三阴性乳腺癌中环状RNA的表达特点及功能意义

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摘要 环状RNA是由前体RNA通过反向剪接形成的一类共价闭合环状分子。在过去, 环状RNA被认为是DNA转录的“噪音”, 不参与生物代谢过程。然而, 最近研究表明, 环状RNA的异常表达可影响包括三阴性乳腺癌在内的多种恶性肿瘤的发生发展。该文综述了环状RNA在肿瘤中的分子机制及其在三阴性乳腺癌细胞增殖、凋亡、迁移、侵袭和药物抗性中的功能。

关键词 肿瘤; 三阴性乳腺癌; 环状RNA; 分子机制; 功能

Expression Characteristics and Functional Significance of Circular RNA in Triple Negative Breast Cancer

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Abstract Circular RNA is a covalently closed circular molecule formed by reverse splicing of precursor RNA. In the past, circular RNA was considered as the “noise” of DNA transcription and did not participate in biological metabolic processes. However, recent studies have shown that abnormal expression of circular RNA can affect the occurrence and development of various malignant tumors, including triple-negative breast cancer. This article reviews the molecular mechanism of circular RNA in tumors and its functions in cell proliferation, apoptosis, migration, invasion, and drug resistance of triple-negative breast cancer.

Keywords tumor; triple-negative breast cancer; circular RNA; molecular mechanism; function

三阴性乳腺癌(triple-negative breast cancer, TNBC)作为乳腺癌亚型之一, 严重威胁着世界女性的健康, 具有不表达雌激素受体(estrogen receptor, ER)、孕激素受体(progestin receptor, PR)、人表皮生长因子受体2(human epithelial growth factor receptor 2, Her2)的特点[1]。其临床特征表现为侵袭性高, 且在局部手术、全身化疗和放射治疗后, 与其他乳腺癌亚型患者相比, TNBC患者更易发生早期复发和远处转移。最近研究表明, 在标准治疗结束后, 持续以低剂量、高频率的“节拍化疗”方式口服卡培他滨能够显著提高早期TNBC患者的5年无病生存期(disease-free survival, FDS)[2]。此外, 免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)帕博利珠单抗(pembrolizumab)联合化疗药物紫杉醇(Paclitaxel, PAX)可以显著提高TNBC患者的病理完全缓解率(pathological complete response, pCR)[3]。晚期TNBC的防治是目前临床面临的更为严峻的挑战, 根据分子亚型进行精准用药治疗, 已成为治疗晚期TNBC的重要策略。为了使TNBC实现更精准的治疗, 近期科学家们就TNBC多组学图谱提出了“复旦分型”,

收稿日期: 2020-10-30 接受日期: 2021-01-13

国家自然科学基金(批准号: 81560451)资助的课题

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Received: October 30, 2020 Accepted: January 13, 2021

This work was supported by the National Natural Science Foundation of China (Grant No.81560451)

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URL: http://www.cjcb.org/arts.asp?id=5492

包括免疫调节型(immunomodulatory, IM)、腔面/雄激素受体型(luminal-AR, LAR)、基底样免疫抑制型(basal-like immune suppressed, BLIS)和间质型(mesenchymal-like, MES), 通过检测病理免疫组化标志物(雄激素受体、CD8、FOXC1、DCLK1), 可以快速知道患者属于哪种亚型, 并通过精准治疗提高TNBC患者的治愈率[4]。尽管诊疗水平的不断上升使TNBC患者的无病生存期FDS得到了实质性的延长, 但是其生存率依然很低。因此, 寻找有效的治疗靶点对于提高TNBC患者的生存率是极具意义的。

环状RNA(circular RNA, circRNA)是共价封闭、无5′端帽和3′poly(A)尾巴的竞争性内源RNA(competing endogenous RNA, ceRNA)。由于不能被核糖核酸酶识别, 因此, circRNA的半衰期比信使RNA(messenger RNA, mRNA)长且结构更加稳定。在过去, circRNA被认为是由错误剪接产生的RNA结构变异体, 是转录的“噪音”[5]。然而, 最近研究表明, circRNA的异常表达可影响包括TNBC在内的多种恶性肿瘤的发生发展, 其通过多种调控机制影响TNBC细胞代谢过程(包括增殖、凋亡、侵袭、迁移和药物敏感性等)。基于此, 本文就circRNA在恶性肿瘤中的分子机制及其在TNBC增殖、凋亡、迁移、侵袭和药物抗性中的作用作一综述。

1 环状RNA在肿瘤中的分子机制

circRNA在肿瘤中有多种作用机制(表1): ①作为ceRNA与mRNA竞争结合微小RNA(microRNA, miRNA)并促进mRNA的表达; ②与蛋白质结合形成circRNP复合体, 调节其结合蛋白的功能和circRNA自身的转运; ③在内部核糖体进入位点(internal ribosome entry site, IRES)和N6-甲基腺苷(N6-methyladenosine, m6A)介导下能编码多肽或者蛋白; ④位于细胞核的外显子–内含子circRNA(exon-intron circRNA, EIciRNA)和内含子circRNA(circular intronic RNA, ciRNA)与RNA聚合酶II(RNA polymerase II, RNA Pol II)形成复合体调节其亲本mRNA的表达水平。下面对circRNA在肿瘤中的潜在机制进行详细介绍。

1.1 环状RNA作为海绵体吸附miRNA并上调其靶基因的表达

miRNA是在真核生物中发现的具有调控功能的一类内源性非编码RNA(noncoding RNA, ncRNA), 其大小约为22个核苷酸[31]。由于circRNA分子含miRNA应答元件(miRNA response element, MRE), 因此和长链非编码RNA(long noncoding RNA, LncRNA)类似, circRNA可以与miRNA结合并上调其靶基因的表达水平[32]。

目前研究表明, circRNA能吸附单个miRNA从而诱导疾病的产生。例如: circRNA_28313可以作为miR-195a的海绵体吸附miR-195a并导致其靶基因集落刺激因子1(colony stimulating factor 1, *CSF1*)的表达升高, 促进了由核因子κB配体受体激活剂(receptor activator of NF-κB ligand, RANKL)和CSF1共同诱导的破骨细胞分化和由小鼠体内卵巢切除(ovariectomize, OVX)引起的骨吸收[33]。另外, 与正常黏膜组织相比, 大肠癌组织中的ciRS-7表达上调, ciRS-7通过吸附miR-7并上调其靶基因表皮生长因子受体(epidermal growth factor receptor, *EGFR*)、*RAF-1*的表达[16], 从而诱导大肠癌的发生。此外, circRNA还可结合多种miRNA并诱导疾病的产生。LIM等和LU等[7,34]报道了circSLC8A1能分别在心肌肥厚和膀胱癌中结合miR-133和miR-130b/494并诱导疾病的发生。类似的, LAI等、CUI等和HAN等[30,35-36]研究发现, circHIPK3能分别靶向miR-221-3p、miR-421和miR-485-3p来促进白内障、神经胶质瘤和肾癌的发生进展。

1.2 通过招募蛋白质调节癌症进程

与LncRNA、mRNA类似, circRNA能通过招募RNA结合蛋白(RNA binding proteins, RBPs)参与癌症进程。例如: 细胞核中的m6A修饰的circNSUN2可以结合蛋白包含1的YTH域(YTH domain containing 1, YTHD1)并促进circNSUN2运出细胞核, 在细胞质中形成circNSUN2/IGF2BP2/HMGA2蛋白质三元复合物, 增强*HMGA2*(high mobility group AT-hook 2) mRNA的稳定性, 从而促进大肠癌转移[17]。在宫颈癌HeLa细胞中, ABDELMOHSEN等[14]发现, 通过招募人抗原R(human antigen R, HuR)并抑制其与聚(A)结合蛋白核1(Poly(A)-binding protein nuclear 1, PABPN1)的结合, 从而阻止了PABPN1的翻译并加速宫颈癌的恶性进程。此外, 存在于乳腺癌细胞中的FLI1外显子环状RNA(FLI1 exonic circular RNA, *FECR1*)募集Tet原癌基因1(Tet oncogene 1, *TET1*)到Fli-1原癌基因(Fli-1 proto-oncogene, *FLI1*)

表1 circRNA在恶性肿瘤中的作用和机制

Table 1 The role and mechanism of circRNA in malignant tumors

肿瘤 Cancer	环状RNA CircRNA	表达 Expression	作用和机制 Function and mechanism	参考文献 References
Bladder cancer	circ_0020394	High	Puerarin impedes cell viability, migration, invasion, and glycolysis, and promots apoptosis in bladder cancer by regulating circ_0020394/miR-328-3p/NRBP1 axis	[6]
	circSLC8A1	Low	CircSLC8A1 acts as a sponge of miR-130b/miR-494 in suppressing bladder cancer progression via regulating PTEN	[7]
	circ_0001944	High	Circ_0001944 promotes the growth and metastasis in bladder cancer cells by acting as a competitive endogenous RNA for miR-548	[8]
Breast cancer	circRNA-MTO	Low	CircRNA-MTO inhibits cell viability by regulating TRAF4/Eg	[9]
	circSMARCA5	Low	CircSMARCA5 enhances the sensitivity of breast cancer cells to cisplatin or bleomycin by down-regulating the expression of SMARC5	[10]
	FECR1	High	FECR1 promotes the metastasis of breast cancer by promoting the expression of FLI1	[11]
	circ_0001982	High	Circ_0001982 promotes cell proliferation and invasion and inhibit apoptosis by reducing miR-143	[12]
Cervical cancer	circE7	High	E7 protein translated by circE7 mediated by M6A promotes tumor progression	[13]
	circPABPN1	High	CircPABPN1 inhibits PABPN1 translation and reduces cervical cancer cell proliferation by preventing the binding of HuR to PABPN1 mRNA	[14]
	circ_0000263	High	Circ_0000263 targets miR-150-5 p/MDM4/p53 axis to promote cell proliferation and migration	[15]
Colorectal cancer	ciRS-7	High	CiRS-7 promote cancer phenotype through miR-7/EGFR/RAF1 axis	[16]
	circNSUN2	High	N(6)-methyladenosine modification of circNSUN2 facilitates cytoplasmic export and stabilizes HMGA2 to promote colorectal liver metastasis	[17]
Esophageal squamous cell carcinoma	circGFRA1	High	CircGFRA1 and miR-188-3p regulats the proliferation of NSCLC cells at least through PI3K/AKT signaling pathway	[18]
	ciRS-7	Low	CiRS-7 inhibits autophagy of ESCC cells by functioning as miR-1299 sponge to target EGFR signaling	[19]
	circRNA_100876	High	Dysregulation of circRNA_100876 expression leads to poor prognosis in ESCC by accelerating cell proliferation and metastasis	[20]
Gastric cancer	circLARP4	Low	CircLARP4 inhibits cell proliferation and invasion through the miR-424/LATS1 axis	[21]
	ciRS-7	High	CiRS-7 promotes carcinogenic phenotype by activating PTEN/PI3K/AKT signal pathway in combination with miR-7	[22]
Glioma	circAKT3	Low	Circular AKT3 RNA inhibits glioblastoma tumorigenicity by competing with active phosphoinositide-dependent kinase-1	[23]
	circFBXW7	Low	CircFBXW7 encodes FBXW7-185aa inhibits cell proliferation and cell cycle progression by shortening the half-life of c-Myc	[24]
	circHIPK3	High	CircHIPK3 elevates CCND2 expression and promotes cell proliferation and invasion through miR-124 in glioma	[25]
Ovarian cancer	circKRT7	High	CircKRT7-miR-29a-3p-COL1A1 axis promotes ovarian cancer cell progression	[26]
	circEPSTI1	High	CircEPSTI1 regulates ovarian cancer progression via decoying miR-942	[27]
Prostate cancer	circHIPK3	High	CircHIPK3 facilitates the G_2/M transition in prostate cancer cells by sponging miR-338-3p	[28]
	circ-0016068	High	Circ-0016068 promotes the growth, migration, and invasion of prostate cancer cells by regulating the miR-330-3p/BMI-1 axis	[29]
Renal carcinoma	circHIPK3	High	CircHIPK3 promotes proliferation and metastasis and inhibits apoptosis of renal cancer cells by inhibiting miR-485-3p	[30]

的启动子区域, 通过上调FLI1的表达来促进乳腺癌的转移[11]。

1.3 通过编码小肽参与肿瘤发生过程

与mRNA的翻译不同, circRNA的翻译是需要通过不依赖帽的机制完成的。研究表明, 含有IRES和m6A的circRNA可以编码肿瘤相关蛋白[37-38]: 一方面, circRNA编码的蛋白可以充当肿瘤抑制因子, 以抑制肿瘤表型。据XIA等[39]报道, circAKT3编码的蛋白AKT3-174aa抑制了神经胶质瘤的发生发展。AKT3-174aa的过表达降低了神经胶质瘤细胞的增殖能力和体内致瘤性, 而AKT3-174aa的低表达增强神经胶质瘤细胞的癌表型。此外, AKT3-174aa与p-PDK1的结合阻止了p-PDK1募集AKT并导致p-AKT(Thr-308)的表达降低, 从而抑制PI3K/AKT信号通路的激活。

另一方面, circRNA编码的蛋白质也能作为一个致癌因子促进肿瘤的发生发展。例如: 由*β-catenin*基因位点产生的circβ-catenin是一种新发现的circRNA, 其在肝癌组织中充当促癌基因发挥作用。研究表明, 位于细胞质中的circβ-catenin在IRES序列的介导下能够编码β-catenin同工型蛋白(β-catenin-370aa), 与全长β-catenin竞争结合糖原合酶激酶3 beta(glycogen synthase kinase 3 beta, GSK3β)而抑制GSK3β诱导的β-catenin降解, 从而通过激活Wnt/β-catenin信号通路促进癌症发生[40]。

1.4 通过直接调节其亲本基因的表达来调控癌症表型

有文献报道, 位于细胞核中的EIcircRNA和ciRNA能够结合RNA Pol II, 并在转录水平上直接调节其亲本基因的表达, 从而参与癌症的发生。

例如: 蔗糖非发酵蛋白2同源(sucrose nonfermenting protein 2 homolog, SMARCA5)是SWI/SNF复合物和具有依赖三磷酸腺苷(adenosine triphosphate, ATP)性质的染色质重塑活性的组分, 在DNA损伤修复的过程中发挥着重要作用。circSMARCA5是由SMARCA5外显子15、外显子16通过反向剪接形成, 在乳腺癌组织中的表达要低于正常乳腺组织, 经实验发现其主要位于细胞核并在转录水平上发挥作用。进一步研究表明, circSMARCA5可以在第15号外显子处终止SMARCA5的转录, 从而降低癌细胞中SMARCA5的表达水平。此外, SMARC5的下调抑制了DNA损伤后的修复功能, 同时增强了乳腺癌细胞对顺铂或博来霉素的敏感性[10]。

2 环状RNA调节三阴性乳腺癌发生进展的分子机制

circRNA在TNBC组织中的表达具有特异性, 失调的circRNA可通过多种分子机制调节细胞的增殖、凋亡、迁移、侵袭和药物敏感性(表2)。目前, 对于TNBC中的circRNA研究还很少, 生物功能研究较为透彻的有circSEPT9、circTADA2A、circAGFA1、circFBXW7、circ-HER2、circUBE2D2、circAMOTL1等。现对这些circRNA进行论述。

2.1 环状RNA参与三阴性乳腺癌增殖、凋亡信号的调控

2.1.1 circSEPT9 circSEPT9是在真核起始因子4A3(eukaryotic initiation factor 4A-III, ELF4A3)介导下由SEPT9(Septin 9)前体mRNA(pre-mRNA)经反向剪接环化形成的circRNA。据报道, circSEPT9在TNBC中发挥致癌作用。在TNBC患者中, circSEPT9高表达组与低表达组相比, 肿瘤体积更大且更易发生淋巴结积累和远处转移。在功能方面, 敲低circSEPT9可以显著抑制细胞增殖, 诱导细胞凋亡; 而circSEPT9的过表达则表现出相反的作用。进一步分析发现, circSEPT9充当miR-637的ceRNA, 进而增强白血病抑制因子(leukemia inhibitory factor, LIF)的表达并激活TNBC中的LIF/Stat3信号通路, 最终导致TNBC的发生发展[41]。

2.1.2 circTADA2A circTADA2A是由转录适配器2A(Transcriptional Adaptor 2A, TADA2A)经反向剪接形成的circRNA, 包含circTADA2A-E6和circTADA2A-E5/E6[70]。

研究发现, circTADA2A在多种癌症进展中起关键作用, circTADA2A扮演着原癌基因和抑癌基因的双重角色, 目前对于circTADA2A出现的不同作用归因于肿瘤微环境的异质性[78]。在骨肉瘤中, circTADA2A通过miR-203a-3p/CREB3轴来促进肿瘤的生长[78], 而在大肠癌中, circTADA2A通过结合miR-374a-3p[78]来抑制糖酵解和体内肿瘤生长。

XU等[70]利用RT-qPCR检测了circTADA2A在TNBC组织以及正常乳腺组织中的表达情况, 结果发现, circTADA2A(尤其是circTADA2A-E6)在TNBC组织中的表达水平要明显低于正常乳腺组织, 并且circTADA2A-E6的下调与淋巴结转移和临床恶性特征显著相关。接下来, 体外细胞实验进一步证实了circTADA2A-E6的抗肿瘤活性, 即过表达circTA-

表2 TNBC中circRNA的作用和机制

Table 2 The function and mechanism of circRNA in TNBC

circRNA名称 circRNA name	实验细胞株 Test cell strain	表达 Expression	TNBC中的作用和机制 The function and mechanism of circRNA in TNBC	其他肿瘤中的作用和机制 The function and mechanism of circRNA in the other tumors	参考文献 References
circSEPT9	BT549, MDA-MB-231	High	The circSEPT9 mediated by E2F1 and EIF4A3 facilitates the carcinogenesis and development of triple-negative breast cancer through circSEPT9/miR-637/LIF axis	Unreported	[41]
circAGFG1	BT549, MDA-MB-231	High	The circRNA circAGFG1 acts as a sponge of miR-195-5p to promote triple-negative breast cancer progression through regulating CCNE1 expression	CircAGFG1 activates YY1/CTNNB1/Wnt/β-catenin pathway axis by combining miR-4262 and miR-185-5p to promote metastasis and dryness colorectal cancer	[42-43]
circGNB1	BT549, MDA-MB-231	High	CircGNB1 facilitates triple-negative breast cancer progression by regulating miR-141-5p-IGF1R axis	Unreported	[44]
circGFRA1	MDA-MB-231, MDA-MB-468, BT549	High	CircGFRA1 and GFRA1 promote cell proliferation and inhibit cell apoptosis by regulating miR-34a	CirGFRA1-miR-188-3p-PI3K/AKT axis plays an important role in the tumorigenesis of non-small cell lung cancer	[18,45]
circ_0131242	BT549, MDA-MB-468	High	Circ_0131242 may promote triple-negative breast cancer progression by sponging has-miR-2682	Unreported	[46]
circEPSTI1	MDA-MB-231, BT549	High	The circEPSTI1-miR-4753/6809-BCL11A axis affects the proliferation and apoptosis of triple-negative breast cancer through the mechanism of ceRNA	CircEPSTI1 regulates ovarian cancer progression via decoying miR-942	[27,47]
circ-UBAP2	BT-20, MDA-MB-231	High	Upregulation of circ-UBAP2 predicts poor prognosis and promotes triple-negative breast cancer progression through the miR-661/MTA1 pathway	CircUBAP2-mediated ceRNA network modulates PAAD (pancreatic adenocarcinoma) by regulating the infiltration and function of immune cells	[48-49]
circANKS1B	MDA-MB-231	High	CircANKS1B/miR-148a/152-3p/USF1 feedback loop promotes cell invasion and metastasis via inducing TGF-β1-mediated EMT in breast cancer	CircANKS1B regulates FOXM1 expression and promotes cell migration and invasion by functioning as a sponge of the miR-149 in colorectal cancer	[50-51]
ciRS-7	MDA-MB-231, BT549	High	CiRS-7 maintains metastatic phenotypes as a ceRNA of miR-1299 to target MMPs	CiRS-7 accelerates ESCC progression through acting as a miR-876-5p sponge to enhance MAGE-A family expression	[52-53]
circKIF4A	MDA-MB-231, BT549	High	CircKIF4A regulates TNBC migration and invasion through miR-375-KIF4A axis	CircKIF4A promotes tumorogenesis of glioma by targeting miR-139-3p to activate Wnt5a signaling	[54-55]
circIFI30	MDA-MB-231, BT549	High	CircIFI30 promote TNBC progression through circIFI30/miR-520b-3p/CD44 axis	Unreported	[56]
circPLK1	MDA-MB-231, HCC38	High	CircPLK1 facilitate through miR-296-5p-PLK1 axis tumor progression by ceRNA mechanism in TNBC	CircPLK1 promotes breast cancer cell proliferation, migration, and invasion by regulating the miR-4500/IGF1 axis	[57-58]
circ-ZEB1	MDA-MB-231, BT549	High	Circular RNA circ-ZEB1 acts as an oncogene in TNBC via sponging miR-448	Circ-ZEB1.33 promotes the proliferation of human HCC by sponging miR-200a-3p and upregulating CDK6	[59-60]
circ_0091074	MDA-MB-231, MDA-MB-468	High	Circ_0091074 can partially reverse the inhibition of breast cancer cell proliferation and invasion caused by miR-1297	Unreported	[61]

续表2

circRNA名称 circRNA name	实验细胞株 Test cell strain	表达 Expression	TNBC中的作用和机制 The function and mechanism of circRNA in TNBC	其他肿瘤中的作用和机制 The function and mechanism of circRNA in the other tumors	参考文献 References
circRAD18	MDA-MB-231, MDA-MB-468, BT549	High	CircRAD18 sponges miR-208a/3164 to promote TNBC progression through regulating IGF1 and FGF2 expression	CircRAD18 promotes breast cancer progression by regulating the miR-613/HK2 axis	[62-63]
circ-TFCP2L1	MDA-MB-231, HCC1937	High	Circ-TFCP2L1 is identified as a sponge of miR-7 functionally targeting PAK1 and further promoting the proliferation and migration of TNBC cells	Unreported	[64]
circHER2	MDA-MB-231, MDA-MB-468	High	Circ-HER2 promotes cell proliferation, invasion, and Pertuzumab sensitivity of TNBC *in vivo* and *in vitro* by encoding HER2-103	Unreported	[65]
circEIF3M	MDA-MB-231	High	CircEIF3M promotes breast cancer progression by promoting cyclin D1 expression	Unreported	[66]
circUBE2D2	MDA-MB-231, BT549	High	CircUBE2D2 (hsa_circ_0005728) promotes cell proliferation, metastasis and chemoresistance in TNBC by regulating miR-512-3p/CDCA3 axis	Upregulated circ-UBE2D2 predicts poor prognosis and promotes breast cancer progression by sponging miR-1236 and miR-1287	[67-68]
circRNA_069718	MDA-MB-468	High	CircRNA_069718 promotes cell proliferation and invasion in triple-negative breast cancer by activating Wnt/β-catenin pathway	Unreported	[69]
circTADA2As	MDA-MB-231	Low	CircTADA2As suppress breast cancer progression and metastasis via targeting miR-203a-3p/SOCS3 axis	Propofol disrupts cell carcinogenesis and aerobic glycolysis by regulating circTADA2A/miR-455-3p/FOXM1 axis in lung cancer	[70-71]
circAHNAK1	MDA-MB-231, BT549	Low	CircAHNAK1 inhibits proliferation and metastasis of triple-negative breast cancer by modulating miR-421 and RASA1	Unreported	[72]
circFBXW7	BT549, 4T1	Low	CircFBXW7 sponges miR-197-3p and encodes the FBXW7-185aa protein to suppress TNBC progression through upregulating FBXW7 expression	CircFBXW7 encodes FBXW7-185aa to inhibit the occurrence of glioma by antagonizing the stability of c-Myc induced by USP28	[24,73]
circITCH	MDA-MB-231, BT-549	Low	CircITCH inhibits proliferation and metastasis by targeting the Wnt/catenin pathway	CircITCH enhances the sensitivity of multiple myeloma cells to bortezomib by regulating the miR-615-3p/PRKCD axis	[74-75]
circAMOTL1	MDA-MB-231	High	CircAMOTL1 through activating AKT and up-regulating the expression of anti-apoptotic protein BCL-2 to promote cancer and increase cell resistance to PAX	CircAMOTL1 promotes the progression of cervical cancer through the miR-485-5p/AMOTL1 axis	[76-77]

DA2A-E6抑制细胞增殖。通过对circTADA2A-E6抗肿瘤活性的分子机制进行探索，结果发现，circTADA2A作为miRNA的海绵体通过miR-203a-3p/SOCS3轴抑制TNBC的形成。

2.2 circRNA调节TNBC细胞迁移和侵袭

2.2.1 circAGFG1 研究表明，circAGFG1在多种肿瘤中起癌基因的作用，例如宫颈癌、非小细胞肺癌和大肠癌。circAGFG1在宫颈癌中通过下调miR-370-3p或者p53来促进细胞的增殖和迁移[79-80]；在非小细胞肺癌中通过上调ZNF281的表达来促进上皮–间质转化(epithelial-mesenchymal transition, EMT)[81]；在大肠癌中通过激活Wnt/β-catenin途径来促进细胞

干性[43]。

YANG等[42]发现, 与癌旁组织和正常细胞相比, circAGFA1在TNBC组织和细胞系中显著上调, 并且circAGFA1的上调与TNBC患者的不良预后呈正相关。circAGFA1的过表达促进TNBC细胞迁移和侵袭, 而敲除circAGFA1呈现出相反的结果。对circAGFA1发挥生物学功能的分子机制进一步分析, 结果表明, circAGFA1通过circAGFA1/miR-195-5P/CCNE1轴正向调控TNBC细胞的迁移和侵袭并促进了TNBC的发生发展。有趣的是, 研究发现, miR-203在非小细胞肺癌中是circAGFG1的下游直接靶基因[81]。此外, 据WANG等[82]报道, 在TNBC中, miR-203下调, 而BIRC5(baculoviral IAP repeat containing 5)和LASP1(LIM and SH3 protein 1)表达上调, 并且miR-203可通过下调BIRC5和LASP1来抑制TNBC的增殖和迁移, 因此, circAGFG1/miR-203/BIRC5/LASP1轴很可能是调控TNBC发生发展的一个潜在分子机制。

2.2.2 circFBXW7 据报道, 由包含7的F-Box和WD重复域(F-Box and WD repeat domain containing 7, FBXW7)衍生的环状RNA(circFBXW7)是一种抑癌circRNA, 在神经胶质瘤和大肠癌中表达下调, 同时使肿瘤细胞的周期和迁移受到抑制[83-85]。在胶质瘤中, circFBXW7通过编码小肽FBXW7-188a或者作为miR-23a-3p的海绵体抑制肿瘤进程, 暗示了circFBXW7可以通过自身编码小肽和作为miRNA的海绵体发挥作用。

有研究发现, circFBXW7在TNBC细胞系中同样低表达, 同时circFBXW7的低表达与较差的临床预后相关[73]。此外, 体外细胞实验(Transwell、迁移)的结果证明了敲低circFBXW7促进了TNBC细胞的迁移和侵袭。YE等[73]分析circFBXW7在TNBC中的抑癌机制, 结果发现, circFBXW7能分别通过靶向miR-197-3p和编码FBXW7-185aa两种不同作用机制来促进其亲本基因的表达, 从而抑制TNBC的发生发展。

2.3 环状RNA在三阴性乳腺癌细胞耐药及化疗药物的敏感性中的作用

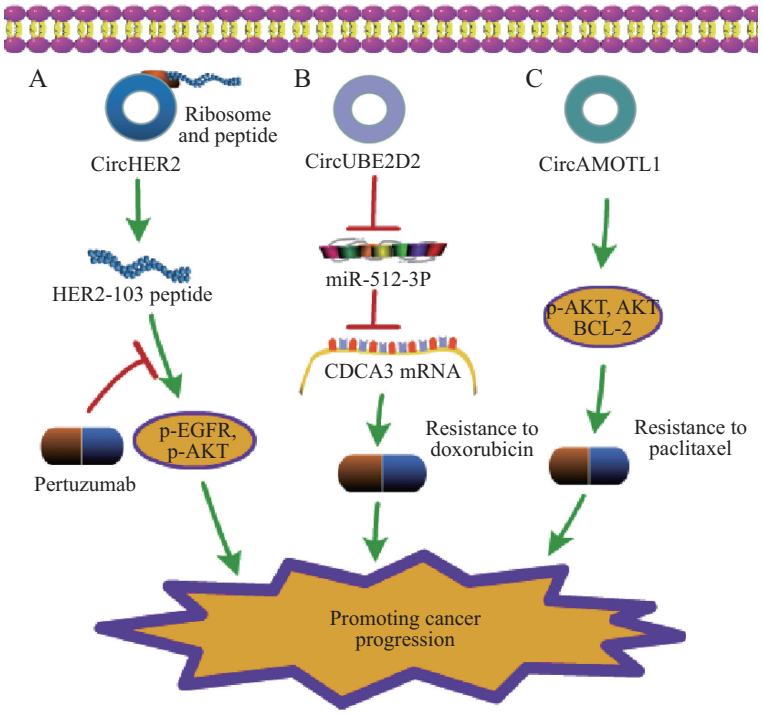
2.3.1 circ-HER2 有效治疗靶点的缺乏和药物抗性的存在是TNBC临床治疗面临的两个挑战。以往人们一直认为内分泌治疗和曲妥珠单抗(Pertuzumab)治疗对TNBC患者没有影响[86]。但最近研究表明, Pertuzumab对环状HER2(circ-HER2)过表达的TNBC患者治疗敏感。

LI等[65]发现, circ-HER2在部分TNBC患者癌组织样本中的表达要显著高于相邻的癌旁组织。通过Kaplan-meiter曲线分析, 发现circ-HER2的表达与TNBC患者的总生存期呈负相关, circ-HER2通过提高p-EGFR激酶活性和p-AKT水平来促进TNBC恶性表型的产生。此外, circ-HER2编码的小肽(HER2-103)与HER2的CR1结构域有相同的氨基酸序列, 提示靶向HER2的Pertuzumab能够拮抗circ-HER2并发挥抑癌作用(图1A), 经过检测发现, Pertuzumab抑制了HER2-103过表达诱导的恶性表型。

2.3.2 circUBE2D2 circUBE2D2是由泛素结合酶E2 D2(ubiquitin conjugating enzyme E2 D2, *UBE2D2*)mRNA的第2~5号外显子经过反向剪接产生的一种circRNA, 在基因组上位于染色体5q31.2。充当miRNA的“海绵体”是circRNA在细胞质中最常见的作用机制。早在2019年, WANG等[68]在乳腺癌组织中发现, circUBE2D2能够结合miR-1236和miR-1287, 并且在乳腺癌中发挥致癌作用。

阿霉素(Doxorubicin, ADM)是临床治疗TNBC的常用化疗药物之一。DOU等[67]发现, circUBE2D2在TNBC组织和细胞系中高表达并且与TNBC患者的不良预后相关, circUBE2D2的沉默可以抑制TNBC细胞的癌症特征并且降低TNBC细胞对阿霉素的抗性。机制研究表明, circUBE2D2可以通过充当miR-512-3p的海绵体来促进细胞分裂周期相关蛋白3(cell division cycle associated 3, CDCA3)的表达从而促进癌症进展和对ADM的抗性(图1B)。

2.3.3 circAMOTL1 血管紧张素样1(angiomotin like 1, AMOTL1)的pre-mRNA经反向剪接形成的环状RNA(circAMOTL1), 在口腔鳞状细胞癌和宫颈癌中都被报道作为一个促癌基因发挥作用[77,87]。已有研究证明, circAMOTL1与TNBC的耐药性有关, 可通过敲低circAMOTL1降低细胞对紫杉醇(PAX)的耐药性。在TNBC细胞中, 发现加入PAX后, circAMOTL1的低表达组与对照组相比, 细胞活力更弱; 过表达后细胞活力增强。这揭示circAMOTL1是TNBC中PAX耐药性的关键调控基因。进一步分析发现, circAMOTL通过激活AKT和上调抗凋亡蛋白BCL-2的表达来促进癌症发生和提高癌细胞对PAX的耐药性[76](图1C)。此外, 有研究发现, circAMOTL1/



A: 帕妥株单抗通过拮抗HER2-103抑制EGFR和AKT信号通路的激活, 从而使表达circ-HER2的TNBC患者从帕妥株单抗中获益; B: CircUBE2D2通过充当miR-512-3p的海绵体上调CDCA3表达, 从而促进TNBC的发展和对阿霉素的抗性; C: circAMOTL1通过激活AKT信号通路、上调抗凋亡蛋白BCL-2的表达促进细胞对紫杉醇耐药。

A: Pertuzumab inhibits the activation of EGFR and AKT signaling pathways by antagonizing HER2-103, so that TNBC patients who express circ-HER2 can benefit from Pertuzumab; B: circUBE2D2 promoted TNBC progression and doxorubicin resistance through acting as a sponge of miR-512-3p to up-regulate CDCA3 expression; C: circAMOTL1 promotes cell resistance to paclitaxel by activating the AKT signaling pathway and increasing the expression of anti-apoptotic protein BCL-2.

图1 CircRNA在TNBC的耐药性和药物敏感性中起着重要作用

Fig.1 CircRNA plays an important role in drug resistance and drug sensitivity of TNBC

miR-485-5p/AMOTL1轴介导宫颈癌的进展, 并且miR-485-5p在乳腺癌组织和TNBC细胞MDA-MB-231[88-90]、MDA-MB-468[89]细胞中表达下调, 而与ER^+乳腺癌相比, AMOTL1在侵袭性更高的ER^-乳腺癌中表达更高并且发挥肿瘤启动子的作用[90], 因此, circAMOTL1/miR-485-5p/AMOTL1轴可能也发生在TNBC中。

3 小结与展望

根据世界卫生组织国际癌症研究机构(international agency for research on cancer, IARC)发布的2020年最新癌症数据统计显示, 乳腺癌代替肺癌, 成为全球第一大癌。TNBC是乳腺癌中侵袭性最强、危害性最大的恶性肿瘤。虽然局部手术和全身化疗、放疗延长了TNBC患者的总生存期(overall survival, OS), 但TNBC患者的复发率和致死率仍然很高。

随着RNA-seq分析技术和生物信息学的不断发展, 越来越多的circRNA在TNBC细胞系中被鉴定出来。研究发现, circRNA具有TNBC细胞定位、组织特异性表达等特征, 在TNBC发生发展过程中发挥着重要的调控作用。在本篇综述中, 我简要概述了circRNA在肿瘤中发挥功能的机制及其在TNBC中参与的功能调节。目前, 对癌症中circRNA的机制研究主要集中在: (1) 作为海绵体吸附miRNA并上调其靶基因的表达, 发挥其生物学功能; (2) 与蛋白质相互作用, 调节癌症进程; (3) 自身编码多肽并通过多肽调节肿瘤发生发展; (4) 在转录和转录后水平调节其亲本基因的表达, 参与癌症发生。此外, 在TNBC中, circRNA在细胞增殖、凋亡、迁移、侵袭和药物抗性中发挥了巨大的调控功能, circRNA可作为TNBC患者诊疗相关的重要靶点。然而, circRNA在TNBC中的研究还处在起步阶段, 目前只有少数的circRNA在TNBC中被鉴定出是癌症诊断的生物标志物, 还有大部分的circRNA在TNBC中的调控功能尚不清楚。此外, 目前关于circRNA在TNBC中的机制研究主要集中于circRNA作为miRNA的ceRNA方

面，而对于circRNA通过编码小肽等方式影响TNBC进展的研究还很少。因此，关于circRNA调节TNBC发生进展的分子机制还有待进一步深入研究。

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