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文献综述 REVIEW

HBx与肝细胞癌发病机制的研究进展

段昌虎, 郜 升

段昌虎, 郜升, 哈尔滨医科大学附属第二医院普外一科 黑龙江省哈尔滨市 150086
段昌虎, 主要从事肝胆胰腺外科的研究.
作者贡献分布: 本文综述由段昌虎完成; 郜升负责审校.
通讯作者: 郜升, 教授, 主任医师, 150086, 黑龙江省哈尔滨市南岗区保健路148号, 哈尔滨医科大学附属第二医院普外一科. taisheng73@gmail.com
电话: 0451-86605356
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Role of hepatitis B virus X protein in hepatocarcinogenesis

Chang-Hu Duan, Sheng Tai

Chang-Hu Duan, Sheng Tai, Department of General Surgery, the 2nd Affiliated Hospital of Harbin Medical University, Harbin 150086, Heilongjiang Province, China
Correspondence to: Sheng Tai, Professor, Chief Physician, Department of General Surgery, the 2nd Affiliated Hospital of Harbin Medical University, 148 Baojian Road, Nangang District, Harbin 150086, Heilongjiang Province, China. taisheng73@gmail.com
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Abstract
Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the third most common cause of cancer-related death. Chronic hepatitis B virus (HBV) infection has been identified as a major risk factor for HCC. Evidence suggests that the HBV X protein (HBx) plays a crucial role in the carcinogenesis of HCC. HBx is a multifunctional regulator that plays a key role in the occurrence, development, invasion and metastasis of cancers. Due to its important roles in the development of HCC, the research on the HBx protein has become a hot topic in recent years. This review describes the latest advances in understanding the role of the HBx protein in hepatocarcinogenesis.

Key Words: Hepatitis B virus; Hepatitis B virus X protein; Hepatocellular carcinoma

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摘要
原发性肝癌(hepatocellular carcinoma, HCC)是世界范围内最常见的恶性肿瘤之一, 其发病率位于所有癌症的第5位, 死亡率为所有癌症的第3位, 严重威胁着人类健康. 在诱发HCC的众多因素中, 乙型肝炎病毒(hepatitis virus, HBV)感染占到5%以上. 随着对HBV和HCC研究的深入, 人们发现HBV中的*x*基因表达产物(hepatitis B virus X protein, HBx)蛋白是一种多功能的调节蛋白, 具有广泛的反式激活功能, 在肝癌的发生、发展到侵袭转移中, 发挥着不可忽视的作用, 成为近年来研究的热点, 本文就近年来对HBx研究进展作一综述.

关键词: 乙型肝炎病毒; 乙型肝炎病毒x蛋白; 肝细胞癌

核心提示: 乙型肝炎病毒(hepatitis B virus)感染是诱发原发性肝癌的主要原因之一, 乙型肝炎病毒x基因的表达产物乙型肝炎病毒X蛋白(hepatitis B virus X protein, HBx)能通干扰宿主细胞转录, 信号转导, 细胞周期, 蛋白质分解, DNA修复, 细胞凋亡和染色体的稳定性等引起肝癌的发生, 同时参与肿瘤侵袭与转移. HBx蛋白在肝癌发生中扮演的角色及其作用机理成为HBV相关肝癌研究的热点内容.

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0 引言
原发性肝癌(hepatocellular carcinoma, HCC)是世界范围内最常见的恶性肿瘤之一, 其发病率位于所有癌症的第5位, 死亡率为所有癌症的

■背景资料
肝细胞癌其发病率和死亡率居高不下. 我国肝癌以乙型肝炎病毒(hepatitis virus, HBV)相关的肝癌患者所占比例较大, 如何提高HBV相关肝癌早期诊断率是亟待解决的难题, 乙型肝炎病毒X蛋白(hepatitis B virus X protein, HBx)在乙型肝炎相关的肝癌的发生发展过程中起着重要作用, 成为研究热点之一.

■同行评议者
姚登福, 教授, 南通大学附属医院

■研发前沿
HBV中的*x*基因表达产物HBx蛋白是一种多功能的调节蛋白, 具有重要功能, 在肝癌的发生、发展以及侵袭转移中, 发挥着不可忽视的作用.

第3位, 严重威胁着人类健康[1,2], 在过去的几十年人们对其进行了一系列流行病学和实验研究, 确定了HCC与乙型肝炎病毒(hepatitis virus, HBV)、丙型肝炎病毒(hepatitis B virus, HCV)、黄曲霉毒素、饮酒等很多因素有关[3,4]. 其中50%-55%的HCC发生是由于持续的HBV感染引起, 在流行地区高达70%-80%肝癌是由HBV感染引起[5,6]. 在HBV的所有基因组中, HBx通过干扰宿主细胞转录、信号转导、细胞周期、蛋白质分解、DNA修复、细胞凋亡和染色体的稳定性等引起肝癌的发生[7-10], 同时HBx通过影响肝肿瘤细胞的迁移能力促进肿瘤的侵袭与转移. 本文就近年来对于HBx研究的进展作一综述.

1 HBx的结构与生物学效应

*HBV*基因组大约32 kb, 具有4个相互重叠的开放读码框架(ORF): S区、C区、P区、X区, 分别编码HBsAg、HBcAg、DNAP和HBx, 其中X-ORF在N端和P-ORF部分重叠, 在C端和前C-ORF部分重叠[11]. *HBx*基因是*HBV*基因组中最小的开放读码框, 其编码基因位于第1376-1837位核苷酸之间, 所编码的HBx蛋白由154个氨基酸组成, 分子量约为17 kDa[12]. 随着对HBV和原发性肝癌研究的深入, 人们发现*x*基因表达的蛋白HBx在HBV相关的肝癌的发生发展中扮演重要角色[4,13,14].

HBx在HCC的形成中起主导作用, 早期体外实验研究证实: 将HBx导入小鼠的肝细胞中, 可引起肝细胞的恶性转化[15,16]; 将*HBx*基因转入小鼠体内, 可干扰正常肝细胞生长, 诱发转基因小鼠肝癌形成, 使肝癌发生率至少增加10倍; 缩短了HCC发生的潜伏期; 增加了促癌剂致肝癌的形成率. 人群调查发现, 早期肝癌形成过程中, HBx发挥着重要作用[17]; HBx抗体在肝癌患者中比患有乙型肝炎而未发生肝癌患者中表达量要高; 另外大量文献报道HBV相关的肝癌发生过程中, HBV整合入宿主细胞的过程中HBx整合入宿主是最重要的一步, 且HBV相关的肝癌患者定期检查发现HBx检出率及稳定性是最高的, 提示HBx在肝癌形成中发挥重要作用[18].

2 HBx的反式激活机制

HBx在肝细胞内的分布与其蛋白表达水平密切相关, 低表达时主要分布在细胞核, 高表达时多聚集在胞浆. HBx不具有结合双链DNA的能力, 但可通过蛋白-蛋白间相互作用发挥其反式转录活性[19]. HBx通过各种信号通路, 包括Ras/Raf有丝分裂原激活蛋白激酶(mitogen-activated protein kinases, MAPK), 蛋白激酶C(protein kinase C, PKC)[20], 核因子κB(nuclear factor κB, NF-κB), 应激活化蛋白激酶(stress-activated protein kinases, SAPK)/c-Jun氨基末端激酶(jun n-terminal kinases, JNK), 磷脂酰肌醇激酶3(phosphatidylinositol 3-hydroxy kinase, PI3K)/蛋白激酶B(protein kinase B, PKB)以及Janus激酶(janus kinase, JAK)/信号转导和转录激活子(signal transducer and activator of transcription, STAT)[21]等各种不同的信号通路, 促进癌症的发生.

2.1 HBx与NF-κB NF-κB是一种分布及作用十分广泛的真核细胞转录因子, HBx通过多种途径激活NF-κB信号通路[22,23], 激活的NF-κB从胞质转入核内, 启动核内靶基因的转录, 调节诸如cyclin D1[24], Calpain Small Subunit 1[25], MTA1[26,27]等一些肝癌相关因子的表达, 从而抑制细胞凋亡, 促进肿瘤细胞存活、增殖及恶性转化, 与肝癌的发生发展关系密切.

2.2 Ras-Raf MAPK信号通路 Ras-Raf MAPK信号通路(膜受体络氨酸蛋白激酶信号传递途径)在肝癌形成过程中起着重要作用[28]. 在该通路中, HBx激活Src激酶, 从而激活Ras, 刺激合成Ras-GTP复合物, 促使Raf磷酸化而活化, 活化的Raf通过一系列反应激活MAPK, MAPK进一步活化AP-1、NF-κB、AP-2等多种转录因子, 导致肝癌的发生. 同时有文献报道HBx介导的Ras-Raf MAPK信号通路也与细胞周期密切相关, 导静止期的细胞脱离G_0期, 重返细胞周期, 可以降低细胞循环周期, 刺激细胞增殖.

2.3 PKC信号通路 PKC是一个磷脂依赖性激酶的大家族, 这些激酶参与细胞生长、分化、凋亡、癌变[29,30]. 野生型或突变的PKC的过度表达可导致无序细胞生长和转化. HBx能够增加内源性PKC的水平, 随后激活AP-1和NF-κB转录因子. 有证据表明, HBx激活NF-κB是一个PKC依赖过程. HBx也可能通过增加内源性激活因子Sn-1, 2-DAG短暂地激活PKC. 最近发现HBx蛋白能与XAP3(一种PKC结合蛋白)和PKC发生相互作用, 从而加速HBx的磷酸化, 增加PKC的自动磷酸化, 上调HBx介导的转录激活.

2.4 JAK-STAT信号通路 JAK-STAT信号通路是近年发现的一条由细胞因子刺激的信号转导通路, 参与细胞的增殖、分化、凋亡以及免疫调节等许多重要的生物学过程. 有专家指出

在乙型肝炎相关的肝癌中STAT3及STAT5过表达, 进一步研究发现HBx通过激酶JAK持续激活STAT蛋白, 从而导致肝癌的发生[31,32]. 有文献报道HBx可以通过下调miRNA Let-7a的表达来上调STAT的表达[33]. 同时有学者指出HBx可形成二聚体与JAK发生对接, 从而激活JAK, 激活的JAK可活化AP-1、NF-κB和SRE增强子, 发挥刺激转录活性的效应.

3 HBx和细胞凋亡的调控

细胞通过凋亡以清除老化的或未参与免疫反应的细胞, 如发生病理性干扰改变, 可对肿瘤生成起作用[32]. 肝细胞的正常凋亡过程发生改变也与肝癌的发生发展密切相关. 关于HBx的表达对细胞凋亡的调控人们进行了大量研究, 但这些研究的结论多种多样, 有研究表明HBx可以促凋亡[34-36], 也有研究得出相反观点, 认为HBx可以抗凋亡[37,38], 还有学者认为HBx对凋亡影响不大.

3.1 HBx促凋亡作用 尽管HBx自身并不能激活细胞凋亡通路, 但是体内及体外实验证实: HBx通过caspase3级联效应, 加速氧化应激状态下MCL-1蛋白的表达缺失发挥促凋亡作用, 导致肝癌的发生[39]. 同样有文献报道了HBx通过增加Bax易位于线粒体, 使得线粒体膜电位缺失而去极化, 导致细胞色素C的释放增加, 发挥促凋亡效应[40]. 国外学者也报道了HBx通过维生素K3介导, 使得线粒体膜去极化发挥促凋亡作用. 大量实验表明, Fas-FasL系统、肿瘤坏死因子α(tumor necrosis factor α, TNF-α)-TNFR等介导引发肝内细胞凋亡. HBx诱导FasL表达, 激活并上调了TNF-α的表达, 诱发肝细胞凋亡.

3.2 HBx抗凋亡作用 文献报道HBx可以调节非caspase依赖途径的两个蛋白[37]: 凋亡诱导因子(apoptosis-inducing factor, AIF)和AIF同源的AMID(mitochondrion-associated inducer of death), 通过免疫共沉淀技术发现HBx与AIF及AMID共同存在于细胞之中, HBx可以减少AIF及AMID介导的细胞凋亡发挥抗凋亡作用, 同时作者提出这种抗凋亡作用还与HBx抑制AIF线粒体-细胞核易位有关. 国内有学者报道HBx可以通过下调促凋亡因子miR192的表达水平来发挥抗细胞凋亡的功能[38]. 通过对原代培养的大鼠肝细胞研究发现HBx加剧NF-κB抗细胞凋亡的作用[41]; 然而, 当HBx诱导的NF-κB抗细胞凋亡途径被阻断时, 线粒体通透性转换孔的活性发生改变, HBx可促细胞凋亡. 可以发现HBx的促凋亡或抗凋亡功能的改变与NF-κB密切相关. 综合来看, HBx与凋亡的两种相互矛盾的结论可能都是不同的研究中或不同细胞系中细胞是否过度表达所导致的结果有关, 另一方面我们发现这些机制大都与线粒体有一定关系, 为我们下一步研究凋亡与肝细胞癌的发生提供了一定思路.

4 HBx调控的DNA修复

*p53*具有促进细胞凋亡、修复DNA损伤、维持细胞基因组稳定性等多种功能, 是维持细胞和机体稳定的重要基因之一, 其缺失或突变许多癌症发生密切相关[42-44]. 文献报道*p53*的突变及多态性对肝细胞癌的形成有着重要作用[45]. HBx抑制P53的DNA修复功能可能包括以下几种机制: (1)在HBV感染的早期, HBx通过不依赖P53途径促进肝细胞的凋亡; 随着肝细胞破坏及再生反复进行, 由于HBx与P53蛋白的相互作用, 导致P53调节DNA修复功能的缺陷, 使受损细胞能顺利通过G_0、G_1期进入DNA合成和分裂期; (2)HBx与P53的结合抑制了P53与DNA修复蛋白XPB、XPD的结合; (3)HBx通过环氧合酶2(COX-2)/PGE2通路诱导Mcl-1的表达, 来阻止P53的促凋亡作用[46]; (4)HBx的C末端区域能与野生型的P53(wtp53)蛋白在胞浆中结合, 阻碍其进入细胞核内, 从而抑制P53的转录, 影响wtp53阻断异常细胞生长, 促使DNA修复的能力; (5)细胞在紫外线照射处理时, HBx蛋白表达量增高能引起P53蛋白高表达, 两者在胞核相互作用抑制P53对DNA的修复功能, 使细胞对紫外线损伤更加敏感.

5 HBx影响表观遗传学的作用

表观遗传学是与遗传学相对应的概念. 遗传学是指基于基因序列改变所致基因表达水平变化, 如基因突变、基因杂合丢失和微卫星不稳定等; 表观遗传学是基于非基因序列改变所致基因表达水平变化, 如DNA甲基化和染色质构象变化等. 近年来研究发现表观遗传学与癌症的发生密切相关[47]. HBx介导的DNA甲基化改变和组蛋白修饰与肝癌的发生密切相关. HBx能够上调甲基转移酶1(DNA methyltransferase 1, DNMT1)的表达, 使得抑癌基因*p16*的启动子区超甲基化从而使P16表达下调, 导致癌症的发生[48]. 同时有文献指出在HBV导致的肝细胞癌中HBx可以通过DNA甲基化下调P16的表达导致肝细胞癌的发生[49]. HBx还能调节表观遗传学相关蛋白,

■相关报道
目前国内外关于HBx与肝癌相关的文献报道较多.这些报道都是通过系统的实验室及临床研究所得出的结论. 所以对我临床工作有一定的指导作用.

■创新盘点

目前关于HBx与肝细胞癌的发生发展有相关性已经得到了公认，本文对HBx在肝癌形成过程中的作用，调控信号通路的参与以及肝癌的发生发展乃至转移机制作的最新进展进行了分析.

通过作用于组蛋白去乙酰化酶(histone deacetylases, HDACs), 激发在一些靶基因周围调节元件的表观遗传学修饰, 诱导肝癌的发生[50]. 另外还有文献报道HBx可以通过调控HBV共价闭合环状DNA(covalently closed circular DNA, cccDNA)的表观遗传学改变来发挥促癌作用[51]. 由此认为HBx可通过表观遗传学的调控参与宿主基因和*HBV*基因的转录表达和复制能力.

6 *HBx*基因突变

新近研究发现肝癌患者组织及血清中存在着高频自发的*HBx*基因突变, 提示HBx的突变与肝癌的发生发展可能有着重要关系[52-54]. 第382至401碱基对缺失的HBx突变体(HBxDelta127), 可以通过活化固醇调节元件结合蛋白-1c(sterol regulatory element binding protein 1c, SREBP-1c)来促进肿瘤细胞的生长[55]. 肝癌组织中羧基端突变的HBx可以使着丝粒蛋白A(centromere protein A, CENP-A)表达升高, 而CENP-A在肝癌组织中的过表达与细胞恶性增殖相关[53]. HBx突变与HCC相关性的研究提供了一个新的视角来研究HCC的发病机制.

7 HBx促进肝癌细胞的侵袭与转移

研究显示在许多肿瘤中, 环氧合酶-2(cyclooxygenase-2, COX-2)及其产物过度表达[56]. 体内及体外实验中均证实HBx通过诱导膜基质金属蛋白酶-1和COX-2的表达可以促进肿瘤细胞的侵袭与转移. 临床患乙型肝炎导致肝癌患者的资料回顾性研究发现, HBx上调基质金属蛋白酶的表达有助有肝癌的转移. 这对我们临床工作中用于早期诊断及判断转移提供了一种新的思路.

8 结论

乙型肝炎相关的肝癌形成过程是一个多因素参与的复杂的过程, *HBx*基因在该过程中发挥了重要作用, 然而关于HBx与肝癌发生发展机制研究结果并不一致, 还存在较多分歧, 因此, 需要更多的综合研究, 全面了解HBx蛋白在肝癌中的作用. 此外, 我们应结合体内和体外两方面的研究结果, 联系临床肝癌发生的特点和病理特征, 为临床乙型肝炎相关的肝癌防治策略的制定提供有力依据.

9 参考文献

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■应用要点
随着人们对HBx研究的深入, 对肝癌的发病机制可以得到更好的认识, 为HBV相关肝癌的早期防治研究有一定意义.

■同行评价
本文内容客观全面，逻辑性较强，较好地反映了国内外该领域的研究进展，具有较重要的临床指导意义和科学价值.

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