综述

miRNAs表达异常在宫颈癌转移机制中的研究进展

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摘要 原发宫颈癌(cervical cancer, CC)的早期转移是导致其治疗效果差的主要原因之一。因此, 全面了解宫颈癌的转移机制至关重要。miRNAs(microRNAs)是一种小的非编码RNA分子, 主要通过转录调控基因的表达, 在肿瘤的发生发展过程中发挥重要的作用。miRNAs通过调节上皮–间质转化(epithelial-mesenchymal transition, EMT)、微血管的形成、细胞外基质(extracellular matrix, ECM)的降解及细胞骨架重构等多种途径影响宫颈癌的转移。该文就miRNAs在宫颈癌转移机制中的研究进展作一综述, 以便为基于miRNAs开发抗宫颈癌转移的靶向药物提供参考依据。

关键词 miRNAs; 宫颈癌; 转移; 分子机制

Research Progress on Abnormal Expression of miRNAs in the Metastasis Mechanism of Cervical Cancer

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Abstract The early metastasis of primary tumor of CC (cervical cancer) is one of the main reasons leading to poor prognosis and response. Therefore, it's very important to comprehensively understand the metastasis mechanism of cervical cancer. miRNAs (microRNAs) are a kind of small non-coding RNAs that regulate gene expression through post-transcriptional silencing, playing an important role in the occurrence and development of tumors. miRNAs affect the metastasis of cervical cancer by regulating EMT (epithelial-mesenchymal transition), microvascular formation, degradation of ECM (extracellular matrix) and cytoskeletal remodeling. This article reviews the research progress of miRNAs in the metastasis mechanism of cervical cancer, in order to provide a reference for the development of targeted drugs against cervical cancer metastasis based on miRNAs.

Keywords miRNAs; cervical cancer; metastasis; molecular mechanisms

宫颈癌(cervical cancer, CC)是目前世界范围内最常见的妇科恶性肿瘤之一, 尤其是在包括中国在内的发展中国家, 其发病率和死亡率逐年上升[1]。尽管随着宫颈癌筛查水平的提高, 越来越多的宫颈癌

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患者得到了早期诊断, 并通过联合治疗提高了治疗效果[2], 但是, 仍然有部分患者发生肿瘤复发及转移, 该病生存率明显下降[3]。目前可供选择的宫颈癌治疗方式有手术、化疗和放射治疗。若宫颈癌患者发生转移或肿瘤处于晚期, 其5年生存率则仅为30%~50%[4]。因此, 遏制宫颈癌转移尤其重要。

微小RNAs(microRNAs, miRNAs)是一种内源性非编码RNA, 通过调控基因的表达来调节细胞的发育、增殖、分化、凋亡、信号转导和肿瘤发生发展等多种重要生物学过程, 近年研究发现, miRNAs表达失常与宫颈癌转移密切相关, 其可通过影响上皮–间质转化(epithelial-mesenchymal transition, EMT)相关转录因子、细胞外基质(extracellular matrix, ECM)降解、微血管形成相关分子及细胞骨架重构等干预肿瘤迁移。本文总结了近年来影响宫颈癌转移的miRNAs及其作用机制, 旨在从分子水平寻找更好的疾病治疗方向。

1 miRNAs概述

miRNAs是一组高度保守的长约20~24 nt的单链非编码RNA分子, 存在于真核细胞中。许多miRNAs具有组织特异性或分化特异性, 它们通过与信使RNA(mRNA)的3′非编码序列(3′ untranslated region, 3′UTR)完全或不完全的碱基互补配对, 使靶基因mRNA降解或蛋白质的翻译被抑制, 从而调控基因的表达[5]。一个miRNA可以有多个靶基因, 而几个miRNA也可以调节同一个基因。因此, miRNA在人类基因组中虽仅占不到3%, 却可以调控人类1/3编码蛋白质的基因表达[6]。

miRNAs在发育、代谢、免疫反应以及肿瘤的发生和转移等许多生物过程中都起着重要作用[7], 其在恶性肿瘤中既可作为致癌基因又可作为抑癌基因: 能够抑制细胞增殖、促进其终末分化的miRNAs为抑癌miRNAs(anti-oncomiRs); 能够促进细胞增殖、抑制分化的miRNAs为致癌miRNAs(oncomiRs)[8]。研究表明, miRNAs(如miR-200家族、let-7家族、miR-34家族等)的异常表达在宫颈癌细胞增殖、侵袭及凋亡等过程中扮演重要的角色。

2 miRNAs在宫颈癌转移中的作用

研究宫颈癌的转移机制对其治疗和预后具有重要意义。宫颈癌细胞主要通过影响EMT相关转录因子、ECM的降解, 如基质金属蛋白酶(matrix metalloproteinases, MMPs)、微血管形成相关分子以及细胞骨架重构等进行转移[9-10]。近年来, 大量研究表明, miRNAs在宫颈癌转移组织中的表达水平呈现不同程度的上调或下调, 表现出对宫颈癌的抑制或促进作用。下面我们将对miRNAs影响宫颈癌EMT、ECM的降解、微血管形成及细胞骨架重构这些方面进行论述。

2.1 miRNAs影响宫颈癌EMT

EMT是指上皮细胞极性以及细胞间的紧密连接丧失, 形态学发生改变, 成为有间质细胞形态和特性的细胞的过程。肿瘤细胞发生浸润和转移的过程中首先出现的形态学变化就是EMT。miRNAs可通过下调E-cadherin、β-catenin等上皮细胞标记蛋白和上调N-cadherin、Vimentin等间质细胞相关蛋白, 使肿瘤发生转移[11]。此外, 一些核转录因子: Twist、Snail、Slug及ZEB(zinc finger E-box binding homeobox)等[12-13], 以及许多信号通路(TGF-β、Wnt, Hedgehog 、MAPK等)在EMT过程中也发挥着重要的作用[14]。

TANG等[15]发现, miR-21在宫颈癌及淋巴结转移组织中过表达, 转染了miR-21的HeLa和SiHa细胞中*ZEB1*和*Snail*的基因表达水平明显提高, 同时E-cadherin蛋白表达减少, N-cadherin、Vimentin蛋白表达增加, 显示出了更强的侵袭力, 这表明miR-21通过增强EMT促进宫颈癌的转移。而YUAN等[16]发现, 被HPV感染的宫颈癌组织中VEGF和miR-21表达水平明显高于癌旁组织, 进一步的实验表明, 两者的表达呈正相关, 其高水平的表达预示着不良预后。有意思的是, ZHANG等[17]发现, miR-21还可以负性调节TIMP3(tissue inhibitor of metalloproteinase 3)的表达促进宫颈癌细胞增殖、存活以及迁移和侵袭活动。可见miR-21能够多靶点、多途径促进宫颈癌的转移。PIAS3(protein inhibitor of activated signal trans-ducer and activators of transcription 3)是一种转录抑制因子, 其低表达与淋巴结转移和晚期临床分期有关。miR-199a-5p通过靶向抑制PIAS3, 上调N-cadherin、Vimentin, 下调E-cadherin, 抑制宫颈癌转移[18]。YANG等[19]发现, miR-G-1受GRSF1(G-rich RNA sequence binding factor 1)调控, 通过上调LMNB1(lamin B1)和TMED5(transmembrane p24 trafficking protein 5)激活Wnt/β-catenin信号通路,

促进EMT及核自噬, 发挥促进宫颈癌转移的作用。INPP1(inositol polyphosphate-1-phosphatase)是一种负责糖酵解和脂质代谢的酶, miR-27a通过靶向结合INPP1, 增强宫颈癌细胞活力, 促进EMT, 增强细胞侵袭转移能力[20]。*SRCIN*(SRC kinase signalling inhibitor 1)是一种肿瘤抑制基因, 在转染了SRCIN过表达质粒的C-33A和HeLa细胞中, EMT过程被抑制, miR-150-5p通过与SRCIN的3′UTR结合逆转了这一过程, 发挥促进细胞增殖迁移的作用[21]。

相反地, 一些miRNAs对宫颈癌的转移具有抑制作用。miR-137和miR-34b分别通过与GREM1(gremlin 1)结合以及调节TGF-β1抑制TGF-β/smad通路, 抑制宫颈癌细胞的EMT和侵袭、迁移[22-23]。GLI1(glioma-associated oncogene 1)是Hedgehog信号通路的转录因子, 在多种癌症的发生发展过程中起到关键的作用, miR-873及miR-584通过靶向抑制GLI1的表达, 上调E-cadherin, 下调N-cadherin和Vimentin, 抑制EMT过程, 从而抑制宫颈癌细胞的增殖、迁移[24-25]。相似地, miR-4429和miR-374b可靶向抑制FOXM1(forkhead box protein M1)来上调E-cadherin, 下调N-cadherin和Vimentin, 发挥抑制宫颈癌细胞增殖、迁移和侵袭的作用[26-27]。KAPORA等[28]发现, miR-505-5p通过抑制CDK5(cyclin-dependent kinase 5)的表达抑制EMT, 此外, 临床结果表明, miR-505-5p的表达与FIGO分期、肿瘤大小、淋巴结转移和组织学分级之间具有紧密的联系。eIF4E(eukaryotic translation initiation factor 4E)是一种限速蛋白, 对翻译的调控至关重要, 在各种类型的癌症中呈现出高表达。抑制eIF4E的表达可上调E-cadherin, 下调N-cadherin、Vimentin以及Snail-1, miR-499a-5p通过抑制eIF4E的表达抑制EMT, 促进宫颈癌细胞的凋亡、增强放射敏感性, 起到抑癌作用[29]。研究表明, miR-377的表达与宫颈癌患者的FIGO分期、淋巴结转移和远处转移密切相关, 进一步了解其机制为miR-377通过负调控ZEB2的表达, 抑制EMT, 阻止肿瘤转移[30]。c-Met参与EMT, 与肿瘤的发生和进展密切相关, miR-1、miR-138和miR-454-3p可抑制c-Met的表达。在宫颈癌组织中, miR-1、miR-138和miR-454-3p表达下调, 解除了对c-Met的抑制, 上调的c-Met表达水平可抑制E-cadherin表达, 促进癌细胞增殖、迁移和浸润, 降低患者生存率[31-33]。此外, Sema4C(semaphorin 4C)通过激活p38 MAPK促进EMT的形成[34], miR-31-3p靶向抑制Sema4C阻断EMT过程, 抑制宫颈癌细胞的转移[35]。

2.2 miRNAs影响ECM的降解

ECM是一个动态的结构, 通过不断地沉积、降解和修饰以维持组织内稳态, 这种特点使其成为抵御肿瘤细胞转移和侵袭的天然屏障。MMPs是一类锌依赖性的内肽酶, 通过降解ECM中的各种蛋白质, 破坏其组织学屏障, 在肿瘤侵袭转移中起关键性作用[36]。MMPs家族包含28个成员, 其中对MMP-2、MMP-9的研究较深入[37]。miRNAs可通过抑制相关MMPs表达, 以及结合组织金属蛋白酶抑制剂(tissue inhibitor of matrix metalloproteinase, TIMP)等途径, 来调控宫颈癌的转移行为。此外, 丝氨酸蛋白酶、半胱氨酸蛋白酶及天门冬氨酸蛋白酶也是溶解ECM的主要蛋白水解酶。

SUN等[38]发现, miR-G-10通过靶向GRSF1(G-rich RNA sequence binding protein), 一方面上调PIK3R3激活PI3K/AKT/NF-κB信号通路, 另一方面, 下调TIMP3促进ADAM17和MMP9表达, 发挥促进宫颈癌细胞侵袭和迁移的作用, 此外, HeLa细胞转染miR-G-10后, caspase-3和PARP[poly (ADP-ribose) polymerase]的表达水平显著降低, 显示出抗细胞凋亡的作用。TIMP2是MMP-2的拮抗剂, YIN等[39]发现, *TIMP2*是miR-130a的靶基因, miR-130a在宫颈癌组织中高表达, 与宫颈癌的临床晚期和淋巴结转移显著相关, 敲除*HPV18 E6*基因可显著抑制HeLa细胞中miR-130a的表达, 抑制HeLa细胞迁移和侵袭, 这些结果表明HPV18 E6通过上调miR-130a, 抑制*TIMP2*的表达, 促进宫颈癌细胞迁移和侵袭。血小板反应蛋白2(thrombospondin, THBS2)是THBS家族的5个成员之一, 能调节糖蛋白在细胞间、细胞与肿瘤之间的黏附和迁移能力, 肿瘤中THBS2的表达与肿瘤的血管生成、侵袭和转移相关。miR-93-5p作为miR-106b-25家族的一员, 在宫颈癌组织和细胞中呈现高表达的状态, miR-93-5p通过靶向抑制THBS2表达, 上调MMP-2和MMP-9, 降解ECM, 促进SiHa细胞的侵袭和迁移[40]。CHEN等[41]发现, *THBS2*也是miR-1246的靶基因, miR-1246通过负调节THBS2促进SiHa细胞的侵袭和迁移。随后, DU等[42]进一步阐明了其作用机制, 即miR-1246在靶向抑制THBS2的基础上, 上调MMP-2和MMP-9的表达, 促进ECM降解。这与miR-93-5p的作用机制高度相似。不仅如此,

研究发现, miR-20a同样通过靶向抑制THBS2的表达促进宫颈癌细胞增殖并抑制细胞自噬及凋亡[43], 但其是否像miR-93-5p及miR-1246一样通过进一步上调MMP-2和MMP-9的表达来促进宫颈癌转移则需进一步的实验验证。可见, THBS2在宫颈癌的转移中具有重要的作用, 当其表达被miRNA抑制时, 宫颈癌将发生转移。HMGA1(high-mobility group AT-hook1)与宫颈癌的晚期临床分期以及淋巴结转移有关, 通过调节细胞周期蛋白D1/E1促进宫颈癌细胞从G_1期过渡到S期, 进一步的研究表明, HMGA1上调miR-221/22表达, 抑制TIMP3, 促进MMP-2和MMP-9表达, 加速宫颈癌细胞增殖、迁移和侵袭, 促进肿瘤的生长[44]。LIU等[45]发现, miR-492在晚期宫颈鳞状细胞癌组织中高表达, 与骨盆淋巴结转移有关, 进一步的研究表明, miR-492与TIMP2的3′UTR结合抑制TIMP2表达, 促进MMP10分泌, 诱导SiHa增殖和迁移, 增强其对放化疗的敏感性。

研究表明, 一些miRNAs对宫颈癌的转移具有抑制作用。胸腺基质淋巴细胞生成素(thymic stromal lymphopoietin, TSLP)具有促进血管生成以及嗜酸性粒细胞募集的作用。缺氧条件下或TGF-β的诱导可引起TSLP水平升高, 这种高水平的TSLP一方面能够促进嗜酸性粒细胞的募集以及肿瘤血管的生成, 另一方面能够通过下调miR-132的表达水平来抑制Ki-67、PCNA(proliferating cell nuclear antigen)、MMP-2和MMP-9的表达, 限制宫颈癌细胞的增殖和侵袭[46]。miR-126通过靶向抑制ZEB1下调MMP-2、MMP-9的表达及JAK2/STAT3信号通路的转导, 抑制宫颈癌细胞增殖、迁移和侵袭[47]。研究发现, miR-484发挥抑制宫颈癌细胞侵袭和迁移的作用是通过下调MMP-14和HNF1A(hepatocyte nuclear factor 1A)的表达实现的, 而EZH2(enhancer of zeste homolog 2)募集的DNMT1(DNA methyltransferases 1)介导了miR-484的甲基化, 从而使其沉默, 解除了对MMP-14和HNF1A的抑制, 使宫颈癌细胞发生侵袭和迁移[48]。此外, HU等[49]发现miR-484抑制EMT过程, 主要是通过与ZEB1和SMAD2 3′UTR区结合并降低其表达来实现的。

2.3 miRNAs调节宫颈癌微血管形成

肿瘤微血管生成是肿瘤生长、发展和转移所需的重要条件。肿瘤细胞和基质细胞通过分泌大量促血管生成因子为血管的生成提供养料, 形成的血管网反过来又为肿瘤提供生长所需的营养和氧气, 并帮助清除肿瘤微环境中的代谢废物和二氧化碳, 为肿瘤扩散及转移创造条件[50]。血管内皮生长因子(vascular endothelial growth factor, VEGF)是调节细胞有丝分裂和内皮细胞通透性的关键血管生成细胞因子, 可促进血管生成的各种过程, 包括内皮细胞增殖、黏附、迁移和趋化性, 其高表达提示肿瘤的生长及新生血管的形成。此外, 促血管生成因子还包括成纤维细胞生长因子-1(fibroblast growth-factor-1, FGF-1)和血小板来源的内皮细胞生长因子(platelet-derived endothelial cell growth factor, PDGF); 抗血管生成因子包括细胞外基质糖蛋白凝血酶反应蛋白-1(extracellular matrix glycoprotein thrombospondin-1, TSP1)、内皮抑素和血管抑素等[51]。

研究表明, miR-221-3p通过多种途径促进肿瘤微血管形成。WEI等[52]发现, Twist2通过上调miR-221-3p增加N-cadherin、Vimentin蛋白表达, 减少E-cadherin蛋白表达, 增强细胞的侵袭性和迁移能力, 促进EMT过程, 同时体内实验也表明miR-221-3p高表达促进了肿瘤的淋巴结转移, 他们发现, *THBS2*是miR-221-3p重要的下游靶基因, 在有淋巴结转移的癌组织中THBS2的表达水平明显低于无淋巴结转移的癌组织, 这表明miR-221-3被Twist2上调并下调其靶基因*THBS2*来促进宫颈癌淋巴结转移。随后, WU等[53]发现, SiHa和C33细胞外泌体中的miR-221-3p同样通过靶向下调THBS2的表达来促进肿瘤的血管生成、侵袭及转移。此外, miR-221-3p还可分别通过抑制血管抑制素-1(vasohibin-1, VASH1)的表达激活AKT和ERK信号通路以及下调MAPK10的表达促进微血管内皮细胞(microvascular endothelial cell, MVEC)对外泌体的摄取来促进血管生成, 促使宫颈癌发生淋巴结转移[54-55]。BABION等[56]和HU等[57]分别发现, miR-9-5p通过靶向SOCS5(suppressor of cytokine signaling 5)促进血管生成以及靶向twist1促进EMT, 发挥促进宫颈癌转移的作用。另有研究发现, miR-205一方面被lncRNA GAS5下调, 对宫颈癌的发展产生抑制作用[58], 另一方面通过下调TSLC1(tumor suppressor lung cancer 1)的表达, 激活AKT信号通路, 上调IL-8、VEGF和bFGF, 促进肿瘤的血管生成及转移[59]。

WANG等[60]发现, miR-129-5p负性调节Hedgehog信号通路的转导和ZIC2(zinc finger protein of the

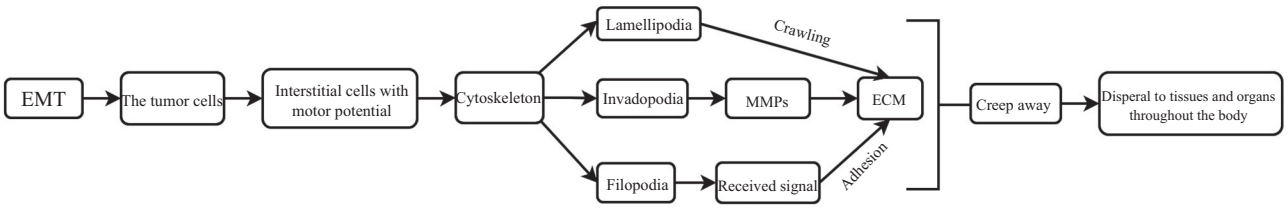

图1 细胞骨架在肿瘤转移中与EMT、ECM的作用关系

Fig.1 The relationships between cytoskeleton and EMT, ECM in tumor metastasis

cerebellum 2)的表达, 降低趋化因子1(chemotactic cytokine 1, CXCL1)、VEGF及血管生成素2(Ang2)的水平, 抑制血管生成, 进一步的体内实验也表明miR-129-5p具有抑制裸鼠体内肿瘤生长和血管生成的能力。此外, FU等[61]发现, miR-125通过靶向抑制VEGF的表达以及PI3K/AKT信号通路的转导, 抑制宫颈癌细胞的增殖、侵袭和迁移。吲哚胺-2,3-双加氧酶(indoleamine-2,3-dioxygenase, IDO)是一种负性免疫调节因子, 通过将色氨酸分解成多种代谢产物, 阻止T细胞的免疫反应, 诱导调节性T细胞(regulatory cells, Tregs)介导的免疫逃逸, miR-218能够负性调节JAK2/STAT3信号通路抑制TGF-β、VEGF、IL-6、PGE2(prostaglandin E2)、COX-2(cyclooxygenase-2)和Survivin的表达, 增强caspase-3活性, 抑制宫颈癌细胞免疫逃逸[62]。癌症干细胞(cancer stem cells, CSC)具有促进肿瘤启动和自我更新的作用, miR-146a可直接靶向VEGF, 下调VEGF的表达, 抑制CDC42/PAK1信号通路的激活, 最终抑制TCs的肿瘤形成和侵袭转移[63]。VEGF是一个家族, 包括VEGF-A、VEGF-B、VEGF-C、VEGF-D、VEGF-E和胎盘生长因子(placental growth factor, PGF)。miR-144通过直接靶向VEGF-A和VEGF-C抑制宫颈癌细胞的生长、迁移和侵袭[64]。静脉血栓栓塞症(venous thromboembolism, VTE)是恶性肿瘤患者的常见并发症和第二大死因, 也可能是肿瘤患者首先出现的临床表现, miR-205-5p和miR-195-5p通过靶向抑制VEGF-A, 抑制肿瘤血管增生, 降低血管通透性, 预防VTE发生[65]。

2.4 miRNAs影响细胞骨架重构

细胞骨架(cytoskeleton)是指真核细胞中的蛋白纤维网络结构, 由微管(microtubule, MT)、微丝(microfilament, MF)及中间纤维(intermediate filament, IF)构成, 具有维持细胞形态及细胞运动的功能。在肿瘤细胞中, 细胞骨架是细胞侵袭性伪足(Invadopodia)、板状伪足(Lamellipodia)以及丝状伪足(Filopodia)形成的结构基础, 在细胞迁移和黏附中发挥作用。细胞骨架中蛋白(特别是肌动连接蛋白、Cortactin和Fascin-1)表达水平的变化会影响细胞的形态及运动性, 影响肿瘤的侵袭及转移。研究发现, 细胞骨架结构和蛋白水平的变化与EMT、ECM密不可分。肿瘤细胞经EMT编辑后, 细胞之间的紧密连接及细胞极性消失, 变成具有运动潜能的间质样细胞。此时, 由E-cadherin介导的细胞–细胞间的连接消失, 单个具有高度侵袭潜能的细胞从团块中分离出来, 细胞质内的细胞骨架通过肌动蛋白推动胞膜形成局部凸起, 其中F-actin(肌动蛋白丝)在细胞骨架调节蛋白的调控下, 在肿瘤细胞与ECM的结合面呈极性延伸, 形成侵袭性伪足, 运输MMPs帮助肿瘤细胞溶解ECM和血管壁等肿瘤屏障[66-67]; 接着肿瘤细胞通过板状伪足及丝状伪足实现向前运动。板状伪足是运动细胞前沿的薄片状质膜凸起性结构, 肿瘤细胞沿着ECM平面爬行时, 细胞骨架推动细胞膜不断地向运动方向突起形成板状伪足, 并通过黏附作用将新形成的板状伪足锚定在ECM上[68-69]; 在运动的过程中, 肿瘤细胞在运动前沿以放射状的形式不停地向细胞微环境中形成丝状伪足, 以感受细胞外信号, 如生长因子、趋化因子和细胞外基质等, 在其顶端形成细胞-ECM连接, 完成细胞与ECM的黏附, 指引板状伪足向信号方向组装, 帮助其向远处爬行, 从而实现肿瘤细胞向全身组织器官播散[70-71](图1)。

HE等[72]发现, miR-145-5p发挥抑制宫颈癌侵袭的作用与下调Fascin的表达有关。c-Src是一种酪氨酸激酶, 主要通过蛋白间的相互作用和激酶结构域的协同作用来调节肌动蛋白细胞骨架和细胞的黏附。YANG等[73]发现, VEGF-C通过c-Src信号通路抑制miR-326的表达, 提高cortactin蛋白水平, 改变细胞骨架, 增强宫颈癌浸润性, 促进宫颈癌细胞侵袭。miR-326还可以与TCF4(transcription factor 4) 3′UTR

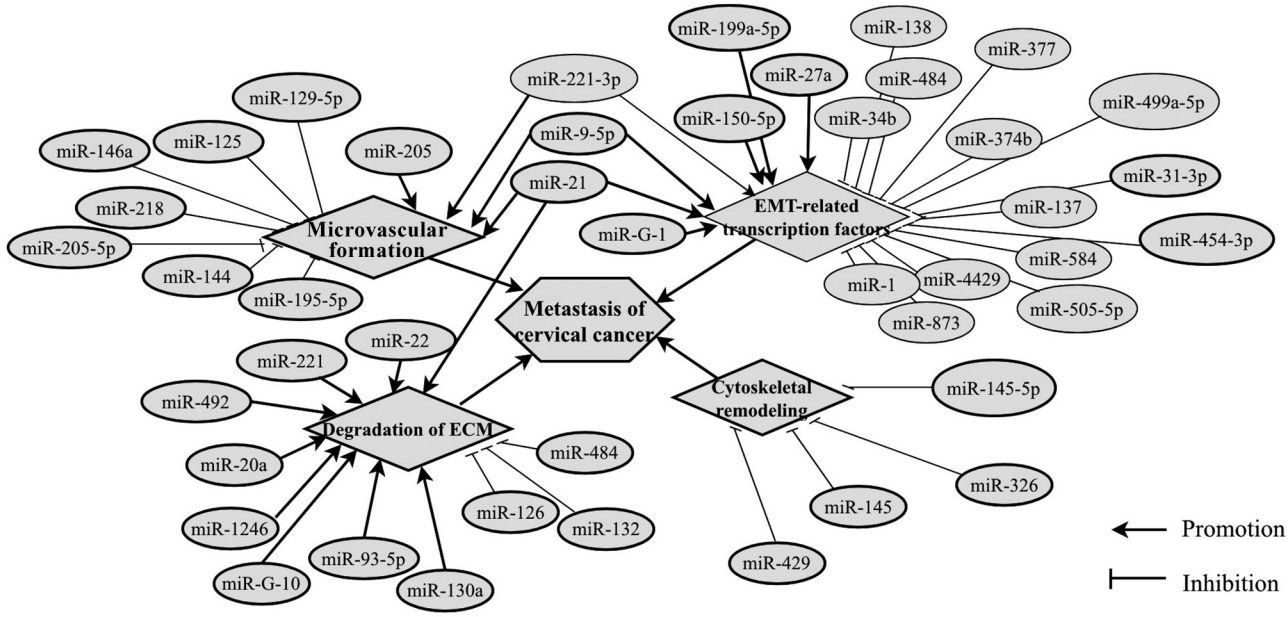

图2 miRNAs异常表达与宫颈癌转移的关系

Fig.2 Relationship between abnormal expression of miRNAs and metastasis of cervical cancer

结合, 抑制其表达, 阻断Wnt/β-catenin信号通路转导, 抑制了Caski细胞增殖和侵袭[74]。肌球蛋白的活性在细胞增殖、凋亡、黏附和迁移的调控中起着关键作用, MYPT1是肌球蛋白磷酸酶的亚单位之一, miR-145通过抑制MYPT1的翻译上调肌球蛋白轻链的磷酸化(phosphorylation of the myosin light chain, pMLC)水平, 使细胞骨架重构, 降低细胞存活率, 抑制细胞迁移和侵袭[75]。既往研究表明, miR-429通过靶向抑制ZEB1和ZEB2, 抑制EMT。WANG等[76]发现, miR-429还可以通过抑制ZEB1和CRKL(Crk-like adapter protein)的表达, 诱导细胞骨架的张力纤维减少, 导致肌动蛋白形态皱缩, 影响细胞骨架重构, 抑制宫颈癌侵袭和迁移能力。

3 小结与展望

宫颈癌的转移是宫颈癌中需重点关注的部分, 随着对miRNAs研究的不断深入, miRNAs显示出了在宫颈癌转移中的调控作用(图2), 这意味着一方面, miRNAs的表达情况有可能成为对宫颈癌是否发生转移进行预测、诊断和预后的生物标志物; 另一方面, miRNAs可能帮助临床制定个性化治疗及靶向治疗方案。然而, 目前关于miRNAs影响宫颈癌转移EMT机制的研究较为深入, 在ECM的降解、血管新生及细胞骨架重构方面研究较少(尤其是细胞骨架重构方面), 因此, 宫颈癌相关miRNAs表达异常的作用机制仍然需要更多的体内及体外实验来进一步探索。近年来发现, 细胞骨架与EMT、ECM联系紧密, 而miRNAs影响宫颈癌侵袭转移或可通过对骨架蛋白的调控实现一元化干预。因此, 在未来的研究中, 可以将关注点放在miRNAs通过调节骨架蛋白进而对肿瘤的侵袭迁移进行调控上, 以期为明确宫颈癌转移机制及抑制宫颈癌转移提供新思路。

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