循环miR-155作为肿瘤生物标志物的研究进展

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摘要 microRNAs(miRNAs)是一类在转录后水平影响生物体基因表达的小分子非编码RNA, 参与调控机体正常发育和疾病发生发展等过程。新近研究发现, 循环miRNA由于具有取样方便和高度稳定性等优点, 迅速成为目前的研究热点。microRNA-155(miR-155)在多种肿瘤中高表达。循环miR-155已被证实与多种肿瘤的发生、发展相关, 可作为一种分子标志物用于肿瘤的早期诊断和实时监测。该文围绕循环miR-155作为肿瘤标志物的研究进展予以综述。

关键词 循环miR-155; 肿瘤; 生物标志物

Recent Advances in Circulating miR-155 As Tumor Biomarker

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Abstract microRNAs (miRNAs) are a class of small non-coding RNAs that regulate gene expression through modulation of post-transcriptional activity. miRNAs have been shown to participate in the regulation of normal cellular function as well as disease development. Circulating miRNAs possess many advantages, including easy sampling and stability. miR-155 is highly expressed in various tumors, and the circulating miR-155 is aberrantly present during the tumor genesis and development. Studies have shown that circulating miR-155 could be used as a tumor marker for early diagnosis and real-time monitoring of tumors. This review discribed the recent progress of circulating miR-155 as tumor biomarker.

Keywords circulating miR-155; tumor; biomarker

microRNAs(miRNAs)是一类长度约21~23个碱基的非编码单链小分子RNA, 能通过碱基互补配对方式识别和结合特定的mRNA来降解或干扰其翻译, 在转录后水平对相关基因的表达起负调控作用[1-2]。早期研究发现, miR-155作为癌基因参与对血液恶性肿瘤的调控[3]。随后的研究发现, miR-155在多种实体瘤内高表达, 参与对细胞的增殖、分化、凋亡等功能的调控[4]。关于miR-155与肿瘤发生、发展的关系及其调控机制已成为目前的研究热点。

病理诊断是肿瘤确诊和治疗方案制定的金标准, 且对制定合适的治疗方案起着重要作用。目前用于病理诊断的组织主要来源于穿刺活检或手术切除样本, 穿刺活检常存在取样困难、可引起创伤、操作可重复性低等缺点。因此, 寻找一种可用于肿瘤早期诊断与预后判断的无创、非侵入性检测技术具有重要意义。最新研究发现, 人类外周血中存在一些来源于肿瘤细胞和血细胞的循环miRNA(circulating miRNA)。这些循环miRNA具有高度稳定性, 能够抵抗RNA酶消化、酸碱处理和反复冻融。在肿瘤患者血液中存在特异性的表达谱[5-6]。目前认为, 循环miRNA主要存在于外泌体(exosome)及微囊泡(microvesicles)内, 此外, 还能与

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基因沉默蛋白Ago2(Argonaute 2)及高密度脂蛋白(high-density lipoprotein, HDL)形成复合物而稳定存在于外周血[7-9]。随后研究表明, 循环miRNA在免疫反应、血管生成、细胞增殖、肿瘤细胞浸润等方面发挥重要作用[10]。Yoon等[11]的研究发现, EB病毒(epstein-barr virus, EBV)阳性的B淋巴瘤细胞Raji分泌的外泌体中包含有miR-155和miR-9, 他们将该外泌体与人视网膜色素上皮细胞(retinal pigment epithelial cell, RPE)ARPE-19共培养16 h, 检测发现, ARPE-19细胞中miR-155及miR-9水平显著升高。相反, 加入内吞抑制剂叠氮钠后miR-155及miR-9水平显著降低。此外, 在共培养ARPE-19细胞中, miR-155水平升高能影响希佩尔林道(von Hippel-Lindau, VHL)/低氧诱导因子-1(hypoxia inducible factor-1, HIF-1)信号通路, 促进血管内皮生长因子(vascular endothelial growth factor, VEGF)表达。这提示, 受体细胞可通过内吞或胞膜融合摄取外泌体, 而在这一过程中miRNA也同时进入受体细胞并可作为内源性因子参与靶基因调节或影响相关信号通路。由于循环miRNA取样方便, 并具有组织特异性和高灵敏性等优点, 已成为目前的研究热点。2008年, Lawrie等[12]首次在弥漫性大B细胞淋巴瘤(diffuse large B-cell lymphoma, DLBCL)患者血清中检测到miR-155, 发现DLBCL患者血清中, miR-155水平显著高于对照组, 提示血清miR-155有可能作为DLBCL的生物标志物。随着研究的深入, 在循环miR-155与肿瘤发生、发展的相关性被揭示的同时, 也发现其在肿瘤早期诊断、实时监测、个体化治疗方案的制定及预后判断中具有重要的意义。本文围绕循环miR-155在肿瘤发生、发展中的作用及其可能的应用价值予以综述。

1 miR-155的生物学特征与功能

miR-155的序列为5′-UUA AUG CUA AUC GUG AUA GGG G-3′, 是位于21号染色体的癌基因*BIC/MIR155HG*的转录产物。miR-155不仅参与炎症反应和免疫反应等多种生物学过程[13-17], 还参与对造血干细胞和B淋巴细胞分化的调节[18]。研究发现, miR-155不仅可作为癌基因参与肺癌[19]、乳腺癌[20-24]、胃癌[25]、肾癌[26]、口腔鳞状细胞癌[27-28]、胰腺癌[29-32]、结直肠癌[33-35] 、淋巴瘤[36-37]和白血病[38-39]等恶性肿瘤的发生、发展, 还与心血管疾病[40-43]密切相关(图1)。miR-155的靶mRNA包括程序性细胞凋亡因子4(programmed cell death 4, *PDCD4*)、肿瘤蛋白p53诱导核蛋白1(tumor protein p53-inducible nuclear protein 1, *TP53INP1*)、叉头框蛋白O3a(forkhead box protein O3a, *FOXO3a*)、母亲DPP同源物4(mothers against decapentaplegic 4, *SMAD4*)、母亲DPP同源物5(mothers against decapentaplegic 5, *SMAD5*)、细胞因子信号传导抑制蛋白1(suppressors of cytokine signaling 1, *SOCS1*)的转录产物等; miR-155通过与这些靶mRNA相结合, 影响c-Jun端激酶2(c-Jun

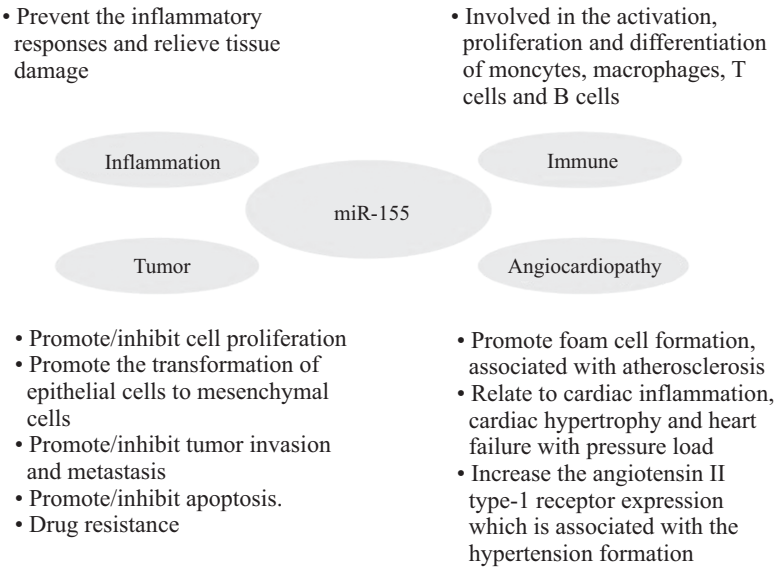

图1 miR-155的生物学特征与功能

Fig.1 Biological characteristics and functions of miR-155

N-terminal kinase 2, JNK2)/信号转导与转录活化因3(signal transducters and activators of transcription 3, STAT3)、磷脂酰肌醇-3-激酶(phosphatidylinositol-3-kinase, PI3K)/丝氨酸/苏氨酸激酶(serine/threonine kinase, AKT)、转化生长因子-β(transforming grow factor-β, TGF-β)/SMAD等信号转导通路, 抑制细胞凋亡、促进细胞增殖及转移, 进而导致肿瘤的发生[22,29,34,44-48]。此外, 有研究显示, miR-155在胃癌[49]、黑色素瘤[50]及卵巢癌[51]等恶性肿瘤中发挥抑癌基因的作用, 通过与细胞周期蛋白D1(cyclin D1)、*SKI*、闭合蛋白1(claudin 1, *CLDN1)*等的靶mRNA相互作用, 抑制细胞增殖、转移, 促进细胞凋亡。

2　循环miR-155与肿瘤

2.1　循环miR-155与血液系统恶性肿瘤

Lawrie等[12]首次对循环miRNA与DLBCL的关系进行了研究, 用RT-qPCR检测了60例DLBCL患者和40例健康人的血清中与肿瘤高度相关的miR-21、miR-155和miR-210, 结果发现, 这3种miRNA水平均显著高于健康人, 且miR-21高表达的DLBCL患者无复发生存期(relapse-free survival, RFS)明显短于miR-21低表达的DLBCL患者。这提示, 循环miRNA如miR-155有可能作为DLBCL的非侵入性诊断标志物。Fang等[52]为深入研究血清miRNA在DLBCL早期诊断中的应用价值, 检测了75例DLBCL患者及77例健康人的血清样本中与淋巴瘤相关的miR-15a、miR-16-1、miR-21, miR-29c、miR-34a和miR-155水平。结果发现, DLBCL患者血清中miR-15a、miR-16-1、miR-21、miR-29c和miR-155的水平明显高于健康人群, 而DLBCL患者血清miR-34a水平低于健康人群。血清miR-155用于诊断DLBCL的受试者工作特征曲线下面积(area under the received operating characteristic curve, AUC)为0.715, 灵敏度为83%, 特异性为65%。这些结果表明, 血清miR-155有潜力作为DLBCL早期诊断新指标。Zhi等[53]研究了循环miRNA与急性白血病发生、发展的关系, 他们用Solexa测序和TaqMan RT-qPCR技术分析了140例急性白血病患者和135例健康人血清, 发现急性白血病患者血清中, miR-10a-5p、miR-93-5p、miR-129-5p、miR-155-5p、miR-181b-5p和miR-320d水平显著高于健康人, 且这6种miRNA能特异性地区分急性白血病患者和健康人。因此他们认为, 循环miRNA有望成为急性白血病早期诊断标志物。综上所述, 循环miR-155可作为血液恶性肿瘤的辅助诊断、疗效监测及预后判断的标志物之一。

2.2　循环miR-155与肺癌

Sanfiorenzo等[54]为研究循环miRNA在非小细胞肺癌(non-small cell lung cancer, NSCLC)早期诊断及预后判断中的作用, 用RT-qPCR对52例I~III A期非小细胞肺癌患者血浆中17种与肿瘤高度相关的miRNA进行了分析。结果发现, 在NSCLC患者血浆中, miR-155-5p、miR-20a-5p、miR-25-3p、miR-296-5p、miR-223-3p、miR-320-3p和miR-191-5p水平显著性升高; 而miR-152-3p、let-7f-5p、miR-24-3p、miR-145-5p、miR-126-3p及miR-199a-5p水平降低; 未在NSCLC患者与健康人血浆中检测到miR-96-5p、miR-129-5p、miR-373-5p及miR-516-5p; miR-155-5p、miR-20a-5p、miR-25-3p、miR-296-5p、let-7f-5p、miR-126-3p、miR-223-3p、miR-152-3p、miR-145-5p、miR-199a-5p及miR-24-3p能够显著区分NSCLC患者与健康人。其联合应用于诊断NSCLC的AUC为0.879, 灵敏度为85%, 特异性为82.9%, 诊断准确性明显高于外周血中用于肺癌常规检测的细胞角蛋白19片段(CYFRA 21-1)、组织多肽特异性抗原(tissue polypeptide specific antigen, TPS)和血癌胚抗原(cancer embryo antigen, CEA)等肿瘤标志物。此外, 他们进一步研究表明, 这11种血浆miRNA用于诊断肺鳞癌的灵敏度(91.3%)显著高于肺腺癌(85.7%)。这些结果表明了上述11种miRNA表达谱在早期筛查NSCLC的临床意义。最后, 他们深入调查了血浆miRNA水平与NSCLC患者无病生存期(disease-free survival, DFS)的关系, 发现血浆中miR-155-5p水平高的NSCLC患者的DFS显著短于miR-155-5p水平低的NSCLC患者。因此他们认为, miR-155-5p与NSCLC患者预后密切相关。Gao等[55]进一步探索了血清miR-155作为肿瘤标志物用于肺腺癌早期诊断的可能性, 分析了36例肺腺癌患者(以32例健康人为对照)血清miR-155、CEA和CA-125水平的诊断价值。结果显示, 血清miR-155、CEA和CA-125用于诊断肺腺癌灵敏度及特异性分别为72.2%和68.7%、58.3%和81.2%、66.7%和90.6%。因此, 血清miR-155诊断肺腺癌灵敏度最高, 而CA-125诊断肺腺癌特异性最高; 当三者联合用于肺腺癌诊断时, 灵敏度和特异性分别为91.6%和65.6%。这些结

果提示, 循环miR-155联合其他肿瘤抗原可作为肺腺癌的早期诊断标志物。Xu等[56]为研究血清中与炎症高度相关的miR-155、miR-221和miR-21与NSCLC患者放射性食管炎之间的相关性, 用RT-qPCR检测102例NSCLC患者血清中3种miRNA的水平, 发现放疗2周内发生放射性食管炎的NSCLC患者血清中3种miRNA水平显著高于无发生放射性食管炎的NSCLC患者。这提示, 上述3种miRNA的表达与放射性食管炎发生密切相关并可作为放疗早期毒性反应监测指标。上述研究结果表明, 循环miR-155可以作为肺癌初步诊断指标, 用于辅助诊断、早期毒性反应监测和预后评估。

2.3 循环miR-155与乳腺癌

循环miR-155用于乳腺癌早期诊断及预后评估也已得到证实。Sun等[57]检测103例乳腺癌患者血清中miR-155水平, 发现乳腺癌患者血清miR-155水平显著高于健康人。其诊断乳腺癌的准确性为80.1%, 灵敏度和特异性分别为65%和81.8%; 并且乳腺癌患者术后血清miR-155的水平显著性低于术前。这些结果提示, miR-155不仅可用于乳腺癌早期诊断, 还可作为手术清除率的辅助标志物。Liu等[58]探讨了循环miRNA是否可作为乳腺癌早期诊断标志物, 并分析其与乳腺癌病理特点的关系及初步探索其生物学功能。研究结果显示, 乳腺癌患者血清miR-155水平显著高于健康人。此外, miR-155水平由高到低依次为三阴性型(ER、PR和HER-2均阴性)>HER-2过表达型(ER和PR阴性、HER-2阳性)>luminal B型(ER阳性和/或PR阳性、HER-2阳性)>luminal A型(ER阳性和/或PR阳性、HER-2阴性)。Sorlie等[59]研究表明, 乳腺癌病理分型与乳腺癌患者预后密切相关, 其中三阴性及HER-2过表达型预后最差, 而luminal A预后最好。因此他们认为, miR-155与乳腺癌分子病理分型及预后评估密切相关。上述研究表明, 循环miR-155可作为肿瘤标志物用于乳腺癌的早期诊断、手术疗效监测和预后判断。

2.4 循环miR-155与胰腺癌

近年来, 循环miR-155与胰腺癌关系的研究也取得一系列进展。Liu等[60]研究了循环miRNA在胰腺癌早期诊断中的意义, 用RT-qPCR检测了140例胰腺癌患者、111例慢性胰腺炎患者和68例健康人血清中与胰腺癌发病高度相关的7种miRNA(miR-16、miR-21、miR-155、miR-181a、miR-181b、miR-196a和miR-210)水平。结果发现, 这7种miRNA在胰腺癌患者血清中水平显著高于慢性胰腺炎患者和健康人群。其中, miR-196a用于胰腺癌诊断准确度最高为81.6%, miR-155诊断胰腺癌的准确度为70.4%。因此他们认为, 这7种血清miRNA均可作为肿瘤标志物用于胰腺癌早期辅助诊断。

2.5 循环miR-155与结直肠癌

结直肠癌是我国常见恶性肿瘤, 世界卫生组织国际癌症研究中心(International Agency for Researchon Cancer, IARC)数据表明, 2012年全世界结直肠癌新发病例约136万, 居恶性肿瘤第3位; 死亡病例约69万, 居恶性肿瘤第4位。因此, 找寻有效肿瘤标志物对提高结直肠癌早期诊断及预后评估十分必要。Lü等[61]检测了146例结直肠癌患者和60例健康人血清中miR-155的水平, 结果发现, 结直肠癌患者血清miR-155水平显著高于健康人; 血清miR-155诊断结直肠癌的AUC为0.776, 灵敏度和特异度分别为58.2%和95%。此外, 他们还分析了血清miR-155水平与临床病理学特征的关系, 结果表明, I期结直肠患者血清中miR-155水平显著性低于II~IV期结直肠癌患者; 而且, 血清miR-155水平高的结直肠患者肿瘤分化程度低及转移能力强。最后, 他们进一步对结直肠癌患者进行生存分析, 发现血清miR-155水平高的结直肠癌患者总体生存率(overall survival, OS)及无进展生存率(progression-free survival, PFS)明显低于miR-155水平低的结直肠癌患者。因此, 他们认为, 血清miR-155不仅可用于结直肠癌早期诊断, 还可作为结直肠癌分期及预后评估的有效指标。

2.6 循环miR-155与食管癌

Liu等[62]用miRNAs芯片和RT-qPCR检测食管癌组织和血浆中miR-155水平, 发现食管癌组织中miR-155水平显著性升高, 然而血浆miR-155的水平却显著性下调。有研究表明, 某些miRNA在肿瘤组织和血清中的水平存在不一致的现象, 如miR-122在肝细胞癌组织中的水平较高, 而在肝细胞癌患者血清中的水平较低[63]。这与此前Lodes等的研究结果一致[64]。Lodes等[64]用miRNA基因芯片技术检测了前列腺癌、结肠癌、卵巢癌、乳腺癌和肺癌患者组织和对应血清, 结果发现, 肿瘤组织和血清中miRNA的表达谱并没有直接对应关系, 他们推测可能是循环miRNA的来源不同于组织miRNA。此外, 他们还发现, 如果病人具有吸烟和饮酒等习惯, 同时存在血浆中miR-

表1　循环miR-155在肿瘤诊断中的临床意义

Table 1　Clinical significance of circulating miR-155 in tumor diagnosis

疾病 Disease	方法 Assay	循环miR-155水平 Circulating miR-155 level	临床意义 Clinical significance	参考文献 References
Diffuse large B-cell lymphoma	RT-qPCR	↑	Early diagnosis	[13,53]
Acute leukemia	Solexa RT-qPCR	↑	Early diagnosis	[54]
Lung cancer	RT-qPCR	↑	Early diagnosis, DFS, early monitoring of radiation esophagitis	[55-57]
Breast cancer	RT-qPCR	↑	Early diagnosis, pathological typing	[58-60]
Pancreatic cancer	RT-qPCR	↑	Early diagnosis	[61]
Colorectal cancer	RT-qPCR	↑	Early diagnosis, clinical staging, prognosis	[62]
Esophagus cancer	RT-qPCR miRNAs Chip	↓	Early diagnosis	[63]
Thyroid carcinoma	RT-qPCR	↑	Early diagnosis	[66]
Endometrial carcinoma	RT-qPCR	↑	Early diagnosis, clinical staging, involved in migration	[67]
Malignant melanoma	RT-qPCR	↑	Involved in migration	[68]

155低表达, 此类病人是食管癌发病的高危患者。这些研究结果表明, 循环miR-155的临床意义尚需进一步研究。对于血清miRNA在凝血过程中是否存在降解, 血清与血浆RNA哪一个更能反映疾病状态, 目前尚无明确答案。

2.7　循环miR-155与其他肿瘤

除上述肿瘤外, 循环miR-155还与甲状腺癌[65]、子宫内膜癌[66]和恶性黑色素瘤[67]的发生、发展密切相关(表1)。Lee等[65]对19例甲状腺良性结节患者和70例甲状腺乳头状癌患者血浆进行研究, 发现甲状腺乳头状癌患者血浆中miR-155的水平显著高于甲状腺良性结节患者; miR-155在甲状腺乳头状癌患者和甲状腺良性结节患者中鉴别诊断中的准确性为69.5%、灵敏度和特异性分别为74.3%和63.2%; 此外还发现, 血浆中miR-155水平与肿瘤直径呈正相关。因此他们提出, 血浆miR-155可作为一项早期诊断甲状腺癌的新指标。Tan等[66]研究了miR-155在子宫内膜癌患者血清中的水平及其临床意义。他们用RT-qPCR检测44例子宫内膜癌患者血清, 结果发现, III~IV期子宫内膜癌患者血清miR-155水平显著高于I~II期子宫内膜癌患者。此外, 有盆腔淋巴结转移的子宫内膜癌患者血清miR-155水平显著高于无转移的患者。这些结果表明, 血清中miR-155与子宫内膜癌分期及转移密切相关, 其有望作为子宫内膜癌病情进展的生物标志物。

3　结语

由于循环miRNA的检测不仅具有组织miRNA用于患者病情诊断和评估的特点, 还具有创伤小、取样方便和可重复操作等优点。因此, 近几年关于循环miRNA的研究突飞猛进。虽然在多种肿瘤中已经发现, 循环miR-155的异常表达, 并能作为一种潜在的肿瘤标志物, 然而由于单一循环miR-155诊断肿瘤特异性和敏感性不高, 目前用于临床仍存在一定问题。首先, 缺乏用于获取及保存血液标本的统一参考标准; 其次, 无规范的检测方法和无明确的表达谱用于联合检测肿瘤的发生、发展。随着对miR-155的深入研究, 科学家们将克服这些困难, 最终将使循环miR-155的检测技术成熟并成为肿瘤早期诊断、个体化治疗方案制定及预后评估的指标之一。

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