miRNAs表达异常与宫颈癌发生发展关系的研究进展

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摘要 宫颈癌(cervical cancer, CC)是严重危害女性健康的疾病之一, 具有高的发病率和死亡率。微小RNA(miRNAs)是一类小分子非编码RNA, 通过转录后沉默来调控基因表达。表达异常的miRNAs主要通过调控细胞周期、细胞凋亡以及多种信号通路的方式参与宫颈癌的发生发展。该文就近年来miRNAs在宫颈癌发生发展、诊断、治疗和预后评估等方面的研究进展做一综述, 以寻求对宫颈癌的防治提供新思路。

关键词 微小RNA; 宫颈癌; 诊断; 治疗; 预后

Research Progress on Abnormal Expression of miRNAs and Development of Cervical Cancer

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Abstract CC (cervical cancer) is one of the diseases that seriously endanger women's health, with high morbidity and mortality. miRNAs (microRNAs) are a class of small non-coding RNAs that regulate gene expression through post-transcriptional silencing. Abnormally expressed miRNAs are involved in the development of cervical cancer mainly by regulating cell cycle, apoptosis and various signaling pathways. In this paper, the research progress of miRNAs in the progress, diagnosis, treatment and prognosis of cervical cancer in recent years is reviewed to seek new ideas for the prevention and treatment of cervical cancer.

Keywords MicroRNAs; cervical cancer; diagnosis; treatment; prognosis

宫颈癌(cervical cancer, CC)是妇科常见的恶性肿瘤之一, 也是女性癌症死亡的第四大原因[1]。尽管在过去的几十年里, 宫颈癌的发病率和死亡率一直在下降, 但宫颈癌易复发、放化疗敏感性低、转移性高及预后极差, 严重威胁着女性的健康[2]。微小RNA(microRNAs, miRNAs)作为一类小分子非编码的内源RNA, 对宫颈癌细胞增殖、侵袭和转移具有调控作用, 其表达失常与宫颈癌的发生发展密切相关[3]。因此, 从分子水平研究miRNAs在宫颈癌发生发展中的作用将有助于指导临床上对宫颈癌的预防、诊断和治疗等。

1 miRNAs的生物学功能

miRNAs是一类存在于真核生物中长约22个核苷酸的内源性非编码小分子RNA, 在转录后调控中起重要作用[4]。miRNAs首先由RNA聚合酶II转录为初级miRNA(pri-miRNA), 再被RNase III Drosha切割成具有发夹结构的pre-miRNA, 随后经Dicer酶切割

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成pre-miRNA, 形成miRNA诱导的沉默复合体(miRNA- induced silencing complex, miRISC)。miRISC通过碱基互补配对方式与靶mRNA的3′UTR序列特异性结合, 导致mRNA去腺苷酸化和降解或直接抑制翻译, 从而调控基因表达。

miRNAs作为一种强大的调节剂, 可广泛调控细胞生长、分化、发育和凋亡等生物学过程[5]。超过一半miRNAs基因位于脆性位点区域, 这些区域的表达失调通常与人类许多疾病有关, 特别是癌症[6]。不同miRNAs对细胞增殖、分化和凋亡的作用是不同的。一些miRNAs表现为抑癌基因作用, 抑制细胞增殖、促进分化; 另一些miRNAs则作为癌基因, 在癌细胞中表达上调, 促进细胞增殖、抑制分化。近年来, 众多研究发现, 宫颈癌中存在多种miRNAs表达失调, 进而引起宫颈细胞增殖、迁移、侵袭、细胞凋亡和上皮间充质转化(epithelial-mesenchymal transition, EMT)等关键生物学过程失调, 导致宫颈癌的发生发展[3,8-9]。

2 miRNAs表达异常与宫颈癌的发生发展

表达失调的miRNAs通过调节宫颈癌细胞增殖、侵袭和转移等多种病理过程进而促进宫颈癌的发生发展。在宫颈癌组织中表达上调并能促进宫颈癌发生发展的miRNAs主要包括: miR-150、miR-378、miR-92a、miR-494和miR-18a; 表达下调并抑制宫颈癌发生发展的miRNAs主要有: miR-218、miR-216b、miR-497、miR-204、miR-638和miRNA-383。上述miRNAs主要从细胞周期、细胞凋亡、Wnt/β-catenin通路、磷酸肌醇3-激酶(PI3K)/AKT通路和MAPK/ERK通路等方面调控宫颈癌的发生发展(表1)。

2.1 miRNAs表达异常影响宫颈癌细胞周期和凋亡

近年研究表明, miR-150、miR-378、miR-494和miR-18a等可通过促进细胞周期蛋白表达, 加速细胞周期进程; 同时抑制细胞促凋亡蛋白的表达, 减少细胞凋亡[8,10-12]。LI等[8]证实, 过表达miR-150可诱导宫颈癌细胞从G_1/G_0进展到S期, 促进细胞增殖和生长, 并发现miRNA-150模拟物可显著上调细胞周期蛋白D1(CyclinD1)并抑制p27、凋亡相关因子配体(fas ligand, FASL)和BIM的表达。另有研究发现, miR-378可直接下调HeLa和SiHa细胞中致瘤性7样蛋白(ST7-like, ST7L)的表达, 加速细胞从G_1期到S期和G_2期, 促进宫颈癌细胞增殖和生长[10]。同样, YANG等[11]研究发现, miR-494可通过抑制磷酸酶和张力蛋白同源物(phosphatase and tensin homologue deleted on chromosome 10, PTEN), 促进宫颈癌细胞增殖和细胞周期进程。当miR-494被下调时, 则出现了CyclinD1表达减少和细胞周期阻滞, 宫颈癌细胞增殖显著减少。此外, DONG等[12]发现, miR-18a通过抑制SOX6, 上调CyclinD1的表达促进宫颈癌细胞周期, 促进细胞增殖。

相反, miR-218、miR-216b、miR-497、miR-204等miRNAs则通过抑制细胞周期蛋白表达, 导致细胞周期阻滞, 抑制宫颈癌增殖和生长[12-15]。ZHANG等[13]发现, miR-218可通过靶向Gli3调节宫颈癌细胞的增殖和凋亡, 当miR-218过表达时, 显著增加凋亡相关蛋白活性和降低细胞周期蛋白的表达, 阻断细胞从G_0/G_1期向S期转变, 抑制宫颈癌细胞增殖, 促进凋亡。此外, TAO等[15]发现, miR-497也可诱导宫颈癌HeLe细胞阻滞于G_0/G_1期, 抑制细胞增殖, 促进凋亡; 而miR-204也可将宫颈癌细胞周期阻滞于G_0/G_1期[16], 抑制肿瘤生长。

2.2 表达异常的miRNAs通过Wnt/β-catenin等通路参与宫颈癌的发生发展

激活Wnt/β-catenin通路可促进宫颈癌细胞增殖和侵袭。DONG等[12]发现, 过表达miR-18a可通过靶向抑制SOX6, 激活Wnt/β-catenin通路, 抑制p53途径, 同时增加程序性死亡配体1(programmed death-ligand 1, PD-L1)的表达, 促进宫颈癌细胞增殖和侵袭。当SOX6过表达时, β-catenin表达和Wnt/β-catenin活性也被下调, 并抑制CyclinD1和PD-L1的表达, 导致miR-18a诱导的CC细胞增殖和侵袭能力降低。同样, LI等[10]发现, miR-378 靶向作用ST7L, 从而激活Wnt/β-catenin途径; 后者可增加下游β-连环蛋白、C-myc和CyclinD1的表达, 减少凋亡并促进宫颈癌细胞增殖。而HE等[14]发现, miR-216b可通过抑制FOXM1的表达, 调节Wnt/β-catenin通路下游靶蛋白cyclinD1、myc和LEF1等的表达, 抑制宫颈癌细胞增殖。WEI等[17]发现, miR-638对Wnt/β-catenin通路也有类似的抑制作用, miR-638过表达时能抑制宫颈癌细胞迁移和侵袭。可见, miR-18a和miR-378通过激活Wnt/β-catenin通路, 促进宫颈癌细胞增殖和侵袭; 而miR-216b和miR-638对Wnt/β-catenin通路有抑制作用, 并抑制宫颈癌细胞增殖和生长。

PTEN/PI3K/AKT信号通路异常激活在宫颈

表1 宫颈癌中表达失调的miRNAs

Table 1 Deregulated miRNAs in cervical cancer

微小RNA miRNA	表达 Expression	靶基因/信号通路 Target gene/signal pathway	功能 Function	参考文献 Reference
miR-150	↑	*FOXO4*	Promote proliferation and metastasis, inhibits apoptosis	[8]
miR-378	↑	*ST7L* Wnt/β-catenin	Promote proliferation and inhibit apoptosis	[10]
miR-494	↑	*PTEN* PI3K/AKT	Promotes proliferation, poor prognosis	[11]
miR-18a	↑	*SOX6* Wnt/β-catenin *P53*	Promotes proliferation and invasion	[12]
miR-92a	↑	*PTEN* MAPK/ERK	Promote proliferation and inhibit apoptosis	[19]
miR-21	↑	PTEN/AKT/HIF-1α	Radiotherapy resistance	[37]
miR-181a	↑	AKT/mTOR *PRKCD*	Chemotherapy resistance, inhibition of apoptosis	[34]
miR-19a	↑	-	Promote proliferation, radiation resistance, and inhibition of apoptosis	[40]
miR-221-3p	↑	*TWIST2*	Promotes lymph node metastasis	[43]
miR-218	↓	*GLi3* AKT/mTOR	Inhibit proliferation, promotes apoptosis, and enhances chemotherapy sensitivity	[13,35]
miR-216b	↓	*FOXM1* Wnt/β-catenin	Inhibit proliferation	[14]
miR-497	↓	*RAF-1* MAKP/ERK	Promotes apoptosis, inhibits proliferation, invasion and metastasis	[15]
miR-204	↓	*EphB2* PI3K/AKT	Inhibit proliferation and invasion	[16]
miR-638	↓	Wnt/β-catenin	Inhibit migration and invasion	[17]
miR-383	↓	*PARP2* PI3K/AKT/mTOR	Inhibit migration and invasion	[18]
miR-25-3p	↓	*Sema4C* *EMT*	Inhibit growth and increase chemosensitivity	[9]
MiR-424	↓	*RBBP6*	Inhibit proliferation	[24]
miR-15a-3p	↓	*TPD52*	Enhanced radiosensitivity	[38]
miR-136	↓	*E2F1* *NF-κB*	Inhibits proliferation, promotes apoptosis, enhances radiosensitivity	[39]
miR-874	↓	*ETS1*	Inhibits proliferation, migration, invasion, metastasis, promotes apoptosis	[42]
miR-375	↓	*SP1*	Inhibit proliferation	[32]

↑: 表达上调; ↓: 表达下调。

↑: upregulated; ↓: downregulated.

癌发生发展中起重要作用。YANG等[10]研究证实, PTEN作为miR-494的直接靶标, 在PI3K/AKT通路中有维持稳态的作用, 并通过PTEN/PI3K/AKT信号通路促进宫颈癌发生发展, 但具体机制有待进一步研究。DUAN等[16]研究表明, 过表达的miR-204可显著抑制宫颈癌细胞的增殖、迁移和侵袭及促进凋亡, 其机制是通过靶向负调控Ephrin B型受体2(ephrin type-B receptor 2, EphB2)并抑制PI3K/AKT信号通路的激

活。另有研究发现, miRNA-383可抑制PI3K-AKT-mTOR信号通路并下调PARP2的表达, 抑制细胞增殖、迁移和侵袭, 从而抑制宫颈癌的发生发展[18]。

LI等[19]在小鼠实验中发现, miR-92a可激活MAPK/ERK通路, 促进宫颈癌的发生发展; 过表达的miR-92a通过靶向抑制PTEN, 增加TNF-α、sIL-2R、ERK1和ERK2的表达, 抑制凋亡, 从而促进细胞增殖和生长。而TAO等[15]研究证明, miR-497能通过靶向作用*RAF-1*基因抑制MAPK/ERK信号通路, 下调宫颈癌细胞中MEK1、ERK1和P38的磷酸化状态, 促进凋亡, 抑制增殖、侵袭和迁移。

2.3 宫颈癌中miRNAs表达失调的主要机制

宫颈癌中miRNAs表达失调可能与miRNA基因多态性[20-21]、DNA甲基化[22,24]以及人乳头瘤病毒(HPV)感染[25-26]等因素有关。有研究发现, 位于miRNAs结合位点上的单核苷酸多态性(single nucleotide polymorphism, SNP)可影响miRNAs基因的表达[20-21]。WANG等[20]对954名子宫颈癌患者中6种miRNAs的SNP(即miR-146a rs2910164、miR-149 rs2292832、miR-196a2 rs11614913、miR-499 rs3746444、miR-605 rs2043556和miR-618 rs2682818)基因分型结果显示, 与TT基因型相比, miR-149 rs2292832 TC/CC基因型增加宫颈癌患癌风险[优势比(odds ratio, OR)=1.21, 95%置信区间(confidence interval, CI)=1.00~1.47]。同样, SRIVASTAVA等[21]对Pre-microRNA基因多态性与宫颈鳞癌进行风险评估, 结果表明miRNA-499 rs 3746444 T/C多态性与宫颈癌的患癌风险显著相关, 并可能在宫颈癌的发生中起重要作用。

miRNAs基因启动子发生DNA异常甲基化导致miRNA表达失调也可能促进宫颈癌的发生发展[22-23]。VARGHESE等[24]对来自正常宫颈上皮(normal cervical epithelium, NCE)、宫颈上皮内瘤变(CIN I-III)和鳞状细胞癌(squamous cell carcinoma, SCC)组织中69个miRNA启动子进行DNA甲基化微阵列研究。结果显示, 在宫颈癌组织中表达下调的miR-424发生高甲基化, 表达上调的miR-200b和miR-34c发生低甲基化。当使用去甲基化剂5-氮杂-2′-脱氧胞苷处理后, 表达上调的miR-424通过靶向RBBP6显著抑制宫颈癌细胞增殖。因此, miRNAs与DNA甲基化的相互作用可能参与了宫颈癌的发生发展。

另有研究表明, 高危型HPV与宫颈癌细胞中miRNA表达失调有高度相关性, 它可能通过病毒E6和E7调节宫颈癌组织中miRNA的表达[25-26]。HAN等[25]用qRT-PCR检测HPV16阳性宫颈癌中8种microRNAs(miR-9-5p、miR-136-5p、miR-148a-3p、miR-190a-5p、miR-199b-5p、miR-382-5p、miR-597-5p和miR-655-3p)的表达水平, 发现miR-148a-3p表达下调与3种HPV16癌基因(*E5*、*E6*、*E7*)有关, 而HPV16癌基因*E6*、*E7*的表达上调可导致miR-199b-5p和miR-190a-5p表达下调。此外, XIA等[26]研究发现, HPV16/18阳性的宫颈癌细胞中miR-3156-3p表达下调与HPV感染诱导的宫颈癌发生有关。而DREHER等[27]对3种HPV(低危型HPV-11、高危型HPV-16、HPV-45)类型的基因组miRNA进行分析, 结果发现有13种miRNA表达类似, 其中miR-181a、miR-125a-5p、miR-502-3p、miR-923、miR-92a-1和miR-500表达上调, 而miR-558、miR-576-3p、miR-606、miR-886- 3p、miR-888、miR-1255a和miR-1274b表达下调。

3 miRNAs与宫颈癌诊断

众多研究发现, 血清中miRNAs是一种有前景的新型非侵入性生物标志物, 检测血清中特异性miRNAs表达类型及水平, 对宫颈癌早期诊断和预后具有重要的临床意义[28-30]。血清miRNAs除了来源于凋亡细胞和坏死细胞释放, 还可通过组织以外泌体形式主动分泌到血液中[31]。血清中的miRNAs通常对RNase具有抗性, 成熟后与蛋白质形成沉默复合物, 很少以游离形式存在, 提高了血清miRNAs的稳定性。基于这些基本特征, 提示血清miRNAs有可能作为肿瘤生物标志物, 用于宫颈癌临床早期诊断和治疗。JIA等[28]对213名宫颈癌患者血清研究发现有12种miRNAs显著上调, 其中miR-21、miR-29a、miR-25、miR-200a和miR-486-5p可以作为宫颈癌诊断的非侵入性的生物标志物。ZHANG等[29]在184名宫颈癌患者血清中鉴定了一组由4种miRNAs构成(miR-16-2、miR-195、miR-2861、miR-497)的非侵入性标志物, 也有可能用于宫颈癌的辅助诊断。而JIANG等[30]研究发现, 血清miR-101水平与宫颈癌的转移和预后密切相关, 且较高水平的血清miR-101可延长宫颈癌患者的存活时间。

宫颈癌细胞miRNAs表达失调与DNA异常高甲基化有关[22-23], miRNAs基因高甲基化可能成为宫颈癌诊断与治疗的潜在指标。STICH等[32]认为, miR-375基因甲基化水平可能用于HPV感染导致的宫颈

癌患者的诊断和监测。ROGERI等[22]证实, miR-124基因高甲基化与宫颈癌上皮内瘤变2等级(CIN2+)具有相关性, 并显示出与HPV试验相似的敏感性和特异性, miR-124基因高甲基化可能是宫颈癌前体病变有希望的生物标志物。YU等[23]发现, miR-10b基因异常甲基化导致的表达水平改变与HPV感染有关, 表明HPV可能通过CpG岛甲基化降低miR-10b的表达。随后分析表明, miR-10b启动子区域甲基化程度有可能成为宫颈癌诊断与治疗的潜在指标。

4 miRNAs与宫颈癌治疗

目前宫颈癌治疗主要采用手术治疗和放疗两种方法, 针对宫颈癌的化疗仍以顺铂为基础的单药或联合化疗为主[33], 特别是对晚期或复发性宫颈癌患者; 但耐药性是导致宫颈癌治疗失败和预后不良的主要原因。许多研究发现, 宫颈癌对化疗药物敏感性与miRNAs表达失调有关[9,34-35]。CHEN等[34]发现, miR-181a能增强宫颈鳞状细胞癌对顺铂等化疗药物的耐药性; 其机制可能是通过靶向作用促凋亡蛋白激酶(protein kinase C delta, PRKCD)降低宫颈癌细胞对顺铂的敏感性, 减少肿瘤细胞凋亡。另有研究表明, miR-218也可通过阻断AKT/mTOR信号通路增强宫颈癌细胞对顺铂的敏感性, 可见miR-218有可能作为宫颈鳞癌患者对顺铂敏感性的预测指标[35]。另外, SONG等[9]发现, miR-25-3p过表达可逆转宫颈癌细胞的EMT表型, 且可通过靶向Sema4C增强宫颈癌细胞对顺铂的敏感性。

放疗特别适用于宫颈癌晚期或发生淋巴结转移的患者, 但放射治疗形成的放疗抵抗也会严重影响着疗效[36]。SONG等[37]报道, miR-21可通过减少细胞自噬, 进而增强宫颈癌细胞的放射抗性。过表达的miR-21能抑制PTEN, 增加p-AKT和缺氧诱导因子-1(hypoxia-inducible factor-1alpha, HIF-1α)的表达, 导致宫颈癌细胞自噬减少。因此, miR-21可通过PTEN/AKT/HIF-1α、AKT-mTOR信号通路减少宫颈癌细胞自噬, 增强放射抗性。WU等[38]对30例宫颈鳞癌分析发现, 放疗后宫颈癌组织中miR-15a-3p表达较放疗前呈显著性增加, 后者可通过靶向TPD52增强癌细胞的敏感性。此外, LU等[39]研究发现, miR-NA-136也可通过NF-κB途径促进宫颈癌细胞凋亡和提高放射敏感性, 而WANG等[40]证实, miR-19a可降低宫颈癌SiHa细胞的放疗敏感性; 当miR-19a被沉默时, 宫颈癌细胞增殖减少, 细胞凋亡增加。

5 miRNAs与宫颈癌的预后

通常把FIGO肿瘤分期、组织学类型、肿瘤浸润深度及淋巴结转移等作为宫颈癌预后判断的重要指标[41-42]。LIAO等[42]证实, 在宫颈癌中表达下调的miR-NA-874与FIGO分期、淋巴结转移有关, 恢复miR-874的表达显著抑制癌细胞增殖、迁移和侵袭, 并发现miRNA-874的作用是依赖于E26转化特异性-1(E26 transformation specific-1, ETS1)。另有研究证实, 转移性宫颈癌组织中高表达的miR-221-3p也具有促进宫颈癌转移的作用, 其可通过靶向负调控TWIST2, 促进EMT, 增强淋巴结转移, 因此, miR-221-3p有可能作为宫颈癌患者预后不良的一个指标[43]。最近Zeng等[44]通过对306例宫颈癌病例进行预后分析, 结果表明hsa-miR-3154、hsa-miR-600和hsa-miR-7-3可 作为宫颈癌的潜在预后标志物, 其中hsa-miR-3154和hsa-miR-7-3的高表达与宫颈癌患者存活时间和更多的死亡病例密切相关, 而hsa-miR-600高表达与延长的存活时间有关。此外, 还有研究发现, miR-34a和miR-206与患者较低的总体存活率相关, 提示miR-34a和miR-206也有可能作为宫颈癌预后不良判断的指标[45]。

6 问题与展望

尽管对宫颈癌的研究已深入分子水平, 对其发病机制也有一定的了解, 但宫颈癌患者在复发、预后及改善生存期方面的效果仍然较差。miRNAs对宫颈癌细胞的增殖、侵袭和转移都有调控作用, 这为临床靶向治疗提供了新的可能性; 且miRNAs作为一种新型的非侵入性生物标志物, 为宫颈癌的辅助诊断、治疗和预后也提供了新的方向和思路。然而, miRNAs要实际运用于临床仍然面临诸多问题或困难, 比如运用miRNAs检测宫颈癌发生的研究不够, 且没有进入临床实践, 也没有足够的miRNAs实验研究成果可以运用到临床。此外, 阐明miRNAs在不同信号通路中的相互作用及其机制, 也是需要探索并解决的问题。miRNAs如何精确作用于相应靶点而不被其他miRNAs所干扰也需要进一步研究。

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