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·专家论坛·

DNA 甲基化与卵巢癌多药耐药及预后的关系

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[摘 要] **目的**:卵巢癌是严重威胁女性健康的疾病,病死率居妇科恶性肿瘤之首。多药耐药是卵巢癌患者术后化疗失败的主要原因,而DNA甲基化则是卵巢癌多药耐药调控的重要机制,因此全面了解DNA甲基化对卵巢癌多药耐药的调控机制对于卵巢癌治疗和预后具有重要意义。通过PubMed数据库检索,笔者共提取了26个与卵巢癌多药耐药调控显著相关的DNA甲基化基因,系统整合分析了这些基因甲基化水平改变对卵巢癌耐药的影响及其分子调控机制。在所有26个基因中,至少一半以上的DNA甲基化基因直接或间接地通过调控细胞凋亡信号通路响应耐药调控,说明该信号通路可能是DNA甲基化基因行使其耐药生物学功能的主要方式。另外,分析这26个卵巢癌耐药相关甲基化基因与患者临床预后的关系,表明上述基因主要与不良预后相关。总之,深入探讨DNA甲基化基因与卵巢癌耐药和预后的潜在关系,对于充分认识DNA甲基化对卵巢癌耐药的调控及提高卵巢癌的疗效和改善预后具有一定的指导意义。

[关键词] DNA甲基化;卵巢癌;耐药;预后
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The relationship of DNA methylation with multidrug resistance and prognosis in ovarian cancer

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[**Abstract**] Ovarian cancer is a malignant tumour that poses a serious threat to women's health. In most cases of ovarian cancer, drug resistance develops in the course of post-surgery chemotherapy. It has been well documented that DNA methylation is one of the important regulatory mechanisms underlying the development of multidrug resistance in ovarian cancer patients. However, the relationship between DNA methylation and drug resistance and clinical prognosis has yet to further understood. Through an electronic search of the PubMed database, we have identified 26 methylated genes that have been reported to be associated with the regulation of ovarian cancer drug resistance. Among these genes, at least half respond to ovarian cancer drug resistance by directly or indirectly regulating signaling pathways involved in cell apoptosis. Moreover, we have performed an integrated analysis of the relationship between these 26 methylated genes and the behav-

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iour and prognosis of malignant ovarian cancer and have found that DNA methylation is primarily associated with poor prognosis. Herein in this review paper, we attempt to present the general information on the 26 identified methylated genes related to drug resistance, outline the putative molecular mechanisms through which DNA methylation affect drug resistance and discuss the possible strategies for reverse how the DNA methylation-induced drug resistance to improve prognosis in malignant ovarian cancer.

[**Keywords**] DNA methylation; ovarian cancer; drug resistance; prognosis

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MHL1	mutL homolog 1
BRCA1	breast cancer 1
FBXO32	F-box protein 32
DNAJC15	DnaJ (Hsp40) homolog, subfamily C, member 15, also known as MCJ
CSAG2	CSAG family, member 2 , also known as TRAG-3
PROM1	prominin 1, also known as CD133
ASS1	argininosuccinate synthase 1
RASSF1	Ras association (RalGDS/AF-6) domain family member 1
PTEN	phosphatase and tensin homolog
TNFRSF10A	tumor necrosis factor receptor superfamily, member 10, also known as DR4
ABCG2	ATP-binding cassette, sub-family G (WHITE), member 2
ZMYND10	zinc finger, MYND-type containing 10
MDR1	ATP-binding cassette, sub-family B (MDR/TAP), member 1, also known as ABCB1
TGFBI	transforming growth factor, beta-induced, 68 kDa
RGS10	regulator of G-protein signaling 10
UCHL1	ubiquitin carboxyl-terminal esterase L1
Sulf-1	sulfatase 1
SFRP	secreted frizzled-related protein
MALmal	T-cell differentiation protein
TUBB3	tubulin, beta 3 class Ⅲ
LITD1	LINE-1 type transposase domain containing 1, also known as LINE1
CLDN4	claudin 4
HOXA9	homeobox A9
HOXA10	homeobox A10
HOXA11	homeobox A11
FANCF	Fanconi anemia, complementation group F

卵巢癌是严重威胁妇女健康常见的恶性肿瘤,其中上皮性恶性肿瘤是其主要种类,占所有卵巢恶性肿瘤的 85% ~90%,病死率为女性生殖道恶性肿瘤之首。约有 70% 的卵巢癌患者发现时已是晚期,而其中绝大多数在手术后的化疗过程中又极易产生耐药,从而大大降低了治疗效果,导致卵巢癌 5 年生存率仅为 30%[1]。因此,多药耐药是现阶段卵巢癌化疗失败的主要原因。已有研究表明,多药耐药是一个多基因或蛋白参与的,多步骤、多因素综合交叉作用的结果,涉及多种不同的调控机制,而表观遗传学调控是卵巢癌多药耐药发生发展的重要调节机制之一[2]。表观遗传学修饰是研究在基因的核酸序列没有改变的情况下,发生的可遗传的基因表达的改变[3],包括 DNA 甲基化、组蛋白修饰、染色质改型和 microRNA 修饰等[4],它们在基因转录调控过程中起着重要作用。作为表观遗传学调控的主要方式之一,DNA 甲基化与卵巢癌多药耐药及卵巢癌预后有密切关系[5],因此,综合研究其作用机制对卵巢癌的诊断和治疗都有重要意义。

DNA 甲基化是指在 DNA 甲基转移酶(DNA methytransferase, DNMT)的作用下,以 S-腺苷-L-甲硫氨酸(S-adenosy-L-methionine, SAM)为甲基供体,将甲基转移到胞嘧啶的 5 位碳原子上,生成 5-甲基胞嘧啶(5-methlcytosine)过程。DNA 甲基化包括全基因组的低甲基化和启动子区 CpG 岛的超甲基化,其中 CpG 岛的超甲基化能导致基因的表达水平下降甚至沉默,并最终在包括卵巢癌在内的肿瘤调控中发挥重要作用[6]。DNA 甲基化在卵巢癌多药耐药调控中发挥着至关重要的作用,本文重点讨论 DNA 甲基化对卵巢癌多药耐药的调控机制及对卵巢癌预后的影响。

1　卵巢癌耐药相关 DNA 甲基化基因的数据挖掘和耐药机制分析

利用 PubMed 数据库检索并筛选出与卵巢癌多药耐药相关的 DNA 甲基化基因文献,共挖掘出 26 个与卵巢癌耐药显著相关的 DNA 甲基化基因,包括 *MLH1*、*BRCA1*、*FBXO32*、*DNAJC15*、*CSAG2*、*PROM1*、*ASS1*、*RASSF1*、*PTEN*、*TNFRSF10A*、*ABCG2*、*ZMYND10*、*MDR1*、*TGFBI*、*RGS10*、*UCHL1*、*Sulf-1*、*SFRP*、

MAL、*TUBB3*、*L1TD1*、*CLDN4*、*HOXA10*、*HOXA9*、*HOXA11* 和 *FANCF*(表 1)。在上述基因中,除 *CSAG2*、*MDR1*、*TUBB3*、*L1TD1*、*FANCF* 和 *HOXA10* 等 6 个基因外,其余所有基因在卵巢癌耐药组织或细胞中均呈高甲基化和低表达状态。据此推测,相对于低甲基化而言,DNA 高/超甲基化状态可能是卵巢癌耐药调控的主要方式。此外,部分基因如 *ABCB1*(*MDR1*)基因和 *MAL* 基因,其甲基化状态及表达水平与肿瘤发生和肿瘤耐药的确切关系尚不明了。比如 Eyre 等[7]发现,*ABCB1*(*MDR1*)基因在卵巢癌紫杉醇耐药细胞中呈现低甲基化和高表达状态,并且通过影响肿瘤干细胞导致卵巢恶性肿瘤的转移及化疗抵抗。Hatle 等[8]指出,该基因在卵巢癌耐药细胞中发生了 DNA 超甲基化,而由其导致的基因下调表达通过 c-Jun/JNK 信号通路参与卵巢癌发生发展及卵巢癌多药耐药的形成。

DNA 甲基化在卵巢癌耐药发生发展中的调控机制比较复杂,其耐药调控机制包括基因错配修复、基因微卫星灶不稳定性、细胞损伤修复缺陷、细胞识别 DNA 能力减弱、细胞增殖异常、细胞凋亡、细胞生长、细胞侵袭及转移、阻止细胞内药物累积以及相关的信号通路等(表 1)。

表 1　26 个 DNA 甲基化基因与卵巢癌多药耐药相关性的综合分析

基因	甲基化状态	基因表达	药 物	耐药调控机制	去甲基化逆转耐药	参考文献
MLH1	高	沉默	铂类	DNA 损伤修复,细胞增殖,细胞凋亡	是	[17-19]
BRCA1	低	上调	顺铂	DNA 修复	否	[20-21]
FBXO32	高	沉默	铂类	细胞凋亡,细胞侵袭,TGF-β/SMAD4 通路	是	[22]
DNAJC15	高	下调	铂类和紫杉醇	阻止细胞内药物累积	是	[8, 23-24]
CSAG2	低	上调	紫杉醇	–	是	[25]
PROM1	低	上调	铂类	肿瘤干细胞通路	否	[25-26]
ASS1	高	沉默	铂类	–	–	[27]
RASSF1	高	沉默	紫杉醇	细胞凋亡,RAS 信号通路	是	[28-29]
PTEN	高	沉默	紫杉醇	细胞凋亡,PI3K/AKT 通路	是	[30-32]
DR4	高	沉默	铂类	细胞凋亡,细胞侵袭;TRAIL	是	[33-34]
ABCG2	低	上调	多药耐药	受基因 BAF57 调控,干扰细胞生长过程及 BCRP/ABCG2 通路	否	[14-15,35]
BLU	高	下调	铂类和紫杉醇类	细胞生长,细胞凋亡,AKT 通路	是	[9, 36]
MDR1	低[7] 高[8]	高[7] 沉默[8]	紫杉醇[7] 多药耐药[8]	信号通路 c-Jun/JNN 通路,药物代谢,细胞凋亡	–	[8,16,38]
TGFBI	高	沉默	紫杉醇	细胞增殖;细胞外基质	是	[39-40]
RGS10	高	下调	铂类	细胞凋亡	是	[41]
UCHL1	高	下调	顺铂	细胞凋亡,细胞增殖, AKT 通路	是	[10]
Sulf-1	高	沉默	铂类	通过调节 Bim 蛋白表达,细胞凋亡,新陈代谢	是	[37,42]
SFRP	高	沉默	顺铂	细胞生长,细胞增殖,细胞侵袭,Wnt 通路;EMT 和 AKT2 信号通路	–	[11, 43]
MAL	高	下调	顺铂	细胞内药物累积	是	[44-45]
TUBB3	低	上调	紫杉醇	–	–	[46-47]
LITD1	低	上调	铂类	调控基因组稳定性	是	[48]
CLDN4	高	沉默	顺铂	细胞侵袭,细胞转移,β-连环蛋白信号通路,P13K/AKT 通路	是	[13, 49-51]
HOXA10	低	上调	铂类	细胞增殖,细胞迁移,细胞侵犯[53]	是	[5,52-53]
HOXA9	高	下调	铂类	Wnt 通路,细胞凋亡	是	[5,54-55]
HOXA11						
FANCF	低	上调	烷化剂和顺铂	基因的错配修复,FA/BRCA 通路,FA 通路	否	[56-57]

–:表示未见相关报道

其中,至少有 11 个基因(*MLH1*、*PTEN*、*FBXO32*、*RASSF1*、*TNFRSF10A*、*BLU*、*RGS10*、*UCHL1*、*MDR1*、*Sulf-1*、*HOXA9*)通过细胞凋亡参与耐药调控,至少有 5 个基因(*MLH1*、*TGFBI*、*UCHL1*、*SFRP*、*HOXA10*)通过细胞增殖参与耐药调控;另外,至少有 5 个基因(*PTEN*、*BLU*、*UCHL1*、*SFRP*、*HOXA10*)通过直接或间接参与 AKT 信号通路调节细胞凋亡和细胞增殖,最终响应多药耐药调控。由此可见,DNA 甲基化基因可能主要通过细胞凋亡或细胞增殖途径而发挥其卵巢癌多药耐药调控作用,而细胞凋亡途径在卵巢癌耐药发生发展中可能显示出更为重要的地位。比如,肿瘤抑制基因 BLU 通过下调 *Bcl-2* 以及上调 *Bax*、*P21* 及 *P53* 发挥抑癌基因的作用,参与细胞凋亡并最终响应卵巢癌细胞对紫杉醇的耐药性[9]。又如 *UCHL1* 在卵巢癌细胞中通过促进细胞凋亡的作用而增加卵巢癌细胞对顺铂化疗的敏感性[10]。此外,肿瘤抑制基因 *SFRP* 参与 *Wnt* 通路的负性调节,与体内多种肿瘤的形成相关。该基因在卵巢癌的耐药组织中为高甲基化改变和基因沉默表达。去甲基化后该基因的重新表达,通过下调 AKT 信号通路调节细胞凋亡,从而增加卵巢癌细胞对铂类的敏感性。*SFRP5* 的重新表达还通过削弱卵巢癌中 Wnt 的信号通路,抑制肿瘤细胞的生长,削弱其致瘤性[11]。近期又有研究[12]表明,基因 *DOK2* 卵巢癌组织中通过细胞调亡机制参与了卡铂耐药的过程。综上结果说明,细胞凋亡可能是 DNA 甲基化基因发挥卵巢癌耐药调控的重要方式,而深入研究 DNA 甲基化基因对细胞凋亡的调节作用有望为逆转卵巢癌耐药提供更多的可能性。

除细胞凋亡、细胞增殖、AKT 信号通路外,DNA 甲基化基因还可以通过其他的机制参与卵巢癌的耐药。如封闭蛋白家族成员 *CLDN4*,在卵巢癌耐药组织中发生高甲基化改变,基因沉默表达。该基因的表达缺失,可以下调 E-钙黏素的表达,激活 β-连环蛋白信号通路,增强去磷酸化作用,增强细胞的侵犯和转移能力,增强卵巢癌顺铂的耐药[13]。又如基因 *ABCG2* 可能在 *BAF57* 的调控下参与了细胞生长的调节过程[14],并且该基因参与的 BCRP/ABCG2 通路与卵巢癌的化疗药物的代谢相关[15],从而参与了卵巢癌的多药耐药。又如基因 *MCJ* 和 *ABCB1*[8,16],通过阻止细胞内药物的累积参与卵巢癌耐药过程。这些卵巢癌甲基化基因参与卵巢癌作用机制的一一揭示,为克服卵巢癌的耐药提供了新的思路。

2　DNA 甲基化基因与卵巢癌预后及卵巢癌耐药逆转

分析部分 DNA 甲基化基因与卵巢癌恶性生物学行为及预后密切相关(表 2)。相当一部分 DNA 甲基化基因与卵巢癌侵袭相关,如 *MLH1*、*FBXO32*、*PROM1*、*RASSF1*、*PTEN*、*SFRP*、*TUBB3*、*L1TD1* 和 *CLDN4* 等,它们在卵巢癌耐药组织或者细胞中均呈现出高甲基化状态,并最终基因沉默表达,导致肿瘤细胞侵袭,其中 *MLH1*、*FBXO32* 和 *TUBB3* 与卵巢癌淋巴结转移相关,值得注意的是 *HOXA10* 的低甲基化与卵巢癌转移行为有关,但是 *HOXA10* 的高表达却会导致卵巢透明细胞腺癌细胞增殖,迁移和侵袭,最终导致患者预后不良[53]。部分 DNA 甲基化改变与卵巢癌的肿瘤类型、病理分级及临床分期等临床病理因素也呈显著相关性。与卵巢癌肿瘤类型或者病理分级相关的有 *MLH1*、*BRCA1*、*PTEN*、*PROM1*、*UCHL1*、*ABCG2*、*L1TD1*、*DR4*、*RASSF1*、*MDRI* 和 *HOXA10*,与卵巢癌临床分期相关的有 *FBXO32*、*RASSF1*、*PTEN*、*UCHL1*、*SFRP*、*MAL*、*TUBB3*、*L1TD1*、*MDR1*、*Sulf-1* 和 *FANCF*。有国内学者[58]指出,相比于其他肿瘤类型,*BRCA1* 的超甲基化在浆液性和高级别卵巢癌中更为常见,而在黏液性和低级别卵巢癌中,*PTEN* 的超甲基化更为多见。除此之外,*MLH1*、*BRCA1*、*ASS1*、*SFRP*、*MDR1*、*CYP39A1*[59]、*SOX1* 及 *LMX1A*[60]等 8 个基因的 DNA 甲基化与卵巢癌复发密切相关。在已报道的 26 个与卵巢癌相关的 DNA 甲基化基因中,除 *PROM1*、*Sulf-1*、*FANCF*、*RGS10* 甲基化与卵巢癌预后无报道或无关联外,其余 22 个基因的甲基化及表达异常均与卵巢癌的预后存在统计学关联性。大多数基因的甲基化及随后基因表达的改变与卵巢癌的预后不良有关,分别表现为 OS 及 PFS 缩短,而少数基因如 *BRCA1* 和 *CSAG2* 等的甲基化改变与较长的 PFS 及 OS[7,61]相关。此外,还有研究指出,基因 *SOX1* 和 *LMX1A* 的甲基化改变除了与晚期卵巢癌密切相关外(Ⅳ期检出率分别为 83.3% 和 58.4%),尚与患者的肿瘤复发和远期生存率相关[61]。

鉴于卵巢癌耐药相关基因的 DNA 甲基化与卵巢癌预后具有显著相关性,因此,联合血浆检测 DNA 甲基化水平可能是卵巢癌临床预测及预后分析的重要途径。事实上,已有研究证明,血浆 DNA 甲基化可以成为早期卵巢癌诊断的生物学标志。在早期卵巢癌患者血浆中,*MLH1*、*BRCA1*、*RASSF1*、*TNFRSF10A* 和 *L1TD1* 等基因的甲基化状态及甲基化水平均发生显著改变。Ibanez 等[62]在 50 例卵巢癌患者血浆 DNA 中,*BRCAl* 和 *RASSF1* 基因在 68% 的患者中其启动子至少有一个处于过甲基化状态,而联合这两个基因及另外 4 个基因(*APC*,*DAPK*,

p14ARF 和 *p16INK4a*)的甲基化状态检测可使卵巢癌诊断的敏感性达到 100%,而 20 例正常女性外周血 DNA 中此 6 种基因全部甲基化阴性,即诊断的特异性也是 100%。由此可见,DNA 甲基化状态的检测,尤其是血浆中 DNA 甲基化水平的检测在卵巢癌诊断中具有广阔的应用前景。这就为早期诊断卵巢癌提供了一个新的途径。

由于 DNA 超甲基化调节导致的基因下调表达在卵巢癌耐药发生发展中发挥着重要作用。因此,充分利用 DNA 甲基化抑制剂等方式来逆转 DNA 的甲基化基因的表达可能是卵巢癌治疗及逆转耐药的一个重要方向。比如,*MLH1*、*FBXO32*、*TRAG-3* 等共有 15 个基因在加入了甲基化抑制剂 5-azacytidine 或 5-aza-2 deoxycytidine 后,大部分卵巢癌细胞对化疗药物的敏感性会不同程度的增加(表 2)。

表 2　卵巢癌耐药调控相关甲基化基因与卵巢癌的预后

基因	甲基化状态	组织学类型	分　级	分　期	侵　袭	复　发	预　后	血浆检测	参考文献
MLH1	高[64]	有关[64]	有关[58]	–	有关,同时与淋巴结转移有关[64]	有关	好(PFS)[5]	是	[19]
BRCA1	高	有关[58]	有关[58]	–	–	有关[65]	好(PFS)[61]	是[62,66]	[20]
FBXO32	高	–	–	有关[67]	有关	–	差(PFS,与 OS 无关)	–	[22]
DNAJC15	高	–	–	–	–	–	差(OS)[24]	–	[23-24]
CSAG2	低	–	–	–	–	–	好(PFS,OS)[7]	–	[25]
PROM1	高	有关[68]	有关[68]	–	有关	–	–	–	[69]
ASS1	高	–	–	–	–	有关	差(PFS,OS)	–	[27]
RASSF1	高	无关[70]	有关[70]	有关[70-72]	有关[64,71,73]	–	差(PFS)[5]	是[62,66]	[28-29]
PTEN	高	有关[58];无关[74,75]	有关[74]	有关[74]	有关,同时与淋巴结转移有关[76]	–	差(OS,PFS)[77]	–	[32]
DR4	高	–	有关[78]	–	–	–	差(OS,PFS)[79]	是[80]	[34]
ABCG2	高	有关[81]	有关[82]	–	有关[83]	–	差(PFS)[81]	-	[35]
BLU	高	–	–	–	–	–	差(PFS,OS)	–	[11,34]
MDR1	低[9];高[8]	无关[84]	有关[85]	有关[86]	–	有关[84]	差(PFS,OS)[85]	–	–
TGFBI	高	无关	无关	无关	–	–	与 OS 相关[87]	–	[31,40,88]
RGS10	高	–	–	–	–	–	无关联	–	[41]
UCHL1	高	有关	有关	有关	–	–	有关	–	[10,43,89]
Sulf-1	高	–	–	有关[42]	–	–	–	–	[90]
SFRP	高	–	–	有关[91,92]	有关	有关	好(OS)	–	[11]
MAL	高	–	–	有关	–	–	差	–	[45,93]
TUBB3	低	–	–	有关	有关,同时与淋巴结转移有关	–	差(PFS,OS)[94]	–	[47]
LITD1	低	有关	有关	有关	有关	–	差(PFS,OS)	是[66]	[48]
CLDN4	高	–	–	–	有关[13,50]	–	与 OS 相关[95]	–	[49]
HOXA10	低[52]	有关[96]	有关[68]	–	有关[53]	–	差(PFS)[53]	–	–
HOXA9,*HOXA11*	高	–	有关[68]		–	–	差(PFS)[94]	是[66]	[54-55]
FANCF	低	–	–	有关[97]	–	–	–	–	[57]

–:无相关研究或报道;有关:文献报道有统计学相关;无关:文献报道无统计学相关;预后好:患者生存期延长;预后差:患者生存期缩短;PFS:无进展生存期;OS:总生存时间

然而,某些基因如 *BRCA1*、*CSAG2*、*PROM1*、*ABCG2*、*L1TD1*、*HOXA10*、*FANCF* 在卵巢癌耐药组织或者细胞中呈现低甲基化状态,对于这些基因低甲基化引起的卵巢癌耐药,使用去甲基化药物反而会使得卵巢癌细胞对化疗药物的敏感性降低或者加重耐药。已有研究证明,一些基因甲基化状态的逆转能有效逆转细胞对卵巢癌化疗药物的耐受性。如 Strathdee 等[63]发现,A2780 顺铂耐药细胞中 *MLHl* 基因的甲基化水平明显高于其在敏感细胞中的水平,而用 DNA 甲基化抑制剂 5-azacytidin 处理 A2780 耐药细胞后能恢复细胞对顺铂的敏感性,同时 *MLHl* 的 DNA 甲基化水平也显著下降,说明卵巢癌细胞药物敏感性的增加至少部分是源于 *MLHl* 基因 DNA 甲基化水平的下降。又如 Kassler 等[29]发现,在卵巢癌紫杉醇耐药细胞中 *RASSF1A* 基因启动子呈高甲基化状态,而强制 *RASSF1A* 基因的高表达会提高卵巢癌细胞对紫杉醇的敏感性,这一结果说明,由 DNA 甲基化导致的 *RASSF1A* 基因的沉默表达是卵巢癌细胞对紫杉醇产生耐药的原因,而通过强制 *RASSF1A* 基因重新表达来模拟基因的去甲基化状态确能有效提高细胞对药物的敏感性。去甲基化药物已被逐渐使用,如目前临床上已使用核苷类 DNMT抑制剂如 5-氮胞苷(5-azacytidine)及其脱氧核糖类似物或氮杂胞苷(5-aza-2 deoxycytidin),及地西他滨等去甲基化药物用于肿瘤化疗。充分检测与卵巢癌耐药相关的 DNA 甲基化基因在一定程度上可以指导临床药物的选择,具有重要临床应用价值。

3　结　语

DNA 甲基化是卵巢癌耐药调控机制研究的一个重要方向。DNA 甲基化基因可能通过细胞凋亡等重要途径参与卵巢癌耐药调控,与卵巢癌临床病理因素和预后密切相关,而去甲基化导致的基因重新表达可能在一定程度上逆转卵巢癌细胞对化疗药物的耐受性,由此可见,去甲基化药物具有深远的临床应用前景。因此,充分了解 DNA 甲基化基因与卵巢癌耐药之间的潜在关系,对于深入阐明甲基化基因对卵巢癌耐药的调控作用机制,以及治疗卵巢癌和提高卵巢癌的预后具有一定的理论指导意义。

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文稿中计量单位使用的要求

本刊严格执行国务院颁发的《中华人民共和国法定计量单位》,全面贯彻国家标准 GB3100-3102-1993《量和单位》的规定,正确使用量和单位的名称和符号。(1)量符号以斜体拉丁和希腊字母表示(pH 用正体除外),例如 *m*(质量)、*t*(时间)、*c*(浓度)、*V*(体积)、*p*(压力)、*F*(力)等。(2)单位符号一律以正体拉丁或希腊字母表示,例如 kg(千克)、m(米)、h(小时)、mol/L(摩尔每升)等。(3)表示人体检验指标的量浓度或质量浓度时,一般使用 L(升)作为检验组成含量单位的分母。(4)表示用药剂量单位时,不能写成 mg/kg/d 的形式,应写成 mg/(kg · d)或 $mg \cdot kg^{-1} \cdot d^{-1}$的形式。(5)单位符号常见书写错误:长度单位符号 A°(埃)已不用,应写作 0.1 nm;时间单位“小时”符号为 h(不是 hr)、“秒”符号为 s(不是 sec);转速单位符号为 r/min(不是 rpm);量浓度单位符号为 mol/L(不是 M、N,也不是 mol/mm^3);力的单位“牛顿”符号为 N[不是 dyn(达因)、kgf(千克力),换算 1 dyn = 10^{-5} N];热量单位“焦耳”符号为 J[不是 cal(卡)、kcal(千卡),换算 1 cal = 4.187 J];放射性活度单位符号为 Bq[不是 Ci(居里),换算 1 Ci = 3.7×10^{10} Bq]。

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