

microRNA-21在肝脏中的作用

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Functions of microRNA-21 in the liver

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Abstract

microRNAs (miRNAs) are a class of newly discovered small RNAs that can regulate every aspect of cellular activity, including differentiation, growth, metabolism, proliferation, apoptosis, viral infection, and tumorigenesis. Recent studies have provided clear evidence that miRNAs are abundant in the liver and participate in all physiological and pathological processes. microRNA-21 (miR-21) is one of the most studied miRNAs and has been demonstrated to be involved in tumorigenesis and some pathological physiological changes. However, there is little

research on the roles of miR-21 in the liver. This paper will review the roles of miR-21 in liver regeneration, liver cell metabolism, immunity activity in liver, and the pathogenesis of human hepatocellular cancer and chronic hepatitis C.

Key Words: microRNA-21; Liver; microRNA

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摘要

microRNAs(miRNAs)是一类新发现的小RNAs, 因其能调控细胞活动的每个方面, 包括分化、生长、代谢、增殖、凋亡和病毒感染、肿瘤生成, 已经成为目前研究的热点。最近已有明确的证据表明, miRNAs在肝脏含量丰富并且参与肝脏生理和病理的各个过程。microRNA-21是目前研究最多的miRNAs之一, 参与多种肿瘤的发生和一些病理生理改变, 但其在肝脏中的研究比较少。本文就microRNA-21在肝再生、肝细胞代谢、肝脏免疫反应及其在肝癌、丙型肝炎等肝病中的作用作一综述。

关键词: microRNA-21; 肝脏; microRNAs

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0 引言

microRNAs(miRNAs)是一类新发现的在进化上高度保守的非编码小RNAs, 长约19-22 nt, 在转录后水平调控基因的表达^[1]。研究表明miRNAs调控人类约1/3的基因, 是细胞分化、增殖、生长、迁移和凋亡的重要调节因子, 在生物发育和生理活动中起着重要的作用^[2]。最近已经有明确的证据表明, miRNAs在肝脏中含量丰富并且调控肝脏功能的各个方面。miRNAs的不正常表达可能是许多肝脏疾病包括病毒性肝炎、肝细胞癌(hepatocellular

■背景资料

miRNAs调节人类约1/3的基因, miRNAs功能失调可能导致人类癌症、心血管疾病、肝病、免疫功能障碍、代谢紊乱等疾病发生。自从5年前被确认为是人类恶性胶质瘤最常见和高度上调的miRNAs, microRNA-21已经引起包括发育学、肿瘤学、干细胞生物学、衰老学等不同领域研究者的注意, 成为被研究最多最透彻的miRNAs之一, 例如microRNA-21已经被证实多种肿瘤性疾病发生密切相关, 还参与心肌肥大等一些病理生理改变, 但目前肝病中作用研究尚少, 是研究热点之一。

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■研究前沿

加强各型肝炎患者相关miRNAs研究,可能有助于从miRNAs基因调控角度阐明肝病的发病机制。目前microRNA-21在肝癌发生中的作用已有较多研究,但在乙型、丙型肝炎等患者发病中的作用尚报道不多。

cancer, HCC)、多囊肝病的一个关键的发病因素^[3],对肝病相关miRNAs进行研究,必将加深对肝病发病机制的理解和认识,也有助于发现肝病新的治疗靶点。自从5年前被认为是人脑恶性胶质瘤最常见和表达高度上调的miRNAs^[4],microRNA-21已经引起包括发育学、肿瘤学、干细胞生物学、衰老学等不同领域研究者的注意,成为被研究最多最透彻的miRNAs之一,如多数研究表明microRNA-21和肿瘤的发生密切相关^[5],同时,在心肌肥大、心力衰竭等一些病理改变中表达升高^[6,7]。目前,microRNA-21在肝脏中的研究尚少,本文就microRNA-21在肝脏中的作用作一综述。

1 microRNA-21和肝再生

microRNA-21在肝再生的增殖期表达上调。细胞再生过程中,原本处于静止期的肝细胞进入细胞周期,分化为实质细胞和间质细胞。与此同时肝组织结构得到恢复。这个过程受到相应基因复杂而精确的调控,其具体表达、调控过程尚未完全阐明。而microRNA-21作为一个具有调节作用的小分子RNA,在肝细胞增殖过程中发挥了重要的作用。Marquez等^[8]切除小鼠的部分肝脏,观察切除术后1、6、12、24、48 h以及7、14 d小鼠肝脏的再生情况,发现和肝切除术前相比,切除术后小鼠肝脏microRNA-21的表达在1、6、12、24和48 h上调,并在12、24 h达到高峰(超过正常2倍),提示microRNA-21在肝再生早期可能参与基因表达调控。microRNA-21基因的启动子受核因子κB(nuclear factor kappa B, NF-κB)、激动蛋白-1(activation protein-1)、核因子IB(nuclear factor I-B, NFIB)和信号传导与转录激活因子-3(signal transducer and activator of transcription 3, STAT3)等转录因子的调节^[9-11],这些转录因子中有很多在肝再生早期被激活^[12]。其中,NF-κB的激活是肝切除术后最早出现的信号转导事件之一^[13,14],有研究显示,NF-κB参与microRNA-21的表达上调^[11,15]。Pellino(Peli1)是一种泛素连接酶,并且是公认的microRNA-21的靶基因。在肝再生早期,microRNA-21和Pellino(Peli1)的水平呈负相关。而Pellino(Peli1)作为IL-1R/TLR信号级联反应的一种衔接蛋白,和IL-1R相关激酶(IL-1R-associated kinase, IRAK)1, IRAK4, TNF受体相关因子6(TNF receptor-associated factor 6)形成复合体,共同参与IL-1R/TLR信号级联反应,激活NF-κB^[16]。因此在肝

再生过程中,Marquez等认为microRNA-21一方面可能在NF-κB作用下表达上调;另一方面microRNA-21通过作用于靶基因Peli1蛋白,间接抑制NF-κB转录因子,和NF-κB形成一种负反馈调节反应^[8]。

2 microRNA-21在肝脏细胞代谢的调控作用

林蛙能适应严寒的环境,能够忍受身体里65%-70%的水凝固成冰。Biggar等^[17]多年致力于林蛙抗冷性的生物化学研究。他们发现,和对照组(从5℃,驯化组抽样)相比,24 h冰冻组(-3℃,冰冻暴露24 h)的林蛙肝脏中的microRNA-21转录水平上升了1.3倍($P<0.05$)。由于在一些恶性胶质瘤和乳腺癌研究中,microRNA-21显示了抗细胞凋亡的作用:在乳腺癌MCF-7细胞株中,microRNA-21可作用于靶基因程序性细胞死亡因子4(programmed cell death protein-4, PDCD4)而抑制细胞凋亡^[18];而在恶性胶质瘤细胞系的研究则显示,如果用寡核苷酸封闭microRNA-21,可导致caspase-3、caspase-7的激活,诱导细胞凋亡^[19]。由此,Biggar推测,在冰冻条件下,microRNA-21发挥了抗凋亡作用,肝脏细胞凋亡可能被抑制,凋亡的抑制是保持长期低代谢率的重要组成部分。肝脏中microRNA-21水平的升高可能对冰冻组林蛙保持长期低代谢率非常重要^[8]。

3 microRNA-21和肝脏的免疫反应

肝脏实质细胞和免疫细胞的相互作用在病毒、细菌、毒物和抗原等造成的肝损伤中扮演了独特的角色。有令人信服的证据表明,miRNAs在先天性免疫和适应性免疫中发挥了重要的调节作用^[20]。Hand等^[21]发现肝脏中缺少Dicer1功能的小鼠不能产生成熟的miRNAs,出现进行性肝细胞损害、凋亡和汇管区炎症表现,更加证明了miRNAs在肝脏免疫系统的重要性。

Hashimi等^[22]发现miRNA-蛋白网络系统(miRNA-protein networks)具有调节单个核细胞来源的树突状细胞(monocyte-derived dendritic cell, MDDC)分化的作用。通过对结合树突状细胞特异性细胞间黏附分子-3的非整合素分子/CD14(dendritic cell-specific intercellular adhesion nonintegrin/CD14, DC-SIGN/CD14)的表达率定量可以发现,抑制microRNA-21使MDDC分化停顿。已经证实Wingless-1(WNT1)和Jagged-1(JAG1)是microRNA-21的靶基因,microRNA-21通过与WNT1和JAG13'端非翻译区结合抑制这两个靶基因的翻译。值得注意的,外加的

WNT1和JAG1也能使MDDC分化停顿, 提示由microRNA-21调节的对内源WNT1和JAG1表达的抑制作用对正常MDDC的分化具有重要的作用. 总之, 抑制microRNA-21, 或者增加Wnt-1和JAG1, 都能导致DC内吞功能的下降.

4 microRNA-21在肝病中的作用研究进展

目前关于microRNA-21在肝病中的研究非常少, 研究比较透彻的是他和HCC的关系. 另外, 最近有研究发现, 慢性丙型病毒性肝炎肝纤维化的程度和microRNA-21的表达水平有着密切的关系. 下面我们就microRNA-21与HCC和慢性丙型肝炎的关系作一阐述.

4.1 microRNA-21与HCC HCC是肝脏最常见的恶性肿瘤, 已有研究证实microRNA-21在HCCs中表达上调^[23,24]. microRNA-21克隆占肝癌细胞株(HepG2, PLC, Huh7)中所有miRNA克隆的16.7%, 而在正常肝脏中这一数值只有0.1%^[25]. 研究表明, microRNA-21通过多种机制促进HCC的发生和细胞的增殖、肿瘤的侵袭、转移密切相关.

4.1.1 microRNA-21促进肝癌细胞增殖: Meng等^[26]应用microRNA-21抑制或过表达试验探讨了microRNA-21对肝癌细胞株促增殖作用: 在HepG2, PLC/PRF-5, SK-HEP-1和SNU-182等肝癌细胞株中, 应用microRNA-21特异性反义寡核苷酸(anti-microRNA-21)降低了细胞增殖, 而给与anti-miR-132则细胞增殖无明显改变; 给肝癌细胞株转染microRNA-21前体(precursors), 则促进了肝癌细胞增殖. 探讨其机制发现, 属于抑癌基因之一的磷酸酶及张力蛋白同源物基因(phosphatase and tensin homolog, PTEN)为microRNA-21的靶基因, 用PTEN siRNA下调PTEN表达, 降低了anti-microRNA-21对肝癌细胞株增殖的抑制作用, 表明microRNA-21对肝癌细胞株的增殖作用是PTEN依赖性的. 在肝癌中PTEN蛋白经常下降或缺失, 与肝癌形成相关^[27,28]; PTEN基因功能的丧失使蛋白激酶B(protein kinase B, PKB, 又称AKT)活性增强, 从而增强哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)激酶途径, 促进肝癌细胞存活和增殖^[29].

4.1.2 microRNA-21增强肝癌细胞侵袭和迁移能力: 上调microRNA-21能抑制PTEN的表达, 如上所述, PTEN降低除了可以促进HCC细胞增殖外, 还能引起局部黏着斑激酶(focal adhesion kinase, FAK)的磷酸化作用, 磷酸化的FAK可以促进细

胞的迁移, 还可以促进金属蛋白酶-2(matrix metalloproteinase-2, MMP-2) (正常肝组织的 21.7 ± 8.7 倍)和金属蛋白酶-9(正常肝组织的 17.5 ± 8.6 倍)表达的增多^[26], 从而增强细胞的侵袭性. 另外, microRNA-21通过抑制PDCD4的表达增强癌细胞的血管内渗作用, 从而启动HCC细胞的迁移^[30].

细胞外基质(extracellular matrix, ECM)成分的降解是HCC浸润和转移的关键. MMP能降解ECM. 而组织中MMPs主要受基质金属蛋白酶组织抑制因子(tissue inhibitor of metalloproteinase, TIMP)抑制. 目前已发现的TIMPs包括TIMP-1、-2、-3、-4四种, TIMP3只存在于ECM中, 是4种TIMP中唯一可以与ECM紧密结合的非可溶性蛋白, 能与MMP非共价结合, 从而抑制MMPs的活性^[31-33]. 反向诱导的含有Kazal基序的富含半胱氨酸的蛋白(reversion-inducing cysteine-rich protein with kazal motifs, RECK)是一种膜定位MMP抑制因子, 能在转录后水平调节多种MMP的分泌和活化, 从而抑制肿瘤的侵袭及迁移^[34,35]. RECK和TIMP3均受microRNA-21的调节, RECK是microRNA-21直接的靶基因, 而TIMP3不受microRNA-21的直接调节, 他作为microRNA-21信号通路的下游效应器发挥作用^[36]. microRNA-21上调能抑制RECK和TIMP3的表达, 导致MMPs的表达升高, 从而增强HCC细胞的侵袭性和迁移能力^[37].

4.2 microRNA-21和慢性丙型病毒性肝炎的关系 丙型肝炎病毒(hepatitis C virus, HCV)是一种正链RNA病毒, 慢性HCV感染引起正常处于静止期的肝细胞迅速地分裂, 导致肝纤维化, 肝硬化, 部分可进展为HCC.

Marquez等^[38]研究表明microRNA-21和HCV、肝纤维化有密切的关系. 他们用斯皮尔曼等级相关(spearman rank correlation)分析发现HCV感染患者肝硬化分期($r = 0.51, P = 0.018$)、外周病毒载量($r = 0.584, P = 0.021$)、血清谷丙转氨酶(glutamic pyruvic transaminase, GPT又称ALT)($r = 0.43, P = 0.05$)、谷草转氨酶(glutamic oxaloacetic transaminase, GOT又称AST)水平($r = 0.452, P = 0.044$)和microRNA-21有关. microRNA-21表达水平在肝纤维化早期是低的, 在肝纤维化进展期中表达上调, 考虑microRNA-21参与调节丙型肝炎肝纤维化发病.

TGF- β 对肝纤维化的发生发展具有关键的作用, SMAD7是TGF- β 信号传导通路的抑制信

■相关报道
Marquez等提出在肝再生过程中, microRNA-21可能通过靶向调节Peli1蛋白, 和NF- κ B形成一种负反馈调节反应.

同行评价

本文选题新颖, 内容丰富, 文献引用合理, 有一定的学术价值.

号蛋白, 有抑制肝纤维化作用. Marquez等的研究发现, SMAD7作为microRNA-21直接的靶基因, 在慢性HCV感染的肝细胞中, microRNA-21的上调可通过抑制SMAD7来促进纤维化^[38]; 另有研究表明TGF- β 促进初级microRNA-21前体(pri-miRNA)加工成为成熟microRNA-21^[39], Marquez等的研究认为, microRNA-21通过抑制TGF- β 信号传导通路的负调节子SMAD7, 在肝纤维化过程中形成了正反馈机制^[38].

5 结论

研究表明, miRNAs功能失调可能导致人类癌症、心血管疾病、肝病, 免疫功能障碍、代谢紊乱等疾病发生. 加强各型肝炎患者相关miRNAs研究, 可能有助于从miRNAs基因调控角度阐明肝病的发病机制. 目前microRNA-21在肝癌发生中的作用已有较多研究, 但在乙型、丙型肝炎等患者发病中的作用尚报道不多, 而我国是病毒性肝炎大国, 进一步积极探讨乙型肝炎、丙型肝炎等相关肝病中microRNA-21表达改变规律, 分析验证其作用靶基因和进行相应功能研究, 并设法对肝脏miRNA-21表达进行调控, 有可能发现乙型肝炎、丙型肝炎相关肝病新的治疗新的靶点和方法.

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