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述评 EDITORIAL

microRNAs在肝脏中的作用

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Roles of microRNAs in the liver

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Abstract

MicroRNAs (miRNAs) are a group of small non-coding RNAs that function as endogenous silencers of numerous target genes. Hundreds of human miRNAs have been identified in the human genome, and they are expressed in a tissue-specific manner and play important roles in cell proliferation, apoptosis, and differentiation. Numerous studies have shown that miRNAs participate in a variety of physiological and pathological processes in the liver. In this review, we will discuss the roles of miRNAs in the processes of liver regeneration (LR), liver immune responses, and the pathogenesis of liver fibrosis and hepatocellular carcinoma (HCC).

Key Words: MicroRNAs; Liver regeneration; Liver immune response; Liver fibrosis; Hepatocellular carcinoma

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摘要

microRNAs(miRNAs)是一类长约18-25个核苷酸序列的内源性非编码单链小RNA, 通过与靶基因序列特异性相互作用, 在转录后水平调节基因表达, 从而调控细胞增殖、分化与凋亡等过程. 大量研究表明, miRNAs参与肝脏的多种生理和病理过程. 本文就近年来miRNAs在肝再生(liver regeneration, LR)、肝脏免疫反应、肝纤维化及肝癌(hepatocellular carcinoma, HCC)形成这4个过程中的作用的研究作一综述.

关键词: microRNAs; **肝再生; 肝脏免疫反应; 肝纤维化; 肝癌**

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0 引言

microRNAs(miRNAs)是一类内源性非编码单链小RNA, 通过与靶序列特异性相互作用, 在转录后水平调节基因表达, miRNAs可调节约30%的人类蛋白编码基因[1]. 目前对于miRNAs的研究, 不仅仅局限于细胞的增生、分化、凋亡过程, 其在病毒感染[2]、炎症反应[3]、脏器纤维化[4]、癌症[5]等方面的研究逐渐成为焦点. 本文将对miRNAs在肝脏中的主要作用作一综述.

1 miRNAs与肝再生

肝细胞是终末分化细胞, 生理状态下绝大多数处于静息状态, 仅约0.1%细胞发生分裂以补偿凋亡的肝细胞. 同时, 肝脏保持着极强的再生能力, 在部分肝切除或肝脏发生急性毒性损伤时, 残留肝实质细胞及非实质细胞迅速增殖, 从而在短时间内恢复肝脏原有体积, 继而自行终止再生过程[6]. 肝再生(liver regeneration, LR)是一个相当复杂且被精密调控的过程, 是增殖与抗

■背景资料
miRNAs可调节约30%的人类蛋白编码基因. 目前对于miRNAs的研究, 不仅仅局限于细胞增生、分化、凋亡过程, 其在病毒感染、炎症反应、脏器纤维化、癌症等方面的研究逐渐成为焦点.

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■研发前沿
目前我们已部分了解了miRNAs在肝脏的再生、免疫反应以及肝纤维化、肝癌发生发展中的作用机制, 但是如何筛选出更为特异性的miRNAs作为诊断的生物标志物、治疗的靶标, 目前尚无定论.

增殖、凋亡与抗凋亡相抗衡的过程, 可分为启动、增生和终止阶段, 多种生长因子和细胞因子参与了这一过程[7]. 近年来, 研究者对LR过程有了更为深入的认识[8], 而miRNAs在LR刺激性反应中的作用也得到了广泛研究.

DGCR8(DiGeorge syndrome critical region gene 8)是miRNAs合成过程中必不可少的部分, 特异性抑制小鼠肝实质细胞中DGCR8的表达, 然后行肝部分切除(2/3), 结果表明, 残余肝细胞中miRNAs合成能力下降, G_1向S期转变过程延迟; 但野生型小鼠肝部分切除(2/3)后, miRNAs则出现明显的特异性表达, 其中miR-21表达上调, miR-378表达下调. miR-21靶向作用于Btg2, 后者是细胞周期抑制因子, 可抑制插头蛋白(fork-head box M1, Fox M1)的激活, 而Fox M1是肝部分切除后肝细胞合成DNA所必需的蛋白; miR-378可抑制尿苷酸脱羧酶(ornithine decarboxylase, ODC)表达, 从而促进肝细胞DNA合成. 由此提出miRNAs在LR过程中发挥重要作用[9]. 核因子κB(nuclear factor kappa B, NF-κB)激活是肝部分切除后最早出现的细胞信号转导事件之一[10], 且NF-κB可参与miR-21的表达上调[11]. 在LR的早期增生阶段, miR-21表达上调, 并靶向作用于白介素-1受体(interleukin 1 recept, IL-1R)/Toll样受体(Toll-like receptor, TLR)信号级联反应的衔接蛋白Pellion, 进而抑制NF-κB激活, 从而形成负反馈调节反应[12]. 大鼠原代培养肝细胞中, 熊去氧胆酸(deoxycholic acid, UDCA)可上调miR-21表达, 后者进一步增强细胞增生和活力, 从而在LR过程中发挥重要作用[13].

转化生长因子(transforming growth factor, TGF)-β是LR过程从增生阶段进入终止阶段的重要因子[14]. miR-23b表达上调可促进大鼠肝细胞株BRL-3A增生, 并部分抑制TGF-β1介导的细胞凋亡; 而TGF-β1又可抑制miR-23b的表达. 在LR终止阶段, 低表达miR-23b可激活TGF-β1/Smad3信号通路, 从而抑制肝细胞继续增生[15]. miR-34a在BRL-3A肝细胞再生终止阶段表达亦上调, 上调的miR-34a可靶向抑制抑制素βB(inhibin βB, INHBB)和Met表达, 最终达到终止LR的目的[16].

小体积移植肝或肝部分切除后残余肝中miRNAs特异性表达, 部分miRNAs表达显著上调、部分miRNAs表达显著下调, 并伴随其靶标-细胞周期相关蛋白的表达异常. 如miR-122a低表达, 其靶标细胞周期蛋白G_1表达则上调; miR-26a过表达显著下调细胞周期蛋白E2的表达, 从而明显降低HepG2细胞株的增生能力[17].

2 miRNAs与肝脏的免疫反应

Chen等[18]首先提出了miRNAs可能在免疫反应过程中发挥重要作用. miRNAs异常表达与系统自身免疫性疾病有关[19]. miRNAs不仅与先天性免疫反应有关, 还与正常或异常适应性免疫反应有关, 从而在获得性免疫性肝病(尤其是病毒性肝炎)中发挥重要作用[20]. 肝脏实质细胞和免疫细胞的相互作用在病毒、细菌、毒物和抗原等引起的肝损伤过程中扮演着独特的角色. Hand等[21]发现肝脏中Dicer1功能缺失的小鼠不能产生成熟的miRNAs, 并出现进行性肝细胞损害、凋亡和汇管区炎症表现, 这一点更加证明了miRNAs在肝脏免疫系统中的重要性.

脂多糖(lipopolysaccharide, LPS)可以上调人类单核巨噬细胞中miR-146a的表达, 后者通过靶向作用于TRAF6而负向调控先天性免疫反应; TRAF6又可进一步调节TLR信号通路[22]. 炎症过程中, LPS可刺激促炎性细胞活素和趋化因子释放, 而泛醇-10又可以抑制上述作用[23]. 随后, 研究表明, LPS刺激可使人类单核细胞细胞株THP-1中miR-146a表达上调, 若用泛醇-10对THP-1细胞株进行预处理, 则结果显示LPS上调miR-146a的作用显著减弱; 同样小鼠体内实验表明, 腹腔注射LPS后, 其肝脏组织中miR-146a表达上调, 而与未予泛醇-10预处理的小鼠相比, 食入泛醇-10 1 wk的小鼠在LPS处理后的miR-146a水平上调不显著. 从而提出泛醇-10通过调节miR-146a表达, 最终调节免疫反应过程[24]. LPS诱导Kupffer细胞激活和TLR4-LPS介导的肿瘤坏死因子(tumor necrosis factor, TNF)-α增多在酒精性肝脏疾病中发挥重要作用; 研究表明, 酒精预处理的巨噬细胞中LPS介导的miR-155表达进一步上调; 酒精性肝病小鼠模型中分离出的Kupffer细胞中miR-155和TNF-α表达显著提高, 且miR-155影响TNF-α mRNA的稳定性, 从而提出miR-155在肝脏免疫中的重要作用[25].

miRNA影响丙型肝炎病毒(hepatitis C virus, HCV)复制[26]. 体外细胞水平研究表明, miR-199a过表达可以抑制HCV复制[27]. 乙醇可以上调大鼠肝窦内皮细胞(liver sinusoidal endothelial cell, LSEC)内单核细胞趋化因子-1(monocyte chemotactic protein-1, MCP-1)、巨噬细胞炎症蛋白-2(macrophage inflammatory protein, MIP-2)、内皮素-1(endothelin-1, ET-1)、缺氧诱导因

子-1(hypoxia-inducible factor-1, HIF-1)的mRNA水平, 亦可以上调大鼠LSEC、Kupffer细胞和人类单核细胞系THP-1中ET-1同源物受体(ET-1 cognate receptor, ET-BR)水平, 且ET-1、ET-BR水平上调与NADPH、HIF-1α的激活有关; 进一步研究表明, miR-199拮抗剂下调上述细胞中miR-199表达后, ET-1和HIF-1mRNA水平相应上调. 从而提出miR-199参与乙醇介导的肝脏炎症免疫过程[28]. miR-196可靶向作用于Bech1(一种碱性亮氨酸拉链)并下调其表达; 过表达miR-196或者低表达Bech1均可以抑制HCV复制; 研究还表明, 过表达miR-196通过下调Bech1表达, 进一步上调血红素加氧酶1(heme oxygenase 1, HMOX1)的表达, 从而预防或减轻HCV感染所致的肝细胞氧化应激以及肝损伤[29]. 此外, miR-122过表达也可促进HCV复制[30,31].

3 miRNAs与肝纤维化

miRNAs在心、肝、肺、肾等脏器纤维化过程中发挥重要作用[4]. 肝纤维化是慢性肝病的共同病理变化, 最终导致肝硬化甚至肝衰竭, 而慢性肝病的病因主要包括病毒感染、酗酒、代谢性疾病等. 肝星状细胞(hepatic stellate cells, HSCs)是参与肝纤维化过程中细胞外基质(extracellular matrix, ECM)形成的主要细胞. 正常情况下, HSCs位于Disse间隙, 在损伤因素刺激或暴露于炎性因子后, 激活的HSCs向损伤部位迁移, 并向肌成纤维样细胞和成纤维细胞转化, 形态学的改变主要包括失去维生素A和出现α平滑肌肌动蛋白(alpha smooth muscle actin, α-SMA), 进而分泌大量的ECM, 引起肝纤维化[32]. 此过程涉及多种细胞因子, 如血小板衍生生长因子(platelet-derived growth factor, PDGF)、TNF-α、TGF-β等, 除了此前传统的信号转导通路外, 近年来, miRNAs参与的信号通路成为研究热点[33], 相应的临床应用价值研究亦日益升温.

已有大量研究表明miRNAs在HSCs激活、增生过程中发挥重要作用, 特异性阻断或促进miRNAs表达可逆转此过程. Guo等[34]研究表明miR-16和miR-15b在大鼠体外活化的HSCs中低表达, 转染miR-16和miR-15b可通过直接抑制线粒体相关抗凋亡蛋白Bcl-2的表达, 进而上调并激活胱门蛋白酶(caspases)-3、8、9, 诱导活化的HSCs凋亡; miR-16还可以负性调控HSCs中细胞周期蛋白D1的表达, 从而使细胞周期停滞在G_1期, 减少HSCs增生[35]. 在活化的HSCs中, miR-27a和miR-27b高表达, 类视黄醛X受体α(retinoid X receptor alpha, RXRα)表达则下调; 抑制HSCs中miR-27a和miR-27b的表达, 或者转染RXRα基因可以使部分HSCs的活化表型逆转为静止表型, 并能够抑制HSCs的增生[36]. 转染miR-150、miR-194, 可抑制LX-2增生, 抑制α-SMA、Ⅰ型胶原蛋白表达, 且两者通过抑制c-myb、rac1表达而起作用[37]. 转染miR-30可以特异性抑制大鼠体外活化HSCs中TGF-β1的表达, 并进一步下调HSCs中α-SMA、Ⅰ型胶原、基质金属蛋白酶-2(matrix metalloproteinases-2, MMP-2)、组织金属蛋白酶抑制因子-1(tissue inhibitors of metalloproteinases-1, TIMP-1)的表达, 从而逆转肝纤维化进程[38].

CCl_4诱导的小鼠肝纤维化组织、人类中重度肝纤维化组织中均发现miR-29家族表达下调; 与正常人或者轻度肝纤维化患者相比, 晚期肝硬化患者血清miR-29a表达显著下调, 并且该作用与肝纤维化的病因有关, 酒精性肝硬化患者miR-29a下调程度较病毒性肝炎患者明显. 细胞水平研究表明, 小鼠HSCs中miR-29b表达下调受TGF-β及炎性因子, 如LPS、NF-κB的调节; 同时, 在小鼠HSCs中, 过表达miR-29b可减少其胶原合成[39]. 细胞核受体法尼醇受体(farnesoid X receptor, FXR)可以上调小鼠、大鼠和人HSCs中miR-29a表达, 并进一步抑制ECM形成, 从而减轻肝纤维化[40]. 由此, 提出miR-29家族有望成为临床诊断肝纤维化的特异性指标, 诱使其过表达是一种新型的治疗肝纤维化的措施. 另外, 干扰素α(interferon-α, IFN-α)可以上调人肝星状细胞株LX-2中miR-29表达, 并进一步负性调控Ⅰ型胶原蛋白的表达, 从而完善了miR-29在IFN-α治疗肝纤维化中的作用机制[41].

Marquez等[42]研究表明无论是感染HCV患者的经皮肝穿刺活检组织、CCl_4诱导小鼠肝纤维化模型的肝组织, 还是体外转染HCV的细胞株中均出现miR-21表达上调; 斯皮尔曼等级相关(spearman rank correlation)分析表明, 在慢性HCV感染患者中, miR-21的表达与肝纤维化分期、外周病毒载量、血清谷丙转氨酶(glutamic pyruvic transaminase, GPT又称ALT)水平、血清谷草转氨酶(glutamic oxaloacetic transaminase, GOT又称AST)水平以及干扰素应答基因MX1表达水平呈正相关. 此外, 研究还指出miR-21表达水平在肝纤维化早期相对较低, 随着肝纤维化程度的加重, miR-21表达上调, 提出肝纤维化程

■相关报道
Murakami等提出miR-199、miR-200家族可促进肝纤维化相关基因TIMP-1、MMP-13、前胶原αⅠ表达增强.

■创新盘点
文章从几大方面详细总结了近几年来miRNAs在肝脏中的研究进展，在肝纤维化和肝癌形成中的作用概括尤为详尽.

度不仅与miR-21表达的量有关, 还与其表达上调所持续的时间有关. 双荧光素酶报告基因检测(luciferase reporter assay)系统检测表明, miR-21可通过直接靶向作用于TGF-β信号传导通路的负性调控因子SMAD7[43], 从而促进肝脏纤维化, 而此前有研究表明TGF-β可促进初级miR-21前体加工成为成熟miR-21[44], 进一步提出肝纤维化过程中的正反馈机制[42].

Murakami等[45]研究表明, 与单纯腹腔内注射橄榄油的对照组小鼠相比, CCl_4诱导的小鼠肝纤维化组织中11种miRNAs表达上调; 而在慢性HCV感染患者的肝纤维化活检组织中10种miRNAs表达上调, 并且与肝纤维化程度密切相关; TGF-β刺激可诱导人肝星状细胞株LX-2中miR-199和miR-200家族成员表达上调, 其上调又进一步使TIMP-1、MMP-13及前胶原α1表达上调; 直接通过对LX-2细胞转染miR-199和miR-200家族, 同样使得上述3个与肝纤维化相关的基因表达增强, 进一步提出了其在临床诊断和治疗中的潜在价值.

酗酒或者代谢综合征引起的脂肪性肝炎是常见的导致肝纤维化的慢性肝病. Dolganiuc等[46]对小鼠酒精性脂肪性肝炎和非酒精性脂肪性肝炎(nonalcoholic steatohepatitis, NASH)模型进行研究, 结果显示5种miRNAs表达异常: miR-705和miR-1224在两组中表达均上调, 同时, miR-182、miR-183和miR-199a-3p在酒精性脂肪性肝炎组织中表达下调, 而在NASH中上调.

4 miRNAs与肝癌

不同肿瘤组织, 包括肝癌(hepatocellular carcinoma, HCC)中存在特异性miRNAs表达谱, 异常表达的miRNAs靶向作用于癌基因或抑癌基因, 故与肿瘤的发生、发展及恶性肿瘤的转移等生物学行为密切相关[5,47]. 近年来, 研究发现循环血中特异性表达的miRNAs有望成为肿瘤诊断、治疗、预后评估的生物标志物[48].

部分miRNA在HCC中表现为表达上调, 其异常表达影响肿瘤细胞的增生、凋亡及迁移和侵袭能力. miR-21是目前研究较多的miRNAs之一, 其在人HCC组织及HCC细胞株中表达上调, 通过靶向抑制磷酸酶张力蛋白同源物基因(phosphatase and tension homologue deleted from chromosome 10, PTEN)、程序性细胞死亡因子4(programmed cell death 4, PDCD4)的表达, 从而抑制肿瘤细胞凋亡、促进肿瘤细胞无限增生, 增强肿瘤细胞侵袭能力; 亦可下调含有Kazal基序的富含半胱氨酸的蛋白(reversion-inducing cysteine-rich protein with kazal motifs, RECK)的表达, 增强肿瘤细胞的侵袭能力[49]. 过表达PTEN诱导HepG2细胞周期停滞在G_1期, 进而降低细胞增殖能力, 且这一过程受PI3K/AKT信号转导通路调节; 划痕试验和基质胶侵袭试验表明PTEN可显著抑制HepG2的迁移和侵袭能力; 同时, PI3K/AKT抑制剂LY294002作用于HepG2亦有类似表现, 进一步研究表明上述作用均通过下调MMP-2和MMP-9的表达而实现, 从而提出PTEN通过PI3K/AKT信号转导通路调节MMPs的表达, 进而调节HepG2的迁移和侵袭能力[50]. HCC组织中PTEN表达下调与肿瘤大小(P = 0.021)、微卫星灶的出现(P = 0.027)、总体生存率(overall survival, OS)(P = 0.035)有显著相关性, 此外, PTEN下调AKT/特异性β1蛋白(specific β1 glycoprotein, SP1)/MMP-2通路进而调节HCC的转移和侵袭能力[51]. RECK是一种膜锚链糖蛋白, 通过抑制MMP-2、MMP-9、膜型基质金属蛋白酶(membrane-type matrix metalloproteinase-1, MT1-MMP)的表达，进而降低肿瘤细胞侵袭能力[52]. PDCD4是一种抑癌因子, 能够上调TIMP-2表达, 进而降低肿瘤细胞的侵袭能力[53].

HCC组织中高表达的miR-30d与肿瘤肝内转移显著正相关; 体外HCC细胞株水平研究显示miR-30d可促进肿瘤细胞迁移和侵袭; 裸鼠体内实验研究表明, miR-30d可促进HCC肝内转移和远处肺转移; 进一步研究表明, miR-30d通过靶向作用于GNAI2, 进而在HCC中调控上述肿瘤细胞生物学行为[54]. miR-17-5p在HCC组织中表达上调, 并依赖于p38丝裂原激活蛋白激酶(mitogen-activated protein kinase, MAPK)激活和热休克蛋白(heat shock protein, SHP)27磷酸化来促进HCC细胞侵袭能力[55]. TGF-β可上调miR-181b表达, 后者通过调节TIMP-3水平, 进而增加MMP-2和MMP-9的生物活性, 从而促进HCC细胞迁移和侵袭[56]. miR-222表达显著上调, 且与患者无病生存率(disease-free survival, DFS)、OS下降显著相关; 抑制HCC细胞株Hep3B和HKCI-9中miR-222表达可以减少AKT磷酸化, 降低肿瘤细胞的转移和侵袭能力, 而这一作用很大程度上是通过miR-222靶标蛋白磷酸酶2(PP2A)的调节亚基PPP2R2A(the protein phosphatase 2A subunit B)实现的[57].

乙型肝炎病毒(hepatitis B virus, HBV)介导

的HCC组织中, miR-602高表达, 其直接靶标Ras相关区域家族1A(Ras association domain family 1A, RASSF1A)则低表达; 转染anti-miR- 602的HCC细胞凋亡增加、增生减少; 研究还表明, miR-602可作为HBV介导的HCC的早期诊断指标[58]. p21-HBx转基因鼠发展为HCC后, HCC组织中miR-29a表达显著上调, 转染HBx的HCC细胞株中miR-29表达亦上调, 从而提出HBx可上调miR-29a的表达; 然而, HCC患者肝组织中HBx与miR-29却无显著相关性.HBx上调miR-29的表达, 后者进一步通过靶向抑制PTEN表达、促进Akt磷酸化, 从而增强HCC细胞株的迁移能力; 此外, miR-29a还可上调HCC细胞株MMP-2 mRNA水平, 同样增强肿瘤细胞迁移能力[59].

同样, 部分miRNAs表达下调, 通过作用于靶标基因来影响肿瘤的生物学行为. HCC患者肿瘤组织中, miR-29表达显著下调, 且与患者DFS具有显著相关性; 体外细胞水平实验显示, 过表达miR-29可促进由血清饥饿、缺氧和化疗药物所致的HCC细胞株凋亡, 其机制主要是miR-29靶向调控抗凋亡基因Bcl-2、Mcl-1的表达, 从而促进细胞色素C释放至胞浆, 通过线粒体途径促进细胞凋亡; 裸鼠体内实验结果显示, 转染miR-29的HCC细胞株致瘤能力下降[60]. HCC细胞株QGY-7703、SMMC-7721中, miR-142-3p表达下调, 过表达miR-142-3p靶向抑制RAC1的表达, 从而抑制癌细胞增生、迁移和侵袭能力[61]. HCC组织中、HCC细胞株HepG2、SK-Hep-1中miR-193b表达下调; 过表达miR-193b可靶向抑制癌基因CCND1的表达, 从而导致细胞周期停滞在G_1期, 进而抑制肿瘤细胞增生; 同时, 过表达miR-193b也可靶向抑制癌基因ETS1表达, 从而降低肿瘤细胞迁移和侵袭能力[62]. 与无转移的HCC患者相比, 有转移的HCC者肿瘤组织let-7g表达下调, 且后者较前者预后差; 进一步研究表明, 过表达let-7g可靶向作用于Ⅰ型胶原蛋白α2, 从而抑制肿瘤细胞增殖能力和迁移能力, 但不影响其侵袭能力[63].

HCC细胞株中miR-124表达下调, 通过靶向作用于细胞周期蛋白依赖激酶6(cyclin-dependent kinase 6, CDK6)、VIM、SMYD3、IQGAP1、ABCE1, 从而介导细胞周期停滞[64]. miR-199a-3p在HCC组织中表达下调, 并可靶向作用于c-Met、mTOR, 从而介导细胞周期停滞在G_1期, 并降低细胞侵袭能力[65]. 表达下调的miR-22与患者DFS有相关性, 且通过上调组蛋白去乙酰化酶4(histone deacetylase 4, HDAC4)表达, 抑制肿瘤细胞增生[66]. miR-122在HCC组织中低表达, miR-122寡核苷酸干预的HCC细胞株凋亡增加、增生减少; 抑制miR-122的表达可以降低HCC细胞中HCV复制能力, 从而为HCV感染而最终导致的HCC提供治疗措施[67,68].

近年来, miRNAs在HCC治疗中的作用机制亦得到了广泛研究. let-7家族可抑制Bcl-xL表达, 增强索拉非尼(首个口服多激酶抑制药)所致的细胞凋亡[69]. 索拉非尼可以上调HCC细胞株HepG2中miR-1274a的表达, 再进一步靶向抑制去整合素-金属蛋白酶9(a disintegrin and metalloproteinase 9, ADAM9)的表达, 从而抑制细胞增生、促进细胞凋亡[70]. 该研究为索拉非尼靶向治疗HCC提出了又一新的作用机制.

■应用要点

理论研究最终应服务于临床, 建立标准化的用于临床诊断、治疗、评估疾病预后的miRNAs优化体系势在必行.

5 结论

近年来, 关于miRNAs在上述领域中的研究已成为热点, 人们对miRNAs的整体认识也在不断提高, 但是仍有大量的问题需要进一步解决: miRNAs自身的表达和功能还受哪些因素的调节? 理论研究的miRNAs调控靶蛋白表达的信息, 怎样有效地应用于临床? 是否能筛选出更为特异性的相关miRNAs作为诊断肝病的生物标记物? 如何建立适合临床应用的miRNAs标准化检测体系? 能否通过阻断或者促进miRNAs合成的调节因素、miRNAs本身及其靶标的表达, 从而达到靶向治疗的目的? 如何达到靶向治疗的最优化? 即便如此, 我们仍然坚信, 随着miRNAs研究的不断深入, 理论与临床将达到完美的结合.

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■同行评价
文章对不同肝病miRNAs的表达、功能及和肝病的关系作了较详细的综述，对临床研究和基础研究有很好的指导和借鉴.

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• 消息 •

《世界华人消化杂志》外文字符标准

本刊讯 本刊论文出现的外文字符应注意大小写、正斜体与上下角标. 静脉注射iv, 肌肉注射im, 腹腔注射ip, 皮下注射sc, 脑室注射icv, 动脉注射ia, 口服*po*, 灌胃ig. s(秒)不能写成S, kg不能写成Kg, mL不能写成ML, lcpm(应写为1/min)÷E%(仪器效率)÷60 = Bq, pH不能写PH或P^H, *H pylori*不能写成HP, T1/2不能写成tl/2或$T_{\frac{1}{2}}$, *V*max不能Vmax, μ不写为英文u. 需排斜体的外文字, 用斜体表示. 如生物学中拉丁学名的属名与种名, 包括亚属、亚种、变种. 如幽门螺杆菌(*Helicobacter pylori*, *H.pylori*), *Ilex pubescens* Hook, *et* Arn.*var.glaber* Chang(命名者勿划横线); 常数*K*; 一些统计学符号(如样本数*n*, 均数mean, 标准差SD, *F*检验, *t*检验和概率*P*, 相关系数*r*); 化学名中标明取代位的元素、旋光性和构型符号(如*N*, *O*, *P*, *S*, *d*, *l*)如*n*-(normal, 正), *N*-(nitrogen, 氮), *o*-(ortho, 邻), *O*-(oxygen, 氧, 习惯不译), *d*-(dextro, 右旋), *p*-(para, 对), 例如*n*-butyl acetate(醋酸正丁酯), *N*-methylacetanilide(N-甲基乙酰苯胺), *o*-cresol(邻甲酚), 3-*O*-methyl-adrenaline(3-O-甲基肾上腺素), *d*-amphetamine(右旋苯丙胺), *l*-dopa(左旋多巴), *p*-aminosalicylic acid(对氨基水杨酸). 拉丁字及缩写*in vitro*, *in vivo*, *in situ*; Ibid, *et al*, *po*, *vs*; 用外文字母代表的物理量, 如*m*(质量), *V*(体积), *F*(力), *p*(压力), *W*(功), *v*(速度), *Q*(热量), *E*(电场强度), S(面积), *t*(时间), *z*(酶活性, kat), *t*(摄氏温度, ℃), *D*(吸收剂量, Gy), *A*(放射性活度, Bq), ρ(密度, 体积质量, g/L), *c*(浓度, mol/L), φ(体积分数, mL/L), *w*(质量分数, mg/g), *b*(质量摩尔浓度, mol/g), *l*(长度), *b*(宽度), *h*(高度), *d*(厚度), *R*(半径), *D*(直径), T_{max}, C_{max}, *V*d, $T_{1/2}$ *Cl*等. 基因符号通常用小写斜体, 如*ras*, *c-myc*; 基因产物用大写正体, 如P16蛋白.