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·综 述·

蛋白磷酸酶2A癌性抑制因子在肿瘤中的作用

Roles of cancerous inhibitor of protein phosphatase 2A in human cancer

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[摘 要] 蛋白磷酸酶2A癌性抑制因子(cancerous inhibitor of protein phosphatase 2A,CIP2A)在绝大多数肿瘤中高表达。CIP2A能够与转录因子c-Myc和蛋白磷酸酶2A(protein phosphatase 2A,PP2A)直接相互作用,抑制PP2A对c-Myc第62位丝氨酸的磷酸化作用,进而阻止c-Myc蛋白降解,该功能是CIP2A促癌作用的重要体现。CIP2A在肿瘤细胞增殖、凋亡、侵袭、迁移、上皮间充质转化(epithelial-mesenchymal transition,EMT)、细胞周期及抗药性等方面发挥着重要的作用;同时,CIP2A也是一些肿瘤诊断和预后的潜在生物标志物。本文就近年来CIP2A在肿瘤中的表达、调控以及其在肿瘤细胞中的作用和其作为潜在抗肿瘤药物靶标的研究作一综述。

[关键词] 蛋白磷酸酶2A癌性抑制因子;蛋白磷酸酶2A;c-Myc;肿瘤
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2002年Soo-Hoo和Zhang等首次在肝癌和胃癌细胞中发现了表观分子量为90 kDa的肿瘤相关自身抗原(p90)[1],2007年p90被鉴定为蛋白磷酸酶2A癌性抑制因子(cancerous inhibitor of protein phosphatase 2A,CIP2A)[2],CIP2A能够直接与转录因子c-Myc相互作用,抑制蛋白磷酸酶2A(protein phosphatase 2A,PP2A)对c-Myc第62位丝氨酸的磷酸化作用,进而阻止c-Myc蛋白降解。随着该功能的阐明,CIP2A在各种肿瘤中的研究开始活跃起来。笔者就近年来CIP2A在肿瘤中的表达及临床意义、调控机制及其在各种肿瘤中的作用,以及其作为肿瘤治疗的潜在靶标等研究进展作一综述,旨在探讨CIP2A在肿瘤进展中的重要作用,并为肿瘤相关基础研究和肿瘤治疗的新靶点提供基础或参考依据。

1 CIP2A在肿瘤中的表达及其临床意义

*CIP2A*基因位于人染色体3q13.13,长度约为43.9 kb,含21个外显子,编码蛋白分子量为102 kD(GenBank accession numberNP_065941.2)。相比正常或癌旁组织,CIP2A在绝大多数实体瘤和血液肿瘤中均高表达(表1)。多数肿瘤患者低生存率与其瘤内CIP2A高表达正相关,且CIP2A对患者预后有指示意义。表1中个别相似研究具有不同的结论。He等[3]报道CIP2A在人肝癌标本中高表达[阳性率为100.0%(136/136)],与患者低生存率相关;而Huang等[4]报道*CIP2A* mRNA在肝癌中的阳性率[77.9%(106/136)]高于癌旁组织[31.6%(43/136)],瘤内mRNA水平与患者预后不相关,而癌旁mRNA水平与患者预后相关。Böckelman等[5]报道CIP2A在结直肠癌中阳性率为87.9%(661/752),与患者低生存率和预后的相关性无统计学意义;Teng等[6]报道CIP2A在结肠癌中阳性率为100.0%(167/167),与患者低生存率相关,对预后有指示意义。这些研究结论的不同可能源于样本量偏小或样本内在基因型的差异。另外,高水平CIP2A对甲状腺乳头状癌、乳腺癌患者具有诊断意义[7-9]。

2 CIP2A在肿瘤细胞中的表达调控机制

CIP2A在各肿瘤细胞中的表达受转录因子[骨髓成红细胞增多症病毒E26癌基因同源物1(erythroblastosis virus E26 oncogene homolog 1,Ets1)、ETS样蛋白1(ets-like protein 1,Elk1)和八聚体结合转录因子4(octamer-binding transcription factor 4,OCT4)等]、蛋白酶[细胞周期检测点激酶1(checkpoint kinase 1,CHK1)和cAMP反应元件结合蛋白(cAMP response element-binding protein,CREB)等]和微小RNA(miRNA)的调控,具有一定的复杂性和细胞特异性。首先,Khanna等[43]报道在胃腺癌细胞和前列

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腺癌细胞中ERK信号通路可通过转录因子Ets1来调控*CIP2A*基因表达。而Pallai等[44]报道在子宫颈癌和子宫内膜癌细胞中转录因子Ets1和Elk1与*CIP2A*基因启动子区结合，协同调控*CIP2A*的基础转录。Ventelä等[11]报道在睾丸癌细胞和胚胎干细胞中OCT4能够直接调控*CIP2A*基因表达。另外，在小鼠胚胎成纤维细胞中激活转录因子2（activating transcription factor 2，ATF2）结合于*CIP2A*基因启动子区的激活蛋白1（activator protein 1，AP-1）结合位点，启动基因转录[45]；胃癌细胞中也很可能有如此规律[46]。Laine等[20]报道在乳腺癌细胞和结肠癌细胞中p53直接靶向调控p21表达，进而抑制CDK，使成视网膜细胞瘤蛋白（retinoblastoma protein，pRb）保持去磷酸化状态，抑制E2F转录因子1（E2F transcription factor 1，E2F1）与*CIP2A*基因启动子区结合，最终下调CIP2A的表达。Choi等[47]报道在乳腺癌细胞中17β-雌二醇能够激活EGFR，进而激活MAPK和PI3K信号通路，使p70核糖体蛋白S6激酶（p70 ribosomal protein S6 kinase，p70S6K）活化，最终激活真核翻译起始因子4B（eukaryotic translation initiation factor 4B，eIF4B）来调控*CIP2A*基因表达。其次，Khanna等[21]报道在胃癌细胞和成纤维肉瘤细胞中敲除*c-Myc*显著下调CIP2A表达（同样敲除*CIP2A*显著下调c-Myc）；c-Myc很可能通过转录因子E2F1来调控*CIP2A*基因表达[48]。

表1 CIP2A在各肿瘤中的表达及其临床意义

肿瘤类型	CIP2A阳性率（%）		与生存率相关	预后指示	参考文献
	肿瘤组织	正常或癌旁组织			
头颈部鳞状细胞癌	78.6（11/14）	0.0（0/9）	-	-	[2]
	80.8（42/52）	-	+	+	[10]
	82.7（43/52）	-	+	-	[11]
鼻咽癌	90.7（254/280）	-	+	+	[12]
舌癌	97.3（71/73）	66.7[a]（2/3）	+	+	[13]
非小细胞肺癌	72.2（65/90）	0.0（0/90）	+	+	[14]
	76.3（74/97）	5.2（5/97）	+	+	[15]
食管鳞状细胞癌	90.0（36/40）	20.0（8/40）	-	×[d]	[16]
食管腺癌	97.3（110/113）	100.0[c]（5/5）	×	+	[17]
乳腺癌	39.4（13/33）	-	+	-	[18]
	35.0（448/1280）	-	+	+	[19]
	46.0（565/1228）	-	-	+	[20]
	100.0（46/46）	28.3（13/46）	-	-	[9]
胃癌	65.0（145/223）	-	+	+	[21]
	67.6（25/37）	-	+	+	[22]
结直肠癌	87.9（661/752）	-	×	×	[5]
	100.0（167/167）	80.0[c]（12/15）	+	+	[6]
肝癌	100.0（136/136）	-	+	+	[3]
	77.9[b]（106/136）	31.6[c]（43/136）	+	+	[4]
胰腺癌	56.3（54/96）	-	+[c]	+[c]	[23]
	70.8（51/72）	11.1（3/27）	+	+	[24]
胆管上皮癌	78.9（45/57）	13.0（3/23）	+	+	[25]
肾癌	70.1（75/107）	31.6（6/19，癌旁） 16.7（1/6，正常）	+	+	[26]
前列腺癌	72.9（43/59）	10.0（2/20）	×	×	[27]
	86.5（109/126）	17.4（16/92）	-	-	[28]
膀胱癌	72.6（85/117）	0.0（0/30）	+	+	[29]
	78.8（63/80）	16.3（13/80）	-	-	[30]
	63.6（63/99）	0.0（0/12）	-	-	[31]
	41.9（18/43）	0.0（0/43）	-	-	[32]
子宫颈癌	52.8（38/72）	0.0（0/15）	-	-	[33]
	60.8（31/51）	5.7（2/35）	-	-	[34]
卵巢癌	82.8（434/524）	-	+	+	[35]
	65.8（100/152）	-	-	-	[36]
皮肤黑色素瘤	100.0（65/65）	0.0（0/30）	+	+	[37]
骨肉瘤	76.5（39/51）	-	-	-	[38]
急性髓性白血病	57.8（67/116）	2.9（1/35）	-	-	[39]
	100.0（203/203）	-	+	+	[40]
慢性髓性白血病	-	-	+	+	[41]
	75.7[c]（56/74）	2.9（1/35）	-	-	[42]

+：相关；−：不祥；×：无关；[a]正常或癌旁组织的CIP2A蛋白表达水平低于肿瘤组织；[b]*CIP2A* mRNA阳性率（其余为CIP2A蛋白阳性率）；[c]癌旁*CIP2A* mRNA水平与患者生存率相关，对预后有指示意义

Khanna等[49]报道在人胃癌、卵巢癌、结肠癌和成神经细胞瘤标本中*CHK1*和*CIP2A*在mRNA表达水平上具有显著相关性，在胃癌细胞中DNA损伤应答激酶（DNA damage response kinases，DNA-PK）使CHK1第345位丝氨酸持续磷酸化，磷酸化的CHK1能够上调*CIP2A*基因表达。Sung等[50]报道在肺腺癌细胞中IL10通过PI3K/蛋白激酶B（protein kinase B，PKB/AKT）信号通路使CREB磷酸化，进而调控*CIP2A*基因表达。Balliu等[51]报道HDAC1在结直肠癌细胞中能够调控*CIP2A*基因表达。但c-Myc、CHK1、CREB和HDAC1是直接还是间接（通过信号通路介导其它转录因子）结合*CIP2A*启动子区进而启动基因表达尚不完全清楚。还有，Jung等[52]报道在口腔癌细胞中miR-375通过多个结合位点直接能够调控*CIP2A*基因表达。Wei等[53]报道在皮肤黑色素瘤细胞中miR-218能够结合*CIP2A*的3′-UTR区调控*CIP2A*基因表达。

3 CIP2A在肿瘤中的作用

蛋白激酶的磷酸化作用和蛋白磷酸酶（protein phosphatase，PP）的去磷酸化作用是细胞内蛋白功能调节和信号转导的最普遍机制之一，两者失衡与囊性纤维化、阿尔茨海默病（Alzheimer diseases，AD）和肿瘤等一些疾病息息相关。根据去磷酸化的氨基酸残基的不同，PP可分成蛋白酪氨酸磷酸酶和丝氨酸/苏氨酸磷酸酶。其中，蛋白磷酸酶1（PP1）和PP2A承担着细胞中绝大多数丝氨酸/苏氨酸磷酸酶的去磷酸化作用[54-55]。研究[56]表明PP2A是一个重要的抑癌磷酸酶，它广泛参与调节细胞能量代谢、周期、DNA复制、增殖和凋亡等生理病理进程。PP2A是由结构亚基A、调节亚基B和催化亚基C组成的异源三聚体。不同亚基的不同异形体之间组合可形成超过80种不同的PP2A，亚基B决定着PP2A的底物特异性和亚细胞定位[56-57]。虽然PP2A底物众多，但其抑癌功能很大程度上与去磷酸化并稳定c-Myc相关[58]。c-Myc属于碱性螺旋-环-螺旋-亮氨酸拉链（basic helix-loop-helix-leucine zipper，bHLH-LZ）转录因子家族，它通常与Myc相关因子X（Myc-associated factor X，Max）形成异源二聚体，结合到靶基因启动子区的E-box（5′-CANNTG-3′）元件，并同时招募其他转录因子，启动靶基因的表达[59]。c-Myc在绝大多数肿瘤中高表达，广泛参与细胞增殖、黏附、分化、迁移、代谢和DNA复制等生理病理进程[60]。CIP2A是PP2A主要的内源性抑制剂，CIP2A、PP2A和c-Myc三者相互作用抑制PP2A对c-Myc第62位丝氨酸的磷酸化作用，稳定c-Myc蛋白，该功能是CIP2A促癌作用的重要体现。

如表2所示，CIP2A在多种肿瘤细胞增殖、凋亡、侵袭、迁移、上皮间充质转化（epithelial-mesenchymal transition，EMT）、细胞周期及抗药性等方面发挥着重要的作用，其分子机制大多与CIP2A、PP2A和c-Myc三者相互作用相关。如图1所示，siRNA沉默*CIP2A*能够导致多发性骨髓瘤细胞内c-Myc蛋白降低，通过失活PI3K/AKT/mTOR信号通路来抑制细胞增殖，诱导细胞凋亡[61-62]。CIP2A在乳腺癌细胞中通过PP2A/PI3K/AKT促进细胞周期蛋白依赖性激酶抑制剂1B（cyclin-dependent kinase inhibitor 1B，CDKN1B/p27Kip1）磷酸化，使其重定位于细胞质，同时通过PP2A/c-Myc抑制*p27Kip1*转录表达，最终促进细胞周期[63]。但是，像这样较为具体的阐明CIP2A调节细胞功能的分子机制的研究仍相对较少。同时，CIP2A也有非依赖PP2A的功能，与Ras、Polo样激酶1（polo-like kinase 1，PLK1）、永离有丝分裂基因A相关激酶2（never in mitosis gene A-related kinase 2，NEK2）等可直接相互作用，进而调节细胞的功能。CIP2A在子宫颈癌细胞中可与Ras直接相互作用，增强Ras-MAPK信号通路，同时通过抑制PP2A对c-Myc去磷酸化，稳定c-Myc，两者共同参与EMT和肿瘤的发生[34]。CIP2A可与PLK1相互作用，增强PLK1的稳定性和活力，促进有丝分裂[64]。CIP2A在子宫颈癌细胞中也可与NEK2相互作用，增强NEK2活性，促进中心体分离[65]。CIP2A在前列腺癌细胞中可与Shugoshin样蛋白1（shugoshin-like 1，Sgol1）相互作用，促进染色体分离，促进细胞周期[66]。CIP2A在前列腺癌细胞中可通过与富含亮氨酸重复序列蛋白59（leucine-rich repeat-containing protein 59，LRRC59）相互作用转运入核，引起细胞周期调控失常[67]。另外，在慢性粒细胞白血病细胞中CIP2A与断裂点簇集区-艾贝尔逊白血病病毒（breakpoint cluster region-Abelson leukemia virus，BCR-ABL）存在正反馈调节，可能促进该疾病发展，但两者是否直接相互作用尚不清楚[42]。

CIP2A的功能发辉与多个信号有关。与CIP2A相关的两个重要的信号通路Ras-MAPK和PK3K-AKT参与肿瘤生物学的功能。此外，CIP2A在肺癌细胞中可增强JNK信号通路，促进细胞增殖，但CIP2A增强JNK信号通路的具体分子机制尚不清楚[68]。以下讨论与CIP2A相关的10个信号通路：（1）Ras-MAPK信号通路。Ras受胞外信号刺激活化，招募Raf在细胞膜上与之结合并将其活化，活化的Raf（MAPKKK）再活化MAPKK，活化的MEK（MAPKK）又接着活化ERK（又称MAPK），最终活化的ERK激活一些转录因子（Elk1、ATF、NF-κB、c-Myc等），引发多种生物学效应[82]。（2）PI3K-AKT信号通路。PI3K

表2 siRNA下调CIP2A对肿瘤细胞的影响和潜在的分子机制

肿瘤细胞		增殖	凋亡	侵袭	迁移	EMT	周期	抗药性	机制	参考文献
星形细胞瘤细胞	A172和U87	↓[a]	↑[b]	–[c]	–	–	–	–	c-Myc ↓, pAKT ↓, BCL2 ↓	[69]
头颈部鳞状细胞癌	UT-SCC-7和UT-SCC-9	↓	–	–	–	–	–	–	c-Myc ↓	[2]
鼻咽癌细胞	CNE-2和SUNE-1	↓	–	–	–	–	–	–	c-Myc ↓	[12]
口腔癌细胞	NCI-60	↓	–	↓	↓	–	–	–	c-Myc ↓	[52]
	SCC-25	↓	–	–	–	–	–	–	–	[70]
非小细胞肺癌细胞	H1299	↓	–	=[d]	–	–	–	–	AKT-mTOR信号通路	[14,71]
	L78	↓	–	–	–	–	–	–	–	[72]
	SPCA1	↓	–	–	–	–	–	↓（顺铂）	AKT信号通路	[72-73]
	A549	↓	–	=	–	–	–	↓（顺铂）	AKT信号通路	[14,72-73]
食管鳞状细胞癌	EC109	↓	↑	–	–	–	=	–	c-Myc ↓	[16]
乳腺癌细胞	MDA-MB-231和BT549	↓	–	↓	–	–	↓	–	PP2A/c-Myc/p27Kip1	[7,63]
胃癌细胞	MKN-28、KATOIII和AGS	↓	–	–	–	–	–	–	c-Myc ↓	[21]
结肠癌细胞	Caco-2	↓	–	–	–	–	–	–	ERK ↓	[74]
	HCT116	↓	–	–	–	–	–	–	c-Myc ↓	[75]
	HT29	↓	–	–	–	–	–	↓（5-氟尿嘧啶、奥沙利铂、SN38）	–	[6]
胰腺癌细胞	SW1990	↓	–	–	–	–	–	↓（吉西他滨）	BCL2 ↓, AKT ↓	[24]
肾透明细胞癌细胞	786-O	–	–	↓	–	↓	–	–	–	[76]
	A498和KRC/Y	=	–	↓	↓	–	–	–	c-Myc ↓	[26]
前列腺癌细胞	LNCaP	↓	–	–	–	–	–	–	–	[77]
	PC-3	–	–	–	–	–	↓	–	CIP2A与Sgol1作用	[66]
	C4-2	↓	–	–	–	–	–	↓（卡巴他赛）	–	[78]
	DU-145	↓	–	↓	↓	–	–	–	c-Myc ↓	[28]
膀胱癌细胞	T24	↓	↑	↓	↓	↓	–	–	–	[29-30]
子宫颈癌细胞	HeLa	↓	–	–	–	↓	–	↓（多柔比星、顺铂和紫杉酚）	c-Myc ↓, P- gp ↓, MEK/ERK信号通路	[33-34,79]
	SiHa和Caski	↓	–	–	–	–	–	–	c-Myc ↓	[33]
卵巢癌细胞	SKOV3^{DDP}	↓	–	–	–	–	–	↓（顺铂）	AKT信号通路	[80]
	A2780和SKOV3	↓	–	–	–	–	↓	↓（紫杉酚）	Cyclin D1 ↓, c-Myc ↓, pRb ↓, Bcl- 2 ↓, Pakt ↓	[36]
黑色素瘤细胞	FEMX1、WM1366、WM983b和WM9	↓	↑	–	–	–	–	–	PI3K/AKT信号通路	[81]
	A375	–	–	↓	↓	–	–	–	–	[37]
骨肉瘤细胞	MG-63	↓	–	↓	—	–	–	–	c-Myc ↓, pAKT ↓	[38]
多发性骨髓瘤细胞	RPMI-8226和NCI-H929	↓	↑	–	–	–	–	–	c-Myc ↓, PI3K/AKT/mTOR信号通路	[61-62]
急性髓细胞白血病细胞	HEL	↓	–	–	–	–	–	–	c-Myc ↓	[40]
	HL60	↓	–	–	–	–	–	–	–	[39]
慢性髓细胞白血病细胞	K562	↓	↑	–	–	–	–	–	c-Myc ↓	[42]

[a]抑制或下调；[b]促进或上调；[c]不详；[d]无明显影响

是由调节亚基(p85)和催化亚基(p110)组成的异源二聚体。受体酪氨酸激酶(receptor tyrosine kinase，RTK)可直接诱导活化PI3K，也可通过活化Ras，进而由活化的Ras诱导活化PI3K。活化的PI3K能将磷脂酰肌醇二磷酸(phosphatidylinositol4,5-bisphosphate，PIP2)转化为PIP3。PIP3作为第二信使通过3-磷脂酰肌醇依赖性蛋白激酶(3-phosphoinositide-dependent kinase1，PDK1)等间接激活AKT，激活的AKT作用于多种底物如mTOR和糖原合成酶激酶-3β(glycogen synthase kinase-3β，GSK-3β)等来调节细胞生存、增殖等功能[82]。(3)c-Myc的磷酸化与降解[83]。ERK磷酸化c-Myc Ser62使其稳定，随后GSK-3β会进一步磷酸化c-MycThr58，紧接着脯氨酰异构酶(prolyl isomerase，PIN-1)可使c-Myc(含Ser62和Thr58两磷酸化位点)由顺式结构转变为反式结构，PP2A可催化反式结构c-Myc(含Ser62和Thr58两磷酸化位点)的Ser62去磷酸化生成反式结构c-Myc(含Thr58磷酸化位点)，该产物可进一步被遍在蛋白连接酶复合体(含FWB7)催化生成泛素化的c-Myc，最终经蛋白酶复合体降解。(4)CIP2A、PP2A和c-Myc三者可直接相互作用，阻碍PP2A对c-Myc Ser62的去磷酸化,进而稳定c-Myc蛋白[2]。(5)CIP2A-PP2A复合物与雷帕霉素靶蛋白复合物1(mammalian target of rapamycin complex 1，mTORC1)相互作用，增强mTORC1活力，进而抑制细胞自噬[84]。(6)CIP2A可与PLK1相互作用，增强PLK1的稳定性和活性，促进有丝分裂[64]。(7)CIP2A也可与NEK2相互作用，增强NEK2活力，促进中心体分离[65]。(8)沉默或抑制*CIP2A*能够导致肿瘤细胞内c-Myc蛋白降低，通过失活PI3K/AKT/mTOR信号通路来抑制细胞增殖，诱导细胞凋亡[61-62]；其中PP2A能够去磷酸化PI3K的Thr308和Ser473，使其失活[85]。(9)CIP2A在乳腺癌细胞中通过PP2A/PI3K/AKT促进p27Kip1磷酸化，使其重定位于胞质，同时通过PP2A/c-Myc抑制*p27Kip1*转录表达，最终促进细胞周期[63]。(10)CIP2A在子宫颈癌细胞中可与Ras直接相互作用，增强Ras-MAPK信号通路，同时通过抑制PP2A对c-Myc去磷酸化进而稳定c-Myc，两者共同参与EMT和肿瘤的发生[34]。详见图1。

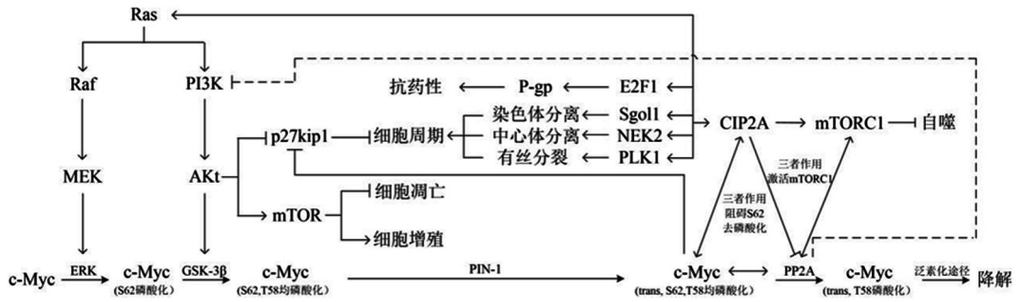

图1 CIP2A的功能与相关信号通路示意图

4 CIP2A为潜在靶标的抗肿瘤研究

笔者将近年来CIP2A作为潜在靶标的抗肿瘤研究总结于表3。表3可见，*CIP2A* siRNA和一些小分子化合物可抑制一些肿瘤细胞增殖和相应的裸鼠移植瘤，该抑制作用与下调CIP2A以及其下游分子的改变(如增加PP2A活性和减弱AKT磷酸化等)相关。一些小分子化合物下调CIP2A的机制已经阐明。染料木素和坦西莫司分别在乳腺癌细胞和结肠癌细胞中通过抑制转录和增强蛋白酶降解两种途径来下调CIP2A[86-87]；拉帕替尼、埃罗替尼衍生物TD52和阿法替尼分别在乳腺癌细胞、肝癌细胞和非小细胞肺癌细胞中干扰转录因子Elk1与*CIP2A*启动子结合，进而下调CIP2A表达[88-90]；新藤黄酸在肝癌细胞中能够诱导CIP2A通过泛素-蛋白酶体途径降解[91]；南蛇藤醇在非小细胞肺癌细胞中结合CIP2A，促进CIP2A与热休克蛋白70羧基末端相互作用蛋白(carboxyl terminus of Hsp70-interacting protein，CHIP)结合，诱导CIP2A降解[92]。有趣的是，他莫昔芬可诱导乳腺癌细胞MDA-MB-231、MDA-MB-468、MDA-MB-453和SK-BR-3凋亡，而对细胞HCC-1937无效[93]；硼替佐米可诱导乳腺癌细胞HCC-1937、MDA-MB-231和MDA-MB-468凋亡，而对细胞MDA-MB-453和MCF-7无效[94]。两者同样在乳腺癌细胞MDA-MB-453和HCC-1937中能够下调CIP2A，但对细胞的作用结果却截然不同，这暗示了硼替佐米或他莫昔芬或许未能像siRNA一样单纯下调CIP2A进而引起细胞变化，它们不一定是直接靶向*CIP2A*，可能有不同的作用机制。另外，埃罗替尼及其衍生物是受体酪氨酸激酶抑制物(EGFR拮抗剂)，但它诱导肝癌

细胞凋亡作用与受体酪氨酸激酶活性无关，而与下调CIP2A表达相关[95]。阿法替尼是ErbB家族受体（包含EGFR）的阻滞剂，但它通过CIP2A/PP2A/AKT信号通路诱导非小细胞肺癌细胞凋亡[90]。还有，高表达CIP2A的慢性粒细胞白血病患者服用二代酪氨酸激酶抑制剂2G TKIs可控制病情恶化[96]。前面提到一些肿瘤中CIP2A高表达与其不良预后相关，而绝大多数正常组织中CIP2A低表达（除精原细胞外）[2,97]。上述研究结果提示CIP2A可作为抗肿瘤药物靶标，然而CIP2A的晶体结构尚未解析，深入探讨当前实验中的这些化合物与CIP2A的相互作用以及针对其结构设计直接相互作用的拮抗剂等均难以进行。

表3 与下调CIP2A相关的抗肿瘤研究

化合物	抑制肿瘤细胞	抑制裸鼠移植瘤	降低抗性	参考文献
CIP2A siRNA	见表2	-[a]	见表2	见表2
	-	口腔癌细胞CAL27移植瘤	-	[98]
	膀胱癌细胞（T24）	膀胱癌细胞T24移植瘤	-	[29]
染料木素	乳腺癌细胞（MCF-7-C3和T47D）	-	-	[86]
拉帕替尼	乳腺癌细胞（HCC 1937、MDA-MB-468和MDA-MB-231）	-	-	[88]
芬戈莫德	乳腺癌细胞（MDA-MB-231和BT-474）	乳腺癌细胞MDA-MB-231移植瘤	-	[99]
他莫昔芬	乳腺癌细胞（MDA-MB-231、MDA-MB-468、MDA-MB-453和SK-BR-3）	乳腺癌细胞MDA-MB-468移植瘤	-	[93]
硼替佐米	乳腺癌细胞（HCC-1937、MDA-MB-231和MDA-MB-468）	乳腺癌细胞HCC-1937移植瘤	-	[94]
	白血病细胞（HL-60和KG-1）	白血病细胞HL-60移植瘤	-	[100]
	头颈部鳞状细胞癌细胞（Ca9-22、SAS和SCC-25）	-	-	[101]
	结肠癌细胞（LoVo）	结肠癌细胞LoVo移植瘤	-	[102]
	子宫颈癌细胞（SiHa）	硼替佐米和放射线联合能抑制子宫颈癌细胞SiHa移植瘤	放射线	[103]
	肝癌细胞（Sk-Hep1和Huh-7）	-	放射线	[103]
硼替佐米及其衍生物	肝癌细胞（Huh-7、Hep3B和Sk-Hep1）	硼替佐米抑制肝癌细胞Huh-7移植瘤	抗死亡受体5抗体CS-1008	[104-106]
葫芦素B	乳腺癌细胞（MCF-7/Adr）	-	多柔比星	[107]
新藤黄酸	肝癌细胞（Hep G2和Bel-7402）	-	-	[91]
埃罗替尼	肝癌细胞（PLC5和Hep3B）	-	-	[108]
	非小细胞肺癌细胞（H358）	非小细胞肺癌细胞H358移植瘤	-	[109]
埃罗替尼衍生物	肝癌细胞（Sk-Hep1）	-	-	[95]
埃罗替尼衍生物TD-19	非小细胞肺癌细胞（H460）	非小细胞肺癌细胞H460移植瘤	-	[110]
埃罗替尼衍生物TD52	肝癌细胞（PLC5、Huh-7、Hep3B和Sk-Hep1）	肝癌细胞PLC5移植瘤	-	[89]
阿法替尼	非小细胞肺癌细胞（H358和H441）	非小细胞肺癌细胞H358移植瘤	-	[90]
南蛇藤醇	非小细胞肺癌细胞（H1975和A549）	非小细胞肺癌细胞H1975和A549移植瘤	-	[92]
乙氧基血根碱	非小细胞肺癌细胞（H1975和A549）	-	顺铂	[111]
坦西莫司	结肠癌细胞（HCT-15和SW480）	坦西莫司和西妥昔单抗联合抑制结肠癌细胞HCT-15移植瘤	西妥昔单抗	[87]

[a]不详

5 结　语

CIP2A在绝大多数肿瘤中高表达，与许多肿瘤患者的不良预后正相关。CIP2A、PP2A和c-Myc三者的相互作用是CIP2A促癌作用的重要体现，CIP2A在肿瘤细胞的增殖、凋亡、侵袭、迁移、EMT、周期及抗

药性等方面发挥着重要的作用。CIP2A可作为潜在的抗肿瘤药物靶标。当前仍有几个重要问题有待解决。(1)CIP2A的晶体结构尚未解析，深入研究CIP2A的功能以及直接相互作用的拮抗剂等均难以进行；(2)CIP2A在细胞增殖和抗药性两方面的功能提示其在具有抗药性和增殖快的肿瘤干细胞中具有重要的作用；(3)CIP2A与相关信号通路深入具体的联系和非依赖PP2A复合物的CIP2A功能还了解较少，有待进一步深入挖掘和研究。

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