

HBx在肿瘤微环境中的作用及其对肝癌发生发展的影响

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Pathophysiological implications of hepatitis B X protein in tumor microenvironment of hepatocellular carcinoma

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Abstract

Hepatitis B X protein (HBx), encoded by hepatitis B virus (HBV), is a multifunctional and potentially oncogenic protein that has significant functions during the progression from chronic hepatitis B to cirrhosis and eventually to hepatocellular carcinoma (HCC). Over the past decades, it has been widely established that chronic inflammation orchestrates a tumor-supporting microenvironment. HCC is a typical chronic inflammation-related cancer and inflammation is the main risk factor for the progression of HCC. As a major viral transactivator, HBx is thought to play a pivotal role in the activation and maintenance of hepatic inflammatory process through interaction with various components of the tumor microenvironment including tumor cell and surrounding peritumoral stroma. Complex interactions between HBx and these cell types in this microenvironment will regulate tumor growth, progression, metastasis, and angiogenesis. In this review, we mainly summarize the current understanding of HBx and its contribution to the inflammatory tumor microenvironment of HBV-related HCC.

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■背景资料

乙型肝炎病毒x蛋白(hepatitis B X protein, HBx)由乙型肝炎病毒(hepatitis B virus, HBV)X基因所编码, 具有广泛的反式激活作用, 大量研究表明HBx可通过与肿瘤微环境中的各组分相互作用在肝脏炎症反应的激活及维持中发挥重要作用, 拮抗HBx蛋白在肿瘤微环境中的活性及功能的相关策略可能成为肝癌治疗中的新靶点及方向。

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■ 研发前沿

HBx与肝癌的关系一直是近年来研究的热点, 本文对HBx在HBV相关性肝癌肿瘤微环境中的作用进行重点阐述, 今后的研究重点应明确不同情况下HBx在亚细胞定位的调控机制, 找出HBx调控肝脏肿瘤微环境所涉及的具体信号通路, 为拮抗HBx的生物学功能提供新方向。

Key Words: Hepatitis B virus; Hepatitis B X protein; Hepatocellular carcinoma; Tumor microenvironment; Inflammation

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摘要

乙型肝炎病毒x蛋白(hepatitis B X protein, HBx)是由乙型肝炎病毒(hepatitis B virus, HBV)所编码的一种多功能潜在性肿瘤蛋白, 其在慢性乙型肝炎, 肝硬化及肝癌过程中发挥着极其重要的作用。既往研究表明慢性炎症能形成一种有利于肿瘤生存的微环境。肝癌是一种典型的慢性炎症相关性肿瘤, 炎症是肝癌侵袭进展的主要危险因素。作为乙型肝炎病毒的主要激活子, HBx可通过与肿瘤微环境中的肿瘤细胞及肿瘤周围基质成分相互作用在肝脏炎症反应的激活及维持中发挥重要作用。HBx与这些细胞成分之间复杂的相互作用将调控肿瘤的生长、侵袭、转移以及血管形成。本文将就此领域相关内容作一述评。

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关键词: 乙型肝炎病毒; 乙型肝炎病毒x蛋白; 肝细胞癌; 肿瘤微环境; 炎症

核心提示: 乙型肝炎病毒x蛋白(hepatitis B X protein)与肿瘤微环境中的肿瘤细胞及肿瘤周围基质成分相互作用将调控肿瘤的生长、侵袭、转移以及血管形成, 肝脏肿瘤微环境的细胞及非细胞成分有望成为肝癌治疗的新靶点。

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0 引言

肝细胞癌(hepatocellular carcinoma, HCC)是一种常见的消化系恶性肿瘤, 世界范围内, 每年约75万人群发生肝癌^[1]。流行病学资料显示乙型肝炎病毒(hepatitis B virus, HBV)感染是肝癌发生的主要危险因素之一, 50%以上的肝癌患者归因于持续的HBV感染^[2]。机体感染HBV后

常导致慢性乙型肝炎并最终进展到肝硬化及肝癌。在过去的几十年, 学者们针对肝癌发生发展的相关机制进行了广泛深入的研究, 然而HBV致癌的确切机制仍不清楚。目前学术界认为HBV可通过多种途径发挥其致癌效应, 其中包括诱导长期的慢性炎症以及HBV相关蛋白的直接致癌作用^[3-5]。在众多的致癌因素中, 乙型肝炎病毒x蛋白(hepatitis B X protein, HBx)作为HBV所编码的一种多功能潜在肿瘤蛋白, 其在HBV的整个生命周期中均发挥着举足轻重的作用。众多研究^[6-9]表明HBx可干扰多种细胞信号通道来调控细胞周期、增殖及凋亡进而发挥其致癌效应。

肿瘤微环境主要由肿瘤细胞、炎性细胞、炎性因子等成分构成。研究^[10-12]证实, 肿瘤微环境可通过各种机制在肿瘤的启动、侵袭、转移及血管形成方面发挥重要调控作用, 其中包括形成有利于肿瘤生存的缺氧环境, microRNAs表达谱的改变, 增加干细胞表型等。在肿瘤微环境中炎性成分占据较大比例, 故又称为“炎性肿瘤微环境”^[13-15]。炎症与肿瘤的关系最早在19世纪被首次提出, 研究发现炎性疾病其肿瘤发生的风险性增加, 且炎性介质存在于大部分肿瘤微环境中, 炎性因子的过表达将促进肿瘤的发生发展, 抑制炎性因子可减少肿瘤的侵袭进展^[16-19]。故目前炎症已被作为肿瘤发生发展及侵袭的六大标志之一^[20]。肝癌是典型的炎症相关肿瘤^[21], 大部分肝癌患者既往有长期的慢性肝脏炎症反应, 而HBx被认为在肝脏的慢性炎症反应中发挥重要的调控作用。进一步阐明肝癌发生发展过程中炎性肿瘤微环境的维持及其潜在机制意义重大。本文将对HBx及其在HBV相关性肝癌肿瘤微环境中的作用进行重点阐述。

1 HBx的基本结构及功能

HBx由HBV X基因所编码, X基因是HBV基因组中最小的开放读码框, 所编码的HBx蛋白由154个氨基酸组成, 分子量约为17 kDa。HBx的基因编码区包含4个重要的结构域, 这些结构域对于转录调控、细胞周期、细胞黏附及胞浆信号通路的调节具有重要作用^[22,23]。HBx具有广泛的反式激活作用, 可激活细胞的多种调控基因并促进HBV的复制^[24]。HBx的功能与其细胞定位密切相关, 在细胞浆内, HBx主要通

过与细胞蛋白相互作用并激活胞浆内一系列信号通路来发挥其反式激活作用, 其中包括Wnt/ β -catenin、核因子- κ B(nuclear factor- κ B, NF- κ B)、JAK/STAT及Ras-Raf-MAPK等信号通路^[25-28]. 在细胞核内, HBx与HBV的基因调控及病毒复制有关. 此外, HBx还可直接与转录因子相互结合并激活细胞转录从而介导细胞增殖、凋亡、细胞周期进展及DNA修复^[6-9,29]. 在线粒体内, HBx可下调线粒体酶, 促进ROS及过氧化脂质的产生从而影响线粒体的稳定^[30-33]. 在内质网内, HBx通过内质网应激在诱导肝脏慢性炎症反应及细胞增殖中发挥重要作用^[34,35]. 据此, 我们提出如下假设HBx在细胞内的不同定位将介导不同的生物学功能, 并通过与肿瘤炎症微环境中的各种成分相互作用来促进肿瘤细胞生长、活化肝星状细胞、诱导上皮向间质转化、增加基质蛋白酶活性、促进肿瘤血管形成并调控抗肿瘤免疫进而影响肝癌患者的生存及预后.

2 肝脏肿瘤微环境

肝脏肿瘤微环境大体可分为细胞及非细胞成分, 前者包括肝癌细胞、肝星状细胞、成纤维细胞、内皮细胞、间质干细胞及免疫细胞; 非细胞成分主要为炎症因子、生长因子以及细胞外基质. 研究^[36]表明: 上皮细胞在癌基因激活或抑癌基因失活等诱因下可分泌某些细胞因子并招募炎症细胞到达肿瘤部位. 此外, 肿瘤细胞可通过上调蛋白酶、细胞因子、趋化因子等炎症介质从而形成有利于肿瘤生存的炎症微环境. 换言之, 肿瘤细胞本身可触发内源性肿瘤相关性炎症反应. 肿瘤细胞与炎症微环境中的基质成分相互作用将调控肿瘤的存活、生长、增殖以及侵袭和转移. 肝癌作为一种常见的慢性炎症相关性肿瘤, 其肿瘤微环境中的各组分在肝癌炎症微环境的维持中扮演着各自的角色. 研究^[37-39]表明: 活化的肝星状细胞可参与慢性肝脏炎症、肝硬化、肝癌等一系列的生理病理过程并在肝癌的侵袭转移中发挥重要作用. 炎症因子作为肿瘤微环境中的主要信号传递者, 其在肝癌发生发展中的作用逐渐被我们所认识. 大量体内及体外实验证实: 肝癌患者其癌组织及血清中炎症因子水平常升高, 如白介素(interleukin, IL)-6、肿瘤坏死因子- α (tumor necrosis factor α , TNF- α)、IL-1 β 、

IL-10、转化生长因子 β (transforming growth factor- β , TGF- β)等, 这些炎症因子可促进肿瘤生长、抑制凋亡、诱导上皮向间质转化并最终促进肝癌的侵袭及转移^[40-43]. 这提示我们, 肝脏肿瘤微环境的细胞及非细胞成分有望成为肝癌治疗的新靶点.

3 HBx与肝脏肿瘤微环境

3.1 HBx与肿瘤细胞 在HBV基因所编码的产物中, HBx作为X基因区所编码的一种重要的病毒蛋白, 其在肝癌组织中常高表达, 且在HBV相关性肝癌的发病机制及侵袭转移过程中发挥关键调控作用. 研究^[6-9]表明HBx可通过其转录调控及反式激活作用来调控肿瘤细胞的生物学行为, 如促进肿瘤细胞增殖、抑制凋亡、增加自噬、加快细胞周期进展等从而影响肝癌的发生发展.

3.2 HBx与免疫细胞 机体感染HBV后, 肝细胞病变很大程度上取决于机体的免疫应答, 尤其是细胞免疫应答, 免疫应答既可清除病毒亦可导致肝细胞损伤. 肿瘤的发生与机体的免疫状态密切相关, 肿瘤可通过各种机制来逃脱机体的免疫监视功能, 并诱导免疫耐受从而形成有利于肿瘤生长及存活的环境. 肿瘤微环境中的免疫细胞可参与先天及适应性免疫应答来影响肿瘤的侵袭及进展. 在众多的免疫细胞中, CD8⁺ T淋巴细胞所介导的免疫应答被认为在HBV的清除、急性肝衰竭、HBV感染的慢性化等过程中发挥关键性的调控作用^[44-46]. 研究报道^[47]HBx可促进CD8⁺ T淋巴细胞的凋亡并减少干扰素- γ 的产生从而降低宿主特异性免疫应答, 而宿主免疫应答功能不足被认为是导致HBV感染慢性化的主要原因之一, 至此HBV可长期存在于病变肝组织内并通过各种机制最终诱导肝细胞癌变. 此外, HBx还可上调免疫应答相关分子的表达如主要组织相容性复合体分子, ICAM-1和Fas配体等从而介导肝脏的炎症反应及免疫调节^[48,49]. 这提示我们HBx一方面可通过上调免疫应答相关分子的表达来促进肝内的炎症反应, 肝内长期的慢性炎症环境将促进肝癌的发生. 另一方面, HBx又可抑制HBV特异性免疫应答从而促进HBV感染慢性化并通过其免疫调节功能来调控宿主对肿瘤的免疫反应, 促进相关免疫细胞的凋亡, 诱导其免疫耐受从而促进肿瘤的存活.

■ 相关报道

研究表明HBx具有广泛的反式激活功能, 其在HBV的整个生命周期中均发挥举足轻重的作用, 主要侧重HBx在调控HBV复制及肝癌发生发展中的作用, 与本文内容相互补充.

■ 创新盘点

本文首次综述了HBx对炎症肿瘤微环境各组分的调控作用及其对肝癌发生发展的影响, 对HBx在细胞内的不同定位及其作用进行了总结和述评。

3.3 HBx与肝星状细胞 肝星状细胞也称肝贮脂细胞, 主要位于肝细胞与肝窦间隙之间, 故又称窦周细胞。正常情况下肝星状细胞的主要功能为储存维生素A并合成少量细胞外基质成分。在肝脏损伤的情况下, 炎性细胞及枯否细胞分泌的炎性因子可激活肝星状细胞, 并转化为具有增殖、迁移、收缩和蛋白质合成功能的肌纤维母细胞。众所周知, 肝星状细胞在肝脏损伤及肝纤维化过程中扮演着重要的角色。此外, 近年来研究表明肝星状细胞还与肝癌的侵袭及转移有关^[50]。HBx作为HBV生命周期的主要调控蛋白, 其可通过调控肝星状细胞的活化进而在肝脏的慢性炎症、肝纤维化形成及肝癌的发生发展中发挥重要作用。目前关于肝星状细胞活化具体机制的研究主要围绕在TGF- β 与PDGF信号通路, 其中TGF- β 被认为在肝星状细胞的活化过程中发挥关键性调控因子的作用。体外研究结果表明HBx可激活旁分泌, 在基因转录及蛋白翻译水平上均可上调细胞因子TGF- β 1。TGF- β 1进一步活化下游信号通路Smad, 促使其进入细胞核内并与DNA结合蛋白相互作用从而激活肝星状细胞。此外, HBx还可通过血小板来源的生长因子 β 信号通路(PDGF- β /PDGFR- β)来活化肝星状细胞并促进其增殖与迁移。活化的肝星状细胞可进一步上调 α 平滑肌肌动蛋白及基质金属蛋白酶(matrix metalloproteinases, MMPs), 促进细胞外基质胶原的异常沉积及肝细胞结构紊乱, 从而介导一系列肝脏病理过程如细胞外基质的重塑、肝纤维化、肿瘤血管形成、肝癌的侵袭及远处转移^[51,52]。

3.4 HBx与炎性细胞因子

3.4.1 HBx与TGF- β : 细胞因子是一类小分子信号蛋白, 他们促进不同细胞间信号的传递并通过与细胞表面的受体及下游的信号通路发挥其功能。TGF- β 是属于一组新近发现的调节细胞生长和分化的TGF- β 超家族, 其属于一种炎症相关的细胞因子, 主要由肿瘤微环境中肿瘤细胞、肿瘤相关的巨噬细胞、调节性T细胞所分泌。在不同类型的肿瘤及肿瘤形成的不同阶段, TGF- β 可发挥抑癌或促癌作用^[53]。HBx与TGF- β 的关系已被众多研究所报道。Murata等^[54]研究表明在早期慢性乙型肝炎患者中, HBx可使肝内TGF- β 信号通路从抑癌的pSmad3C到促癌的pSmad3L信号通路转变从而直接参与肝癌

的形成。此外, HBx还可激活旁分泌上调TGF- β 来发挥其生物活性。上调的TGF- β 除了参与肝星状细胞的活化, 其作为促侵袭肿瘤微环境中的重要调控子, 还可与干细胞信号通路如Wnt、Ras等相互协同来诱导上皮向间质转换(epithelial-mesenchymal transition, EMT)或通过改变肿瘤中所浸润的免疫细胞表型来形成一种有利于EMT的肿瘤微环境。EMT形成后, 肿瘤细胞将具有侵袭、转移及干细胞的特性^[55,56]。

3.4.2 HBx与IL家族: IL即是由多种细胞产生并作用于多种细胞的一类细胞因子, 其种类繁多, 功能复杂, 并在免疫细胞的成熟、活化及免疫调节等一系列过程中均发挥重要作用。在肝脏慢性炎症反应中, 炎性细胞因子可被大量释放, 肝内细胞因子的活化参与了肝脏慢性炎症及肝脏损伤的病理过程。炎性因子的平衡决定了免疫反应的最终结局, 故目前炎性因子已作为肝病患者的潜在治疗靶点, 而HBx可在转录水平诱导促炎细胞因子的产生从而在肝脏慢性炎症过程中发挥重要作用^[57,58]。既往研究结果表明, HBx可通过Toll样受体接头蛋白髓样分化因子88(toll-like Receptor adaptor protein myeloid differentiation factor 88, MyD88)依赖的方式来激活NF- κ B及MAP激酶从而促进IL-6的合成与分泌。IL-6作为肝癌发生发展过程中主要促炎细胞因子之一, 其在HBV相关性肝癌患者的癌组织及血浆中常升高, 且可激活下游转录因子STAT3来促进肝癌的侵袭转移并与肝癌患者的预后差相关^[59,60]。此外, HBx还可在选择性调控其他促炎细胞因子如IL-8、IL-18、IL-23、TNF- α 等并参与调节免疫细胞之间的相互作用^[61,62]。这些细胞因子在肝癌的发生发展中扮演着各自的角色, 其中IL-8可调控肿瘤的生长并与肝细胞恶性转化及肝癌的侵袭转移有关^[63,64]。IL-18作为新型的促炎细胞因子, 其在肝癌患者的血清中常升高, 研究^[65,66]报道其可作为HBV相关性肝癌患者的诊断指标。这提示我们由HBx表达上调的细胞因子在肝癌的形成过程中有可能是一种促肿瘤趋化因子, HBx正是通过调控上述免疫细胞因子的表达来促进肝细胞的恶性转化、肿瘤的增殖并抑制抗肿瘤免疫反应从而促进肝癌的发生发展。

3.4.3 HBx与TNF- α : 如前所述, 肝脏长期的慢性的炎症反应介导了肝癌的发生发展, 肝脏炎症反应启动后, 肿瘤细胞可活跃的招募炎性细

胞浸润, 这些细胞可释放相应的炎症因子及趋化因子^[67]。作为经典的促炎细胞因子, TNF- α 主要由炎症细胞所分泌并可调控细胞的存活、增殖、分化及免疫应答从而参与炎症相关的肿瘤形成。既往体内体外实验模型中均表明TNF- α 在肿瘤发生发展过程中扮演着重要的角色^[68]。HBx与TNF- α 的关系早在1998年即有文献报道HBx可在基因转录水平上调肝细胞内TNF- α 的表达。上调的炎症因子TNF- α 可参与肝脏炎症反应及肝病的进展并与肝癌的发生有关^[69]。此外, TNF- α 还可通过上调血管生成因子、MMPs等从而促进肿瘤血管形成并活化生存信号通路从而介导肿瘤的发生发展^[70]。这表明HBV的病毒蛋白可通过调控某些炎症细胞因子的表达来介导肝内炎症反应及肝病的进展。进一步阐明肝内炎症细胞因子的调控机制有望为我们靶向干预治疗提供新策略。

3.4.4 HBx与环氧合酶-2: 环氧合酶(cyclooxygenase, COX)是花生四烯酸代谢的限速酶, 目前COX有两个亚型, 即COX-1和COX-2, 其中COX-2是一种诱导酶, 在组织损伤、炎症等情况下表达增强且与肿瘤的发生发展、新生血管的形成以及转移密切相关。研究报道^[71-73]COX-2在慢性肝炎、肝硬化及肝癌中常高表达, HBx在肝癌组织中的表达与COX-2相关, HBx可通过激活COX-2/PGE(2)信号通路来阻断P53介导的凋亡从而产生抗凋亡效应, 并可依赖COX-2的活性来上调MT1-MMP的表达从而促进肝癌的侵袭及转移。此外, HBx还可通过与线粒体蛋白COXIII共定位来上调COX-2的表达从而促进肝癌细胞的生长^[74]。总而言之, HBx可通过多种途径来维持COX-2的活性, COX-2作为一种重要的存活因子其可介导HBx一系列的致癌效应。

4 结论

HBx作为HBV所编码的一种多功能潜在肿瘤蛋白, 其可通过激活一系列的细胞信号通路在慢性乙型肝炎、肝硬化及肝癌的疾病进展中均发挥着极其重要的作用。在HBV相关性肝癌的发生发展中, HBx可通过不同的机制与肝癌肿瘤微环境中的肿瘤细胞、免疫细胞、肝星状细胞及炎症因子等成分相互作用并介导肝癌的不同生物学行为, 如增殖、抗凋亡、侵袭

转移、肿瘤血管形成、细胞周期调控等。HBx与肿瘤微环境各组分间的复杂相互作用最终将形成有利于肝癌存活及进展的炎症微环境。HBx已成为肝癌发生发展及预后判断的重要生物学指标, 拮抗HBx蛋白在肿瘤微环境中的活性及功能的相关策略可能成为肝癌治疗中的新靶点及方向。

应用要点

本文揭示了HBx在肝脏炎症性肿瘤微环境中的作用及其对肝癌发生发展的影响, 指出了今后研究的可能方向, 为HBV相关性肝癌的治疗提供了新的靶点。

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同行评价

本文从HBx的结构、细胞内不同定位的功能展开阐述,重点讨论HBx在炎症肿瘤微环境中的作用及其对肝癌发生发展的影响,并提出了今后研究的可能方向,为读者了解HBx在HBV相关性肝癌肿瘤微环境中的作用的研究进展提供了借鉴。

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