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文献综述 REVIEW

HBX促进肝细胞癌发生发展的分子机制

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Molecular mechanism of hepatitis B virus X-associated hepatocarcinogenesis

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Abstract
Hepatocellular carcinoma (HCC) is one of the most common malignant diseases and has the fourth highest mortality rate worldwide. Chronic hepatitis B virus (HBV) infection is one of the most important etiological factors for HCC. Current studies show that the hepatitis B virus X (*HBX*) gene plays an important role in the development of HBV-associated HCC. HBX protein is a multifunctional regulator. Though interacting with different host factors, HBX takes part in many cell physiological activities, such as signal transduction, gene transcription, cell cycle progression, apoptosis and autophagy. This review will discuss the biological role of HBX protein in the development of HCC based on the current state of knowledge on this protein.

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), 是一种常见的恶性度较高的疾病. 其死亡率在世界排名第4位. 慢性乙型肝炎病毒(hepatitis B virus, HBV)的感染, 是其发病的一个重要因素. 目前证据表明乙型肝炎病毒X蛋白(hepatitis B virus X, *HBX*)基因在HBV介导的HCC中发挥着重要作用. HBX蛋白是一种多功能的调节蛋白, 通过与不同的宿主细胞因子相互作用, 来参与细胞信号的传导、转录、细胞周期、凋亡、自噬等多种细胞活动. 本文依据目前研究水平探讨HBX蛋白在HCC发生发展中的生物学作用.

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, HBV)感染是诱发原发性肝癌的主要原因之一, 乙型肝炎病毒X蛋白(hepatitis B virus X protein, HBX)能通过干扰宿主细胞转录、信号转导、细胞周期、DNA修复、细胞凋亡、自噬以及染色体稳定性等引起肝癌的发生, 同时参与肿瘤细胞的侵袭和转移, HBX蛋白在肝癌发生中扮演重要角色, 其租用机制成为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)是世界上主要的恶性疾病之一, 2000年发病率高

■背景资料
原发性肝癌是临床上最常见的恶性肿瘤之一, 其发病率和死亡率居高不下, 我国肝癌以乙型肝炎病毒(hepatitis B virus, HBV)相关的肝癌患者所占比例较大, *HBV*基因可以编码多种蛋白, 其中乙型肝炎病毒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, 为研究HBV相关肝癌发生发展机制, HBx成为研究热点之一.

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HBx蛋白是一种多功能的调节蛋白, 具有重要功能, 在HBV相关肝癌的发生发展以及侵袭转移中起到重要作用, 其研究意义不可忽视.

达50多万例[1]. 全世界HCC患者约75%-80%是由于持续感染乙型肝炎病毒(hepatitis B virus, HBV)(50%-55%)或者丙型肝炎病毒(hepatitis C virus, HCV)(25%-30%)[2,3]. 尽管实验表明HBV是引起HCC的主要因素[4], 然而其机制还不是很清楚. 经过对HBV相关的HCC广泛研究发现, 许多因素参与其中. 大量证据表明乙型肝炎病毒X蛋白(hepatitis B virus X protein, *HBX*)基因及其表达产物发挥着重要作用. 在HCC发生过程中, HBV DNA整合入宿主细胞中, *HBX*基因也包含在内, 且其仍然保持其活性. HBX引起HCC发生发展的机制已经被各种体内外实验研究, 然而具体机制尚不明了. 本文主要依据目前的研究结果阐述HBX在HBV相关HCC中的作用.

1 *HBX*基因与HBX蛋白

HBV基因组是一个长度为3.2 kb的部分双链环形基因组, 该基因组拥有4个重叠的开放阅读框架, 分别编码病毒包膜乙型肝炎表面抗原(hepatitis B surface antigen, HBsAg)、乙型肝炎核心抗体(hepatitis B core antibody, HBcAb)、病毒聚合酶(DNA polymerase, DNAP)和HBX蛋白[5]. 其中HBX蛋白作为一个重要的转录因子, 因其在肝癌的发生发展中发挥的多效性的作用而备受瞩目. 在哺乳动物噬肝病毒中, *HBX*基因编码的HBX蛋白是一种演化过程中高度保守的蛋白, 是病毒复制过程中至关重要的蛋白. HBX蛋白是由452个碱基构成的基因编码的长度为154氨基酸的蛋白质, 其分子量为17 kDa[6]. 作为一个多功能管理者, HBX通过与宿主细胞内不同的细胞因子相互作用参与许多细胞代谢过程的管理, 其中包括信号转导、转录、细胞周期、DNA损伤修复、自噬、凋亡、细胞增殖和基因稳定等[7].

2 HBX与表观遗传学改变

表观遗传学的改变是指在不改变DNA碱基序列的基础上, 改变基因的表达, 这些改变可以被视为基因的“开关”, 并最终决定哪些蛋白被转录[7]. 细胞内主要通过DNA的甲基化、组蛋白的修饰和相关RNA的沉默3种方式对基因进行表观沉默[7,8].

2.1 HBX参与宿主细胞DNA甲基化的过程 可逆性DNA甲基化主要发生在胞嘧啶-鸟嘌呤二聚体区域(CpGs), 甲基基团通过转甲基酶被添加到该区域胞嘧啶的第5位碳原子上[9]. DNA甲基化主要由DNA转甲基酶家族(a family of DNA methyltransferases, DNMTs)来构建, DNMTs家族主要有三个成员(DNMT1、DNMT3A和DNMT3B)参与催化特定的转甲基过程[10]. DNMT1主要参与复制过程中DNA甲基化的重建, DNMT3A和DNMT3B则是介导新的DNA甲基化过程[8]. 目前研究表明这3种DNMTs成员都可以被招募到抑癌基因的启动子上, 引起该区域的高甲基化并降低其表达[10]. 而致癌基因启动子上的DNMTs则被释放, 导致其低甲基化及相应基因的高表达[11]. HBX增强DNMT的活性, 并导致宿主细胞中抑癌基因CpG区域异常甲基化[12]. 这些基因参与细胞周期的管理、细胞生长、去分化、侵袭、凋亡、免疫逃逸以及异生代谢等多种生理活动, 且这些活动都与HBV介导的肝癌的发生发展密切相关[13]. HBX可以通过自身反式激活活性提高DNMT1和DNMT3A的表达, 致使一些具有肿瘤抑制活性基因的启动子高甲基化[14]. 例如负性调节细胞周期的*P16*基因[14]; 与肿瘤侵袭和去分化密切相关的钙黏蛋白基因(*E-cadherin*)[15]; 介导生长抑制信号传导通路的胰岛素样生长因子(insulin-like growth factor, IGF)结合蛋白3(IGF binding protein 3, IGFBP-3)[16]. 进来一些研究表明HBX可以使启动子低甲基化来提高相应基因的表达, 这些基因包括一些促进肿瘤发生相关的基因, 例如视黄醛脱氢酶1(retinal dehydrogenase 1, *Raldh1*); 血浆视黄醇结合蛋白前体(retinol-binding protein precursor, *RBP*); 细胞视黄醇结合蛋白I(cellular retinol-binding protein 1, *CRBP1*); 以及钙黏素6基因[17,18].

2.2 HBX可以导致异常的组蛋白修饰 DNA甲基化状态的改变在HBX介导的肝癌中并不是孤立存在的, 其发生通常伴有其他表观遗传学的改变, 例如组蛋白的修饰. 其主要作用是激起和维持基因的活性状态[19]. 组蛋白修饰在生理上通过与基因转录、复制及DNA修复过程中相关的各种关键蛋白相互作用, 来管理DNA序列的使用权限. 在肝癌细胞中组蛋白修饰状态通常发证反常的改变, 这些改变可以影响细胞的基因表达, 从而干扰细胞的正常活动. 目前在HBX介导的肝癌细胞中, 对于组蛋白修饰改变研究比较热的就是组蛋白赖氨酸残基的乙酰化和甲基化修饰. 乙酰化修饰主要由组蛋白乙酰转移酶

(histone acetyltransferases, HAT)和组蛋白脱乙酰酶(histone deacetylases, HDAC). 目前研究表明HBX促进HBV诱导的肝癌的发生机制之一就是通过使特定的肿瘤相关基因乙酰化来实现的. 例如, HBX可以占据宿主目的基因的启动子, 增加cAMP反应元件结合蛋白(cAMP-response element binding protein, CREB)结合蛋白(CREB binding protein, CBP)/p300转录复合体(内源性乙酰酶)在该区域的聚集量, 从而导致组蛋白的乙酰化和基因的高表达[20]. 这一机制在HBX引起的细胞因子白介素-8(interleukin-8, IL-8)和增殖细胞核抗原(proliferating cell nuclear antigen, PCNA)的高表达中也有发现[21]. HBX还可以通过导致特定的抑癌基因组蛋白脱乙酰化诱导肝癌的发生. 例如, HBX抑制CDH1和IGFBP-3的表达机制就是分别招募转录因子mSin3A/HDAC1复合体和Sp1/HDAC1复合体(内源性脱乙酰酶)到各自的基因的组蛋白上, 使其脱乙酰化[22,23]. 进来有研究表明HBX也可以导致组蛋白甲基化, 特别是H3组蛋白赖氨酸4(H3-K4). SET和MYND结构域3(SET and MYND domain-containing 3, SMYD3)的组蛋白H3-K4特异性甲基转移酶(histone methyltransferase, HMT), 可以提高该区域的基因的转录活性[24]. HBX通过提高SMYD3表达, 反式激活一些致癌基因, 比如*C-MYC*[25], 其过度表达对肝癌的发生发展起到重要作用.

2.3 HBX介导肝癌细胞中miRNA的改变 HBX可以上调一些miRNAs的表达量, 例如可以靶向沉默肿瘤抑制基因*RASSF1A*的miRNA-602(miR-602)[26]; 沉默PTEN以提高肿瘤转移的miR-29a和miR-148a[27,28]等. HBX也可以下调一些miRNAs的量, 例如用以沉默肿瘤转移相关基因*MTA1*的miR-661[29]; 靶向作用于DNMT3A的miR-101[30]等.

然而, HBX在调控宿主细胞基因表达中的主要角色, 是作为一种转录因子调控miRNAs的表达还是作为一种辅因子影响DNA甲基化和组蛋白的改变, 还需要进一步探究.

3 HBX、衰老和端粒末端的改变

衰老可以阻止受损细胞的增殖, 同时通过提高肿瘤抑制因子的表达来减少恶变的风险[31]. 肝硬化患者的肝脏中, 可以观察到衰老表型占优势的肝细胞增殖率的降低以及端粒的缩短和细胞周期阻滞[32]. 端粒是一种结合在真核细胞染色体末端的DNA-蛋白复合体, 用以保护染色体终末端防止其被降解. 从正常的肝细胞到慢性肝炎细胞, 端粒是逐渐缩短的, 肝癌细胞中最短[33]. HBX可以作为端粒酶启动子阻遏蛋白*Myc*基因相关锌指(Myc-associated zinc finger, MAZ)的辅阻遏物, 通过提高MAZ蛋白与端粒酶启动子结合能力, 从而抑制端粒酶转录, 导致端粒逐渐缩短[34]. 所以, 在衰老的肝硬化组织中, 肝细胞想要恶变需要绕过衰老机制并且能够在端粒极度缩短的情况下存活.

另外, 有证据表明乙型肝炎病毒DNA序列可以整合到端粒酶基因组中, 并导致端粒酶表达失调[35,36]. 而且, HBX还可以提高端粒酶的表达[37]. 在肝癌细胞中, 尽管端粒酶活性提高, 但是端粒始终很短, 这可以导致端粒稳定性差、染色体稳定性差以及多倍体的出现[37]. 总之, 大部分肝癌细胞的染色体都表现出高度的不稳定性, 类似于衰老逐渐累积的细胞, 这一点已经在肝硬化患者的肝脏组织中的得到证实, 并且这一不稳定性频率会随着细胞的癌变程度提高[38].

4 HBX与自噬

自噬是一种在进化上保守的细胞新陈代谢过程, 可以使细胞通过降解自身细胞质中的蛋白提供自身所需要的营养物质, 从而使细胞能够在饥饿等恶劣条件下存活[39]. 根据物质的性质以及运送到溶酶体的方式, 可以将自噬分为巨大囊泡自噬(macroautophagy)、微小囊泡自噬(microautophagy)和分子伴侣介导的自噬(chaperone-mediated autophagy)[40]. 自噬过程的最初阶段是形成一个双膜的囊泡结构, 叫做初级自噬囊泡(autophagosomes), 用以将需要降解的物质从细胞质中隔离出来. 初级自噬囊泡形成后与溶酶体结合形成单膜的次级自噬囊泡(autolysosomes), 使得囊泡内的物质在多种水解酶及高度酸性的环境下被充分反应, 最终降解为氨基酸、脂肪酸、碳水化合物和核苷酸在细胞内被利用[41]. 自噬在肝癌细胞对索拉菲尼等化疗药物产生的抵抗过程中发挥着重要作用[42]. HBX可以通过多种机制来提高细胞的自噬水平.

4.1 HBX与Beclin1 HBX通过激活死亡相关蛋白激酶(death-associated protein kinase, DAPK), 提高Beclin1的表达量来提高自噬[43-45]. Beclin1可以与磷脂酰肌醇3-激酶(phosphatidylinositol 3-kinase, PI3K)形成复合体VPS34, 参与初级自噬囊

■相关报道
HBx蛋白已经被广泛研究, 其诱导肝癌发生发展的相关机制也已经通过细胞及动物实验得到证实, 目前国内外关于HBx的文献报道较多, 对于指导临床工作有一定的意义.

■创新盘点
本文对HBx在肝癌的发生发展过程中的作用, 调控信号通路的参与以及肝癌的转移机制的最新进展进行了分析.

泡的形成[46].

4.2 HBX与PI3K/蛋白激酶B(protein kinase B, PKB或AKT)信号传导通路 HBX可以通过激活PI3K/AKT信号传导通路增强自噬[47,48]. HBX实现这一过程主要是通过抑制肿瘤抑制因子PTEN来完成的. PTEN通过其去磷酸化作用阻止PI3K下游靶蛋白PIP2生成PIP3, 从而抑制PI3K/AKT信号传导通路[49]. HBX提高细胞内反应活性氧(reactive oxygen species, ROS)的量, 氧化PTEN蛋白, 使其失活, 从而间接激活PI3K/AKT信号传导通路, 增强自噬的表达[47,48]. PI3K蛋白家族对于细胞的增殖、分化和转移等有着重要的作用, 该蛋白家族主要有3个亚型, 其中第三亚型(PI3K Ⅲ)是唯一存在于哺乳动物细胞中的亚型, 也叫VPS34, 可以与Beclin1结合参与自噬初级自噬囊泡的形成[46,49].

4.3 HBX与溶酶体 HBX除了可以提高自噬的表达量, 还可以抑制自噬的降解. 近来有研究表明HBX可以通过抑制溶酶体的成熟, 影响其活性, 阻止自噬囊泡的降解[50].

5 HBX对凋亡的影响

维持正常的组织代谢平衡主要依靠细胞增殖和程序性细胞死亡(即凋亡). 凋亡主要负责清除感染、损伤和癌变的细胞以及在组织细胞发展过程中出现在错误地方的细胞. HBX在凋亡方面的影响对于肝癌的发展起到非常重要的作用, 其影响机制较为复杂, 因为HBX同时具有抗凋亡和促凋亡两种活性. 这明显矛盾的作用还没有被解释清楚, 目前较为合理的解释就是高表达的HBX可以促进凋亡, 而低表达的HBX则抑制凋亡[51].

5.1 HBX的抗凋亡作用 HBX可以抑制P53相关凋亡途径. HBX在细胞浆中与P53形成复合体, 阻止其进入细胞核, 从而阻止了P53在转录过程中的反式激活效应以及与其他转录因子的相互作用[52,53], 致使许多P53介导凋亡途径的相关基因表达受限, 例如*P21*、*Bax*、*Fas*等[54]. 另外HBX还可以通过上调凋亡抑制蛋白生存素(survivin)来抑制凋亡[55]. 生存素还可以与HBX反应蛋白(HBX interacting protein, HBXIP)形成复合体Survivin-HbXIP, 该复合体可以与半胱氨天冬氨酶9前体(pro-Caspase9)结合, 阻止其对凋亡蛋白酶活性因子1(apoptotic protease activating factor-1, Apaf1)的招募, 抑制线粒体凋亡途径的初始阶段[7]. HBX还可以通过核因子-κB(nuclear factor-kappa B, NF-κB)和CREB途径, 提高甲硫氨酸腺苷转移酶Ⅱα的表达, 致使S-腺苷-甲硫氨酸(S-adenosyl-methionine, SAM)量减少, 来抑制凋亡[56]. HBX也可以通过提高Wnt/β-catenin信号通路抑制凋亡[57]以及扰乱线粒体动态平衡, 增强线粒体的分裂和自我吞噬来削弱凋亡[58].

5.2 HBX的促凋亡作用 实验研究表明HBX可以通过许多不同的机制来促进凋亡的发生, 例如使Fas/FasL、Bax/Bcl-2等信号通路功能失调; 增强cFADD样IL-1β转化酶(cFADD like IL-1β-converting enzyme, cFLICE)的活性; 提高热休克蛋白60(HSP60)、HSP70、DNA损伤结合蛋白1(DNA damage-binding protein 1, DDB1)以及NF-κB等蛋白的表达[59-61]. 另外, 研究表明HBV病毒复制时, HBX可以提高细胞对凋亡杀伤的敏感性; 且细胞用以抵抗凋亡的TNFα, 在HBX的作用下含量也明显降低[62].

6 HBX与肝癌转移

HBX诱导的肝癌患者, 其复发率和转移率较高, 然而具体机制尚不明朗[63]. 近来研究表明HBX可以通过激活PI3K/AKT/糖原合成酶激酶-3β(glycogen synthase kinase-3β, GSK-3β)信号传导通路稳定Snail蛋白, 引起肝癌细胞的上皮间质转化, 从而促进肝癌细胞浸润转移[64]. HBV DNA整合入宿主细胞DNA时通常会导致HBV DNA的截断, 且主要发生在HBX蛋白的C'末端. 实验证明, HBX蛋白自然条件下C'末端被截短24个氨基酸可以提高HepG2细胞的浸润能力, 且可以增强基质金属蛋白酶10(matrix metalloproteinases 10, MMP10)的转录, 提高肝癌细胞的转移能力[65]. 另有报道称, HBX可以通过细胞外信号调节激酶(细胞外调节蛋白激酶)/CREB通路提高FoxM1(肝癌细胞转移的一个重要管理者)表达活性来促进肝癌细胞的转移[66]. HBX还可以通过提高HSP90α蛋白和转移相关蛋白1(metastasis-associated protein 1, MTA1)诱导肝癌细胞转移[67]. 另外, HBX引起细胞转移表型改变之外, 还可以通过自身或与生长因子相互作用提高细胞的运动能力[63]. 总之, 这些在公认的HBX相关的分子机制基础上寻找到的线索, 都为HBV相关的肝癌浸润转移提供了依据.

7 结论

HCC是一种较为流行且致命性较高的一种癌

症, 目前的研究主要为了阐明其发生的分子机制以便制定更好的治疗方案. HBV是诱发HCC的一个主要危险因素, 但是HBV相关HCC的发病机制尚不完全明了. 实验表明HBX蛋白在肝癌的发生中发挥着重要作用, 这些数据让我们了解了HBX蛋白的细胞转化的潜力, 然而还需要进一步探究. 充分理解HBX蛋白在HCC发生过程中的作用可能为HCC患者的治疗提供新的治疗方案.

■应用要点
随着国内外研究对HBx促进肝癌发生发展机制进行全面深入剖析, 对其作用机制得到了更好的认识, 对HBV相关肝癌的诊断及治疗研究有一定意义.

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■同行评价
本综述主要探讨*HBx*基因在HBV介导的HCC中的重要作用, 整篇综述内容详实, 叙述逻辑性强, 是一篇比较优秀的综述.

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