microRNA调控肿瘤形成相关的因素及信号通路

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摘要 miRNA(microRNA)作为单链非编码RNA, 通过结合靶mRNA的非翻译区而抑制蛋白质编码基因的表达。已有研究表明, miRNA可通过ceRNA、外泌体、环境等因素调控肿瘤的形成。绝大多数miRNA对肿瘤细胞的增殖、凋亡与自噬、细胞周期、细胞的迁移和侵袭以及能量代谢具有调节作用, 故miRNA可作为一种新颖的生物标志物, 并已成为肿瘤治疗中极具吸引力的靶点。同时, 该文回顾了miRNA调控肿瘤形成相关的信号通路, 并深入讨论了JAK/STAT3、Wnt/β-catenin、PI3K/AKT三种常见的信号通路, 旨在为了解肿瘤发生发展的机制提供良好的基础, 为发现新的肿瘤治疗途径和肿瘤治疗靶点奠定基础。

关键词 miRNA; 肿瘤形成; 信号通路

Factors and Signaling Pathways Related to microRNA Regulation of Tumor Formation

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Abstract miRNA (microRNA) acts as a single-stranded non-coding RNA that inhibits the expression of protein coding genes through binding to the untranslated regions of target mRNA. Previous research has established that miRNA can regulate tumor formation through some factors such as ceRNA, exosomes and environment. The majority of miRNA exhibites regulatory effects on essential processes of tumor cells, including proliferation, apoptosis and autophagy, cell cycle, cell migration and invasion, energy metabolism and so on. Thus, miRNAs has emerged as a promising biomarker for targeted-tumor therapy. This article undertakes an in-depth review of the signaling pathways linked with miRNA regulationg of tumor formation, with a particular focus on the interplay among JAK/STAT3, Wnt/β-catenin and PI3K/AKT pathways. By providing a sound basis for understanding the mechanisms involved in tumor genesis and development, this article aims to lay the groundwork for discovering new tumor treatment pathways and cancer therapy targets.

Keywords miRNA; tumor formation; signaling pathways

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微小RNA(microRNA, miRNA)作为一种内源性且相对保守的长度仅为21~25个核苷酸的单链非编码RNA, 在胚胎发生、细胞分化、血管生成、神经发育以及肿瘤发生等多种细胞生理事件中发挥重要作用[1-2]。研究发现, 体细胞突变以及肿瘤细胞表观基因组的改变会解除细胞内信号通路的调控, 最终导致肿瘤细胞的异常生长、生存和侵袭。miRNA可通过表观遗传基因调节多种生物学过程(包括调控细胞增殖、迁移、侵袭、糖酵解、细胞凋亡、肿瘤干细胞样表型、化疗耐药和上皮–间充质转化等)从而控制肿瘤的发生和发展[3]。miRNA已被证明可以抑制重要的癌症相关基因的表达, 并有望在癌症的诊断和治疗中发挥作用[4], 已有研究表明miRNA功能丧失可影响癌症的进展, 因此, miRNA替代疗法已成为治疗恶性肿瘤的有希望的治疗策略[5]。为了更加清晰地阐明miRNA调控肿瘤形成相关的信号通路, 经过查阅相关文献, 本文对miRNA调控肿瘤发生的研究现状和涉及的主要信号通路进行阐述, 为发现新的肿瘤治疗途径以及癌症治疗靶点提供理论依据。

1 miRNA参与调控肿瘤形成

1.1 竞争内源性RNA调控

miRNA可与编码蛋白质的mRNA的3′-非翻译区(3′-UTR)结合, 在转录后抑制蛋白质编码基因表达, 从而对进化产生影响, 因此其在动物、植物、微生物中发挥重要的基因调控作用[6]。miRNA的功能主要由第2到7位的核苷酸组成的种子区决定, miRNA可与mRNA靶标的3′-UTR中的一个或多个互补序列结合[7]。miRNA与其宿主基因共享启动子或独立转录, 可通过调节与宿主生物学功能相关的靶基因, 与宿主基因发挥协同或拮抗作用[8]; miRNA能够同时抑制多个靶基因, 被认为是肿瘤发生过程的关键介质[9], 亦有学者认为健康细胞分泌的miRNA可向附近的癌细胞发送生长抑制信号[10]。随着有关非编码RNA的研究的飞速发展, 科学家们发现作用于肿瘤细胞的非编码RNA并非由单一RNA组成的。

竞争内源性RNA(competing endogenous RNA, ceRNA)是一类转录本, 可以在转录后竞争性地调节miRNA, 并可以通过ceRNA-miRNA-mRNA轴参与广泛的生物过程[11]。ceRNA调控机制以lncRNA-miRNA-mRNA和circRNA-miRNA-mRNA调控网络为主, 相关研究已经证实了ceRNA通过调控miRNA在肿瘤发生发展中发挥作用[12]。在表1中, 作者通过查阅文献总结分析了近三年(2021年~2023年)在人类肿瘤疾病的研究中受ceRNA网络调控的miRNA, 并对miRNA的靶基因的作用途径及影响作用作简要说明。

1.2 外泌体调控

外泌体参与了体内肿瘤转移、血管生成、免疫逃逸、代谢和耐药的过程, miRNA通过外泌体转移到受体细胞, 此过程构成了生理细胞通讯的一种重要形式。受外泌体调控的非编码RNA可以作为内源性调节因子, 直接与癌症的发生和进展相关[22]。例如, 在胃癌患者血清外泌体中发现miR-122-5p表达下调抑制胃癌细胞增殖和转移, 且miR-122-5p在体内抑制肿瘤生长, 该过程与miR-122-5p靶基因*GIT1*有关[23]。表2中整理了近年来作为肿瘤标志物的外泌体miRNA, 并对其靶基因及影响作用作了简要说明。从表2中已收集到的文献中可以推断, 外泌体大多来源于血浆或血清, 外泌体中的miRNA通过靶基因调控肿瘤的形式多样, 并且转运到癌细胞中的miRNA会对肿瘤微环境产生影响。

1.3 环境因素调控

研究表明, 环境因素会增加实体肿瘤血管生成、生长因子和基因的不稳定性, 并促进肿瘤侵袭和转移[36]。缺氧能够降低癌细胞中核糖核酸酶3和Dicer酶的表达量, 抑制AGO2(Argonaute 2)的磷酸化, 干扰Dicer与AGO2的结合, 抑制miRNA从前体到成熟体的加工[37]。研究发现非小细胞肺癌(non-small cell lung cancer, NSCLC)肿瘤组织中*Bcl-w*表达与缺氧有关, miR-519d-3p可通过调节*Bcl-w*和缺氧诱导因子(hypoxia-inducible factor 1-alpha, *HIF-1a*)的表达抑制缺氧诱导的肿瘤发生, 可作为NSCLC的诊断和靶向治疗标志物[38]。缺氧时, 骨髓细胞通过下调干扰因子调节因子4(interferon regulatory factor 4, *IRF4*)来获得抗凋亡能力, 此时miR-210表达水平上调, 这与18S RNA碱基甲基转移酶DIMT1直接下调有关[39]。在未成熟胶质母细胞瘤细胞缺氧时, miR-210表达同样上调[40]。综上所述, 缺氧会抑制miRNA的加工进程, 从而影响细胞的正常生理过程, 引发癌变并阻碍相关癌症的诊断。

2 miRNA对肿瘤细胞的影响

2.1 影响细胞增殖

*Glypicans*作为生长因子的辅助受体影响细胞

表1 受ceRNA网络调控的miRNA(2021年~2023年)

Table 1 miRNA regulated by ceRNA networks (2021-2023)

ceRNA类型 ceRNA types	miRNA类型 miRNA types	疾病 Diseases	靶基因/途径 Target gene/pathway	影响作用 Influence	参考文献 Reference
MALAT1	miR-26a/26b	Breast cancer	*ST8SIA4*	It regulates the tumorigenicity of breast cancer cells	[13]
LncRNA ABHD11-AS1	Many miRNAs	Gastric cancer and thyroid cancer	PI3K/AKT	Clinical biomarker	[14]
circ-0005105	miR-20a-3p	Pancreatic ductal adenocarcinoma	*COL11A1*	Reduce tumorigenicity and metastasis of pancreatic duct adenocyte	[15]
circ-ABCB10	miR-588	Squamous carcinoma of larynx	*CXCR4*	Involved in malignant progression of laryngeal squamous cells	[16]
lncRNA AGAP2-AS1	miR-3064-5p	Cervical cancer	*SIRT1*	Promote cell proliferation	[17]
circ_0001402	miR-625-5p	Squamous cell carcinoma of skin	*KPNA4*	It affects the tumorigenicity of squamous cell carcinoma of skin	[18]
LncRNA HULC	miR-372	Hepatocellular carcinoma	*PRKACB*	Influence tumor growth	[19]
LncRNA RPPH1	miR-122	Hepatocellular carcinoma	Wnt/β-catenin	Provide therapeutic targets for patients with liver cancer	[20]
lncRNAs, mRNAs	hsa-miR-17, hsa-miR-93, hsa-miR-150, hsa-miR-25, hsamiR-125b	Prostatic cancer	*PCA3*, *H19*, *RND3*, *ITGB8*	Diagnostic biomarkers for prostate cancer	[21]

表2 作为潜在肿瘤标志物的外泌体miRNA

Table 2 Exosome miRNA as potential tumor marker

外泌体来源 Exosome source	miRNA类型 miRNA types	疾病 Diseases	靶基因/途径 Target gene/pathway	影响作用 Influence	参考文献 References
Plasma	miR-125a-5p/miR-141-5p	Prostate cancer	PI3K/AKT/mTOR	Indirectly predict the possibility of tumor development	[24]
Plasma	miR-21, miR-181a-5p	Thyroid carcinoma	*OTUD6B-AS1*	Differentiation of different thyroid cancers	[25]
Serum	miR-25, miR-130b, miR-425	Colorectal cancer	PTEN/PI3K/AKT	Promote metastasis of colorectal cancer	[26]
Serum	miR-1247-3p	Liver cancer	*B4GALT3*	Promote lung metastasis of liver cancer	[27]
Serum	miR-139-5p	Bladder cancer	*PRC1*	Inhibition of tumor formation	[28]
Serum	miR-7977	Lung adenocarcinoma	Unknown	Promote A549 cell proliferation and invasion, and inhibit cell apoptosis	[29]
Serum	miR-1468-5p	Cervical cancer	*HMBOX1* & JAK2/STAT3	Promote tumor immune escape	[30]
Wide range of sources	miR-21	Various cancers	Multiple pathways	Promote the development of cancer	[31]
Serum and tissue	miR-21-5p, miR-142-5p, miR-150-5p, miR-320a-3p, miR-4433b-5p	Breast cancer	Multiple pathways	Promote chemotherapy resistance	[32-33]
Plasma and macrophage	miR-223, miR-320d, miR-4479, miR-6763-5p	Epithelial ovarian cancer	PTEN/PI3K/AKT	Promote chemotherapy resistance	[34-35]

增殖, 是miR-509-3p在黑色素瘤中的作用靶点[41]。*Glypican-3*是一种癌基因, 在肝细胞癌(hepato cellular carcinoma, HCC)和肝母细胞瘤等肝脏恶性肿瘤中频繁上调, miR-4510通过直接靶向*Glypican-3*并调控Wnt/β-catenin信号通路的转录活性来实现抑癌作用[42]。miR-125a过表达可抑制人胚肾细胞系293T(human embryonic kidney cell 293T, HEK293T)细胞的增殖, miR-125a通过靶向*Glypican-4*基因影响细胞增殖, 增加了miRNA作为抑制细胞增殖的治疗策略的可行性[43]。*GPC5*(Glypican-5)是硫酸乙酰肝素蛋白多糖的一员, 可抑制肿瘤细胞增殖, 抑制miR-301b会使*GPC5*的表达上调从而抑制胶质瘤细胞的增殖和侵袭[44]。由此可见, miRNA对肿瘤细胞的影响绝大多数是通过调控不同的生长因子实现的, 其通过这种途径只是对肿瘤的增殖起到简单的外部介导作用, 随着研究的不断深入, 科研人员发现miRNA也可通过介导基因的转录来影响肿瘤的发生。

对基因转录水平的研究更清晰地阐明了miRNA如何通过不同的基因影响肿瘤的增殖, 为更好地研究miRNA调控肿瘤形成的机制提供了理论依据。HCC细胞中miR-15a低表达可靶向上调转录因子4, 抑制HCC细胞的增殖、迁移和侵袭, 抑制体内HCC成瘤和转移从而延缓HCC的发生发展[45]。在上皮性卵巢癌细胞(epithelial ovarian cancer cell, EOCC)中发现抑制miR-200a表达可使上皮–间充质转化相关转录因子*ZEB2*表达上调, 影响细胞成瘤, miR-200a可能是EOCC预后评估和治疗干预的潜在标志物[46]。过表达miR-339通过靶向调控*ZNF689*基因的表达, 显著抑制胃癌细胞的增殖、侵袭和迁移[47]。表观遗传抑制因子促进细胞增殖, miR-150通过直接和间接机制调控表观遗传抑制因子*NMT3A*和*DNMT3B*的水平。miR-150作为一种肿瘤抑制因子, 通过提高肿瘤抑制因子的水平和降低细胞周期调节因子的水平, 下调表观遗传抑制因子, 抑制细胞增殖并诱导S期阻滞[48]。

2.2 影响细胞凋亡与自噬

miRNA主要通过影响凋亡通路及自噬通路相关基因和蛋白质之间的相互作用, 从而影响肿瘤的发生发展。肿瘤干细胞(cancer stem cells, CSCs)因其多能性而能够推动肿瘤的发生。ZHOU等[49]从两个胰腺癌异种移植物中分离出两种不同表型的胰腺癌干细胞(pancreatic cancer stem cells, PCSCs), 通过全转录组测序发现479个mRNA和15个miRNA在PCSCs中特异性表达, 其中miR-146b-3p下调最显著。miR-146b-3p在胰腺癌组织和细胞系MIA Paca-2(CSC^{high})中表达下调。恢复miR-146b-3p表达可抑制MIA Paca-2(CSC^{high})的细胞增殖, 此过程通过增加细胞的G_1期、减少S期, 诱导细胞凋亡, 最终抑制细胞成瘤; 进一步研究发现, miR-146b-3p可通过作用于DYRK2和GLI2从而激活Hedgehog通路并直接靶向MAP3K10。miR-7-5p通过下调丝裂铁蛋白从而降低铁水平来抑制抗辐射细胞铁死亡, 并且miR-9和miR-137通过降低细胞内谷胱甘肽水平来促进铁死亡[50]。在胶质母细胞肿瘤亚型的研究中发现miR-93的异常表达与细胞自噬有关, miR-93可影响胶质瘤干细胞(glioma stem cells, GSCs)表型以及耐药性, miR-93通过同时抑制多种自噬调节因子改变GSC自噬活性, 揭示了miR-93在自噬调节中的关键作用[51]。miR-124在胶质瘤组织中的表达降低, 可导致细胞外基质金属蛋白酶诱导物的表达增加, 从而抑制胶质瘤发展[52]。在神经胶质瘤的研究中发现, 调控细胞自噬的mRNA与AKT2相互作用, AKT2抑制miR-193a-3p表达后可抑制神经胶质瘤细胞增殖并促进细胞凋亡[53]。

2.3 影响细胞周期

研究表明, 细胞周期蛋白依赖性激酶1(cyclin-dependent kinase 1, CDK1)参与宫颈癌细胞周期改变, 在宫颈癌细胞中miR-495-3p和miR-143-3p可共同靶向CDK1, 导致其表达下调, 抑制宫颈癌细胞增殖, 促进细胞凋亡, 在体内降低宫颈癌细胞的成瘤性[54]。lncRNA EVADR在结直肠癌(colorectal cancer, CRC)中高度上调, 在EVADR的全长cDNA(EVADR-v1)扩增过程中, 发现了一个新的短变体(EVADR-v2)。生物信息学分析和双荧光素酶检测证实, EVADR可作为海绵与miR-7和miR-29b相互作用, EVADR-v1/-v2过表达后, CRC细胞的细胞周期和迁移情况发生改变, 早期/晚期凋亡率降低, Bax/Bcl2值降低[55]。GHEIDARI等[56]发现miR-429在多形性胶质母细胞瘤(glioblastoma, GBM)中表达下调, 并利用生物信息学工具预测了几个与ERBB信号通路相关的靶基因; 在GBM细胞中用慢病毒载体过表达miR-429, 结果发现miR-429通过ERBB途径直接靶向癌基因*MYC*、*BCL2*和*EGFR*, 并显著降低靶基因的表达水平, 诱导细胞周期停

滞。在肝癌放疗耐药组织和细胞中, miR-302a-3p的表达量显著降低, 细胞周期抑制剂可逆转miR-302a-3p下调对肝癌放疗敏感性的抑制作用; 进一步的研究表明miR-302a-3p/MCL1轴可通过诱导G_0/G_1期停滞来增强肝癌细胞的放射敏感性[57]。HASSAN等[58]发现, 通过使用miR-122模拟物和miR-221抑制剂靶向*SENP1*和*ARF4*基因, 可使细胞周期蛋白D1、转化生长因子-β和β-连环蛋白基因的表达下调, 诱导肿瘤的凋亡和坏死。ZHOU等[59]发现, *CDK1*在肝细胞癌组织和细胞中高表达, 沉默*CDK1*可调节肝癌细胞的细胞周期, 抑制DNA复制和细胞增殖。在肝癌细胞中, miR-195-5p可降低*CDK1*水平, 且抑制G_1期到S期的转变, 诱导DNA损伤反应, 抑制DNA复制和细胞增殖。综上所述, miRNA可以通过调控CDK1、细胞周期蛋白D1、细胞周期通路相关基因、G_0/G_1期停滞以及抑制G_1期到S期的转变来影响肿瘤细胞的细胞周期, 这可为癌症的临床治疗提供理论依据。

2.4 影响细胞迁移和侵袭

癌组织易侵袭和转移通常会导致预后不良, 例如高级别卵巢浆液性癌是一种因癌细胞转移而预后不良的卵巢癌, 迫切需要新的治疗靶点, miRNA通过调节下游靶基因及相关通路, 提高或降低肿瘤细胞的迁移和侵袭能力。LIU等[60]发现, 细胞质聚腺苷酸化元件结合蛋白3(cytoplasmic polyadenylation element binding protein 3, CPEB3)作为miR-301b-3p的靶蛋白与其表达水平呈负相关, 并在高级别卵巢浆液性癌组织和细胞系中下调, miR-301b-3p通过诱导表皮生长因子受体和下游转移相关蛋白p38及细胞外信号调节激酶1/2(extracellular signal-regulated kinase 1/2, ERK1/2)生成, 最终靶向CPEB3/EGFR轴并加速高级别卵巢浆液性癌的迁移和侵袭。无独有偶, 骨转移瘤在影响四肢骨骼的同时容易发生肺转移。骨肉瘤相关体外实验的结果表明, *RAB22A*作为癌基因家族的成员是miRNA-151a-3p的潜在靶基因, 受lncRNA SNHG3正调控, 但受miR-151a-3p负调控, miR-151a-3p敲除可以促进骨肉瘤细胞的侵袭和迁移, *RAB22A*的过度表达也可促进骨肉瘤细胞的侵袭和迁移[61]。随着研究的深入, ZHANG等[62]发现miR-338-3p过表达可通过靶向MAP3K2调控ERK1/2信号通路, 从而抑制人肺腺癌细胞的迁移、侵袭和增殖, 此研究加入miR-338-3p抑制剂后, *MAP3K2*、*p-ERK1/2*、*MMP2*、*MMP3*、*MMP9*、细胞周期蛋白A2和细胞周期蛋白D1的表达水平升高, 导致人肺腺癌细胞的迁移和侵袭增加, 而加入miR-338-3p模拟物的结果与此相反。LIU等[63]发现抑制miR-196-5p的表达可显著抑制胆管癌细胞的增殖和转移, 且*HAND1c*和β-catenin沉默均能逆转miR-196-5p上调带来的细胞异常增殖和迁移, 所以*HAND1*/Wnt/β-catenin信号通路的激活是miR-196-5p发挥作用的重要条件。

2.5 影响细胞能量代谢

一些miRNA对多个代谢基因进行正向和负向调节, 使肿瘤细胞能够在不利条件下存活, 并产生恶性肿瘤的相关特性, 如细胞黏附、迁移和侵袭增加, 三羧酸循环和头合成脂肪酸减弱、无氧糖酵解和自噬增加。一些信号通路因子、低氧诱导因子、磷脂酰肌醇-3激酶、蛋白激酶B、哺乳动物靶标雷帕霉素、磷酸酶以及胰岛素信号通路中的张力蛋白的同系物, 均受miRNA调控[64]。QUIRICO等[65]通过分析miR-455-3p、miR-122、miR-30a-5p、miR-203、miR-181d、miR-7、miR-489-3p、miR-155、miR-422a和miR-146b-5p后发现在癌症中, miRNA可控制糖酵解途径中葡萄糖的代谢。与此同时, SUN等[66]发现通过PI3K/AKT/mTOR/HIF-1α途径下调miR-21的表达, 可抑制顺铂耐药的肺癌细胞株的糖代谢而促进癌细胞死亡。miR-125还可以和天然化合物结合来共同调节与癌症相关的线粒体功能障碍和能量代谢[67], 由此可见, miRNA在癌细胞的代谢重编程中发挥着非常重要的作用, 并且可同时调控转录和转录后水平。

3 miRNA调控肿瘤形成相关的主要信号通路

恶性肿瘤的发生发展始于一系列遗传和表观遗传事件, 这导致多种信号通路发生改变, 靶向这些信号通路也被认为在癌症治疗中具有临床价值[68]。作者通过查阅文献在表3中列举出了miRNA调控肿瘤形成相关的信号通路。如表3所述, 交叉分析可知miRNA调控肿瘤形成相关的主要通路为Wnt/β-catenin信号通路、JAK(Janus kinase)/STAT3(signal transducer and activator of transcription 3)信号通路、PI3K/AKT/mTOR信号通路。miRNA占基因的1%~3%, 但调节人类30%以上基因的表达, 可见miRNA通过调节基因的表达, 参与调控肿瘤形成相关的信号通路, 在有关肿瘤的研究

表3 miRNA影响肿瘤形成相关的信号通路

Table 3 miRNA affected signaling pathways related to tumor formation

miRNA类型 miRNA types	信号通路 Signaling pathway	疾病 Disease	影响作用 Influence	参考文献 Reference
Many miRNAs	PI3K/AKT/mTOR, Wnt/β-catenin, JAK/STAT, MAPK	Breast cancer	Provide treatment options	[69]
Many miRNAs	Notch, TGF-β, Wnt, STAT3, AKT, EGFR	Glioma	Study the pathogenesis and regulation of drug resistance	[70]
Many miRNAs	Wnt/β-catenin, PTEN/AKT/mTOR, TGF-β, KRAS, VEGFR, EGFR, p53	Colorectal cancer	Control of cellular processes in colorectal cancer	[71]
Twenty-two kinds miRNAs	PI3K/AKT, Wnt, AMPK, MAPK	Fourteen types of cancer	Play a role in cancer inhibition	[72]
miR-411	MAPK, PI3K/AKT/mTOR, p53, Ras, NF-κB, Wnt/β-catenin	Multiple cancers	Regulate cell proliferation, invasion, migration, apoptosis and colony, and the formation of cancer cells	[73]
miR-1275	PI3K/AKT, ERK/JNK, MAPK, Wnt	Liver cancer, breast cancer, lung cancer, gastrointestinal cancer, urogenital tract cancer	It helps to study the development of many types of cancer	[74]

中意义重大。

3.1 JAK/STAT3信号通路

miRNA通过直接或间接影响细胞因子信号转导抑制因子家族成员JAK、STAT3及调控其他细胞增殖、凋亡、迁移、侵袭和EMT相关基因的表达从而参与肿瘤形成[75]。抗癌药物可通过miRNA来抑制JAK/STAT3信号通路, 目前已经在骨肉瘤细胞[76]和肺癌细胞[77]中得到证明。JAK/STAT3信号参与细胞增殖、细胞周期等多种生物学过程[78-79], 因此, miRNA可通过细胞内外的不同途径激活JAK/STAT3信号通路来影响细胞的增殖。*STAT3*在激活前存在于细胞质中, 在细胞因子和致癌因子的作用下, *STAT3*磷酸活化并在细胞核中过表达, 此过程促进细胞增殖和恶性转化, 阻碍细胞凋亡, 具有致癌作用[80]。

miR-301a过表达会增强胰腺癌细胞的侵袭、血管生成和迁移能力, 抑制靶基因细胞因子信号抑制因子5(suppressor of cytokine signaling 5, *SOCS5*)的表达, 导致JAK/STAT3激活[81]。卵巢肿瘤细胞外小泡富含miR-141-3p, 转染miR-141-3p后的小细胞外小泡使*SOCS5*的表达水平显著降低, 导致内皮细胞JAK/STAT3通路激活, miR-141-3p能够促进内皮细胞迁移和血管生成, 进而调控卵巢肿瘤发病机制[82]。GSCs是胶质瘤发生和发展的关键, miR-30在原发性胶质瘤细胞的GSCs中过度表达, 而下调miR-30则能抑制JAK/STAT3通路, 降低GSCs的致瘤性。miR-30通过靶向mRNA的3′-UTR来降低*SOCS3*的表达量[83], 应用同样的原理, miR-30e-5p通过靶向泛素特异性肽酶22(ubiquitin specific peptidase 22, USP22)介导的JAK/STAT3信号, 抑制NSCLC肿瘤的发生[84]。另外, NSCLC患者的miR-410表达水平较高, *SOCS3*表达水平较低, miR-410通过靶向抑制*SOCS3*的表达, 促进JAK/STAT3信号通路的激活和细胞增殖, 为未来肺癌的治疗提供了线索[85]。miR-500a-3p水平在肝癌组织和细胞中显著升高, 上调miR-500a-3p可增强体外肿瘤干细胞的球体形成能力, 并增加其数量比例和肿瘤相关因子的表达水平, miR-500a-3p通过靶向JAK/STAT3信号通路的多种负性调节因子, 包括*SOCS2*、*SOCS4*和*PTPN11*, 促进肿瘤细胞增殖; STAT3信号通路激活, 使得miR-500a-3p下调并沉默细胞中的*SOCS2*、*SOCS4*和*PTPN11*的表达, 这个过程可逆转miR-500a-3p过表达引起的STAT3信号活性抑制和肿瘤细胞中癌症干细胞表型增加的现象[86]。

另有研究发现, JAK1和JAK2的口服抑制剂通过抑制白细胞介素-6(interleukin 6, IL-6)受体依赖性JAK/STAT信号转导在胶质母细胞瘤血管生成中发挥重要作用, 抑制剂治疗诱导的miR-17a-3p和miR-20a过表达可能在下调JAK2、STAT3和PI3K蛋白中起主要作用[87]。在宫颈腺癌中, miR-9启动子高甲基化后, 下调并抑制HeLa细胞的IL-6表达从而发挥抑癌作用, HeLa细胞去甲基化处理可增加成熟miR-9的表达量, 消除其对IL-6的抑制, 使IL-6/JAK/STAT3通路激活, 最终产生抑癌作用[88]。miR-515-5p的过表达

抑制了肝癌细胞在体外和体内的迁移和侵袭，miR-515-5p可直接结合到IL-6的3′-UTR，抑制JAK/STAT3信号通路的激活，IL-6的过表达则使JAK/STAT3信号通路激活[89]。图1总结了miRNA参与JAK/STAT3信号通路调控的机制，并通过调节该通路影响肿瘤细胞的增殖情况。

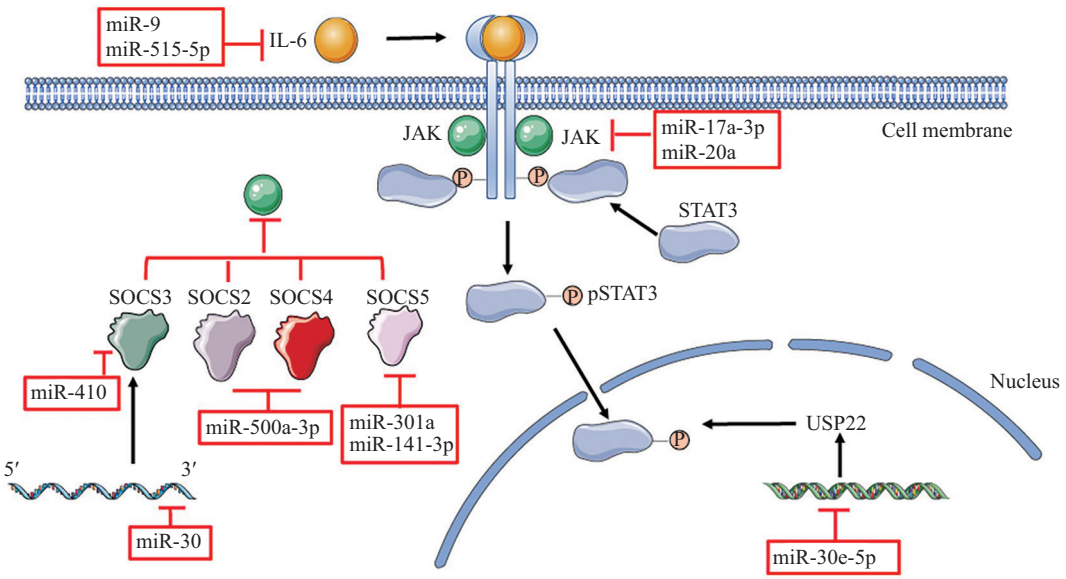
3.2 Wnt/β-catenin信号通路

Wnt/β-catenin参与人类的发育、生长和细胞内稳态维持[90]，Wnt通过β-catenin激活靶基因的表达[91]。β-catenin是一种可在细胞间连接处与细胞黏附分子E-钙黏蛋白相互作用的蛋白质，已被证明是肿瘤发生中Wnt信号通路的最重要的介导物之一[92]。CSCs几乎在所有种类的癌症中都能被检测到，具有自我更新和分化能力，可增强肿瘤细胞的成瘤性。miRNA通过控制干细胞自我更新的级联信号，即Wnt、Notch和Hedgehog通路，影响CSCs的功能[93]。

在Wnt/β-catenin信号通路中，miRNA主要通过调控信号通路中的关键因子，如以相关蛋白及基因为靶点，影响肿瘤细胞的成瘤性。在研究直肠癌干细胞(colorectal cancer stem cells, CRCSCs)自我更新的潜在机制过程中发现，miR-8063的表达明显下调，异质核糖核蛋白A/B(heterogeneous nuclear ribonucleoprotein A/B, hnRNP A/B)的表达明显上调，当hnRNP A/B过表达后，直肠癌干细胞集落形成能力和成瘤性增强，Wnt/β-catenin信号通路中关键蛋白Wnt3a、Wnt5a和β-catenin的表达上调，而miR-8063的表达缺失会削弱其对hnRNP A/B的抑制作用，miR-8063在CRCSCs中过表达后，hnRNP A/B、Wnt3a、Wnt5a和β-catenin的表达下调，CSCs的自我更新能力减弱，miR-8063可激活Wnt/β-catenin信号通路，促进CRCSCs的自我更新[94]。miR-664已被证明在皮肤鳞状细胞癌(squamous cell carcinoma, SCC)中含量升高，可增强SCC细胞的迁移和侵袭能力，*ARMC8*(armadillo repeat containing 8)基因作为miR-664的直接作用靶点抑制Wnt/β-catenin信号通路和cSCC中的上皮–间充质转化[95]。

3.3 PI3K/AKT信号通路

PI3K/AKT通路是一条重要的细胞内信号转导



在细胞质内，miR-500a-3p负向调控SOCS3和SOCS4，miR-30和miR-410抑制SOCS3，miR-301a和miR-141-3p抑制SOCS5，从而介导JAK/STAT3激活，促进肿瘤发生发展；在细胞核中，miR-30c-5p通过靶向调控USP22，介导JAK/STAT3信号。与此相反，在细胞外，miR-9和miR-515-5p通过抑制IL-6，抑制JAK/STAT3途径激活而发挥抑癌作用。在细胞内胞质中，miR-17a-3p和miR-20a的上调可抑制JAK、STAT3和PI3K蛋白表达，从而抑制JAK/STAT3途径激活。

In the cytoplasm, miR-500a-3p exerts a negative influence on SOCS3 and SOCS4, miR-30 and miR-410 mediate JAK/STAT3 activation by inhibiting SOCS3, as well as miR-301a and miR-141-3p mediate JAK/STAT3 activation by inhibiting SOCS5. MiR-30c-5p mediates the JAK/STAT3 signaling by targeting USP22 in the nucleus. Conversely, extracellular miR-9 and miR-515-5p have anti-cancer properties by inhibiting IL-6 and curbing the activation of the JAK/STAT3 pathway. Intracellular cytoplasm upregulation of miR-17a-3p and miR-20a inhibits JAK, STAT3, and PI3K proteins, thereby preventing JAK/STAT3 pathway activation.

图1 miRNA影响细胞增殖的机制

Fig.1 The mechanism of miRNA impacting cell proliferation

通路, 调节细胞增殖、凋亡、代谢和血管生成等生物学过程, 有研究表明, 该信号通路的失控与不同类型人类恶性肿瘤的发生和发展有关[96]。HASHEMI等[97]研究发现, miRNA、lncRNA和circRNA等上游调控因子调节PI3K/AKT信号转导, 刺激PI3K/AKT信号通路可促进前列腺癌细胞存活, 减少细胞凋亡, PI3K/AKT信号通路可刺激EMT, 促进前列腺癌细胞的转移, 沉默PI3K/AKT信号会影响前列腺癌细胞的生长和转移。CHI等[98]研究miR-194-5p在胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)进展中起关键作用的分子机制, 发现miR-194-5p通过调控PVRL3/miR-194-5p/SOCS2轴激活PI3K/AKT信号通路, 调控PDAC的增殖和转移。在PI3K/AKT信号通路中, miRNA主要通过信号转导参与基因的上游调控, 进而影响肿瘤增殖通路, 这与以上两种通路作用方式存在明显的区别, 虽有较少文献讲解miRNA参与此条通路的相关知识, 但miRNA在PI3K/AKT信号通路中发挥的作用具有深远的研究意义。

4 miRNA在临床医学中的应用

由于miRNA的稳定性, 肿瘤进展过程中异常表达的基因和miRNA可作为肿瘤诊断和预后的生物标志物, 在肿瘤诊断中可通过检测miRNA的甲基化水平来监控肿瘤变化。研究发现, 在非小细胞肺癌及其组织学亚型中一些高甲基化miRNA存在甲基化水平的变化, 在胰腺癌和鳞状细胞肺癌中, miR-124-1、miR-124-3、miR125B-1、miR129-2、miR137、miR1258和miR339的甲基化水平明显高于邻近组织学特征未变的肺组织样本, 在鳞状细胞肺癌中, miR-124-2的甲基化水平也显著较高[99]。

miRNA的比较重要的另外一种功能是在临床中可作为某一种或几种癌症的诊断标志物。HUANG等[100]通过对全局miRNA表达进行分析, 共鉴定出9个与胃肠癌预后有关的miRNA, 其中, miR-194是唯一一个与胃癌、结直肠癌和肝癌的总生存期、疾病特异性生存期和无进展间期均显著相关的miRNA, 可见miR-194是预测胃肠癌的最佳预后生物标志物。RUI等[101]通过分析血清外切体中miRNA的比例和分布, 发现miRNA是血清外切体中最重要的组成成分, 3个来自血清外切体的miRNA(miR-122-5p、let-7d-5p和miR-4255p)对诊断肝癌具有重要价值, 可成为肝癌诊断的生物标志物。关于血清来源的miRNA let-7及其所调控的通路已成为耐药癌症的新治疗靶点, 已经有较多文献报道。let-7家族调节包括*KRAS*基因在内的多种致癌基因, 其还可作为头颈癌的预测性生物标志物, 并已被证明在致癌作用中发挥关键作用[102]。血清let-7-A1、miR-143和miR-145表达下调可能对埃及慢性丙型肝炎患者中肝细胞癌的发生发展有重要影响, 可作为肝细胞癌诊断的生物标志物[103]。let-7作为最早发现的miRNA, 研究发现其和miR-21协同调控对肺癌的作用大于单一miRNA的作用。miR-21和let-7是肺癌中重要的差异表达miRNA, 对于多种基因参与的肺癌来说, 这两个miRNA的协同调控将为未来肺癌的治疗提供新的靶点和方向[104]。WANG等[105]研究表明血浆外切体miR-320d、miR-4479和miR-6763-5p可作为卵巢上皮性癌的诊断标志物, WROBLEWSKA等[106]发现血清外切体源的hsa-miR-191-5p可作为一种新的葡萄膜黑色素瘤早期检测的生物标志物。ABO-ELELA等[107]发现, miR-133a、miR-574-3p和miR-27a可作为早期诊断结直肠癌的较好的无创性标志物, 具有较高的敏感性和特异性, 有助于早期发现结直肠癌, 且对于这种广泛传播的恶性肿瘤可通过手术进行干预, 以改善结直肠癌患者的预后和提高患者的生存率。

除了在肿瘤诊断中可使用miRNA外, miRNA还显示出作为治疗靶点的潜力。在恶性胶质瘤治疗中, 研究发现使用miRNA的3个主要考虑因素[108]: (1) 递送方法, 尽管miRNA体积小, 在血清中稳定, 实现全身给药效率仍不佳。通过局部递送和基于纳米颗粒的递送, 可以让miRNA跨越血脑屏障, 到达肿瘤细胞, 这种方法具有更高的稳定性和效率。(2) 靶点的特异性, 肿瘤特异性表面受体作为识别靶点, 可确保miRNA传递到正确位置的特异性。(3) 目标基因的特异性, miRNA靶向多个基因的能力是其治疗应用的限制因素, 以miRNA为基础的药物的主要障碍是以感兴趣的基因为靶点, 以避免非特定靶点。所以需要更多的研究来提高基于miRNA的药物的特异性, 以进行靶向治疗。

5 展望

在肿瘤发展早期检测miRNA可增加治疗成功的机会。circRNA-miRNA分子相互作用是癌症早期检测和预后中重要的研究领域, 其不仅对提高患者

生存率至关重要, 而且对癌症预防也至关重要。根据miRNA的表达与肿瘤发生发展及治疗之间的关联, 可将miRNA确定为疾病诊断和预后的潜在生物标志物。miRNA已经被发现是一种新颖的、非常有前途的生物标志物, 也是新的治疗方法的有吸引力的工具和靶点。本文通过探讨miRNA参与调控肿瘤形成的方式以及对肿瘤细胞的影响, 阐明miRNA影响肿瘤发生的机制, 并对三条常见的JAK/STAT3信号通路、Wnt/β-catenin信号通路和PI3K/AKT信号通路进行总结分析, 为miRNA后续研究提供帮助。

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