体内的长度约18-25个核苷酸的非编码小分子RNA, 具有调节基因表达的功能, 参与细胞增殖、分化、凋亡等多种重要细胞活动的调控. miRNA基因以多种形式存在于基因组中, 近来研究发现miRNA具有癌基因或抑癌基因样作用, 多种miRNA在大肠癌组织及大肠癌细胞系中异常表达, 本文就近年来有关miRNA与大肠癌关系作一综述.

1 miRNA的生物学特点
1.1 miRNA发现与命名 miRNA是一类由内源基因编码的长度约为18-25个核苷酸的非编码单链RNA分子, 由具有发夹结构的约70-90个碱基大小的单链RNA前体经过Dicer酶加工后生成. 成熟miRNA的5'端带有磷酸基团(-HPO_4), 3'端带有羟基(-OH), 其本身不具有开放阅读框(ORF), 不编码任何蛋白质, 而是在蛋白质合成中调节其他基因. miRNA的研究始于1993年, Lee等[1]在秀丽新小杆线虫中发现了第1个miRNA, 并命名为

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lin-4. 2000年Pasquinelli等[2,3]又在对线虫发育调控研究中发现了let-7, 从而揭开了miRNA的研究序幕. 随后多个研究小组在包括人类[4-6]、果蝇[7-9]、植物[10-12]等多种生物物种中鉴别出数百个miRNA, 至2007年5月提交并已证实的在动植物和病毒中有4 584个miRNA.

miRNA具有高度保守性、时序表达特异性和组织表达特异性, 广泛地存在于多种真核生物中, 从低等生物到人类都有其存在的痕迹[13,15]. miRNA简写为miR, 其命名根据被克隆的先后顺序加上阿拉伯数字组成, 如miR-21; 若高度同源的miRNA则在数字后面加上英文小写字母(a、b、c), 如miR-199a和miR-199b; 由不同染色体上的DNA序列转录加工而成的具有相同成熟序列的miRNA, 则在后面加上阿拉伯数字加以区别, 如miR-199a-1和miR-199a-2; 如果1个前体的2个臂分别加工产生miRNA, 则根据克隆实验, 在表达水平较低的miRNA后面加“*”, 如miR-199a和miR-199a*, 也可以将物种缩写置于miRNA之前, 如has-miR-195; 在确定命名规则之前发现的miRNA则保留原来的名字, 如let-7, lin-4.

1.2 miRNA合成及作用机制 miRNA的合成是十分复杂的生理过程: 首先, 细胞核内的miRNA基因转录成pri-microRNA(pri-miRNA), 由细胞核内的酶Drosha RNase将其剪切成miRNA前体(pre-miRNA), 核内的转运蛋白将pre-miRNA转运到细胞质中. 然后细胞质中的另一种酶Dicer把miRNA前体剪切成双链miRNA. 成熟的miRNA与其互补链结合成双螺旋结构, 然后双螺旋打开, 其中1条会与RNA诱导的基因沉默复合物(RNA-induced silencing complex, RISC)形成非对称的RISC复合物(asymmetric RISC assembly), 该非对称RISC复合物能够与目标靶mRNA相结合.

目前普遍认为miRNA主要通过2种机制介导转录后基因调节: 一种是mRNA的降解, 而另一种是翻译抑制. 关于miRNA与靶基因的作用方式有3种: (1)当miRNA与靶基因的mRNA序列互补配对程度高时, 通过RISC切割酶Argonaute(Ago-2)作用引起靶基因在互补区的特异性断裂, 从而导致基因沉默; (2)当miRNA与靶mRNA序列配对程度低时, 抑制其翻译过程, 从而调控靶基因的表达. 以线虫lin-4为代表, 这种miRNA是目前发现最多的种类, 但其具体机制还不清楚; (3)同时具有以上2种作用方式, 代表为let-7.

2 大肠癌中差异表达miRNA

2.1 大肠癌中高表达miRNA miRNA是一类新发现的具有调节基因功能的小分子RNA, 癌组织与正常组织相比, 高表达的定义为原癌基因性miRNA. 目前已经发现多种miRNA在大肠癌组织中呈高表达, 如let-7b、miR-9、miR-17-3p、miR-21、miR-29b-2、miR-31、 miR-132、miR-141、miR-142-3p、miR-182、miR-194、miR-194等[16-23]. miR-21是目前唯一的在几乎所有肿瘤中表达上调的miRNA, 其参与了肿瘤细胞的增殖、迁移、浸润以及肿瘤的血管生成等多个环节. Schetter等[24]通过检测197例结肠癌组织中miRNA的表达, 发现37种miRNA的表达存在差异, 其中miR-20a、miR-21、miR-106a、miR-181b及miR-203的表达升高, 而又以miR-21的升高最显著, 且其在结肠癌中的高表达与较差的分化、较差的化疗疗效及较低的生存率相关. Yamamichi等[25]采用原位杂交技术分析了miR-21在结直肠癌发展的不同期别中的表达, 结果发现miR-21的表达从癌前病变到晚期癌逐渐增加. PDCD4是与结直肠癌发生、发展密切相关的miR-2l靶基因之一, Chang等[26]提出, miR-21和PDCD4呈负相关, 提示miR-21通过降解mRNA在后转录水平调节PDCD4表达, 进而提示药物调节miR-21/PDCD4轴可能是结直肠癌新的治疗策略.

2.2 大肠癌中低表达miRNA 癌组织与正常组织相比, 低表达的定义为抑癌基因性miRNA. 目前已经发现多种miRNA在大肠癌组织中呈低表达, 如let-7a、miR-15b、miR-25、miR-30c、miR-92、miR-125、miR-127、miR-143、miR-145、miR-148、miR-191、miR-299、miR-451、miR-486-3p等[27-33]. Akao等[34]发现结肠癌细胞中miR-143和miR-145表达极度下调, 提示两者可能发挥抑癌作用. 该研究还显示, 人结肠癌细胞株DLD-1和SW480转染miR-143和miR-145后, 肿瘤细胞生长显著受抑. 且证实ERK5是miR-143的靶基因. Chen等[35]发现miR-143通过抑制癌基因KRAS蛋白表达而抑制人结肠癌细胞株LoVo生长. Shi等[36]发现miR-145靶向下调胰岛素受体底物-1(IRS-1)蛋白表达, 引起人结肠癌细胞生长停滞. Gregersen等[37]证实在结肠癌细胞中, YES和STATl是miR-145的直接靶分子, miR-145的表达量与癌细胞的分化程度、远处转移或浸润生长密切相关.

■研发前沿
近年来研究证实miRNA与大肠癌相关基因表达调控密切相关, 这些发现极大地扩展了大肠癌的发病机制, 为大肠癌的诊断和分子靶向治疗提供了新的思路和手段.

■创新盘点
本文对多种miRNA在大肠癌组织及大肠癌细胞系中异常表达，及miRNA在大肠癌中的作用机制作一综述. 为进一步阐明大肠癌发生、发展, 包括肿瘤的药物治疗和分子靶向疗法提供新的着眼点.

3 miRNA在大肠癌发生中的作用

3.1 miRNA参与大肠癌细胞增殖 Monzo等[38]发现, miR-17-5p及其靶分子E2F转录因子1(E2F transcription factor 1, E2F1)在人类结肠的早期胚胎发育和肿瘤的发生中存在着相似的表达模式, 且肿瘤的恶性程度越高, 其表达模式越接近胚胎中的表达, 提示胚胎发育期结肠组织中miR-17-5p的高表达可通过下调E2F1的表达促进细胞的增殖; 而结肠癌发生过程中miR-17-5p的表达重新被激活, 并导致了细胞的恶性增殖. Akao等[39]用RT-PCR 技术在结肠癌组织及细胞系DLD-1、SW480、COLO-201中均检测到miR-143、miR-145表达水平下降. 进一步研究发现在增殖期的细胞中miR-143表达下降, 而在凋亡的细胞中表达升高. 将miR-143、miR-145的前体分别转染至细胞系DLD-1、SW480中, 可检测miR-143、miR-145表达水平升高, 还可观察到剂量依赖性细胞生长抑制作用, 提示miR-143、miR-145有抑制癌细胞生长增殖作用. Tazawa等[40]对25例结肠癌组织进行检测, 其中9例(36%)miR-34a表达较周围正常组织明显下降. 把miR-34a导入大肠癌细胞系HCT116和PKO中, 观察到细胞增殖受到完全抑制, 并呈现出衰老样表现型. 应用免疫印迹和基因表达微阵列技术进一步研究发现, miR-34a通过对E2F信号通路的负性调节以及p53信号通路的正性调节, 发挥抑制肿瘤细胞增殖的作用, miR-34a表达失调导致细胞增殖失控, 与大肠癌的发生密切相关.

3.2 miRNA参与大肠癌血管新生 血管新生涉及一系列基因的激活、表达及其调控作用. 近年来, 随着人们对miRNA研究的兴起, 人们发现miRNA在血管新生的调控中起着至关重要的作用. miR-27a是一种具有癌基因作用样的miRNA, 目前发现的其下游靶基因主要有抑制素、ZBTBl0mRNA、Myt-1以及Wee-1等[41-45]. 有些实验也证实ZBTBl0 mRNA是miR-27a的靶目标. ZBTBl0被认为是一种锌指蛋白, 可以抑制特殊蛋白(specificity protein, Sp)转录因子和Sp依赖的基因的表达[46], 而Sp转录因子Spl、Sp3和Sp4在结肠癌肿瘤细胞中高度表达, Sp可以调节VEGF、VEGFRl、VEGFR2等血管源性基因的表达以及抗凋亡基因存活素的表达[47]. Myt-1和Wee-1也是miR-27a的靶目标, 他们可以抑制Cdc2的活性. 通过下调miR-27a的水平, ZBTBl0和Myt-1的表达增强, 从而在G_2/M检查点处抑制结肠肿瘤细胞的生长[45].

3.3 miRNA参与调控大肠癌细胞周期 近来认为miRNAs控制超过30%的编码蛋白基因的表达[48], 许多miRNA的靶基因调节细胞周期[49-52]. Wang[53]等通过无偏的微点阵生物信息学方法分析敲除miR-21的结肠肿瘤细胞, 认为细胞周期调节因子Cdc25A可能也是miR-21的靶目标. 他们发现血清缺乏和DNA损伤会诱导miR-21的产生, 而miR-21通过识别Cdc25A的3'-非翻译区域(3'-UTR)抑制Cdc25A的表达, 进而负向调控细胞G_1-S的转换, 同时参与构成DNA损伤诱导的G_2-M检查点. 因此认为miR-21在机体应激后通过调节Cdc25A参与细胞周期的调节, 从而成为潜在的癌基因.

3.4 miRNA参与大肠癌侵袭转移 大肠癌的复发转移涉及miRNA的调节作用, 他们作为生物标志可准确地诊断大肠癌, 并且能辅助预测大肠癌的复发转移. 目前许多研究揭示miR-21在大肠癌中高表达, 并参与肿瘤浸润转移[54-63]. 有报道指出, 侵袭和迁移的肿瘤细胞miRNA的表达量整体降低, PTEN抑制细胞侵袭, 阻止细胞外基质金属蛋白酶(matrix metalloproteases, MMP)的表达, 而miR-21通过与靶PTEN基因的结合促进了细胞侵袭和迁移[64]. 最近报道了另一条转移途径: 在结肠癌中, miR-21通过下调Pdcd4的表达而促进癌细胞内渗、侵袭和转移, 抑制miR-21和miR-17-92的活性与降低肿瘤的生长、侵袭、转移相关[65]. miRNA在缓解和防止肿瘤复发中有着潜在的重要作用, 他们可能成为肿瘤基因治疗的重要靶点. Zhang等[66]通过分析LoVo, SW480, HT29和Caco-2 4种大肠癌细胞株发现, 11个miRNAs(hsa-let-7i、hsa-let-7g、hsa-miR-30a、hsa-let-7a、hsa-let-7e、hsa-miR-7、hsa-miR-584、hsa-miR-98、hsa-miR-149、hsa-miR-429、hsa-miR-10a)与大肠癌复发转移密切相关, 其中hsa-let-7i在大肠癌复发转移中表达量最高.

4 结论

目前研究已证实miRNA在大肠癌细胞增殖、凋亡、侵袭或肿瘤血管形成等过程中都发挥着重要的作用. 国内外已有很多大肠癌中miRNA表达谱的研究[67], 有关miRNA与大肠癌关系的研究也在不断深入, 但迄今为止许多与大肠癌相关的miRNA仍不为人知, 有关其表达调节的研究也不全面, 且对miRNA参与大肠癌的作用机制尚未完全明确. 相信随着今后对有关研究的

深入和技术的不断进步, 可为进一步阐明大肠癌发生、发展, 包括肿瘤的药物治疗和分子靶向疗法提供新的着眼点.

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■同行评价

该论文阐述了近年来有关miRNA的定义、作用机制及与大肠癌的关系. 有助于人们对miRNA的理解, 并继续研究其与肿瘤的关系, 有一定研究价值.

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• 消息 •

《世界华人消化杂志》外文字符标准

本刊讯 本刊论文出现的外文字符应注意大小写、正斜体与上下角标. 静脉注射iv, 肌肉注射im, 腹腔注射ip, 皮下注射sc, 脑室注射icv, 动脉注射ia, 口服*po*, 灌胃ig. s(秒)不能写成S, kg不能写成Kg, mL不能写成ML, lcpm(应写为1/min)÷E%(仪器效率)÷60 = Bq, pH不能写PH或P^H, *H pylori*不能写成HP, T1/2不能写成tl/2或$T_{\frac{1}{2}}$, *V*max不能Vmax, μ不写为英文u. 需排斜体的外文字, 用斜体表示. 如生物学中拉丁学名的属名与种名, 包括亚属、亚种、变种. 如幽门螺杆菌(*Helicobacter pylori*, *H.pylori*), *Ilex pubescens* Hook, *et* Arn.*var.glaber* Chang(命名者勿划横线); 常数*K*; 一些统计学符号(如样本数*n*, 均数mean, 标准差SD, *F*检验, *t*检验和概率*P*, 相关系数*r*); 化学名中标明取代位的元素、旋光性和构型符号(如*N*, *O*, *P*, *S*, *d*, *l*)如*n*-(normal, 正), *N*-(nitrogen, 氮), *o*-(ortho, 邻), *O*-(oxygen, 氧, 习惯不译), *d*-(dextro, 右旋), *p*-(para, 对), 例如*n*-butyl acetate(醋酸正丁酯), *N*-methylacetanilide(N-甲基乙酰苯胺), *o*-cresol(邻甲酚), 3-*O*-methyl-adrenaline(3-O-甲基肾上腺素), *d*-amphetamine(右旋苯丙胺), *l*-dopa(左旋多巴), *p*-aminosalicylic acid(对氨基水杨酸). 拉丁字及缩写*in vitro*, *in vivo*, *in situ*; Ibid, *et al*, *po*, *vs*; 用外文字母代表的物理量, 如*m*(质量), *V*(体积), *F*(力), *p*(压力), *W*(功), *v*(速度), *Q*(热量), *E*(电场强度), S(面积), *t*(时间), *z*(酶活性, kat), *t*(摄氏温度, ℃), *D*(吸收剂量, Gy), *A*(放射性活度, Bq), ρ(密度, 体积质量, g/L), *c*(浓度, mol/L), φ(体积分数, mL/L), *w*(质量分数, mg/g), *b*(质量摩尔浓度, mol/g), *l*(长度), *b*(宽度), *h*(高度), *d*(厚度), *R*(半径), *D*(直径), T_{max}, C_{max}, *V*d, $T_{1/2}$ *Cl*等. 基因符号通常用小写斜体, 如*ras*, *c-myc*; 基因产物用大写正体, 如P16蛋白.