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甲状腺癌分子标记物的研究进展

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[摘 要] 近年来，大量甲状腺癌相关的分子标志物相继被发现。这些标志物也许可用来作为诊断的工具，或是预测患者的预后，甚至作为潜在的治疗靶点。比如在对甲状腺进行细针穿刺细胞学检查后，某些分子标志物可以协助诊断，为肿瘤的危险程度分级，进而优化甲状腺癌患者的手术方式以及术后的管理。

[关键词] 甲状腺癌；分子标志物；治疗靶点

Research progress of thyroid cancer molecular markers

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Abstract In recent years, a large number of thyroid cancer related molecular markers have been found. These markers may be used as a diagnostic tool, or to predict the prognosis of patients, even as potential therapeutic targets. Such as in the thyroid fine needle puncture cytological examination, some molecular markers could help diagnose, to the degree of danger of tumor classification, thus optimizing the operation of thyroid carcinoma and postoperative management.

Keywords thyroid cancer; molecular markers; therapeutic targets

甲状腺癌是内分泌系统中常见恶性肿瘤之一，目前其发病率仍呈上升趋势[1-3]。近年来，在甲状腺癌的发生发展机制的研究中取得了明显的进步，不少甲状腺癌相关的基因及标记物被先后报道。BRAF、RAS、RET/PTC、PAX8/PPARγ这些基因标记物为甲状腺癌的诊断及治疗起到了一定的辅助作用。本文结合目前研究较多且和甲状腺癌关系较为密切的基因和分子标记物作一综述。

1 甲状腺癌发生相关的基因标记物

肿瘤是一种多基因病，其发生发展过程复杂，常涉及到多个基因的变化。就甲状腺癌(thyroid cancer，TC)而言，主要表现为基因突变。

在最常见的两种甲状腺癌——乳头状癌和滤泡状癌中，主要的基因突变类型有4种：BRAF基因突变、RAS基因突变以及RET/PTC基因和PAX8基因的过氧化物酶增殖激活受体γ(PPARγ)的重

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排，目前认为它们对甲状腺癌的诊断和预后的价值最高。在甲状腺乳头状癌中，所有这些突变和重排都会激活有丝分裂原活化蛋白激酶(mitogen-activated protein kinase，MAPK)通路；在超过70%的甲状腺乳头状癌中发现存在着这些单独出现的基因突变[1-4]。约75%的滤泡状癌中存在着RAS突变或者存在PAX8/PPARγ重排[5]。

另一种类型基因突变是PI3K/AKT信号转导通路中TP53和CTNNB1基因，这一突变在高分化甲状腺癌中罕见，而在低分化和未分化甲状腺癌中的突变率较高[6-9]。此外还有一种基因变异：TRK重排，在甲状腺乳头状癌中的发生，但突变率很低[10-12]。

1.1 BRAF

据报道[2,13-14]，BRAF基因突变是目前已知最常见的甲状腺乳头状癌的基因变异，发生率约为35%~70%。其中绝大多数(>95%)的突变发生在核苷酸1799(T1799A)的蛋白质残基600(V600E)中，由于胸腺嘧啶取代了腺嘌呤，造成缬氨酸变成了谷氨酸。这一突变结构性激活了BRAF激酶，形成了长期对MAPK信号通路的慢性刺激，是导致甲状腺细胞肿瘤源性重要原因。其他较少见的甲状腺乳头状癌BRAF的激活机制，包括K601E点突变、密码子600周围小框内插入或删除[15]、以及AKAP9/BRAF基因的重排，这些突变与电离辐射造成的甲状腺癌相关[16]。

BRAF基因的V600E突变与甲状腺乳头状癌的病理学改变有密切的关系。在高大细胞型乳头状癌中发生率有70%~80%，而在普通乳头状癌中的发生率约为60%[1,13,17]。许多BRAF阳性的甲状腺肿瘤在镜下表现出经典的乳头状结构伴有灶性突出的高突细胞征象或边界不清的高突细胞征象。而在甲状腺乳头状癌的滤泡亚型中，BRAF的V600E突变发生率则只有约10%。另一种BRAF基因的点突变K601E，整体上比较罕见，大多出现在甲状腺乳头状癌的滤泡亚型中[18-19]。在未分化和低分化甲状腺癌中也可以观察到BRAF的V600E突变[17,20-21]，然而在甲状腺滤泡癌和甲状腺良性肿瘤中没有发现BRAF的V600E突变。因此，BRAF基因可以用来作为鉴别甲状腺乳头状癌和其它类型的甲状腺肿瘤的分子标志物。

除了在高大细胞型乳头状癌中的发生率较高，BRAF基因的V600E突变也被发现与甲状腺癌的侵袭性相关，以及更高的肿瘤分期，伴有淋巴结或远处转移等[17,20,22-23]。

1.2 RET/PTC

RET/PTC重排是甲状腺乳头状癌中的另一种基因改变[24]，是由RET酪氨酸激酶受体基因的3'端和其它无相关基因的5'端的融合所造成的。包括两种最常见的重排类型：RET/PTC1和RET/PTC3，是由定位于10号染色体上的RET及其融合基因——H4和NCOA4(也被称为ELE1)在染色体内的倒置所致[25-27]。另外包括RET/PTC2和九个新近发现的RET/PTC类型是染色体间的易位[28]。所有的重排类型包含完整的RET受体酪氨酸激酶结构域，它们激活RET/PTC融合蛋白，进而造成RAS-RAF-MAPK级联反应，最终启动甲状腺肿瘤的发生。

成人甲状腺乳头状癌中存在着约10%~20%的RET/PTC重排，由于检测方法敏感性的差异和一些地域性因素的影响，不同研究结果存在较大差异[29-30]。曾经接受电离辐射的患者发生RET/PTC重排的几率较大(50%~80%)，在甲状腺乳头状癌患者中，儿童和青壮年(40%~70%)出现RET/PTC重排的几率也较高[31-34]。RET/PTC重排在肿瘤细胞内的分布也有所不同，大部分肿瘤细胞中存在着克隆型的RET/PTC，只有小部分(<1%)的肿瘤细胞中存在非克隆型的RET/PTC[35-36]。虽然在甲状腺腺瘤和其他良性甲状腺病变中也发现有RET/PTC，但是我们仍可以认为克隆型的RET/PTC(如在肿瘤的大部分细胞内出现重排)可能是甲状腺乳头状癌发病的成因之一[29,35]。有两组研究报告[37-39]称在甲状腺透明变性小梁肿瘤细胞中发现RET/PTC重排。在其中一项研究中，4例肿瘤标本中以免疫组织化学方法检出RET蛋白，而其中3例以RT-PCR方法发现存在RET/PTC1重排[37]。在另一项研究中，8例甲状腺透明变性小梁肿瘤中有6例存在RET/PTC1重排[38]。这些发现提示，甲状腺透明变性小梁肿瘤可能是乳头状癌的一种变异，然而这些研究没有调查是否大多数这类肿瘤细胞中存在着RET/PTC，因此无法提供确凿的关于乳头状癌和透明变性小梁肿瘤之间有密切联系的生物学证据。

在甲状腺乳头状癌中RET/PTC1是最常见的，占所有重排类型的60%~70%，RET/PTC3占20%~30%，RET/PTC2和其他重排类型<5%[11,40]。在RET/PTC表达阳性特别是存在RET/PTC1重排的甲状腺乳头状癌中，表现为患者年龄较轻，淋巴结转移率较高[1]。在大多数RET/PTC表达阳性尤其是RET/PTC1重排的肿瘤中，呈现典型的乳头状结构，微小乳头状癌中RET/PTC1重排的出现更

加显著[40-42]，甲状腺乳头状癌的滤泡亚型中RET/PT的出现率较低[34,40]。切尔诺贝利事故后遭遇辐射患甲状腺乳头状癌的儿童中，RET/PTC的不同类型与乳头状癌的亚型之间有强相关性——表现为硬癌与RET/PTC3相关，普通乳头状癌与RET/PTC1相关[31-32,43]。不过，目前尚不清楚在一般人群中是否存在这样的相关性。在散发甲状腺乳头状癌中硬癌亚型和一般乳头状癌与RET/PTC的关系的研究中，病例数较少，并没有发现它们之间存在这样的相关性[44]。

1.3 RAS

RAS基因点突变并不局限于某种特定类型的甲状腺肿瘤。在甲状腺滤泡癌、乳头状癌和滤泡性腺瘤中都有发现。三种人类RAS基因(HRAS，KRAS和NRAS)编码高度相关的G蛋白，传递从细胞膜受体到各种细胞内靶点的信号。RAS基因特定位点的突变，一方面增加其对GTP的亲和力(12和13密码子突变)，一方面灭活其催化GTP酶的功能(第61位密码子的突变)，造成永久的RAS激活，及其下游MAPK和PI3K/Akt信号通路中靶分子的长期刺激。

在甲状腺肿瘤中，虽然所有三种RAS基因的不同突变都有发现，但涉及NRAS密码子61和HRAS密码子61的突变是最常见的。在甲状腺乳头状癌中，RAS的突变率约为15%~20%[45-50]。带有RAS基因突变的甲状腺乳头状癌，几乎都伴有组织学上的滤泡样变化，这种突变也与肿瘤细胞核形态不明显、更多的核修饰以及低淋巴结转移率相关[1,51]。在40%~50%的滤泡性甲状腺癌中发现有RAS突变[48,52-56]。20%~40%的滤泡性腺瘤中也有RAS突变[45,52-55]，其中微滤泡形态的RAS突变较多[52]。嗜酸性细胞肿瘤中RAS突变率较低，只有在0%~4%的甲状腺腺瘤和15%~25%的甲状腺癌中存在[54,57-58]。在甲状腺腺瘤的冷结节和结节性甲状腺肿中也发现少量的RAS突变[45,54,59]。这些结节中胶质丰富呈巨滤泡样结构，虽然它们可能是甲状腺癌，但还是应该诊断为甲状腺滤泡样腺瘤。

1.4 PAX8/PPARγ

PAX8/PPARγ重排是染色体2和3，t(23)(q13;P25)之间易位的结果，导致编码甲状腺特定配对域转录因子的PAX8和PPARγ基因之间的融合[60]。PAX8/PPARγ重排可导致PPARγ蛋白的过表达，这种基因变异导致细胞转化的机制尚未完全了解。

30%~40%的常规型滤泡癌中存在PAX8/PPARγ表达，而在嗜酸性细胞癌中少见[5,61-62]。表达PAX8/PPARγ的肿瘤特征表现为：患者年龄多较小、肿瘤体积较小、有癌巢样生长结构并多伴有血管浸润[5,19,61]。在一小部分(2%~10%)滤泡性腺瘤和(<5%)乳头状癌滤泡亚型中也发现有这种重排[5,19,62-63]。PAX8/PPARγ表达阳性的滤泡性腺瘤通常伴有厚壁囊样结构，在免疫组织化学上显示出类甲状腺癌的特征。这表明他们可能已经是(原位)滤泡样癌或是在免疫组织化学检查中被忽视的恶性肿瘤征象[5]。有研究[19]表明，滤泡性腺瘤和乳头状癌滤泡亚型中PAX8/PPARγ重排的发生率高。另一种类型的PPARγ基因融合，CREB3L2/PPARγ，曾在42例滤泡癌中发现了1例[64]。

2 甲状腺癌发展及预后的分子标志物

2.1 BRAF

BRAF V600E突变通常被认为是一个可靠的乳头状癌的预后指标。它与肿瘤的高侵袭性行为相关，在大多数大样本研究中都得到证实。在许多研究中，BRAF V600E突变同肿瘤的高侵袭性相关，如高大细胞型，侵犯甲状腺包膜、更高的肿瘤分期及淋巴结或远处转移等。更重要的是，BRAF的V600E是患者治疗效果不佳和肿瘤复发的独立预测因子[22,65-66]。最近的一项对102位患者随访15年的研究[67]表明，BRAF V600E突变是肿瘤相关死亡事件的独立危险因素。在手术切除肿瘤样本和甲状腺细针穿刺标本中，BRAF V600E突变都显示出与无疾病生存期密切相关性[68]。

甲状腺细胞BRAF V600E突变导致BRAF的激活，造成钠碘转运体(Na+/I-symporter，NIS)和其他碘化物代谢体的功能失常，使得BRAF突变的肿瘤的摄取碘131的能力下降，以及肿瘤复发后治疗失败[8,69-70]。BRAF突变也使得肿瘤具有去分化，低分化和未分化的趋势，这也是导致患者预后不佳的原因。

BRAF突变对甲状腺微小乳头状癌(偶然发现的直径小于1 cm的肿瘤)患者预后的影响也特别重要，这些肿瘤通常在手术切除的较大良性甲状腺结节中被发现。大多数微小癌可以经手术切除治愈，然而部分也会转移、复发，导致患者死亡，所以也需要积极的治疗[71]。将BRAF突变来鉴别微小癌中侵袭性强的肿瘤应用于临床仍还需进一步研究。最近的几项研究[72-74]表明，甲状腺微小癌中BRAF的突变与肿瘤突破包膜和淋巴结转移都有密切相关性。

2.2 RAS

RAS基因突变预测肿瘤侵袭性的能力尚有待研究，因为在良性的滤泡腺瘤中也存在这种突变，RAS状态本身不能被用于预测肿瘤的预后。然而一些研究证实，侵袭性滤泡癌和乳头状癌中的RAS突变可能代表更差的预后，但这一结论尚未得到更多的研究的证实。

一些研究[46,48,75-76]发现RAS基因突变与滤泡癌的转移行为，特别是骨转移有相关性，这可能是RAS促进肿瘤去分化成未分化癌的作所致。在一项随访14年91例乳头状癌患者的系列报道中，RAS突变同肿瘤的高侵袭性相关，RAS突变的患者发生远处转移的几率较高，病死率也明显增加[47]。另一方面，肿瘤侵袭性较低的乳头状癌滤泡亚型中，也经常发现RAS突变[51,77]。因此，在侵袭性强的高分化乳头状癌中RAS突变是广泛存在的，容易导致广泛转移和肿瘤去分化，带来更高的病死率。但是RAS突变不能作为针对所有类型甲状腺癌的通用预后指标。

3 甲状腺癌分子标志物在临床中的应用

3.1 细针穿刺 (fine needle aspiration，FNA) 样本的分子分析

细胞学穿刺检查是目前大多数病例中最可靠的甲状腺结节的诊断以及判断良恶性的方法，然而其中也有10%~40%的标本不能确切诊断为恶性肿瘤[78-81]。不确定的细胞学表现一般包括一下几种：不确定的滤泡性病变(follicular lesion of undetermined significance，FLUS)、滤泡性肿瘤/Hurthle细胞肿瘤和怀疑为恶性的肿瘤，它们与恶性肿瘤的相关性分别为5%~10%、20%~30%和50%~75%[82]。由于缺乏明确的诊断，这些患者必需接受手术治疗，但是最终只有8%~17%的手术切除的甲状腺结节是恶性的[83-84]。很多细胞学检测不确定结果和恶性肿瘤的患者的治疗上存在欠缺之处，因为其中很多患者最初接受了甲状腺腺叶切除后，由于诊断为恶性肿瘤，又必需再接受一次完整的甲状腺切除手术。

对活检样品进行分子检测能显著提高甲状腺结节的细胞学诊断的准确性。迄今为止对BRAF突变的检测积累了最多的经验。在18个前瞻性和回顾性研究中，一共对2 766个活检样品进行了BRAF突变的测试[68,85-101]。在581例BRAF阳性的结节中，有580例被确诊为甲状腺乳头状癌，1例被确诊为良性结节[101]，假阳性率仅为0.2%。并且这唯一一例良性结节病理诊断是“非典型结节性增生”，且并没有利用免疫组织化学技术[102]。更重要的是，BRAF阳性的病例中有15%~40%是不确定的或细胞学检查不能确诊的[86-87,91,94,96-97]，这表明BRAF基因检测对细胞学不确定的结节明确诊断是很有帮助的。

除BRAF以外，一些研究还探讨了对细胞学标本进行RET/PTC，TRK，或RAS基因突变进行检测的可能性[97,103-104]。最近有研究[87,105]提供了一种同时检测BRAF、RAS、RET/PTC和PAX8/PPARγ突变的实用工具，认为综合检测一系列基因突变比检测单一基因的突变对细胞学诊断提供更大的帮助。一项前瞻性研究对470例活检样品进行了测试，其中32例存在上述基因的突变[87]。任何一种基因的突变都是一个预测癌症明显标志，其中31例(97%)的突变阳性的结节，在手术后证实为恶性肿瘤，仅有1例(3%)是甲状腺腺瘤。这项研究表明，测试一系列基因的突变对于细胞学诊断不确定的甲状腺结节是特别有用的，尤其是对于低风险组的病例(如FLUS)，在这一组中，阳性突变的病例100%印证恶性肿瘤的诊断，突变阴性的结节证明都是良性的。此外，这项研究表明，分子检测可以使细胞学诊断的假阴性率从2.1%下降到0.9%。另一项只集中于FLUS组细胞学标本的研究表明，基因突变的检测，对于恶性肿瘤有100%的阳性预测值和92%的阴性预测值[105]。对于BRAF，RET/PTC和PAX8/PPARγ突变的检测，在这两项研究中都具有对恶性肿瘤的100%的阳性预测值[87,105]。RAS基因突变检测有着仅次于BRAF检测的重要性，它对样本的诊断价值也很高—对恶性肿瘤的阳性诊断率约为87%~100%。更重要的是，对于乳头状癌滤泡亚型和滤泡状癌这两类依据细胞学很难确诊的肿瘤，可以通过检测RAS基因突变来确诊。对分子标志物检测的经验积累，已反映在美国甲状腺协会最近公布的甲状腺结节和分化型甲状腺癌的诊疗指南中[106]。该指南建议对于细胞学检查不确定的病例，使用分子标记物(如BRAF基因，RAS，RET/PTC，和PAX8/PPARγ)检测来帮助诊断。

3.2 手术切除肿瘤的分子分析

手术切除的甲状腺样本的分子检测于乳头状癌的诊断价值相当有限。当病理学诊断怀疑是乳头状癌时，同时进行BRAF和RET/PTC的检测，如果表达是阳性则提示乳头状癌的可能性很大。然而，带有这些基因变异的肿瘤多在病理学上表现

为经典的乳头状癌征象或高细胞变化，因此其组织学诊断通常很容易。病理学确诊相对困难的乳头状癌滤泡亚型，往往带有RAS突变。但是RAS基因突变不能作为诊断恶性肿瘤的依据——其也可以在滤泡性腺瘤中出现。

在滤泡癌中，PAX8/PPARγ重排的检测有显著的诊断价值，这种突变是滤泡癌的典型表现，虽然如前所述，它也可以在一小部分滤泡性腺瘤中出现。PAX8/PPARγ阳性时，多伴有肿瘤血管或包膜外浸润。许多PAX8/PPARγ阳性的滤泡状肿瘤中都可以检测到肿瘤突破甲状腺包膜的病理征象[5,61,107]。

4 结语

尽管目前已经发现大量甲状腺相关的基因及标记物，且这些标记物在甲状腺癌的诊断及治疗中也发挥了一定的作用，但甲状腺癌的发生发展是一个涉及多基因的变化过程，单纯依赖某一基因或标记物的检测都有一定的局限性，如何联合多个基因进行检测以提高灵敏度和特异度是未来努力的方向。

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