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人 8-羟基鸟嘌呤 DNA 糖苷酶 1 基因低表达增加肺腺癌细胞对博来霉素的敏感性

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摘要: 目的 研究 DNA 碱基切除修复基因人 8-羟基鸟嘌呤 DNA 糖苷酶 1(hOGG1)低表达增加肺腺癌细胞对博来霉素(BLM)的敏感性的作用,为化疗增敏提供更多的实验依据。**方法** 以肺腺癌 A549 细胞和通过稳定转染 hOGG1 核酶而获得的 hOGG1 低表达的 A549-R 细胞为研究对象,用 MTT 试验和集落形成抑制试验测定不同浓度 BLM 处理后两种细胞的存活率和形成集落的能力;体外微核试验及单细胞凝胶电泳检测两种细胞微核率及 DNA 损伤与修复的差异。**结果** BLM 作用下 A549-R 细胞的 IC_{50} 及集落形成率显著低于 A549 细胞;BLM 可诱导两种细胞的微核率增高,而在相同浓度下 A549-R 细胞微核率较 A549 细胞更高;单细胞凝胶电泳结果显示,BLM 作用下两种细胞均有不同程度 DNA 损伤,A549-R 细胞的拖尾率和 DNA 迁移长度显著大于 A549 细胞;损伤后 A549 细胞修复发生较 A549-R 早,与 A549 细胞相比 A549-R 细胞更不易修复。**结论** hOGG1 低表达使肺腺癌细胞 DNA 修复能力降低,从而使其对 BLM 的敏感性增强。

关键词: 基因表达; 人 8-羟基鸟嘌呤 DNA 糖苷酶; 博来霉素; 腺癌; 肺; DNA 损伤

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博来霉素(bleomycin, BLM)是目前临床常用的一种广谱抗肿瘤药物,其治疗机制在于 BLM 介导的 DNA 氧化断裂及多种自由基的形成[1],BLM 的耐药性在很大程度上限制了其临床应用。研究发现,DNA 氧化损伤修复对于肿瘤的形成、治疗及耐药都起着非常重要的作用,临床治疗中常出现的肿瘤细胞耐药性与其 DNA 氧化损伤修复能力增加有关,DNA 修复相关酶活性增高也是肿瘤对化疗药物产生抗性的一个重要因素[1,2]。分子肿瘤学研究提示,与 DNA 修复有关分子是化学药物耐药的主要原因之一[3,4],从研究 DNA 修复入手,降低肿瘤细胞对 DNA 氧化损伤的修复能力将为肿瘤治疗和耐药性逆转开辟新的途径。人 8-羟基鸟嘌呤 DNA 糖苷酶 1 (human 8-oxoguanine DNA glycosylase-1, hOGG1)是 DNA 氧化损伤修复途径中的关键酶,本文以肺腺癌 A549 细胞和通过稳定转染 hOGG1 核酶而获得的 hOGG1 低表达的 A549-R 细胞为研究对象,比较两种细胞在 BLM 处理后存活率及 DNA 损伤修复能力的变化,以研究 hOGG1 低表达影响肺腺癌细胞对 BLM 敏感性的效应,从而为在基因水平进行化疗增敏提供更多实验依据。

1 材料与方法

1.1 试剂和仪器

BLM, Nippon Kayaku; G418, Invitrogen; 低熔点琼脂糖, Amresco; 噻唑蓝(MTT), Fluka; 溴化乙锭(ethidium bromide, EB), Amresco; 吖啶橙(acridine orange, AO), Sigma; 酶标仪(Microplate Reader), Bio-Rad; 荧光显微镜及倒置显微镜, Leica。

1.2 细胞培养

A549 细胞购于华神集团成都基因治疗肿瘤药物工程技术研究中心, A549-R(hOGG-1 低表达的 A549)细胞由本实验室构建,即通过稳定转染 hOGG1 核酶真核表达载体 pcDNA3.1(+)-RZ 的 A549 细胞[5],经鉴定该细胞可稳定表达核酶基因,并持续有效抑制 hOGG1 的表达(hOGG1 的表达比 A549 细胞低 61.1%)[6]。两种细胞均接种于含

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10%小牛血清的DMEM培养液中,37℃,5% CO_2培养箱中培养,A549-R细胞中持续加入800 mg·L^{-1}的G418。

1.3 MTT试验

细胞接种于96孔培养板,每孔200 μL培养液中含1×10^5个细胞,37℃培养24 h后更换培养液并加入0, 0.25, 0.5, 1, 2.5, 10, 25, 50和100 mg·L^{-1}的BLM,每个浓度设置8个复孔,同时设空白对照。受试物和细胞作用72 h后吸去培养液,D-Hanks液洗涤细胞1次,每孔加入含5 g·L^{-1} MTT的培养液100 μL,继续孵育4 h,弃去培养液,每孔加入150 μL DMSO,震荡2 min,使蓝色结晶充分溶解,于酶标仪上测定570 nm波长的光吸收值并计算存活率,将浓度的对数值和存活率拟和得到直线方程后计算出半数抑制浓度(IC_{50}),试验重复3次。

1.4 集落形成抑制试验

细胞接种于24孔培养板,每孔0.5 mL培养液中含200个细胞,待细胞贴壁后更换培养液并加入0.01,0.05,0.1,0.25和0.5 mg·L^{-1}的BLM,每个浓度设置3个复孔,同时设空白对照,将细胞置于37℃,5% CO_2培养箱中连续培养10 d,弃去培养液,以pH为7.4的磷酸盐缓冲液(PBS)洗涤细胞3次,甲醇固定20min,10% Giemsa染色15 min,蒸馏水冲洗,自然风干,于解剖显微镜下计数每孔中集落数(含50个细胞以上的为1个集落),每孔计数2次。试验重复3次。计算集落形成率和集落形成抑制率:集落形成率=各试验组平均集落形成数/接种细胞总数×100%;集落形成抑制率=(对照组平均集落形成数-各剂量组平均集落形成数)/对照组平均集落形成数×100%。

1.5 体外微核试验检测细胞染色体的损伤

将细胞接种于6孔板中,每孔1 mL培养液中含1×10^6个细胞,37℃培养。当细胞长到对数生长期时,按MTT法测定结果,以无明显细胞毒性的浓度作为受试物的最高浓度(5 mg·L^{-1}),每孔加入10 μL受试物,同时设空白对照,37℃作用24 h后弃培养液,2.5 g·L^{-1}胰酶消化细胞,离心后沉淀用0.075 mol·L^{-1} KCl低渗处理,3∶1甲醇冰醋酸固定3次,沉淀用含1%冰醋酸的甲醇制成悬液,滴2滴于冰冻的洁净玻片上,每个剂量滴4张片子,室温下自然干燥,最后用40 mg·L^{-1}的AO 50 μL染色,立即在荧光显微镜下观察结果每张片子计数2000个细胞并计算微核率。试验重复3次。

1.6 彗星试验检测细胞的DNA损伤

细胞消化后,制成1×10^8 L^{-1}的细胞悬液,按每管1 mL分装于EP管中。每管加入10 μL不同浓度受试物,使其终浓度分别为0.05,0.25,0.5,1,5和10 mg·L^{-1}。37℃水浴染毒3 h,PBS洗涤3次后收获细胞,立即进行彗星试验。每张片子计数200个细胞计算细胞拖尾率,并计数30个拖尾细胞的尾长计算平均DNA迁移长度。试验重复3次。

1.7 改良彗星试验检测细胞DNA损伤的修复

选择5及10 mg·L^{-1}作为DNA损伤修复试验的浓度。按照前述方法并以PBS洗涤3次后加入新培养液(不含BLM),37℃培养箱中培养,分别于0,0.5,1,2,3和6 h后收获细胞,按同样的方法进行彗星试验。观察不同孵育时间细胞拖尾率和彗星DNA迁移长度的减少。试验重复3次。

1.8 计量资料用$\bar{x}\pm s$表示,SPSS11.5软件对指标进行单因素方差分析,两两比较应用LSD法分析。

2 结果

2.1 博来霉素对细胞存活率的影响

A549细胞及A549-R细胞的存活率均随BLM浓度的增加而呈下降趋势(图1),且低浓度(<25 mg·L^{-1})时,两种细胞存活率随浓度增加而降低的趋势更明显;在设计的浓度范围(0.25,0.5,1,2.5,10,25,50和100 mg·L^{-1})内A549-R细胞的存活率

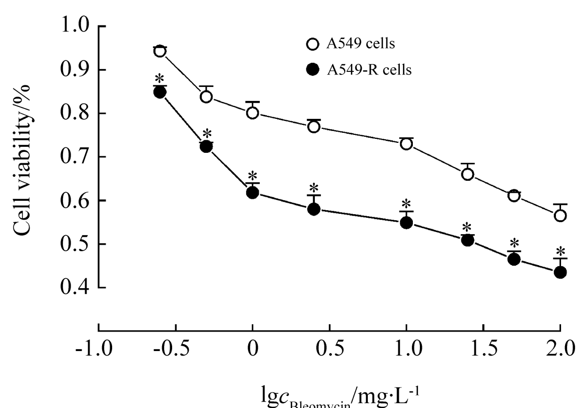

Fig1. Effect of bleomycin on the cell viability of A549 cells and A549-R cells. A549 cell and A549-R cells were treated by 0, 0.25, 0.5, 1, 2.5, 10, 25, 50 and 100 mg·L^{-1} bleomycin for 72 h. Cell viability was detected by MTT test. Cell viability = ($A_{\text{Test group}}/A_{\text{Control group}}$)×100%. $\bar{x}\pm s$, $n=3$. $^{*}P<0.05$, compared with the corresponding of A549 cells by one-way ANOVA and LSD tests.

均在 A549 细胞以下,A549-R 细胞的 IC_{50}为(60.01 ± 3.39)mg·L^{-1},明显低于 A549 细胞(93.85 ± 8.72) mg·L^{-1}(n = 3, P < 0.05)。

2.2 博来霉素对细胞集落形成能力的影响

由表 1 结果可以看出,在 0.01,0.05,0.1,0.25 和 0.5 mg·L^{-1}的剂量下,两种细胞的集落形成率均随 BLM 浓度的增加而降低,各浓度组与对照组比较,差异均有统计学意义,并呈现良好的浓度-效应关系。当 BLM 浓度达到 0.5 mg·L^{-1}时,镜下观察两种细胞均零星分散,未见到完整细胞集落,细胞的集落形成能力被完全抑制(图 2);而在其他浓度,A549-R 细胞的集落形成率明显低于相同浓度下的 A549 细胞,两者差异有统计学意义。

2.3 博来霉素对两种细胞微核形成的影响

如表 2 结果所示,微核试验中 BLM 导致的染色体损伤在所设计的剂量范围(0.05,0.25,1 和 5 mg·L^{-1})内,除0.05 mg·L^{-1}组 A549 细胞与空白对照组微核率差别无统计学意义外,其他剂量两种细胞与各自的空白对照组比较,差异均有统计学意义,并呈现良好的剂量-效应关系,两种细胞的微核率随着 BLM 浓度的增加而增加。相同剂量水平,除 5 mg·L^{-1}组外,A549-R 细胞的微核率均高于 A549 细胞。

2.4 博来霉素对细胞 DNA 的损伤及修复的影响

如表 3 结果所示,随着 BLM 浓度的增加,两种细胞的拖尾率和拖尾细胞 DNA 迁移长度均增加,各浓度组拖尾率和拖尾细胞DNA迁移长度与对照组

Tab 1. Effect of bleomycin on the colony forming ability of A549 cells and A549-R cells

Bleomycin /mg · L^{-1}	Number of colony forming		Rate of colony forming/%		Inhibitory rate of colony forming/%	
	A549 cells	A549-R cells	A549 cells	A549-R cells	A549 cells	A549-R cells
0	93.7 ± 3.8	91.5 ± 4.1	46.9 ± 1.1	45.7 ± 1.3	–	–
0.01	85.4 ± 4.9	66.3 ± 3.7 *	42.7 ± 1.9 *	33.2 ± 1.2 *#	8.9 ± 0.5 *	27.5 ± 1.1 *#
0.05	72.6 ± 3.7 *	61.2 ± 2.2 *	35.3 ± 1.0 *	30.6 ± 1.8 *#	22.5 ± 0.9 *	33.1 ± 0.7 *#
0.1	51.3 ± 1.8 *	40.6 ± 1.4 *	25.7 ± 1.3 *	20.3 ± 0.9 *#	45.3 ± 1.4 *	55.6 ± 1.9 *#
0.25	22.7 ± 0.5 *	15.1 ± 0.9 *	11.4 ± 0.7 *	7.6 ± 0.4 *#	75.8 ± 2.6 *	83.5 ± 2.5 *#
0.5	0.0 ± 0.0 *	0.0 ± 0.0 *	–	–	–	–

A549 cells and A549-R cells (A549 cells with low expression of human 8-oxoguanine DNA glycosylase-1) were planted in 24 welled culture plants, treated with BLM for 10 d. Rate of colony forming(%) = (average number of colony/cell count of planting) × 100%。Inhibitory rate of colony forming(%) = [(average number of colony of control group – average number of colony of test group)/average number of colony of control group] × 100%. $\bar{x} \pm s$, n = 3(experiment times). $^*P$ < 0.05, compared with control group; $^{\#}P$ < 0.05, compared with the corresponding A549 cells by one-way ANOVA and LSD tests.

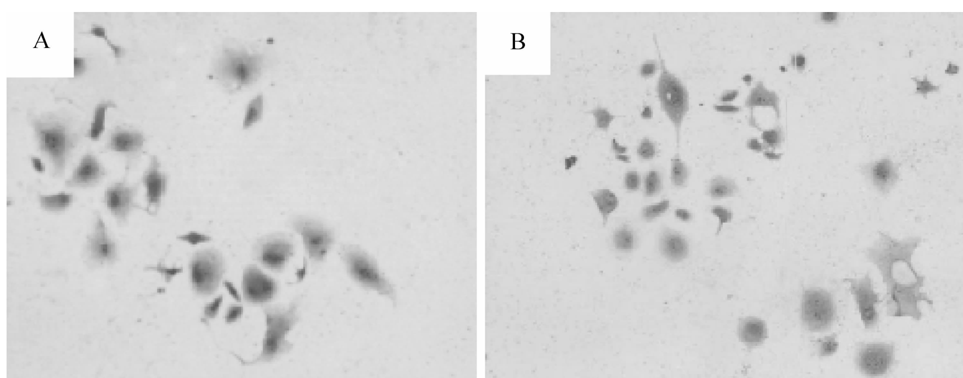

Fig 2. Photographs of A549 and A549-R cells exposed to 0.5 mg·L^{-1} bleomycin. (200 ×) A: A549 cells exposed to 0.5 mg·L^{-1} bleomycin; B: A549-R cells exposed to 0.5 mg·L^{-1} bleomycin. For either A549 cells or A549-R cells, no cell clone could be observed but a few scattered cells.

Tab 2. Effect of bleomycin on the rates of micronucleated cells

Bleomycin /mg · L^{-1}	Rate of micronucleated cells/ ‰	
	A549 cells	549-R cells
0	33.2 ± 5.4	30.4 ± 3.2
0.05	38.4 ± 6.7	52.6 ± 5.5 $^{*\#}$
0.25	48.6 ± 4.9 *	59.9 ± 5.0 $^{*\#}$
1	53.7 ± 2.7 *	74.3 ± 6.1 $^{*\#}$
5	55.2 ± 4.5 *	59.6 ± 4.3 *

A549 cells and A549-R cells were treated with bleomycin for 24 h. $\bar{x} \pm s$, $n = 3$ (experiment times). $^{*}P < 0.05$, compared with 0 mg · L^{-1}; $^{\#}P < 0.05$, compared with the corresponding A549 cells by one-way ANOVA and LSD tests.

比较差异有统计学意义，在相同BLM浓度下，A549-R细胞的拖尾率高于A549细胞，拖尾细胞的DNA迁移长度较A549细胞长，差异有统计学意义。A549-R细胞在5 mg·L^{-1}时拖尾细胞形态发生明显变化，尾部面积增大，细胞核变小(图3A)，10 mg·L^{-1}时多数细胞呈现类似凋忘的形态(图3B)；而A549细胞在前述两个浓度下形态无明显变化(图3C，D)。

从表4结果可见，随着修复时间的延长，两种细胞的拖尾率和拖尾细胞DNA迁移长度均有降低，两个浓度组的A549细胞在0.5 h后即出现明显的修

Tab 3. Effect of bleomycin on DNA damage of A549 and A549-R cells

Bleomycin /mg · L^{-1}	Comet cell rate/%		DNA migration length / μm	
	A549 cells	A549-R cells	A549 cells	A549-R cell
0	3.1 ± 0.1	2.9 ± 0.5	5.8 ± 0.2	5.6 ± 0.5
0. 05	7.2 ± 0.8	26.5 ± 1.2 $^{*\#}$	15.7 ± 0.5 *	33.9 ± 0.7 $^{*\#}$
0. 25	43.6 ± 1.9 *	60.8 ± 2.7 $^{*\#}$	24.4 ± 1.1 *	47.3 ± 1.3 $^{*\#}$
0.5	52.3 ± 3.6 *	74.9 ± 3.7 $^{*\#}$	41.9 ± 2.0 *	66.8 ± 2.9 $^{*\#}$
1	71.2 ± 5.6 *	100.0 ± 0.0 $^{*\#}$	51.1 ± 1.8 *	69.1 ± 2.0 $^{*\#}$
5	100.0 ± 0.0 *	100.0 ± 0.0 *	62.3 ± 2.2 *	101.8 ± 3.4 $^{*\#}$
10	100.0 ± 0.0 *	100.0 ± 0.0 *	98.5 ± 2.6 *	151.2 ± 4.5 $^{*\#}$

Cells were treated with bleomycin for 3 h. Comet cell rate and DNA migration length were detected by comet assay. Comet cell rate indicates the percentage of DNA damaged cells in 200 total cells observed, DNA migration length is the average value of the tail length of 30 comet cells, and diameter of nucleus is not included. $\bar{x} \pm s$, $n = 3$ (experiment times). $^{*}P < 0.05$, compared with 0 mg · L^{-1}; $^{\#}P < 0.05$, compared with the corresponding A549 cells. The comet cell rate and DNA migration rength were statistically analyzed by one-way ANOVA and LSD tests.

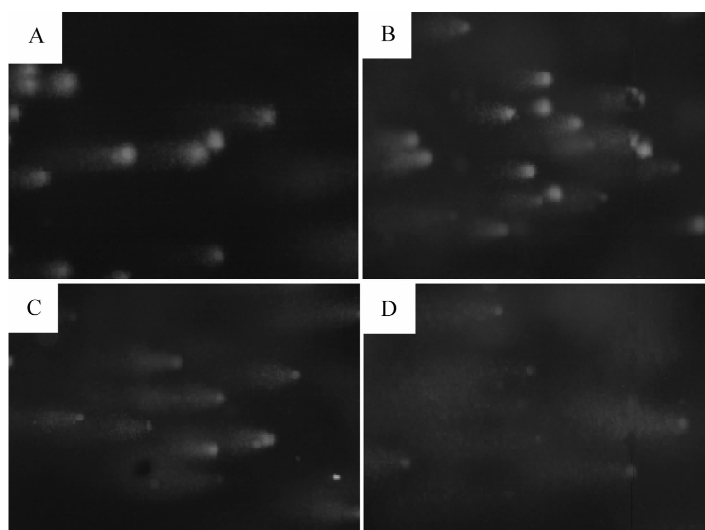

Fig 3. Photographs of A549 cells and A549-R cells exhibiting DNA migration induced by bleomycin. (200×) A, B: A549 cells exposed to 5 and 10 mg · L^{-1} bleomycin, respectively; C, D: A549-R cells exposed to 5 and 10 mg · L^{-1} bleomycin, respectively. A549-R cells showed obvious morphologic changes when exposed to 5 mg · L^{-1} bleomycin, and most of them were similar to apoptosis cells. While above phenomenon couldn't be observed in A549 cells.

Tab 4.　Effect of bleomycin on DNA damage repair of A549 and A549-R cell

Bleomycin /mg · L^{-1}	Incubation time / h	Comet cell rate/%		DNA migration length/μm	
		A549 cells	A549-R cells	A549 cells	A549-R cells
5	0	100.0 ± 0.0	100.0 ± 0.0	62.3 ± 2.2	101.8 ± 2.4$^{\#}$
	0.5	91.2 ± 2.2*	100.0 ± 0.0	50.9 ± 2.4*	99.2 ± 3.7$^{*\#}$
	1	85.1 ± 2.3*	100.0 ± 0.0	45.3 ± 3.8*	85.6 ± 3.5$^{*\#}$
	2	55.7 ± 1.9*	88.4 ± 2.7*	37.5 ± 2.9*	82.3 ± 2.8$^{*\#}$
	3	24.3 ± 0.5*	52.4 ± 1.6*	3.2 ± 0.1*	24.6 ± 1.4$^{*\#}$
	6	0.0 ± 0.0*	0.0 ± 0.0*	0.0 ± 0.0*	0.0 ± 0.0$^{*\#}$
10	0	100.0 ± 0.0	100.0 ± 0.0	98.5 ± 2.6	151.2 ± 4.5$^{\#}$
	0.5	100.0 ± 0.0	100.0 ± 0.0	79.6 ± 2.3*	105.2 ± 2.1$^{*\#}$
	1	100.0 ± 0.0	100.0 ± 0.0	66.8 ± 2.0*	100.5 ± 2.9$^{*\#}$
	2	80.0 ± 1.3*	100.0 ± 0.0	57.8 ± 2.7*	85.6 ± 2.5$^{*\#}$
	3	57.1 ± 1.5*	75.6 ± 1.9*	31.5 ± 1.4*	65.3 ± 2.1$^{*\#}$
	6	0.0 ± 0.0*	21.3 ± 2.0*	0.0 ± 0.0*	26.4 ± 0.6$^{*\#}$

DNA repair ability of cells was reflected by detecting comet cell rate and DNA migration length after DNA-damaged cells incubated in fresh culture medium without bleomycin for different time. $\bar{x} \pm s$, $n = 3$. $^{*}P < 0.05$, compared with 0 h; $^{\#}P < 0.05$, compared with the corresponding A549 cells.

复现象,拖尾率和拖尾细胞 DNA 迁移长度与 0 h 比较差异有统计学意义,而 5 和 10 mg·L^{-1}浓度组的 A549-R 细胞在 1 h 后拖尾细胞形态恢复正常,2 h 后拖尾率和拖尾细胞 DNA 迁移长度才有明显降低。10 mg·L^{-1}浓度组的 A549 细胞在 6 h 后其 DNA 损伤已完全修复,而此时 A549-R 细胞拖尾率为(21.3 ± 2.0)%,拖尾细胞 DNA 迁移长度(26.4 ± 0.6) μm。

3　讨论

hOGG1 是人体细胞中 DNA 氧化损伤修复的关键酶,具有特异性切除和修复活性氧自由基引起的 DNA 加合物 8-羟基脱氧鸟嘌呤(8-OHdG)的作用。本研究通过 MTT 试验及集落形成抑制试验比较了肺腺癌 A549 细胞和通过稳定转染 hOGG1 核酶而获得的 hOGG1 低表达的 A549-R 细胞对 BLM 的敏感性。结果显示,A549-R 细胞的 IC_{50} 明显低于 A549 细胞;在试验设计的剂量范围内 A549-R 细胞的集落形成率明显低于 A549 细胞,而集落形成抑制率则高于 A549 细胞,转染 hOGG1 核酶后细胞对 BLM 的敏感性增高。

DNA 是 BLM 作用的主要靶,在 BLM 介导的 DNA 断裂过程中产生的多种自由基有明显致 DNA 和染色体断裂的作用[7],本研究采用彗星试验和微核试验比较了两种细胞在 BLM 作用下的微核率和 DNA 损伤及修复能力,结果表明 A549-R 细胞在 BLM 作用下微核率明显高于 A549 细胞,说明 A549-R 细胞对 BLM 造成的染色体损伤较 A549 细胞更敏感。A549 细胞对 BLM 造成 DNA 损伤修复发生较早,5 mg · L^{-1}组在 0.5 h 后即有明显修复,而 A549-R 细胞在 2 h 后才有明显的修复现象,10 mg · L^{-1}组 A549 细胞 6h 后 DNA 损伤已完全修复,而此时的 A549-R 细胞的 DNA 损伤现象仍较明显。这显示 A549-R 细胞的修复能力较 A549 细胞更低,也说明通过转染 hOGG1 核酶而使肺腺癌细胞 hOGG1 表达降低,其清除 8-OHdG 的作用受到抑制,对 DNA 氧化损伤的修复能力下降。

综上所述,与 A549 细胞相比,hOGG1 低表达的 A549-R 细胞在 BLM 作用下 DNA 更易于发生损伤,损伤后难以修复,细胞存活率及集落形成能力下降,表明 hOGG1 低表达可以增加肺腺癌细胞对 BLM 的敏感性,降低肿瘤细胞 hOGG1 活性可能是化疗增敏的一条新途径。

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Low expression of human 8-oxoguanine DNA glycosylase-1 gene increases sensitivity of human lung adenocarcinoma cells to bleomycin

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Abstract: **AIM** To investigate the effect of low expression of human 8-oxoguanine DNA glycosylase (hOGG) 1 gene on sensitivity of lung adenocarcinoma cells to bleomycin, and provide more experimental evidence of sensitizing the response of tumor to chemotherapy. **METHODS** Human lung adenocarcinoma A549 cells and A549-R cells into which ribozyme gene inhibited the hOGG1 mRNA expression and transfected were studied. The cell viability and the ability of colony forming after treatment of bleomycin of different concentrations detected by MTT test and colony forming inhibition test. Micronucleus rate, DNA damage and repair were detected by micronucleus test *in vitro* and single cell gel electrophoresis assay. **RESULTS** The cell viability after treatment of bleomycin was decreased, IC_{50} of bleomycin and the ability of colony forming was significantly lower in A549-R cells than in A549 cells. The micronucleus rate in A549-R cells was higher than A549 cells statistically. DNA damage of A549-R cells induced by bleomycin of different concentrations was more serious than A549 cells both in comet cell rate and DNA migration length. The DNA repair after treatment of bleomycin happened earlier in A549 cells than in A549-R cells. The repair capability in A549-R cells was significantly lower than A549 cells. **CONCLUSION** Down-regulation of the expression of hOGG1 can decrease the DNA repair capability of A549 cells, and increase the sensitivity of cells to bleomycin.

Key words: gene expression; human 8-oxoguanine DNA glycosylase; bleomycin; adenocarcinoma; lung; DNA damage

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