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PIK3CA基因突变与HR阳性且HER2阴性乳腺癌的关系

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摘　要

PIK3CA靶向药物也在临床上得到开发和试验验证。PI3K抑制剂已批准用于PIK3CA突变、激素受体阳性且HER2阴性(HR+/HER2−)晚期乳腺癌患者。然而并非所有患者都能从靶向治疗获益且大多数患者不可避免地会出现内分泌抵抗。PIK3CA突变状态作为HR+/HER2−乳腺癌生物标志物的预后和预测价值，作为分子靶点用于乳腺癌的常规治疗等方面仍存在争议。

关键词

乳腺癌，ER，HR，HR+/HER2−，PIK3CA

The Relationship between PIK3CA Mutation and Hormone Receptor Positive and HER2 Negative Breast Cancer

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Abstract

PIK3CA targeted drugs have also been developed and tested clinically. PI3K inhibitor has been approved for use in patients with PIK3CA mutation, hormone receptor positive and HER2 negative

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(HR+/HER2−) advanced breast cancer. However, not all patients can benefit from targeted therapy and most patients will inevitably develop endocrine resistance. The PIK3CA mutation status as a biomarker of HR+/HER2 breast cancer and its predictive value, as a molecular target for routine treatment of breast cancer, is still controversial.

Keywords

Breast Cancer, ER, HR, HR+/HER2−, PIK3CA

1. 引言

乳腺癌(Breast Cancer)是最常见的女性恶性肿瘤之一。2020 年全球新增 230 万新病例，这占所有癌症病例的 11.7%，有 685,000 死亡病例[1] [2]。PIK3CA 是近年来发现的乳腺癌又一常见突变基因，PIK3CA 突变存在于高达 40%的 HR+/HER2−乳腺癌患者中[3] [4]。

2. PIK3CA 基因的分子病理特征

磷脂酰肌醇-3-激酶(PI3K)在细胞内介导不同的过程，包括生长、增殖和存活，并且经常参与癌发生、肿瘤进展和转移[5]。PI3K 的失调会在许多癌症中启动丝氨酸/苏氨酸激酶 AKT 的活性，从而调节一系列下游蛋白质从而导致肿瘤的发生和发展[6]。三十年前 Arafeh 和 Samules [7]发现并总结 PI3K/AKT/mTOR 信号通路与致癌和癌症进展相关[8]。PI3 激酶将磷脂酰肌醇(4,5)-二磷酸(PIP2)转化为磷脂酰肌醇(3,4,5)-三磷酸(PIP3)，随后激活 AKT 并调控细胞生长和存活所需的下流信号通路。PI3K 激活在生理上被肿瘤抑制磷酸酶和张力蛋白同系物(PTEN)消除，后者将 PIP3 转化回 PIP2 [9]。PIP3 肽水平取决于 PI3K 和 PTEN 之间的竞争。PI3K 的过度激活以及 PTEN 表达的降低导致 AKT 的激活和表达水平升高，从而在病理上促进细胞周期进程[9]。已确定存在三类 PI3K：I 类(Ia、Ib)、II 类和 III 类。与细胞调节相关性最强的是 Ia 类 PI3K，它们充当调节和催化亚基的异源二聚体[10]。I 类 PI3 激酶 p110α 的催化亚基由 PIK3CA 基因编码，总基因组大小为 86,190 个碱基对，包含 21 个外显子，最终转录本为 3207 个碱基对，编码 1068 个氨基酸的蛋白质。p110α 蛋白有五个结构域：连接调节亚基的衔接子结合结构域、Ras 结合结构域、结合 PIP2 和 PIP3 的 C2 结构域、螺旋结构域和激酶结构域[11]。PIK3CA 基因的体细胞突变在人类癌症中最为普遍，在原发性乳腺癌中的突变率高达 40% [12] [13]。最常见的三个位点：Exon9 中的 COSMIC 760 (发生率为 17%)和 E545K 突变，Exon19 中的 COSMIC 763 (发生率 17%)影响 E545，Exon20 中的 COSMIC 775 (发生率 35%)改变 H1047 [14]。PIK3CA 高频率突变具有激酶活性，当野生型和突变型克隆通过尾静脉注射到裸鼠体内，野生型没有肿瘤形成，而突变型克隆在不同部位形成肿瘤，并伴有微转移和浸润[15] [16]。此外，PIK3CA 突变被认为是乳腺癌发展的早期事件，即使在较小体积的肿瘤和非浸润性前驱病变(如 DCIS)中也能检测到其突变[17]。研究发现 PIK3CA 基因突变患者有更高的生存率(Dumont 等人、Pang 等人[18] [19])，而 Sobhani 等人及 Fan 等人的研究结果则支持 PIK3CA 突变与较低的生存率[20] [21]之间存在关联。这些相矛盾的结果可能是由于人群差异、样本含量大小、亚组分布和治疗类型方面的异质性所致。

3. PIK3CA 基因在 HR+/HER2−乳腺癌中的突变及临床意义

根据免疫组织化学(IHC)，大多数乳腺癌呈激素受体(HR)阳性，并且缺乏皮生长因子受体 2 (HER2)扩增(HR+/HER2−)，占 50 岁以下女性的病例的 65%和 50 岁以上女性病例的 75% [22]。HR+/HER2−乳腺癌是一个异质性亚群，大多数 HR+/HER2−肿瘤属于 Luminal 亚型[23]。低级别(高分化)肿瘤通常具有较高的 HR 表达以及较低的增殖率，而中级别和高级肿瘤可能具有较低水平的 ER 并且可能缺乏 PR 表达，具有较高的细胞增殖率[24]。肿瘤在雌激素受体(ER)和孕激素受体(PR)表达水平(由 ER 驱动)、组织学分级、增殖程度(通过 Ki-67 或其他指标测量)、基因表达模式以及分子类型方面各不相同[23] [24]。PIK3CA 基因突变存在于大约 40% HR+/HER2−乳腺癌患者中[12] [13]且与这些特征高度相关，研究 PIK3CA 基因突变与乳腺癌潜在联系具有重要的临床意义。最近，TEAM 以摘要形式发表的研究发现，进行了辅助内分泌治疗的绝经后 ER+乳腺癌患者中 PIK3CA 基因突变发生率为 39.8% (1702/4272) [25]。也有研究发现有 PIK3CA 基因突变并未接受 PI3K 抑制剂治疗的 HR+/HER2−乳腺癌患者无转移生存率较接受 PI3K 抑制剂治疗者低[26]。一项涉及 278 名女性的四项新辅助内分泌治疗乳腺癌试验的回顾性汇总分析发现 PIK3CA 突变与内分泌治疗耐药性相关[27]。内分泌治疗耐药是临床治疗乳腺癌患者时常见的治疗挑战，且其机制尚未被完全解读。PIK3CA 基因在 HR+/HER2−乳腺癌中的临床意义研究前景广阔，可为临床制定治疗策略提供理论基础。

4. PIK3CA 基因与 HR+/HER2−乳腺癌靶向治疗及预后的关系

晚期 HR+/HER2−阴性乳腺癌的标准化治疗包括内分泌治疗、联合或不联合使用细胞周期蛋白依赖性激酶 4 和 6 (CDK4/6)抑制剂[28]。PI3K 抑制剂与内分泌治疗联合使用的原理是协同抑制 PI3K 和 ER 通路[29]。早期原发性乳腺癌发生 PIK3CA 基因突变，就可以在其微转移的腋窝淋巴结中发现同样的突变基因，并用特定的方法检查出微量的突变 DNA 分子，这可能成为早期检测乳腺癌微转移结节的一种分子诊断手段[30] [31]。PIK3CA 的突变是与 HR+/HER2−转移性乳腺癌标准辅助化疗的结局高度相关的预后指标[32]。最近的一项研究也发现不仅在 PI3K 抑制剂治疗组中 PIK3CA 突变可能作为 HR+/HER2−乳腺癌不良预后的重要预测因子，而且在非 PI3K 抑制治疗组也有同样的结果[33]。数据表明 PIK3CA 突变是具有 PI3K 通路依赖性的晚期或转移性 HR+/HER2−乳腺癌的相关治疗靶点。2020 年 5 月 28 日，欧洲药品管理局批准了 alpelisib 联合氟维司群用于治疗 HR+/HER2−的绝经后女性患者和男性患者[34]。SOLAR-1 III 期临床试验调查了 alpelisib (一种特异性 I 类 PI3K 抑制剂加氟维司组对比安慰剂加氟维司组对转移性 HR+/HER2 乳腺癌患者的疗效和安全性)接受内分泌治疗的癌患者中，约 85.6%的患者出现了内分泌抵抗[35]。Ramirez-Ardila 等人也描述了晚期 HR+/HER2−乳腺癌对不同治疗的反应[36]，研究结果指出。Stemke-Hale 等的研究中没有发现 PIK3CA 突变与辅助他莫昔芬的作用之间存在关联[37]。也有一些作者描述了 PIK3CA 突变 HR+/HER2−乳腺癌对他莫昔芬的耐药性之间的正向联系，此类晚期患者生存率更低，产生耐药的周期更短[38] [39]，而其他作者发现如果检测到 PIK3CA 突变表示肿瘤对他莫昔芬的敏感性偏高[40]。必须承认，这些联系复杂且涉及多重机制，且仍缺乏更加有力的前瞻性研究。同时这也表示了 PIK3CA 基因组畸变可预测 HR+/HER2−乳腺癌疾病进展及肿瘤对药物治疗的反应，这也意味着 PIK3CA 基因突变的检测可作为预测患者预后的辅助因子、可以识别可能受益于 PI3K 靶向治疗的目标患者。

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