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文献综述 REVIEW

HBx诱导甲胎蛋白表达对肝细胞恶性转化的影响及其调控机制

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HBx induced expression of alpha fetoprotein drives malignant transformation of liver cells

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Abstract

The development of hepatocellular carcinoma (HCC) is closely related to hepatitis B virus (HBV) infection, and HBV-X protein (HBx) plays a critical role in the malignant transformation of liver cells. HBx stimulates the expression of alpha fetoprotein (AFP) *via* restraining the transcription activity of P53 in the early stage of HCC genesis. Recently, studies have indicated that HBx preferentially promotes AFP expression during the malignant transformation of hepatic cells, and AFP accelerates the expression of malignant behavior related molecules through activating the phosphatidylinositol-3 kinase (PI3K)/protein kinas A (AKT) signaling pathway. These results suggest that AFP may be an important factor for HBx driven hepatocarcinogenesis. The discovery of novel function of AFP implicates that AFP can be used not only as a tumor marker for HBV-related HCC but also as a target for HCC therapy.

背景资料
肝细胞癌(hepatocellular carcinoma, HCC)是严重威胁人类健康的恶性肿瘤, 在全球范围内肿瘤相关性死亡因素中排名第3位. 乙型肝炎病毒(hepatitis B virus, HBV)感染是导致肝细胞恶性转化的重要生物因素, 在肝细胞恶性转化的早期, HBV表达的X蛋白(HBx)激活甲胎蛋白(alpha fetoprotein, AFP)表达, AFP表达后能激活细胞生长和恶性转化的信号途径以及基因的表达, 所以AFP表达能预警HCC发生. 本文综述了HBx诱导AFP表达在肝癌发生发展过程中的作用及其调控机制研究的最新成果.

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研发前沿

HBx优先诱导AFP及其受体(AFPR)的表达, 但AFP如何通过AFPR发挥其生物学功能是一个尚未阐明的科学问题. 因此, 研究AFPR的结构及功能是阐明AFP功能的关键环节, 也是探索AFP作为治疗肝癌新靶点的核心问题.

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Key Words: Hepatitis B virus X protein; Alpha fetoprotein; Hepatocarcinogenesis

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摘要

肝细胞癌(hepatocellular carcinoma, HCC)发生与肝细胞感染乙型肝炎病毒(hepatitis B virus, HBV)密切相关, HBV在复制时表达的X蛋白(HBx)在肝细胞恶性转化过程中发挥关键性作用. 甲胎蛋白(alpha fetoprotein, AFP)是HCC发生早期表达的蛋白质, HBx通过抑制P53对*AFP*基因的阻遏作用诱导AFP表达. 近期研究发现, 在HBx诱导的肝细胞恶性转化过程, 优先促进AFP表达, AFP通过激活磷酸肌醇-3激酶(phosphatidylinositol-3 kinase, PI3K)/蛋白激酶-A(protein kinas A, AKT)信号途径刺激肝细胞恶性行为分子的表达, 提示AFP的表达可能是HBx驱动肝癌发生的重要因素和先锋分子. AFP新功能的发现, 可以利用AFP的表达预警HBV相关肝癌的发生, AFP可能作为肝癌治疗的新靶点.

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关键词: 乙型肝炎病毒-X蛋白; 甲胎蛋白; 肝癌发生

核心提示: 该文综述了乙型肝炎病毒(hepatitis B virus, HBV)-X蛋白(HBV-X protein, HBx)诱导甲胎蛋白(alpha fetoprotein, AFP)表达在肝癌发生发展过程中的作用及其调控机制研究的最新成果, 显示在感染HBV过程中, HBx能优先诱导AFP表达, 通过AFP的作用驱动肝癌的发生. 因此研究AFP在肝细胞恶性转化中的调控作用及其对癌基因表达的调节机制是探索AFP发挥促癌作用的生物学功能的关键问题. 肝炎病毒感染后导致AFP表达升高能预警HBV相关肝细胞恶性转化, AFP可能作为生物治疗肝癌的新靶点.

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0 引言

肝细胞癌(hepatocellular carcinoma, HCC)是严重威胁人类健康的恶性肿瘤. 全世界每年新诊断的HCC患者约60多万例, 其中近50%发生在中国, 而肝癌的发病率仍有不断上升的趋势[1]. 全世界的总人口中, 有8%的人群感染乙型肝炎病毒(hepatitis B virus, HBV)或丙型肝炎病毒, 感染这些肝炎病毒是导致肝癌发生率不断升高的重要原因[2]. 研究[3,4]已经证明, HBV感染是导致肝细胞恶性转化的关键生物因素. 但是HBV没有直接诱导肝癌发生的功能[5,6], HBV通过表达X蛋白(HBx)影响肝细胞内的凋亡信号、生长信号以及转录调节因子的作用, 导致肝细胞的异常增生和其他恶性行为. 在肝细胞恶性转化的早期, HBx激活沉默的甲胎蛋白(α-fetoprotein, *AFP*)基因促进AFP表达, 通过AFP的作用驱动肝癌的发生.

1 HBx诱导AFP表达在肝癌发生、发展过程中的作用

肝细胞感染HBV是诱发肝癌的重要因素. 80%以上的肝癌发生与感染HBV或丙型肝炎病毒有关, HBV等肝炎病毒可诱导肝细胞恶性转化[7-10], 但是HBV本身并没有直接激发肝细胞癌变的功能[5,6], 其通过诱导肝细胞内的驱动癌变的基因表达发挥诱癌作用, 而AFP表达是肝细胞恶性转化过程的早期事件, 暗示*AFP*基因表达可能与肝细胞恶性转化密切相关. AFP是胚胎时期高表达的蛋白质, 人出生2年后, *AFP*基因基本处于关闭状态, 但是在HBV相关的肝癌发生过程, *AFP*基因重新被激活而表达, 所以临床上, 采用血清AFP含量变化监测HCC的发生, 到目前为止, AFP还是诊断肝癌一个重要的指标[11], 但是AFP为何在肝细胞恶性转化过程中高表达以及表达后发挥怎样的生物学作用并不清楚. AFP是肝癌细胞高表达的特异性蛋白质, 许多肝癌患者(70%-80%)在发病期间都有*AFP*基因高表达的特征. 以往研究认为, AFP在肝癌发生过程具有免疫抑制作用, AFP通过抑制免疫细胞或细胞因子[12,13], 导致恶性转化的肝细胞逃避免疫监视得以在体内生存和转移. 但是, 近期研

究[14,15]发现AFP的高表达与肝癌、胃癌等恶性肿瘤细胞的恶性行为正相关, 而且研究[16]发现AFP具有促进肝癌细胞增殖相关基因表达的生物学功能. 我们前期研究[17]发现, 在肝癌细胞膜上存在2种不同亲和常数的AFP受体, AFP与其受体结合后通过cAMP和Ca^{2+}传递的信号途径诱导*N-Ras*和*c-myc*等基因的表达, 从而促进肝癌细胞增殖. Ogden等[18]和Arima等[19]研究发现, HBx能通过抑制p53对*AFP*基因启动子的阻遏作用, 导致*AFP*基因被激活而表达. 近期我们研究显示, HBV在诱导肝癌恶性转化过程中, 优先选择驱动AFP和AFP受体(AFPR)表达, 通过AFP激活磷脂酰肌醇-3激酶(phosphoinositide 3 kinase, PI3K)/蛋白激酶B(protein kinase B, AKT)信号途径诱导癌基因*Ras*、*Src*等的表达, 促进肝细胞恶性转化和肝癌细胞增殖[20,21]. AFP是肝细胞恶性转化的早期高表达的特异性蛋白质, 也就是在肝癌发生的早期, 肝细胞表达的AFP不仅有抑制免疫监视作用, 更为重要的是, AFP还能促进恶性转化的细胞生长. 这些研究结果显示, AFP不仅能抑制机体的免疫监视, 而且也能促进癌细胞增殖, AFP在肝癌的发生、发展中发挥抑制免疫和促进癌细胞生长的双重作用. 提示AFP是驱动肝癌发生、发展的一个重要的“先锋因子”.

2 AFP调控肝癌转移关键因子的表达及其作用

细胞具有转移性是细胞恶性转化的重要标志. 肝癌细胞具有强大的转移能力, 其表达的促进转移相关因子发挥重要作用. 癌细胞转移具有离巢、侵袭和定向迁移的特性, 细胞黏附分子或趋化分子增多是促进癌细胞离巢主要原因, 在诸多细胞黏附分子中, 细胞角蛋白-19(keratin 19, K19)和上皮细胞黏附分子(epithelial cell adhesion molecule, EpCAM)是两个关键的调控肝癌细胞转移的黏附分子, 这两个因子不仅能促进癌细胞离巢, 而且也能增强癌细胞在原发病灶的侵袭力[22-24]; 而趋化因子受体(CXC chemokine receptor, CXCR)的表达, 也是决定癌细胞定向转移并植入其他组织器官的一个关键因素[25,26], 其中CXCR4是一个重要的促进癌细胞转移的分子[27,28]. 这些分子均能调控癌细胞的恶性行为, 特别是侵袭转移行为. 角蛋白在不同的正常上皮细胞和皮肤毛发内表达, 发挥着极其重要的生理功能. K19是分子量最小的酸性角蛋白, 在正常肝细胞内不表达, 但在多种肿瘤中表达, 包括乳腺癌、肺癌、肝癌[22,29,30]. 研究[31]发现, K19通过促进细胞外基质降解或细胞移动来给肿瘤细胞提供高度的转移潜力, 例如K19重组到层黏连蛋白(一种所有基底膜上的主要蛋白质)可引发免疫反应破坏基底膜, 从而促进肝癌细胞的侵袭. 在肿瘤的发生和发展过程, EpCAM是一个与癌细胞转移密切相关的膜分子, EpCAM的作用能消除E-钙黏连素介导的细胞和细胞之间的黏连, 增加了癌细胞离巢能力, 而且EpCAM过表达能激活Wnt信号促进癌细胞的增殖和迁移[32,33]. 在肝癌细胞的转移过程中, 癌细胞高表达K19、EpCAM和CXCR4的协同作用不仅能破坏正常组织的包围, 而且也能促进癌组织的血管生成以及对正常组织的侵袭, 导致癌细胞离巢和定向转移. Cai等[34]临床观察发现在肝癌发生和复发过程中, AFP的表达与K19、EpCAM呈正相关性, 我们前期研究结果也发现, HBx诱导AFP表达后能刺激正常肝细胞的CXCR4表达, 显示AFP可能通过调控K19、EpCAM和CXCR4等分子的表达促进肝癌细胞转移. 研究[35]已经证明, 癌细胞转移不是癌变过程的晚期事件, 在细胞恶变的早期, 癌细胞就开始离巢转移. 因为AFP表达是肝细胞恶性转化过程的早期事件, 而且我们研究[20]发现AFP具有激活PI3K/AKT信号传递诱导肝癌发生的功能, 由于PI3K/AKT信号的激活是导致肝癌细胞转移的关键信号[36-38]. PI3K/AKT信号的激活能促进*K19*、*EpCAM*和*CXCR4*等基因的表达, 在肝细胞恶性转化的早期, 肝细胞表达的AFP不仅具有诱导肝细胞恶变的生物学功能, 而且还能通过激活PI3K/AKT信号驱动肝癌细胞转移.

3 HBx诱导AFP表达调控肝癌细胞恶性行为的作用机制

正常肝细胞在HBV感染后如何转化为恶性肝癌细胞的机制并不清楚. 在HBV复制过程中所表达的HBx能优先诱导AFP表达, 而AFP表达后调控凋亡信号或生长信号的传递可能是HBV诱发肝癌的主要调控原因. 我们研究[38]结果显示AFP能抑制Caspase信号传

相关报道
目前研究已经证明在HBV感染过程中其X蛋白能通过抑制P53对*AFP*基因启动子的阻碍作用促进AFP表达, 从而通过AFP激活PI3K/AKT信号途径驱动肝细胞恶性转化和肝癌细胞转移, 提示AFP可能是一个诱导肝癌发生的重要因子.

创新盘点

HBV诱导肝细胞恶性转化过程中, 其HBx蛋白优先激活AFP, AFP能与PTEN作用, 激活PI3K/AKT信号传递诱导IL-6表达, 也能促进与细胞恶性转化相关因子Ras、Src和CXCR4等表达. 本文综合介绍了AFP的这些功能.

递, Zhang等[39]也发现沉默AFP表达可促进Caspase的表达, 抑制肝癌细胞生长, AFP还能与维甲酸受体-β结合抑制维甲酸受体传递的信号途径, 导致肝癌细胞耐受维甲酸诱导的分化和凋亡作用[40-42]. 这些研究结果提示, 在肝癌的发生过程, AFP发挥抑制凋亡信号的传递作用, 也就是AFP通过抑制这些信号的传递, 对抗肿瘤坏死因子家族或维甲酸的凋亡诱导作用, 从而导致感染HBV的肝细胞在恶变早期逃避免疫监视作用或抗肿瘤药物的作用. PTEN(phosphate and tension homologue deleted on chromosome 10)是目前研究发现的具有抑制PI3K/AKT信号传递的蛋白质分子, PTEN不仅具有信号调节分子作用, 而且在维持正常细胞基因的稳定性、阻止细胞的恶变和转移发挥至关重要的作用[43,44]. 近期研究[20,21,45]显示AFP能与PTEN分子相互作用, 通过抑制PTEN的磷酸酶活性激活能够PI3K/AKT信号传递, 促进与细胞恶性转化相关因子Ras、Src和CXCR4等的表达; 近期研究[5]发现, 肝细胞感染HBV后诱发白介素-6(interleukin-6, IL-6)等炎症因子刺激炎症反应, IL-6的表达与HBV感染呈正相关性, 在化学药物和HBx诱导肝癌发生过程, 肝细胞分泌IL-6, IL-6通过自分泌的作用方式与其受体结合后[46,47], 诱导肝细胞变为肝癌干细胞, 因此IL-6被认为是诱导肝细胞转化为肝干细胞的关键细胞因子[48]. IL-6的表达受PI3K/AKT信号的调控[49,50], 由于肝细胞在感染HBV后通过自然重编程形式逆转为干细胞, 而干细胞的存在是癌变的细胞基础, 所以HBx诱导AFP表达后, 不仅通过激活PI3K/AKT信号途径诱导IL-6表达, 促进肝细胞自然重编程回归到干细胞状态, 而且也能通过PI3K/AKT信号途径诱导*Src*、*Ras*和*CXCR4*等与细胞恶性转化密切相关的基因表达, 促使肝干细胞恶性转化. 因此, AFP调控HBV诱导恶性行为的作用机制主要是通过细胞内的信号调节分子样作用发挥生物学效应, 即抑制Caspase信号传递导致感染HBV的肝细胞逃避免疫监控; 激活PI3K/AKT信号途径诱导肝癌干细胞的生成以及促进细胞恶性行为相关基因的表达.

4 结论

目前研究结果基本证实HBV感染肝细胞后通过自身复制产生HBx, 在保证病毒繁殖的过程中诱发肝细胞恶性转化[4], HBx调节信号传递和p53等转录因子优先诱导AFP表达, 通过AFP的作用抑制凋亡信号以及激活生长信号传递, 导致感染HBV的肝细胞得以在体内生存; 同时肝细胞感染HBV后诱导AFP表达激发机体产生炎症因子, 特别是IL-6等, 在慢性炎症的刺激过程, IL-6通过自分泌的作用诱发肝细胞重编程返祖回到干细胞状态, 由于AFP能激活PI3K/AKT信号刺激癌基因的表达, 导致干细胞向恶性方向转化. 这些结果显示AFP可能是HBV诱导肝细胞恶变、复发和耐药的一个重要分子. 但是, AFP为何在胚胎时期是一个诱导胚胎干细胞分化和增殖的分子, 而在肝细胞恶性转化时却发挥促癌作用? 这是非常值得探索的科学问题, 揭开AFP的这些生物学功能, 可利用AFP的表达预警HBV相关肝细胞恶性转化, AFP还可能被利用为生物治疗肝癌的新靶点.

5 参考文献

1 Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014; 64: 9-29 [PMID: 24399786 DOI: 10.3322/caac.21208]

2 El-Serag HB. Hepatocellular carcinoma. *N Engl J Med* 2011; 365: 1118-1127 [PMID: 21992124 DOI: 10.1056/NEJMra1001683]

3 Kekulé AS, Lauer U, Weiss L, Luber B, Hofschneider PH. Hepatitis B virus transactivator HBx uses a tumour promoter signalling pathway. *Nature* 1993; 361: 742-745 [PMID: 8441471 DOI: 10.1038/361742a0]

4 Rawat S, Bouchard MJ. The Hepatitis B Virus (HBV) HBx Protein Activates AKT To Simultaneously Regulate HBV Replication and Hepatocyte Survival. *J Virol* 2015; 89: 999-1012 [PMID: 25355887 DOI: 10.1128/JVI.02440-14]

5 Wang C, Yang W, Yan HX, Luo T, Zhang J, Tang L, Wu FQ, Zhang HL, Yu LX, Zheng LY, Li YQ, Dong W, He YQ, Liu Q, Zou SS, Lin Y, Hu L, Li Z, Wu MC, Wang HY. Hepatitis B virus X (HBx) induces tumorigenicity of hepatic progenitor cells in 3,5-diethoxycarbonyl-1,4-dihydrocollidine-treated HBx transgenic mice. *Hepatology* 2012; 55: 108-120 [PMID: 21932402 DOI: 10.1002/hep.24675]

6 Kim CM, Koike K, Saito I, Miyamura T, Jay G. HBx gene of hepatitis B virus induces liver cancer in transgenic mice. *Nature* 1991; 351: 317-320 [PMID: 2034275 DOI: 10.1038/351317a0]

7 Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; 61: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

8 Liu S, Zhang H, Gu C, Yin J, He Y, Xie J, Cao G. Associations between hepatitis B virus mutations

and the risk of hepatocellular carcinoma: a meta-analysis. *J Natl Cancer Inst* 2009; 101: 1066-1082 [PMID: 19574418 DOI: 10.1093/jnci/djp180]
9 Zampino R, Pisaturo MA, Cirillo G, Marrone A, Macera M, Rinaldi L, Stanzione M, Durante-Mangoni E, Gentile I, Sagnelli E, Signoriello G, Miraglia Del Giudice E, Adinolfi LE, Coppola N. Hepatocellular carcinoma in chronic HBV-HCV co-infection is correlated to fibrosis and disease duration. *Ann Hepatol* 2015; 14: 75-82 [PMID: 25536644]
10 Liu N, Jiao T, Huang Y, Liu W, Li Z, Ye X. HBV regulates apoptosis and tumorigenesis through miR15a-Smad7-TGF-β pathway. *J Virol* 2014 Dec 24. *[Epub ahead of print]* [PMID: 25540364]
11 El-Serag HB, Kanwal F. α-Fetoprotein in hepatocellular carcinoma surveillance: mend it but do not end it. *Clin Gastroenterol Hepatol* 2013; 11: 441-443 [PMID: 23376321 DOI: 10.1016/j.cgh.2012.12.046]
12 Um SH, Mulhall C, Alisa A, Ives AR, Karani J, Williams R, Bertoletti A, Behboudi S. Alpha-fetoprotein impairs APC function and induces their apoptosis. *J Immunol* 2004; 173: 1772-1778 [PMID: 15265907 DOI: 10.4049/jimmunol.173.3.1772]
13 Yamamoto M, Tatsumi T, Miyagi T, Tsunematsu H, Aketa H, Hosui A, Kanto T, Hiramatsu N, Hayashi N, Takehara T. α-Fetoprotein impairs activation of natural killer cells by inhibiting the function of dendritic cells. *Clin Exp Immunol* 2011; 165: 211-219 [PMID: 21592114 DOI: 10.1111/j.1365-2249.2011.04421.x]
14 Zhang Q, Shang L, Zang Y, Chen X, Zhang L, Wang Y, Wang L, Liu Y, Mao S, Shen Z. α-Fetoprotein is a potential survival predictor in hepatocellular carcinoma patients with hepatitis B selected for liver transplantation. *Eur J Gastroenterol Hepatol* 2014; 26: 544-552 [PMID: 24614696 DOI: 10.1097/MEG.0000000000000029]
15 Liu X, Sheng W, Wang Y. An analysis of clinicopathological features and prognosis by comparing hepatoid adenocarcinoma of the stomach with AFP-producing gastric cancer. *J Surg Oncol* 2012; 106: 299-303 [PMID: 22389029 DOI: 10.1002/jso.23073]
16 Parpart S, Roessler S, Dong F, Rao V, Takai A, Ji J, Qin LX, Ye QH, Jia HL, Tang ZY, Wang XW. Modulation of miR-29 expression by α-fetoprotein is linked to the hepatocellular carcinoma epigenome. *Hepatology* 2014; 60: 872-883 [PMID: 24798303 DOI: 10.1002/hep.27200]
17 Li MS, Li PF, He SP, Du GG, Li G. The promoting molecular mechanism of alpha-fetoprotein on the growth of human hepatoma Bel7402 cell line. *World J Gastroenterol* 2002; 8: 469-475 [PMID: 12046072]
18 Ogden SK, Lee KC, Barton MC. Hepatitis B viral transactivator HBx alleviates p53-mediated repression of alpha-fetoprotein gene expression. *J Biol Chem* 2000; 275: 27806-27814 [PMID: 10842185 DOI: 10.1074/jbc.M004449200]
19 Arima T, Nakao K, Nakata K, Ishikawa H, Ichikawa T, Hamasaki K, Ishii N, Eguchi K. Transactivation of human alpha-fetoprotein gene by X-gene product of hepatitis B virus in human hepatoma cells. *Int J Mol Med* 2002; 9: 397-400 [PMID: 11891535 DOI: 10.3892/ijmm.9.4.397]
20 Li M, Zhu M, Li W, Lu Y, Xie X, Wu Y, Zheng S. Alpha-fetoprotein receptor as an early indicator of HBx-driven hepatocarcinogenesis and its applications in tracing cancer cell metastasis. *Cancer Lett* 2013; 330: 170-180 [PMID: 23211536 DOI: 10.1016/j.canlet.2012.11.042]
21 Li M, Li H, Li C, Wang S, Jiang W, Liu Z, Zhou S, Liu X, McNutt MA, Li G. Alpha-fetoprotein: a new member of intracellular signal molecules in regulation of the PI3K/AKT signaling in human hepatoma cell lines. *Int J Cancer* 2011; 128: 524-532 [PMID: 20473866 DOI: 10.1002/ijc.25373]
22 Govaere O, Komuta M, Berkers J, Spee B, Janssen C, de Luca F, Katoonizadeh A, Wouters J, van Kempen LC, Durnez A, Verslype C, De Kock J, Rogiers V, van Grunsven LA, Topal B, Pirenne J, Vankelecom H, Nevens F, van den Oord J, Pinzani M, Roskams T. Keratin 19: a key role player in the invasion of human hepatocellular carcinomas. *Gut* 2014; 63: 674-685 [PMID: 23958557 DOI: 10.1136/gutjnl-2012-304351]
23 Schulze K, Gasch C, Staufer K, Nashan B, Lohse AW, Pantel K, Riethdorf S, Wege H. Presence of EpCAM-positive circulating tumor cells as biomarker for systemic disease strongly correlates to survival in patients with hepatocellular carcinoma. *Int J Cancer* 2013; 133: 2165-2171 [PMID: 23616258 DOI: 10.1002/ijc.28230]
24 Schimanski CC, Bahre R, Gockel I, Müller A, Frerichs K, Hörner V, Teufel A, Simiantonaki N, Biesterfeld S, Wehler T, Schuler M, Achenbach T, Junginger T, Galle PR, Moehler M. Dissemination of hepatocellular carcinoma is mediated via chemokine receptor CXCR4. *Br J Cancer* 2006; 95: 210-217 [PMID: 16819541 DOI: 10.1038/sj.bjc.6603251]
25 Xiang ZL, Zeng ZC, Tang ZY, Fan J, Zhuang PY, Liang Y, Tan YS, He J. Chemokine receptor CXCR4 expression in hepatocellular carcinoma patients increases the risk of bone metastases and poor survival. *BMC Cancer* 2009; 9: 176 [PMID: 19508713 DOI: 10.1186/1471-2407-9-176]
26 Bertran E, Crosas-Molist E, Sancho P, Caja L, Lopez-Luque J, Navarro E, Egea G, Lastra R, Serrano T, Ramos E, Fabregat I. Overactivation of the TGF-β pathway confers a mesenchymal-like phenotype and CXCR4-dependent migratory properties to liver tumor cells. *Hepatology* 2013; 58: 2032-2044 [PMID: 23813475 DOI: 10.1002/hep.26597]
27 Drury LJ, Ziarek JJ, Gravel S, Veldkamp CT, Takekoshi T, Hwang ST, Heveker N, Volkman BF, Dwinell MB. Monomeric and dimeric CXCL12 inhibit metastasis through distinct CXCR4 interactions and signaling pathways. *Proc Natl Acad Sci U S A* 2011; 108: 17655-17660 [PMID: 21990345 DOI: 10.1073/pnas.1101133108]
28 Ma N, Pang H, Shen W, Zhang F, Cui Z, Wang J, Wang J, Liu L, Zhang H. Downregulation of CXCR4 by SDF-KDEL in SBC-5 cells inhibits their

应用要点

HBx诱导AFP表达促进肝细胞的恶性转化, 提示AFP具有驱动肝细胞恶性转化的生物学功能, 而且研究证明AFP还具有抗凋亡诱导的功能. AFP的这些功能预示其是肝细胞恶性转化的先锋因子及肝癌细胞耐药的新靶点, 为肝癌的生物治疗提供了新的思路和策略.

同行评价
本文对指导该领域的科研具有较高的学术价值.

migration in vitro and organ metastasis in vivo. *Int J Mol Med* 2015; 35: 425-432 [PMID: 25504108 DOI: 10.3892/ijmm.2014.2033]
29 Meleady P, Clynes M. Bromodeoxyuridine increases keratin 19 protein expression at a posttranscriptional level in two human lung tumor cell lines. *In Vitro Cell Dev Biol Anim* 2001; 37: 536-542 [PMID: 11669288]
30 Mackinder MA, Evans CA, Chowdry J, Staton CA, Corfe BM. Alteration in composition of keratin intermediate filaments in a model of breast cancer progression and the potential to reverse hallmarks of metastasis. *Cancer Biomark* 2012; 12: 49-64 [PMID: 23396250 DOI: 10.3233/CBM-120293]
31 van Sprundel RG, van den Ingh TS, Desmet VJ, Katoonizadeh A, Penning LC, Rothuizen J, Roskams T, Spee B. Keratin 19 marks poor differentiation and a more aggressive behaviour in canine and human hepatocellular tumours. *Comp Hepatol* 2010; 9: 4 [PMID: 20167095 DOI: 10.1186/1476-5926-9-4]
32 Winter MJ, Nagelkerken B, Mertens AE, Rees-Bakker HA, Briaire-de Bruijn IH, Litvinov SV. Expression of Ep-CAM shifts the state of cadherin-mediated adhesions from strong to weak. *Exp Cell Res* 2003; 285: 50-58 [PMID: 12681286 DOI: 10.1016/S0014-4827(02)00045-9]
33 Maetzel D, Denzel S, Mack B, Canis M, Went P, Benk M, Kieu C, Papior P, Baeuerle PA, Munz M, Gires O. Nuclear signalling by tumour-associated antigen EpCAM. *Nat Cell Biol* 2009; 11: 162-171 [PMID: 19136966 DOI: 10.1038/ncb1824]
34 Cai X, Zhai J, Kaplan DE, Zhang Y, Zhou L, Chen X, Qian G, Zhao Q, Li Y, Gao L, Cong W, Zhu M, Yan Z, Shi L, Wu D, Wei L, Shen F, Wu M. Background progenitor activation is associated with recurrence after hepatectomy of combined hepatocellular-cholangiocarcinoma. *Hepatology* 2012; 56: 1804-1816 [PMID: 22684921 DOI: 10.1002/hep.25874]
35 Podsypanina K, Du YC, Jechlinger M, Beverly LJ, Hambardzumyan D, Varmus H. Seeding and propagation of untransformed mouse mammary cells in the lung. *Science* 2008; 321: 1841-1844 [PMID: 18755941 DOI: 10.1126/science.1161621]
36 Wang H, Xu L, Zhu X, Wang P, Chi H, Meng Z. Activation of phosphatidylinositol 3-kinase/Akt signaling mediates sorafenib-induced invasion and metastasis in hepatocellular carcinoma. *Oncol Rep* 2014; 32: 1465-1472 [PMID: 25070581 DOI: 10.3892/or.2014.3352]
37 Bai H, Weng Y, Bai S, Jiang Y, Li B, He F, Zhang R, Yan S, Deng F, Wang J, Shi Q. CCL5 secreted from bone marrow stromal cells stimulates the migration and invasion of Huh7 hepatocellular carcinoma cells via the PI3K-Akt pathway. *Int J Oncol* 2014; 45: 333-343 [PMID: 24806733 DOI: 10.3892/ijo.2014.2421]
38 Li M, Li H, Li C, Zhou S, Guo L, Liu H, Jiang W, Liu X, Li P, McNutt MA, Li G. Alpha fetoprotein is a novel protein-binding partner for caspase-3 and blocks the apoptotic signaling pathway in human hepatoma cells. *Int J Cancer* 2009; 124: 2845-2854 [PMID: 19267404 DOI: 10.1002/ijc.24272]
39 Zhang L, He T, Cui H, Wang Y, Huang C, Han F. Effects of AFP gene silencing on apoptosis and proliferation of a hepatocellular carcinoma cell line. *Discov Med* 2012; 14: 115-124 [PMID: 22935208]
40 Wang S, Jiang W, Chen X, Zhang C, Li H, Hou W, Liu Z, McNutt MA, Lu F, Li G. Alpha-fetoprotein acts as a novel signal molecule and mediates transcription of Fn14 in human hepatocellular carcinoma. *J Hepatol* 2012; 57: 322-329 [PMID: 22521346 DOI: 10.1016/j.jhep.2012.03.029]
41 Li C, Wang S, Jiang W, Li H, Liu Z, Zhang C, McNutt MA, Li G. Impact of intracellular alpha fetoprotein on retinoic acid receptors-mediated expression of GADD153 in human hepatoma cell lines. *Int J Cancer* 2012; 130: 754-764 [PMID: 21365646 DOI: 10.1002/ijc.26025]
42 Li M, Li H, Li C, Guo L, Liu H, Zhou S, Liu X, Chen Z, Shi S, Wei J, McNutt MA, Li G. Cytoplasmic alpha-fetoprotein functions as a co-repressor in RA-RAR signaling to promote the growth of human hepatoma Bel 7402 cells. *Cancer Lett* 2009; 285: 190-199 [PMID: 19501957 DOI: 10.1016/j.canlet.2009.05.014]
43 Bassi C, Ho J, Srikumar T, Dowling RJ, Gorrini C, Miller SJ, Mak TW, Neel BG, Raught B, Stambolic V. Nuclear PTEN controls DNA repair and sensitivity to genotoxic stress. *Science* 2013; 341: 395-399 [PMID: 23888040 DOI: 10.1126/science.1236188]
44 Seton-Rogers S. Tumour suppressors: PTEN surprise. *Nat Rev Cancer* 2013; 13: 520 [PMID: 23822982 DOI: 10.1038/nrc3569]
45 Zheng L, Gong W, Liang P, Huang X, You N, Han KQ, Li YM, Li J. Effects of AFP-activated PI3K/Akt signaling pathway on cell proliferation of liver cancer. *Tumour Biol* 2014; 35: 4095-4099 [PMID: 24425104 DOI: 10.1007/s13277-013-1535-z]
46 Kao JT, Lai HC, Tsai SM, Lin PC, Chuang PH, Yu CJ, Cheng KS, Su WP, Hsu PN, Peng CY, Wu YY. Rather than interleukin-27, interleukin-6 expresses positive correlation with liver severity in naïve hepatitis B infection patients. *Liver Int* 2012; 32: 928-936 [PMID: 22230324 DOI: 10.1111/j.1478-3231.2011.02742.x]
47 Li CH, Xu F, Chow S, Feng L, Yin D, Ng TB, Chen Y. Hepatitis B virus X protein promotes hepatocellular carcinoma transformation through interleukin-6 activation of microRNA-21 expression. *Eur J Cancer* 2014; 50: 2560-2569 [PMID: 25087183 DOI: 10.1016/j.ejca.2014.07.008]
48 He G, Dhar D, Nakagawa H, Font-Burgada J, Ogata H, Jiang Y, Shalapour S, Seki E, Yost SE, Jepsen K, Frazer KA, Harismendy O, Hatziapostolou M, Iliopoulos D, Suetsugu A, Hoffman RM, Tateishi R, Koike K, Karin M. Identification of liver cancer progenitors whose malignant progression depends on autocrine IL-6 signaling. *Cell* 2013; 155: 384-396 [PMID: 24120137 DOI: 10.1016/j.cell.2013.09.031]
49 Frampton G, Invernizzi P, Bernuzzi F, Pae HY, Quinn M, Horvat D, Galindo C, Huang L, McMillin M, Cooper B, Rimassa L, DeMorrow

S. Interleukin-6-driven progranulin expression increases cholangiocarcinoma growth by an Akt-dependent mechanism. *Gut* 2012; 61: 268-277 [PMID: 22068162 DOI: 10.1136/gutjnl-2011-300643]
50 Codeluppi S, Fernandez-Zafra T, Sandor K, Kjell J, Liu Q, Abrams M, Olson L, Gray NS, Svensson CI, Uhlén P. Interleukin-6 secretion by astrocytes is dynamically regulated by PI3K-mTOR-calcium signaling. *PLoS One* 2014; 9: e92649 [PMID: 24667246 DOI: 10.1371/journal.pone.0092649]

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