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· 文献综述 ·

循环游离DNA在甲状腺癌诊疗中的应用

李宁^{1,2}, 朱春悦^{2,3}, 洪方成², 冯哲明^{1,2}, 郑玉鑫^{2,3}, 张风华²

(1.河北医科大学 研究生学院, 河北 石家庄 050051; 2.河北省人民医院 腺体外科, 河北 石家庄 050051; 3.华北理工大学 研究生学院, 河北 石家庄 050051)

摘要

甲状腺癌是最常见的内分泌肿瘤。近年,随着世界范围内疾病筛查力度加强及生活方式变化,甲状腺癌发病率呈逐年上升趋势。目前甲状腺癌的诊疗结果监测主要依赖于侵入性组织活检或涉及辐射暴露的重复成像,虽大部分甲状腺癌患者预后较好,但在发生广泛转移时复发及病死率较高。因此,建立一种无创、简便易重复的检测技术应用于甲状腺癌的早期诊断及复发监测等方面显得尤为重要。液体活检是一种非侵入性检测技术,可从患者的血液、尿液等体液中提取循环肿瘤细胞(CTC)、循环游离DNA(cfDNA)、miRNA等生物样本进行分析,以获得有价值的生物信息,使临床医生能够反复多次地对患者肿瘤情况进行动态了解,达到精准诊疗的目的,其中cfDNA检测技术最为重要。cfDNA是一种存在于动、植物和人的体液中的无细胞状态的胞外DNA,对血液中cfDNA进行定量分析、完整性检测、特定基因突变及基因甲基化分析可在恶性肿瘤的早期诊断、预测转移、复发及监测疗效等方面发挥作用。因其具有无创性与较高的特异度及灵敏度,逐渐成为了癌症诊疗研究中的一大热点,但其产生的机制至今仍不明确。近年来,评估cfDNA检测在甲状腺癌中作用的相关文献有所增加,进一步表明cfDNA检测技术可在甲状腺癌的诊治及疾病监测方面发挥重要作用,成为克服甲状腺癌常规检查及监测方法局限性的一种有价值的工具。笔者就cfDNA在甲状腺癌诊疗中的最新研究进展作一综述。

关键词

甲状腺肿瘤/诊断; 游离核酸; 液体活组织检查; 综述
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Application of circulating free DNA in diagnosis and treatment of thyroid cancer

LI Ning^{1,2}, ZHU Chunyue^{2,3}, HONG Fangcheng², FENG Zheming^{1,2}, ZHENG Yuxin^{2,3}, ZHANG Fenghua²

(1. Graduate School, Hebei Medicine University, Shijiazhuang 050051, China; 2. Department of Gland Surgery, Hebei General Hospital, Shijiazhuang 050051, China; 3. Graduate School, North China University of Science and Technology, Shijiazhuang 050051, China)

Abstract

Thyroid cancer (TC) is the most common endocrine tumor. In recent years, with the population-based disease screening programs worldwide and the lifestyle changes, the incidence rate of thyroid cancer keeps rising. At present, the monitoring of diagnosis and treatment results of thyroid cancer mainly depends on invasive tissue biopsy or repeated imaging procedures with radiation exposure. Although the

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作者简介: 李宁, 河北医科大学研究生学院/河北省人民医院硕士研究生, 主要从事甲状腺癌基础方面的研究。

通信作者: 张风华, Email: z139338@126.com

prognosis of most thyroid cancer patients is favorable, the recurrence and mortality rates are relatively high when extensive metastasis occurs. Therefore, developing a non-invasive, simple and repeatable detection technique in the early diagnosis and recurrence monitoring of thyroid cancer is particularly important. Liquid biopsy is a non-invasive testing procedure that can extract circulating tumor cells (CTC), circulating free DNA (cfDNA), microRNAs (miRNAs) and other biological samples from patients' blood, urine and other body fluids for analysis to obtain valuable biological information for tumor diagnosis and treatment, by which the clinicians can repeatedly and dynamically analyze the development of the patients'tumor, so as to achieve the purpose of accurate medical treatment. Among them, the cfDNA detection technique is the most important. It is a kind of acellular extracellular DNA existing in the body fluids of animals, plants and humans. Through the quantitative analysis, integrity detection, specific gene mutation and gene methylation analysis of cfDNA in blood, it plays a role in the early diagnosis, prediction of metastasis, recurrence and treatment effect monitoring of malignant tumors. Because of its non-invasive, high specificity and sensitivity, it has gradually become a hot spot in the research of cancer diagnosis and treatment, and its mechanism is still not fully understood so far. In recent years, the relevant literature evaluating the role of cfDNA detection in thyroid cancer has increased, which further shows that cfDNA detection technique can play an important role in the diagnosis, treatment and disease monitoring of thyroid cancer, and become a valuable tool to overcome the limitations of routine examination and monitoring methods of thyroid cancer. Therefore, cfDNA may become a new molecular marker to judge the effect of diagnosis and treatment of thyroid cancer. Here, the authors review the latest research progress of cfDNA in the diagnosis and treatment of thyroid cancer.

Key words

Thyroid Neoplasms/diag; Cell-Free Nucleic Acids; Liquid Biopsy; Review

CLC number: R736.1

甲状腺癌是最常见的内分泌癌类型, 约占肿瘤总数的2%^[1]。在过去的30年里, 甲状腺癌发病率在全世界范围内呈上升趋势, 在中国, 甲状腺癌已跃升至女性恶性肿瘤的第3位, 且发病出现年轻化趋势, 已成为我国30岁以下女性增长最快的恶性肿瘤^[2]。目前甲状腺癌诊断主要依靠甲状腺超声及细针穿刺(fine needle aspiration, FNA), 但是由于肿瘤的异质性, 使用FNA评估的甲状腺结节中有15%~30%无法鉴别良恶性^[3]。在甲状腺癌的复发检测方面, 目前依赖于颈部的超声等影像学检查和连续的甲状腺球蛋白(thyroglobulin, Tg)测量, 然而Tg具有器官特异度, 但不具有肿瘤特异度, 在有残留甲状腺组织的治愈患者中仍然可以检测到, 同时部分患者体内存在甲状腺球蛋白抗体干扰Tg水平的测量, 这些因素都会对甲状腺癌复发的监测造成阻碍。循环游离DNA(circulating free DNA, cfDNA)是肿瘤细胞通过坏死或凋亡过程释放的胞外核酸片段^[4], 携带有肿

瘤组织基因, 作为液体活组织检查的主要组成部分cfDNA检测技术显示了无创、快速、易于重复的优点, 是肿瘤遗传和表观遗传学改变的实时代表^[5]。近几年循环中高水平的cfDNA被发现与癌症的诊断和进展有关, 并显示出作为癌症反应生物标志物的潜在特征^[6], 在癌症的诊治和预测转移等方面发挥作用。下面将围绕cfDNA在甲状腺癌早期诊断、转移、预后等方面的应用展开阐述。

1 cfDNA在甲状腺癌早期诊断中的应用

cfDNA已被证明在乳腺癌、胰腺癌、结直肠癌等多种癌症的诊断中具有重要的临床应用价值^[7-11], 在甲状腺癌中可通过评估cfDNA的定量分析、完整性、突变基因及甲基化水平协助甲状腺癌的早期诊断^[12], 这为甲状腺癌的早期诊断提供了一种新的检测指标。

1.1 cfDNA定量分析及完整性检测在甲状腺癌早期诊断中的应用

循环游离DNA完整性 (circulating free DNA integrity, cfDI) 是指血浆或血清中较长的DNA片段与较短片段的浓度之比。在细胞凋亡过程中, 正常细胞会在血液中释放大约180~200 bp小而均匀DNA片段, 而肿瘤细胞会释放出较长且不均匀的DNA片段, 导致癌症患者的cfDI提高^[13]。cfDI已被证实在区分肝脏、乳腺以及肾脏结节良恶性方面发挥有效作用, 成为癌症诊断和预后的一个有前途的生物标志物^[14-16]。Salvianti等^[17]通过基于定量2个不同长度的扩增子 (分别为67和180 bp) 来评估cfDI (180/67) 在甲状腺癌患者与良性甲状腺结节患者两者之间的差异, 发现甲状腺癌患者较良性结节患者及健康人cfDI更高, 这一发现支持cfDI可能成为甲状腺结节早期鉴别诊断的一个标志物。

绝大多数cfDNA是由非肿瘤细胞释放的, 由肿瘤细胞凋亡或坏死后释放的一小部分cfDNA被称为循环肿瘤DNA (circulation tumor DNA, ctDNA)^[18]。ctDNA分为核DNA和线粒体DNA (mitochondrial DNA, mtDNA)。近年来大部分研究都集中在核DNA, 近年提出mtDNA可区分良恶性肿瘤, 也可能为癌症诊断和预后提供重要信息^[19-20]。最近一项研究^[21]使用定量荧光PCR技术分析了甲状腺癌、结节性甲状腺肿患者和正常人血液中mtDNA的水平, 发现在甲状腺癌患者血浆中mtDNA的完整性比值明显增高, 但是甲状腺癌细胞释放完整mtDNA的机制尚需要进一步研究。

此外, 多项研究^[17, 21-24]通过对cfDNA定量分析发现, 甲状腺癌中cfDNA浓度水平较甲状腺良性疾病及健康者明显增高, 表明cfDNA的定量分析可成为甲状腺癌早期诊断的潜在指标。对于细针穿刺结果性质不明的甲状腺结节, 可通过cfDNA定量检测进一步鉴别良恶性结节, 诊断甲状腺恶性结节的敏感度为100%, 特异度为92.3%^[23]。亦可在常规参数如降钙素 (calcitonin, CT) 无法应用时, 作为甲状腺髓样癌 (medullary thyroid carcinoma, MTC) 的诊断指标^[25]。

1.2 cfDNA基因突变分析在甲状腺癌早期诊断中的应用

有研究^[22]对甲状腺癌患者、良性甲状腺疾病患者及健康者进行cfDNA中特定基因的检测, 对比

结果发现, BRAFV600E基线水平在甲状腺癌患者体内的百分比明显增高。Cradic等^[26]采集173例甲状腺乳头状癌 (papillary thyroid carcinoma, PTC) 患者及20例非PTC患者血液行BRAF1799A检测, 发现该基因突变在PTC患者中检出率是11.6%, 而在非PTC患者的血液及石蜡包块样本中均为未发现该基因突变, 由此可见BRAF1799A的检测可能在甲状腺癌诊断中发挥作用, 但需进一步研究证实。

1.3 cfDNA基因甲基化水平检测在甲状腺癌早期诊断中的应用

除了cfDNA基因突变外, 血清DNA甲基化评估作为一种新的甲状腺癌诊断工具于2006年被提出^[27]。如TIMP3、DAPK等肿瘤抑制基因启动子区域的异常甲基化使基因处于失活状态, 进而导致甲状腺癌的发生^[28]。目前关于甲状腺癌早期筛查常用的异常甲基化状态的基因有RASSF1^[29]; Calca、Cdh1、TIMP3、DAPK、RAR β ^[27]; SLC5A8、SLC26A4^[30]。近几年提出甲基转移酶甲基化状态在甲状腺癌早期诊断中也发挥着重要作用, 循环中DNA甲基转移酶基因 (MGMT和DNMT1) 启动子区域甲基化状态在甲状腺癌的早期诊断中有较高的灵敏度及特异度^[30]。

2 cfDNA在预测甲状腺癌转移中的应用

甲状腺癌切除术术前主要依靠影像学以及细针穿刺活检来评估甲状腺癌转移情况, 然而有些转移灶单纯依靠术前影像学检测很难发现。cfDNA检测在预测局部晚期或转移性甲状腺癌中具有一定作用, 可以弥补传统检测方法的不足。

PTC中BRAFV600E突变的全球发生率约为45%^[31], 在中国更高达85%^[32]。在PTC患者中BRAFV600E的表达与预后不良相关^[33], 建议对携带该基因突变的患者进行积极干预和规律随访, 以防止肿瘤复发。研究^[34-40]发现, 血液循环中BRAFV600E突变与甲状腺癌的腺体外侵犯、转移以及肿瘤较强的侵袭性有关。BRAFV600E突变亦是甲状腺癌发生对侧淋巴结转移的一个重要危险因素, 且与甲状腺癌较高侵袭性和转移性相关^[41]。有研究^[35]表明, NRAS基因突变在cfDNA中的敏感度为50.00%, 特异度为98.18%, 但其在肿瘤中的低频率限制了其独立应用, 可采用NRAS突变与血浆

BRAFV600E检测联合的方法监测甲状腺癌转移情况。

同样, cfDNA基因甲基化状态在甲状腺癌转移方面也具有一定的预测功能, 如: RAS结合域家族蛋白1 (RASSF1) 和钠转运体编码基因 (SLC5A5) 的甲基化水平与疾病侵袭性相关^[42]; SLC5A8基因通过促凋亡作用发挥抑癌功能, 其甲基化状态已在不同的癌症中观察到^[43], SLC5A8的高甲基化状态与甲状腺癌的分期、多灶性和腺体外侵犯呈正相关^[44]。基于对PTC患者血液中cfDNA定量检测分析发现, cfDNA的高检出率与肿瘤大小、远处转移及侵袭性密切相关^[45]。

3 cfDNA在预测甲状腺癌预后中的应用

ctDNA在预测甲状腺癌预后中的效果明显优于其他影像学检测和蛋白标志物检测。多项研究表明cfDNA中特定基因突变的检出率与甲状腺癌总生存率及不良预后有关, 如PIK3CA^[46]、BRAFV600E^[47-48]、RET^[49]。有研究^[47, 50]发现在转移性MTC患者中RET基因和BRAF基因突变更为常见, 可预测其不良预后。同时发现在分化型甲状腺癌 (differentiated thyroid carcinoma, DTC) 和间变型甲状腺癌 (anaplastic thyroid cancer, ATC) 患者中, 循环中NRAS和TP53突变的高表达状态会增加肿瘤进展的可能性^[47]。

目前对于甲状腺癌术后复发监测主要依靠影像学检查及常规生物学标志物的检测, 研究^[47]发现通过cfDNA检测技术可以更早发现常规影像学检测不到的微小残留病灶及复发迹象, 可成为一种重要的补充检测方法。通过对甲状腺癌患者中持续疾病状态 (persistent disease, PD) 及无疾病状态 (no evidence of disease, NED) 两类患者血浆中的cfDNA检测, 发现在PD患者中cfDNA百分比明显高于NED患者。与传统检测方法相比, cfDNA在检测疾病状态和肿瘤负担方面具有更高的敏感度和特异性^[45]。Patel等^[36]通过对甲状腺癌术前、术后血浆样本中BRAFV600E基因突变表达丰度差异的检测来判断微小病灶残留及预测甲状腺癌术后复发。此外有研究^[26, 39, 51]已证实BRAFT1799A突变与PTC的局部侵袭性、淋巴结转移和复发率有关, 这说明BRAFT1799A可能成为预测PTC预后的潜在标记物。

4 cfDNA在监测甲状腺癌治疗反应中的应用

当前甲状腺癌的治疗方式以手术和放疗为主, 靶向治疗逐步应用于晚期放射性碘难治性甲状腺癌患者的治疗, 提高其无进展生存期^[52]。在治疗期间, cfDNA液体活检技术可作为识别细胞分子特征的微创方法, 帮助预测疾病进展、纵向监测肿瘤细胞对治疗药物的反应、提供个性化治疗^[53]。而且, 治疗期间总cfDNA水平的变化在监测治疗反应及指导治疗方面的作用已在肝癌^[54]、黑色素瘤^[55]等多种癌症中得到证实。cfDNA水平较传统标志物在反馈治疗反应及疾病状态变化方面具有更高的灵敏度^[37]。通过检测循环中的BRAFV600E^[22]和RET^[804M]^[56]可筛选出可能导致治疗耐药的新突变基因, 动态观察治疗反应, 及时终止无效治疗, 针对性指导药物选择。

Salviant等^[17]对17例患者治疗前后血浆中cfDI水平进行对比, 发现无论是否进行放射性治疗, 治疗后的cfDI均低于治疗前, 这说明cfDI检测可能在监测治疗方面发挥作用, 但仍需要进一步的研究。

5 总结与展望

综上所述, cfDNA检测技术除具有简单、无创等优点外, 与传统标记物相比还具有更高的敏感度, 已在甲状腺癌的早期诊断、微小残留病灶、预后及治疗反应监测中显示其独特的优势。但血液样本的选择、cfDNA的检测方法等可能会导致cfDNA检测灵敏度及敏感度降低, 进而影响最终检测结果。因此, 还需继续深入了解cfDNA脱落机制以及开发更灵敏的检测方法并检验其在甲状腺癌的诊疗中的应用效果。

利益冲突: 所有作者均声明不存在利益冲突。

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