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文献综述 REVIEW

MicroRNAs在肝细胞肝癌中作用的研究进展

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背景资料
肝细胞肝癌(hepatocellular carcinoma, HCC)在我国居恶性肿瘤发病率的第4位, 恶性肿瘤死亡的第2位, 严重威胁着人们的身体健康. miRNAs在个体发育、细胞增殖、分化及肿瘤发生等过程中发挥重要作用. 研究显示miRNAs与HCC发生发展关系密切.

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Roles of microRNAs in hepatocellular carcinoma

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Abstract
MicroRNAs (miRNAs) are small, non-coding RNA molecules consisting of 22 nucleotides, regulating the expression of target genes at the post-transcriptional or translational level. miRNAs play important roles in several physiological and physiopathological processes such as individual development, cell proliferation, apoptosis, differentiation and tumorigenesis. miRNAs may promote the development of malignant tumors by participating in the regulation of oncogenes and tumor suppressor genes, or they may function as oncogenes or tumor suppressor genes themselves. Studies have indicated that miRNAs are closely associated with hepatocellular carcinoma (HCC) formation and progression. In this review, we summarize the recent knowledge about the roles of miRNAs in the occurrence and development of HCC, as well as the value of miRNAs in the diagnosis and therapy of HCC.

Key Words: Hepatocellular carcinoma; MicroRNA; Diagnosis

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摘要
MicroRNAs(miRNAs)是近年来发现的长度约为22 nt的一类非编码小分子RNA, 通过在转录后或翻译水平调节靶基因功能, 进而在生物个体发育、细胞增殖、凋亡、分化、肿瘤发生等生理及病理过程中发挥重要作用. miRNAs可能通过参与调控癌基因和抑癌基因的表达, 促进恶性肿瘤的发生发展, 或者其本身就是潜在的癌基因或抑癌基因. 越来越多的研究显示miRNAs与肝细胞肝癌(hepatocellular carcinoma, HCC)关系密切. 本

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文就miRNAs在HCC发生发展中的作用以及在HCC诊断与治疗中的应用价值等方面的研究进展作一综述.

关键词: 肝细胞性肝癌; 微小RNA; 诊断

核心提示: miRNAs的异常表达与肝细胞肝癌(hepatocellular carcinoma, HCC)发生发展密切相关, 可作为HCC早期诊断的标志物及用于HCC预后的判断, 通过调控miRNAs表达可增加HCC细胞对化疗药物的敏感性及改善化疗药物抵抗, 为HCC治疗提供新策略.

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0 引言

肝细胞肝癌(hepatocellular carcinoma, HCC)是常见的消化系恶性肿瘤之一, 世界范围内居常见癌症的第5位, 处于癌症相关死亡病因的第3位[1], 在我国居恶性肿瘤发病率的第4位, 处于肿瘤死亡的第2位[2,3]. HCC恶性程度高、病情进展快, 发病较隐匿, 多数患者在诊断时即已出现肝内或肝外转移, 失去了根治性手术治疗的机会, 而且放、化疗效果也不理想[4]. HCC的发生与乙型肝炎病毒(hepatitis B virus, HBV)及丙型肝炎病毒(hepatitis C virus)感染、慢性酒精摄入、非酒精性脂肪性肝病及环境因素等有关[5], 癌变过程中涉及多种基因的异常改变[6].

MicroRNAs(miRNAs)是近年来新发现的长度约为22 nt一类非编码小分子RNA, 在生物个体发育、细胞增殖、分化及肿瘤发生等生理及病理过程中发挥重要作用[7,8]. 近来研究[9]报道多种miRNAs可能通过参与调控癌基因和抑癌基因的表达, 促进肿瘤的发生发展, 或者其本身就是潜在的癌基因或抑癌基因. 越来越多的研究显示miRNAs与HCC发生发展关系密切, 本文总结了miRNAs在HCC发生发展中的作用及其在HCC诊断与治疗中的应用价值等方面的最新进展, 为进一步研究提供参考.

1 miRNA的合成与作用

miRNA在一系列RNaseⅡ内切酶和转运蛋白的作用下, 逐步被剪切、转运, 再剪切并加工完成[10]. 在细胞核内首先由RNA聚合酶Ⅱ转录生成初级转录产物, 然后被剪切成miRNA前体, 在转运蛋白5的作用下被运送到细胞质中, 被另一种RNaseⅢ-Dicer核酸内切酶复合物剪切成miRNA双链RNA, 其中的一条链结合到RNA介导的沉默复合物, 另一条链被降解[11-13]. miRNA主要通过与靶基因mRNA的3'端基因非翻译区(untranslated regions, UTR)区互补结合发挥作用, 当两者能完全互补配对结合时, 可导致靶基因mRNA的降解; 当两者不完全互补时, 则抑制靶基因mRNA的翻译, 影响靶基因蛋白的表达, 而对靶基因mRNA无影响[14,15]. miRNA通过在转录后或翻译水平调节靶基因功能, 进而调控细胞增殖、凋亡、代谢等多种生物学活动[7,16]. 研究显示miRNAs参与了恶性肿瘤的发生, 被认为是癌基因及抑癌基因的调控因子, 多数miRNA可作为恶性肿瘤潜在的生物学标志物. miRNA的靶点及其相关信号通路的发现有助于恶性肿瘤治疗方案的研发[17].

研发前沿
HCC发生过程中涉及到多种miRNA的异常改变, 目前研究集中于miRNAs在HCC中的作用与机制, 需要进一步临床大规模筛选HCC特异性高的miRNAs, 以及针对异常表达miRNAs设计靶点以提高HCC治疗效果.

2 miRNA与HCC发生发展

越来越多的研究显示HCC组织中存在miRNA异常表达. Murakami等[18]采用miRNA芯片技术对HCC组织、HCC周围正常肝组织及慢性肝炎细针穿刺组织进行研究, 鉴定出差异表达的miRNA有30个, 进一步研究发现, 与肝癌分化程度相关的miRNA有miR-92、miR-20、miR-18等, 而且其表达水平与肝癌分化程度呈负相关. Wojcicka等[19]研究也表明miRNA的异常表达与HCC发生发展相关, 在HCC组织中有10种miRNAs表达明显上调, 有16种miRNAs表达明显下调, 而包括miR-199a-3p/miR-199b-3p等在内的miRNAs的变化可能发生在HCC癌变的早期, 即慢性肝炎、肝硬化时就已出现.

2.1 癌性miRNA 研究[20]认为在HCC组织中明显上调、高表达的miRNAs在HCC的发展过程中呈现出类似癌基因的作用. Wang等[21]应用实时定量PCR检测(real-time quantitative PCR, qRT-PCR)方法分析HCC早期阶段miRNAs的表达情况, 发现miR-155、miR-221、miR-222和miR-21表达上调, 其中miR-155的异常表达促进癌细胞的增殖. miR-21被作为癌基因, 可通过抑制抑癌基因*PTEN*和*MAP2K3*促进肝脏肿瘤生长和转移[22]; miR-21还通过调节PDCD4

相关报道
国外学者首次采用miRNA芯片技术检测HCC组织、癌周正常肝组织及慢性肝炎细针穿刺组织中miRNA的表达, 发现了30个差异表达的miRNA, 部分与HCC分化程度显著相关. 该报道开启了miRNAs与HCC关系研究的热潮.

蛋白在促进HCC发生和发展中起着重要作用[23]. 研究[24]报道miR-224、miR-34a、miR-362-5p在HCC组织中表达显著上调, 而且与HCC的发展密切相关. 应用siRNA抑制HCC细胞miR-362-5p表达可显著降低细胞的增殖、克隆形成、侵袭和迁移及裸鼠肝癌的生长和转移, 进一步研究[25]发现miR-362-5p通过靶基因*CYLD*激活NF-κB信号通路促进HCC的进展.

Yu等[26]研究发现miR-543在HCC组织和HCC细胞株中表达明显升高, 而且miR-543能够促进肝癌HepG2细胞的增殖潜能及侵袭力, miR-543通过靶基因*PAQR3*在HCC中发挥类似癌基因作用. Chuang等[27]报道miR-494通过直接靶向调控*TET1*(ten eleven translocation 1)基因, 使多种侵袭抑制miRNAs的基因组DNA去甲基化从而使基因沉默, 进而导致HCC的血管浸润. Yuan等[28]等报道miR-106a在36例HCC组织中的表达较癌旁正常肝组织中表达明显升高, miR-106a启动子的甲基化状态与其表达呈负相关, 进一步研究证实miR-106a的靶基因是*TP53INP1*和*CDKN1A*. 与低表达miR-106a的肝癌细胞株相比, 高表达miR-106a的HCC细胞株具有更强的侵袭性、更快的细胞周期进程及更多的凋亡抵抗. Kan等[29]报道miR-520g在HCC组织中表达上调, 并与肿瘤复发、转移等密切相关, 功能研究显示miR-520g能促进HCC细胞的侵袭、迁移和上皮间质转化(epithelial-mesenchymal transition, EMT), 而Smad7是其作用的直接靶点. miR-181a在HCC组织中表达明显上调, 而在TGF-β处理后miR-181a也是上调miRNA之一, miR-181a过表达能够诱导细胞发生EMT样变化[30]. Yau等[31]报道miR-106b在HCC中过度表达, 且与肿瘤分级显著相关, miR-106b可通过过表达Rho GTP酶、RhoA和RhoC来促进细胞迁移, 而且miR-106b过表达能促进HCC的转移, 这些作用都与EMT过程的激活有关.

2.2 抑癌性miRNA 另一类miRNA称为“抑癌性miRNA”, 即在正常组织中高表达、肿瘤组织中低表达, 如miR-122、miR-126、miR-375等[20]. miR-122、miR-125a/b、miR-26、miR-199和miR-375在HCC组织中表达下调, 部分miRNA在HCC的进展中发挥关键作用[24]. miR-122表达下调导致染色体的不稳定性, 从而解除细胞周期G_1期相关蛋白的调控, 间接地通过细胞周期调节蛋白P53依赖途径发挥作用, 使PPZA磷酸酶去磷酸化, 激活Mdm-2导致p53失活, 抑制肝癌细胞的增殖, 促进癌细胞的凋亡[32]. miR-122还可抑制血管内皮细胞的分化, 抑制肿瘤血管的生成[33]. 此外, 有报道[34]认为在非酒精性脂肪性肝病发生癌变过程中miR-122基因的沉默是个早期事件, miR-122可作为评估患者发生HCC风险的理想指标. Bandopadhyay等[35]报道miRNA-21、miRNA-222和miRNA-145在HCC中发挥肿瘤抑制基因的作用, 其下游靶基因有*PTEN*、*p27*和*MAP3K*. Lin等[36]研究发现miR-744在HCC组织及细胞株中均明显下调, 而恢复miR-744的表达能降低HCC细胞的增殖及引起细胞周期G_1期阻滞, miR-744可能通过靶向调控*c-myc*基因在HCC中发挥肿瘤抑制基因的功能. 研究[37]报道在HCC中miR-1285-3p也充当抑癌基因, 而且血清中miR-1285-3p和miR-4741还能预测HCC对经皮肝动脉化疗栓塞术的治疗反应. miR-148b在HCC组织的表达显著低于正常对照肝组织, 而且miR-148b的异常表达与HCC血管浸润及TNM分期显著相关[38].

研究[39]发现miR-26b在多种HCC细胞株如HepG2、MHCC97H、Hep3B及MHCC97L等中表达下降, 且与HCC的分级显著相关, 而恢复miR-26b表达能够抑制HCC细胞株的侵袭及迁移力, 同时伴随上皮标志物E-cadherin表达的降低、间质标志物Vimentin表达的增高以及USP9X和Smad4蛋白表达受抑, miR-26b可能通过USP9X、Smad4和TGF-β信号通路抑制HCC细胞的EMT. Zhou等[40]报道在众多的miRNAs中, miR-125b在HCC组织中表达下调, 与HCC细胞分化程度明显相关, miR-125b的过表达可抑制HCC细胞的EMT; miR-125b主要通过作用于Smad2和Smad4来抑制EMT, 改善EMT相关的HCC化疗耐药等. Kim等[41]报道miR-31主要通过调节细胞周期相关蛋白(如HDAC2、CDK2)及EMT相关蛋白(如N-cadherin、E-cadherin、Vimentin等)的表达在HCC中发挥抑癌基因的功能.

3 miRNA与HCC诊断

miRNA在组织中含量稳定, 而血液中含有大量RNA酶(RNase), 可能会影响血液中miRNA的检测, 但研究[42]显示miRNA在血液中表达水平

稳定. 研究[43,44]认为可能是某种保护miRNA的附加结构, 如膜性物质包裹miRNA分子, 避免其与RNase接触, 或是某种物质能够对miRNA进行保护性的修饰或结合, 使miRNA免于被降解, 从而对血液miRNA起到保护作用. 因此有越来越多的研究探讨检测血清中miRNA的表达水平在恶性肿瘤患者中的诊断价值.

多项研究[45]报道血清中miRNAs的检测可用于HCC患者的诊断. Qi等[46]检测HCC患者和健康对照组中血清miR-122、miR-222、miR-223、miR-21、miR-221、miR-301的表达水平, 发现HCC中miR-122、miR-222、miR-223的表达显著上调(P<0.05), miR-21表达显著下调(P<0.01), 而miR-221、miR-301的表达水平与健康对照组之间比较差异无统计学意义(P>0.05); 对于HBV感染患者发生HCC组和未发生HCC组之间miR-222、miR-223及miR-21的表达水平比较无显著性差异(P>0.05), 并发HCC组血清miR-122表达水平明显高于未合并HCC组(P<0.05), 提示血清miR-122可作为在HBV感染者筛查HCC潜在的分子标志物. 日本学者也报道miR-21在HCC患者的血浆中和组织中表达增高, 血浆miR-21可作为HCC的诊断标志物[47]. Gong等[24]也报道血清miR-21的变化能够比甲胎蛋白(α-fetoprotein, AFP)更早、更准确地反映HCC的发生, miR-21可作为HCC的早期诊断标志物.

Meng等[48]检测合并HBV感染的HCC和慢性肝脏病患者血清中miR-155-5p、miR-24-3p、miR-490-3p、miR-210-3p、and miR-335-5p的表达水平, 结果发现血清中miR-24-3p水平明显升高, 且与HCC患者血管浸润密切相关, 而血清miR-24-3p水平能够很好地鉴别HCC与慢性肝脏病, 曲线下面积(area under the curve, AUC)是0.636(95%CI: 0.524-0.748), 当联合AFP时, AUC可增加至0.834%(95%CI: 0.745-0.923, P<0.001), 联合检测血清miR-24-3p和AFP较单一指标能够显著增加HCC诊断的准确度. 另有报道[49]miR-125和miR-233可用于HBV阳性或伴有乙型病毒性肝炎的HCC患者早期诊断.

我们前期研究[50]应用qRT-PCR方法检测HCC、慢性肝炎及正常对照人群血浆miR-143和miR-215的水平, 并应用ROC曲线分析miR-143和miR-215对于慢性肝炎及肝癌的诊断价值, 结果显示miR-143和miR-215在HCC、慢性肝炎患者血浆中表达上调, 血清miR-143和miR-215可作为HCC患者诊断的潜在的标志物. Jiang等[51]检测27例HCC患者、31例慢性肝脏病患者及50例健康人群血清中miR-106b、miR-10b及miR-181a的表达水平, 结果发现三者可以很好地鉴别HCC与慢性肝脏病及健康对照, 血清miR-106b、miR-10b及miR-181a可作为准确且无创的HCC初步筛选的生物学标志物. 虽然研究报道显示部分miRNA在HCC的诊断价值, 但还需进一步大规模的临床研究来证实循环miRNAs在HCC筛查的临床意义.

创新盘点

本文重点讨论了miRNAs在HCC发生发展、诊断、治疗及预后判断中作用及机制的最新进展, 为HCC早期诊断、有效治疗等方面引入了新思路和新策略.

4 miRNA与HCC治疗

miRNA有癌基因和抑癌基因的作用, 而且miRNA还可以影响化疗效果, 因此可以可通过调控miRNA开展对肿瘤的治疗[52]. 针对miRNA治疗肿瘤主要有两个策略, 一种策略是针对在肿瘤组织中上调的miRNA, 通过应用反义技术抑制miRNA的表达, 可以抑制肿瘤细胞的增殖或诱导其凋亡, 另一种策略是转染pre-miRNA或直接使用人工合成特异性miRNA, 恢复肿瘤组织细胞miRNA表达, 进而起到抑制肿瘤细胞增殖的作用.

通过应用寡核苷酸技术沉默肿瘤组织中高表达的miRNA, 可抑制肿瘤细胞的增殖和转移. 腺病毒载体介导或小分子螯合物能够降低肝癌细胞中miR-221的表达水平, 使CDKN1B/p27蛋白表达增加, 进而促进肝癌细胞Hep3B的凋亡[53]. 将抗miR-184导入肝癌HepG2细胞沉默miR-184表达, 可抑制肝癌细胞增殖, 并通过调节Caspase3/7的表达促进肝癌细胞的凋亡[54].

应用腺病毒载体介导miR-122转染到人HCC细胞株HepG、Hep3B、Huh7及PLC/PRF/5等中, 能提高miR-122在HCC细胞中的表达, 促进细胞凋亡及使细胞周期停滞, 从而抑制HCC细胞的增殖[55]. 研究[56]显示miR-26a在肝癌组织中表达明显下调, 而构建miR-26a自身互补型腺病毒载体注入小鼠肝癌模型, 肿瘤生长明显受到抑制. 应用脂质体^{TM}2000将miR-206转染至HepG2细胞, 可引起细胞增殖受抑、凋亡增加[57]. 恢复或上调miR-34a表达

应用要点
本文系统阐述了miRNAs与HCC的关系, 希望引起更多研究者关注miRNA在HCC发生中的具体作用, 以期发现有价值的miRNAs用于HCC的诊断及治疗.

及功能可以预防肿瘤细胞对化疗药物抵抗, 小分子激活剂Rubone可激活miR-34a表达, 抑制肝癌的生长[58].

Yin等[59]报道miR-193b可作为肝癌化疗药物顺铂的增敏剂, 主要通过Caspase3通路、靶向调控Mcl-1来发挥作用. Huang等[60]研究显示紫杉醇可诱导miR-877表达上调进而抑制肝癌细胞的增殖, miR-877通过靶向调控*FoxM1*基因影响肝癌细胞株对化疗药物的敏感性. 有研究[61]报道miR-141通过下调KEAP1表达在5-FU耐药中发挥关键作用, 而其可通过激活Nrf2依赖的抗氧化途径克服肝癌细胞对5-Fu的耐药, miR-141可成为HCC治疗的一个潜在靶点.

5 miRNA与HCC预后

目前临床中评价HCC预后依据主要包括临床病理学分期及AFP等, 一些生物学标志物的预后价值处于研究探索中. 研究[45,62]报道血清miRNAs的检测可预判和监测治疗反应, 能够用于HCC患者预后判断. 血清中miR-21、miR-520g、miR-140的水平与HCC患者预后密切相关[24,29,63]. 研究[38]对HCC患者进行生存分析, 结果显示miR-148b是HCC的独立预后因素, 类似的研究显示血清miR-24-3p水平是HBV相关HCC患者独立预后因素[48]. 研究[64]检测327例HCC组织标本中miRNAs的表达情况, 并分析与HCC患者预后的关系, 结果发现共有7种miRNAs与患者生存期显著相关(P<0.001), 其中hsa-miR-326、hsa-miR-3677、hsa-miR-511-1、hsa-miR-511-2、hsa-miR-9-1和hsa-miR-9-2与HCC总体生存率呈负相关, 而hsa-miR-30d与之呈正相关, 建立在检测这7种miRNAs基础上的预后模型, 可用于判断HCC患者生存.

6 结论

miRNA在肿瘤中的研究已取得较大的进展, 为HCC诊断、治疗、预后判断等方面引入了新思路、新策略. 由于HCC发生机制极其复杂, 发生过程中涉及到多个miRNA的异常改变, 因此除了深入研究miRNA的具体作用及机制, 还需要临床大规模研究包括不同病因、不同性别、不同年龄段及不同阶段HCC患者血清miRNA表达水平变化, 筛选出HCC特异性高的miRNA. 血清中miRNA检测虽具有创伤小、可重复的优势, 尚需要可靠的内源性参照物提高检测的准确性, 以期达到很好地在临床上应用于HCC的诊断. 而针对多种过表达或低表达miRNA设计能够增强治疗效果的有效的调控方案还需要深入的探讨与研究.

7 参考文献

1 Centers for Disease Control and Prevention (CDC). Hepatocellular carcinoma - United States, 2001-2006. *MMWR Morb Mortal Wkly Rep* 2010; 59: 517-520 [PMID: 20448528]
2 Liu XY, Xu JF. Liver resection for young patients with large hepatocellular carcinoma: a single center experience from China. *World J Surg Oncol* 2014; 12: 175 [PMID: 24894964]
3 陈万青, 张思维, 曾红梅, 郑荣寿, 邹小农, 赵平, 吴良有, 李光琳, 赫捷. 中国2010年恶性肿瘤发病与死亡. 中国肿瘤 2014; 23: 1-10
4 Morise Z, Kawabe N, Tomishige H, Nagata H, Kawase J, Arakawa S, Yoshida R, Isetani M. Recent advances in liver resection for hepatocellular carcinoma. *Front Surg* 2014; 1: 21 [PMID: 25593945 DOI: 10.3389/fsurg.2014.00021]
5 Mlynarsky L, Menachem Y, Shibolet O. Treatment of hepatocellular carcinoma: Steps forward but still a long way to go. *World J Hepatol* 2015; 7: 566-574 [PMID: 25848480 DOI: 10.4254/wjh.v7.i3.566]
6 Nault JC. Pathogenesis of hepatocellular carcinoma according to aetiology. *Best Pract Res Clin Gastroenterol* 2014; 28: 937-947 [PMID: 25260319 DOI: 10.1016/j.bpg.2014.08.006]
7 Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004; 116: 281-297 [PMID: 14744438]
8 Thorsen SB, Obad S, Jensen NF, Stenvang J, Kauppinen S. The therapeutic potential of microRNAs in cancer. *Cancer J* 2012; 18: 275-284 [PMID: 22647365 DOI: 10.1097/PPO.0b013e318258b5d6]
9 Zhang B, Pan X, Cobb GP, Anderson TA. microRNAs as oncogenes and tumor suppressors. *Dev Biol* 2007; 302: 1-12 [PMID: 16989803]
10 Lee Y, Ahn C, Han J, Choi H, Kim J, Yim J, Lee J, Provost P, Rådmark O, Kim S, Kim VN. The nuclear RNase III Drosha initiates microRNA processing. *Nature* 2003; 425: 415-419 [PMID: 14508493]
11 Liu W, Mao SY, Zhu WY. Impact of tiny miRNAs on cancers. *World J Gastroenterol* 2007; 13: 497-502 [PMID: 17278213]
12 He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. *Nat Rev Genet* 2004; 5: 522-531 [PMID: 15211354]
13 Gregory RI, Shiekhattar R. MicroRNA biogenesis and cancer. *Cancer Res* 2005; 65: 3509-3512 [PMID: 15867338]
14 Gregory RI, Chendrimada TP, Cooch N, Shiekhattar R. Human RISC couples microRNA biogenesis and posttranscriptional gene silencing. *Cell* 2005; 123: 631-640 [PMID: 16271387]
15 Tang F, Hajkova P, O'Carroll D, Lee C, Tarakhovsky A, Lao K, Surani MA. MicroRNAs are tightly associated with RNA-induced gene silencing

complexes in vivo. *Biochem Biophys Res Commun* 2008; 372: 24-29 [PMID: 18474225 DOI: 10.1016/j.bbrc.2008.04.137]
16 Taylor MA, Schiemann WP. Therapeutic Opportunities for Targeting microRNAs in Cancer. *Mol Cell Ther* 2014; 2: 1-13 [PMID: 25717380 DOI: 10.1186/2052-8426-2-30]
17 Zhu Z, Zhang X, Wang G, Zheng H. Role of MicroRNAs in Hepatocellular Carcinoma. *Hepat Mon* 2014; 14: e18672 [PMID: 25337143 DOI: 10.5812/hepatmon.18672]
18 Murakami Y, Yasuda T, Saigo K, Urashima T, Toyoda H, Okanoue T, Shimotohno K. Comprehensive analysis of microRNA expression patterns in hepatocellular carcinoma and nontumorous tissues. *Oncogene* 2006; 25: 2537-2545 [PMID: 16331254]
19 Wojcicka A, Swierniak M, Kornasiewicz O, Gierlikowski W, Maciag M, Kolanowska M, Kotlarek M, Gornicka B, Koperski L, Niewinski G, Krawczyk M, Jazdzewski K. Next generation sequencing reveals microRNA isoforms in liver cirrhosis and hepatocellular carcinoma. *Int J Biochem Cell Biol* 2014; 53: 208-217 [PMID: 24875649 DOI: 10.1016/j.biocel.2014.05.020]
20 Song Y, Wang F, Huang Q, Cao Y, Zhao Y, Yang C. MicroRNAs Contribute to Hepatocellular Carcinoma. *Mini Rev Med Chem* 2015; 15: 459-466 [PMID: 25807945]
21 Wong QW, Lung RW, Law PT, Lai PB, Chan KY, To KF, Wong N. MicroRNA-223 is commonly repressed in hepatocellular carcinoma and potentiates expression of Stathmin1. *Gastroenterology* 2008; 135: 257-269 [PMID: 18555017 DOI: 10.1053/j.gastro.2008.04.003]
22 Xu G, Zhang Y, Wei J, Jia W, Ge Z, Zhang Z, Liu X. MicroRNA-21 promotes hepatocellular carcinoma HepG2 cell proliferation through repression of mitogen-activated protein kinase-kinase 3. *BMC Cancer* 2013; 13: 469 [PMID: 24112539 DOI: 10.1186/1471-2407-13-469]
23 Wang X, Zhang J, Zhou L, Lu P, Zheng ZG, Sun W, Wang JL, Yang XS, Li XL, Xia N, Zhang N, Dou KF. Significance of serum microRNA-21 in diagnosis of hepatocellular carcinoma (HCC): clinical analyses of patients and an HCC rat model. *Int J Clin Exp Pathol* 2015; 8: 1466-1478 [PMID: 25973032]
24 Gong J, He XX, Tian A. Emerging role of microRNA in hepatocellular carcinoma (Review). *Oncol Lett* 2015; 9: 1027-1033 [PMID: 25663852]
25 Ni F, Zhao H, Cui H, Wu Z, Chen L, Hu Z, Guo C, Liu Y, Chen Z, Wang X, Chen D, Wei H, Wang S. MicroRNA-362-5p promotes tumor growth and metastasis by targeting CYLD in hepatocellular carcinoma. *Cancer Lett* 2015; 356: 809-818 [PMID: 25449782 DOI: 10.1016/j.canlet.2014.10.041]
26 Yu L, Zhou L, Cheng Y, Sun L, Fan J, Liang J, Guo M, Liu N, Zhu L. MicroRNA-543 acts as an oncogene by targeting PAQR3 in hepatocellular carcinoma. *Am J Cancer Res* 2014; 4: 897-906 [PMID: 25520877]
27 Chuang KH, Whitney-Miller CL, Chu CY, Zhou Z, Dokus MK, Schmit S, Barry CT. MicroRNA-494 is a master epigenetic regulator of multiple invasion-suppressor microRNAs by targeting ten eleven translocation 1 in invasive human hepatocellular carcinoma tumors. *Hepatology* 2015; 62: 466-480 [PMID: 25820676 DOI: 10.1002/hep.27816]
28 Yuan R, Zhi Q, Zhao H, Han Y, Gao L, Wang B, Kou Z, Guo Z, He S, Xue X, Hu H. Upregulated expression of miR-106a by DNA hypomethylation plays an oncogenic role in hepatocellular carcinoma. *Tumour Biol* 2015; 36: 3093-3100 [PMID: 25510666 DOI: 10.1007/s13277-014-2945-2]
29 Kan H, Guo W, Huang Y, Liu D. MicroRNA-520g induces epithelial-mesenchymal transition and promotes metastasis of hepatocellular carcinoma by targeting SMAD7. *FEBS Lett* 2015; 589: 102-109 [PMID: 25436421 DOI: 10.1016/j.febslet.2014.11.031]
30 Brockhausen J, Tay SS, Grzelak CA, Bertolino P, Bowen DG, d'Avigdor WM, Teoh N, Pok S, Shackel N, Gamble JR, Vadas M, McCaughan GW. miR-181a mediates TGF-β-induced hepatocyte EMT and is dysregulated in cirrhosis and hepatocellular cancer. *Liver Int* 2015; 35: 240-253 [PMID: 24576072 DOI: 10.1111/liv.12517]
31 Yau WL, Lam CS, Ng L, Chow AK, Chan ST, Chan JY, Wo JY, Ng KT, Man K, Poon RT, Pang RW. Over-expression of miR-106b promotes cell migration and metastasis in hepatocellular carcinoma by activating epithelial-mesenchymal transition process. *PLoS One* 2013; 8: e57882 [PMID: 23483935 DOI: 10.1371/journal.pone.0057882]
32 Fornari F, Gramantieri L, Giovannini C, Veronese A, Ferracin M, Sabbioni S, Calin GA, Grazi GL, Croce CM, Tavolari S, Chieco P, Negrini M, Bolondi L. MiR-122/cyclin G1 interaction modulates p53 activity and affects doxorubicin sensitivity of human hepatocarcinoma cells. *Cancer Res* 2009; 69: 5761-5767 [PMID: 19584283 DOI: 10.1158/0008-5472.CAN-08-4797]
33 Bai S, Nasser MW, Wang B, Hsu SH, Datta J, Kutay H, Yadav A, Nuovo G, Kumar P, Ghoshal K. MicroRNA-122 inhibits tumorigenic properties of hepatocellular carcinoma cells and sensitizes these cells to sorafenib. *J Biol Chem* 2009; 284: 32015-32027 [PMID: 19726678 DOI: 10.1074/jbc.M109.016774]
34 Takaki Y, Saito Y, Takasugi A, Toshimitsu K, Yamada S, Muramatsu T, Kimura M, Sugiyama K, Suzuki H, Arai E, Ojima H, Kanai Y, Saito H. Silencing of microRNA-122 is an early event during hepatocarcinogenesis from non-alcoholic steatohepatitis. *Cancer Sci* 2014; 105: 1254-1260 [PMID: 25117675 DOI: 10.1111/cas.12498]
35 Bandopadhyay M, Banerjee A, Sarkar N, Panigrahi R, Datta S, Pal A, Singh SP, Biswas A, Chakrabarti S, Chakravarty R. Tumor suppressor micro RNA miR-145 and onco micro RNAs miR-21 and miR-222 expressions are differentially modulated by hepatitis B virus X protein in malignant hepatocytes. *BMC Cancer* 2014; 14: 721 [PMID: 25260533 DOI: 10.1186/1471-2407-14-721]
36 Lin F, Ding R, Zheng S, Xing D, Hong W, Zhou Z, Shen J. Decrease expression of microRNA-744 promotes cell proliferation by targeting c-Myc in human hepatocellular carcinoma. *Cancer Cell Int* 2014; 14: 58 [PMID: 24991193 DOI: 10.1186/1475-2867-14-58]
37 Liu J, Yan J, Zhou C, Ma Q, Jin Q, Yang Z. miR-1285-3p acts as a potential tumor suppressor miRNA via downregulating JUN expression in hepatocellular carcinoma. *Tumour Biol* 2015;

同行评价

本文就miRNAs在HCC的研究进展和最新动态作了系统性、全面性的综合分析，总结其在HCC诊断、治疗、预后中的作用以及对化疗药物的敏感性和耐药性方面的影响，对临床有一定的指导意义. 文章条理清晰、通顺简练.

36: 219-225 [PMID: 25230788 DOI: 10.1007/s13277-014-2622-5]
38 Zhang Z, Zheng W, Hai J. MicroRNA-148b expression is decreased in hepatocellular carcinoma and associated with prognosis. *Med Oncol* 2014; 31: 984 [PMID: 24805877 DOI: 10.1007/s12032-014-0984-6]
39 Shen G, Lin Y, Yang X, Zhang J, Xu Z, Jia H. MicroRNA-26b inhibits epithelial-mesenchymal transition in hepatocellular carcinoma by targeting USP9X. *BMC Cancer* 2014; 14: 393 [PMID: 24890815 DOI: 10.1186/1471-2407-14-393]
40 Zhou JN, Zeng Q, Wang HY, Zhang B, Li ST, Nan X, Cao N, Fu CJ, Yan XL, Jia YL, Wang JX, Zhao AH, Li ZW, Li YH, Xie XY, Zhang XM, Dong Y, Xu YC, He LJ, Yue W, Pei XT. MicroRNA-125b attenuates epithelial-mesenchymal transitions and targets stem-like liver cancer cells through small mothers against decapentaplegic 2 and 4. *Hepatology* 2015; 62: 801-815 [PMID: 25953743 DOI: 10.1002/hep.27887]
41 Kim HS, Lee KS, Bae HJ, Eun JW, Shen Q, Park SJ, Shin WC, Yang HD, Park M, Park WS, Kang YK, Nam SW. MicroRNA-31 functions as a tumor suppressor by regulating cell cycle and epithelial-mesenchymal transition regulatory proteins in liver cancer. *Oncotarget* 2015; 6: 8089-8102 [PMID: 25797269]
42 Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, Peterson A, Noteboom J, O'Briant KC, Allen A, Lin DW, Urban N, Drescher CW, Knudsen BS, Stirewalt DL, Gentleman R, Vessella RL, Nelson PS, Martin DB, Tewari M. Circulating microRNAs as stable blood-based markers for cancer detection. *Proc Natl Acad Sci USA* 2008; 105: 10513-10518 [PMID: 18663219 DOI: 10.1073/pnas.0804549105]
43 Chen X, Ba Y, Ma L, Cai X, Yin Y, Wang K, Guo J, Zhang Y, Chen J, Guo X, Li Q, Li X, Wang W, Zhang Y, Wang J, Jiang X, Xiang Y, Xu C, Zheng P, Zhang J, Li R, Zhang H, Shang X, Gong T, Ning G, Wang J, Zen K, Zhang J, Zhang CY. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. *Cell Res* 2008; 18: 997-1006 [PMID: 18766170 DOI: 10.1038/cr.2008.282]
44 Kosaka N, Iguchi H, Ochiya T. Circulating microRNA in body fluid: a new potential biomarker for cancer diagnosis and prognosis. *Cancer Sci* 2010; 101: 2087-2092 [PMID: 20624164 DOI: 10.1111/j.1349-7006.2010.01650.x]
45 He S, Zhang DC, Wei C. MicroRNAs as biomarkers for hepatocellular carcinoma diagnosis and prognosis. *Clin Res Hepatol Gastroenterol* 2015; 39: 426-434 [PMID: 25746139 DOI: 10.1016/j.clinre.2015.01.006]
46 Qi P, Cheng SQ, Wang H, Li N, Chen YF, Gao CF. Serum microRNAs as biomarkers for hepatocellular carcinoma in Chinese patients with chronic hepatitis B virus infection. *PLoS One* 2011; 6: e28486 [PMID: 22174818 DOI: 10.1371/journal.pone.0028486]
47 Tomimaru Y, Eguchi H, Nagano H, Wada H, Kobayashi S, Marubashi S, Tanemura M, Tomokuni A, Takemasa I, Umeshita K, Kanto T, Doki Y, Mori M. Circulating microRNA-21 as a novel biomarker for hepatocellular carcinoma. *J Hepatol* 2012; 56: 167-175 [PMID: 21749846 DOI: 10.1016/j.jhep.2011.04.026]
48 Meng FL, Wang W, Jia WD. Diagnostic and prognostic significance of serum miR-24-3p in HBV-related hepatocellular carcinoma. *Med Oncol* 2014; 31: 177 [PMID: 25129312 DOI: 10.1007/s12032-014-0177-3]
49 Giray BG, Emekdas G, Tezcan S, Ulger M, Serin MS, Sezgin O, Altintas E, Tiftik EN. Profiles of serum microRNAs; miR-125b-5p and miR223-3p serve as novel biomarkers for HBV-positive hepatocellular carcinoma. *Mol Biol Rep* 2014; 41: 4513-4519 [PMID: 24595450 DOI: 10.1007/s11033-014-3322-3]
50 Zhang ZQ, Meng H, Wang N, Liang LN, Liu LN, Lu SM, Luan Y. Serum microRNA 143 and microRNA 215 as potential biomarkers for the diagnosis of chronic hepatitis and hepatocellular carcinoma. *Diagn Pathol* 2014; 9: 135 [PMID: 24993656 DOI: 10.1186/1746-1596-9-135]
51 Jiang L, Cheng Q, Zhang BH, Zhang MZ. Circulating microRNAs as biomarkers in hepatocellular carcinoma screening: a validation set from China. *Medicine* (Baltimore) 2015; 94: e603 [PMID: 25761179 DOI: 10.1097/MD.0000000000000603]
52 Hung CH, Chiu YC, Chen CH, Hu TH. MicroRNAs in hepatocellular carcinoma: carcinogenesis, progression, and therapeutic target. *Biomed Res Int* 2014; 2014: 486407 [PMID: 24800233 DOI: 10.1155/2014/486407]
53 Moshiri F, Callegari E, D'Abundo L, Corrà F, Lupini L, Sabbioni S, Negrini M. Inhibiting the oncogenic mir-221 by microRNA sponge: toward microRNA-based therapeutics for hepatocellular carcinoma. *Gastroenterol Hepatol Bed Bench* 2014; 7: 43-54 [PMID: 25436097]
54 Gao B, Gao K, Li L, Huang Z, Lin L. miR-184 functions as an oncogenic regulator in hepatocellular carcinoma (HCC). *Biomed Pharmacother* 2014; 68: 143-148 [PMID: 24183204 DOI: 10.1016/j.biopha.2013.09.005]
55 Ma L, Liu J, Shen J, Liu L, Wu J, Li W, Luo J, Chen Q, Qian C. Expression of miR-122 mediated by adenoviral vector induces apoptosis and cell cycle arrest of cancer cells. *Cancer Biol Ther* 2010; 9: 554-561 [PMID: 20150764]
56 Kota J, Chivukula RR, O'Donnell KA, Wentzel EA, Montgomery CL, Hwang HW, Chang TC, Vivekanandan P, Torbenson M, Clark KR, Mendell JR, Mendell JT. Therapeutic microRNA delivery suppresses tumorigenesis in a murine liver cancer model. *Cell* 2009; 137: 1005-1017 [PMID: 19524505 DOI: 10.1016/j.cell.2009.04.021]
57 Liu W, Xu C, Wan H, Liu C, Wen C, Lu H, Wan F. MicroRNA-206 overexpression promotes apoptosis, induces cell cycle arrest and inhibits the migration of human hepatocellular carcinoma HepG2 cells. *Int J Mol Med* 2014; 34: 420-428 [PMID: 24919811 DOI: 10.3892/ijmm.2014.1800]
58 Xiao Z, Li CH, Chan SL, Xu F, Feng L, Wang Y, Jiang JD, Sung JJ, Cheng CH, Chen Y. A small-molecule modulator of the tumor-suppressor miR34a inhibits the growth of hepatocellular carcinoma. *Cancer Res* 2014; 74: 6236-6247 [PMID: 25217526 DOI: 10.1158/0008-5472.CAN-14-0855]

59 Yin W, Nie Y, Zhang Z, Xie L, He X. miR-193b acts as a cisplatin sensitizer via the caspase-3-dependent pathway in HCC chemotherapy. *Oncol Rep* 2015; 34: 368-374 [PMID: 25997995 DOI: 10.3892/or.2015.3996]
60 Huang X, Qin J, Lu S. Up-regulation of miR-877 induced by paclitaxel inhibits hepatocellular carcinoma cell proliferation though targeting FOXM1. *Int J Clin Exp Pathol* 2015; 8: 1515-1524 [PMID: 25973036]
61 Shi L, Wu L, Chen Z, Yang J, Chen X, Yu F, Zheng F, Lin X. MiR-141 Activates Nrf2-Dependent Antioxidant Pathway via Down-Regulating the Expression of Keap1 Conferring the Resistance of Hepatocellular Carcinoma Cells to 5-Fluorouracil. *Cell Physiol Biochem* 2015; 35: 2333-2348 [PMID: 25896253 DOI: 10.1159/000374036]
62 Anwar SL, Lehmann U. MicroRNAs: Emerging Novel Clinical Biomarkers for Hepatocellular Carcinomas. *J Clin Med* 2015; 4: 1631-1650 [PMID: 26295264 DOI: 10.3390/jcm4081631]
63 Yang H, Fang F, Chang R, Yang L. MicroRNA-140-5p suppresses tumor growth and metastasis by targeting transforming growth factor β receptor 1 and fibroblast growth factor 9 in hepatocellular carcinoma. *Hepatology* 2013; 58: 205-217 [PMID: 23401231 DOI: 10.1002/hep.26315]
64 Zhang J, Chong CC, Chen GG, Lai PB. A Seven-microRNA Expression Signature Predicts Survival in Hepatocellular Carcinoma. *PLoS One* 2015; 10: e0128628 [PMID: 26046780 DOI: 10.1371/journal.pone.0128628]

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本刊讯 本刊采用“顺序编码制”的著录方法, 即以文中出现顺序用阿拉伯数字编号排序. 提倡对国内同行近年已发表的相关研究论文给予充分的反映, 并在文内引用处右上角加方括号注明角码. 文中如列作者姓名, 则需在“Pang等”的右上角注角码号; 若正文中仅引用某文献中的论述, 则在该论述的句末右上角注码号. 如马连生[1]报告……, 研究[2-5]认为……; PCR方法敏感性高[6-7]. 文献序号作正文叙述时, 用与正文同号的数字并排, 如本实验方法见文献[8]. 所引参考文献必须以近2-3年SCIE, PubMed,《中国科技论文统计源期刊》和《中文核心期刊要目总览》收录的学术类期刊为准, 通常应只引用与其观点或数据密切相关的国内外期刊中的最新文献, 包括世界华人消化杂志(http://www.wjgnet.com/1009-3079/index.jsp)和*World Journal of Gastroenterology*(http://www.wjgnet.com/1007-9327/index.jsp). 期刊: 序号, 作者(列出全体作者). 文题, 刊名, 年, 卷, 起页-止页, PMID编号 ; 书籍: 序号, 作者(列出全部),书名, 卷次, 版次, 出版地, 出版社, 年, 起页-止页.

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