WCJD 世界华人消化杂志®

在线投稿: http://www.baishideng.com/wcjd/ch/index.aspx
帮助平台: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.11569/wcjd.v24.i20.3128

世界华人消化杂志 2016年7月18日; 24(20): 3128-3134
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 REVIEW

MicroRNA在急性胰腺炎中的研究进展

邓力珲, 夏 庆

背景资料
微小RNA(microRNAs, miRNAs)是一类非编码的转录后调节的小RNA分子, 参与机体生长发育过程以及多种疾病发生过程. 近年来的研究资料显示, miRNAs参与了急性胰腺炎(acute pancreatitis, AP)的疾病过程, 但miRNAs在AP中的作用尚不明确, 需要深入研究.

邓力珲, 夏庆, 四川大学华西医院中西医结合科 四川省成都市 610041

邓力珲, 助理研究员, 主要从事重症急性胰腺炎的基础与临床研究.

基金项目: 国家自然科学基金资助项目, No. 81300358; 高等学校博士学科点专项科研基金资助项目, No. 20130181120050.

作者贡献分布: 本文综述由邓力珲完成; 夏庆审校.

通讯作者: 夏庆, 教授, 主任医师, 610041, 四川省成都市武侯区国学巷37号, 四川大学华西医院中西医结合科.
xiaqing@medmail.com.cn
电话: 028-85423373

收稿日期: 2016-05-23
修回日期: 2016-06-17
接受日期: 2016-06-27
在线出版日期: 2016-07-18

MicroRNAs in acute pancreatitis

Li-Hui Deng, Qing Xia

Li-Hui Deng, Qing Xia, Department of Integrated Traditional and Western Medicine, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Supported by: National Natural Science Foundation of China, No. 81300358; Research Fund for the Doctoral Program of Higher Education of China, No. 20130181120050.

Correspondence to: Qing Xia, Professor, Chief Physician, Department of Integrated Traditional and Western Medicine, West China Hospital, Sichuan University, 37 Guoxue Alley, Wuhou District, Chengdu 610041, Sichuan Province, China. xiaqing@medmail.com.cn

Received: 2016-05-23
Revised: 2016-06-17
Accepted: 2016-06-27
Published online: 2016-07-18

Abstract
Acute pancreatitis is an acute inflammatory condition of the pancreas that can develop into a complicated clinical course with severe local and systemic complications, resulting in a prolonged clinical course with considerable mortality. MicroRNAs (miRNAs), a class of small non-coding RNA molecules that negatively regulate gene expression, have potential value in clinical research and biomarker discovery. In recent years, accumulating evidence suggests that miRNAs may act as potential biomarkers for pancreatic tissue injury, and much attention has been paid to those miRNAs involved in acute pancreatitis. However, the role of miRNAs in acute pancreatitis has been validated in very few clinical studies. A better understanding of the role that miRNAs play in acute pancreatitis can lead to the development of new diagnostic and prognostic tools for future clinical applications.

Key Words: Acute pancreatitis; Biomarker; MicroRNA; Gene expression regulation; Pancreatic injury

Deng LH, Xia Q. MicroRNAs in acute pancreatitis. Shijie Huaren Xiaohua Zazhi 2016; 24(20): 3128-3134
URL: http://www.wjgnet.com/1009-3079/full/v24/i20/3128.htm DOI: http://dx.doi.org/10.11569/wcjd.v24.i20.3128

摘要
急性胰腺炎(acute pancreatitis, AP)是临床常见的胰腺外分泌腺急性炎症性疾病, 可引起严重的局部和全身并发症, 死亡率高. 微小

同行评议者
梁国刚, 教授, 大连医科大学附属第一医院; 张淑坤, 副研究员, 南开医院急腹症研究所 细胞及分子生物学实验室

RNA(microRNA, miRNA)是一类非编码的转录后调控因子, 随着miRNA研究的深入, 多项研究显示miRNA参与机体生长发育过程以及多种疾病发生过程. miRNA在AP发病过程中的作用尚不明确. 本文总结近年来的研究结果, 对AP与相关miRNA的研究进展作一综述.

关键词: 急性胰腺炎; 生物标志物; 微小RNA; 基因表达调控; 胰腺损伤

核心提示: 急性胰腺炎(acute pancreatitis, AP)发病机制不明, 早期预警疾病的严重程度可能改善预后降低病死率. 近年来的研究显示, 微小RNA参与了胰腺损伤和AP的发病过程, 在AP的发生和发展过程中起到重要作用.

邓力珲, 夏庆. MicroRNA在急性胰腺炎中的研究进展. 世界华人消化杂志 2016; 24(20): 3128-3134 URL: http://www.wjgnet.com/1009-3079/full/v24/i20/3128.htm DOI: http://dx.doi.org/10.11569/wcjd.v24.i20.3128

0 引言

急性胰腺炎(acute pancreatitis, AP)是胰腺外分泌腺的急性炎症性疾病, 目前该病发病机制仍未完全明了, 还没有特异性治疗方法, 一旦发展为重症急性胰腺炎(sever acute pancreatitis, SAP), 病死率高达36%-50%, 给个人家庭和社会造成了巨大的经济和心理负担[1,2]. 微小RNA(microRNA, miRNA)是一类约由19-24个核苷酸组成的内源性非编码单链RNA分子, 抑制mRNA的翻译过程最终阻断蛋白质合成[3]. 诸多研究表明miRNA参与机体生长发育以及多种疾病发生过程. 近年来的研究资料显示, miRNA参与了AP的发病机制, 可能作为胰腺炎的生物标志物.

1 miRNA的生物合成、作用机制和功能

1993年Lee等[4]在秀隐杆线虫发育的研究中首次发现了控制细胞发育时序的长度约为22 nt的小分子miRNA Lin-4, Reinhart等[5]在线虫中发现另一种调控发育时序的miRNA let-7, 研究发现miRNA广泛存在各自动物、植物和病毒中, 随后miRNA逐步受到关注.

miRNA由基因组DNA在RNA聚合酶Ⅱ用下转录为pri-miRNA, 经RNA聚合酶Ⅲ剪切为约70 nt的具有茎环结构的pre-miRNA, 再通过exportin-5由细胞核转运至细胞质, 在胞质中由RNaseⅡ核酸酶Dicer酶切断pre-miRNA的末端袢环, 形成19-24个核苷酸组成的成熟miRNA[6-13]. 成熟的miRNA整合到RNA诱导的基因沉默复合物(RNA induced silencing complex)中, 该复合体能够结合至靶mRNA上, 或阻碍了该基因的翻译, 或引起基因的降解, 最终抑制靶基因表达阻碍蛋白的合成.

由于miRNA在基因表达调控方面起重要作用, 参与生命体的个体发育、细胞分化、增殖、凋亡、病毒侵染和炎症反应等生命过程[14]. 同时miRNA的表达失调可以引起人类多种疾病, 在疾病的诊断、治疗和指导预后中发挥重要的调控作用[15-18].

2 外周血循环中的miRNA

近年来研究发现miRNA具有组织特异性[19-22], 除此之外, miRNA在血液、尿液、唾液、眼泪、胸水、支气管灌洗液、脑脊髓液等不同的细胞外体液中均可稳定表达[23,24]. 2007年, Lawrie等[25]首次检测到了血循环中的miRNA. miRNAs进入体内循环的机制尚不清楚, 目前认为循环中的miRNAs并不是单纯的细胞溶解产物, 可能是包裹于微粒体内或简单的由argonaute 2或nucleophosmin保护而防止其发生降解[26-28]. 循环miRNA表达稳定, RNA酶、高温、极低或极高的pH环境等处理条件, 长时间储存以及多次冻融均不会影响其表达的含量[29]. 越来越多的研究支持循环miRNA成为新一类生物标志物, 例如, 风湿性关节炎患者, 即便抗环瓜氨酸多肽抗体阴性, 血浆miR-24和miR-125a-5p也可以作为潜在的诊断标志物; 心血管疾病患者血循环中miR-1和miR-133a主要来源于受损的心肌, 可作为心肌细胞死亡的标志物[30]; 血清miRNA-146a和miR-223可以作为脓毒血症的新标志物, 具有高特异性和敏感性[31]; 循环miR-323-3p可作为异位妊娠的标志物[32]; 大量研究认为循环miRNA鉴别病变的良恶性质、早期诊断恶性肿瘤、鉴别恶性肿瘤的组织来源、预测肿瘤病变的预后, 甚至筛查化疗的敏感性指导临床诊疗方案[33-40].

3 miRNA与AP的研究进展

AP的具体发病机制还没有完全明确, miRNA这

研发前沿

miRNAs具有组织特异性, 还可在细胞外体液中稳定表达, 循环miRNAs成为新一类生物标志物, 已成为研究的热点. 目前已在AP患者的血清中筛选及检测到一些能够预测AP严重程度的miRNAs.

相关报道
大量文献报道miRNA参与生命体的个体发育、细胞分化、增殖、凋亡、病毒侵染和炎症反应等生命过程, 在疾病的诊断、治疗和指导预后中发挥重要的调控作用, miRNAs也参与了胰腺损伤和AP的发病过程.

一类小分子在整个疾病过程中作用也所知甚少. 随着对胰腺中miRNA认识的深入, 越来越多的研究者开始着手研究miRNA与AP的关系.

3.1 miRNAs在胰腺损伤和AP中的作用 miR-216(包括高度同源的miR-216a和miR-216b)是胰腺组织特异性表达的miRNA[41-44], 当组织受损伤时, 组织特异性miRNA释放入血, 因此可作为组织损伤的标志物. Kong等[45]检测SD大鼠的多种组织器官后发现, miR-216a在胰腺中的表达量最高, 提示miR-216a在胰腺组织中特异性表达, 精氨酸诱导的AP大鼠血清中miR-216a表达增高, 优于淀粉酶、脂肪酶等生化指标, 可作为胰腺损伤检测的特异性标志物. 该观点被Endo等[46]的研究结果进一步证实. Usborne等[47]分别用雨蛙肽和1-氰基-2-羟基-3-丁烯(cyanohydroxybutene)引起大鼠外分泌胰腺损伤模型中发现miR-216a在胰腺损伤后的24 h达高峰, 是AP的潜在标志物. Goodwin等[48]分别在大鼠和小鼠中使用雨蛙肽、*L*-精氨酸和胰管结扎三种经典造模方式, 虽然在不同模型中血清miRNA-216a表达有差异, 但其还是能较好的反映胰腺损伤. Zhang等[49]研究发现转化生长因子-β(transforming growth factor-β, TGF-β)刺激大鼠胰腺腺泡细胞株后可引起剂量依赖性miRNA-216a升高, TGF-β抑制剂可显著降低胰腺组织和血清中的miRNA-216a的表达量, 同时发现miRNA-216a通过作用于PTEN和Smad7参与AP病机过程中的PI3K/Akt信号通路和TGF-β通路. 王春全等[50]对60例患AP患者的外周血样本进行检测发现其外周血细胞miR-216a的表达显著高于健康对照者, 提示miRNA可作为AP的诊断依据之一. 值得提出的是, Blenkiron等[51]在AP模型大鼠的肠系膜淋巴结中检测到miR-216a, -375, -217, -148a等7个miRNAs在AP大鼠肠系膜淋巴结有所增加, 且上调程度与AP严重程度呈正相关; 在临床研究中, 血浆miR-216a在轻症和中度AP患者中都显著升高. 该研究首次证明miRNA稳定存在于AP大鼠血液和淋巴结中, AP患者血循环中也存在特定miRNA的改变, 提出miRNA可被探索作为AP新的生物标志物.

除了miR-216, 一些文献报道了其他miRNAs在AP动物中的作用. Tian等[52]观察到SAP过度的炎症反应导致肿瘤坏死因子α等炎症因子过度释放, 诱导肠上皮miR-155过度表达, 使*RhoA*基因转录后表达失调而抑制RhoA蛋白合成, 从而下调紧密黏连蛋白1(zonula occludens-1, ZO-1)和E-钙黏蛋白(E-cadherin, ED)的表达, 这两种蛋白是AJC的重要组成部分, 过程最终导致SAP肠屏障功能障碍. miR-19b在ANP大鼠和TLC-S处理的AR42J细胞中miR-19b 表达升高, 其表达升高与胰腺腺泡细胞坏死的程度相关, 其表达确实可降低腺泡细胞坏死率[53]. miR-9的表达与胰腺纤维化呈正相关, 提示miR-9可作为AP转化为慢性胰腺炎的标志物, 参与AP的转归[54]. 血清miRNA可作为早期筛选AP中胰腺上皮内瘤变等良性肿瘤的生物标志物[55].

3.2 miRNA调控腺泡细胞凋亡与自噬 秦涛等[56]在大鼠AP凋亡相关miRNA表达谱的研究中发现, 其中有5条miRNA上调, 有3条miRNA下调. 付强等[57]用miRNA芯片技术筛选出miR-19b、miR-15b、miR-92、miR-99b、miR-363、miR-135a、miR-22、miR-614等八种可能与AP腺泡细胞凋亡相关的miRNA. Qin等[58]在轻度水肿性胰腺炎小鼠模型中发现, AP胰腺组织中miR-22和miR-135a在胰腺组织中表达显著升高, 上调的miR-22和miR-135a分别通过抑制ErbB3和Ptk2的表达来促进腺泡细胞的凋亡,从而在轻症AP中起到保护作用.

miRNAs调节自噬相关基因的表达参与维持自噬的过程[59], 饥饿诱导AR42J细胞建立胰腺腺泡细胞自噬模型, 用miRNA芯片检测到10个差异表达miRNAs, 生物信息学分析预测miRNAs的靶基因, 分析差异表达miRNA的功能. 结果显示仅仅有miR-148b-3p表达下调, 预测593个靶基因, 为自噬推动的AP发病机制与治疗提供了新的靶向. miR-141直接抑制小鼠hepal-6细胞HMGB1表达, 精氨酸AP体内模型中miR-141调节自噬下游蛋白Beclin-1表达, 减少自噬体和自噬溶酶体的形成, 降低LC3-Ⅱ水平, 升高自噬负调节蛋白p62, miR-141或可为AP的治疗提供基因治疗的新靶点[60]. miR-21与AP腺泡细胞损伤和坏死性凋亡有关, miR-21基因缺失能保护雨蛙肽或精氨酸诱导的小鼠AP, 降低TNF导致的全身炎症反应综合征, miR-21能负性调节肿瘤抑制基因相关的死亡受体调节的体内凋亡通路而增强细胞坏死, 可能作为阻断胰腺病理性坏死的治疗靶点[61].

3.3 血清miRNA作为预测AP的生物标志物 在

不同程度AP患者的外周血中发现, 血清miR-92b, miR-10a, 和miR-7在AP患者中表达降低, 可能有助于早期诊断AP, 并且miR-551b-5p可以作为预测AP严重性的潜在标志物[62]. 研究[63]发现高甘油三酯血症AP患者血清miR-24-3p, 361-5p, 246和222-3p显著升高, miR-181a-5p显著性下调, 这5个miRNA在区分重症AP与中度重症AP方面均显示较好的敏感性和特异性, 其中尤以miR-181a-5p最为显著; miR-181a-5p是唯一表达下调的miRNA, 与甘油三酯、总胆固醇和空腹血糖呈负相关, 而与钙离子呈正相关, 这些研究数据表明血清miRNA具有很好的HTAP生物标志物的潜力. 还有研究[64]检测到AP患者血清miR-126-5p, -148a-3p, -216a-5p, -551b-5p, 以及miR-375的表达, 结果显示miR-126-5p和miR-551b-5p能够预测AP的严重程度.

4 展望

将miRNAs应用于AP的早期诊断, 研究AP及其并发症的发生机制, 为AP的治疗提供新的治疗途径. 通过调节miRNAs的表达研究调控相关蛋白表达, 也将是一种新型治疗手段. 更多或更大样本量的临床研究需要进行来进一步证实miRNA在临床早期预测AP病情严重程度中的价值, 可能在临床应用中会有良好的发展前景, 带来生物标志物领域的新变革.

5 结论

探索无创、简便、准确可靠的预测病情方式, 早期及时筛选出真正危重的患者, 采取积极的救治方法和手段, 对于降低SAP总体病死率具有十分重要的意义. miRNAs在AP中表现出异常表达, 而这些异常表达的 miRNAs 可能在疾病的临床诊断中有重要作用, 同时具备成为疾病生物标志物的潜力, 可以用于预测AP的严重程度或预后.

6 参考文献

1 Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 2013; 108: 1400-115; 1416 [PMID: 23896955 DOI: 10.1038/ajg.2013.218]

2 Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; 62: 102-111 [PMID: 23100216 DOI: 10.1136/gutjnl-2012-302779]

3 Bartel DP. MicroRNAs: target recognition and regulatory functions. *Cell* 2009; 136: 215-233 [PMID: 19167326 DOI: 10.1016/j.cell.2009.01.002]

4 Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* 1993; 75: 843-854 [PMID: 8252621]

5 Reinhart BJ, Slack FJ, Basson M, Pasquinelli AE, Bettinger JC, Rougvie AE, Horvitz HR, Ruvkun G. The 21-nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegans. *Nature* 2000; 403: 901-906 [PMID: 10706289]

6 Zeng Y, Cullen BR. Efficient processing of primary microRNA hairpins by Drosha requires flanking nonstructured RNA sequences. *J Biol Chem* 2005; 280: 27595-27603 [PMID: 15932881]

7 Tomari Y, Du T, Zamore PD. Sorting of Drosophila small silencing RNAs. *Cell* 2007; 130: 299-308 [PMID: 17662944]

8 Meister G, Landthaler M, Patkaniowska A, Dorsett Y, Teng G, Tuschl T. Human Argonaute2 mediates RNA cleavage targeted by miRNAs and siRNAs. *Mol Cell* 2004; 15: 185-197 [PMID: 15260970]

9 Liu J, Carmell MA, Rivas FV, Marsden CG, Thomson JM, Song JJ, Hammond SM, Joshua-Tor L, Hannon GJ. Argonaute2 is the catalytic engine of mammalian RNAi. *Science* 2004; 305: 1437-1441 [PMID: 15284456]

10 Hutvágner G, McLachlan J, Pasquinelli AE, Bálint E, Tuschl T, Zamore PD. A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA. *Science* 2001; 293: 834-838 [PMID: 11452083]

11 Cullen BR. Transcription and processing of human microRNA precursors. *Mol Cell* 2004; 16: 861-865 [PMID: 15610730]

12 Chendrimada TP, Gregory RI, Kumaraswamy E, Norman J, Cooch N, Nishikura K, Shiekhattar R. TRBP recruits the Dicer complex to Ago2 for microRNA processing and gene silencing. *Nature* 2005; 436: 740-744 [PMID: 15973356]

13 Agrawal N, Dasaradhi PV, Mohmmed A, Malhotra P, Bhatnagar RK, Mukherjee SK. RNA interference: biology, mechanism, and applications. *Microbiol Mol Biol Rev* 2003; 67: 657-685 [PMID: 14665679]

14 Kloosterman WP, Plasterk RH. The diverse functions of microRNAs in animal development and disease. *Dev Cell* 2006; 11: 441-450 [PMID: 17011485]

15 Costinean S, Zanesi N, Pekarsky Y, Tili E, Volinia S, Heerema N, Croce CM. Pre-B cell proliferation and lymphoblastic leukemia/high-grade lymphoma in E(mu)-miR155 transgenic mice. *Proc Natl Acad Sci USA* 2006; 103: 7024-7029 [PMID: 16641092]

16 Hunter MP, Ismail N, Zhang X, Aguda BD, Lee EJ, Yu L, Xiao T, Schafer J, Lee ML, Schmittgen TD, Nana-Sinkam SP, Jarjoura D, Marsh CB. Detection of microRNA expression in human peripheral blood microvesicles. *PLoS One* 2008; 3: e3694 [PMID: 19002258 DOI: 10.1371/journal.pone.0003694]

17 Gandy SZ, Linnstaedt SD, Muralidhar S,

创新盘点

目前基础与临床研究结果支持循环miRNA成为新一类生物标志物. 研究发现, miRNA在各系统疾病中有表达谱变化, 其在胰腺炎中表达变化对疾病的诊断、病情严重程度预警、预后判断等方面有一定的意义.

应用要点

AP至今尚无特异性治疗. 发现调节AP发病的关键miRNAs, 或可找到AP的治疗靶点; 若能筛选鉴定出反映AP病情变化发展、预警重症患者的miRNAs, 则可作为疾病生物标志物开发转化应用, 有理论和实际意义.

Cashman KA, Rosenthal LJ, Casey JL. RNA editing of the human herpesvirus 8 kaposin transcript eliminates its transforming activity and is induced during lytic replication. *J Virol* 2007; 81: 13544-13551 [PMID: 17913828]

18 Macha MA, Seshacharyulu P, Krishn SR, Pai P, Rachagani S, Jain M, Batra SK. MicroRNAs (miRNAs) as biomarker(s) for prognosis and diagnosis of gastrointestinal (GI) cancers. *Curr Pharm Des* 2014; 20: 5287-5297 [PMID: 24479799]

19 Girard M, Jacquemin E, Munnich A, Lyonnet S, Henrion-Caude A. miR-122, a paradigm for the role of microRNAs in the liver. *J Hepatol* 2008; 48: 648-656 [PMID: 18291553 DOI: 10.1016/j.jhep.2008.01.019]

20 Tömböl Z, Szabó PM, Molnár V, Wiener Z, Tölgyesi G, Horányi J, Riesz P, Reismann P, Patócs A, Likó I, Gaillard RC, Falus A, Rácz K, Igaz P. Integrative molecular bioinformatics study of human adrenocortical tumors: microRNA, tissue-specific target prediction, and pathway analysis. *Endocr Relat Cancer* 2009; 16: 895-906 [PMID: 19546168 DOI: 10.1677/ERC-09-0096]

21 Rosenberg MI, Georges SA, Asawachaicharn A, Analau E, Tapscott SJ. MyoD inhibits Fstl1 and Utrn expression by inducing transcription of miR-206. *J Cell Biol* 2006; 175: 77-85 [PMID: 17030984]

22 Beuvink I, Kolb FA, Budach W, Garnier A, Lange J, Natt F, Dengler U, Hall J, Filipowicz W, Weiler J. A novel microarray approach reveals new tissue-specific signatures of known and predicted mammalian microRNAs. *Nucleic Acids Res* 2007; 35: e52 [PMID: 17355992]

23 Weber JA, Baxter DH, Zhang S, Huang DY, Huang KH, Lee MJ, Galas DJ, Wang K. The microRNA spectrum in 12 body fluids. *Clin Chem* 2010; 56: 1733-1741 [PMID: 20847327 DOI: 10.1373/clinchem.2010.147405]

24 Molina-Pinelo S, Suárez R, Pastor MD, Nogal A, Márquez-Martín E, Martín-Juan J, Carnero A, Paz-Ares L. Association between the miRNA signatures in plasma and bronchoalveolar fluid in respiratory pathologies. *Dis Markers* 2012; 32: 221-230 [PMID: 22430188 DOI: 10.3233/DMA-2011-0882]

25 Lawrie CH, Gal S, Dunlop HM, Pushkaran B, Liggins AP, Pulford K, Banham AH, Pezzella F, Boultwood J, Wainscoat JS, Hatton CS, Harris AL. Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma. *Br J Haematol* 2008; 141: 672-675 [PMID: 18318758 DOI: 10.1111/j.1365-2141.2008.07077.x]

26 Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol* 2007; 9: 654-659 [PMID: 17486113]

27 Arroyo JD, Chevillet JR, Kroh EM, Ruf IK, Pritchard CC, Gibson DF, Mitchell PS, Bennett CF, Pogosova-Agadjanyan EL, Stirewalt DL, Tait JF, Tewari M. Argonaute2 complexes carry a population of circulating microRNAs independent of vesicles in human plasma. *Proc Natl Acad Sci USA* 2011; 108: 5003-5008 [PMID: 21383194 DOI: 10.1073/pnas.1019055108]

28 Wang K, Zhang S, Weber J, Baxter D, Galas DJ. Export of microRNAs and microRNA-protective protein by mammalian cells. *Nucleic Acids Res* 2010; 38: 7248-7259 [PMID: 20615901 DOI: 10.1093/nar/gkq601]

29 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]

30 Kuwabara Y, Ono K, Horie T, Nishi H, Nagao K, Kinoshita M, Watanabe S, Baba O, Kojima Y, Shizuta S, Imai M, Tamura T, Kita T, Kimura T. Increased microRNA-1 and microRNA-133a levels in serum of patients with cardiovascular disease indicate myocardial damage. *Circ Cardiovasc Genet* 2011; 4: 446-454 [PMID: 21642241 DOI: 10.1161/CIRCGENETICS.110.958975]

31 Wang JF, Yu ML, Yu G, Bian JJ, Deng XM, Wan XJ, Zhu KM. Serum miR-146a and miR-223 as potential new biomarkers for sepsis. *Biochem Biophys Res Commun* 2010; 394: 184-188 [PMID: 20188071 DOI: 10.1016/j.bbrc.2010.02.145]

32 Zhao Z, Zhao Q, Warrick J, Lockwood CM, Woodworth A, Moley KH, Gronowski AM. Circulating microRNA miR-323-3p as a biomarker of ectopic pregnancy. *Clin Chem* 2012; 58: 896-905 [PMID: 22395025 DOI: 10.1373/clinchem.2011.179283]

33 De Guire V, Robitaille R, Tétreault N, Guérin R, Ménard C, Bambace N, Sapieha P. Circulating miRNAs as sensitive and specific biomarkers for the diagnosis and monitoring of human diseases: promises and challenges. *Clin Biochem* 2013; 46: 846-860 [PMID: 23562576 DOI: 10.1016/j.clinbiochem.2013.03.015]

34 Li C, Li JF, Cai Q, Qiu QQ, Yan M, Liu BY, Zhu ZG. MiRNA-199a-3p: A potential circulating diagnostic biomarker for early gastric cancer. *J Surg Oncol* 2013; 108: 89-92 [PMID: 23733518 DOI: 10.1002/jso.23358]

35 Wang H, Tan G, Dong L, Cheng L, Li K, Wang Z, Luo H. Circulating MiR-125b as a marker predicting chemoresistance in breast cancer. *PLoS One* 2012; 7: e34210 [PMID: 22523546 DOI: 10.1371/journal.pone.0034210]

36 Nair N, Kumar S, Gongora E, Gupta S. Circulating miRNA as novel markers for diastolic dysfunction. *Mol Cell Biochem* 2013; 376: 33-40 [PMID: 23247724 DOI: 10.1007/s11010-012-1546-x]

37 Friedman RC, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. *Genome Res* 2009; 19: 92-105 [PMID: 18955434]

38 Murata K, Furu M, Yoshitomi H, Ishikawa M, Shibuya H, Hashimoto M, Imura Y, Fujii T, Ito H, Mimori T, Matsuda S. Comprehensive microRNA analysis identifies miR-24 and miR-125a-5p as plasma biomarkers for rheumatoid arthritis. *PLoS One* 2013; 8: e69118 [PMID: 23874885 DOI:

10.1371/journal.pone.0069118]
39 Kumar P, Dezso Z, MacKenzie C, Oestreicher J, Agoulnik S, Byrne M, Bernier F, Yanagimachi M, Aoshima K, Oda Y. Circulating miRNA biomarkers for Alzheimer's disease. *PLoS One* 2013; 8: e69807 [PMID: 23922807 DOI: 10.1371/journal.pone.0069807]
40 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]
41 Sood P, Krek A, Zavolan M, Macino G, Rajewsky N. Cell-type-specific signatures of microRNAs on target mRNA expression. *Proc Natl Acad Sci USA* 2006; 103: 2746-2751 [PMID: 16477010]
42 Szafranska AE, Davison TS, John J, Cannon T, Sipos B, Maghnouj A, Labourier E, Hahn SA. MicroRNA expression alterations are linked to tumorigenesis and non-neoplastic processes in pancreatic ductal adenocarcinoma. *Oncogene* 2007; 26: 4442-4452 [PMID: 17237814]
43 Baskerville S, Bartel DP. Microarray profiling of microRNAs reveals frequent coexpression with neighboring miRNAs and host genes. *RNA* 2005; 11: 241-247 [PMID: 15701730]
44 Shingara J, Keiger K, Shelton J, Laosinchai-Wolf W, Powers P, Conrad R, Brown D, Labourier E. An optimized isolation and labeling platform for accurate microRNA expression profiling. *RNA* 2005; 11: 1461-1470 [PMID: 16043497]
45 Kong XY, Du YQ, Li L, Liu JQ, Wang GK, Zhu JQ, Man XH, Gong YF, Xiao LN, Zheng YZ, Deng SX, Gu JJ, Li ZS. Plasma miR-216a as a potential marker of pancreatic injury in a rat model of acute pancreatitis. *World J Gastroenterol* 2010; 16: 4599-4604 [PMID: 20857533 DOI: 10.3748/wjg.v16.i36.4599]
46 Endo K, Weng H, Kito N, Fukushima Y, Iwai N. MiR-216a and miR-216b as markers for acute phased pancreatic injury. *Biomed Res* 2013; 34: 179-188 [PMID: 23995054]
47 Usborne AL, Smith AT, Engle SK, Watson DE, Sullivan JM, Walgren JL. Biomarkers of exocrine pancreatic injury in 2 rat acute pancreatitis models. *Toxicol Pathol* 2014; 42: 195-203 [PMID: 24285669 DOI: 10.1177/0192623313512030]
48 Goodwin D, Rosenzweig B, Zhang J, Xu L, Stewart S, Thompson K, Rouse R. Evaluation of miR-216a and miR-217 as potential biomarkers of acute pancreatic injury in rats and mice. *Biomarkers* 2014; 19: 517-529 [PMID: 25059555 DOI: 10.3109/1354750X.2014.944217]
49 Zhang J, Ning X, Cui W, Bi M, Zhang D, Zhang J. Transforming growth factor (TGF)-β-induced microRNA-216a promotes acute pancreatitis via Akt and TGF-β pathway in mice. *Dig Dis Sci* 2015; 60: 127-135 [PMID: 25501921 DOI: 10.1007/s10620-014-3261-9]
50 王春全, 陈景祥, 杨进军, 唐小卿, 简华刚. miR-216a在急性胰腺炎患者外周血的表达及临床意义. 免疫学杂志 2013; 29: 47-49
51 Blenkiron C, Askelund KJ, Shanbhag ST, Chakraborty M, Petrov MS, Delahunt B, Windsor JA, Phillips AR. MicroRNAs in mesenteric lymph and plasma during acute pancreatitis. *Ann Surg* 2014; 260: 341-347 [PMID: 24509209 DOI: 10.1097/SLA.0000000000000447]
52 Tian R, Wang RL, Xie H, Jin W, Yu KL. Overexpressed miRNA-155 dysregulates intestinal epithelial apical junctional complex in severe acute pancreatitis. *World J Gastroenterol* 2013; 19: 8282-8291 [PMID: 24363519 DOI: 10.3748/wjg.v19.i45.8282]
53 Hu MX, Zhang HW, Fu Q, Qin T, Liu CJ, Wang YZ, Tang Q, Chen YX. Functional role of MicroRNA-19b in acinar cell necrosis in acute necrotizing pancreatitis. *J Huazhong Univ Sci Technolog Med Sci* 2016; 36: 221-225 [PMID: 27072966 DOI: 10.1007/s11596-016-1570-2]
54 韩非, 王春友, 章孟詹. 血浆miR-9在小鼠急性胰腺炎向慢性胰腺炎转化过程中的表达及意义. 中华实验外科杂志 2012; 29: 560-565
55 Hong X, Zhang J, Wu Q, Wang W, Ye AY, Song W, Dai H, Wang X, Wu F, You L, Wu W, Zhao Y. Challenges in detecting pre-malignant pancreatic lesions during acute pancreatitis using a serum microRNA assay: a study based on KrasG12D transgenic mice. *Oncotarget* 2016 Mar 17. *[Epub ahead of print]* [PMID: 27009811 DOI: 10.18632/oncotarget.8148]
56 秦涛, 李杰, 张宏伟, 刘传江, 刘健康. 大鼠急性胰腺炎凋亡相关微小RNA表达谱分析. 中华实验外科杂志 2011; 28: 416-418
57 付强, 张宏伟, 秦涛, 刘传江, 胡明星, 唐强, 王玉柱, 薛飞, 张莉. 微小RNA-92b在大鼠急性胰腺炎中对腺泡细胞凋亡的影响. 中华实验外科杂志 2013; 30: 1672-167558
58 Qin T, Fu Q, Pan YF, Liu CJ, Wang YZ, Hu MX, Tang Q, Zhang HW. Expressions of miR-22 and miR-135a in acute pancreatitis. *J Huazhong Univ Sci Technolog Med Sci* 2014; 34: 225-233 [PMID: 24710937]
59 Gao B, Wang D, Sun W, Meng X, Zhang W, Xue D. Differentially expressed microRNA identification and target gene function analysis in starvation-induced autophagy of AR42J pancreatic acinar cells. *Mol Med Rep* 2016; 14: 590-598 [PMID: 27175615 DOI: 10.3892/mmr.2016.5240]
60 Zhu H, Huang L, Zhu S, Li X, Li Z, Yu C, Yu X. Regulation of autophagy by systemic admission of microRNA-141 to target HMGB1 in l-arginine-induced acute pancreatitis in vivo. *Pancreatology* 2016; 16: 337-346 [PMID: 27017485 DOI: 10.1016/j.pan.2016.03.004]
61 Ma X, Conklin DJ, Li F, Dai Z, Hua X, Li Y, Xu-Monette ZY, Young KH, Xiong W, Wysoczynski M, Sithu SD, Srivastava S, Bhatnagar A, Li Y. The oncogenic microRNA miR-21 promotes regulated necrosis in mice. *Nat Commun* 2015; 6: 7151 [PMID: 25990308 DOI: 10.1038/ncomms8151]
62 Liu P, Xia L, Zhang WL, Ke HJ, Su T, Deng LB, Chen YX, Lv NH. Identification of serum microRNAs as diagnostic and prognostic biomarkers for acute pancreatitis. *Pancreatology* 2014; 14: 159-166 [PMID: 24854610 DOI: 10.1016/j.pan.2014.03.019]
63 An F, Zhan Q, Xia M, Jiang L, Lu G, Huang M, Guo J, Liu S. From moderately severe to severe hypertriglyceridemia induced acute pancreatitis:

名词解释

miRNAs: 是一类约为19-24个核苷酸的内源性非编码单链RNA, 由70-90个碱基大小的单链前体pre-miRNA, 经Dicer加工产生为成熟miRNA, 诱导靶mRNA的翻译抑制或剪切降解.

同行评价
作者总结近年来AP与miRNA的基础与临床研究结果, 对深入研究AP的发病机制具有一定指导作用, 并有助于推动miRNA作为该疾病生物标志物的研究, 具有良好的科学意义和学术价值.

circulating miRNAs play role as potential biomarkers. *PLoS One* 2014; 9: e111058 [PMID: 25365448 DOI: 10.1371/journal.pone.0111058]
64 Kuśnierz-Cabala B, Nowak E, Sporek M, Kowalik A, Kuźniewski M, Enguita FJ, Stępień E. Serum levels of unique miR-551-5p and endothelial-specific miR-126a-5p allow discrimination of patients in the early phase of acute pancreatitis. *Pancreatology* 2015; 15: 344-351 [PMID: 26094040 DOI: 10.1016/j.pan.2015.05.475]

编辑: 郭鹏 电编: 闫晋利

ISSN 1009-3079 (print) ISSN 2219-2859 (online) DOI: 10.11569

• 消息 •

《世界华人消化杂志》修回稿须知

本刊讯 为了保证作者来稿及时发表, 同时保护作者与《世界华人消化杂志》的合法权益, 本刊对修回稿要求如下.

1 修回稿信件

来稿包括所有作者签名的作者投稿函. 内容包括: (1)保证无重复发表或一稿多投; (2)是否有经济利益或其他关系造成的利益冲突; (3)所有作者均审读过该文并同意发表, 所有作者均符合作者条件, 所有作者均同意该文代表其真实研究成果, 保证文责自负; (4)列出通讯作者的姓名、地址、电话、传真和电子邮件; 通讯作者应负责与其他作者联系, 修改并最终审核复核稿; (5)列出作者贡献分布; (6)来稿应附有作者工作单位的推荐信, 保证无泄密, 如果是几个单位合作的论文, 则需要提供所有参与单位的推荐信; (7)愿将印刷版和电子版出版权转让给本刊编辑部.

2 稿件修改

来稿经同行专家审查后, 认为内容需要修改、补充或删节时, 本刊编辑部将把原稿连同审稿意见、编辑意见发给作者修改, 而作者必须于15天内将单位介绍信、作者复核要点承诺书、版权转让信等书面材料电子版发回编辑部, 同时将修改后的电子稿件上传至在线办公系统; 逾期发回的, 作重新投稿处理.

3 版权

本论文发表后作者享有非专有权, 文责由作者自负. 作者可在本单位或本人著作集中汇编出版以及用于宣讲和交流, 但应注明发表于《世界华人消化杂志》××年; 卷(期): 起止页码. 如有国内外其他单位和个人复制、翻译出版等商业活动, 须征得《世界华人消化杂志》编辑部书面同意, 其编辑版权属本刊所有. 编辑部可将文章在《中国学术期刊光盘版》等媒体上长期发布; 作者允许该文章被美国《化学文摘》、《荷兰医学文摘库/医学文摘》、俄罗斯《文摘杂志》等国外相关文摘与检索系统收录.