

论文

转染结构性雄烷受体对丝裂霉素C和5-氮丙啶-3-羟甲基-1-甲基吲哚-4,7-二酮的细胞毒性的影响

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摘要:

研究丝裂霉素C(MMC)及其衍生物5-氮丙啶-3-羟甲基-1-甲基吲哚-4,7-二酮 [5-(aziridin-1-yl)-3-hydroxymethyl-1-methylindole-4,7-dione, 629] 的细胞毒性, 以及结构性雄烷受体(constitutive androstane receptor, CAR)转染对其生物学效应的影响。将质粒mCAR/pCR3转染HepG2细胞, 经G418耐药性筛选获得转染CAR的g2car细胞, 以转染空载体pCR3(HepG2/pCR3)作为对照。用RT-PCR检测质粒和CYP2B6 mRNA的表达, 用MTT法评价MMC和629对g2car细胞和HepG2细胞在有氧和乏氧条件下的细胞毒性。RT-PCR检测到CAR和CYP2B6 mRNA在g2car细胞中有表达, 在HepG2细胞中无表达; 此外, 在乏氧情况下, MMC和629的细胞毒性比在有氧情况下均有所增加(p<0.05), 并且转染CAR以后, 两者的细胞毒性均增加, 但对MMC的影响较明显(p<0.05), 对629的影响不明显(p>0.05)。提示CAR可在转录水平调节药物的代谢, 提高药物的毒性; CYP2B6可以主要代谢MMC, 但不主要代谢629。转染CAR基因可以增加细胞CYP2B6 mRNA的表达, 并可引起MMC和629毒性的改变。

关键词: 丝裂霉素C 5-氮丙啶-3-羟甲基-1-甲基吲哚-4,7-二酮 细胞毒性 生物还原活性物 结构性雄烷受体 细胞色素P450

Effect of constitutive androstane receptor on the cytotoxicity of mitomycin C and 5-(aziridin-1-yl)-3-hydroxymethyl-1-methylindole-4,7-dione

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Abstract:

This study is to evaluate the cytotoxicity of mitomycin C (MMC) and its analogue 5-(aziridin-1-yl)-3-hydroxymethyl-1-methylindole-4,7-dione (629) as well as the effect of transfection of constitutive androstane receptor (CAR) on their biological effects. HepG2 cells were transfected with the plasmids mCAR1/pCR3 mediated by liposome. Vector pCR3 was used as control. Transfected cells were screened by G418 resistance and limiting dilution. The expressions of plasmid mCAR1/pCR3 and CYP2B6 mRNA were detected by RT-PCR; Cytotoxicities of MMC and 629 in vitro were evaluated in g2car cells and HepG2 cells by MTT method under anaerobic and aerobic conditions. mRNA expression of CAR and CYP2B6 can not be detected in HepG2 cells and HepG2/pCR3 cells but can in g2car cells. It is shown that plasmid mCAR1/pCR3 was transfected into g2car cells successfully and target CYP2B6 was transactivated by CAR. To compare with aerobic and anaerobic, the cytotoxicities of MMC and 629 to HepG2 cells and g2car cells had significantly enhanced (p<0.05), and transfect CAR gene can improve the cytotoxicity of MMC (p<0.05), but not 629 (p>0.05). Furthermore, CYP2B6 is one master enzyme for the metabolism of MMC and not 629. Transfection of CAR can increase expression of CYP2B6 mRNA in HepG2 cells, and can affect cytotoxicities of MMC and 629.

Keywords: 5-(aziridin-1-yl)-3-hydroxymethyl-1-methylindole-4,7-dione cytotoxicity bioreductive drugs constitutive androstane receptor cytochrome P-450 mitomycin C

收稿日期 2006-07-22 修回日期 网络版发布日期

DOI:

基金项目:

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