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甲状腺癌的分子靶向治疗研究进展

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Advances in molecular targeted therapy of thyroid carcinoma

Summary Thyroid carcinoma is the most common endocrine maligancy, and the worldwide incidence has been rising in recent years. Differentiated thyroid carcinoma is the most common thyroid malignancy, which include thyroid papillary carcinoma and follicular thyroid carcinoma, accounting for about 90 percent of thyroid carcinoma incidence. Currently, surgical treatment, iodine radiotherapy and TSH suppressive therapy are the commonly accepted effective treatments for differentiated thyroid carcinoma, and most patients can be cured. But there are still some patients not sensitive to the general treatments, who have lost the treatment of opportunity. Molecular targeted therapy is an agonistic or suppressive treatment for molecular biology targets of malignant tumor, and currently is a frontier research in the field of malignancy treatment. By retrieving and analyzing the related literature of molecular targeted therapy of thyroid carcinoma through PUBMED in the past 5 years, the article introduced the current status of molecular targeted therapy of thyroid carcinoma.

Key words thyroid neoplasms; molecular therapy; targeted therapy

1 概述

甲状腺癌是最常见的内分泌系统恶性肿瘤，约占人类所有恶性肿瘤发病率的1%[1-3]。甲状腺乳头状癌和甲状腺滤泡状癌属于分化型甲状腺癌，是最常见的甲状腺癌类型，约占90%[4-5]。手术治疗、^{131}碘放射治疗、TSH抑制治疗是有效可靠的治疗方式[1,6-8]，而系统性化疗方案不敏感。但仍有部分类型甲状腺癌无法获得可靠疗效及发生远处转移，其中包括手术无法完整切除的甲状腺癌病灶，对手术治疗、^{131}碘放射治疗、TSH抑制难治性的分化型甲状腺癌及髓样癌，甲状腺癌术后复发、转移病灶等[2,8-10]。随着对疾病的认识逐渐深入到分子层面，通过对甲状腺癌发病分子生物学行为的靶向干预而控制、治疗甲状腺癌，已经成为探索甲状腺癌疾病诊疗方式的前沿领域。疾病治疗已进入一个全新的分子时代，甲状腺癌的分子治疗时代也随之展开。

2 分化型甲状腺癌相关信号传导通路

2.1 MAPK信号传导通路

MAPK信号传导通路存在于多种肿瘤的发生发展过程中，通过接受配体与受体酪氨酸激酶结合级联激活下游RAS、RAF、MEK1/2、ERK并将信号传入细胞核中起到促进细胞生长和生存的生物学作用[3,8]。RAF也称为MAPKKK，MEK也称为MAPKK，ERK也称为MAPK，体现出对细胞生长信号通过级联反应瀑布样放大的信号传导特点[6,11-13]。MAPK信号传导通路是甲状腺癌分子靶向治疗研究最多的领域，现有大多数临床指南推荐使用靶向治疗药物作用于该通路的不同靶点，目前大部分药物临床试验研究针对该通路的不同靶点[2,7,8,14-15]。

2.2 PI3K/Akt信号传导通路

PI3K/Akt信号传导通路是甲状腺癌相关的另一条重要的信号传导通路[2,16]。通路起始通过配体与血管表皮生长因子受体（VEGFR）结合，级联激活通路下游磷脂酰肌醇3-激酶（PI3K），蛋白激酶B（PKB、Akt），哺乳动物雷柏霉素靶蛋白（mTOR）。信号最终通过激活细胞核内基因并转录，促进细胞生长，并减少甲状腺细胞摄碘[5,8,17]。

2.3 PPARγ信号传导通路

PPARγ信号传导通路是胞外生长因子信号通

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过一系列级联反应信号传导，传导入细胞核内引起基因转录激活的最终通路[18-19]。目前研究显示MAPK 信号传导通路、TAK1/MKK3，6/p38 信号传导通路均能通过 PPARγ 将生长因子信号传递进入细胞核内并造成分子生物学效应[20]。

3　分化型甲状腺癌相关基因突变

3.1　RET/PTC 基因突变

RET 基因编码络氨酸激酶受体的跨膜结构域，其突变首次发现于甲状腺乳头状癌并与电离辐射暴露高度关联[3,6,21]。最经典的案例就是 1986 年切尔洛贝利核电站爆炸事件后，受影响区域罹患甲状腺乳头状癌的新生儿多检测有 RET/PTC 3 型基因突变，而核泄漏幸存者中罹患高侵袭性甲状腺癌被检测出带有 RET/PTC 1 型基因突变[6,22]。

3.2　BRAFV600E 转位突变

BRAF 是 RAF 亚型，该突变主要作用于 MAPK 肿瘤信号传导通路[6,7,15,23]。BRAF 基因编码 MAPK 肿瘤信号传导通路中的丝氨酸/苏氨酸蛋白激酶，该酶可将信号由 Ras 传导至 MEK1/2[6,21]。有文献报道 BRAFV600E 转位突变见于 44%的分化型甲状腺乳头状癌及 24%的髓样癌，且表达与甲状腺癌肿瘤的复发和转移存在关联[21,23]。而 BRAFV600E 转位突变作为独立于 RAS、RET 的独立基因突变不仅表现出 PTC 的分子特异性，而且对甲状腺癌复发率高、侵袭性强起到一定的预测作用[7,21,23-25]。

3.3　RAS 突变

RAS 突变通过 MAPK 信号传导通路及 PI3K/Akt 信号传导通路发挥调控甲状腺癌细胞生长的作用[6,15,26]。但 RAS 突变同时见于甲状腺良性病变及分化型甲状腺癌中[6,24,26]。RAS 突变甲状腺癌多表现为甲状腺滤泡状结构，因此带有 RAS 突变的 PTC 患者同样也被称为滤泡转化型甲状腺乳头状癌（FVPTC）[6,26]。但 RAS 突变相关甲状腺癌多表现为局限性病灶，少有侵袭及远处转移[6,26]。

3.4　PAX8/PPARγ 融合突变

PAX8/PPARγ 融合突变是甲状腺滤泡状癌中最常见的基因突变[6,18,24]。PAX8/PPARγ 融合突变产物 PAX8/PPARγ 融合蛋白在甲状腺滤泡状癌、甲状腺滤泡状腺瘤、FVPTC 中均有不同程度的表达[6,27]。

4　甲状腺癌的靶向治疗

4.1　酪氨酸激酶抑制剂

酪氨酸激酶抑制剂（TKI）是针对于 BRAF 信号传导通路的抑制药物[1]。作用靶点主要为 BRAF、VEGFR1-3、RET、PDGFR 等[3,6,18]。其作用原理主要依靠抑制 VEGFR 及下游信号传导通路的激活而抑制肿瘤细胞血管形成和肿瘤细胞生长[6,10]。

索拉菲尼（sorafenib）是最为经典的口服型 TKI 药物，在一系列Ⅱ期对照药物临床试验中取得明显疗效[4,6,10,23,28]。曲美替尼（trametinib）是 MEK 抑制药物，与索拉菲尼联合使用对一线索拉菲尼不敏感的分化型甲状腺癌有一定疗效[4,23]。局部晚期甲状腺癌的维罗非尼（vemurafenib）新辅助治疗方案也表现出良好的疗效[4,23]。除此之外，达拉非尼（dabrafenib）等部分 TKIs 的使用能够增强初期[131]碘放射治疗效果不佳的甲状腺癌术后复发患者放疗敏感性[4,23]。

TKI 抑制剂作为 ATA、ESMO 等甲状腺临床指南推荐的甲状腺癌的靶向治疗药物[1]，在目前的药物临床试验和临床实践中显示出良好的疗效和前景[9,28]，是针对分化型甲状腺癌术后复发和经常规治疗效果不佳者的重要补充[9]。

4.2　环氧酶 2 抑制剂

环氧酶 2（COX-2）参与了多种肿瘤的发生和进展，研究表明在分化型甲状腺癌中 COX-2 的表达要明显高于甲状腺良性病变及正常甲状腺组织，特别是检测有 RET/PTC 突变的甲状腺癌组织[6,29-30]。在一系列 II 期临床试验中 COX-2 抑制剂的使用表现出良好的疾病转归，却因心血管系统毒性而停止观察[6]。

4.3　PPARγ 激动剂

PPARγ 激动剂在甲状腺癌治疗中主要通过促甲状腺癌细胞分化、停止肿瘤细胞生长周期、诱导细胞凋亡发挥生物学作用[6]。代表药物为罗格列酮（rosiglitazone）[6,19]。目前尚缺少药物临床试验资料，其药物疗效及安全性尚在进一步探索之中。

4.4　mTOR 拮抗剂

依维莫司（Everolimus）是 mTOR 结构类似物，通过拮抗 mTOR 而降低 PI3K/Akt 信号传导通路激活，对抑制甲状腺癌细胞生长和提高[131]碘放射治疗无效甲状腺癌放疗敏感性有重要的意义[2,8,17]。

综上所述，甲状腺癌的分子靶向治疗研究取得了一定的成果，并拥有良好的使用价值和应用前景。近年来，甲状腺癌的发病率逐年升高引起了全球范围内对甲状腺疾病的重视加强，而目前针对甲状腺癌的治疗方式也显示出可靠的疗效[5,17]。但随着人类疾病谱的不断变化，必然带来对疾病新的认识和治疗手段的匮乏。众多文献中提到的放射性碘放疗难治性分化型甲状腺癌（radioactive iodine refractory）就是随着疾病谱改变而出现的缺乏有效治疗手段的典型例证[5,8,10,18]。人类肿瘤的生物学行为拥有相似之处，在分子生物学研究层面上有重叠的部分。许多新的观点和方法来源于旧问题的解决和实践经验的积累。甲状腺癌作为日益增长的内分泌恶性肿瘤，在进一步的研究中是否

能够借鉴对其他内分泌恶性肿瘤的有效治疗经验，可为今后的研究提供重要的思路。分子靶向治疗也将成为甲状腺癌疾病治疗不可或缺的组成部分。

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