世界华人消化杂志®
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世界华人消化杂志 2013年11月28日; 21(33): 3678-3682
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

姜黄素抗肝癌分子机制的研究进展

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■背景资料
已报道姜黄素对肺癌、乳腺癌、胃癌、结肠癌、白血病、黑色素瘤等均有效, 肝细胞性肝癌是常见恶性肿瘤之一, 大量研究表明姜黄素具有抗肝癌细胞生长的作用.

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收稿日期: 2013-05-10 修回日期: 2013-07-22
接受日期: 2013-07-31 在线出版日期: 2013-11-28

Molecular mechanisms behind anti-cancer effects of curcumin in hepatocellular carcinoma

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Received: 2013-05-10 Revised: 2013-07-22
Accepted: 2013-07-31 Published online: 2013-11-28

Abstract
Primary liver cancer, also known as hepatocellular carcinoma (HCC), is one of the most lethal cancers worldwide. Most HCC cases are reported in the developing countries in Asia and Africa. Viral hepatitis, alcoholism as well as dietary carcinogens, such as aflatoxins and nitrosoamines, contribute to HCC. Surgical resection is the best treatment for early HCC, and Chinese medicine is one of the main measures for the treatment of advanced HCC. Numerous studies show that curcumin has anti-cancer, anti-oxidant and anti-inflammatory properties. This article will discuss the mechanisms behind anti-cancer effects of curcumin in HCC.

Key Words: Curcumin; Hepatocellular carcinoma; Molecular mechanism

Liu J, Tang SX. Molecular mechanisms behind anti-cancer effects of curcumin in hepatocellular carcinoma. Shijie Huaren Xiaohua Zazhi 2013; 21(33): 3678-3682 URL: http://www.wjgnet.com/1009-3079/21/3678.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i33.3678

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摘要
原发性肝癌, 也称之为肝细胞性肝癌(hepatocellular carcinoma, HCC), 是世界上常见的恶性肿瘤之一, 东南亚国家地区和热带非洲的肝细胞癌发病率最高; 病毒性肝炎, 酒精及肝毒性物质(黄曲霉毒素或亚硝胺)均能导致肝细胞癌发病, 手术切除是治疗早期肝癌的主要方式. 中药是治疗中晚期肝癌的主要措施之一. 姜黄素, 最主要的是多酚姜黄色素, 大量研究表明, 姜黄素有抗癌、抗氧化及抗炎的特性, 本文章就姜黄素抗人肝细胞癌生长作用机制的研究进展进行综述.

关键词: 姜黄素; 肝癌; 分子机制

核心提示: 姜黄素具有抗肝癌作用, 其分子机制为通过作用于一系列的分子信号通路发挥抗肝癌细胞生长作用.

刘婕, 唐世孝. 姜黄素抗肝癌分子机制的研究进展. 世界华人消化杂志 2013; 21(33): 3678-3682 URL: http://www.wjgnet.com/1009-3079/21/3678.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i33.3678

0 引言
原发性肝癌, 尤其是肝细胞肝癌, 是常见的消化系恶性肿瘤之一, 男性肝癌病死率居各种肿瘤病死率的第5位, 女性第8位[1,2], 全世界肝细胞性肝癌(hepatocellular carcinoma, HCC)年死亡人数高达700000例[3], 2006年我国调查数据显示, 男性肝癌发病率占第3位, 女性肝癌发病率占第4位; 肝细胞癌发病率急剧增加, 尤其在亚洲发展中国家, 如中国、撒哈拉沙漠以南的非洲、欧洲中部和南部、南美洲大陆[4,5]. 绝大多数的HCC是感染乙型或丙型肝炎而发病, 肥胖、酒精性、非酒精性肝硬化、肝毒性药物(黄曲霉素

或亚硝胺)等[3,6-8]也是HCC重要致病因素, 外科手术是治疗早期肝癌的主要措施, 肝移植往往受到供体的限制, 且复发率高达50%[9], 一些区域性治疗方法也有一定的限制性, 如经肝动脉栓塞、经动脉化疗栓塞、钇-90(90γ)微球植入性的动脉给药. 在肝癌治疗手段中, 化疗越来越占据重要位置, 但目前临床上用的化疗药物主要存在: (1)毒性太大; (2)选择性差; 对免疫系统、正常组织影响大; (3)对实体瘤作用不佳; (4)耐药性高等问题. 中医中药已成为中晚期肝癌的主要治疗方法, 故联合中药并降低化疗药物的使用剂量在保持原疗效水平时既能减轻患者的不良反应, 也能提高治疗肝癌的临床效果[10].

姜黄类包括酚型和非酚型, 在亚洲南部, 姜黄最早作为防腐剂、抗菌及抗炎药治疗感染、呼吸疾病、水肿及风湿病[11-14], 后来发现其还具有抗癌、护肝、护心、抗风湿炎等特性[15-19]. Goel等[18]从姜黄中分离出去甲氧基姜黄素、姜黄素和双去甲氧基姜黄素, 并比较了3种类型的细胞毒性、抗氧化及抗肿瘤活性, 得出活性最高的是双去甲氧基姜黄素, 去甲氧基姜黄素次之, 姜黄素最差; 商用姜黄素是姜黄素(77%)、去甲氧基姜黄素(18%)及双去甲氧基姜黄素(5%)的混合物[18,20,21]; 近几十年姜黄素被广泛用于治疗慢性疾病, 如糖尿病、类风湿性关节炎、癌症, 大量的临床前研究及临床研究表明, 姜黄素有明显的抗肿瘤作用[22].

1 姜黄素的药理作用

姜黄素是从姜科姜黄属植物姜黄根茎中提取的一种酚型色素, 自1985年印度Packard等[23]首次提出姜黄和姜黄素可能具有抗肿瘤作用, 随后大量的研究证实.

姜黄素具有抗氧化、抗炎、抗感染、抑制肿瘤生长等药理作用, 炎症瀑布反应在慢性疾病发病机制中占主要作用, 姜黄素因具有抗炎的作用故可用于治疗慢性疾病[24,25]. 研究表明姜黄素具有抑制转录因子[核因子κB(nuclear factor κB, NF-κB)、过氧化物酶体增殖剂激活受体-γ(peroxisome proliferators-activated receptor-γ, PPAP-γ)、p53]、蛋白激酶(EGFR、PKA、PKC等)、基因表达[细胞周期蛋白(CyclinD1)、环氧化酶2抑制剂(cyclooxygense 2, COX2)、基质金属蛋白酶(matrix metalloproteinase-9, MMP9)、肿瘤坏死因子(tumor necrosis factor, TNF)、白介素-12(interleukin-12, IL-12)]及其他[Bcl-2、细胞间黏附分子-1(intercellular adhesion molecular-1, ICAM-1)]的作用, 并通过改变一系列的信号通路发挥抗炎、抗氧化及抗肿瘤的作用[26-28]; 如姜黄素能够抑制NF-κB[29], 而NF-κB能调节炎症中介物如细胞活素类、趋化因子及蛋白激酶[30,31](IL-1、IL-6、IL-8、肿瘤坏死因子-α及环加氧酶)的活性[32-34], 从而发挥抗炎作用, 且*NF-κB*基因产物能调节细胞凋亡及增殖, 阻止肿瘤细胞的侵犯及血管的再生; 姜黄素还能与大量信号蛋白(转录因子、生长因子、黏附分子及抗凋亡蛋白)相互作用, 抑制癌细胞的增殖和凋亡及肿瘤的侵袭和转移[35-40]. 姜黄素抗肿瘤的分子机制[41]可能包括以下: (1)下调前癌基因*CyclinD1*的表达; (2)诱导肿瘤细胞的停滞与凋亡; (3)抑制CyclinD-依赖性蛋白激酶4(cyclin-dependentproteinkinases 4, CDK4); (4)抑制金属蛋白酶和肿瘤血管形成; (5)抑制细胞色素P450(cytochrome P450, CYP450)同工酶活性; (6)下调核转录因子(NF-κB), 抑制可诱导性NO合成酶、COX2的活性; (7)改变微丝的结构和功能; (8)上调GADDi53的转录.

2 姜黄素抗肝癌的作用

细胞凋亡主要通过死亡受体(外源性)通路和线粒体依赖性的细胞凋亡(内源性)通路, 并由一系列的促凋亡和抗凋亡调节因子控制, 外源性和内源性通路在形成具有裂解活性的Caspase3处汇合, 进一步导致DNA、核蛋白和细胞骨架崩解. 凋亡受体属于肿瘤坏死因子家族, 结构上均具有相同的细胞内部分一“死亡区域”, 凋亡受体通路通过激活死亡受体, 形成死亡诱导信号复合物而启动凋亡过程. 如Fas相关死亡结构域蛋白(fas-associated death domain protein, FADD)可介导Caspase8活化而触发细胞的凋亡. 线粒体通路则常与Bcl-2家族有关, Bcl-2家族成员中部分为促凋亡蛋白, 部分为抗凋亡蛋白. 二者的组成比例决定细胞对凋亡的敏感性. 当细胞损伤发生时, 促凋亡蛋白自从胞质转移到线粒体膜上与抗凋亡蛋白相作用, 导致线粒体膜穿孔, 细胞色素C漏出, 而启动凋亡过程.

姜黄素抗肝癌机制认为可能主要与诱导肿瘤细胞凋亡有关, 其通过调控抑癌基因、癌基因及其蛋白的表达、诱导细胞周期停滞及调控细胞凋亡信号等途径来实现, 其还可以通过抗氧化、免疫调节、影响激素水平及上调GADD153的转录等机制发挥抗肿瘤的作用.

■研发前沿
姜黄素具有抗肝癌细胞生长的作用, 但其分子机制尚不完全清楚, 问题在于需要设计及系统性评价姜黄素抗肝癌生长作用的临床实验.

■相关报道
Jun、Takuto等均证实姜黄素具有抗不同肝癌细胞株生长的作用, 但其分子机制主要与诱导肿瘤细胞凋亡有关.

王伟章等[42]研究表明, 姜黄素能够显著地上调肝癌细胞Huh中的Bcl-2家族促凋亡蛋白Bad的表达, 并诱导cytochromes从线粒体释放至胞浆中以及活化Caspase3蛋白, 表明通过激活线粒体凋亡通路诱导肝癌细胞Huh7的凋亡. Yu等[43]研究表明姜黄素能够诱导人肝细胞癌SMMC-7721的凋亡, 且具有浓度依赖性, 主要通过增加Bax蛋白的表达, 降低Bcl-2蛋白表达. 孙军等研究结果表明, 在缺氧条件下, 姜黄素通过抑制肝癌细胞BEL-7402中VEGF的mRNA和蛋白表达来抗肝癌血管生成、抑制癌细胞的生长和转移; 随着缺氧时间延长, VEGF的蛋白和mRNA表达增强, 郭志松等[44]通过研究姜黄素对肝癌HepG2细胞和肝脏正常L-02细胞的生长抑制作用及其机制表明, 姜黄素阻滞HepG2细胞周期于G_1期, 此过程中Caspase3、Caspase8、Caspase9被激活, DR5蛋白表达上升, Bcl-2/Bax蛋白表达比率下降, 得出姜黄素能够选择性杀伤HepG2细胞, 并通过外源性通路和内源性通路两条通路促其凋亡. 姜黄素通过下调血管内皮生长因子-A抑制Hepal-6细胞的生长[45]; Wang等[46]研究表明其还能通过下调Chk1蛋白表达及阻滞细胞在G_2/M期来抑制肝癌细胞的凋亡; Wang等[47]研究表明姜黄素通过激活p38上调Fas和Fasl的蛋白及mRNA水平的表达诱导肝癌Huh7细胞的凋亡. Fujii等[48]发现肝癌细胞HepG2具有高Mg^{2+}活性的外核苷酸酶活性, 姜黄素可能通过降低ecto-ATPase活性及影响外在依赖ATP反应来诱导肝癌细胞HepG2的凋亡; Wang等[49]也证实姜黄素可能通过破坏线粒体膜及阻止游离Ca^{2+}离子的积聚来诱导肝癌细胞HepG2的凋亡; Cheng等[50]研究表明姜黄素通过增加内质网的负担及破坏线粒体功能来抑制人肝癌J5细胞增殖, 并呈时间及浓度依赖方式, 其机制通过下调Calnexin、PDI及Ero1-Lα的表达和上调Calreticulin的表达来诱导非折叠朊蛋白的反应, 也通过裂解Caspase12和ATF6诱导GADD153的表达, 并把ATF6转移至细胞核, 还通过下调TCTP、Mcl-1及Bcl-2的表达来诱导线粒体的功能障碍, 且通过降低Cdc2的表达来阻滞肝癌细胞在G_2/M时期.

3 结论

姜黄素因具有抗炎、抗氧化及抑制肿瘤生长等作用而被广泛用于治疗胃癌、结肠癌、类风湿性关节炎等慢性疾病, 大量体外实验证实其能通过作用于一系列的分子信号通路发挥抗肝癌细胞生长作用, 但临床上姜黄素被用于治疗肝癌还需要做大量的实验研究, 成功的关键在于设计系统性评价姜黄素抗肝癌生长作用的临床实验. 肝癌的治疗方式为综合性治疗, 单一使用姜黄素治疗肝癌的效果欠佳, 联合化疗治疗肝癌将成为后续的研究热点.

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■创新盘点
通过列举一系列姜黄素抗肝癌细胞生长的研究, 证明姜黄素具有抗肝癌的作用,其分子机制尚不完全清楚.

■同行评价

姜黄素具有抗癌、抗氧化及抑制炎症反应的作用, 近年越来越受到人们的关注. 本文作者就姜黄素对肝癌细胞抑制的分子机制进行了综述.

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