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· 文献综述 ·

分化型甲状腺癌颈部淋巴结转移相关分子的研究进展

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摘要

分化型甲状腺癌 (DTC) 呈惰性进展且预后良好, 但其易在早期即出现颈部淋巴结转移 (LNM), 与术后复发及不良预后密切相关。高分辨率超声、CT扫描、细针穿刺针吸活检是术前判断是否存在颈部LNM及转移范围的常用手段, 随着分子生物学技术的发展, DTC预后相关分子机制的研究取得了很大进步, 有望为术前精准评估颈部LNM、个体化制定手术方案、减少不必要的淋巴结清扫提供新的无创且准确的评价方式。在此, 笔者结合目前临床的研究总结并探讨分子标志物与DTC颈部LNM的关系及其在诊断和预后中的潜在价值。

关键词

甲状腺肿瘤; 淋巴转移; 颈, 生物标记; 综述

中图分类号: R736.1

Research progress of molecular signatures associated with cervical lymph node metastasis in differentiated thyroid carcinoma

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Abstract

Differentiated thyroid carcinoma (DTC) exhibits an indolent progression and a favorable prognosis, but it is prone to early cervical lymph node metastasis (LNM), which is closely associated with postoperative recurrence and poor prognosis. High-resolution ultrasound, CT scanning, and fine-needle aspiration biopsy are commonly used methods for preoperative assessment of the presence and extent of cervical LNM. With the development of molecular biology techniques, significant progress has been made in the understanding of molecular mechanisms related to the prognosis of DTC. It holds the promise of providing new non-invasive and accurate ways to preoperatively assess cervical LNM, individualize surgical plans, and reduce unnecessary lymph node dissection. Here, the authors, based on current clinical research, summarize and discuss the relationship between molecular biomarkers and cervical

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LNM in DTC, as well as their potential value in diagnosis and prognosis.

Key words

Thyroid Neoplasms; Lymphatic Metastasis; Neck, Biomarkers; Review

CLC number: R736.1

甲状腺癌是内分泌系统，也是头颈部最常见的恶性肿瘤，据统计^[1-2]2020年全球新发甲状腺癌58.6万例，占全球癌症诊断的3%，在女性恶性肿瘤中位列第四位，是近10年发病率增长最快的肿瘤。据美国SEER数据库^[3]统计，甲状腺乳头状癌（papillary thyroid carcinoma, PTC）占有甲状腺癌的89.1%；甲状腺滤泡癌（follicular thyroid carcinoma, FTC）和嗜酸细胞癌（oncocytic carcinoma, OCA）占7.9%；甲状腺髓样癌（medullary thyroid carcinoma, MTC）占1.8%；甲状腺未分化癌（anaplastic thyroid carcinoma, ATC）占1.0%；甲状腺岛状癌占0.2%，其中PTC和FTC统称为分化型甲状腺癌（differentiated thyroid carcinoma, DTC）。虽然DTC预后良好，5年生存率由2003年的67.5%提升至2015年的84.3%，部分发达欧美国家可达98%^[4-5]，但极易早期就出现颈部淋巴结转移（lymph node metastasis, LNM），15%~50%患者初诊时即出现颈部LNM^[6]，20%~69%可出现侧颈部LNM^[7]，LNM与较短的无病生存期存在显著关联，这可能会增加颈部复发风险从而影响预后^[8-9]。由此可见术前精准评估LNM在DTC临床诊治工作中的重要性。

分子标志物检测是近年进展迅速的一种诊断方式，有望成为影像学和病理学鉴别DTC侵袭性疾病特征如LNM的有力辅助手段。本文旨在总结并探讨各分子标志物检测在DTC术前预测颈部LNM中的应用价值，以期指导DTC患者颈部淋巴结清扫范围选择，避免过度手术或手术不足导致的医疗资源浪费或不必要的手术创伤。

1 DTC颈部LNM特点

DTC通常沿颈部淋巴引流途径呈逐站转移，最常发生于靠近甲状腺腺体的中央区淋巴结（VI区），而后经气管旁淋巴结引流，向上转移至颈静脉链淋巴结（II~IV区）及颈后三角区淋巴结（V区），向下转移至上纵隔淋巴结（VII区），以多区转移为主（占81.4%），仅单区转移较少见^[10]，部分可

出现跳跃性转移，即无中央区（VI区）转移，出现侧区（II~V区）转移，发生率约为1.6%~21.8%，年龄>45岁、肿瘤大小<5 mm、肿瘤位于甲状腺锥体叶或腺叶上极都是出现跳跃转移的危险因素^[11]。对于侧区淋巴结而言，一项囊括了18篇研究的Meta分析^[12]指出转移率由高至低分别为：III区（70.5%）>IV区（66.3%）>II区（53.4%）>V区（25.3%）>I区（3%）。Li等^[13]分析发现中央区LNM数量≥3枚以及II区LNM是V区LNM的独立危险因素，其中V区LNM以Vb区更多见，Song等^[14]对46例行治疗性侧颈清扫的PTC患者研究发现并无患者出现Va区的LNM。

2 DTC相关信号转导通路

甲状腺癌发病的分子机制主要与丝裂原活化蛋白激酶（mitogen-activated protein kinase, MAPK）和磷脂酰肌醇-3-激酶/蛋白激酶B（phosphatidylinositol-3-kinase/protein kinase B, PI3K/Akt）信号通路的失调有关，但其确切的进展机制仍未阐明（图1）。PTC常常携带激活MAPK，又称细胞外信号调节激酶（extracellular signal-regulated kinase, ERK）信号通路的遗传学变异，其中RET重排和NTRK1重排、BRAF突变、RAS突变在MAPK激活级联反应中连续发生，但PTC通常只包含上述单一驱动基因改变，仅约9%的PTC同时存在端粒酶逆转录酶基因（telomerase reverse transcriptase, TERT）启动子区突变和BRAF或RAS突变，这种PTC的侵袭性高于仅携带一种驱动基因改变的PTC^[15]。FTC多由PI3K/Akt信号通路转导的基因突变所致，包括PAX8/PPAR- γ -1重排以及HRAS、NRAS和KRAS原癌基因突变等，该通路的主要参与分子包括磷酸酶和张力蛋白同源物缺失（phosphatase and tensin homolog deleted on chromosome ten, PTEN）、PI3K、Akt和哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin, mTOR），PTEN是对抗Akt激活来抑制PI3K信号的关键负调节因子^[16]，mTOR是PI3K相关激酶蛋白家族的成员，参

与识别营养信号和调节细胞生长和增殖^[17]。生长因子和细胞因子等通过相应受体,激活 PI3K,或通过激活 RAS 激活 PI3K,进而活化 Akt 和 mTOR。mTOR 控制细胞内核糖体合成和 mRNA 的翻译,参与膜蛋白转运和蛋白质降解,进而调控细胞生长、增殖和代谢。

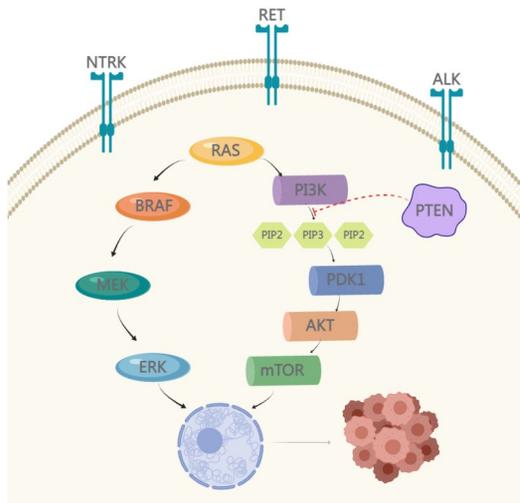


图 1 DTC 相关信号转导通路图

Figure 1 Signal pathways associated with DTC

3 分子标志物在 DTC 颈部 LNM 预测中的作用

3.1 BRAF^{V600E} 突变

BRAF^{V600E} 是近年来 PTC 诊断中常检的基因靶点, BRAF 基因 T1799A 突变导致 BRAF 蛋白中 V600E 氨基酸由缬氨酸变为谷氨酸,激活 BRAF/MEK/MAPK 信号通路,促进肿瘤发生、细胞增殖和转移,在 PTC 中的发生率为 29%~69%,与 PTC 发病机制相关,与良性肿瘤或 FTC 的发病机制无关^[18-19]。在一些研究^[20-21]指出 BRAF^{V600E} 突变可以强烈预测 LNM,且与 PTC 包膜外侵犯、较晚的 TNM 分期、持续性疾病、疾病复发密切相关,但仍有许多研究^[22-23]表明 BRAF^{V600E} 突变阳性与 PTC 侵袭性临床病理特征,尤其是 LNM 之间并无关联,作为独立分子标志物预测 LNM 乃至预后的价值需进一步研究。文献数据报道的不一致性可能与研究患者群体的异质性有关,如不同研究中患者年龄、肿瘤大小、地理位置、肿瘤分期、是否与 TERT 基因突变共存等存在显著差异。Silver 等^[24]将 121 例 PTC 患者按肿瘤直径分为两组:直径≤1 cm 组和直

径 1.1~1.5 cm 组,即甲状腺微小乳头状癌(papillary thyroid microcarcinoma, PTMC)组和小 PTC 组,研究发现小 PTC 组中 BRAF^{V600E} 突变与 LNM 呈显著相关($P=0.0016$),而 PTMC 组中 BRAF^{V600E} 突变与 LNM 无关。Zha 等^[25]也得出相似结论,肿瘤直径>1 cm、BRAF^{V600E} 突变阳性组 LNM 发生率是肿瘤直径≤1 cm、BRAF^{V600E} 突变阴性组的 2.55 倍($P=0.036$),调整年龄和性别后仍差异显著。这些研究显示尚未有充分证据将 BRAF^{V600E} 突变纳入 PTMC 患者危险分层,指导积极检测(acute surveillance, AS)或手术方案的选择。Wang 等^[26]发现亚洲、欧洲和美洲 PTC 患者中, BRAF^{V600E} 突变阳性 LNM 发生率分别是 BRAF^{V600E} 突变阴性的 1.24、1.27、2.07 倍。Zhang 等^[27]发现与白种人和亚洲人亚组相比,非洲亚组的这种关联更为显著($OR=5.96$)。因此当 PTC 患者检测到 BRAF^{V600E} 突变阳性时,还应考虑地理位置及种族影响,评估其 LNM 状态。

3.2 RAS 突变

约 30% 的 FTC 中存在 RAS 突变,其中 NRAS 突变较 HRAS、KRAS 突变更常见,RAS 突变属于弱驱动突变,在良性甲状腺肿瘤,如 14%~48% 的滤泡型腺瘤(follicular adenoma, FA)中也很常见。迄今为止,很少有文献讨论 RAS 突变与 LNM 的关联,这可能与 FTC 较少发生 LNM,而多通过血行转移有关。Medici 等^[28]指出 RAS 突变阳性的结节无论是 FA,还是 FTC,均无包括 LNM 在内的侵袭性临床病理特征,其中 5 个样本具有长期前瞻性超声随访(平均 8.3 年),也均未显示 LNM 迹象,这提示虽然 RAS 突变阳性会增加结节恶性风险,但也均为低风险癌症表型。Fukahori 等^[29]报道的 58 例 FTC 中 RAS 突变也均与 LNM 无关($P=0.41$)。

3.3 TERT 启动子基因突变

TERT 启动子区域存在 C228T 和 C250T 两个突变热点,TERT C228T 和 C250T 突变在 PTC、FTC 中的发生率分别为 10% vs. 2%、30% vs. 5%^[30]。Bae 等^[31]发现 222 例 DTC 患者中 TERT 启动子突变阳性与 LNM ($P=0.011$)、侧区 LNM ($P<0.001$) 有显著相关性,TERT 启动子突变主要出现在更具侵袭性的病例中,如存在远处转移、高细胞变体 PTC、广泛浸润型 FTC 等,且 TERT 启动子突变在 BRAF^{V600E} 突变阳性的 PTC 中更为常见,但也有研究发现 TERT 启动子突变与 LNM 之间没有显著关联,这可能与研究中大多数患者没有或仅进行了有限的颈

部淋巴结清扫术、研究人群异质性、患者数过少等有关。

TERT启动子突变与BRAF^{V600E}或RAS突变共存已被证实会增加DTC侵袭性及不良预后风险,但与LNM的关系尚未产生定论。Xing等^[32]在507例PTC患者中同时检测BRAF^{V600E}和TERT C228T突变,观察到两种突变均阴性、仅存在BRAF^{V600E}突变和TERT C228T突变,两种突变共存组LNM发生率分别为20.2%、42.4%、38.5%、63.6%,差异均具有统计学意义($P<0.05$),发现PTC患者LNM与BRAF^{V600E}和TERT C228T突变均有显著关联,当两种突变共存时,LNM发生率更高且可显著提示复发与远处转移,在PTC总体和CPTC亚组分析研究中,这些结果均成立,且TERT C228T与BRAF突变也有显著相关性,二者对PTC患者LNM与远期预后的影响具有增量和协同作用。这可能与BRAF^{V600E}激活的MAPK通路通过生成和增强ETS因子与TERT启动因子的相互作用,促进TERT基因的上调有关^[33-34]。但Ren等^[35]通过对342例PTC患者进行分子检测发现TERT启动子突变与BRAF^{V600E}共存与中央区LNM、侧区LNM、LNM转移枚数 >5 、累及或切除淋巴结数均无关。至于TERT启动子突变和RAS突变共存病例也没有表现出LNM迹象^[29]。

3.4 RET和NTRK重排

PTC与3种不同的跨膜酪氨酸激酶基因重排有关:RET、NTRK1和NTRK3,RET重排所得的嵌合基因被称为RET/PTC,NTRK重排所得的嵌合基因被称为TRK,其产生的嵌合蛋白具备非配体依赖性激活的酪氨酸激酶活性。早期的一些研究认为无法发现RET重排与PTC的任何临床病理特征包括LNM存在密切关联,相较之下RET/PTC3通常使PTC具备更有侵袭性的表型,但也与LNM无关,后来Zhou等^[36]在50例PTC患者中研究发现,8例存在RET重排,且RET/PTC与LNM显著相关,RET/PTC阳性患者局部扩散率和淋巴结受累率均高于RET/PTC阴性病例,在5例RET/PTC和BRAF^{V600E}突变共存患者中,相关性进一步增强,且RET/PTC阳性组NF- κ B、IL-1 β 、IL-6、TNF- α 、TGF- β 的表达增加,提示RET/PTC可能增强NF- κ B的活性、炎症介质的表达和淋巴结的转移。NTRK1/3重排在成人PTC中罕见,发生率为2.3%~6.7%,有限证据表明其可能与频繁的LNM相关,Chu等^[37]在11例NTRK重排甲状腺癌患者中研究发现,初诊时所有患者

原发病灶均具有多结节生长模式,以广泛的淋巴管浸润和颈部LNM为特征。但由于RET重排、NTRK重排发生阳性率太低、样本量太小,这些结论仍需要更多的证据支持。

3.5 基质金属蛋白酶家族(matrix metalloproteinase, MMP)

MMP中MMP-9是肿瘤发生过程中基底膜降解、包膜外侵犯、侵袭性增强的关键性酶之一,Liu等^[38]纳入112例PTC患者,研究发现MMP-9表达显著上调,且存在中央区LNM、侧区LNM或晚期肿瘤LNM(III+IV)的MMP-9表达水平更高。Zhang等^[39]发现PTC伴与不伴LNM患者MMP-9表达强度差异有统计学意义,MMP-9的强表达(+++)主要见于伴有LNM的PTC(80.95%,17/21)。Li等^[40]发现MMP-9的mRNA和蛋白表达水平与LNM显著相关,同时TGF- β 1、SNAIL和MMP-9蛋白表达之间存在显著相关性,任何两个或全部三个分子的同时表达与LNM的相关性比单独表达强。Bumber等^[41]发现PTC患者MMP-1和TIMP-1表达水平与LNM相关,在侧区LNM组的表达水平最高,可被视为侧区LNM的预测因素,而MMP-2、MMP-9的表达水平与侧区LNM无关。

3.6 Ki-67

Ki-67增殖指数是细胞增殖的标志物,被认为是甲状腺癌预后分类的可靠标志物。Zhou等^[42]报道了108例PTMC中Ki-67与中央区LNM有显著关联($P<0.01$),可作为判断临床进展和判断预后的重要指标。Lei等^[43]研究发现PTC患者中Ki-67指数 $>3\%$ 与中央区淋巴结转移(CLNM)显著相关,当Ki-67指数 $>5\%$ 时,更能提示CLNM和更高的淋巴结受累率。Matsuse等^[44]和Aydogan等^[45]却得出了直接相反的结果,即Ki-67与LNM、临床侧区LNM(N1b)、病理证实的LNM(pN1)均无显著相关,只与远处转移有关。文献数据的不一致性可能与各研究中患者群体的Ki-67增值指数范围存在明显差异。Matsuse等^[44]称Ki-67结合TERT启动子或BRAF^{V600E}突变虽与LNM关联缺乏统计学差异,却在预测PTC复发方面表现出色,复发危险比为6.225~8.8,因此需要更多研究发现Ki-67与其他分子突变组合对LNM的预测价值。

3.7 其他分子标志物

血管内皮生长因子C(VEGF-C)引导肿瘤相关淋巴管生长并促进循淋巴系统传播,Šelemetjev

研究^[46-47]发现 PTC 患者中, VEGF-C 协同活性 MMP-9 或 survivin 蛋白的高水平表达与 LNM 显著相关 ($P<0.005$), 抑癌基因 PTEN 丢失可诱导成纤维细胞迁移和增殖从而促进 FTC 进展^[48], 韩国一项研究^[49]表明无论组织学亚型如何, PTEN 丢失都与 LNM 相关 ($P=0.007$)。半乳糖凝集素 3 (galectin 3, GAL3) 在细胞黏附、肿瘤发生发展过程中起重要作用, 研究发现 GAL3 在 PTC 原发病灶中高表达与 LNM 显著相关, 在 LNM 病灶中却低表达, 提示 LNM 病灶中 GAL3 下调可能是促进肿瘤细胞从原发病灶中释放出来发生 LNM 的原因。Yu 等^[50]在 60 例 PTC 患者中抽取血标本检测 GAL3 和环状 RNA (circular RNAs, circRNA) 中的 circRNA-UMAD1, 研究发现二者可作为协同外周血分子标志物预测 PTC 患者是否存在 LNM, 在有 LNM 的 PTC 患者外周血中, GAL3 和 circRNA-UMAD1 表达均显著升高, 受试者工作特征曲线 (receiver operating characteristic, ROC) 下面积 (the area under the curve, AUC) 为 0.87, 较单一标志物预测 LNM 的敏感度、特异度均有所增加。血浆和尿液外泌体蛋白含量丰富, Chen 等^[51]研究发现血浆中两种微小 RNA (microRNA, miRNA), miR-6774-3p 和 miR-6879-5p 对 PTC 患者 LNM 具有良好的诊断效率, 其组合可使诊断预测效能进一步提高。Huang 等^[52]发现尿液中甲状腺球蛋白 (U-Ex-Tg) 浓度升高与 IV 区 LNM 相关。

DTC 总体上来讲是高度可治愈的, 但仍有相当一部分患者出现区域 LNM, 出现侵袭性肿瘤行为和高疾病复发率、病死率。目前, 术前评估是否有区域 LNM 主要通过影像学手段, 或对明显肿大的淋巴结进行粗针穿刺病理活检, 分子检测无疑提供了一种无创、有可能会更加准确敏感的新思路, 虽然临床研究数据目前仍存在矛盾和争议点, 但联合应用几种分子标志物预测 LNM 情况、亚组分析等研究正在开展, 以期为临床上 DTC 淋巴结清扫问题提供解决新思路。

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