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文献综述 REVIEW

# 肝癌相关基因及相互作用的研究进展

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## Advances in genes and gene interaction of hepatocellular carcinoma

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## Abstract
Multigenes and multigene interaction are involved in the development, recurrence and metastasis of hepatocellular carcinoma, while aberrant gene expression is the significant cause of recurrence and metastasis. Researches on gene changes and gene interaction in hepatitis, liver cirrhosis and hepatocellular carcinoma are important for identifying the development, elucidating the pathogenesis, and guiding the prognosis and therapy of hepatocellular carcinoma.

Key Words: Hepatocellular carcinoma; Gene expression; Interaction

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## 摘要
肝癌的发生、发展、复发与转移是一个多基因、多途径相互作用的过程, 基因表达的异常是肿瘤发生发展以及肿瘤浸润、转移的重要因素. 研究从正常肝组织到肝炎、肝硬化、肝癌的发展过程中基因的改变及基因间相互作用的关系, 对于明确肝癌的发生发展过程, 阐明肿瘤的发病机制和肿瘤的治疗与预后都有重要的意义.

关键词: 肝癌; 基因表达; 相互作用

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## 0 引言
原发性肝癌是世界范围内发病率最高的恶性肿瘤之一, 也是我国最常见且恶性程度最高的肿瘤之一. 目前手术切除仍是治疗原发性肝癌的首选方法. 然而根治性切除后患者的5年复发率高、转移率高, 这成为肝癌临床治疗的难题. 因此, 分子水平研究原发性肝癌的发生、发展、复发、转移的机制, 并针对此寻找有效的早期诊断指标及治疗措施成为当今肝癌研究中的重点和难点. 本文就细胞增殖、转移相关的基因及与其他基因间相互作用的关系作一综述.

## 1 与肝癌细胞增殖相关的基因
### 1.1 肝癌中PTEN、ppM1A和Smad2之间的关系
PTEN是抑癌基因, 分布在肝细胞的胞核、胞质、胞膜中, 抑癌机制由如下几条途径共同完成[1]: (1)通过对FAK的去磷酸化抑制细胞转移及浸润[2]. (2)通过PIP3去磷酸化阻止细胞生长及促进细胞凋亡[3-4]. (3)通过抑制MAPK细胞传导途径抑制细胞生长分化[5]; ppM1A分布在胞核、胞质中, 是丝氨酸/苏氨酸蛋白磷酸激酶PP2C家族成员, 其调节细胞应激反应如p38, JNK激酶级联反应[6], ppM1A使磷酸激酶过表达从而激活抑癌基因TP53/P53[7], 导致细胞周期$G_2$/M期停滞; Smad2分布在胞核和胞核周围的胞质中, 是TGF-β信号途径的重要调节因子[8-13], 抑制细胞生长, 促进凋亡. Wu *et al*[14]通过Envision免疫组

■背景资料
原发性肝癌是世界范围内发病率最高的恶性肿瘤之一, 也是我国最常见且恶性程度最高的肿瘤之一. 分子水平研究原发性肝癌的发生、发展、复发、转移的机制, 并针对此寻找有效的早期诊断指标及治疗措施成为当今肝癌研究中的重点和难点. 本文对肝癌相关基因的研究新进展、基因间的相互作用等研究成果作一综述.

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■研发前沿
对基因间相互作用关系的明确将对基因作用机制的研究提供帮助.

化技术检测31例肝癌组织、25例癌旁组织、13例非癌组织中PTEN、ppM1A、Smad2的表达情况显示PTEN、ppM1A在癌变过程中从细胞核转移到细胞质中, Smad2从细胞质转移到细胞核中, 且Lin *et al*[15]证明ppM1A能使TGF-β激活的Smad2/3去磷酸化, 说明ppM1A从细胞核向细胞质转移将导致Smad2细胞核积聚, 暗示基因分布位置与肝癌发生有关.

microRNA-21(miR-21)调节PTEN的表达. microRNAs(miRNAs)是非编码RNAs, 调节基因的表达. Meng *et al*[16]研究显示miR-21在肝癌和其细胞系中高表达, 在肝癌细胞系中抑制miR-21的表达, 增加了PTEN的表达, 减少了肿瘤细胞增殖、侵入、转移; 增加miR-21的表达, 增加细胞的增殖、侵入和转移, 而且正常肝细胞转染miR-21前体, 增加了细胞运动能力. miR-21以PTEN为直接靶目标, 调节PTEN表达, 且miR-21调节PTEN下游的MMP2(matrix metallopeptidase 2)和MMP9的表达, 以此促进miR-21的细胞侵入作用, 由此可见miR-21通过调节PTEN及依赖PTEN的信号途径促进肝癌的发生、发展.

1.2 GPC3 GPC3是glypican家族成员之一, 是细胞表面蛋白多糖, 调节细胞生长. 目前关于GPC3调节细胞增殖的报道不一致. Capurro *et al*[17]报道GPC3促进PLCPRF-5, HLF肝癌细胞系的细胞增殖, 而最近报道GPC3在肝癌细胞增殖中呈负向调节, 通过抑制FGF2介导的细胞增长抑制了SNU423细胞的表达, 阻碍GPC3表达增加了肝癌细胞系的增长[18-19]. Kwack *et al*[20]报道GPC3下调E-cadherin, 上调MMP-2, 减少了肝癌细胞和I型胶原和纤维连接蛋白的黏附, 增加细胞迁徙和浸润, 这与Peters *et a*[21]报道的GPC3抑制浸润、转移不一致. GPC3在卵巢癌细胞系、鼠间皮瘤细胞系、乳腺癌细胞系中沉默而肝癌组织甚至肝癌患者的血清中可检测到GPC3表达变化. 不同研究中GPC3调节细胞增殖及基因表达的不一致可能是由于使用不同的细胞系及不同类型的肝癌标本.

■相关报道
Kwack *et al*对GPC3近几年的研究成果总结、对比, 发现GPC3下调E-cadherin, 上调MMP-2, 减少了肝癌细胞和Ⅰ型胶原和纤维连接蛋白的黏附, 增加细胞迁徙和浸润.

1.3 肝癌中Pin1与Nek6的关系 Pin1通过与NIMA(never in mitosis, gene A)相互作用, 减弱有丝分裂启动区活性, 调节有丝分裂, 在肝癌中高表达. Chen *et al*[22]通过GST pull-down assay、免疫沉淀和免疫荧光检测40例肝癌标本中Pin1和Nek6之间的关系, 研究结果表明Nek6抑制Pin1表达, 减弱有丝分裂, 在细胞周期中起关键作用. 在多种癌中已有实验数据证明Pin1与许多癌蛋白的上调关系密切, 如CyclinD1[23-29]、β-catenin[30-34]的上调促进细胞增殖, 肝癌中基因之间的关系也有待证明. 然而现阶段关于Pin1和Nek6与肝癌和其他肿瘤的关系的研究仅限于Nek6 mRNA水平, 无商业化的Nek6抗体试剂盒可利用.

1.4 CCND1 CCND1蛋白与CDK4/6结合, 激活CDK4/6的蛋白激酶, 促使Rb磷酸化而释放与其结合的转录因子E2F, 促进DNA的合成, 加快细胞由$G_1$期进入S期, 从而导致细胞失控性生长[35-36]. CCND1在肝细胞癌组织中表达较高, 癌组织分化程度越低, 其阳性表达率越高, 且与肝癌侵袭性明显相关[37-40]. Park *et al*[41]研究表明在肝炎后肝癌中, 由HBx介导的NF-2/BCL3(B-cell CLL/lymphoma 3)复合体上调, 该复合体作用于CCND1启动子从而导致CCND1上调. 通过小干扰RNA阻止HBx上调BCL3的表达, 最终导致CCND1下调; 通过p53降解HBx, HBx下调, 使HBx介导的BCL3、CCND1上调被损害, 说明HBx介导的BCL3、CCND1上调对肝癌的发生发展起重要作用.

1.5 肝癌中KLF6基因变异 KLF6是具有锌指结构的肿瘤抑制基因, 调节细胞生长的信号转导途径, 参与细胞分化、细胞增殖、坏死和血管发生. KLF6通过上调细胞周期抑制因子p21抑制肿瘤生长, 而癌组织中的KLF6变异体不能上调p21的表达[42]. Pan *et al*[43]报道实验中有15%的标本KLF6发生体细胞突变. 而Boyault *et al*[44]报道实验中KLF6即未发现KLF6有体细胞突变, 也未发现有种系突变. Song *et al*[45]研究了85例肝癌标本, 结果显示KLF6的第二外显子无单链构象多态性, 即没有发现突变; 85例标本中有5例在一个或多个位点有等位基因缺失; 85例标本中1例发生甲基化. 对于KLF6变异报道的不一致, 可能由于肿瘤标本不同, 标本来源的患者种族不同, 所处的地理位置不同, 危险因素也不同, 以及标本的肿瘤分级不同.

## 2 与肝癌复发转移相关的基因

2.1 ANGPT ANGPT调节内皮与周围间质、基质间的相互作用, 促进血管的成熟性和稳定性, 与肿瘤浸润、复发、转移有关. Ang-1(angiopioetin-1)和Ang-2(angiopioetin-2)是ANGPT家族成员. Ang-1与Tie-2(Tyrosine-protein kinase receptor)结合促进自身磷酸化, Ang-2与Tie-2

结合抑制自身磷酸化, 大量实验证明Ang-2诱导血管生成反应[46]. Zhang *et al*[47]通过RT-PCR法检测38个患者的肝癌组织和癌旁组织中Ang-1、Ang-2、Tie-2、VEGF mRNA表达情况以及和临床的关系, 结果显示Ang-2在肝癌中明显高于癌旁组织, 有统计学意义; Ang-1与Tie-2 mRNA在肝癌组织和癌旁组织中无统计学差异; Ang-2、VEGF、Ang-2/Ang-1与除组织学分级外的临床病理参数相关. Ang-2/Ang-1与MVD(microvessel density)及VEGF正相关. 已有报道证明VEGF、ANGPT/Tie2系统在正常肺组织恶变为非小细胞肺癌的过程中起重要的作用[48], 有关其在肝癌发生发展中的机制有待进一步研究.

2.2 RhoC RhoC是GTPases的Ras超家族成员之一, 参与细胞骨架重建, Rho蛋白导致肌动蛋白和肌球蛋白聚集在黏着斑复合体, 导致肝癌细胞极性丧失, 增加细胞移动性, 参与肝癌的转移. RhoC在炎性乳腺癌[49-50], 前列腺癌[51]中高表达, 在肝癌中RhoC mRNA和蛋白表达水平在转移病灶和肿瘤血栓处高于原发灶, 参与肝癌的血管侵入[52-54]. 近期研究表明Rho GTPase参与自分泌运动因子(autocrine motility factor, AMF)信号途径[55], Caceres *et al*[56]通过RT-PCR检测了25例患者的肝癌组织, 癌旁组织中AMFR, RhoC的表达, 显示所有标本中均表达AMFR(autocrine motility factor receptor)、RhoC, 且肝癌组织中表达高于癌旁组织; 肝外转移灶明显高于肝内转移灶; AMFR表达低的患者复发率低, AMFR表达高的患者复发率高. AMFR与RhoC成正相关暗示RhoC可能参与AMF信号途径. 以上结果表明RhoC、AMFR可以作为肝癌的分子标记, 明确RhoC、AMFR之间的关系将对肝癌的发生机制提供一定的帮助.

2.3 RhoA RhoA调节张力丝和黏着斑形成, 在乳腺癌[57-58]、肺癌[59-60]、头颈癌[61]和卵巢癌[62]中高表达. Wang *et al*[63]通过免疫组化技术检测64个肝癌患者癌组织和正常组织中Rho蛋白的表达结果显示在恶性组织中染色强, 在良性组织弱; 通过免疫印迹法和RT-PCR检测显示癌组织中RhoA mRNA和蛋白质水平明显高于相应的癌旁组织, 且在伴有静脉浸润、卫星灶损害、PTNM分期Ⅲ/Ⅳ的肝癌组织中RhoA水平相对较高, 具有统计学差异, 说明RhoA在肝癌进展、转移中具有一定的意义. 大量数据已表明在肿瘤组织中RhoA、RhoC、ROCK(Rho-kinase)蛋白水平高, 在低分化肿瘤组织和转移的淋巴结中表达更高, 这些数据说明Rho细胞内信号途径可能决定了恶性肿瘤的转移潜能, RhoA/Rho-kinase途径介导的细胞浸润可能与肿瘤进展相关.

**■创新盘点**
从对单个基因的研究上升到基因间相互作用的研究是本文比较新颖的地方.

## 3 与肝癌相关的生长因子

3.1TGF-β TGF-β调节细胞增殖和分化, 参与胚胎发育调节, 促进细胞外基质形成和抑制免疫等. 在肿瘤发生初期, 他通过诱导生长抑制途径, 起到了抑制因子的作用, 然而在肿瘤发生后期, TGF-β起到了促进肿瘤血管生成, 促进肿瘤细胞浸润、侵入、转移和免疫抑制的作用. 目前已经在前列腺癌[64-65]、乳腺癌[66]、胃癌[67]等肿瘤中, 发现在其信号转导途径中至少有一个成分发生改变. TGF-β1是TGF-β的一个亚型, 几乎参与了所有的病理和生理过程, 如阻止细胞周期$G_1$期, 抑制细胞增殖, 促进细胞坏死, TGFβ1/Smads信号通路与肿瘤的发生发展有着密切的关系[68-69]. TGF-β1逃离了由TGF-β抑制的细胞增殖, 在肝癌组织中高表达, 在癌旁组织表达相对较低; 在HBV-DNA阳性组95%表达TGF-β1, 在HBV-DNA阴性组64%, TGF-β1表达与肝癌分化程度, 和HBV复制有关[70-71], 但与肿瘤大小, 数量无关. 外周血中TGF-β1诊断肝癌的敏感性和特异性分别是90%、94%, 联合AFP能提高检出率到97%, 因此外周血中TGF-β1mRNA可以作为HBV诱导的肝癌诊断和预后的生物标记[72].

3.2 IGF-Ⅱ IGF-Ⅱ是与胰岛素相关的促有丝分裂多肽, 调节转录, 是一种胚胎型生长因子, 常常共表达IGF-Ⅱ和IGF-Ⅰ受体, 在肝癌中高表达[73-74], 推测其在多种肿瘤细胞中作为一个自分泌因子[75]. 肝癌被看作是血管多分布肿瘤, IGF-Ⅱ可能是低氧诱导的血管源性生长因子, 在低氧环境中诱导VEGF增长, 在人类肝癌细胞中呈时间依赖的方式增加VEGF mRNA和其蛋白水平, 所以IGF-Ⅱ可能在肝癌的新生血管形成中起重要的作用. IGF-Ⅱ中P4活化与HBV基因产物间的关系, 证实HBV-X蛋白增加, 导致内皮性IGF-Ⅱ表达增加且病毒复制, 使胚胎型IGF-Ⅱ基因活化, 使IGF-Ⅱ呈高水平状态[76-77]. HBV-X抗原使Sp1磷酸化增加与DNA的结合力, 可能是调节IGF-Ⅱ基因转录和表达的重要机制, 从而在细胞癌变过程中促进细胞的分裂. IGF-ⅡmRNA在外周血中的表达与肿瘤分级有关; 肝外转移患者血清中IGF-Ⅱ mRNA 100%表达, AFP阴性肝癌中有35%表达IGF-Ⅱ mRNA. 综上诉述IGF-Ⅱ可以作

■应用要点
本文对肝癌基因研究新进展做了综述, 为今后基因的研究方向提供参考.

为肝癌肝外转移、预后及复发的分子标记[72].

## 4 结论

尽管基因研究在肝癌中取得了较大进展, 但目前尚需对以下问题进行深入研究: (1)一些基因在不同的标本中表达不同, 如GPC3在有些细胞系中上调, 有些细胞系中下调, 所以关于基因表达水平及调节机制还需进一步通过体内实验明确. (2)现阶段多数研究以肝组织为标本, 从诊断意义上讲, 外周血中基因的检测及其生物学指标的研究, 将有可能为临床肿瘤的早期诊断、预后监测及跟踪随访等提供一系列方便、快捷、特异、无创或微创的分子生物学检测手段. (3)进一步通过芯片技术确定基因在不同组织中的表达情况和基因之间的关系, 对明确基因之间的相互作用奠定一定的理论基础. (4)每个基因参与的信号途径及在信号途径中的作用机制还了解甚少, 许多的研究结果也仅限于实验水平的推测, 信号途径的明确是我们今后研究的一大挑战, 信号通路中具体的信号传递过程及调控环节的详尽研究, 将有助于我们深入理解细胞间的相互作用以及人体中正常的生理过程和某些疾病的发生机制. 总之, 通过多方面、多领域的研究, 阐明肝炎向肝硬化、肝癌发展过程中的机制对肝癌的预防、诊断、治疗、预后评估有重要的意义.

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**■同行评价**

本文对肝癌相关基因及基因间相互作用作了一定分析, 文章通顺, 条理清楚, 但学术价值一般.

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