·肿瘤机理·

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GADD45A 与肿瘤治疗

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摘 要: 生长阻滞和 *DNA* 损伤基因 45*A* (*growth arrest and DNA damage-inducible* 45*A*, *GADD*45*A*)是第 1 个被发现的由 P53 激活的应激诱导基因, 同时也是 P63、P73、BRCA1 及 MYC 的靶标基因。*GADD*45*A* 作为 DNA 损伤修复基因, 受 P53 依赖(电离辐射诱导)和独立于 P53 (紫外线诱导)的途径调节, 参与 DNA 损伤修复、细胞周期阻滞、凋亡、自噬、血管形成等生物学功能, 与肿瘤发生发展密切相关。在大多数肿瘤的治疗中, 化疗药物直接或者间接(如脱甲基化、乙酰化)上调其表达水平, 提高癌细胞药物敏感性; 同时, 在放射治疗过程, 过表达 *GADD*45*A* 可干预放射抵抗。然而, 在少数肿瘤的治疗中, *GADD*45*A* 的表达反而能够提高癌细胞的存活率。本文主要对 *GADD*45*A* 在肿瘤治疗中所发挥的作用及机制进行综述。

关键词: 生长阻滞和 *DNA* 损伤基因 45*A* (*GADD*45*A*); 肿瘤治疗; 凋亡; 细胞周期阻滞; 细胞耐药; 放疗敏感
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GADD45A and Tumor Therapy

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Abstract: *Growth arrest and DNA damage-inducible* 45*A* (*GADD*45*A*) is the first P53 activated stress-induced gene, which is also a target gene of P63, P73, BRCA1 and MYC. As a DNA damage repair gene, *GADD*45*A* is regulated by P53 dependent (induced by ionizing radiation) and P53 independent (induced by ultraviolet light) pathways, and participates in DNA damage repair, cell cycle arrest, apoptosis, autophagy, angiogenesis and other biological functions, which are closely related to tumorigenesis and tumor development. In the treatment of most tumors, chemotherapeutics directly or indirectly (e.g. demethylation and acetylation) upregulates *GADD*45*A* expression and improves the drug sensitivity of cancer cells. Meanwhile, overexpression of *GADD*45*A* can interfere with radiation resistance during radiotherapy. However, for a few tumors, the expression of *GADD*45*A* can increase the survival rate of cancer cells. Here the roles and mechanism of *GADD*45*A* in tumor therapy are mainly reviewed.

Key words: *growth arrest and DNA damage-inducible* 45*A* (*GADD*45*A*); tumor therapy; apoptosis; cell cycle arrest; cell resistance; radiotherapy sensitivity

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美国癌症学会在线发表的《2018 年全球癌症统计数据》指出, 我国癌症发病率、死亡率均居全球第一[1]。显然, 癌症已成为威胁我国国民生命健康的一大因素。肿瘤的发生发展是一个复杂的过程, 其中 DNA 损伤修复机制的缺陷与之密切相关。肿瘤抑制因子 P53 及其调控的 DNA 损伤修复蛋白, 在多种生物学功能中发挥关键作用。

生长阻滞和 *DNA* 损伤基因 45*A* (*growth arrest and DNA damage-inducible* 45*A*, *GADD*45*A*)是第 1 个被发现的经由 P53 激活的应激诱导基因, 又名 *GADD*45 或 *DDIT*1, 位于人染色体 1p31.1~31.2[2], 共有 3 个转录本, 大小分别为 135 2 bp、125 0 bp

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和 111 4 bp。其编码的生长阻滞与 DNA 损伤诱导蛋白 GADD45α 的相对分子质量为 18.4 kD, 主要定位于细胞核, 与 GADD45β、GADD45γ、GADD34、GADD153 共同构成 GADD 家族[3]。大量研究表明, *GADD45A* 可以诱导 DNA 损伤修复[4-5]、细胞接触抑制[6]、细胞周期阻滞[7]、细胞凋亡和衰老[8], 抑制肿瘤转移[9]、血管形成[10]和自噬[11]。*GADD45A* 不仅与基因组的稳定性有关, 而且与肿瘤的发生发展关系密切, 并在肿瘤治疗中发挥着不同甚至相反的作用。

1　*GADD45A* 在肿瘤发生发展中的作用机制

文献显示, 与正常组织相比, *GADD45A* 在多种肿瘤(结直肠癌[5, 12]、乳腺癌[13]、膀胱癌[14]、宫颈癌[15]等)中的表达水平均有不同程度的下调。相反, *GADD45A* 表达高的食道癌病人的整体生存率明显升高[16]。

研究表明, *GADD45A* 响应紫外线辐射信号从而调节核苷酸切除 DNA 修复, 是保护表皮免受紫外线诱导形成皮肤肿瘤的关键因素[4]。P53 蛋白与 DNA 聚合酶β作用可激活 *GADD45A* 的转录, 增强其与增殖细胞核抗原(proliferating cell nuclear antigen, PCNA)的相互作用, 形成无嘧啶核酸内切酶 1/氧化还原因子 1 (apyrimidinic endonuclease 1/redox factor 1, APE1/Ref1)-GADD45α-PCNA 蛋白复合物并定位于人结肠癌细胞的细胞核, 从而促进碱基切除修复[5]。在 P53 功能正常的情况下, GADD45α 减少细胞周期蛋白 cyclin B1 的核水平, 并通过改变亚细胞定位来抑制 Cdc2 激酶活性, 诱导细胞周期 G2/M 阻滞和生长抑制[7]。已有研究报道, *GADD45A* 通过增强β连环素(β-catenin)与小窝蛋白 1 (caveolin-1)的相互作用, 诱导β-catenin 从胞核和胞质易位至细胞膜而增强其稳定性, 以维持细胞间黏附/接触抑制, 抑制肿瘤的发生[6, 17]。在 Ras 蛋白驱动的乳腺癌中, *GADD45A* 可以激活 c-Jun 氨基端激酶(c-Jun N-terminal kinase, JNK)通路, 促进癌细胞的凋亡; 同时, 其也可以激活 P38, 促进乳腺癌细胞的衰老[8]。在髓母细胞瘤细胞中过表达 *GADD45A*, 可上调 P53 的表达, 进而经基质金属蛋白酶-9 (matrix metallopeptidase-9, MMP-9)抑制肿瘤细胞转移[9]。过表达 *GADD45A* 可以破坏哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)与信号转导及转录活化因子 3 (signal transducer and activator of transcription 3, STAT3)的联系, 抑制 STAT3 的磷酸化, 并导致血管内皮生长因子α (vascular endothelial growth factor alpha, VEGFα)的表达下调, 进而抑制宫颈癌细胞血管形成[10]。此外, *GADD45A* 通过与 Beclin1 相互作用, 破坏 Beclin1-PIK3C3 (phosphatidylinositol 3-kinase, catalytic subunit type 3)复合物, 损坏自噬起始复合物的形成, 进而抑制食管癌细胞自噬[11]。*GADD45A* 在上述恶性肿瘤中涉及的主要生物学功能如表 1 所示, 发挥这些生物学功能所涉及的信号通路如图 1 所示。

2　*GADD45A* 在肿瘤化学治疗中的作用

2.1　*GADD45A* 与化疗药物

化疗药物主要通过影响肿瘤细胞的基因表达或者信号通路, 使肿瘤细胞受到抑制或致死, 以达到治疗肿瘤的效果。研究表明, *GADD45A* 可能是多种化疗药物的作用靶点之一。非甾体类抗炎药(non-steroidal anti-inflammatory drugs, NSAIDs)能够诱导黑色素瘤、卵巢癌、血癌细胞表达黑色素瘤分化相关基因-7/白细胞介素-24 (melanoma differentiation associated gene-7/interleukin-24, MDA-7/IL-24), 激活 *GADD45A* 及下游促分裂原活化的蛋白激酶(mitogen-activated protein kinase, M-

表 1　*GADD45A* 在肿瘤进展中的作用
Table 1　The role of *GADD45A* in tumor progression

Biological function	Tumor type	Promotion/Inhibition
DNA damage repair	Skin cancer[4], colorectal cancer[5]	Promotion
Apoptosis	Breast cancer[8]	Promotion
Cell cycle arrest	Colorectal cancer[7]	Promotion
Autophagy	Esophageal cancer[11]	Inhibition
Angiogenesis	Cervical cancer[10]	Inhibition
Metastasis	Medulloblastoma[9]	Inhibition
Cell senescence	Breast cancer[8]	Promotion
Cell-cell adhesion/contact inhibition	Cervical cancer, colorectal cancer, glioma[6, 17]	Promotion

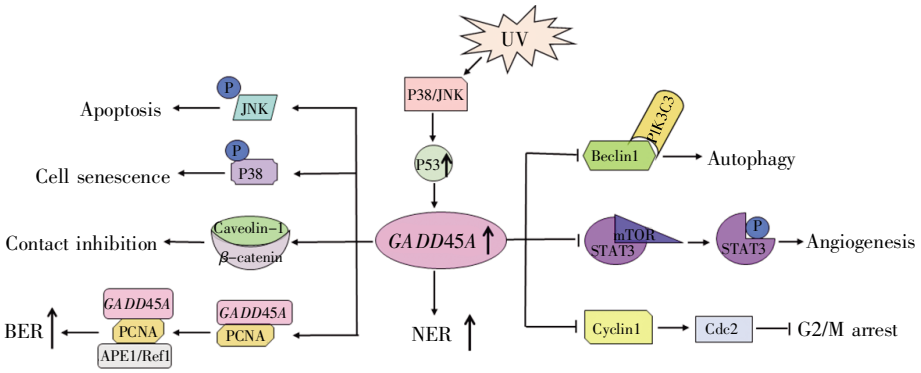

图 1 *GADD45A* 在肿瘤发生发展中的作用机制

NER: 核苷酸切除修复; BER: 碱基切除修复。

Fig.1 Mechanism of *GADD45A* in tumorigenesis

NER: Nucleotide excision repair; BER: Base excision repair.

APK)/JNK 以促发凋亡, 同时抑制 Cdc2-cyclin B 检查点激酶以激发生长阻滞[18~20]。5-氟尿嘧啶(5-fluorouracil, 5-FU)治疗可使结肠癌细胞 S 期阻滞, P53 积累, 同时上调 *GADD45A* 并通过 FAS 途径诱导凋亡[21~22]。在人结肠癌细胞中, 黄芩素诱导孕酮和 *GADD45A* 的上调, 促进 MAPK 的激活, 并在 *GADD45A* 和 JNK/P38 之间形成正反馈环, 从而引起肿瘤细胞明显的凋亡反应[12]。黄连素激活 P53 及其与线粒体 Bax 和 Bim 相互作用的下游靶标 GADD45α, 诱导 B 细胞淋巴瘤细胞凋亡[23]。穿心莲中分离出的 14-脱氧-11, 12-二脱氢穿心莲内酯(14-deoxy-11,12-didehydroandrographolide, 14-DDA)可诱导内质网液泡和自噬体的形成, 激活 *GADD45A*, 并通过 *GADD45A*/P38 MAPK/DDIT3 通路诱导乳腺癌细胞发生自噬而死亡[24]。

在一些优化的化疗药物中, *GADD45A* 也显示出其作为治疗靶点的潜在可能性。顺铂类似物 PN149 可有效规避顺铂耐药性, 提高 P53 水平, 上调 *GADD45A*, 诱导凋亡和细胞周期阻滞, 提高肿瘤治疗效果[25]。滔罗定(taurolidine, TRD)能够降低肿瘤坏死因子相关凋亡诱导配体(tumor necrosis factor related apoptosis-inducing ligand, TRAIL)的毒性和剂量, 上调 *GADD45A*, 触发食道癌细胞凋亡[26]。具有抗癌作用的绿茶儿茶素与抗癌药物(如他莫昔芬、COX-2 抑制剂和维甲酸等)联用, 可以增加 GADD45α 的表达, 诱导癌细胞凋亡[27]。拓扑异构酶Ⅱ α 抑制剂视黄酸 B (retigeric acid B, RB)可激活 ATM (ataxia telangiectasia mutated)、ATR (ataxia telangiectasia and RAD3), 并进一步通过激活其下游 P53 的表达上调 *GADD45A*, 最终诱导细胞凋亡[28]。砷(As)作为一种用于急性早幼粒细胞白血病(acute promyelocytic leukemia, APL)和多发性骨髓瘤(multiple myeloma, MM)的有效化学治疗剂, 在肝癌中可通过触发 *GADD45A* 活化 JNKs/AP-1 细胞死亡途径, 有效诱导癌细胞凋亡, 而对于正常肝细胞的毒害作用很小[29]。庆大霉素是常用的抗微生物剂, 其可通过上调 *GADD45A* 抑制胃癌细胞增殖, 诱发细胞凋亡[30]。

2.2 *GADD45A* 与肿瘤细胞耐药性

化学疗法是治疗癌症的有效手段之一, 但癌细胞可以同时对多种药物产生抗药性, 甚至是对新的药物都有耐药性, 这严重阻碍了化学疗法的有效性[31]。现有研究显示, *GADD45A* 基因同样展现出了其在肿瘤耐药性中的作用, 有望为癌症化疗耐药的预防提供新靶标。

在肺鳞癌患者中, 顺铂治疗导致 lncRNA SF-TA1P 呈现高表达, 并通过上调 hnRNP U-*GADD-45A* 轴来增强凋亡, 进而增高癌细胞的药物敏感性[32]。Chk1 抑制剂可通过抑制 ATR/Chk1 诱导 *GADD45A* 的表达, 从而有效地触发高危髓母细胞瘤(c-Myc 高表达)的死亡, 因此靶向 ATR/Chk1 可有效地增强顺铂的抗癌功效, 并且在非癌性神经元细胞中具有良好的耐受性[33]。在胆管癌细胞中敲除高表达的 *S100P* 基因可上调 *GADD45A*, 抑制细胞的增殖, 促进细胞周期阻滞, 增加化疗药物敏感性[34]。在淋巴瘤细胞中沉默 *PKCη* 基因可诱导 *GADD45A* 表达升高, 激活 P38, 进而促进细胞周期阻滞, 使细胞对化疗药物敏感[35]。雌二醇通过激活长期雌激素剥夺(long-term estrogen deprivation, LTED)乳腺癌细胞的 AMP 活化蛋白激酶(AMP activated protein kinase, AMPK), 上调 FOXO3 的靶基因 *Bim*、*FasL* 和 *GADD45A*, 介导凋亡和

G2/M 期阻滞; 相反, 雌二醇抑制野生型乳腺癌细胞 AMPK 的激活, 并阻止细胞的凋亡, 最终提高雌激素依赖的乳腺癌细胞对雌二醇的敏感性[36]。分泌簇蛋白(secretory clusterin, sCLU)在肝癌组织中过表达导致总生存率差、耐药性高, 而过表达 *GADD45A* 可通过影响 Akt 激酶的磷酸化水平调控线粒体凋亡, 克服细胞耐药性[37]。尽管在多种癌症中过表达 *GADD45A* 可以明显提高细胞的药物敏感性, 但也有研究显示 *GADD45A* 可以保护黑色素瘤细胞和胶质瘤细胞免受化疗药物毒性[38~39], 这体现了 *GADD45A* 功能的复杂性。

2.3 *GADD45A* 与靶向表观遗传的小分子药物

肿瘤细胞的致癌作用不仅与遗传改变有关, 还涉及表观遗传修饰改变, 例如 DNA 甲基化、组蛋白修饰和非编码 RNA 表达, 从而使其逃避化学疗法和宿主免疫监视。越来越多的证据表明, 由表观遗传变化控制的基因表达对癌症的发生和进展也至关重要[40~41], 因而可以使用小分子药物靶向表观遗传酶和调节蛋白, 使其成为肿瘤治疗干预的良好靶标[42~44]。

研究表明, GADD45α 是一种参与维持基因组稳定性、DNA 修复和抑制细胞生长的核蛋白[45~46], 通过促进 DNA 修复来缓解表观遗传基因沉默, 从而使整体 DNA 脱甲基[47]。葡萄糖剥夺可以上调 DNA 甲基化沉默的 *GADD45A* 的表达, 为癌症治疗提供了新的策略[48]。DNA 甲基化酶(DNA methylase, DNMT)抑制剂地西他滨处理细胞能够激活 *GADD45A* 的表达, 诱导基因组 DNA 脱甲基[49~50], 而 PRIMA-1 (P53 reactivation and induction of massive apoptosis)通过抑制 DNMT 及上调 *GADD45A* 的表达, 诱导 P53 突变型癌细胞发生整体 DNA的脱甲基[51], 最终诱导癌细胞对抗肿瘤药物的敏化作用[49~51]。相关研究报道, 地西他滨联合相应小分子抑制剂能够调控细胞周期相关基因 *GADD45A* 和 *CDKIN1A* 的表达, 上调 MEK/ERK、JAK-STAT 和 NF-κB, 增加脱甲基效率, 抑制霍奇金淋巴瘤细胞生长, 提高地西他滨的治疗效果[52]。

此外, *GADD45A* 也被证明在一些靶向组蛋白修饰酶的小分子药物的作用通路中发挥作用。组蛋白去乙酰化酶抑制剂(histone deacetylase inhibitor, HDACi) PCI-24781 处理骨肿瘤细胞使乙酰化组蛋白积累, 诱导 *GADD45A* 表达, 激发凋亡, 逆转细胞耐药性, 使其对化疗药物更加敏感[53~54]。曲古菌素(trichostatin A, TSA)是一种特异的组蛋白去乙酰化酶类型Ⅰ和Ⅱ抑制剂, 通过 ATM 介导的通路诱导 *GADD45A* 表达, 导致肿瘤细胞凋亡[55~56]。小分子药物 LBH589 则通过组蛋白(H3K9 和 H4K8)的乙酰化上调 *GADD45A*, 诱导细胞周期停滞和凋亡[57]。我们课题组也发现, 新型组蛋白去乙酰化酶抑制剂 PXD101 能够显著抑制胶质瘤细胞的增殖、转移, 促进凋亡, 而进一步的机制研究显示 *GADD45A* 是其发挥抑瘤作用的重要靶标(数据尚未发表)。

3 *GADD45A* 在肿瘤放射治疗中的作用

电离辐射(ionizing radiation, IR)治疗也是癌症患者常用的治疗方法之一[58], 不仅有助于局部控制目标病灶, 而且还可以控制远端的转移灶[59]。IR 治疗的临床功效归因于其诱导 DNA 损伤导致直接的肿瘤细胞死亡[60]。无论放射敏感还是放射抵抗的肿瘤, 探究使肿瘤细胞对 IR 敏感的分子和机制可以为癌症治疗提供新的分子靶标。

众所周知, 正常细胞通过葡萄糖氧化提供能量, 而癌细胞则通过瓦博格效应(Warburg effect)改变自身的遗传和表观状态, 从而促进癌细胞的生长和侵袭[61]。研究发现, 用糖酵解抑制剂 2-脱氧-D-葡萄糖(2-deoxy-D-glucose, 2-DG)预处理癌细胞, 经 IR 处理后可激活 *GADD45A* 的表达, 诱发细胞死亡[62]。在人舌鳞状细胞癌中, IR 可以诱导癌细胞表达 *GADD45A*, 增加癌细胞对 IR 的敏感性[63]。对于髓母细胞瘤, IR 处理可以激发肿瘤细胞 *GADD45A* 的表达, 促进细胞周期的阻滞, 还可以下调 MMP-9, 抑制肿瘤转移, 使髓母细胞瘤细胞对放射治疗敏感[9]。在宫颈癌细胞中, *GADD45A* 通过抑制内皮型一氧化氮合酶(endothelial nitric oxide synthase, eNOS)和诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS), 进一步抑制 NO 调节 APE1 的胞质定位, 从而增强宫颈癌细胞的放射敏感性; 相反, *GADD45A* 表达的降低显著促进放射抵抗的发展[15]。对于一些具有放射抵抗的癌症, 例如胰腺癌, 放射增敏剂 DPS (darinaparsin)结合放射线治疗能激发 *GADD45A* 表达, 同时保护正常肠隐窝上皮细胞, 诱导癌细胞在 G1/S 和 G2/M 发生细胞周期阻滞[64]。胶毒素(gliotoxin)结合放射治疗可抑制 *GADD45A* -P38-NF-κB 介导的生存途径, 激发肝癌细胞凋亡, 从而提高放疗效果[65]。此外, 肿瘤周围微环境中的癌症相关成纤维细胞及癌细胞之间的串扰可降低 GADD45α 水平,

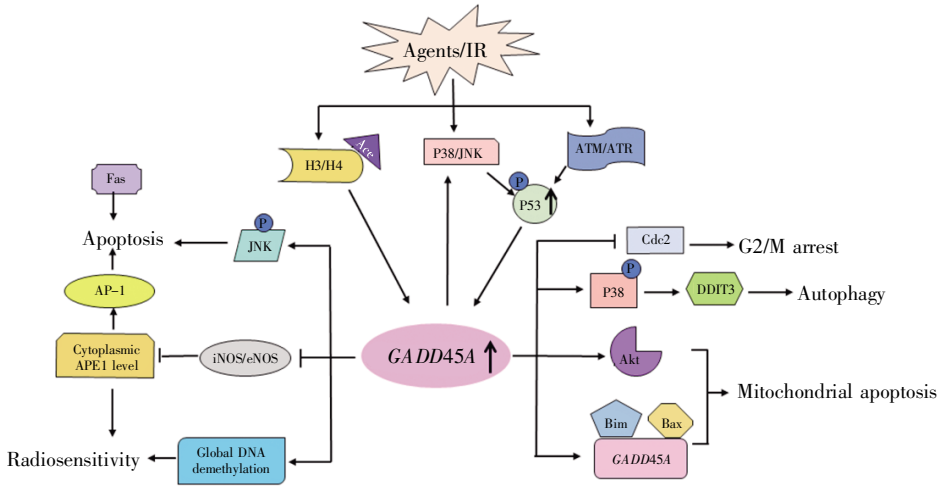

图 2 *GADD45A* 在肿瘤治疗中的作用机制

Fig.2 The roles of *GADD45A* in tumor therapy

表 2 *GADD45A* 在肿瘤治疗中的作用

Table 2 The roles of *GADD45A* in tumor therapy

	Therapy	Biological function	Tumor type
Chemotherapy	NSAIDs	Apoptosis activation	Melanoma, ovarian cancer, acute myeloid leukemia[18-20]
	Baicalein	Apoptosis activation	Colon cancer[12]
	Cisplatin	Apoptosis activation	Lung cancer, medulloblastoma[32-33]
	PN149	Apoptosis activation	Bladder cancer[25]
	TRD	Apoptosis activation	Squamous cancer[26]
	RB	Apoptosis activation	Prostate cancer[28]
	Arsenite	Apoptosis activation	Liver cancer, gastric cancer[29]
	Gentamicin	Apoptosis activation	Gastric cancer[30]
	Combination green tea catechins and anticancer drugs	Apoptosis activation	Lung cancer[27]
	Estradiol	Apoptosis activation	LTED breast cells[36]
	Estradiol	Apoptosis inhibition	Wild type breast cells[36]
	5-FU	Apoptosis-regulatory pathways (FAS)	Colon cancer[21-22]
	Berberine	Mitochondrial apoptosis	B cell lymphoma 9[23]
	Combination anticancer drugs with over-expression of *GADD45A*	Mitochondrial apoptosis	Hepatocellular carcinoma[37]
	NSAIDs	Cell cycle arrest	Melanoma[18]
	PN149	Cell cycle arrest	Bladder cancer[25]
	Combination anticancer drugs with over-expression of *GADD45A*	Cell cycle arrest	Cholangiocarcinoma[34]
	Estradiol	Cell cycle arrest	Breast cancer[36]
	14-DDA	Autophagy activation	Breast cancer[24]
	Methylase inhibitor 5-aza-2′-deoxycytidine	Demethylation	Pancreatic cancer[49]
	PRIMA-1	Demethylation	Thyroid cancer[51]
	Combination 5-aza-2′-deoxycytidine with small molecular weight inhibitors	Demethylation	Hodgkin lymphoma[52]
	PCI-24781	Acetylation	Bone sarcoma[53-54]
	TSA	Acetylation	Colon cancer, cervical cancer[55-56]
	LBH589	Acetylation	Leukemia[57]
Radiotherapy	Glycolytic inhibitor 2-DG	Apoptosis	Glioma[62]
	Over-expression of *GADD45A*	Apoptosis	Tongue squamous cell carcinoma, cervical cancer[63, 66]
	Gliotoxin	Cell cycle arrest	Hepatocellular carcinoma[65]
	DPS	Cell cycle arrest	Thyroid cancer[64]
	IR	Cell cycle arrest	Medulloblastoma[9]

进而抵抗放射治疗[66]。

4　总结与展望

综上所述, 作为一个细胞生长阻滞和 DNA 损伤调节基因, *GADD45A* 参与了调控细胞周期、细胞凋亡、DNA 损伤修复、自噬、信号转导等多种生物学过程, 在维持基因组稳定性和抑制肿瘤发生发展的过程中发挥重要的作用。正如表 2 和图2所示, *GADD45A* 在癌症治疗中具有两面性, 其作为抑癌基因还是促癌基因发挥作用, 可能与肿瘤类型、涉及的信号通路以及其所处的肿瘤微环境密不可分。目前的研究对 *GADD45A* 的了解还比较有限, 因此, 未来亟需从基础研究与临床转化的角度, 寻找 *GADD45A* 上、下游新的调控分子, 筛选和鉴定其新的互作蛋白质或 RNA 分子, 挖掘其与肿瘤微环境(如外泌体、肿瘤相关成纤维细胞、免疫细胞等)的联系, 以及其在表观遗传修饰(甲基化、组蛋白修饰等)中扮演的角色。总的来讲, 深入研究 *GADD45A* 在重要生理与病理发生中的机制, 可为肿瘤临床治疗提供新靶标及相关治疗策略, 在抗肿瘤中具有重要价值。

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