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AID、BRAFV600E与甲状腺乳头状癌相关性研究

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摘　要

近年来，全球范围内甲状腺乳头状癌(papillary thyroid carcinoma, PTC)的发病率递增，已成为头颈外科最常见的恶性肿瘤之一。国内外学者对PTC的机制研究成为临床和基础研究的热点，其发生、发展过程涉及多种遗传和表观遗传学改变，其中B型丝氨酸/苏氨酸蛋白激酶(B typeserine/threonine protein kinases, BRAF)密码子600处谷氨酸通常替换缬氨酸(BRAFV600E)在PTC中发生突变频率颇高；活性诱导性胞嘧啶脱氨基酶(activation-induced cytidine deaminase, AID)的累积异常表达可引起癌基因或抑制基因突变，AID高表达可能与BRAFV600E突变型PTC具有交互作用，要通过AID基因水平改变来影响细胞的分化程度、调控肿瘤的生长和转移概率，还需要进一步的研究。本文拟针对PTC与BRAFV600E、ADI之间的关联性作一综述。

关键词

甲状腺乳头状癌，BRAFV600E，AID

Research Progress in the Correlation between AID, BRAFV600E and Papillary Thyroid Carcinoma

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Abstract

The incidence rate of papillary thyroid carcinoma (PTC) has increased globally and become one of the most common malignant tumors in head surgery. Research on the mechanism of PTC by global scholars has become a hotspot in clinical and basic research. Its occurrence and development process involves a variety of genetic and epigenetic changes. Glutamic acid at codon 600 of B type serine/threonine protein kinases (BRAF) usually replaces valine (BRAFV600E) in PTC with high mutation frequency. Activation induced cytosine deaminase (AID) is induced to express under the stimulation of inflammation and/or infection. The accumulated abnormal expression can cause the mutation of oncogene or suppressorgene, and may interact with BRAFV600E mutant PTC. Further research is needed to affect the degree of cell differentiation and regulate the growth and metastasis probability of tumor through endogenous changes of AID gene level. This overview aims to make a summary of the correlation between PTC and BRAFV600E, AID.

Keywords

Papillary Thyroid Carcinoma (PTC), BRAFV600E, AID

1. 引言

甲状腺癌的发病率在恶性肿瘤中增长最快，在女性恶性肿瘤中则更高；甲状腺乳头状癌(Thyroid papillary carcinoma, PTC)是甲状腺癌病理分型中的一种，占全部甲状腺癌的 85%~90% [1]。PTC 起源于内胚层来源的滤泡上皮细胞，进展缓慢，恶性程度不高[2]。碘摄入量、桥本甲状腺炎、肥胖、糖尿病、暴露于射线等是其发生、发展的危险因素[3]。该病近年来由于患者对甲状腺疾病的重视程度增加以及多检查技术的普及，甲状腺癌发病率不断上升，主要见于青壮年，临床上治疗预后良好。现有治疗方法主要包括外科手术、放射性 I 131 射频消融术、内分泌治疗等均可取得较好的治疗效果[4]。先有较多临床研究发现年龄 ＜45 岁是 PTC 复发和转移的独立危险因素，复发且合并远处转移患者预后较差[5]。

2. PTC 的发生发展与 BRAFV600E 基因的相关性

PTC 发生的关键分子机制主要经由 MAPK 级联通路的组成性激活。丝分裂原激活的蛋白激酶/细胞外信号调节激酶(MAPK/ERK)信号通路转导途径是哺乳动物体内高度保守的受体蛋白激酶信号转导途径，Ras、Raf、MEK 和 ERK 蛋白就是该通路中的关键因子，共同调节着细胞的生长、分化、应激、炎症等多种重要的生理/病理效应。正常情况下，启动膜受体的初始信号 RAS 分子，募集至胞膜后触发启动 MAP 激酶的磷酸化，按顺序激活 MEK，在生长因子、细胞因子、神经递质等因素的刺激下发生顺序磷酸化，激活 ERK，发挥协调细胞功能调控作用[6]，内环境的稳定可由磷酸酶和促新陈代谢的双向通信进行高度调节以维持。当上游基因癌基因异常或微环境的改变/炎症刺激诱发使得 MAPK/ERK 信号转导通路的异常激活，转导信号在特定的关键因子积聚，使得有序的通路被破坏，对细胞的适应性控制变得不再可控，细胞生长分裂发生改变，最终 PTC 形成[7]。鼠类肉瘤滤过性毒菌致癌同源体 B1 (v-raf murine sarcoma viral oncogene homolog B1, BRAF)，位于人类 7 号染色体上，编码 RAF 家族丝氨酸/苏氨酸蛋白激酶，不依赖

RAS 信号通路，激活下游 MEK 和 ERK 蛋白信号通路，导致细胞影响细胞分裂、分化不可控，微环境的改变和促上皮－间质转化(epithelial-mesenchymal transition, EMT)的发生[8] [9]，促进肿瘤细胞发生、增殖和存活。较多研究发现 BRAF V600E 突变是 PTC 最常见的基因突变，BRAFV600E 密码子 600 处谷氨酸通常替换缬氨酸，存在于 29%~83%的 PTC 中[10]，有较高的特异性，临床侵袭性更高，动态风险评估较高，淋巴结转移及复发的概率较野生型高，总体预后相对差。

炎症刺激在肿瘤的发生、发展过程中起重要作用[11]；肿瘤组织中除肿瘤细胞外，约 80%由细胞外环境基质细胞和炎症细胞组成，共同构成了有利于肿瘤细胞生长的微环境[12]。慢性炎症过程中淋巴细胞、中性粒细胞均与肿瘤进展相关，其中中性粒细胞/淋巴细胞计数比值(neutrophil-to-lymphocyte ratio, NLR)和血小板/淋巴细胞计数比值(platelet-to-lymphocyte ratio, PLR)是临床研究中有价值的炎症指标，分别反映了 NE 或 PLT 与 LY 免疫反应之间的平衡关系。有研究发现高 NLR 与血清中促炎因子如 TNF-α、IL-6、IL-8、IL-12 等升高密切相关[13] [14]。NLR 升高反映肿瘤细胞周围微环境的变化、免疫系统平衡被打破、特异性抗肿瘤免疫活性的降低[15] [16]，构成有利于肿瘤侵袭转移的微环境。有国内外大量临床研究证实 NLR 和 PLR 与包括 PTC 内的多种癌症的发生、发展及预后密切相关[17]-[23]。Shrestha 等[24]回顾性研究发现，NLR 和 PLR 增加与淋巴结转移、甲状腺外扩散、肿瘤多灶性和双侧性有关；Huang 等[25]对 764 例诊断 PTC 患者回顾性分析发现 NLR、PLR 与 PTC 侵袭性临床病理特征和术后复发密切相关。林琳等[26]对 100 例分化型甲状腺癌进行分析，结果显示 NLR 与对甲状腺癌的诊断具有诊断价值。Gong 等[27]对 161 例甲状腺癌患者进行回顾性分析，结果显示患者肿瘤组织病理特性差、淋巴结易转移与 NLR 升高显著相关。有文献报道，在 PTC 发展的过程中 BRAFV600E 突变与 NLR 有明显相互作用[28]。中性粒细胞促进肿瘤的生长及转移，其机制与抑制肿瘤坏死因子-α (TNF-α)的分泌，促进基质金属蛋白酶-9 (matrix metallopro-teinase 9, MMP-9)、趋化因子、成纤维细胞生长因子-2 (fibroblast growth factor-2, FGF-2)和血管内皮生长因子(vascular endothelial growth factor, VEGF)等的分泌有关。高迁移率族蛋白 1 (high mobility group protein 1, HMGB1)、MMP-9 均在 PTC 患者中异常表达，与肿瘤侵袭、转移相关，且可辅助 PTC 的诊断和预后。HMGB1 已被证实可通过 MAPK 信号通路影响肿瘤发生发展[29]，并且 MAPK 信号通路可上调 MMP-9 的表达[30]。肿瘤相关成纤维细胞(cancer associated fibroblasts, CAF)源于静息状态的成纤维细胞、间充质干细胞或通过 EMT 转化而来，与 PTC 的侵袭相关；刘磊等[31]人发现 CAF 增生提示肿瘤侵袭能力增强，BRAFV600E 突变的 PTC 细胞可能与 CAF 相互作用，改变肿瘤微环境，使 PTC 更易发生腺外侵犯。Oksana Sulaieva 等[32]人发现淋巴结转移与 PTC 中 VEGF 表达的增加有关。

由此可见，甲状腺乳头状癌的发生、发展离不开基因改变和肿瘤的微环境共同作用。

3. AID 基因与 PTC 的相关性

载脂蛋 B 编辑酶催化多肽(apolipoprotein B mRNA-editing enzyme, catalyticpolypeptide-like，APOBEC)家族的成员中的活性诱导性胞嘧啶脱氨基酶(activation-induced cytidine deaminase, AID)的异常表达可导致癌基因的激活或抑制基因发生突变，可导致癌症的发生和促进癌症的转移[33]。AID 是在 B 细胞正常生发中心表达的基因编辑酶，其靶向免疫球蛋白基因能促进对抗原的亲和力并改变 B 细胞受体在适应性免疫中发挥关键作用[34]。上皮细胞慢性癌变过程中 AID 通过改变基因序列参与肿瘤的发生、发展已成为研究的热点，B 细胞淋巴瘤中 AID 的异常表达在国内外已达成广泛的共识[35]。但现在有更多的研究表明 AID 参与肿瘤还存在于非 B 细胞的恶性肿瘤中，如膀胱癌、乳腺癌、黑色素瘤、消化系统肿瘤等。Zhifei Che 等[36]人发现激活 AID 表达促进恶性表型和 EMT。Denise P 等[37]人已经发现有证据表明，恶性和非恶性乳腺上皮细胞的 EMT 需要 AID，AID 在乳腺上皮细胞系中炎症刺激下被诱导并在 EMT 过程中发挥关键作用；研究表明 EMT 的异常调控改变了微环境促进 PTC 中肿瘤的发生并增加了 PTC 侵袭性

和转移性。Taichiro Nonaka 等[38]人发现 AID 在人多种消化系统癌症、黑色素瘤中表达；这些研究的一个普遍发现是促炎细胞因子和/或感染可通过 NFκB 通路诱导 AID 的表达[39]。通常在细胞质中 NF-κB 信号通路处于失活状态，是由细胞外炎症因子、紫外线等外界的刺激时，细胞外信号因子与细胞膜上的肿瘤坏死因子(Tumor Necrosis Factor, TNF)受体(TNFR)结合，TNF 积聚并于细胞质中 TNFR1 相关死亡结构域蛋白(TRADD)分子发生相互作用，TRADD 招募肿瘤坏死因子受体相关因子(TRAF)。受体蛋白接受刺激后先活化 IκB 激酶(IKK)，释放 NF-κB。自由的 NF-κB 会进入细胞核，与有 NF-κB 结合位点的基因结合，启动转录进程。尽管现有研究 AID 在 PTC 中的表达甚少，但已证实 NF-κB 信号通路的活性增加在 PTC 存在[40]，受 BRAFV600E 基因的调控，不仅参与甲状腺癌的发生、发展，而且可以促进炎症和构成肿瘤微环境的分子产生，同时也能增加抗凋亡因子如 BCL2 以及促有丝分裂因子如 c-MYC 和细胞周期蛋白 D1 的表达[41]。

4. BRAFV600E 突变、AID 与 PTC 相关性

慢性炎症刺激和基因突变常使机体内微环境改变、诱导基因突变进而导致恶性肿瘤的发生、发展；而肿瘤的发生又诱发了免疫系统的失调，二者之间存在着交互作用。BRAFV600E 突变型 PTC 与 NLR 的升高有交互作用，NLR 是有意义的炎症指标，既能反应特异性免疫系统的失调，又能反应细胞微环境平衡被破坏。AID 的表达是在促炎细胞因子和/或感染的作用下通过 NFκB 信号通路被诱导，MAPK 信号通路在 NFκB 通路可被调节激活；MAPK 级联通路的组成性激活又是 PTC 发生的关键分子机制；同时 BRAFV600E 能明显促进甲状腺细胞中的 IKKα/β 和 IκBα 的磷酸化，BRAFV600E 能通过调节 NF-κB 的活性来促进甲状腺细胞增殖和迁移[42]。部分研究已证实 AID 在 EMT 过程中发挥关键作用，PTC 有可能是在 EMT 的基础之上发生的，EMT 增加了肿瘤细胞的侵袭性和转移性。由此大胆猜想 AID 与 BRAFV600E 突变型 PTC 之间是具有交互作用。

5. 展望

综上所述，大多数研究提示 AID 异常累积表达使原癌基因的激活和/或抑癌基因的突变促进肿瘤细胞发生、发展，其高表达可能与 BRAFV600E 突变型 PTC 具有交互作用。但由于目前对 AID 与 BRAFV600E 突变型 PTC 直接关系目前尚缺乏研究，要想通过内源性的 AID 基因水平改变来影响细胞的分化程度、调控肿瘤的生长和转移概率，还需要进一步的研究，来证实其临床应用的有效性、安全性与实用性。

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