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文献综述 REVIEW

肝缺氧诱导因子-1α与肝癌发生、发展及治疗研究新进展

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Advances in understanding the relationship between hepatic hypoxia-inducible factor-1 alpha and hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is characterized by hypoxia due to robust cell proliferation. Hypoxia can promote tumor cell proliferation, metastasis and neovasculogenesis, inhibit differentiation and apoptosis, and decrease chemosensitivity and radiosensitivity. Hypoxia-inducible factor-1α (HIF-1α) is a key mediator of physiological and pathological hypoxia response and controls the transcription of numerous genes that are of pivotal importance for angiogenesis and cellular metabolism. Therefore, HIF-1α is closely related with the proliferation, metastasis and apoptosis of HCC cells. Recently, HIF-1α-based gene therapy has become a novel adjunctive strategy for the management of HCC. This review focuses on the relationship between HIF-1α and the progression and therapy of HCC.

Key Words: Hypoxia-inducible factor-1 alpha; Hepatocellular carcinoma; Gene therapy

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摘要

失控的增殖导致缺氧(hypoxia)是肝细胞癌(HCC)形成的特征性微环境. 缺氧可促进癌细胞增殖、转移、血管新生、抑制癌细胞分化、凋亡以及对放化疗耐受. 缺氧诱导因子-1α(HIF-1α)是介导生理性和病理性低氧反应的关键转录因子, 在转录水平上调控百余种靶基因, 参与调节血管新生及糖代谢等过程, 与HCC生长、浸润、转移和预后等密切相关. 近年来以HIF-1α为靶点的基因疗法如RNA干扰、反义技术和自杀基因技术等, 成为HCC辅助治疗的新策略. 本文综述了HIF-1α转录水平异常与HCC发生、发展及靶向HIF-1α基因治疗HCC的新进展.

关键词: 缺氧诱导因子-1α; 肝细胞癌; 基因治疗

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0 引言

肝细胞肝癌(hepatocellular carcinoma, HCC)是以血供丰富、进展迅速及化疗耐药著称的恶性肿瘤[1]. HCC由肝炎病毒(HBV、HCV)的慢性感染或在肝硬化基础上发展而来, 因肝内纤维化破坏脉管系统及癌基因激活/抑癌基因失活等使癌细胞增殖失控导致缺氧. 缺氧诱导因子-1α(hypoxia-inducible factor-1 alpha, HIF-1α)是调节氧稳态的重要转录因子, 通过下游靶基因调控肿瘤能量代谢、血管生成和转移等环节, 促进HCC发生与发展. 他还可通过上调Ⅰ型纤溶酶原激活物抑制剂(plasminogen activator inhibitor, PAI-1)、肾上腺髓质素-1(adrenomedullin-1,

■背景资料
缺氧诱导因子-1α(HIF-1α)是介导生理性和病理性低氧反应的关键转录因子, 在转录水平上调控百余种靶基因, 参与调节血管新生及糖代谢等过程, 与HCC生长、浸润、转移和预后等密切相关.

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肝癌细胞缺氧, 核内HIF-1α积聚, 诱导多种生长因子表达上调, 诱发肝癌形成, 以HIF-1α为靶点的基因疗法如RNA干扰、反义技术和自杀基因技术等, 成为HCC辅助治疗的新策略.

ADM-1)和肾上腺髓质素-2(adrenomedullin-2, ADM-2)促肝纤维化形成[2]. HCC患者HIF-1α转录水平上呈高表达者, 总体生存率和无病生存率较低表达者明显减低, 且静脉及淋巴结转移率较高. 在肝癌等多种肿瘤中HIF-1α过表达, 缺氧和HIF-1α转录异常共同促进HCC进展, 并对传统疗法耐受. 随着RNA干扰、自杀基因等技术日趋成熟, 已开展了靶向HIF-1α基因治疗HCC的研究, 本文就HIF-1α转录水平上异常与HCC发生发展及靶向HIF-1α基因治疗的研究进展作一综述.

1 HIF-1α转录机制及在肝细胞恶性转化时的表达

HIF-1是由氧调节的α亚基和组成性表达的β亚基(芳香烃受体核转运蛋白, ARNT)构成的异二聚体转录因子. α亚基具有结合DNA及异二聚体化的bHLH/PAS结构域, 一个氧依赖降解区域(oxygen-dependent domain, ODD)和两个转录激活区域(N-TAD和C-TAD). 常氧下, 脯氨酸羟化酶(PHD1、PHD2和PHD3)羟化HIF-1α ODD区402位和564位脯氨酸残基, 经pVHL-E3泛素连接酶-S26蛋白酶体途径降解, HIF抑制因子FIH羟化803位天冬氨酸残基, 阻止其与共转录因子环腺苷酸反应元件结合蛋白p300/CBP结合, 抑制转录启动; 缺氧下, 羟基化作用消除, C-TAD与p300/CBP结合, α亚基稳定后转入核内, 与β亚基异二聚体化, 作用于缺氧反应基因启动子区域的缺氧反应元件(hypoxia-response element, HRE), 激活下游靶基因转录. β亚基缺少ODD区域, 且只含有一个TAD区, 不受氧浓度的调节. 除了氧分压, 生长因子刺激、癌基因激活、抑癌基因失活、Ca^{2+}信号和ROS等均可在常氧下诱导HIF-1α产生[3]. HIF-1α的活性调节与HIF-1α稳定性、磷酸化和氧化还原条件的改变、共辅助激活蛋白的相互作用有关. PI3K/Akt/FRAP/mTOR/4E-BP、MEK1/ERK/MAPK等信号通路, 在调节HIF-1α中也起重要作用. 羟基化、泛素化、乙酰化、巯基化和磷酸化也均参与调节HIF-1α的半衰期和转录活性[4], 可作为一种细胞缺氧状态下的防御机制[5,6].

肝内实体瘤存在缺氧微环境, 癌细胞增殖、浸润对缺氧的适应性调节即依赖于HIF-1α. 人HCC及癌周组织中HIF-1α分布主要定位于胞质, 部分位于胞核. 癌灶组织HIF-1α表达均匀, 肿瘤坏死区周围及肿瘤浸润边缘HIF-1α表达增多; 癌旁组织中靠近肿瘤边缘被压扁的肝组织条索中及中央静脉周围HIF-1α表达明显, 癌周组织表达明显强于其癌灶组织, 表明HIF-1α表达增强与癌周组织的增生活跃密切相关, 且HIF-1α表达强度与分化程度负相关, 表达率与肿瘤直径正相关, 与HBsAg、肿瘤数目间未见明显相关[7]. 在鼠肝癌发生发展过程中, 肝癌形成的早期阶段, 即变性期, HIF-1α在转录水平和蛋白水平上既已过表达, 表现为肝细胞变性、癌前和癌变组HIF-1α在基因和蛋白表达上呈动态梯度增高, 且外周血中亦可检测到HIF-1α的表达变化, 同时基因序列与GenBank中基因源序列同源性分析完全一致[8].

2 肝炎病毒慢性感染与HIF-1α表达

HBV感染在我国肝癌病因中居首. HBx, 即HBV编码蛋白, 可诱导HIF-1α ODD的氨基酸残基去乙酰化, PHD和VHL与HIF-1α分离, 从而稳定HIF-1α表达. 在HBx转基因小鼠和HBV感染的HCC患者中, 转移相关蛋白-1(metastasis-associated 1, MTA1)和组蛋白去乙酰酶(histone deacetylase 1, HDAC1)蛋白水平增高, 且癌组织与周围非肿瘤硬化结节相比, MTA1和HDAC1蛋白水平也明显升高, HBx上调MTA1/HDAC1复合体的表达, MTA1通过HDAC1去乙酰化HIF-1α, 中和乙酰基转移酶(acetyltransferase 1, ARD1)的作用, 两者协调一致促进HIF-1α稳定表达, 在HBV相关肝癌血管新生和转移中发挥重要作用[9,10]. HBx稳定HIF-1α后, 可诱导核转录因子C/EBP-β, 转录激活多重耐药相关基因(multi-drug resistance protein 1, MDR1), 增强其活性, 使肝癌治疗从化疗敏感转变为化疗耐受[11]. 体外研究也表明HBx过表达上调HIF-1α, 两者显著相关, HIF-1α可作为HBV相关肝癌患者的预后指标[12].

HCV感染极易致慢性化是肝硬化和HCC发生的主要原因之一. HCV活化NF-κB、STAT-3、PI3K/AKT和P42/P44丝裂酶原蛋白激酶, 稳定HIF-1α, 促进HCV感染的细胞释放促血管生成因子, 诱导血管新生及肝细胞恶性转化[13]. HCV阳性患者中其TGF-β2、VEGF和CD34表达较阴性患者显著升高. HCV核心蛋白可激活HIF-1α、E2F1、ASK1、JNK/P38、ERK、AP-1、ATF-2和CREB等多种途径上调TGF、VEGF和CD34, 诱导血管新生. HCV通过影响线粒体呼吸链活性产生一系列氧化应激反应, 导致线粒体氧化应激磷酸化受损, 转向依赖于非氧化应

激糖代谢, 而不影响细胞增殖. HCV感染的细胞和慢性丙型肝炎患者肝活检均证实HCV可上调HIF-1α, 并转录激活HIF-1α的靶基因如糖代谢相关基因等, 参与HCC的发生发展, 使患者对抗氧化应激治疗敏感性下降[14].

HCV核心蛋白转染HepG2细胞后激活NF-κB, 进而增强TGF-α转录活性, 最终活化MAPK/ERK通路刺激细胞增殖. 核心蛋白能直接和P53、P73和pRb等肿瘤抑制蛋白结合, 调节Cyclin-依赖激酶(cyclin-dependent kinase, CDK)抑制因子P21/Waf的表达, 而P21/Waf是P53的转录调控靶位, 核心蛋白通过直接调节Cyclin/CDK复合物的功能, 参与细胞周期异常改变和肿瘤的发生. 此外, 核心蛋白还能与LZIP蛋白、hnRNP K蛋白和RNA解旋酶DEADbox DDX3蛋白等结合. 在表达核心蛋白的细胞和转基因小鼠模型中证实core能与线粒体蛋白伴侣分子Prohibitin结合, 破坏Prohibitin与线粒体DNA编码的细胞色素C氧化酶(cytochrome coxidase, COX)的相互作用, 导致COX活性下降, 线粒体功能障碍, 肝细胞氧化应激损伤.

3 HIF-1α表达与多种信号通路间关系

3.1 NF-κB NF-κB信号途径的活化在HCC发生发展过程中起重要作用. 缺氧激活IKKβ, 使IκB磷酸化, NF-κB与其分离并活化[15]. 但HIF-1α与NF-κB的关系不甚明了. 资料报道不一, 如HIF-1α可激活NF-κB, NF-κB可调控HIF-1α的转录, HIF-1α的激活与NF-κB的抑制可共存[16-18]. NF-κB抑制因子IκB-α, 可作用于FIH, 使其与HIF-1α分离, 减少803位天冬氨酸羟基化, 增强其转录活性[19]. NF-κB结合于HIF-1α距起始位点-197/188 bp的启动子区, 调节常氧HIF-1α mRNA和蛋白基础水平, 进而上调VEGF、GLUT1、GLUT2[20,21]等.

3.2 MicroRNA 缺氧除通过HIF-1α介导的经典途径促进HCC发生发展, 近来研究发现还可通过作用于缺氧调节的MicroRNA(HRMs)扩大其促血管新生、细胞增殖、糖酵解、DNA损伤、抗凋亡等靶效应. 缺氧条件下HIF-1α上调或下调许多HRMs, 如上调MicroRNA-21、MicroRNA-155等, 下调MicroRNA-26、MicroRNA-101、MicroRNA-122等, 均与HCC有密切关系[22]. MicroRNA-21、MicroRNA-155通过下调PTEN和C/EBPβ促肝癌形成[23,24]. MicroRNA-26水平下降可活化NF-κB信号通路促HCC形成[25]. MicroRNA-101在肝癌组织及肝癌细胞中表达均减少, 异位表达的MicroRNA-101通过抑制Mcl-1发挥促凋亡效应, 明显抑制肝癌细胞集落和裸鼠HCC形成[26]. MicroRNA-122在体内体外研究中均可敲除靶基因ADAM-17, 抑制血管生成、瘤体形成、肝内转移、侵袭等, 而在HCC患者中其表达明显下调[27].

3.3 MIF 巨噬细胞移动抑制因子(macrophage migration inhibition factor, MIF)不仅是炎症因子, 而且具有内分泌和酶的活性, 被认为是胞内信号分子, 参与血管生成, 肿瘤进展. 缺氧条件下HIF-1α上调MIF的表达, MIF又可通过P53途径稳定HIF-1α, 进一步促进癌细胞增殖、生长、侵袭等[28]. 人MIF在5'-非翻译区域含有HRE, 定位于转录起始位点+25区域附近, cAMP反应元件CRE, 即转录因子CREB结合位点, 定位于-20区域附近, 常氧下CREB抑制HIF-1α活性, 而缺氧时CREB降解, 允许HIF-1α转录激活启动子, 促使MIF在肝癌中过表达, 下调P27水平[29]. HBx可借助MIF促进HBV感染者发展为肝癌[30,31]. MIF单抗作用于HepG2细胞后, 阻断细胞周期G_0/G_1期, 减少CyclinD1、VEGF和IL-6分泌, 抑制细胞增殖.

3.4 其他 肝细胞缺氧, 核内HIF-1α积聚, 诱导多种生长因子及Ⅰ型胶原纤维表达上调, 而在HIF-1α缺陷小鼠上述表达均降低, HIF-1α作为促肝纤维化因子调节剂, 诱发肝癌形成[2,32]. Rac和Id-1稳定HIF-1α, 上调VEGF表达, 诱导血管新生, 促进癌细胞侵袭[33,34]. 缺氧时组蛋白脱甲基酶JMJD1A、JMJD2B HRE结合丰富的HIF, 且启动子区域募集了大量RNA聚合酶Ⅱ, HIF可直接靶向jumonji蛋白, 使之去甲基化, 促进肝癌发生与发展[35]. HCC中HIF-1α上调FoxM1表达, 降低P21核内水平, 升高CyclinB1和CyclinD1, 使其获得易感性表型, 参与癌细胞增生、血管生成、凋亡抵抗[36,37]. HIF-1α转录激活多种糖酵解相关基因, 且HIF-1α高表达者癌侵袭率高, 生存率低[38]. HIF靶基因自分泌活动因子vimentin, fibronectin, keratins 14、18和19, MMP2, uPAR, cathepsin D, uPAR, c-Met和CXCR4均参与肝癌浸润转移[39].

4 HIF-1α表达与肝癌基因治疗

缺氧条件下, HIF-1α转染5-FU处理的HepG2细胞后, MDR1、MRP1和LRP表达上调, 参与耐药形成[40]. 放疗后瘤细胞再氧和, 活性氧刺激HIF-

■创新盘点
肝癌组织内广泛低氧, HIF-1α表达调节下游基因, 促血管生成、癌细胞增殖、转移和凋亡等过程, 对传统放、化疗耐受, 抗血管疗法易致缺氧, HIF-1α过表达是监测肝癌复发的良好指标.

■应用要点
靶向HIF-1α或HRE的基因治疗, 敲除目的基因后, 导致基因功能性缺失. 故抑制HIF-1α过表达, 阻断对下游基因的激活, 对肝癌治疗具有新的应用前景.

1α核内积聚, 翻译增加, 抑制内皮细胞凋亡, 降低血管损伤, 增加放疗抵抗, 抑制放疗后HIF-1α活性, 可加强血管破坏, 显著提高放疗敏感性[41]. 兔VX2肝癌模型表明TAE显著激活HIF-1α, 靶向促血管生成因子, 推动残余癌复发[42]. HIF-1α常导致单一治疗失败, 故以HIF-1α或HRE为靶点的基因治疗可作为HCC治疗的辅助手段.

4.1 siRNA与shRNA 外源性双链RNA结合同源互补靶mRNA引发的转录后基因沉默. HIF-1α siRNA转染HepG2细胞后, HIF-1α及其靶基因VEGF在mRNA和蛋白水平均下调, 缺氧下发挥抗肝癌血管生成效应[43]. HSP70-2缺氧下高表达, 加强对缺氧诱导凋亡的抵抗, HIF-1α siRNA转染HCC细胞后, HSP70-2表达减少[44,45]. 体外研究表明HIF-1α siRNA转染依托泊甙处理的HepG2细胞, 上调Bak的表达, 活化P53和caspase, 增加缺氧下细胞凋亡, 恢复药物敏感性[45]. 腺病毒介导的HIF-1α shRNA转染人外周血祖细胞, 可显著下调HIF-1α及VEGF的表达, 抑制其克隆形成、分化、增殖、迁移[46]. HIF-1α siRNA可消除缺氧刺激下Hep3B的迁移能力[47]. VEGF siRNA可使Ang、单核细胞化学吸引蛋白(monocyte chemotactic protein 1, MCP-1)、IL-6、IL-8和TGF-β1下调, 而靶向HIF-1α siRNA虽可使VEGF、Ang和TGF-β1减少, 但上调IL-6、IL-8、MCP-1, 故两者联合更有效抑制血管新生[48]. 靶向HIF-1α和VEGF的siRNA共转染入人脐静脉内皮细胞和视网膜局部缺血C57BL/6J鼠模型中发现HIF-1α siRNA联合VEGF siRNA显著下调两者mRNA及蛋白水平的表达, 体内体外研究均最大效应的抑制了VEGF的表达[49]. 经腹膜腔内注射siRNA(HIF-1α)/PEI, HIF-1α及PAI-1表达下调, 同时降低PAI-1活性, 减少术后腹部黏附[50].

4.2 MicroRNA MicroRNA是内源性的大小与siRNA相仿的非编码RNAs, 通过与靶mRNA3'-端非翻译区结合发挥调节作用. 现仅发现唯一直接靶向HIF-1α的microRNA, 即miR-17-92, 位于13q31.3. 经等量标记试剂iTRAQ联合生物信息靶向预测的质谱分析, HIF-1α是miR-17-92的直接靶点, 可被其负性调节. 但miR-17-92仅在常氧下负性调节HIF-1α, 缺氧条件下miR-17-92表达, 均不影响其过表达[51]. 对miR-17-92负性调节肝癌HIF-1α的研究有待探讨.

4.3 反义DNA或反义RNA 利用DNA或RNA分子通过碱基配对原则与目的基因的mRNA互补结合, 通过各种机制使其降解或抑制其编码蛋白的翻译, 从而抑制目的基因表达. HIF-1α反义寡核苷酸技术可抑制肝癌细胞增殖, 降低HIF-1α mRNA和蛋白质表达[52]. 体内研究证实, 反义HIF-1α可协同多柔比星下调VEGF的表达, 抑制肿瘤生长, 血管生成, 细胞增殖, 诱导凋亡, 增强多柔比星抗肝癌疗效[53]. 反义寡核苷酸靶向VEGF启动子区HIF-1α结合位点, 下调VEGF RNA及蛋白水平, 显著抑制VEGF表达, 抗血管新生, 抑制癌细胞生长[54]. 反义HIF-1α下调HIF-1α表达, 增加X线诱导的缺氧细胞凋亡, 增强放疗敏感性[55].

缺氧不仅反式激活端粒逆转录酶基因(hTERT)启动子活性, 增加内源性hTERT表达, HIF-1α反义寡核苷酸下调hTERT表达, 表明缺氧条件下HIF-1α介导hTERT上调, 端粒酶活性增高, 为肝癌治疗抵抗的原因之一[56]. 经门静脉注入腺相关病毒介导的反义HIF-1α, 在鼠肝中长期局限性表达, 可逆转TAE致缺氧引起的HIF-1α、VEGF、GLUT-1、LDH-A和增殖核抗原升高, 控制血管新生和癌细胞增殖, 抑制瘤体生长, 加强TAE疗效[57].

4.4 核酶 核酶为具有酶活性的分子, 可定点切割目的基因, 有效阻断其表达. 靶向HIF-1α的核酶基因真核表达载体转染肝癌细胞Hep3B, 低氧条件诱导后HIF-1α表达明显下降, 转录活性下调[58]. 靶向hTERT启动子、AFP等核酶基因对肝癌研究较多[59,60], 而靶向HIF-1α核酶基因真核表达载体研究较少.

4.5 自杀基因 酶/前体药物治疗(GDEPT)即将自杀基因导入肿瘤细胞, 介导无活性前体或低毒性药物代谢为毒性产物, 杀伤肿瘤细胞. 自杀基因体系包括单纯疱疹病毒-胸苷激酶基因(HSV-TK)、水痘带状疱疹病毒-胸苷激酶基因(VZV-TK)、大肠杆菌胞嘧啶脱氨酶(EC-CD)等. 整合HRE的嘌呤核苷酸磷酸化酶(PNP)/9-6-甲基嘌呤(Mep-dR)自杀基因体系具有明显抗肝癌效应[61]. 整合HRE的Bax自杀基因, 缺氧诱导下, 上调Bax表达, 增强其介导的细胞凋亡, 抑制瘤体生长. 胞嘧啶脱氨酶(CD), 是一种前体药物激活酶, 可将无活性的5-氟胞嘧啶转化为有活性的5-氟尿嘧啶(5-FU), HIF上调启动子序列插入HRE的可编码CD的自杀基因表达, 克服缺氧诱导对5-FU耐药性产生, 可用于肝癌治疗研究. 构建受VEGF启动子调控的, 融合HIF-1α ODD区的白喉毒素表达载体(DT-A), 其下游含有EPO mRNA

结合蛋白(ERBP)序列, 常氧下DT-A经pVHL和氧介导途径降解, 缺氧下ERPB结合序列稳定mRNA. 体内研究表明缺氧下其可诱导凋亡, 抑制肿瘤生长, 而对常氧正常组织损伤较小[62].

5 结论

肝癌实体瘤内广泛低氧, HIF-1α过表达, 调节百余种下游靶基因, 编码EPO、VEGF、HO-1和iNOs、GLUT-1、糖酵解酶和3-磷酸甘油醛脱氢酶、IGF-Ⅱ、IGF结合蛋白和酪氨酸羟化酶等, 调控血管生成、细胞代谢、癌细胞增殖、转移、凋亡等过程, 促进肿瘤的发生发展及对传统放、化疗耐受, 导致预后不良. TAE/TACE导致缺氧, 促进血管形成, 而抗血管疗法更进一步导致缺氧, 从而形成恶性循环, 利于肝癌复发. 肝癌切除术后, HIF-1α伴或不伴有Ang-2过表达的患者无病生存期较低表达长, 是监测肝癌复发的良好指标[63]. 靶向HIF-1α或HRE的基因治疗, 敲除目的基因后, 导致基因功能性缺失. 故抑制HIF-1α过表达, 阻断对下游基因的激活, 对肝癌治疗具有新的应用前景.

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■同行评价

本文主要总结了HIF-1α转录水平异常与HCC发生、发展及靶向HIF-1α基因治疗HCC的研究进展, 对指导下一步研究方向具有一定的意义, 内容上有一定的新颖性.

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• 消息 •

《世界华人消化杂志》入选《中国学术期刊评价研究报告 – RCCSE权威、核心期刊排行榜与指南》

本刊讯 《中国学术期刊评价研究报告-RCCSE权威、核心期刊排行榜与指南》由中国科学评价研究中心、武汉大学图书馆和信息管理学院联合研发, 采用定量评价和定性分析相结合的方法, 对我国万种期刊大致浏览、反复比较和分析研究, 得出了65个学术期刊排行榜, 其中《世界华人消化杂志》位居396种临床医学类期刊第45位. (编辑部主任: 李军亮 2010-01-08)