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述评 EDITORIAL

非编码RNA调节异常在肝细胞癌发生发展中的作用

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Abnormal regulation of non-coding RNAs plays a role in development and progression of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is an aggressive tumor with a poor prognosis. Non-coding RNAs (ncRNAs) are RNAs transcribed from the genome but not translated into protein. In recent years, ncRNAs have been recognized to be key factors in tumorigenesis because of their ability to regulate multiple targets, cell proliferation, differentiation, apoptosis, and development. In this review, we discuss the pathological significance of ncRNAs (microRNAs, long-chain non-coding RNAs, and cyclic RNAs) in the development and progression of HCC. We also discuss the potential role of ncRNAs in the diagnosis and treatment of HCC.

Key Words: Hepatocellular carcinoma; MicroRNA; LncRNA

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摘要

肝细胞癌(hepatocellular carcinoma, HCC)是一种预后较差、侵袭性较强的肿瘤. 非编码RNA(non-coding RNAs, ncRNAs)是从基因组中转录出来但不被翻译成蛋白质的RNA. 近年来, 因其具有调节多种靶点、调节细胞增殖、分化、凋亡和发育的能力, ncRNAs成为肿瘤发生发展的关键因素. 在本文中, 我们讨论了ncRNAs(microRNA、长链非编码RNA和环状RNA)及在HCC发生和发展中的病理意义, 探讨ncRNA对HCC的诊断和治疗潜力.

关键词: 肝细胞癌; microRNA; 长链非编码RNA

核心提要: 研究发现非编码RNA在肿瘤的发生发展与转移中作用重要, 具较强诊断和治疗潜力, 利于精准诊疗. 但这些研究仍处于起步阶段, 进一步研究肝脏ncRNAs与疾病进展的关系将是解决包括肝细胞癌在内的肝脏疾病的关键.

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0 引言

肝细胞癌(hepatocellular carcinoma, HCC)是常见恶性肿瘤之一, 恶性程度极高, 侵袭能力强, 易转移, 预后较差, 严重危害人类健康. HCC是多种基因突变包括表观遗传改变、染色体易位、缺失和增加等都存在的复杂疾病, 其产生的确切分子机制尚不完全清楚. HCC细胞极易侵袭门静脉系统形成癌栓, HCC门静脉癌栓的形成是影响HCC预后的重要因素. HCC起病隐匿, 早期缺乏明显的临床症状, 研究发现高效的HCC标志物有助于诊断HCC, 提高疗效, 改善预后. 目前HCC的诊断主要依靠甲胎蛋白(alpha fetoprotein, AFP)和影像学技术. 然而, AFP敏感性较低, 诊断早期HCC的能力有限[1]. 近来有证据表明非编码RNA(Non-coding RNAs, ncRNAs)与HCC的发生、发展、诊断、治疗和预后等密切相关, 可作为HCC早期诊断的新型分子标志物和新的有效治疗靶点.

HCC发生过程复杂. 肝脏多次暴露于非酒精性脂肪肝(nonalcoholic fatty liver disease, NAFLD)、酗酒和病毒感染等容易引起纤维化和肝硬化的疾病后, 经过一系列不良增生和发育变化, 最终发展成HCC. 从微观角度看, HCC则是癌基因和抑癌基因在细胞增殖、血管生成、凋亡、细胞迁移和转移等过程中的调控紊乱所致. 其中, c-MET信号通路[2]、磷脂酰肌3-激酶(PI3 K/Akt/mTOR通路)[3]、Wnt/β-catenin通路[4]、TGF-β信号路径[5]等是影响细胞增殖、侵袭和转移的关键分子通路.

ncRNAs是由DNA转录但不翻译成蛋白质的功能性RNA. ncRNAs通过与DNA或RNA结合调节基因表达, 导致其基因转录和翻译过程中降解或改变[5]. ncRNAs作为一类特殊的RNA分子, 包括微小RNA(microRNA, miRNA)、长链非编码RNA(long non-coding RNA, lncRNA)和环状RNA(circle RNA, circRNA), 具有调控基因表达、参与表观遗传修饰、细胞增殖及细胞凋亡等多种生命活动的功能, 参与生长、分化、发育、免疫, 甚至在肿瘤的形成等多种生物学进程.

ncRNAs在HCC中的研究是目前比较前沿的研究领域, 现就ncRNAs(主要包括miRNA、lncRNA和circRNA)在HCC中的研究进展进行述评.

1 miRNA与HCC

ncRNAs中研究最多的是miRNA, miRNA是一种内源性小ncRNAs分子, 大约由21-25个核苷酸组成, 主要促进靶基因的转录后调控. 原代miRNA通过RNA聚合酶Ⅱ从miRNA基因转录而来[6]. 大于60%的蛋白编码基因的翻译由miRNA调控[7]. miRNA调节细胞增殖、凋亡、分化和发育. 一个miRNA能够抑制多个基因的表达, 多个miRNA也能共同作用一个靶点.

miRNA在肝脏中扮演着维持肝脏稳态的关键角色. miRNA失调与肝脏疾病(如病毒感染、炎症、脂糖代谢等)相关, 并促进HCC进展. miR-122, miR-192, miR-21, miR-223, miR-26a, miR-27a and miR-801等7个miRNA联合诊断早期HCC, 对小于2 cm的HCC诊断准确率接近90%, 效果优于传统检测方法[8].

1.1 miRNA促进HCC发生和进展 在HCC中, miRNA失调导致靶基因异常表达, 促进异常细胞生长、分化、血管生成导致HCC的发生、进展、侵袭和转移. 肝细胞特异性Dicer-1 KO小鼠自发形成HCC意味着肝脏miRNA在HCC中发挥重要生物学作用[9]. 此外, Dicer-1 KO小鼠肝脏中4种肝脏特异性miRNA(miR-122、-148a、-192和-194)明显下调.

在肝细胞中, miR-122对维持肝细胞分化和脂质代谢调节等生理功能至关重要[10]. miR-122 KO小鼠在经历肝炎、脂肪肝、纤维化后, 发展为自发性HCC[11]. 在NASH啮鼠模型中, miR-122水平在HCC发生和进展过程中降低[12], 其靶基因, 包括ADAM10、血清应答因子、胰岛素类生长因子1受体[13]和Wnt1[14], 参与HCC进展. 在HCC患者中, miR-122低表达与不良预后和转移相关[15], 其缺失促进细胞迁移和侵袭等运动特性. 此外, miR-122和c-Myc之间的负反馈循环促进HCC进展. miR-122通过靶向调节Tfdp2和E2f1来抑制c-Myc的表达, 而c-Myc则通过转录抑制miR-122表达[16]. miR-122还通过靶向调控Snail1和Snail2以及抑制Wnt/b-catenin通路, 抑制HCC中的EMT[17], 过表达miR-122可减弱EMT启动子基因Ga12对c-Met、ERK、STAT3、Akt/mTOR通路的影响, 抑制HCC的增殖和凋亡[18].

miR-148a抑制与HCC中a-胎蛋白水平高、TNM分期差、无复发生存率低有关. 门静脉肿瘤血栓患者中miR-148a水平下降[19]. 研究发现miR-148a在HCC微血管浸润患者中水平也比较低. 小鼠miR-148a缺失促进二乙基亚硝胺诱导HCC形成[20]. 同样, 肝脏PTEN缺失的小鼠miR-148a过表达抑制肿瘤生长[21]. 此外, miR-148a失调

与HCC预后不良有关. 在原位肝移植模型中, miR-148a上调通过直接抑制c-Met进而抑制EMT和细胞侵袭, 减少锌指转录因子Snail的核积聚[15], 抑制细胞向肺部迁移; 其降低导致HPIP/AKT/ERK/FOXO4/ATF5/mTOR通路激活, 促进EMT、侵袭和转移[14]. 而miR-148a靶点之一的USP4过表达通过激活TGF-b通路促进HCC进展[22].

miR-192失调与HCC预后不良相关[23]. HCC患者miR-192水平降低, 在微血管浸润或肿瘤体积较大的标本中miR-192水平更低[18]. miR-192通过靶向溶质载体家族39成员6(SLC39A6)抑制HCC细胞转移, 进而上调E-cadherin, 下调锌指转录因子Snail表达; 以转录后方式抑制lncRNA HOTTIP表达, 降低HCC细胞生存能力[24]; 抑制p53介导的ZEB2, 抑制HCC细胞中EMT[25]. Mir-194监管肝脏Wnt配体的膜受体信号Fzd6. 体外实验显示miR-194在肝上皮细胞中高度表达, 在二乙基亚硝胺诱导的FXR$^{-/-}$ HCC模型中表达水平降低[26]. 研究发现miR-194抑制多个与EMT和转移相关的基因(如CDH2和RAC1). 另外, HNF1a是肝细胞功能的重要调控因子, 其过表达可重建miR-192、194等肝脏特异性基因的表达, 抑制细胞增殖[27].

1.2 miRNA在HCC临床应用中的意义 miRNA可作为HCC的重要预后标志物. 比如miR-122水平与HCC的肿瘤大小和转移负相关[28], miR-148a失调与HCC患者生存率降低有关[29]. miR-192也是HCC患者预后的独立预测因子[23]. miR-194的降低与HCC患者肿瘤大小、组织学分级、肝内转移等临床病理参数存在显著相关性[29]. 此外, miR-199a可作为HCC患者无瘤生存降低的独立预测因子. miR-135a上调在HCC门静脉肿瘤血栓中得到证实[30].

血清miR-221水平升高与HCC患者肿瘤大小、TNM分期和总生存率相关. 此外, 循环miR-221水平与晚期HCC患者索拉非尼治疗反应相关, 可用于预测治疗反应率[31]. 在血液标本中, miR-21、miR-148a、miR-192和miR-224对HCC具有显著的预测价值[32]. HCC患者血清中miR-20a-5p、miR-320a、miR-324-3p和miR-375水平升高, 可诊断早期HCC[33]. miR-15b和miR-130b水平也升高[31], 与HCC传统血清标志物相比, 血清miR-16敏感性更高[34].

随研究进展, 专注于调控miRNA的策略将是治疗HCC的一种新方法. 多种miRNA在不同肝脏疾病中的调控已显示出其在治疗HCC中的潜在有效性. miR-122是一种肝特异性肿瘤抑制因子, 向miR-122 KO小鼠中注射miR-122a表现为HCC癌变和进展受损, 上调miR-122可能是一种成功治疗HCC的策略[35]. 另一项研究证实, 瘤内注射miR-122能增强异种移植模型中索拉非尼对HCC的抗肿瘤作用[36]. 此外, miR-26a在HCC小鼠模型中通过诱导肿瘤特异性细胞周期阻滞和凋亡抑制肿瘤发生. 相反, 通过释放anti-miR-221寡核苷酸抑制致癌基因miR-221可使肿瘤生长显著下降[37].

2 lncRNA与HCC

LncRNA长度超过200 nt, 转录和处理与蛋白编码基因相同, 是哺乳动物非编码转录组的主要组成部分. 其保守性差, 基因表达调控机制尚不完全清楚[38]. 近年来大量研究表明lncRNA通过在转录、转录后以及表观遗传水平参与基因的表达调控, 并以此影响肿瘤细胞的增殖、凋亡、侵袭及转移等过程, 与HCC发生、发展的病理生理机制及患者预后密切相关. 因此lncRNA有潜力作为疾病诊断的标志物和潜在的药物靶点, 研究成果将有助于开发新型靶向治疗方案, 意义重大.

2.1 lncRNA与HCC发生发展的关系 HULC是高度保守的lncRNA, 也是HCC中上调最多的基因. HULC与HCC患者的PTEN、miR-15a表达负相关, 促进恶性进展[39]. HULC作为miR-9、miR-107和miR-372等miRNA海绵, 分别诱导PPARA、E2F1和CREB, 从而促进HCC发展[40]. lncRNA MALAT1在HCC中上调, 通过上调SRSF1和激活mTOR通路发挥致癌基因的作用[41].

相比之下, 人类母系表达基因3(MEG3)、AOC4P和DREHL ncRNA具有肿瘤抑制作用. MEG3被认为是HCC的独立预后因素, 因为与HCC患者中MEG3的高表达相比, MEG3的低表达与较差的总生存率和无复发生存率相关[42]. MEG3过表达明显抑制细胞生长, 激活细胞凋亡[43]. 同样, 在HCC患者中AOC4P表达显著抑制, 与TNM分期、包膜浸润、血管浸润呈负相关[44].

LncRNA在EMT和转移中也发挥着关键作用. LncRNA-NEF被EMT抑制因子FOXA2转录激活, 显著抑制EMT和细胞迁移[45]. LncRNA CPS1-IT1通过抑制HIF-1a和抑制EMT发挥抑癌作用[46]. ZEB1-as1通过上调ZEB1促进EMT和转移[47], 在HCC样本尤其是转移瘤组织中升高.

HULC还通过与miR-200a竞争, 诱导EMT, 促进肿瘤进展和转移[48]. Jang等[48]发现HULC的表达与TNM分期、肝内转移、HCC复发和术后生存相关. LncRNA-ATB在HCC组织中也显著升高, 且与肝内或肝外转移呈正相关. Li等[49]研究发现, LINC01138高表达的HCC患者肿瘤体积较大, 且高表达与HCC患者的AFP含量以及乙肝表面抗原阳性呈正相关, 而且高表达HCC患者预后较差. 体外与体内功能实验揭示LINC01138可以显著促进HCC细胞的增殖、侵袭与转移能力. Zhang等[50]在HCC中通过RNA-Seq的方法鉴定到了一种肿瘤特异性

的LIN28B转录本变异体LIN28B-TST, 并且发现该转录本的表达受DNA甲基化的调控, 该转录本编码一种具有外加N端氨基酸序列的蛋白异构体, 对于促进肿瘤的增殖生长具有重要作用.

2.2 lncRNA与HCC临床诊治中的潜在应用价值 lncRNA在肝组织中特异性表达. 通过meta分析发现AFAP-AS1、HOTTIP、ZEB-1-AS1等27种LncRNA高表达与预后不良密切相关, GAS5、MEG3、XIST等18种LncRNA低表达会加剧恶化[51].

HCC患者HULC水平升高, 且与Edmondson组织学分级呈正相关[52]. UCA1和WRAP53的表达增加也与肿瘤恶性程度相关. 此外, 结合LncRNA和血清AFP联合检测可提高HCC诊断的敏感性[53]. 分析血清中uc001ncr和AX800134表达情况发现LncRNA有可能成为诊断HCC的新型标志物, 尤其当早期HCCAFP小于等于400 ng/mL时[44].

除此之外, RP11-160H22.5、XLOC_014172和LOC149086等3种潜在的诊断lncRNA也被提出, 其中XLOC_014172和LOC149086在转移性HCC患者中均显著升高[54]. 总结出HCC相关ncRNA, 如HULC, Linc00152, HEIH, HOTTIP, HOTAIR, MALAT1, DILC, ZFAS1, MEG3, PRAL, LALR1, LET, MVIH, PCNA-AS, TUC338, UC001NCR.

MRX34是包裹在脂质体纳米颗粒中的miR-34a合成版本, 在一期临床试验中显示出HCC抗肿瘤活性[55]. 第一种miRNA靶向药物米雷韦森(miravirsen), 一种lna修饰的anti-miR-122 DNA-RNA杂化寡核苷酸, 正在进行慢性丙肝治疗的Ⅱ期临床试验[56].

3 环状RNA与HCC

circRNA是封闭的环状分子, 作为ncRNA家族的一部分, circRNA通常以组织和发育阶段特异性方式表达, 而且表达丰度高. 它在疾病的变化发展中先于蛋白类标志物, 在血清中表达很稳定, 因此它作为HCC早期诊断及预后的标志物具有很好的临床应用前景.

3.1 环状RNA在HCC发生、进展中的作用 环状RNA在HCC的发生发展发挥着重要作用. CDRIas (Hsa_circ_0001946)通过靶向抑制miR-7功能提高HCC细胞的增殖能力[57]; circMT01(Hsa_circ_0007874)通过充当miR-9的分子海绵进而提高P21表达实现抑癌作用[58]; circRNA_000839(Hsa circ_0000497)可能通过与miR-200b和RhoA的相互作用影响HCC发生和发展[59]; circITC H通过抑制Wnt/p -Catenin pathway信号通路抑制HCC[60]. Hsa circ_0001649可通过靶向SHPRH基因来发挥其抑制HCC的作用[61]CircHIPK3 (Hsa_circ_0000284)可以作为miR-124的分子海绵促进HCC细胞生长[62]; 与HCC的发生密切相关的circFUT8 (Hsa_circ_0003028), circZFR(Hsa circ_103809)以及circIP011(Hsa circ_0007915)可靶向多个miRNA发挥作用[63]; cSMARCAS(Hsa_circ_0001445)通过充当miR-17-3p和miR-181b-5p的分子海绵促进抑癌基因TIMP3的表达, 从而抑制HCC细胞的增殖和转移; CircC3P1通过对miR-4641的海绵作用促进PCK1的表达, 从而发挥其抑制HCC生长及转移的作用[64].

3.2 环状RNA在HCC诊断与治疗中的应用 circRNA有望成为理想的HCC分子标志物. Yao等[65]通过建立受试者工作特征曲线(receiver operating characteristic curve, ROC)评估circZKSCANI(Hsa_circ_0001727)在鉴别HCC组织及邻近正常组织时的价值, 发现其受试者工作特征曲线下面积((area under curve, AUC)为0.834, 灵敏度为82.2%, 特异度为72.4%; Qin等[66]通过ROC曲线评估Hsa_circ_0001649在鉴别HCC组织及邻近正常组织的AUC为0.63, 灵敏度为0.81, 特异度为0.69. Shang等[67]发现Hsa circ_0005075鉴别HCC组织和癌旁正常组织时AUC为0.94, 灵敏度为83.3%, 特异度为90.0%; ROC曲线评估血浆Hsa circ_0001445诊断HCC患者较AFP具有更高的灵敏度, 在鉴别HCC患者和正常人时其AUC为0.862, 灵敏度为71.2%, 特异度为94.2%.

另外, Hsa_circ_0016788可以通过miR-486/CDK4信号通路促进HCC细胞生长, 表明Hsa_circ_0016788在HCC治疗中具有很大的研究价值[68]. Hsa circ_0067934可以通过抑制miR-1324的功能以及激活FZD5/β-catenin信号通路提高HCC细胞增殖、转移、侵袭的能力, 提示Hsa_circ_0067934/miR-1324/FZD5/β-catenin信号轴有望成为HCC治疗的新靶标[69].

4 结论

ncRNAs的异常表达与人类各种疾病尤其与恶性肿瘤的发生发展密切相关, 相关研究已成为当今HCC研究领域的热点和重要科学问题. 近年研究对ncRNAs在人类恶性肿瘤特别是HCC中的作用、分子机制及临床意义进行了深入系统的探索, 取得系列创新性研究成果, 充分揭示ncRNAs不仅在肿瘤的发生发展与转移中发挥重要作用, 而且可作为癌症诊断与分型、转移复发与预后预测分子标志物; 另外, ncRNAs还可以作为癌症治疗靶标及新的治疗手段, 为肿瘤精准诊断与精准治疗带来新的机遇.

然而, ncRNAs数量繁多, 大部分ncRNAs功能及调控机制有待进一步明确. 虽然已经发现多种与HCC发生发展及转移密切相关的ncRNAs. 而且, 几种基于

ncRNAs的癌症治疗方法已在临床试验中得到检验, 但这些研究仍处于起步阶段. 因此, 进一步研究肝脏ncRNA与疾病进展的关系将是解决包括HCC在内的肝脏疾病的关键.

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