

原发性肝癌DNA修复酶hOGG1, hMTH1基因表达与DNA氧化损伤的修复

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Expression of DNA repair genes hMTH1 and hOGG1 and repair of oxidative damage of DNA in hepatocellular carcinoma

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Abstract

AIM: To study the regulatory effect of expression of hMTH1 and hOGG1 genes on the oxidative DNA-adduct 8-OHdG levels in hepatocellular carcinoma (HCC) and non-tumorous liver tissue in order to elucidate the role of the DNA repair enzymes in hepatocarcinogenesis.

METHODS: A reverse transcription (RT)/real-time-polymerase chain reaction (PCR) assay was used to semi-quantify mRNA of hMTH1 and hOGG1 in HCC and non-tumorous liver tissue from 23 patients with HCC. 8-OHdG levels were determined by HPLC/ECD.

RESULTS: The median of 8-OHdG levels in non-tumorous liver tissue was significantly (133 vs 56 nmol/g DNA, $P < 0.01$) higher than that in HCC tissue. This was correlated with the severity of inflammation in non-tumorous liver tissues. The expression of hMTH1 was significantly (0.476 vs 0.256 , $P < 0.05$) higher in HCC tissue than that in non-tumorous liver tissue. No difference of expression of hOGG1 between non-tumorous liver and HCC tissue was seen. A significant correlation was detected between the expression of hMTH1 and hOGG1 ($r = 0.81$, $P < 0.01$).

CONCLUSION: Elevated 8-OHdG levels in non-tumorous liver are likely due to the increased generation of reactive oxygen intermediates by infiltrating inflammatory cells. The expression of DNA repair enzymes hOGG1 and hMTH1 may involve cooperatively in the repair oxidative DNA adduct 8-

OHdG and have a potential role in hepatocarcinogenesis.

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摘要

目的:探讨DNA修复酶hOGG1和hMTH1基因表达对DNA氧化损伤产物8-OHdG的修复调控及其在肝癌发生和防御机制中的作用。

方法:RT/实时PCR定量检测23例HCC患者癌和癌旁组织中hOGG1和hMTH1基因的表达,HPLC/ECD法测定其8-OHdG含量。

结果:HCC患者癌旁组织8-OHdG含量明显高于癌组织(133 vs 56 nmol/g DNA, $P < 0.01$),且与炎症程度密切相关。而癌组织中hMTH1表达较癌旁组织显著升高(0.476 vs 0.256 , $P < 0.05$)。hOGG1表达在HCC和癌旁组织间无显著差异。但hOGG1和hMTH1表达之间存在显著的相关性($r = 0.81$, $P < 0.01$)。

结论:慢性肝脏炎症反应可能是肝细胞内DNA氧化损伤及肝细胞癌变的重要原因。DNA修复酶hOGG1和hMTH1可能协同参与肝细胞内DNA氧化损伤的修复,在肝癌发生和防御机制中起到作用。

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0 引言

原发性肝癌 (hepatocellular carcinoma, HCC) 发病率高, 预后差。其癌变是一个多步骤的渐进过程, 慢性肝炎和肝硬化过程中基因突变的积累在 HCC 发生中的作用已得到广泛认同^[1-3]。DNA 氧化损伤是引起基因组不稳定以及基因突变的常见原因^[4]。反应性氧化产物 (reactive oxygen species, ROS) 的生成超过抗氧化酶如过氧化物歧化酶 (manganese superoxide dismutase, Mn-SOD) 和谷胱甘肽过氧化物酶 (glutathione peroxidase, GSH-Px) 以及 DNA 修复酶修复能力时可产生氧应激 (oxidative stress), 导致细胞内 DNA 氧化损伤产物的积聚^[5-7]。8-羟基脱氧鸟核苷酸 (8-hydroxydeoxyguanosine, 8-OHdG) 是

一种主要的DNA氧化损伤产物,可在细胞DNA复制中通过G-T或A-C碱基颠换导致DNA误读,参与癌变发生过程^[8-9].参与8-OHdG所致基因突变修复的hMTH1(human MutT homologue)基因编码产物可通过水解核苷酸池中的游离8-OHdG而阻止8-OHdG误配入DNA^[10-11].hOGG1(human OGG1/MutM homologue)可通过其糖苷酶活性切除DNA双链中与碱基C配对的8-OHdG^[12].因此,hMTH1和hOGG1可能在人类基因组DNA氧化损伤的修复中起重要作用,但迄今尚未见其在HCC发生中的研究报道.我们观察HCC癌组织与癌旁组织中DNA修复酶hMTH1和hOGG1基因表达水平与8-OHdG含量并比较其相互关系,旨在探讨DNA修复酶hMTH1及hOGG1基因表达在HCC发生与防御机制中的作用与地位.

1 材料和方法

1.1 材料 HCC患者23例,男16例,女7例.中位数年龄59(40-71)岁.取手术切除的癌组织与癌旁组织,液氮冷却后储存于-80℃冰箱中待检.所有病例均由二位有经验的病理医师独立诊断,并按Edmondson和Steiner分级标准分为G1、G2和G3期.癌旁组织的炎症程度按HAI评分标准评定,并将病例分为炎症组($n=8$)和无炎症组($n=15$).

1.2 方法 根据Shigenaga(Methods Enzymol 1994;234:16)的方法略加改良,应用高效液相色谱仪并电化学检测器(high pressure liquid chromatography/electrochemical detection, HPLC/ECD, Waters)检测组织中8-OHdG含量.一种铁离子螯合物-甲磺酸去铁胺(deferoxamine mesylate, DFAM, Sigma)用于防止标本处理过程中人为产生8-OHdG. DNA抽提采用Gupta法.用核酸酶P1和碱性磷酸酶消化处理DNA,所得核苷酸溶液用Ultrafree-MW 5000离心滤过管(Sigma)以5 000 g离心过滤50 min.滤过液即可注入HPLC/ECD进行检测.用含已知浓度的标准脱氧鸟核苷酸(dG)和8-OHdG溶液作为标准参照.测量结果应用相应软件处理,所得8-OHdG含量以nmol 8-OHdG/g DNA表示.用Trizol试剂(life technologies, Inc.)根据产品说明书抽提总RNA.取总RNA 2 μg用随机引物(random primer, promega)在反转录酶MMLV(Promega)作用下反转录生成第一链cDNA. PCR引物由Gibco公司合成.外标准物为相应引物的PCR扩增产物经GenElute™PCR DNA纯化试剂盒(Sigma)洗涤纯化获得,并根据需要分别稀释为 10^{-3} , 10^{-4} , 10^{-5} , 10^{-6} , 10^{-7} 和 10^{-8} mg/L.

采用实时PCR技术半定量检测hMTH1, hOGG1, Mn-SOD和GSH-Px在HCC组织和癌旁组织中的表达.β-actin作为内对照. PCR反应体积为10 μL,其中含引物各0.5 μmol/L, 2.5 μmol/L MgCl₂和1 μL LightCycler™ DNA Master SYBR Green I, 1 μL来自2 μg总RNA的cDNA以及1 μL序列稀释的外标准物分别作为模板.

采用LightCycler系统(Roche Diagnostics, Inc)扩增测量循环条件,95℃预变性30 s后,95℃变性1 s,β-actin, hMTH1, hOGG1, Mn-SOD和GSH-Px分别在60, 60, 64, 62和58℃下退火3 s,72℃下分别延伸30, 15, 15, 16和14 s,均扩增40个循环周期.定量分析采用LightCycler软件,β-actin, hMTH1, hOGG1, Mn-SOD和GSH-Px经融点曲线分析确定其特异性后选定相应定量测量温度分别为86, 87, 86, 84和85℃.所有测量重复2次,取其平均值,结果以目标基因与β-actin基因表达的比值表示.所有PCR扩增片段大小均经溴化乙锭染色的琼胶显影所证实.

统计学处理 癌和癌旁组织间配对比较采用Wilcoxon检验,两组间非配对检验采用Mann-Whitney检验,相关分析采用Pearson法.

hOGG1	5' -ACA CTG GAG TGG TGT ACT AGCG-3'	Genbank: AB000410
	5' -GCG ATG TTG TTG TTG GAG G-3'	
hMTH1	5' -AGC CTC AGC GAG TTC TCC TG-3'	Genbank: AK026631
	5' -GAT CTG GCC CAC CTT GTG C-3'	
Mn-SOD	5' -GAG ATG TTA CAG CCC AGA TAG C-3'	Genbank: Y00472
	5' -AAT CCC CAG CAG TGG AAT AAG G-3'	
GSH-Px	5' -TGC TCG GCT TCC CGT GCA A-3'	Genbank: M21304
	5' -ACC GTT CAC CTC GCA CTT CT-3'	
β-Actin	5' -CGG GAA ATC GTG CGT GAC AT-3'	Genbank: NM001101
	5' -GAA CTT TGG GGG ATG CTC GC-3'	

2 结果

HPLC/ECD检测的结果表明,癌旁组织8-OHdG含量明显高于HCC组织($P<0.01$,表1).癌旁组织中炎症组($n=8$)8-OHdG含量的中位数为228(142-256) nmol/g DNA,无炎症组($n=15$)为76(34-224) nmol/g DNA,差异有显著性($P<0.05$).应用LightCycler实时PCR半定量测定HCC及癌旁组织中hMTH1和hOGG1的表达.HCC组织和癌旁组织hMTH1表达的中位数分别为0.476和0.256(hMTH1/β-actin×100),差异有显著性($P<0.05$,图1).而hOGG1的表达在癌组织和癌旁组织间没有显著差异.在癌旁组织中,炎症组和非炎症组间hMTH1和hOGG1的表达也无显著差异.

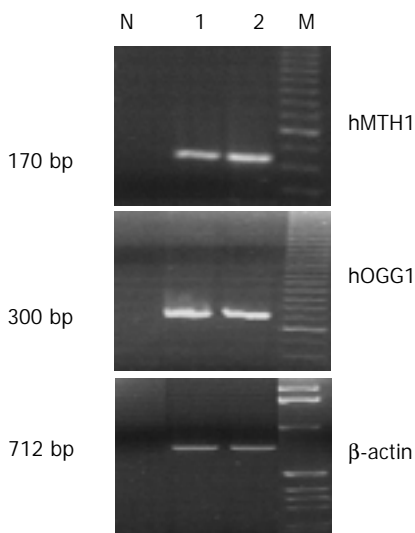
为了观察8-OHdG含量以及hMTH1, hOGG1表达和肿瘤临床分期期间的关系,21例HCC患者根据Edmondson和Steiner分类标准分为2组:早期组(G_1 ; $n=7$)和晚期组(G_2/G_3 ; $n=16$).结果两组间均无显著差异.HCC和癌旁组织中8-OHdG含量分别与hMTH1, hOGG1表达之间的相关分析均无显著相关性($r=-0.18$, $P=0.243$; $r=-0.20$, $P=0.19$).hMTH1和hOGG1表达间存在极显著的相关性($r=0.81$, $P<0.01$;图2).本组HCC病例癌组织和癌旁组织间Mn-SOD和GSH-Px表达无显著差异(表1).癌旁组织中无炎症组和炎症组间Mn-SOD和GSH-Px表达也无显著差异.

表1 HCC及癌旁组织8-OHdG含量,hMTH1, hOGG1, Mn-SOD和GSH-Px的表达

M (n = 23)

组织	8-OHdG含量 (nmol/g DNA)	hMTH1 mRNA (hMTH1/ β -actin \times 100)	hOGG1 mRNA (hOGG1/ β -actin \times 100)	Mn-SOD mRNA (Mn-SOD/ β -actin)	GSH-Px mRNA (GSH-Px/ β -actin)
癌旁	133 (27-387)	0.256 (0.062-1.917)	1.256 (0.392-5.782)	0.190 (0.114-1.114)	1.652 (0.615-9.082)
HCC	56 (16-361) ^b	0.476 (0.083-4.861) ^a	1.196 (0.370-6.687)	0.186 (0.010-1.257)	0.980 (0.211-13.931)

^aP < 0.05, ^bP < 0.01, vs 癌旁.



M:marker, N:阴性对照,1:癌旁组织,2:HCC组织
图1 RT/实时PCR扩增产物的凝胶电泳条带.

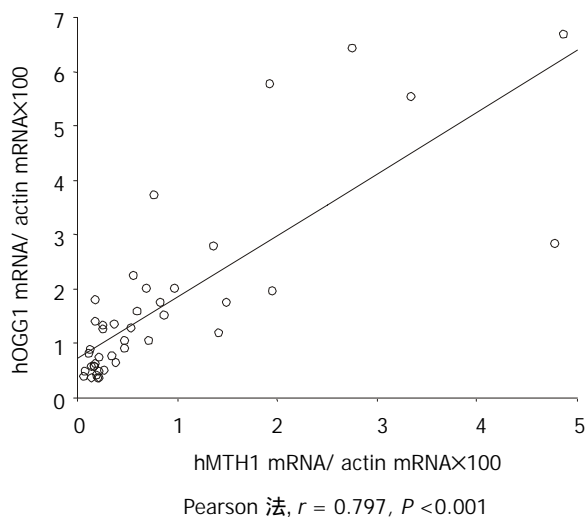


图2 HCC和癌旁组织hMTH1表达与hOGG1表达间的相关性.

3 讨论

8-OHdG 是一种由细胞内氧应激所引起的有致突变作用的DNA氧化损伤产物^[13]. 氧应激主要由细胞内代谢, γ -射线和金属离子转换等所引起^[14-17]. 许多报道表明肿瘤组织内DNA中8-OHdG含量明显高于癌旁组织^[18,19]. Shimoda et al^[20]的观察发现8-OHdG含量在慢性肝炎组织中明显升高,而在肝硬化和肝癌组织中并无显著升高. 近来研究表明DNA修复系统缺陷可导致基因组不稳定性及DNA突变率升高,从而导致肿瘤发生^[21-23]. 新近在HBV和HCV相关性慢性肝病的研究中发现DNA

氧化损伤产物8-OHdG含量与癌基因c-myc的表达呈正相关^[24]. 因此,本研究在比较肝癌组织和癌旁组织中氧应激标志物8-OHdG含量的基础上进一步观察了具备清除8-OHdG能力的DNA修复酶hMTH1、hOGG1以及抗氧化酶Mn-SOD和GSH-Px mRNA表达的变化,并分析其与8-OHdG含量之间的相互关系. 结果表明,8-OHdG含量在癌旁组织明显高于肝癌组织,在癌旁组织中炎症组明显高于无炎症组. 而抗氧化酶Mn-SOD和GSH-Px表达在肝癌和癌旁组织间无明显差异,且在癌旁组织中与有无炎症无关,这表明肝癌癌旁组织中8-OHdG含量升高可能为ROS产生过多所致,这与癌旁组织中炎症细胞浸润过度释放氧自由基有关.

核苷酸池中游离鸟苷的氧化比其在DNA中更迅速,因此,DNA修复酶hMTH1通过水解核苷酸池中游离8-OHdG在DNA氧化损伤的修复中起着首要作用^[25]. Kennedy et al^[26]对SV-40转化的非肿瘤性支气管上皮细胞(SV-40 transformed non-tumorigenic human bronchial epithelial cell, BEAS-2B)和肺癌细胞系的研究以及Okamoto et al^[27]在肾癌组织中的研究均显示8-OHdG含量在转化细胞和肿瘤细胞内明显升高. 本研究也发现hMTH1在肝癌组织中的表达明显增加. 因此,肝癌组织中8-OHdG含量相对较低可能为上调表达的hMTH1的清除效应. 肿瘤细胞中hMTH1基因过度表达有助于减少细胞内核苷酸池中游离8-OHdG的浓度,进而防止8-OHdG在DNA复制中错配入细胞DNA,以保持细胞DNA的完整性. 肿瘤细胞代谢相对活跃,因而可持续产生较高的氧应激,这可能是肿瘤细胞持续表达hMTH1的原因. 所以,hMTH1表达既能作为反映肝细胞内DNA修复能力的指标,也可作为氧应激反应程度的指标.

hOGG1基因编码产物的主要功能是切除DNA双链中与碱基C配对的8-OHdG,从而恢复基因组中正常的G:C配对,在防止8-OHdG的致突变作用中也起着十分重要的作用^[11]. Konto et al^[28]的研究发现hOGG1表达在人类结肠癌组织中明显升高,且与8-OHdG含量呈明显比例关系. 但我们的研究发现hOGG1表达在肝癌和癌旁组织间无显著差异,这可能与组织特异性有关. 另外,在人类肺癌和肾癌组织的研究也未发现癌组织和癌旁组织间hOGG1表达的差异,但发现了三种纯和性突变^[29]. 在前列腺癌患者中也发现了二种hOGG1基因序列变异(11657A/G和Ser326Cys),其修复酶活性降低可能与癌发生有关^[30]. 随后在大规模的肺癌临床病例对照研究中发现了一种与肺癌发生密切相关的基因

多态位点hOGG1Ser326Cys, 其修复酶活性降低, 使得患肝癌的易感性增加^[31,32]. 是否hOGG1 基因突变和/或多态位点也在肝癌的发生发展中起作用有待于进一步大规模的临床病例对照研究.

此外, 本研究还发现了肝癌和癌旁组织中hOGG1 和hMTH1 表达之间存在着明显的相关关系, 提示二者在修复氧化性DNA 损伤产物8-OHdG 中可能存在一定的协同关系. 前者主要功能是切除DNA 中与碱基C 错配的8-OHdG, 后者则水解核苷酸池中游离的8-OHdG. 因此, 推测DNA 修复酶hOGG1 和hMTH1 可能通过协同作用调节细胞内8-OHdG 浓度, 修复其所致的碱基错配和可能引起的关键基因突变, 在肝癌发生的防御机制中起到作用.

总之, 通过本组病例观察可初步得出如下结论:(1) 肝癌癌旁组织中升高的8-OHdG 浓度主要是由于炎症反应时炎性细胞过多释放氧自由基所致, 由此推测, 肝脏慢性炎症反应可能通过引起肝细胞内DNA 氧化损伤, 进而导致肝细胞的癌变;(2) 肝癌组织中8-OHdG 含量相对较低可能与上调表达的hMTH1 的调节有关;(3) hMTH1 表达水平可作为反映肝细胞内氧应激水平以及DNA 氧化损伤修复能力的指标;(4) DNA 修复酶hOGG1 和hMTH1 可能协同参与肝细胞内与8-OHdG 相关的DNA 氧化损伤的修复, 在肝癌的发生和防御机制中起着重要的作用. 其表达不足或基因多态位点与突变可能参与肝癌的发生和防御机制.

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