MiRNA介导circRNA调控肿瘤的发展

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摘要 CircRNA(circular RNA)是一种具有特殊环形结构的ncRNA(non-coding RNA), 并具有多种生物学功能。随着研究的深入, 发现circRNA能够通过海绵吸附抑制miRNA(micro RNA)的表达, 进而调控各系统肿瘤的发展。此外, 一种circRNA也可参与调控一种或多种miRNA的表达, 这一发现有助于寻求肿瘤诊断的生物标记物及治疗靶点。因此该文通过综述国内外最新的有关circRNA通过miRNA调控肿瘤的研究, 为进一步探究circRNA调节各种癌症疾病的发生和发展的具体机制奠定基础, 也为相关疾病的治疗和预防提供更加可靠的理论依据。

关键词 circRNA; miRNA; 肿瘤

MiRNA-Mediated CircRNA Regulates the Development of Tumors

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Abstract CircRNA (circular RNA) is a kind of ncRNA (non-coding RNA) with a special circular structure and has a variety of biological functions. With the deepening of research, circRNA was found to inhibit the expression of miRNA (micro RNA) through sponge adsorption, thus regulating the development of tumors in various systems. Furthermore, one circRNA can also involved in the regulation of the expression of one or more miRNAs. This finding is helpful to seek biomarkers for tumor diagnosis and therapeutic targets. Therefore, this paper reviews the latest domestic and foreign studies on circRNA regulates tumors through miRNA, which lays a foundation for further study on exploring the mechanism of circRNA regulating the occurrence and development of various cancer diseases, as well as provides a reliable theoretical basis for the treatment and prevention of related diseases.

Keywords circRNA; miRNA; tumors

随着人类对基因的不断探索, 具有蛋白编码功能的基因序列在人类基因组中不足2%[1], 因此对于非编码RNA(non-coding RNA, ncRNA)的研究逐渐增多。近些年来研究表明, ncRNA在调控转录过程、参与mRNA的翻译过程、加工修饰RNA、调节细胞增殖分化以及调控肿瘤的发生发展中都起到重要作用[2]。NcRNA根据其功能可分为具有调控功能的调节性ncRNA(lncRNA、siRNA、miRNA等)以及组成性的管家非编码RNA(tRNA、rRNA、snRNA等), 作为调节性ncRNA的一种, 微小RNA(micro RNA, miRNA)在基因调控中占据了一席之地。MiRNA是一类长度为20~24个核苷酸的ncRNA分子, 因为其复杂的调控模式, 人类大约有三分之一的基因通过miRNA进行调控[3], 除了可参与调控基因表达外, 还

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可以调控蛋白质翻译过程、参与细胞分化、在植物中调控生长发育等[4-5], 其在生命进程中发挥的作用不容小觑。2002年, CALIN等[6]发现, miRNA下调与慢性淋巴细胞白血病具有相关性, 这为miRNA也可参与调控肿瘤的发生提供了证据。

CircRNA是共价闭合圆形结构, 由基因剪切后形成的特殊ncRNA分子构成, 因多数来源为外显子, 所以也被称为外显子circRNA[8]。CircRNA表达稳定、不易降解、不受RNA外切酶影响, 但可通过small RNAs的介导降解[9]。最初circRNA在病原体中被发现, 由于测序条件有限, SANGER等[10]将其视为一种类病毒, 1979年HSU等[11]将在HeLa细胞胞质中观察到的circRNA分子当作“DNA错误剪切的垃圾”。直至1993年, CAPEL等[12]发现, 小鼠*Sry*基因的circRNA可能会在小鼠睾丸中发挥特定功能, circRNA才逐渐进入研究者的视野中。2012年, SALZMAN等[13]首次提出, circRNA可通过反向剪切mRNA得到, 并且参与人类细胞的基因表达。随着近些年研究的深入和科技的发展, circRNA具有的生物学功能逐渐被发现, 海绵吸附miRNA、调控多肽的翻译进程、影响蛋白质结合, 进而调控细胞增殖等[14]。

在SALMENA等[15]提出将ncRNA使用miRNA的响应元件(miRNA response elements, MREs)来进行转录调控的方式称作竞争性内源RNA(competing endogenous RNA, ceRNA)之后, circRNA通过MREs实现“miRNA的海绵作用”已在越来越丰富的研究中得到充分证实[16], 尤其是在PIWECKA等[17]首次以完整敲除circRNA序列小鼠模型印证了circCdr1as的敲除能够使与其互作的miR-7下调, miR-671上调, 且其他差异表达的部分miRNA与癌症相关之后, 更加肯定了circRNA与miRNA可直接互作, 并可共同参与肿瘤发展。但是circRNA通过miRNA调控肿瘤发展的具体机制仍存在较多的困惑, 因此本文通过综述国内外最新的有关circRNA通过miRNA调控肿瘤的研究, 为进一步探究circRNA调节各种癌症疾病的发生和发展的具体机制奠定基础。

1 MiRNA介导circRNA调控各系统肿瘤

根据人们对circRNA逐渐丰富的研究可知, circRNA不仅可与单个miRNA互作, 一种circRNA也参与调控一个或多个miRNA的表达, 如circZFR既可以靶向miR-130a、miR-107抑制胃癌细胞的增殖[18], 也可以靶向miR-1261促进甲状腺癌细胞的增殖[19]。这证明, circRNA是研究肿瘤发展分子机制的关键靶点, miRNA介导circRNA调控各系统肿瘤的发展(表1), 为肿瘤治疗与预后等提供一系列参考依据。

1.1 呼吸系统

在人体呼吸系统中, 上呼吸道肿瘤常发于咽、喉。下咽癌(hypopharyngeal carcinoma, HCa)是一种原发性恶性肿瘤, 占上呼吸道恶性肿瘤的3%~5%, 早期具有诊断困难、患者预后差、生存率低等特点[56], 确定其生物标志物迫在眉睫。FENG等[20]通过对HCa患者肿瘤组织的circRNA序列分析后发现, hsa_circ_0008287和hsa_circ_0005027在HCa中显著下调, 并且能共同结合miR-548c-3p, 从而影响表皮生长因子受体(epidermal growth factor receptor, ErbB)、Hippo通路的表达, 显示出它们在HCa中可能存在的重要作用。患有喉癌(laryngeal cancer)后, 发声、呼吸、吞咽困难等症状会给患者带来极大的生活压力[57]。通过基因芯片分析喉鳞状细胞癌(laryngeal squamous cell carcinoma, LSCC)患者喉黏膜组织, 发现hsa_circ_0044520和hsa_circ_0044529在LSCC组织中显著上调, 可能通过共同靶向has_miR_4726_5p和has_miR_4640_5p, 抑制这些miRNA的表达, 导致其调控的靶基因上调, 从而影响LSCC的发生[21]。

肺癌(lung cancer)包括非小细胞肺癌(non-small cell lung cancer, NSCLC)、肺腺癌(lung adenocarcinoma, LUAD)等多种类型, 患者生存率低, 预后差[58]。CHEN等[22]发现, 在肺癌组织中将hsa_circ_100395过表达, 海绵吸附miR-1228, 能够消除miR-1228对TCF21(transcription factor 21)的抑制作用, 从而抑制肺癌细胞的侵袭进程。研究NSCLC中circRNA的表达发现, circZFR的高表达能够通过海绵化miR-101-3p, 促进CUL4B(cullin-4B)表达, 发挥致癌作用[23]; CircFGFR1的表达上调, 作为miR-381-3p的海绵, 上调miR-381-3p及其靶基因*CXCR4*(C-X-C motif chemokine receptor 4)的表达, 进而促进癌细胞的增殖及抗程序性细胞死亡-1(anti-programmed cell death-1, PD-1)的治疗, 增加NSCLC细胞抗药性[24]; CircSMARCA5的表达下调, 通过miR-19b-3p调控HOXA9(homeobox A9)发挥抑癌作用[25]。LUAD中, 强制上调circMTO1能够通过抑制miR-17, 促进

表1 MiRNA介导circRNA调控各系统肿瘤

Table 1 MiRNA-mediated circRNA regulates various systemic tumors

系统 System	肿瘤 Tumor	CircRNA	表达变化 Expression changes	MiRNA	参考文献 References
Respiratory system	HCa	Hsa_circ_0008287	Down	MiR-548c-3p	[20]
		Hsa_circ_0005027	Down		
	LSCC	Hsa_circ_0044520/ Hsa_circ_0044529	Up	Has_miR_4726_5p/ Has_miR_4640_5p	[21]
	Lung cancer	Hsa_circ_100395	Down	MiR-1228	[22]
		CircZFR	Down	MiR-101-3p	[23]
		CircFGFR1	Up	MiR-381-3p	[24]
		CircSMARCA5	Down	MiR-19b-3p	[25]
		CircMTO1	Down	MiR-17	[26]
Digestive system	OSCC	CircDOCK1	Down	MiR-196a-5p	[27]
	ESCC	CircFOXO3	Down	MiR-23a	[28]
	GC	CricRHOBTB3	Down	MiR-654-3p	[29]
		CircPSMC3	Down	MiR-296-5p	[30]
	CRC	Circ0026344	Down	MiR-183	[31]
		Hsa_circ_102958	Up	MiR-585	[32]
	HCC	CircMTO1	Down	MiR-9	[33]
	PDAC	Hsa_circ_0000977	Up	Hsa-miR-874-3p	[34]
Motor system	Bone cancer	Circ9119	Down	MiR-26a	[35]
	OS	CircNASP	Up	MiR-1253	[36]
		CircCDR1as	Up	MiR-7	[37]
Nervous system	Glioma	Hsa_circ_0014359	Up	MiR-153	[38]
		CircNFIX	Up	MiR-34a-5p	[39]
	GBM	CircNT5E	Up	MiR-422a	[40]
Circulatory system	AML	CircPAN3	Up	MiR-153-5p/miR-183-5p	[41]
		Circ0004136	Up	MiR-142	[42]
Endocrine system	PTC	Hsa_circ_0058124	Up	MiR-218-5p	[43]
		CircNEK6	Up	MiR-370-3p	[44]
		CircFOXM1	Up	MiR-1179	[45]
Genital system	Breast cancer	CircTFF1	Up	MiR-326	[46]
		CircKIF4A	Up	MiR-375	[47]
	Ovarian cancer	CircCELSR1	Up	MiR-1252	[48]
	CC	Circ000284	Up	MiR-506	[49]
		Circ8924	Up	MiR-518d-5p/miR-519-5p	[50]
		Hsa_circ_0007534	Up	MiR-498	[51]
Urinary system	RCC	CircRAPGEF5	Down	MiR-27a-3p	[52]
	Bladder cancer	CircPTPRA	Down	MiR-636	[53]
		CircCEP128	Up	MiR-145-5p	[54]
		Hsa_circ_0001165	Up	Hsa-miR-187-3p	[55]
		Hsa_circ_0001085	Down	Hsa-miR-196b-5p/ Hsa-miR-451a	[55]

HCa: 下咽癌; LSCC: 喉鳞状细胞癌; OSCC: 口腔鳞状细胞癌; ESCC: 食管鳞状细胞癌; GC: 胃癌; CRC: 结直肠癌; HCC: 肝细胞癌; PDAC: 胰腺导管腺癌; OS: 骨肉瘤; GBM: 多形性胶质母细胞瘤; AML: 急性髓系白血病; PTC: 甲状腺乳头状癌; CC: 宫颈癌; RCC: 肾细胞癌; PCa: 前列腺癌。

HCa: hypopharyngeal carcinoma; LSCC: laryngeal squamous cell carcinoma; OSCC: oral squamous cell carcinoma; ESCC: esophageal squamous cell carcinoma; GC: gastric carcinoma; CRC: colorectal cancer; HCC: hepatocellular carcinoma; PDAC: pancreatic ductal adenocarcinoma; OS: osteosarcoma; GBM: glioblastoma multiform; AML: acute myelocytic leukemia; PTC: papillary thyroid carcinoma; CC: cervical cancer; RCC: renal cell carcinoma; PCa: prostate cancer.

QKI-5(RNA-binding protein QKI splice variants 5)的表达增加, 使Notch信号通路失活, 抑制LUAD细胞的生长与增殖[26]。肺癌作为多发肿瘤之一, 对其各个类型调控机制的研究与其他肿瘤相比较为丰富, 这大大推进了肺癌治疗的进程。

1.2 消化系统

消化器官的稳定健康是人体进行正常生理活动的重要环节。据统计约90%的口腔癌发病组织起源为鳞状细胞[59]。WANG等[27]在口腔鳞状细胞癌(oral squamous cell carcinoma, OSCC)组织中发现, circDOCK1的沉默导致miR-196a-5p水平上调, BIRC3(baculovirus IAP repeat sequence 3)形成减少, circDOCK1作为潜在靶点参与了OSCC的细胞凋亡过程。食管鳞状细胞癌(esophageal squamous cell carcinoma, ESCC)在食管癌病例中占比高并且无明显早期症状, 复发率高[60]。研究表明, 过表达circFOXO3能够通过海绵化miR-23a, 上调PTEN(phosphatase and tensin homolog)水平, 从而抑制ESCC细胞的生长与迁移[28]。胃癌(gastric carcinoma, GC)是起源于胃黏膜上皮的恶性肿瘤, 在GC组织中cricRHOBTB3[29]、circPSMC3[30]等表达均下调, 过表达上述circRNA, 抑制其靶向miRNA(miR-654-3p、miR-296-5p)的表达, 进而影响p21、PTEN通路, 减缓GC细胞的生长、增殖等过程, 抑制肿瘤发展。大肠癌即结肠直肠癌(colorectal cancer, CRC), 有研究者发现, 在CRC中将circ0026344过表达, 可对miR-183进行负调控, 从而逆转其对Wnt/β-catenin通路的抑制作用, 减缓CRC细胞的转移进程[31]; hsa_circ_102958不仅参与GC的调控, 而且在CRC组织中表达显著升高, 从而抑制miR-585的表达, 加速癌细胞增殖与迁移[32], 再次印证了同一circRNA在不同肿瘤调控中扮演的角色不同。

对于消化腺, 肝细胞癌(hepatocellular carcinoma, HCC)因为复发率和转移率高导致其预后差, 死亡率高[61]。HAN等[33]发现, circMTO1低表达的HCC患者生存期较短, miR-9水平的升高可造成下游p21表达下调, 可尝试通过提高circMTO1水平, 为提升患者生存期提供条件。胰腺癌(pancreatic cancer)因易与胃肠道疾病混淆, 接诊患者多为中晚期, 五年生存率不到4%[62]。胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)在胰腺癌中较为常见, hsa_circ_0000977在PDAC组织中的表达异常上调, 可通过海绵化hsa-miR-874-3p使PLK1(polo-like kinase 1)过表达, 从而加速PDAC细胞的生长侵袭[34], 此调控轴从理论上为胰腺癌的治疗提供了应对策略。

1.3 运动系统

骨癌(bone cancer)是发生于骨骼或骨骼附属组织的恶性骨肿瘤, 骨的癌变会直接导致人体运动能力的受损甚至丧失, 而对继发性骨癌形成的骨痛还未形成有效的治疗方法。虽然有研究人员从小鼠骨癌疼痛模型中的circRNA分析得出过表达circ9119可通过靶向吸附miR-26a, 升高TLR3(Toll-like receptor 3)水平, 改善恶性疼痛[35], 但在人骨癌组织中是否同样适用还没有定论。

骨肉瘤(osteosarcoma, OS)是原发于长骨的恶性骨肿瘤, 有效治疗后的高转移率导致了11%~30%的极低生存率[63]。CircRNA被发现可从多个方面参与OS的发生发展, 如在OS组织中的cricNASP水平显著升高, 并且作为miR-1253靶向FOXF1(forkhead box protein F1)的海绵, 可通过CircNASP的敲低, 抑制FOXF1升高对OS细胞的生长促进作用, 从而降低OS细胞生长侵袭的速度[36]; 同样地, 将OS组织中高表达的circCDR1as敲低后, 可恢复miR-7的抑癌作用, 通过影响上皮–间质转化(epithelial-mesenchymal transition, EMT)进程、阻断细胞周期等方式, 促进OS细胞凋亡[37]。上述研究结果充分说明了circRNA在调控OS发展中的潜在意义。

1.4 神经系统

脑在人体机能调控中不断进行着复杂精密的工作, 癌变的后果不堪设想。胶质瘤(glioma)是颅内常见的恶性肿瘤, 患者生存率较低[64]。SHI等[38]发现在胶质瘤细胞中, hsa_circ_0014359表达上调与miR-153表达下调有关, 沉默hsa_circ_0014359可提高miR-153表达水平, 抑制PI3K-Akt通路活性, 降低胶质瘤细胞迁移速率, 抑制细胞活性。XU等[39]通过对胶质瘤组织和正常组织中差异表达的circRNA进行筛选后发现, circNFIX的表达显著上调, 其海绵靶点是miR-34a-5p, 它可直接靶向NOTCH1, 故可设法通过下调CircNFIX水平, 抑制NOTCH1、Notch信号通路, 实现对胶质瘤细胞的生长抑制作用。

胶质母细胞瘤又叫多形性胶母细胞瘤(Glioblastoma multiform, GBM), 是中枢神经系统最常见的恶性脑肿瘤, 预后差, 患者中位总生存期只有约15个月[65]。WANG等[40]对GBM组织中功能性miRNA

的海绵结构进行探索, 发现了来自于NT5E基因的circNT5E不仅可直接结合miR-422a, 抑制其活性, 而且circNT5E还可作为其他miRNA的海绵, 在GBM中具有肿瘤调控的作用, 由此确定circNT5E可能是GBM中一个重要的调控因子。

1.5 循环系统

所有非淋巴细胞来源的急性白血病都可归为急性髓系白血病(acute myelocytic leukemia, AML)的范畴, 因为部分患者临床上未表现出细胞遗传学异常, 增加了疾病风险性[66], 所以寻求更为准确的生物标志物可对AML的治疗和预后工作提供理论支持。有证据表明, circPAN3在AML中显著上调, 并且通过对miR-153-5p或miR-183-5p的海绵作用, 提高了XIAP(X-linked inhibitor of apoptosis protein)的表达水平, 降低了AML细胞对抗阿霉素[doxorubicin (ADM)-resistant]的耐药性[41]。另外, YUAN等[42]在小儿AML中发现, circ0004136水平显著上调, 它可靶向多个AML相关miRNA, 如miR-29a、miR-142, 通过对其海绵化, 加速AML细胞增殖。故下调上述circRNA可从不同方面实现对AML细胞的抑制, 提供了AML的肿瘤控制思路。

1.6 内分泌系统

甲状腺癌(thyroid carcinoma)是较常见的甲状腺恶性肿瘤, 在大多数国家中, 甲状腺乳头状癌(papillary thyroid carcinoma, PTC)的发病率长期处于上升趋势[67]。在PTC中, hsa_circ_0058124的表达上调, 能够作为miR-218-5p的ceRNA下调NOTCH3/GATAD2A信号轴, 在PTC发展进程中发挥致癌因子作用[43]。CHEN等[44]通过对甲状腺癌组织细胞中mRNA和蛋白表达进行检测后发现, circNEK6和FZD8(frizzled-8)表达增加, 其miRNA靶点是miR-370-3p, 可激活Wnt通路, 促进甲状腺癌细胞的生长与侵袭。PTC虽然预后较好, 但癌细胞的侵袭和转移速率快, 在PTC组织中circFOXM1[45]的表达上调, 导致miR-1179水平的降低以及HMGB1(high-mobility group box 1)通路的激活, 促进PTC的发展, circFOXM1可能是PTC治疗的一个较理想靶点。

1.7 生殖系统

在有关生殖系统癌变的研究中, 更多的注意力集中在女性生殖系统上。在生殖腺方面, 乳腺癌(breast cancer)是全球女性常发的, 发生于乳腺上皮组织的恶性肿瘤[68]。有证据表明, circTFF1在乳腺癌中的下调能够通过海绵化miR-326, 增加TFF1(trefoil factor family 1)表达水平, 抑制乳腺癌的发生[46]; 乳腺癌中的另一个ceRNA调控机制是circKIF4A的下调能够通过减弱对miR-375的海绵作用, 上调KIF4A水平, 对三阴性乳腺癌(triple-negative breast cancer, TNBC)细胞的增殖和迁移产生抑制作用[47]。卵巢癌(ovarian cancer)的五年生存率仅为15%~30%[69]。为缓解卵巢癌的预后不良, ZHANG等[48]对早期卵巢癌细胞对紫杉醇(paclitaxel, PTX)等药物的耐药性进行研究, 发现circCELSR1在卵巢癌组织耐PTX细胞中高表达, 作为miR-1252的海绵, circCELSR1水平的下调可导致卵巢癌细胞周期阻滞, 增加细胞凋亡, 并因其与卵巢癌细胞的化学药物敏感性高度相关, 可为卵巢癌的临床治疗提供理论基础。

子宫是女性生殖道主要器官之一, 宫颈癌(cervical cancer, CC)的发生常伴有恶性HPV感染, 有超三分之一患者因其复发和进展速度快而死亡[70], 越来越多研究者专注于RNA在CC中的特异性作用。Circ000284[49]、circ8924[50]、hsa_circ_0007534[51]等被发现在CC组织中显著上调, 将其下调能够提升miR-506、miR-518d-5p/miR-519-5p和miR-498表达水平, 实现对CC细胞生长、增殖及迁移的抑制作用, 有望完善CC的治疗策略。

1.8 泌尿系统

泌尿系统任何器官的病变都可以对整个系统甚至整个机体造成不利影响。肾癌又称肾细胞癌(renal cell carcinoma, RCC), 由于癌细胞的迁移速率快和易复发等特性导致其预后性差[71]。CHEN等[52]已经证实, 在PTC中起促进作用的circRAPGEF5在RCC组织中也存在显著下调, 它的海绵化靶点miR-27a-3p可与抑癌基因TXNIP互作, 上调circRAPGEF5水平可实现对RCC细胞增殖和迁移的抑制作用, 此途径可成为RCC预后的参考。膀胱癌(bladder cancer)发生于膀胱黏膜上, 具有复发率高、转移速率快、五年生存率低等特点[72]。HE等[53]研究发现, 在膀胱癌组织中下调的circPTPRA可海绵化miR-636, 抑制KLF9(kruppel like factor 9)的表达, 同时促进膀胱癌细胞的增殖; 而另有研究表明, circCEP128在膀胱癌中的表达上调, 海绵化miR-145-5p使其表达降低, 并间接促进SOX11(transcription factor SOX-11)的表达, 加速膀胱癌细胞的凋亡, 从另一个角度影响膀胱癌进程[54]。

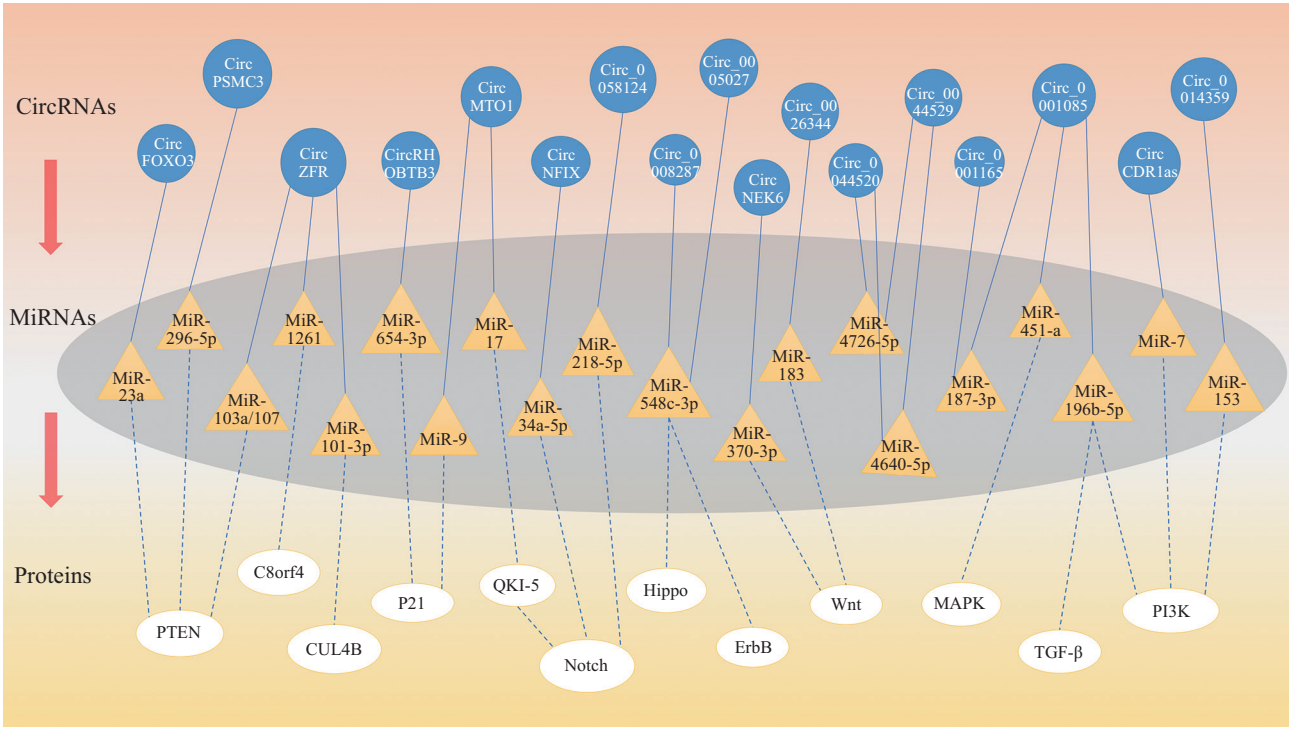

图1　肿瘤中的部分circRNA-miRNA调控网络

Fig.1　Some circRNA-miRNA regulatory networks in tumors

前列腺作为男性特有泌尿器官, 前列腺癌(prostate cancer, PCa)在男性致死肿瘤中排名第二[73], 其健康状况不容忽视。在PCa中, hsa_circ_0001165的表达上调, 通过结合hsa-miR-187-3p诱导PCa细胞的EMT进程, 从而加速其迁移速率; hsa_circ_0001085的表达下调, 与hsa-miR-196b-5p、hsa-miR-451a结合, 激活磷脂酰肌醇3-激酶/苏氨酸蛋白激酶(phosphatidylinositide 3-kinases/serine-threonine kinase, PI3K-Akt)、转化生长因子-β(transforming growth factor-β, TGF-β)、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)等信号通路[55], 这些分子机制的逐步阐明为PCa的治疗提供了理论依据。

2　小结

在对miRNA介导circRNA调控肿瘤的研究现状中不难看出, circRNA的miRNA海绵作用在肿瘤中可参与构成庞大的调控网络(图1)。随着研究的深入, 可以发现circRNA和miRNA的单向或双向作用在转录调控中产生了复杂的影响, 并且某些circRNA在多个肿瘤中都可以进行调控, 如circZFR不仅可通过miR-130a/PTEN、miR-101-3p/CUL4B等通路对胃癌、肺癌进程产生调节作用, 而且在膀胱癌、肾癌、非小细胞肺癌、肝癌等组织中差异表达, 类似的circRNA还有has_circ_102958、circRAPGEF5等。在某些常见肿瘤, 如肺癌、大肠癌、宫颈癌中, 已发现的可能对调控肿瘤有重要影响的circRNA-miRNA调控轴越来越多, circRNA的海绵作用也可通过Wnt、PI3K、Notch等通路影响肿瘤细胞的生长、增殖、迁移等生理进程, 而这些调控网络的干预效果还需要在更深入的研究和临床试验中得到证实。上述发现对于miRNA介导circRNA调控肿瘤的发展和发生的机制的研究奠定了理论基础, 同时circRNA也可能成为肿瘤早期诊断的重要标志物, 为肿瘤的治疗争取更充足的时间, 在提高肿瘤治愈率、减少肿瘤患者的痛苦及死亡率等方面发挥重要作用。

参考文献 (References)

[1] CONSORTIUM E P. An integrated encyclopedia of DNA elements in the human genome [J]. Nature, 2012, 489(7414): 57-74.

[2] CHOWDHURY D, CHOI Y E, BRAULT M E. Charity begins at home: non-coding RNA functions in DNA repair [J]. Nat Rev Mol Cell Biol, 2013, 14(3): 181-9.

[3] ANDO Y, LEUNG A K. Methods for studying microRNA functions during stress [J]. Methods Mol Biol, 2015, 1292:

115-28.
[4] VASHISHT D, NODINE M D. MicroRNA functions in plant embryos [J]. Biochem Soc Trans, 2014, 42(2): 352-7.
[5] ALVAREZ-GARCIA I, MISKA E A. MicroRNA functions in animal development and human disease [J]. Development, 2005, 132(21): 4653-62.
[6] CALIN G A, DUMITRU C D, SHIMIZU M, et al. Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia [J]. Proc Natl Acad Sci USA, 2002, 99(24): 15524-9.
[7] COCQUERELLE C, MASCREZ B, HETUIN D, et al. Mis-splicing yields circular RNA molecules [J]. FASEB J, 1993, 7(1): 155-60.
[8] JECK W R, SORRENTINO J A, WANG K, et al. Circular RNAs are abundant, conserved, and associated with ALU repeats [J]. RNA, 2013, 19(2): 141-57.
[9] YU C Y, LI T C, WU Y Y, et al. The circular RNA circBIRC6 participates in the molecular circuitry controlling human pluripotency [J]. Nat Commun, 2017, 8(1): 1149.
[10] SANGER H, KLOTZ G, RIESNER D, et al. Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures [J]. Proc Natl Acad Sci USA, 1976, 73(11): 3852-6.
[11] HSU M T, COCA-PRADOS M. Electron microscopic evidence for the circular form of RNA in the cytoplasm of eukaryotic cells [J]. Nature, 1979, 280(5720): 339-40.
[12] CAPEL B, SWAIN A, NICOLIS S, et al. Circular transcripts of the testis-determining gene Sry in adult mouse testis [J]. Cell, 1993, 73(5): 1019-30.
[13] SALZMAN J, GAWAD C, WANG P L, et al. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types [J]. PLoS One, 2012, 7(2): e30733.
[14] LI X, YANG L, CHEN L L. The biogenesis, functions, and challenges of circular RNAs [J]. Mol Cell, 2018, 71(3): 428-42.
[15] SALMENA L, POLISENO L, TAY Y, et al. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language [J]? Cell, 2011, 146(3): 353-8.
[16] KULCHESKI F R, CHRISTOFF A P, MARGIS R. Circular RNAs are miRNA sponges and can be used as a new class of biomarker [J]. J Biotechnol, 2016, 238: 42-51.
[17] PIWECKA M, GLAZAR P, HERNANDEZ-MIRANDA L R, et al. Loss of a mammalian circular RNA locus causes miRNA deregulation and affects brain function [J]. Science, 2017, 357(6357): eaam8526.
[18] LIU T, LIU S, XU Y, et al. Circular RNA-ZFR inhibited cell proliferation and promoted apoptosis in gastric cancer by sponging miR-130a/miR-107 and modulating PTEN [J]. Cancer Res Treat, 2018, 50(4): 1396-417.
[19] WEI H, PAN L, TAO D, et al. Circular RNA circZFR contributes to papillary thyroid cancer cell proliferation and invasion by sponging miR-1261 and facilitating C8orf4 expression [J]. Biochem Biophys Res Commun, 2018, 503(1): 56-61.
[20] FENG C, LI Y, LIN Y, et al. CircRNA-associated ceRNA network reveals ErbB and Hippo signaling pathways in hypopharyngeal cancer [J]. Int J Mol Med, 2019, 43(1): 127-42.
[21] FAN Y, XIA X, ZHU Y, et al. Circular RNA expression profile in laryngeal squamous cell carcinoma revealed by microarray [J]. Cell Physiol Biochem, 2018, 50(1): 342-52.
[22] CHEN D, MA W, KE Z, et al. CircRNA hsa_circ_100395 regulates miR-1228/TCF21 pathway to inhibit lung cancer progression [J]. Cell Cycle, 2018, 17(16): 2080-90.
[23] ZHANG H, WANG X, HU B, et al. Circular RNA ZFR accelerates non-small cell lung cancer progression by acting as a miR-101-3p sponge to enhance CUL4B expression [J]. Artif Cells Nanomed Biotechnol, 2019, 47(1): 3410-6.
[24] ZHANG P F, PEI X, LI K S, et al. Circular RNA circFGFR1 promotes progression and anti-PD-1 resistance by sponging miR-381-3p in non-small cell lung cancer cells [J]. Mol Cancer, 2019, 18(1): 179.
[25] WANG Y, LI H, LU H, et al. Circular RNA SMARCA5 inhibits the proliferation, migration, and invasion of non-small cell lung cancer by miR-19b-3p/HOXA9 axis [J]. Onco Targets Ther, 2019, 12: 7055-65.
[26] ZHANG B, CHEN M, JIANG N, et al. A regulatory circuit of circ-MTO1/miR-17/QKI-5 inhibits the proliferation of lung adenocarcinoma [J]. Cancer Biol Ther, 2019, 20(8): 1127-35.
[27] WANG L, WEI Y, YAN Y, et al. CircDOCK1 suppresses cell apoptosis via inhibition of miR196a5p by targeting BIRC3 in OSCC [J]. Oncol Rep, 2018, 39(3): 951-66.
[28] XING Y, ZHA W J, LI X M, et al. Circular RNA circ-Foxo3 inhibits esophageal squamous cell cancer progression via the miR-23a/PTEN axis [J]. J Cell Biochem, 2020, 121(3): 2595-605.
[29] DENG G, MOU T, HE J, et al. Circular RNA circRHOBTB3 acts as a sponge for miR-654-3p inhibiting gastric cancer growth [J]. J Exp Clin Cancer Res, 2020, 39(1): 1.
[30] RONG D, LU C, ZHANG B, et al. CircPSMC3 suppresses the proliferation and metastasis of gastric cancer by acting as a competitive endogenous RNA through sponging miR-296-5p [J]. Mol Cancer, 2019, 18(1): 25.
[31] SHEN T, CHENG X, LIU X, et al. Circ_0026344 restrains metastasis of human colorectal cancer cells via miR-183 [J]. Artif Cells Nanomed Biotechnol, 2019, 47(1): 4038-45.
[32] LI R, WU B, XIA J, et al. Circular RNA hsa_circRNA_102958 promotes tumorigenesis of colorectal cancer via miR-585/CD-C25B axis [J]. Cancer Manag Res, 2019, 11: 6887-93.
[33] HAN D, LI J, WANG H, et al. Circular RNA circMTO1 acts as the sponge of microRNA-9 to suppress hepatocellular carcinoma progression [J]. Hepatology, 2017, 66(4): 1151-64.
[34] HUANG W J, WANG Y, LIU S, et al. Silencing circular RNA hsa_circ_0000977 suppresses pancreatic ductal adenocarcinoma progression by stimulating miR-874-3p and inhibiting PLK1 expression [J]. Cancer Lett, 2018, 422: 70-80.
[35] ZHANG Z, ZHANG X, ZHANG Y, et al. Spinal circRNA-9119 suppresses nociception by mediating the miR-26a-TLR3 axis in a bone cancer pain mouse model [J]. J Mol Neurosci, 2020, 70(1): 9-18.
[36] HUANG L, CHEN M, PAN J, et al. Circular RNA circNASP modulates the malignant behaviors in osteosarcoma via miR-1253/FOXF1 pathway [J]. Biochem Biophys Res Commun, 2018, 500(2): 511-7.
[37] XU B, YANG T, WANG Z, et al. CircRNA CDR1as/miR-7 signals promote tumor growth of osteosarcoma with a potential therapeutic and diagnostic value [J]. Cancer Manag Res, 2018,

10: 4871-80.
[38] SHI F, SHI Z, ZHAO Y, et al. CircRNA hsa-circ-0014359 promotes glioma progression by regulating miR-153/PI3K signaling [J]. Biochem Biophys Res Commun, 2019, 510(4): 614-20.
[39] XU H, ZHANG Y, QI L, et al. NFIX circular RNA promotes glioma progression by regulating miR-34a-5p via Notch signaling pathway [J]. Front Mol Neurosci, 2018, 11: 225.
[40] WANG R, ZHANG S, CHEN X, et al. CircNT5E acts as a sponge of miR-422a to promote glioblastoma tumorigenesis [J]. Cancer Res, 2018, 78(17): 4812-25.
[41] SHANG J, CHEN W M, WANG Z H, et al. CircPAN3 mediates drug resistance in acute myeloid leukemia through the miR-153-5p/miR-183-5p-XIAP axis [J]. Exp Hematol, 2019, 70: 42-54 e3.
[42] YUAN D M, MA J, FANG W B. Identification of non-coding RNA regulatory networks in pediatric acute myeloid leukemia reveals circ-0004136 could promote cell proliferation by sponging miR-142 [J]. Eur Rev Med Pharmacol Sci, 2019, 23(21): 9251-8.
[43] YAO Y, CHEN X, YANG H, et al. Hsa_circ_0058124 promotes papillary thyroid cancer tumorigenesis and invasiveness through the NOTCH3/GATAD2A axis [J]. J Exp Clin Cancer Res, 2019, 38(1): 318.
[44] CHEN F, FENG Z, ZHU J, et al. Emerging roles of circRNA_NEK6 targeting miR-370-3p in the proliferation and invasion of thyroid cancer via Wnt signaling pathway [J]. Cancer Biol Ther, 2018, 19(12): 1139-52.
[45] YE M, HOU H, SHEN M, et al. Circular RNA circFOXM1 plays a role in papillary thyroid carcinoma by sponging miR-1179 and regulating HMGB1 expression [J]. Mol Ther Nucleic Acids, 2019, 19: 741-50.
[46] PAN G, MAO A, LIU J, et al. Circular RNA hsa_circ_0061825 (circ-TFF1) contributes to breast cancer progression through targeting miR-326/TFF1 signalling [J]. Cell Prolif, 2020, 53(2): e12720.
[47] TANG H, HUANG X, WANG J, et al. circKIF4A acts as a prognostic factor and mediator to regulate the progression of triple-negative breast cancer [J]. Mol Cancer, 2019, 18(1): 23.
[48] ZHANG S, CHENG J, QUAN C, et al. circCELSR1 (hsa_circ_0063809) contributes to paclitaxel resistance of ovarian cancer cells by regulating FOXR2 expression via miR-1252 [J]. Mol Ther Nucleic Acids, 2019, 19: 718-30.
[49] MA H B, YAO Y N, YU J J, et al. Extensive profiling of circular RNAs and the potential regulatory role of circRNA-000284 in cell proliferation and invasion of cervical cancer via sponging miR-506 [J]. Am J Transl Res, 2018, 10(2): 592-604.
[50] LIU J, WANG D, LONG Z, et al. CircRNA8924 promotes cervical cancer cell proliferation, migration and invasion by competitively binding to miR-518d-5p/519-5p family and modulating the expression of CBX8 [J]. Cell Physiol Biochem, 2018, 48(1): 173-84.
[51] RONG X, GAO W, YANG X, et al. Downregulation of hsa_circ_0007534 restricts the proliferation and invasion of cervical cancer through regulating miR-498/BMI-1 signaling [J]. Life Sci, 2019, 235: 116785.
[52] CHEN Q, LIU T, BAO Y, et al. CircRNA cRAPGEF5 inhibits the growth and metastasis of renal cell carcinoma via the miR-27a-3p/TXNIP pathway [J]. Cancer Lett, 2020, 469: 68-77.
[53] HE Q, HUANG L, YAN D, et al. CircPTPRA acts as a tumor suppressor in bladder cancer by sponging miR-636 and upregulating KLF9 [J]. Aging, 2019, 11(23): 11314-28.
[54] WU Z, HUANG W, WANG X, et al. Circular RNA CEP128 acts as a sponge of miR-145-5p in promoting the bladder cancer progression via regulating SOX11 [J]. Mol Med, 2018, 24(1): 40.
[55] YAN Z, XIAO Y, CHEN Y, et al. Screening and identification of epithelial-to-mesenchymal transition-related circRNA and miRNA in prostate cancer [J]. Pathol Res Pract, 2020, 216(2): 152784.
[56] M C L, C L M, R B G, et al. Hypopharyngeal cancer: analysis of the evolution and treatment results [J]. Acta Otorrinolaringol Esp, 2009, 60(1): 3-8.
[57] LUO J, WU J, LV K, et al. Analysis of postsurgical health-related quality of life and quality of voice of patients with laryngeal carcinoma [J]. Medicine, 2016, 95(1): e2363.
[58] GUPTA G P, MASSAGUE J. Cancer metastasis: building a framework [J]. Cell, 2006, 127(4): 679-95.
[59] LINGEN M W, KALMAR J R, KARRISON T, et al. Critical evaluation of diagnostic aids for the detection of oral cancer [J]. Oral Oncol, 2008, 44(1): 10-22.
[60] HUANG F L, YU S J. Esophageal cancer: risk factors, genetic association, and treatment [J]. Asian J Surg, 2018, 41(3): 210-5.
[61] RAZA A, SOOD G K. Hepatocellular carcinoma review: current treatment, and evidence-based medicine [J]. World J Gastroenterol, 2014, 20(15): 4115-27.
[62] SHAO F, HUANG M, MENG F, et al. Circular RNA signature predicts gemcitabine resistance of pancreatic ductal adenocarcinoma [J]. Front Pharmacol, 2018, 9: 584.
[63] OMER N, LE DELEY M C, PIPERNO-NEUMANN S, et al. Phase-II trials in osteosarcoma recurrences: a systematic review of past experience [J]. Eur J Cancer, 2017, 75: 98-108.
[64] ALLEMANI C, WEIR H K, CARREIRA H, et al. Global surveillance of cancer survival 1995-2009: analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2) [J]. Lancet, 2015, 385(9972): 977-1010.
[65] WELLER M, VAN DEN BENT M, HOPKINS K, et al. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma [J]. Lancet Oncol, 2014, 15(9): e395-403.
[66] DOHNER H, ESTEY E H, AMADORI S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet [J]. Blood, 2010, 115(3): 453-74.
[67] LA VECCHIA C, MALVEZZI M, BOSETTI C, et al. Thyroid cancer mortality and incidence: a global overview [J]. Int J Cancer, 2015, 136(9): 2187-95.
[68] SIEGEL R L, MILLER K D, JEMAL A. Cancer statistics, 2016 [J]. CA Cancer J Clin, 2016, 66(1): 7-30.
[69] PINATO D J, GRAHAM J, GABRA H, et al. Evolving concepts in the management of drug resistant ovarian cancer: dose dense chemotherapy and the reversal of clinical platinum resistance [J]. Cancer Treat Rev, 2013, 39(2): 153-60.
[70] KIM M K, JO H, KONG H J, et al. Postoperative nomogram

predicting risk of recurrence after radical hysterectomy for early-stage cervical cancer [J]. Int J Gynecol Cancer, 2010, 20(9): 1581-6.

[71] ZNAOR A, LORTET-TIEULENT J, LAVERSANNE M, et al. International variations and trends in renal cell carcinoma incidence and mortality [J]. Eur Urol, 2015, 67(3): 519-30.

[72] AMIN M B, SMITH S C, REUTER V E, et al. Update for the practicing pathologist: The International Consultation On Urologic Disease-European association of urology consultation on bladder cancer [J]. Mod Pathol, 2015, 28(5): 612-30.

[73] CENTER M M, JEMAL A, LORTET-TIEULENT J, et al. International variation in prostate cancer incidence and mortality rates [J]. Eur Urol, 2012, 61(6): 1079-92.