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文献综述 REVIEW

慢性肝脏炎症与肝癌关系的研究进展

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Chronic liver inflammation and liver cancer

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Abstract

Chronic hepadnavirus infection, alcohol abuse, nonalcoholic fatty liver disease and contact with chemical poisons can lead to chronic liver inflammation. Current studies suggest that chronic inflammation of the liver is an important factor contributing to the occurrence, development and prognosis of liver cancer. Liver cancer is highly malignant and has a poor prognosis and high incidence. For better tumor prevention and treatment, it is important to fully understand the relationship between chronic liver inflammation and liver cancer. In this paper, we review recent progress in understanding the relationship between chronic liver inflammation and liver cancer.

Key Words: Chronic liver disease; Inflammation; Liver cancer

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摘要

慢性嗜肝病毒感染、长期饮酒、非酒精性脂肪肝、接触化学毒物等可引起肝脏慢性炎症, 目前研究认为肝脏的慢性炎症是影响肝细胞癌变发生、进展和转归的重要因素, 而肝癌是恶性程度高、预后差、发病率较高恶性肿瘤.充分认识慢性炎症与肝癌的关系, 通过减少慢性炎症生癌、促癌的作用, 对于肿瘤的防治具有重要的意义. 本文就慢性肝脏炎症与肝癌的相关性研究作一综述.

关键词: 慢性肝病; 炎症; 肝癌

核心提示: 肝癌的发生是一个多因素、多途径的复杂病理过程, 近年来的研究发现肝脏的慢性炎症与肝癌的发生、进展及预后有密切联系, 通过对其综述, 寻找肝癌防治的新思路.

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0 引言

癌症是一种增生异常性疾病, 表现为细胞形态转换、细胞凋亡失调、不受控制的细胞增殖、侵袭、血管生成和转移, 已经成为世界性的公共卫生挑战[1]. 临床和流行病学研究表明慢性感染、炎症和癌症密切相关[2,3], 慢性肝炎-肝硬化-肝癌已经被广泛认可为慢性肝病疾病发展的线路图[4]. 本文就慢性肝脏炎症与肝癌的关系做如下综述.

■背景资料
肝细胞癌是我国发病率较高的消化系肿瘤, 其发病呈上升趋势, 大部分肝癌在慢性肝病基础上发生, 如何阻断慢性肝病向肝脏恶性肿瘤的进展已经成为临床的研究热点和难点.

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■研发前沿
目前造成肝脏慢性炎症的病因学治疗已经获得很大的进展, 但是针对引起肝脏肿瘤病变的慢性非可控性炎症和癌周炎症的治疗是研究热点.

1 流行病学

1.1 肝癌发病率 原发性肝癌(primary liver cancer, PLC)是恶性程度高、预后凶险的肿瘤病变, 在全球恶性肿瘤的发病率中排名第5位, 死亡率排名第2位, 5年生存率只有9%. 据统计, 2008年全球共有74.8万新发肝癌病例, 死亡人数为69.5万, 其中50%在发生中国[5]. 2012中国肿瘤登记年报资料显示: 在我国恶性肿瘤中, 肝癌发病率排名第4位, 为28.71/10万; 死亡率排名第2位, 为26.04/10万[6].

1.2 肝癌危险因素 全球范围内, 50%-80%的肝癌与感染乙型肝炎病毒(hepatitis B virus, HBV)相关, 10%-25%的肝癌与感染丙型肝炎病毒(hepatitis C virus, HCV)相关[7,8]. 欧洲8国109118例男性和254870例女性饮酒与肿瘤相关性的研究显示: 过量饮酒导致肝癌的发生率男性为3.3%, 女性为0.54%[9]. 非酒精性脂肪肝病(nonalcoholic fatty liver disease, NAFLD)患者肝癌发病率为0.14%, 非酒精性脂肪性肝炎(nonalcoholic steatohepatitis, NASH)患者肝癌发病率为1.6%[10]. 在发达国家, NASH占未明原因肝癌原因的6.9%-50%[11]. 一项对173643例糖尿病患者和650620例非糖尿病患者10-15年的追踪观察发现: 糖尿病患者肝癌的发生率是非糖尿病患者的2倍, 认为糖尿病是肝癌的独立危险因素[12]. 对11个关于超重与肝癌相关性研究的Meta分析显示: 相对于正常体质量人群, 超重人群罹患肝癌的相对危险度为1.17, 肥胖人群罹患肝癌的相对危险度为1.89[13]. 相较于体质量指数(body mass index, BMI)正常的患者, BMI>35 kg/m^{2}的男性肝癌死亡率高4.52倍, 女性肝癌死亡率高1.68倍[14].

2 炎症启动肝癌

目前认为肝癌的发生发展是一个多因素、多阶段的过程, HBV感染、HCV感染、饮酒、肥胖、接触黄曲霉素B1等是肝癌发生的高危因素: 在发展中国家, 肝癌患者中60%为慢性乙型肝炎患者, 33%为慢性丙型肝炎患者; 在欧美等发达国家, 酒精性肝硬化、肥胖、非酒精性脂肪肝是肝癌的高危因素[15,16].

2.1 活性氧(reactive oxygen species, ROS)和活性氮(reactive nitrogen species, RNS) 接触传染性病原体(病毒)或有毒物质(乙醇、黄曲霉素B1)会诱发炎症, 激活的炎症细胞产生ROS和RNS中间体, ROS、RNS引起DNA损伤和基因组不稳定, 导致相邻的上皮细胞突变; 炎症细胞产生的细胞因子可以提高癌前病变细胞内ROS和RNS, 增加DNA的损伤和基因组的不稳定性[17,18]. 炎症诱导的突变可以导致错配修复基因的失活或抑制; ROS可以直接氧化失活错配修复酶[19,20].

2.2 活化诱导胞嘧啶核苷脱氨酶(activation-induced cytidine deaminase, AID) AID是核苷脱氨酶家族中的一员, 通过参与体细胞高度突变和种类转换重组, 维持免疫球蛋白基因的多样性[21]. 当双链DNA破坏时, AID容易出错的加入, 从而导致基因的不稳定性、增加突变的发生, AID在多种肿瘤组织中过表达[22]. 通过建立AID转基因小鼠模型(AID is expressed in cells producing tissue-nonspecific alkaline phosphatase, TNAP-AID), 发现TNAP-AID小鼠90 wk肝癌发生率为27%, 同时伴有甲胎蛋白(alpha fetoprotein, AFP)的表达和抑癌基因*p53*的突变[23].

2.3 DNA损伤 乙型肝炎病毒是DNA病毒, 他可以整合进入宿主基因组, 引起内源基因表达的改变和基因组不稳定[24]. 丙型肝炎病毒作为单链RNA, 编译的核心蛋白、NS3蛋白、NS4B蛋白和NS5A蛋白与许多细胞蛋白质交互作用并在细胞和体内模型中表现出致癌性[25,26].

DNA损伤既可以作为炎症的结果参与肿瘤的发生; 也可以作为始动因素引起炎症, 从而诱发肿瘤的发生. 乙醇的代谢产物乙醛具有直接的DNA不良反应[27]; 在二乙基亚硝胺致小鼠肝癌模型中, 小鼠细胞DNA损伤引起细胞的坏死、凋亡, 由此导致炎症反应, 最终引发肿瘤[28].

3 炎症促进肝癌进展

慢性炎症诱发免疫细胞产生细胞因子、转录因子、核因子-κB(nuclear factor-κB, NF-κB)、信号转导和转录激活因子3(signal transducer and activators of transcription, STAT3)等的活化促进了癌前病变细胞的生存、增殖、生长、血管生成和入侵, 并通过诱导产生、吸引新的趋化因子以维持肿瘤相关的炎症状态, 最终导致肿瘤的进展和扩散[18].

3.1 STAT3 STAT是一个胞浆蛋白家族. 这一信号分子既可以作为受体与细胞核之间的信号传导子, 也可以作为转录因子. 迄今为止, 已有7个STAT相继被克隆, 在正常生理状态下, STATs的激活仅持续数分钟至几小时, 对于正

常细胞的生理功能, 如胚胎发育、器官形成、免疫功能的完善、细胞的生长分化等, 起着关键性作用[29]. 近年来研究发现, STATs具有强烈的抑制细胞凋亡, 促进细胞增殖的作用, 参与了人类恶性肿瘤的发生、发展和演进, 其中以STAT3尤为活跃[30].

STAT3由多种细胞因子、生长因子和致癌蛋白激活. 持续激活STAT3引起STAT3磷酸化和下游基因启动通过各种蛋白产物作用增加肿瘤细胞增殖、生存和入侵, 抑制细胞凋亡、促进肿瘤转移并抑制抗肿瘤免疫[30,31]. 其中, 与抗肿瘤凋亡和增殖相关的蛋白有Bcl-xL、Mcl-1、Bcl-2、Fas、Cyclin D1、survivin和c-Myc; 与肿瘤迁移和侵袭有关的有基质金属蛋白酶1(matrix metallopeptidase 1, MMP-1)、MMP-2、MMP-9和MMP-10; 与肿瘤血管生成相关的有血管内皮生长因子(vascular endothelial growth facto, VEGF)、碱性成纤维细胞生长因子(basic fibroblast growth factor, bFGF)和低氧诱导因子-1α(hypoxia inducible factor-1α, HIF-1α), 与肿瘤免疫逃避相关的有IP-10、RANTES[29].

人类慢性肝病和肝脏肿瘤所分泌的白介素-6(interleukin-6, IL-6)、肝脏炎症活动引起氧化应激是主要激活STAT3的因素, 大约60%的人类肝癌标本中STAT3处于活化状态, STAT3阳性的肿瘤更具有侵袭性, 预后更差[32-34]. 二乙基亚硝胺诱发肝细胞特异性STAT3缺陷小鼠($STAT3^{\triangle hep}$)发生肝癌, 其肿瘤发生率明显下降, 且瘤体较小[33]. 体内和体外研究显示, 通过抑制STAT3可以提高肝癌细胞的化学敏感性, 抑制异种移植模型的人肝癌细胞生长和转移[35,36]. 肥胖(高脂饮食)C57/BL6小鼠血清IL-6和TNF呈高表达, 引起肝脏慢性炎症, 并通过激活STAT3信号通路诱发肝癌的发生[37].

男性肝癌患者的数量为女性的3-5倍[38], 通过对人体肝癌组织的研究发现, 雌激素信号可以分别在转录水平调节膜蛋白PTPRO及IL-1α表达, 进而调控STAT3的磷酸化而影响肝癌的发生, 男性患者由于失去雌激素的保护而影响PTPRO及IL-1α表达, 最终导致肝癌发生男性明显多于女性[39,40].

3.2 NF-κB NF-κB是一类二聚核转录因子, 存在于所有真核细胞中[41], NF-κB蛋白家族由NF-κB1(p105和p50)、NF-κB2(p100和p52)、RelA(p65)、RelB和c-Rel组成[42]. 在未受刺激的情况下, 大部分的NF-κB二聚体通过与细胞质中的抑制因子IκB(IκBα、IκBβ、IκBε)中的一个结合而以无活性的状态存在. 在TNF、IL-1β等促炎因子的刺激下, IκB激酶(inhibitor of nuclear factor kappa-B kinase, IKK)的调节亚基被激活, 导致IκB磷酸化和泛素介导的变性, 活化的NF-κB进入细胞核内与DNA结合, 通过诱导靶基因的转录而发挥相关生理病理功能[43].

肝细胞IKK依赖性NF-κB信号通过保护肝细胞而抑制肝癌: 在没有接触任何已知致癌物的情况下, 肝细胞IKKγ/NEMO敲除大鼠($Ikk\gamma^{\triangle hep}$)表现出自发的肝损伤, 并随之发生肝炎、肝纤维化、肝细胞癌[44].

激活的肝细胞IKK/NF-κB信号通路通过维持炎症反应促进肿瘤进展: $Mdr2^{-/-}$大鼠肝癌模型中, 抑制NF-κB的激活可以延缓并减少肿瘤的发展[45]. LTα:β转基因鼠(慢性肝脏炎症模型, 能表达IL-1β、IFNγ、IL-6等炎症因子)和$Ikk\beta^{\triangle hep}$鼠的杂交鼠可以阻止肝脏炎症并减少肝癌的发生, 提示IKKβ的激活具有促瘤作用, 而这种促瘤作用是基于维持慢性炎症基础的[46]. 激活的肝枯否氏细胞IKKβ/NF-κB信号通路通过IL-6和炎症反应促进肿瘤进展[47].

4 控炎与肝癌的防治

充分认识炎症与肿瘤的关系, 大多数肿瘤是可以预防和治疗的[18]. Meta分析显示: 经拉米夫定抗病毒治疗的乙型肝炎患者肝癌发病率较未抗病毒者明显下降[3.3/(百人•年) *vs* 9.7/(百人•年), $P<0.0001$][48]. 丙型肝炎抗病毒治疗的Meta分析显示: 相较于抗病毒无应答的患者, 获得持续抗病毒应答疗效的丙型肝炎患者的肝癌发生相对危险度为0.35[49]. 目前, 针对相关炎症通路的分子靶向治疗的基础研究正在广泛开展, 但是针对肝癌的研究较少; 同时, 限于疗效与相关制剂生物安全性问题, 临床应用尚未得到广泛的认可.

5 结论

PLC的发生是一个多因素、多途径参与的复杂病理过程. 研究显示肝脏慢性炎症在PLC的发生、发展中发挥重要的作用, 慢性非可控性炎症通过ROS、RNS、AID、DNA损伤等诱发肝癌, 通过激活NF-κB、STAT3等信号通路促进肿瘤的增殖、生长和入侵. 有效控制肝脏慢性炎症, 可以减少肝癌的发生率, 延缓肝癌的进展,

■相关报道

Berasain认为转录因子中的核转录因子(nuclear factor-κB, NF-κB)、信号转导和转录激活因子3(signal transdueers and activators of transcription, STAT3), 细胞因子中的白介素-6(interleukin-6, IL-6)、IL-1α、表皮生长因子受体(epidermal growth factor receptor, EGFR), Toll样受体(Toll-like receptor, TLR)等在炎症导致肝癌的过程中具有重要的作用.

■应用要点
本文提出肝脏慢性炎症在肝癌的发生发展的重要作用, 但是目前尚无确切的特异性抗肝脏慢性炎症防治的肿瘤临床应用资料, 有待进一步研究.

减少肿瘤手术、介入治疗、药物治疗后的复发, 延长肝癌患者的生存时间, 提高生活质量.

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