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文献综述 REVIEW

人肝癌细胞系HepG2在遗传毒物检测中的应用及其进展

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Application of human hepatoma cell line HepG2 and its progress in the detection of genotoxicants

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Abstract
Genotoxicity test is widely used in the detection of various carcinogens and mutagens. HepG2 is derived from human hepatoblastoma, and it retains the activities of drug-metabolizing enzymes. It has been demonstrated that various carcinogens can be detected in genotoxicity test with HepG2 cells at several endpoints, whereas negative results have been obtained with non-carcinogens.

Key Words: Human hepatoma cell line; HepG2 cell line; Genotoxicant; *In vitro* genotoxicity test

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摘要
外来化合物的体外遗传毒性实验常用于各种致癌物和致突变物的快速筛选. HepG2是一种分化好的人肝胚细胞瘤细胞系, 保留了较完整的代谢酶及其活性. 以HepG2细胞作为实验系统检测各种致癌及非致癌物, 在多个观察终点均获得相应的阳性及阴性结果.

关键词: 人肝癌细胞系; HepG2细胞系; 遗传毒物; 体外遗传毒性实验

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0 引言
一直以来, 遗传毒物的检测普遍受到人们的重视. 对于体外遗传毒性实验来说, 细胞的代谢系统将在很大程度上影响实验的结果. 而人肝癌细胞系HepG2保留了较完整的生物转化代谢Ⅰ相酶和Ⅱ相酶[1], 这意味着该细胞系既可作为外来化合物攻击遗传物质的靶细胞, 同时又是外来化合物的活化系统, 不需依赖传统外源性活化系统的加入. 自从1979年, Aden *et al*[2]从一个阿根廷男孩的原发性肝胚细胞瘤中分离出HepG2细胞, 科研人员多年来对其在遗传毒理学实验中的应用进行了深入的探索和广泛的研究.

1 HepG2细胞内的生物转化代谢酶
HepG2细胞来源于人类肝胚细胞瘤[2], 其所含的生物转化代谢酶与人正常肝实质细胞具有同源性. 虽然HepG2是一种肿瘤细胞, 但是他的分化程度较高[3-4], 并且保留了较完整的生物转化代谢酶, 因此, 用这种细胞做遗传毒性实验, 不需加入外源性活化系统[5-8]. 人类原代肝实质细胞经分离后, 只能经历有限的几次分裂, 其内在的代谢酶很快失去活性[9], 而HepG2细胞作为分化好的细胞系, 其内在的药物代谢酶活性稳定, 不会随着传代次数的增多而降低[10-12]. 以上3点使得HepG2细胞较其他的外来化合物遗传毒性检测系统更具优势.

HepG2内保留了多种细胞色素P450 (cytochrome P450, CYP)同工酶, 不同的同工酶负责激活不同的前致突变物, 所以HepG2细胞可广泛的应用于各种可疑致突变物的快速筛检[13-14]. 其中CYP 1A针对多环芳烃(polycyclic

■背景资料
自从1979年, Aden *et al*从一个阿根廷男孩的原发性肝胚细胞瘤中分离出HepG2细胞, 科研人员多年来对其在遗传毒理学实验中的应用进行了深入的探索和广泛的研究, 近年来, 又获得了可喜的进展, 出现了更多的遗传毒性实验观察终点.

■研发前沿
对于体外遗传毒性实验来说, 细胞的代谢系统将在很大程度上影响实验的结果, 而人肝癌细胞系HepG2保留了较完整的生物转化代谢Ⅰ相酶和Ⅱ相酶, 这意味着该细胞系既可作为外来化合物攻击遗传物质的靶细胞, 同时又是外来化合物的活化系统, 不需依赖传统外源性活化系统的加入.

aromatic hydrocarbons, PAH)类及芳香胺类[15-16], CYP 3A对硝基芘及黄曲霉素类具有特异性[17]. CYP 2B可以激活很多种结构互不相关的化合物[18]. 环氧化物水解酶是一种Ⅱ相代谢酶, 可以水解多环芳烃环氧化物为二氢二醇, 接着被CYP 1A进一步活化为最终的致突变物——二氢二醇环氧化物[19-22]. 除了CYP同工酶, HepG2细胞内还保留了其他氧化还原酶, 参与电子传递, 活性氧的生成和清除[23].

需要特别指出的是, HepG2细胞内CYP 1A2和CYP 2E1的含量很少或检测不到[24]. CYP 1A2对于活化芳香胺起着重要的作用, 但是即使没有这种酶, 芳香胺依然对HepG2细胞表现出明显的遗传毒性, 这可能是因为HepG2细胞内CYP 1A1含量丰富, 芳香胺依然可以被CYP 1A1活化[25-29]. CYP 2E1在活化亚硝胺的过程中起着至关重要的作用[30], 大多数亚硝胺类物质对HepG2细胞仅表现出轻微或不具有遗传毒性, 可能和HepG2细胞内这种酶的缺失有关[31-32].

2 HepG2细胞在体外遗传毒性实验中的应用

2.1 遗传毒性实验的观察终点 HepG2细胞系成功分离后不久, Diamond *et al*[33]报道, 已知致癌物苯并(a)芘[B(a)P]在实验终点为抗6-硫化鸟嘌呤(6-TG^r)时获得了阳性结果. 从此以后, 人们不断探索更多的实验观察终点. 现在比较常用的方法是微核(micronucleus, MN)实验[34]和单细胞凝胶电泳(single cell gel electrophoresis, SCGE)实验[35]. 人们注意到, MN实验结果阳性的化合物, SCGE实验结果往往也是阳性, 这一现象不仅对于HepG2细胞, 其他细胞株也是这样[13,36]. 但是橘霉素是个特例, 他能够引起HepG2细胞微核率显著增加, 但是SCGE实验结果阴性, Knasmuller *et al*[37]利用一种着丝点特异性荧光原位杂交(fluorescence in situ hybridization, FISH)探针, 发现这种真菌霉素可以诱发非整倍体, 没法通过SCGE实验检测到. 此外在HepG2细胞内还可观察到的遗传毒性实验终点有姐妹染色单体交换(sister-chromatid exchange, SCE)[38], 程序外DNA合成(unscheduled DNA synthesis, UDS)[39-40]等. 因为染色体很小, 对HepG2细胞分裂中期的分析十分费时[34]. Kohda *et al*[41]利用ICRF-193-一种Ⅱ型拓扑异构酶抑制剂, 延长分裂中期染色体长度. 在不久的将来, 这项技术可以缩短HepG2细胞染色体畸变分析(chromosome aberration analysis, CA)的时间.

另一项检测HepG2细胞内遗传性损伤的新技术是荧光分析DNA解旋(fluorometric analysis of DNA unwinding, FADU)实验, 可以用于检测DNA双链断裂[42]. Smith *et al*[43]把四环素阻遏蛋白及融合有绿色荧光蛋白的操纵序列转染给HepG2细胞, 当外源性化合物引起四环素阻遏蛋白基因突变时, 可以检测到荧光. 这个新方法比MN实验更敏感, 特别适用于当受试物浓度较高, 细胞生长已经停滞时.

2.2 外源性化合物对HepG2细胞遗传毒性实验结果 迄今采用不同的实验终点已检测了数十种外源性化合物的遗传毒性, 主要结果如下: (1)真菌霉素类. 黄曲霉素B_1在实验终点为UDS, MN和SCGE时, 获得阳性结果[24,39,44]. 已知啮齿动物致癌物赭曲霉毒素A(ochratoxin A, OTA)和伏马菌素B_1(fumonisin B_1, FB_1)可能对人致癌(IARC, 1993)[45-46], 在其他体外遗传毒性实验中结果为阴性, 在HepG2细胞, 实验终点为SCGE时, 结果呈阳性[47-48]; (2)PAH类. 已知致癌物B(a)P在实验终点为MN, SCE和SCGE时, 均获阳性结果[24,34,49]. 已知啮齿动物强致癌物二甲基苯并蒽, 在实验终点为MN时, 结果呈阳性, 已知非致癌物芘在实验终点为SCE和MN时, 结果呈阴性[34]; (3)亚硝胺类. 如前所述, 可能由于CYP 2E1酶的缺失, HepG2细胞对大多数亚硝胺类物质不敏感. 已知致癌物1-亚硝胺在UDS和6-TG^{r}实验中获得阴性结果[31-32]. 已知啮齿动物致癌物吡咯烷亚硝胺, 在MN实验中也获得阴性结果[24]; (4)芳香胺和杂环芳香胺类. 已知致癌物联苯胺, SCE实验结果呈阳性[50]. 非致癌物4-乙酰氨基芴, MN实验结果呈阴性[51]. 已知啮齿动物致癌物2-氨基-3-甲基-咪唑并(4, 5-f)喹啉(IQ), MN实验结果呈阳性[52]; (5)某些具有生物活性的天然植物成分.

近年来很多营养学家和毒理学工作者也利用HepG2细胞研究一些天然植物成分的抗突变效应, 但却发现某些植物成分在稍高一些剂量下表现出遗传毒性[53-58]. 十字花科蔬菜中硫甙的水解产物——异硫氰酸酯, 在实验终点为SCGE和MN时, 结果为阳性[59-61]. 一种黄酮化合物白杨素, MN实验结果呈阳性[62]. 从以上结果可以看出, 并不是所有的植物成分都具有防护效应(例如上述物质), 如果摄入较多, 就可能对人体造成健康危害.

以上实验结果表明, 除了亚硝胺类, HepG2细胞对其他外来化合物的遗传毒性的检测还是比较灵敏的.

2.3 影响HepG2细胞遗传毒性实验结果的因素 随着各种外来化合物在HepG2细胞内遗传毒性实验资料的不断积累, 研究发现, 同一种化合物在不同的实验中表现出遗传毒性的剂量范围不尽相同, 甚至出入较大[13]. 这表明实验结果可能被某些因素所影响. Majer *et al*[24]利用3种不同来源的HepG2细胞克隆, 在同样的实验条件下, 研究B(a)P诱导MN的情况. 结果发现, 不同克隆对B(a)P的敏感性存在明显差异, 其中的一个克隆甚至比另一个敏感4倍多. 这一研究结果表明, 选择不同的HepG2细胞克隆, 可能对实验结果产生影响. 培养基的成分也可能对实验结果产生影响. 如前所述, HepG2细胞内的生物转化代谢酶在活化外来化合物的过程中至关重要. Doostdar *et al*[63]和Feng *et al*[64]都报道, 培养基的配方和成分不同, 对HepG2细胞内Ⅰ相酶的活性影响很大.

基于以上因素对实验结果的影响, 当HepG2细胞用于遗传毒性实验, 细胞克隆的来源及细胞的培养条件等还需进一步标准化.

3 某些转基因的HepG2细胞在遗传毒性实验中的应用

为了研究病毒性肝炎的发病机制及药物的疗效, 人们常把特定的基因转染入HepG2细胞[65-67], 或者为了获得更敏感的遗传毒性实验终点, 弥补HepG2细胞某些生物转化代谢酶的缺陷, 有人也采用了这项技术.

HepG2细胞内缺少CYP 2E1, 使得其对亚硝胺类化合物的敏感性较低, 现在能够持续表达CYP 2E1的转染基因已经成功构建. Kessova *et al*[68]创建了一种具有CYP 2E1酶活性的HepG2细胞系, 这样就可以检测出亚硝胺类化合物的遗传毒性. 除此以外, Hu *et al*[69]指出, 转染谷胱甘肽S-转移酶Pi(GSTP)等位基因变异体的HepG2细胞, 对二氢二醇环氧苯并芘(BPDE)加合物具有防护作用. Tashiro *et al*[70]也指出, 将GSTP转染入HepG2细胞, 可以减轻阿霉素的毒性.

总之, HepG2细胞保存了较为完整的生物转化代谢酶. 除了亚硝胺类物质, 业已采用HepG2细胞检测了多种已知的致突变物和非致突变物, 均获得相应的阳性或阴性结果. 而通过转基因技术, 可以使HepG2细胞持续表达CYP 2E1, 从而提高对亚硝胺类物质的敏感性. 研究发现, 并不是所有的天然植物成分都具有防护效应, 某些植物成分在稍高一些剂量下对HepG2细胞表现出遗传毒性. 近些年来, 随着更多的遗传毒性实验终点的出现, HepG2细胞被广泛的应用于各种外来化合物遗传毒性的快速筛选, 成为体外遗传毒性实验的理想细胞系.

HepG2细胞的来源及培养基组分等因素可能影响遗传毒性实验结果, 细胞克隆的选择及培养条件等有待进一步标准化.

■应用要点

近些年来, 随着更多的遗传毒性实验终点的出现, HepG2细胞被广泛的应用于各种外来化合物遗传毒性的快速筛选, 成为体外遗传毒性实验的理想细胞系.

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■名词解释
1 单细胞凝胶电泳实验: 又称彗星实验, 用来检测外来化合物对细胞DNA的损伤情况.
2 微核: 是细胞染色体受损后, 在有丝分裂期不能结合进子代核, 而在胞质中形成的小核, 所以微核实验是检测外来化合物遗传毒性的重要方法.

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■同行评价

本文综述了以HepG2细胞作为试验系统检测各种致癌及非致癌物, 在多个观察终点均获得相应的阳性及阴性结果, 较详细探讨最新的研究进展. 文章论点明确, 文笔流畅, 有学术参考价值, 是一篇较好的综述.

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• 消息 •

第十九届全国中西医结合消化会议征文通知

本刊讯 中国中西医结合学会消化系统疾病专业委员会决定于2007-08下旬在石家庄市召开第十九届全国中西医结合消化学术交流会, 并同时举办全国中西医结合消化疾病诊治新进展学习班.

1 征文内容和要求

征文内容: (1)有关消化系统疾病包括食管、胃、肝、胰等诊疗、实验研究进展; (2)中西医结合对慢性肝炎(病)、肝纤维化临床诊治以及基础、实验研究; (3)中西医结合对消化系统肿瘤诊治经验与实验研究; (4)中西医结合对“淤血症”以及脾胃学说与脾虚证研究进展. 征文要求: 来稿请附800字论文摘要, 并附软盘或发电子邮件至211zyke@163.com或czs.xiaohua@163.com(尽量以电子邮件发送). 征文请于2007-06-30前邮寄.

2 学习班招收对象

学习班招收对象: 从事中西医结合、中医或西医消化专业医师以上人员. 参加学习班者授予国家继续教育学分12分；在大会有论文报告者另授继续教育学分6分.

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