miRNAs表达异常与卵巢癌发生发展的研究进展

王钰[1] 杨兴业[1] 万福生[2]*

([1]南昌大学第二临床医学院, 南昌 330006; [2]南昌大学基础医学院生物化学与分子生物学教研室, 南昌 330006)

摘要 微小RNAs(microRNAs, miRNAs)是一类长度约22 nt的内源性非编码RNAs, 主要通过转录后沉默调控基因的表达, 参与细胞增殖、分化、凋亡等重要病理生理过程以及某些肿瘤的发生发展与转移。miRNAs在卵巢癌细胞中存在广泛差异性表达, 有望通过干扰miRNAs的生物发生(即放大miRNAs的抑癌作用或减弱miRNAs的致癌作用)达到预防和治疗卵巢癌的作用。该文对近年来miRNAs在卵巢癌发生发展中作用的研究结果进行综述, 希望能为卵巢癌的临床治疗提供新思路。

关键词 微小RNAs; 卵巢癌; 细胞增殖; 凋亡; 侵袭转移

Research Progress on Abnormal Expression of miRNAs in Oncogenesis and Development of Ovarian Cancer

WANG Yu[1], YANG Xingye[1], WAN Fusheng[2]*

([1]*The Second Clinical Medical College of Nanchang University Nanchang 330006, China*;
[2]*Department of Biochemistry and Molecular Biology, Medical College of Nanchang University, Nanchang 330006, China*)

Abstract miRNAs (microRNAs) are a group of endogenous non-coding RNAs of approximately 22 nucleotides in length, which are involved in cell proliferation, differentiation, apoptosis and other important pathophysiological processes. It has been known that miRNAs regulate gene expression by mediating post-transcriptional silencing. miRNAs are also implicated in tumor initiation, progression and metastasis. Widely differentially expressed miRNAs are expected to prevent and treat ovarian cancer by interfering with its biosynthesis, in other words, inhibiting the expression of oncogenic miRNAs or promoting the function of tumor suppressor miRNAs can accomplish the goal. This paper reviews recent researches on roles of miRNAs in the occurrence and development of ovarian cancer, to provide new prescriptions for clinical treatment.

Keywords microRNAs; ovarian cancer; cell proliferation; apoptosis; metastasis

据美国癌症协会统计, 卵巢癌是女性五大致命癌症之一[1]。由于卵巢癌发病隐匿, 早期多无症状, 绝大多数患者就诊时已处在疾病的中晚期或已远处转移, 5年病死率达53%[2], 居妇科恶性肿瘤首位。卵巢癌病因和发病机制迄今尚未明确, 目前以手术为主配合铂类及紫杉烷类的联合化疗是治疗卵巢癌的主要方式, 但术后复发、转移和出现耐药性的发生率极高, 临床对新型分子靶向治疗的需求日益增加。研究表明, 微小RNAs(microRNAs, miRNAs)在卵巢癌发生发展中发挥着重要作用[3], 这对于开发治疗卵巢癌的新方法至关重要。本文就近年来miRNAs在卵巢癌发生发展中的作用及研究进展作一综述,

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*通讯作者。Tel: 0791-86360228, E-mail: wanfs01@163.com
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*Corresponding author. Tel: +86-791-86360228, E-mail: wanfs01@163.com
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希望能为miRNAs在卵巢癌的临床早期诊断、治疗及其预后判断等相关研究提供有价值的参考。

1 miRNAs概述

miRNAs是一类长约为22 nt的非编码核苷酸序列[4]。编码miRNA的基因首先由RNA聚合酶II转录为初级miRNA(pri-miRNA)再由Drosha-DGCR8(DiGeorge syndrome critical region gene 8)复合物处理生成小于100 bp的前体miRNA(pre-miRNA), 再经RNAse III样内切核酸酶Dicer加工形成miRNA双链体, 随后双链miRNA解链, 其中1条单链与RISC(RNA induced silencing complex)结合, 形成miRISC复合物。该复合物会与靶mRNA的3′非翻译区位点碱基互补配对, 导致靶mRNAs降解或使靶mRNAs翻译受抑制, 从而沉默靶基因表达[4-5]。现已知, miRNAs广泛参与细胞增殖、分化、凋亡及代谢等多种生物学过程, 且在肿瘤演进中发挥重要功能[6]。根据miRNAs的生物效应可以将它们分为致癌miRNAs和抑癌miRNAs 2类, 在癌细胞中通过转录后沉默抑癌基因且促进癌症发展的上调miRNAs被认为是致癌miRNAs, 而通过沉默原癌基因抑制癌症发展的下调miRNAs被称为肿瘤抑制miRNAs[3,7]。通常miRNAs的表达具有空间特异性, 即表现为组织特异性或细胞特异性。miRNAs具有特定的肿瘤组织学特征, 一种miRNA在多种癌症中其表达水平也不相同, 即使在同一癌症的不同细胞系中的表达水平也不同。

在卵巢癌中有多种miRNAs表达失调, 且这些miRNAs与卵巢癌的发病及进展密切相关，它们参与并调控了卵巢癌细胞增殖、凋亡、侵袭、迁移等多个发生发展过程。

2 miRNAs表达失调与卵巢癌细胞增殖

细胞过度增殖是卵巢细胞恶性病变的重要原因之一。最近研究发现, 多种miRNAs在卵巢癌细胞的增殖过程中发挥着重要作用, 例如miR-223-3p、miR-18b、miR-205和miR-216a在卵巢癌中表达上调, 这些miRNAs可明显促进卵巢癌细胞增殖[8-11]。然而, 也有众多miRNAs如let-7c、miR-23b、miR-34a、miR-34c、miR-145、miR-491-5p、miR-519a、miR-542-3p、miR-193a-3p、miR-1271、miR-491-5p、miRNA-574-3p、miR-634和miRNA-936在卵巢癌中表达明显下调, 这些miRNAs发挥抑制卵巢癌发生发展的作用[12-23]。

2.1 miRNAs与细胞周期调节因子

let-7c、miR-23b、miR-634、miR-542-3p和miR-145通过调控某些细胞周期调节因子的表达而发挥抑癌作用[12-16]。ZHANG等[12]发现, let-7c可以靶向调控*CDC25a*基因, 因后者是CDC25磷酸酶家族中的一员, 故let-7c导致细胞周期阻滞, 进而抑制卵巢癌细胞的恶性增殖。miRNAs通过下调细胞周期蛋白(cyclin)、细胞周期蛋白依赖性激酶(cyclin-dependent kinase, CDK)以及E2F转录因子家族等直接阻遏细胞周期转换的驱动因子的表达并抑制细胞周期进程。如: miR-23b和miR-634靶向作用*CCNG1*基因, 导致cyclin G1表达下调, 抑制卵巢癌细胞增殖[13-14]; miR-542-3p靶向下调*CDK*基因表达, 中断其在细胞周期中的驱动作用, 从而抑制卵巢癌细胞增殖[15]; miR-145通过直接靶向*CCND2*和*E2F3*基因, 导致卵巢癌细胞G_1期停滞并抑制卵巢癌细胞增殖[16]。

2.2 miRNAs与SRY相关的HMG转录因子家族

SRY相关的HMG转录因子家族(sex determining region Y-related high mobility group box family)编码的SOX蛋白具有调节基因转录的作用。miR-223-3p在卵巢癌细胞系(SKOV3、OVCAR3、A2780、ES2)中过表达。FANG等[8]根据荧光素酶报告基因分析、蛋白质印迹分析和qRT-PCR分析得出, *SOX11*为miR-223-3p的靶基因, miR-223-3p可以抑制靶基因*SOX11*的表达, 因*SOX11*过表达可削弱卵巢癌细胞的增殖和侵袭, 故SOX11表达明显下调加速了卵巢癌细胞的生长、迁移和侵袭。XIAO等[17]报道, miR-34c通过靶向*SOX9*, 下调SOX9、β-catenin和c-Myc蛋白水平, 抑制卵巢癌细胞增殖。SOX9蛋白在A2780、SKOV3和OVCAR-3细胞系中显著上调, 高SOX9表达会加强卵巢癌细胞增殖、转移和对顺铂处理的化学耐药性, 上调miR-34c则显着抑制了癌细胞的活力和DNA合成能力。

2.3 miRNAs与肿瘤增殖相关的信号通路

研究显示, 多种miRNAs(miR-18b、miR-205、miR-216a)靶向*PTEN*基因, 消除PTEN对AKT信号通路的负调控, 激活PI3K/AKT信号通路, 进而促进卵巢癌细胞增殖和转移[9-11]。miRNAs能通过影响细胞增殖信号通路如Ras和AKT中信号分子的活性, 实现对癌细胞增殖的抑制作用[14,18-22]。miR-

1271对mTOR的沉默可以抑制卵巢癌增殖, 促进顺铂诱导的耐药细胞(SKOV3/DDP)凋亡; miR-34a在体内外减少IL-6R的表达, 抑制高级别浆液性卵巢癌细胞KF28和A2780增殖。另有荧光素酶报告基因测定表明, miR-193a-3p不仅靶向生长因子受体结合蛋白7(growth factor receptor bound protein 7, GRB7), 而且靶向其他信号分子如ERBB4、SOS2和KRAS, 完全抑制在卵巢癌中异常激活的MAPK/ERK信号通路; miR-634靶向Ras-MAPK途径组分GRB2、ERK2和RSK2; miR-491-5p和miRNA-574-3p靶向表皮生长因子受体(epidermal growth factor receptor, EGFR), 抑制AKT和MAPK信号通路的激活, 上述miRNAs通过实现对增殖相关信号通路的负调控达到抑制卵巢癌细胞生长增殖的目的。miRNA-936通过靶向*FGF2*基因使p-PI3K和p-Akt蛋白水平显著下调, 导致PI3K/AKT通路失活以抑制上皮性卵巢癌SKOV3和CAOV-3细胞的增殖、迁移和侵袭。用miR-936模拟物转染以过表达miR-936时卵巢癌细胞的增殖, 迁移和侵袭能力被显著抑制。值得注意的是, 研究人员发现, miR-936不仅在体外对上皮性卵巢癌细胞有抑增殖作用, 而且在裸鼠异种移植模型中上调miR-936对体内肿瘤生长具有类似的抗肿瘤作用[23]。

3 miRNAs表达失调与卵巢癌细胞凋亡

miRNAs参与调控卵巢癌细胞的凋亡过程, 如miR-23b、miR-145、miR-491-5p以及miR-519a能促进卵巢癌细胞凋亡, 而miR-221和miR-183有助于卵巢癌细胞逃避凋亡, 加速肿瘤的发生发展[13,16,21,24-27]。

HUA等[16]研究发现, miR-145能激活促凋亡基因*Bax*表达, 并抑制抗凋亡基因*BCL-2*表达而诱导卵巢癌细胞凋亡。miR-23b和miR-491-5p能下调BCL-XL表达, miR-519a通过抑制MCL-L和BCL-XL的表达促进癌细胞凋亡[13,21,24]。XIE等[25]发现, 在卵巢癌细胞中miR-221表达异常升高, 且miR-221表达水平越高, 患者的生存率就越低, 预后也越差。miR-221通过抑制BCL-2修饰因子(B-cell lymphoma 2 modifying factor, BMF)的表达来发挥其拮抗凋亡、促进卵巢癌细胞增殖的作用。凋亡蛋白酶激活因子1(apoptotic protease activating factor 1, *APAF-1*)基因也被确认为miR-221的直接靶标, miRNA-221能靶向作用*APAF-1*基因, 抑制凋亡, 促进卵巢癌细胞增殖[26]。此外, miR-183作用于TGF-β信号通路下游分子CoSMAD 即Smad4, 使Smad4表达受限, TGF-β通路被抑制, cyclin D1和抗凋亡基因*BCL-2*的表达上调, 促凋亡因子BAX、p21和p27以及凋亡蛋白酶caspase-3和caspase-9的表达降低, 从而抑制卵巢癌细胞凋亡[27]。

4 miRNAs表达失调与卵巢癌侵袭转移

肿瘤侵袭转移是导致卵巢癌高死亡率的重要原因, 卵巢癌的侵袭转移与miRNAs表达异常密切相关。miRNAs在卵巢癌侵袭转移中表现出两种效应[30-45], 在卵巢癌中表达增强并促进卵巢癌细胞侵袭转移的主要有miR-27a、miR-590-3p、miR-520h、miR-301b-3p以及miR-205; 与卵巢癌侵袭转移抑制有关且表达水平显著降低的有miR-203、miR-200s、miR-199a-5p、miR-138、miR-16、miR-122、miR-219-5p、miR-124、miR-148a、miR-34和miR-30a-5p。miRNAs通过影响上皮–间质转化(epithelial-mesenchymal transitions, EMT)、基质金属蛋白酶(matrix metalloproteinases, MMPs)活性、血管增生、免疫逃逸等途经[28]参与肿瘤的侵袭转移, 间接影响患者的生存期并与患者病情的预后效果相关联。

4.1 miRNAs表达失调与EMT

EMT是肿瘤侵袭转移早期的一个重要病理生理过程, 也是肿瘤细胞发生浸润和转移过程中首先发生的形态学变化, 在肿瘤侵袭转移过程中起了关键性作用[29]。WANG等[30]发现, miR-27a在卵巢癌细胞(HO8910和OV90)中表达显著升高, 且能促进EMT过程, 增强细胞侵袭转移能力。接受miR-27a模拟物转染的卵巢癌细胞系表现出增殖和迁移能力的增加, 而在miR-27a抑制剂的作用下, 细胞增殖和迁移均受到抑制。双重荧光素酶测定表明, 肿瘤抑制因子1(forkhead box O1, FOXO1)是miR-27a的直接靶标, miR-27a通过靶向*FOXO1*基因, 下调FOXO1表达, 激活Wnt/β-catenin信号传导, 促进卵巢癌的侵袭转移。与之相似的是, miR-590-3p靶向*FOXO3*和*CCNG2*基因, 增强β-catenin活性, 导致卵巢肿瘤的侵袭性增强[31]。miR-520h能直接结合*Smad7*基因, miR-520h不仅可以抑制Smad7蛋白表达还能增加Snail蛋白水平。Smad7作为一种通用的TGF-β信号抑制剂, 其表达降低能激活TGF-β信号通路。miR-520h沉默*Smad7*基因, 启动TGF-β信号转导通路, 进而诱导EMT, 促进卵巢肿瘤转移[32]。此外miR-301b-3p可促使EGFR、p38和ERK1/2过表达, 加速卵巢癌

的恶化; 而miR-205则通过靶向作用*ZEB1*、*Smad4*和*VEGF*增强卵巢癌的侵袭转移[33-34]。miR-203靶向抑制*BIRC5*基因, 下调Survivin蛋白水平, 阻碍TGF-β信号途径传导。作为*BIRC5*基因编码产物的survivin是凋亡抑制蛋白((inhibitor of apoptosis protein, IAP)家族的一员, 它能抑制半胱天冬酶又称凋亡蛋白酶caspase的活化, 具有阻止细胞凋亡和促进细胞增殖的双重作用。Survivin与肿瘤侵袭和化学抗性密切相关。可见, miR-203通过转录后抑制*BIRC5*基因, 阻碍卵巢癌SKOV3和OVCAR3细胞的EMT过程和肿瘤的侵袭转移[35]。miR-200s家族由miR-200a、miR-200b、miR-200c, miR-141和miR-429 5个成员组成, 它们通过靶向E盒结合锌指蛋白家族1/2(zinc finger e-box binding homeobox 1/2, ZEB1/2)、SMAD家族及Snail家族有效抑制EMT并诱导卵巢癌MET。miR-200c还可通过靶向血管内皮生长因子(vascular endothelial growth factor, VEGF)、IL-8和趋化因子配体1(CXC motif chemokine ligand 1, CXCL1), 阻断肿瘤血管的生成[36]。由此可见, miRNAs在卵巢癌细胞的EMT中发挥重要作用。

4.2 miRNAs表达失调与MMPs

MMPs在肿瘤侵袭过程中发挥重要作用[28]。MMPs家族降解细胞外基质(extracellular matrix, ECM), 使瘤细胞穿过组织屏障向周围浸润, 从而加速肿瘤的转移。MMPs是降解细胞外基质的重要酶类, 在卵巢癌中MMP-2和MMP-9被认为与癌细胞的迁移密切相关。miR-199-5p、miR-16、miR-122能抑制相关MMPs的表达, 减少卵巢癌细胞的转移扩散。

HIF-1α(hypoxia-inducible factor-1α)、NF-κB1具有正向调控MMP-2和MMP-9的作用。研究发现, miR-199a-5p和miR-138分别通过靶向作用*NF-κB1* mRNA和*HIF-1α* mRNA的3′非翻译区, 抑制MMP-2、MMP-9的表达, 从而有效降低了卵巢癌的侵袭转移过程[37-38]。另有研究称, miR-16发挥抑制卵巢癌侵袭转移的作用与下调MMP-2和MMP-9的表达水平有关[39]。而miR-122能直接与介导胶原蛋白成熟的脯氨酰-4-羟化酶亚基α-1(proline 4-hydroxylase alpha polypeptide 1, *P4HA1*)的mRNA 3′非翻译区结合并下调其表达水平, 使卵巢癌SKOV3和OVCAR3细胞中E-cadherin的表达增加, vimentin、MMP-2和MMP-14的表达减少, 抑制卵巢癌转移[40]。

4.3 miRNAs表达失调与肿瘤转移相关的信号通路

现已知, Wnt/β-catenin信号通路、鞘氨醇激酶(sphingosine kinase, SphK)/鞘氨醇-1-磷酸(sphingosine-1-phosphate, S1P)/鞘氨醇-1-磷酸受体(sphingosine-1-phosphate receptor, S1PR)参与调控卵巢癌细胞的转移行为。

有研究显示, miR-219-5p靶向作用Twist, 负性调节Wnt/β-catenin信号通路, 抑制上皮性卵巢癌细胞的增殖、迁移和侵袭[41]。JIA等[44]认为, miR-16也能通过抑制Wnt/β-catenin信号通路减弱卵巢癌的侵袭转移。*SphK1*和*S1PR1*分别被确定为miR-124和miR-148a的直接靶标, miR-124靶向抑制SphK1蛋白的表达, miR-148a靶向抑制S1PR1蛋白的表达, 它们共同阻断SphK/S1P/S1PR信号通路诱发的卵巢癌侵袭转移。过表达的miR-124和miR-148a负向调节SphK1、S1PR1蛋白水平, 阻断卵巢癌细胞的迁移和侵袭。相反地, miR-124、miR-148a的表达降低而SphK1、S1PR1表达的恢复可以克服miRNAs诱导的细胞迁移和侵袭的抑制[42-43]。异常的Notch信号传导可诱导癌症干细胞(cancer stem cell, CSC)的自我更新[46], 有研究报道, 在卵巢癌组织中miR-34和miR-30a-5p的表达显著下调, 但Notch1表达却显著上调, miR-34、miR-30a-5p可通过直接靶向*Notch1*基因, 下调Notch1表达, 抑制Notch信号通路激活, 最终抑制卵巢癌的EMT过程和侵袭转移[44-45]。

5 miRNAs在卵巢癌诊断中的作用

卵巢癌往往起病隐匿, 加之转移性高且缺乏特异性诊断性生物标记物, 对患者的病情诊断滞后, 多数卵巢癌患者确诊时已处于疾病的中晚期或有远处转移。

目前, CA125与HE4联合检测可用于评估卵巢癌风险, 有助于监测肿瘤进展或复发, 但临床仍渴望更快速、廉价、便捷的新型生物标志物。近日, 有学者通过qRT-PCR评估116名健康人与110名卵巢癌患者的血清样本发现了5种可能用于检测和预测卵巢癌的血清miRNAs: miR-200c-3p、miR-346、miR-127-3p、miR-143-3p和miR-205-5p。与正常控制组对比发现, 以上5种循环miRNAs在患者组血清中显著高表达, 其中miR-200c-3p、miR-346和miR-127-3p的表达水平与肿瘤的远处转移及分级有关, miR-205-5p与患者血清CA125水平相关联。这意味着, 以

上5种血清miRNAs有望成为卵巢癌进展和预后的特异性生物标志物[47]。WU等[48]利用生物信息学meta分析对比血清miRNA表达水平发现, miR-200成员(miR-200a、miR-200b、miR-200c、miR-429)和miR-25可能成为预测卵巢癌的分子标志物。

6 miRNAs在卵巢癌化疗耐药性中的作用

除手术外, 目前以铂类和紫杉烷类联合用药为主的化疗是治疗卵巢癌的主要手段, 但随之而来的耐药性使化疗疗效大幅降低并导致预后不良。耐药性不仅是卵巢癌治疗失败的重要原因, 更是肿瘤复发和转移的主要原因。最新发现, miRNAs对卵巢癌化疗药物的耐药性具有双向调节作用, 一些miRNAs在卵巢癌中的表达上调并能增强卵巢癌细胞对化疗药物产生耐药性如miR-27a、miR-622; 但也有一些表达被下调的miRNAs能阻抑卵巢癌细胞对化疗药物产生耐药性, 提高药物敏感性如miR-1271、miR-34c、miR-142-5p及miR-383-5p[17-18,49-52]。

miR-27a通过靶向*CUL5*(Cullin5)基因促进卵巢癌的发展, 降低卵巢癌细胞对顺铂和多西紫杉醇的敏感性, 使得患者化疗预后较差[49]。miR-622可诱导具有BRCA1/2突变的高级别浆液性卵巢癌细胞对PARPi和铂的抗性[52], 使得患者铂化疗的预后较差。miR-1271靶向沉默mTOR抑制癌细胞增殖, 增强顺铂诱导的耐药细胞(SKOV3/DDP)凋亡[18]。XIAO等[17]的研究显示, miR-34c通过靶向下调SOX9、β-catenin和c-Myc蛋白水平, 降低卵巢癌细胞对顺铂的化学耐药性。需注意, miR-142-5p能与多种抗凋亡因子(XIAP、BIRC3、BCL-2、BCL2L2和MCL-L)特异性结合, 促进顺铂诱导的卵巢癌细胞凋亡, 提高卵巢癌细胞对顺铂的敏感性及疗效[50]。JIANG等[51]证明, miR-383-5p通过下调*TRIM27*基因表达, 抑制PI3K/AKT途径, 增强卵巢癌细胞对紫杉醇的化学敏感性。

7 结语

卵巢癌作为女性健康的一大杀手, 病死率远高于其他妇科恶性肿瘤。miRNAs能够通过转录后沉默基因表达, 调控卵巢癌细胞的增殖、凋亡、侵袭、转移及耐药等重要过程, 参与卵巢癌的发生发展(图1和表1)。卵巢癌中miRNAs的异常表达可以使癌基因或肿瘤抑制因子的表达水平发生改变, 意味着miRNAs在卵巢癌的早期诊断和治疗及预后方面有望成为新型生物靶标。但是, 卵巢癌在分子水平上具有高度异质性, 是否存在miRNAs对一类卵

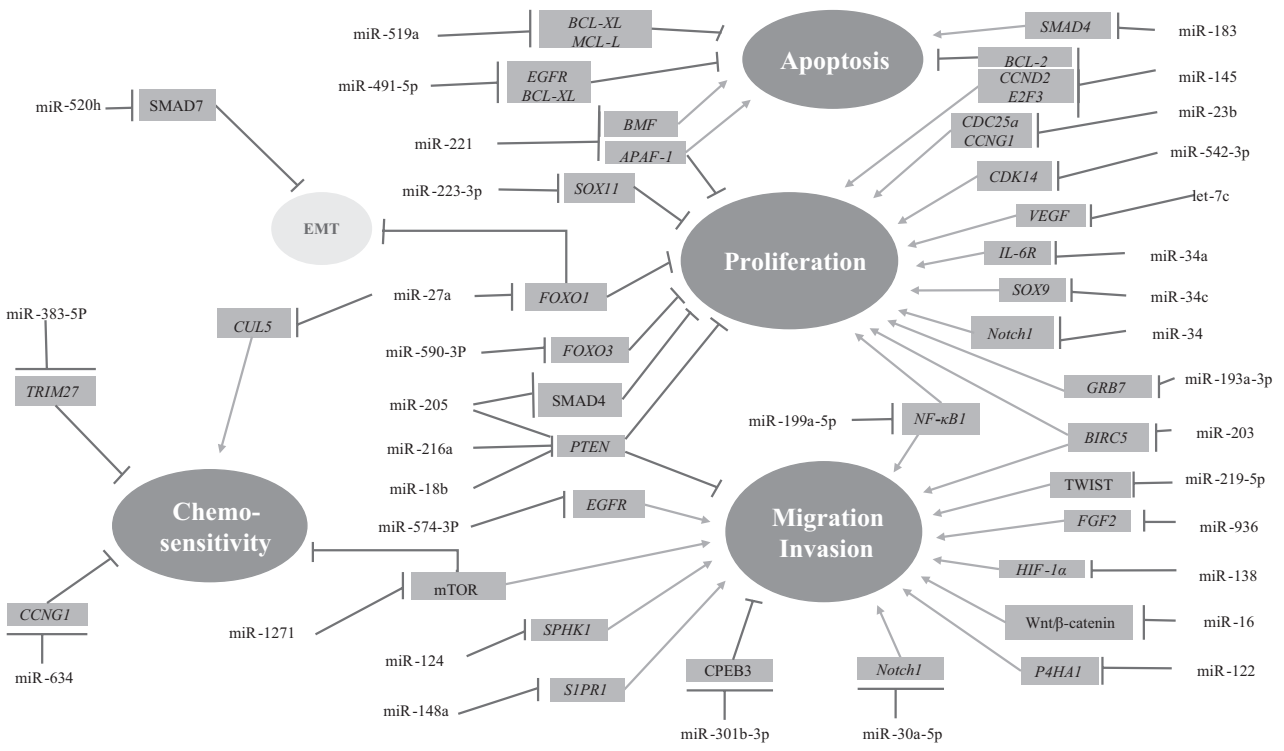

图1 miRNAs在卵巢癌发生发展中的调节机制

Fig.1 miRNAs regulatory mechanisms in the occurrence and development of ovarian cancer

表1 卵巢癌中表达失调的miRNAs

Table 1 Deregulated miRNAs in ovarian 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-223-3p	↑	*SOX11*	Promote proliferation and invasion	[8]
miR-18b	↑	*PTEN*	Promote migration and invasion	[9]
miR-205	↑	PTEN/Smad4, *ZEB1*	Promote proliferation and invasion	[10,34]
miR-216a	↑	*PTEN*	Promote metastasis	[11]
miR-221	↑	*BMF*, *APAF-1*	Promote proliferation and inhibit apoptosis, poor prognosis	[25-26]
miR-183	↑	TGF-β/Smad4	Inhibit apoptosis	[27]
miR-27a	↑	*FOXO1*, *CUL5*	Promote proliferation, invasion and metastasis, enhance chemoresistance	[30,49]
miR-590-3P	↑	*FOXO3*, *CCNG2*	Promote proliferation and invasion	[31]
miR-520h	↑	TGF-β1/c-Myb/Smad7	Promote metastasis	[32]
miR-301b-3p	↑	CPEB3/EGFR	Promote migration and invasion	[33]
miR-622	↑	–	Inhibit proliferation	[52]
let-7c	↓	*VEGF*	Inhibit proliferation	[12]
miR-23b	↓	*CDC25a*, *CCNG1*	Inhibit proliferation	[13]
miR-634	↓	*CCNG1*	Inhibit chemoresistance	[14]
miR-542-3p	↓	*CDK14*	Inhibit proliferation and invasion	[15]
miR-145	↓	*CCND2*, *E2F3*, *BCL-2*	Inhibit proliferation and invasion	[16]
miR-34c	↓	*SOX9*	Inhibit proliferation	[17]
miR-1271	↓	mTOR	Inhibit proliferation and cisplatin resistance	[18]
miR-34a	↓	*IL-6R*	Inhibit proliferation	[19]
miR-193a-3p	↓	*GRB7*	Inhibit invasion and metastasis	[20]
		MAPK/ERK	–	
miR-491-5p	↓	*EGFR, BCL-XL*	Inhibit proliferation, promote apoptosis	[21]
miR-574-3P	↓	*EGFR*	Inhibit proliferation and chemoresistance	[22]
miR-936	↓	*FGF2*	Inhibit invasion and metastasis	[23]
		PI3K/AKt	–	
miR-519a	↓	*MCL-L*, *BCL-XL*	Inhibit proliferation	[24]
miR-203	↓	*BIRC5*, *TGF-β*	Inhibit metastasis	[35]
miR-200s	↓	*ZEB1/2*, *Smad*, *Snail*	Inhibit metastasis	[36]
		VEGF, *IL-8*, *CXCL1*		
miR-199a-5p	↓	*NF-κB1*	Inhibit proliferation and invasion	[37]
miR-138	↓	*HIF-1α*	Inhibit invasion and metastasis	[38]
miR-16	↓	Wnt/β-catenin	Inhibit migration and invasion	[39]
miR-122	↓	*P4HA1*	Inhibit metastasis	[40]
miR-219-5p	↓	Twist/Wnt/β-catenin	Inhibit proliferation, invasion and metastasis	[41]
miR-124	↓	*SphK1*	Inhibit migration and invasion	[42]
miR-148a	↓	*S1PR1*	Inhibit migration and invasion	[43]
miR-34	↓	*Notch1*	Inhibit proliferation and invasion	[44]
miR-30a-5p	↓	*Notch1*	Inhibit metastasis	[45]
miR-383-5p	↓	*TRIM27*	Inhibit proliferation and chemoresistance	[51]

↑: 表达上调; ↓: 表达下调; –: 未提及。

↑: upregulated; ↓: downregulated; –: not mentioned.

巢癌细胞的特定基因发挥特异性结合作用目前尚未知, miRNAs如何准确定位靶组织以及靶向治疗的安全性和可靠性仍尚待解决。今后需全面了解卵巢癌患者外泌体miRNAs时空表达谱及生物学意义, 阐明miRNAs在体内外卵巢癌细胞中的具体效用, 尤其是需着力于体内实验的开展。有望借助外源性miRNAs模拟物修复癌细胞中表达下调的抑癌miRNAs的作用, 抑制特定miRNAs的生物合成或效用减弱miRNAs的致癌作用, 达到抑制卵巢癌的演进、提高生存率的效果并改善预后。

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