

PI3K/AKT/mTOR信号通路与乳腺癌多药耐药性研究进展

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摘要

乳腺癌多药耐药是导致乳腺癌治疗失败的主要原因。PI3K/AKT/mTOR信号通路异常激活与乳腺癌的发生发展及耐药性密切相关, 抑制该通路是改善乳腺癌治疗效果和克服耐药的可行途径。目前, 许多PI3K/AKT/mTOR信号通路抑制剂通过联合标准疗法克服乳腺癌的多药耐药正处于临床前或临床研究。本文综述了PI3K/AKT/mTOR通路在乳腺癌多药耐药中的作用以及通过抑制该通路克服乳腺癌多药耐药的策略研究。

关键词

乳腺癌, PI3K/AKT/mTOR信号通路, 多药耐药, 抑制剂

Research Progress on PI3K/AKT/mTOR Signaling Pathway and Multidrug Resistance in Breast Cancer

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Abstract

Multidrug resistance of breast cancer is the main cause of treatment failure of breast cancer. The abnormal activation of PI3K/AKT/mTOR signaling pathway is closely related to the occurrence, development and drug resistance of breast cancer. Inhibiting PI3K/AKT/mTOR signaling pathway is an effective way to improve the therapeutic effect of breast cancer and overcome drug resistance. At present, several PI3K/AKT/mTOR signaling pathway inhibitors are in preclinical or clinical research to overcome multidrug resistance of breast cancer. This article reviews the role of PI3K/AKT/mTOR pathway in breast cancer multidrug resistance and the research progress of strategies to overcome breast cancer multidrug resistance by inhibiting this pathway.

Keywords

Breast Cancer, PI3K/AKT/mTOR Signaling Pathway, Multidrug Resistance, Inhibitors

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1. 引言

乳腺癌发病率高、死亡率高,是世界上女性最常见的恶性肿瘤之一[1]。其中早期乳腺癌占 90%,治疗方式除了手术和放射治疗,还包括分子靶向药物治疗。晚期乳腺癌采用基于全身疗法的多种手段综合治疗。乳腺癌分子亚型主要包括 HER2 阳性、激素受体阳性(PR+和/或 ER+)及三阴性乳腺癌(ER、PR 和 HER2 均不表达) [2]。这些亚型的不同特征决定了其治疗策略的多样性。对于 HER2 阳性的患者,靶向药物是重要选择;而 PR+和 ER+患者则可通过内分泌治疗来控制病情。三阴性乳腺癌由于缺乏特定靶点,通常采用化疗和免疫治疗相结合的方式进行治疗。此外,PARP 抑制剂也为部分具有 BRCA 突变的患者提供了新的治疗希望。由于抗癌药物的广泛应用,乳腺癌患者的总体生存率有所提高,但药物长期使用造成多药耐药(Multidrug Resistance, MDR)严重限制了药物治疗的效果,成为临床治疗中的一大挑战[3]。

PI3K/AKT/mTOR 信号转导通路参与细胞内生物学过程,该通路的异常激活与乳腺癌发生发展和治疗耐药性密切相关[4]。目前,PI3K/AKT/mTOR 信号通路已成为克服乳腺癌耐药的新靶点。本文对 PI3K/AKT/mTOR 信号通路异常激活引起乳腺癌多药耐药的机制进行了归纳,讨论了目前的治疗策略与临床实践,并对未来的研究趋势进行了预测。

2. PI3K/AKT/mTOR 信号通路与乳腺癌发生发展

2.1. PI3K/AKT/mTOR 通路的组成和分子调控机制

PI3K/AKT/mTOR 信号通路是细胞内一个非常重要的传导网络,体现在负责调控细胞生存、增殖、代谢以及血管生成等方面[5]。该通路的关键因子包括磷脂酰肌醇 3 激酶(PI3K)、蛋白激酶 B (PKB 或 AKT)和哺乳动物雷帕霉素靶蛋白(mTOR),这些激酶通过级联反应激活下游效应分子,从而实现对细胞功能的调控[4]。

PI3K 是这一信号通路的上游效应分子,分为三类,其中 Class I PI3Ks 是研究最为广泛的异二聚体,

由一个催化亚基(p110)和一个调节亚基(p85)组成[4]。PI3K 的激活方式主要通过受体酪氨酸激酶直接结合和通过适配蛋白间接结合。当细胞外生长因子与受体酪氨酸激酶直接结合时, p85 将 PI3K 招募到细胞膜上, 导致 p110 的催化活性增加, 进而磷酸化磷脂酰肌醇 3,4-二磷酸(PIP₂)生成磷脂酰肌醇 3,4,5-三磷酸(PIP₃) [6]。PI3K 的 p85 亚基与适配蛋白上的磷酸化酪氨酸残基结合, 从而激活 PI3K [6]。

第二信使 PIP₃ 的生成是激活 AKT 的关键步骤。AKT 与膜上的 PIP₃ 的对接, 导致 AKT 的构象变化, 暴露出苏氨酸位点(Thr308)和丝氨酸位点(Ser473), PIP₃ 结合磷酸肌醇依赖性激酶 1 (PDK1)磷酸化 Thr308 位点、mTORC2 磷酸化 Ser473 位点而激活 AKT [7]。AKT 激活后能够触发下游蛋白的激活, 这包括 mTORC、细胞周期蛋白依赖性激酶(CDKs)、 β -catenin, 进而干预细胞的生长、代谢和转移[8]。

2.2. PI3K/AKT/mTOR 信号通路的激活与乳腺癌发生发展

在正常细胞中, PI3K/AKT/mTOR 信号通路受到严格的调控, 以保证细胞的正常生长和分化。然而, 在许多类型的癌症中, 包括胃癌、结直肠癌、卵巢癌、乳腺癌、非小细胞肺癌等, 该通路常因基因突变、表观遗传改变或上游信号分子的异常而过度激活[9]-[14]。

除此之外, 乳腺癌的多个亚型中经常发生 PI3K/AKT/mTOR 信号通路异常激活。TNBC 具有侵袭性强、复发早、进展快等特性, 该通路异常激活在 TNBC 中较为常见[15]。约 30%~40%的晚期 ER+乳腺癌具有激活性 PIK3CA 突变, 这些突变与肿瘤的发生发展和耐药性密切相关[16]。此外, 在 HER2 阳性乳腺癌中, PI3K/AKT/mTOR 信号通路的异常激活也与耐药性的产生有关[17]。

PIK3CA 是编码 PI3K 的 p110 α 催化亚基的基因, PIK3CA 突变主要集中在三个“热点”(H1047R、E542K 和 E545K), 这些突变可促进细胞增殖、侵袭、染色体不稳定和免疫抑制环境[18]。除了 PIK3CA 基因突变, 抑癌基因 PTEN 的缺失也可能导致该通路的异常激活, 从而导致癌症发生[19]。PTEN 的缺失通过不同方式发生, 包括体细胞突变、杂合性缺失、表观遗传修饰和蛋白质不稳定性。

2.3. PI3K/AKT/mTOR 信号通路抑制剂

PI3K 抑制剂可分为泛 PI3K 抑制剂, 如 buparlisib (BKM120)、pictilisib (GDC-0941)和 Copanlisib (BAY 80-6946); 亚型选择性 PI3K 抑制剂, 如 taselisib (GDC-0032)、alpelisib (BYL719)、Inavolisib (GDC-0077)和 Serabelisib (TAK-117); AKT/mTOR 双重抑制剂, 如 BEZ235、GSK2126458、SF1126、BGT226 及 XL-765。

Alpelisib (BYL719)是第一个特异性靶向 p110 α 亚型的口服 PI3K 抑制剂[20], 也是首个被批准联合 Fulvestrant 用于 PIK3CA 突变的 HR+/HER2 转移性乳腺癌患者的 PI3K 抑制剂[21]。Taselisib (GDC-0032)是另一种亚型选择性 PI3K 抑制剂, 对 p110 α 突变型有更高的抑制作用[22]。Buparlisib (BKM120)和 Pictilisib (GDC-0941)是口服泛 PI3K 抑制剂, 可抑制 I 类 PI3K 的所有四种亚型[23] [24]。针对 PI3K/mTOR 信号通路的双重阻断剂, BEZ235 展现出了对 I 类 PI3K 的不同亚型以及 mTOR 激酶活性的广泛抑制作用[25]。

基于结构属性和作用位点, AKT 抑制剂可分为针对 PH 结构域的抑制剂、能够引发构象变化的抑制剂, 以及与 ATP 进行竞争性结合的抑制剂。目前研究认为较有效的是 ATP 竞争性抑制剂, 其中 Ipatasertib (GDC-0068)和 Capivasertib (AZD-5363)治疗乳腺癌的临床研究正在进行[26]。

第一代 mTOR 抑制剂依维莫司(Everolimus)和替西莫司(Temsirolimus)仍是目前研究的焦点。Everolimus 是首个被批准用于 HR+/HER2-乳腺癌的 mTOR 抑制剂, 在几项临床试验中显示出改善乳腺癌患者的无进展生存期(PFS) [27] [28]。此外 Everolimus 联合其他药物如 Fulvestrant、卡培他滨等, 联用能够有效阻止乳腺癌进展[29] [30]。在一项随机III期试验中, Temsirolimus 联合 Letrozole 作为一线治疗

方案在未接受芳香酶抑制剂治疗的晚期 HR 阳性乳腺癌患者中并没有改善总 PFS [31]。

PI3K/AKT/mTOR 信号通路的异常激活与乳腺癌细胞对药物治疗产生耐药性密切相关, 阻断该信号通路可以提高药物的敏感性并逆转耐药[32]。综合目前的研究来看, PI3K/AKT 抑制剂与其他抗肿瘤治疗手段的联合使用有望解决乳腺癌的耐药问题。

3. PI3K/AKT/mTOR 信号通路与乳腺癌多药耐药

3.1. PI3K/AKT/mTOR 信号通路与乳腺癌内分泌治疗耐药

内分泌治疗药物是 ER+乳腺癌最重要的治疗选择之一, 例如选择性雌激素受体调节剂他莫昔芬(Tamoxifen), 以及选择性雌激素受体降解剂氟维司群(Fulvestrant), 还有芳香化酶抑制剂, 包括来曲唑(Letrozole)和依西美坦(Exemestane), 均是关键的治疗手段。约 50%患者由于内源性或获得性的内分泌治疗耐药, 导致疾病进展和预后不良[33]。目前已知的乳腺癌内分泌耐药机制主要与 ER 异常有关, 包括 ER 表达水平的改变、ER 基因突变、ER 翻译后修饰、ER 共激活因子异常, 以及 ER 与各种细胞内信号分子的相互作用, 如 HER2、EGFR、PI3K/AKT/mTOR 和 MAPK/ERK 等[34]。

PI3K/AKT 通路异常激活是乳腺癌患者内分泌治疗耐药的原因之一。在接受内分泌治疗的原发性和转移性乳腺癌患者, 其转移性肿瘤病灶中 p-mTOR 表达增加, 提示可能 PI3K/AKT/mTOR 通路的代偿性激活而产生内分泌治疗耐药[35]。在雌激素缺乏的情况下, PI3K 和 AKT 可以磷酸化 ER α 的 Ser167 位点独立激活 ER α , 抑制他莫昔芬诱导的乳腺癌细胞凋亡, 导致乳腺癌细胞对内分泌治疗失去敏感性[36]。肿瘤相关巨噬细胞(TAM)分泌的 CC-趋化因子配体 2 (CCL2)激活 PI3K/Akt/mTOR 信号传导并增加乳腺癌细胞的内分泌抵抗力, 促进肿瘤微环境(TME)中的内分泌耐药[37]。

现有研究表明, PI3K/AKT/mTOR 信号通路抑制剂与乳腺癌的内分泌疗法相结合是一种对抗乳腺癌耐药的有效治疗方案。PI3K/AKT/mTOR 通路抑制剂 buparlisib、Everolimus 或 BGT226 与 Fulvestrant 联合使用, 通过促进 MCF7 细胞凋亡来逆转内分泌治疗的耐药性[38]。此外, Letrozole 耐药 MCF-7/AROM-1 细胞中 AKT/mTOR/S6K1 通路激活, BEZ235 处理促进了 Letrozole 耐药细胞的凋亡, 并且耐药细胞比亲本细胞对 Everolimus 更敏感[39]。因此, 抑制 PI3K/AKT/mTOR 通路可能有助于恢复雌激素受体阳性(ER+)乳腺癌对激素治疗的敏感性, 并通过促进细胞凋亡来克服内分泌治疗的抵抗性。

PI3K/AKT/mTOR 通路激活与内分泌治疗耐药的关系已经在临床研究中得到了循证医学证据支持。BOLERO-2 研究评估了 Everolimus 联合 Exemestane 在内分泌治疗后疾病进展的绝经后 HR+晚期乳腺癌患者中的疗效, 联合治疗显著改善了无进展生存期(PFS), 中位 PFS 从 4.1 个月提高到 10.6 个月[40]。TAMRAD 研究中 Everolimus 联合 Tamoxifen 的临床获益率(CBR)显著提高(61% vs 42%) [41]。BELLE-2 试验评估了 Buparlisib 联合 Fulvestrant 在芳香酶抑制剂治疗后疾病进展的 HR+/HER2-乳腺癌患者中的疗效。研究结果显示, PIK3CA 突变患者从 Buparlisib 治疗中获益更多[42]。FAKTION 试验中, AKT 抑制剂 Capivasertib 联合 Fulvestrant 也改善芳香酶抑制剂耐药晚期乳腺癌的 PFS 和 OS [43]。此外, LORELEI 研究评估了 Letrozole 联合 PI3K α 抑制剂 taselisib 在早期乳腺癌的新辅助治疗中的疗效, 研究结果显示, Letrozole 联合 PI3K α 抑制剂 taselisib 显示出协同抗肿瘤作用[44]。

3.2. PI3K/AKT/mTOR 信号通路与乳腺癌化疗耐药

在乳腺癌的治疗中, 化疗依旧是主要的治疗手段, 然而, 化疗失败经常发生在获得性耐药出现之后。目前关于乳腺癌化疗耐药的潜在机制尚未明确阐明, 归因于多种因素, 包括药物积累减少、药物-靶点相互作用减少、肿瘤干细胞数量增加等[45]。另外, PI3K/AKT/mTOR 通路的激活会增加多药耐药相关蛋白(如 P-糖蛋白、BCRP 和 MRP1)的表达和活性, 这些蛋白可将化疗药物从细胞中置换出来, 降低细胞内

药物浓度, 诱发耐药[46]。研究显示, 他莫昔芬耐药 MCF7 和 T47D 细胞中, PI3K 通路过度活化导致 BARD1 和 BRCA1 表达升高, 增强了 DNA 损伤修复能力, 导致乳腺癌顺铂和阿霉素耐药[47]。

多项临床前研究表明, PI3K/AKT/mTOR 抑制剂在逆转乳腺癌化疗耐药方面具有重要作用。PI3K 抑制剂 BKM120 或 BYL719 可以降低 BARD1 和 BRCA1 的表达, 从而逆转乳腺癌对蒽环和铂类的耐药[47]。AKT 抑制剂 MK-2206 联合 GLUT1 抑制剂 WZB117 通过触发 DNA 损伤反应及阻断 AKT 磷酸化, 诱导 MCF-7 与 MDA-MB-231 乳腺癌细胞的凋亡[48]。另外, 泛 PI3K 抑制剂 BKM120 通过抑制 PI3K/AKT/NF- κ B 信号通路, 在敏感和 MDR 乳腺癌细胞中都显示出强大的抗肿瘤能力, 并且 BKM120 与多柔比星联合显示出更好的协同作用[49]。

Neo PHOEBE 试验显示, 在 HER2+早期乳腺癌患者的紫杉烷-曲妥珠单抗组合治疗中加入 PI3K 抑制剂 buparlisib 治疗效果并不理想[50]。但是在另一个 LOTUS 研究中, 无法手术的局部晚期或转移性原发性 TNBC 患者给予 AKT 抑制剂 Ipatasertib 联合紫杉醇, 结果显示 Ipatasertib 联合紫杉醇治疗对比安慰剂联合紫杉醇治疗可以延长患者的 PFS, 在 Ipatasertib 治疗 PTEN 表达低的亚组中中位 PFS 延长, 在 PIK3CA/AKT1 变异人群中中位 PFS 也显著延长, 这是支持 AKT 靶向治疗 TNBC 的第一个临床试验结果[51]。

3.3. PI3K/AKT/mTOR 信号通路与乳腺癌靶向治疗耐药

除了曲妥珠单抗(Trastuzumab)、帕妥珠单抗(Pertuzumab)伊尼妥单抗(Inebilizumab)等单克隆抗体药物外, 近些年在 HER2 阳性乳腺癌治疗领域还涌现了以拉帕替尼(Lapatinib)、培利替尼(pelitinib)为代表的小分子酪氨酸激酶抑制剂(TKI), 以及抗体药物偶联物, 如恩美曲妥珠单抗(T-DM1), 这些新药为患者提供了更多的治疗选择。

然而, 在这些创新药物的应用中, 获得性耐药的出现仍然是一个不可避免的阻碍[52]。尽管治疗手段不断进步, 但对于耐药机制的深入理解和有效应对策略的开发, 依然是未来研究的重点方向。HER2 结构变化的常见形式是 HER2 截短突变体(p95-HER2), p95HER2 缺乏曲妥珠单抗结合部位, 但保留了激酶活性, 通过自发形成同源二聚体, 导致细胞增殖。靶向治疗会导致 HER2+的乳腺癌 ER 表达增加, 从而导致细胞存活。其他受体如 HER3 也可在 HER2 肿瘤中过度表达, 激活下游 PI3K/AKT 通路, 促进肿瘤细胞存活并导致对 HER2 靶向治疗产生耐药[52]。此外, 研究发现 HER2 阳性乳腺癌患者接受抗 HER2 治疗后 PIK3CA 突变与较差的预后相关, 提示 PI3K/AKT/mTOR 通路的激活可能是 HER2 治疗耐药的重要机制[53]。

一些研究已经证明抑制 PI3K/AKT/mTOR 通路是解决抗 HER2 治疗耐药问题的新方法。泛 PI3K 抑制剂 NVP-BKM120 联合 HER2 靶向治疗, 显著抑制 PIK3CA 突变肿瘤移植瘤的生长[54]。通过将 Lapatinib 与 mTOR 抑制剂 INK-128 联合使用同时阻断 PI3K/Akt/mTOR 和 ERK 通路, 在抗 HER2 治疗难治性乳腺癌模型中协同诱导细胞死亡和肿瘤消退[55]。单克隆抗体如曲妥珠单抗通过靶向 ErbB 受体治疗乳腺癌, 研究发现抑制 PI3K/AKT/mTOR 可以重新恢复 ErbB 靶向药物(pelitinib、canertinib)敏感性, 使用 PI3K/mTOR 双重抑制剂 NVP-BEZ235 与 pelitinib 或 canertinib 组合对 ErbB 靶向药物耐药的乳腺癌细胞通过协同生长抑制作用来克服耐药[56]。

临床试验结果显示, 在 BOLERO-1 和 BOLERO-3 研究中 Everolimus 联合 Trastuzumab 治疗组 PFS 均显著延长, 表明 Everolimus 在增强抗 HER2 治疗效果方面具有潜力[57] [58]。NeoPHOEBE 试验显示, 在 HER2+原发性乳腺癌患者中联合应用泛 PI3K 抑制剂 buparlisib 后, HER2 靶向治疗曲妥珠单抗的抗肿瘤效果增强[50]。NeoSphere 研究招募局部晚期、炎症性乳腺癌和早期 HER2 阳性乳腺癌患者, 其中使用 Trastuzumab、Pertuzumab 和多西他赛三种药物联合治疗组的患者较 Trastuzumab + Pertuzumab 治疗组,

病理完全缓解(pCR)得到改善, 且没有显著增加不良反应[59]。

3.4. PI3K/AKT/mTOR 信号通路与乳腺癌 PARP 抑制剂耐药

PARP 抑制剂可以阻断肿瘤细胞中聚 ADP 核糖聚合酶(PARP)的功能, 干扰 DNA 单链断裂的修复过程, 从而在 BRCA1/2 突变的乳腺癌患者中发挥显著的治疗作用[60]。目前, 奥拉帕利(Olaparib)和塔拉唑帕尼(Talazoparib), 这两种 PARP 抑制剂已获得 FDA 的批准, 用于治疗 BRCA1/2 突变的转移性乳腺癌患者。与标准化疗相比, 奥拉帕尼改善了 BRCA 突变的 HER2-转移性乳腺癌患者的 PFS [61]。然而, 随着获得性耐药的逐渐出现, 迫切需要开发克服乳腺癌对 PARP 此外, 研究发现 FLT1 (VEGFR1)通过激活 AKT 促进细胞存活和抑制细胞毒性免疫反应导致 PARP 抑制剂耐药; 使用 axitinib 阻断 FLT1 信号传导, 使小鼠 PARP 抑制剂耐药肿瘤对 PARP 抑制剂治疗重新敏感[62]。

同源重组修复(Homologous recombination repair, HRR)是 PARP 抑制剂耐药的主要原因, 除此之外还涉及 DNA 复制叉保护、逆转突变、表观遗传修饰、ADP-核糖基化恢复(PARylation)和信号通路相互作用等[63]。

PARP 抑制剂可能会诱导细胞启动保护机制, 从而激活 PI3K/AKT/mTOR 信号通路帮助肿瘤细胞修复 DNA 损伤, 并抵消了 PARP 抑制剂的疗效[64]。研究发现, 抑制 PARP 可抑制 ATM 的多聚 ADP 核糖基化, 促进 ATM-NEMO 相互作用, 进而促进该复合物的胞质转位, 形成 p-ATM-NEMO-AKT-mTOR 细胞保护信号小体[65]。

3.5. PI3K/AKT/mTOR 信号通路与乳腺癌 CDK4/6 抑制剂耐药

目前, 已有三种 FDA 批准的 CDK4/6 抑制剂, 分别是帕博西尼(Palbociclib)、瑞博西尼(Ribociclib)和阿贝西利(Abemaciclib)。达尔西利(Dalpiciclib)是中国自主研发的 CDK4/6 抑制剂。这些抑制剂被用于治疗内分泌治疗耐药的乳腺癌患者以及其他类型的癌症患者, 显著延长了患者的生存期[66]。尽管如此, 这些抑制剂使用导致获得性耐药是不可避免的, 导致乳腺癌患者病情进一步恶化, 抑制剂耐药机制的深入研究以及新治疗策略开发刻不容缓。

迄今为止, CDK4/6 抑制剂耐药的原因比较复杂, 包括 RB1 或 FAT1 缺失突变、CDK4/6 过表达或扩增、细胞周期蛋白 E1 的过表达和 PI3K/mTOR 介导的 CDK2 激活[67]。CDK4/6 抑制剂联合 PI3K/AKT/mTOR 抑制剂逆转在乳腺癌中的耐药已经被证实是行之有效的途径。PDK1 激活是 ER 阳性乳腺癌中 Palbociclib 耐药的关键原因, 用 PDK1 抑制剂或 CDK2 抑制剂 dinaciclib 处理能够增加 ribociclib 耐药细胞对 CDK4/6 抑制剂敏感性[68]。mTORC1/2 抑制剂 AZD2014 可以抑制 CDK4/6 抑制剂耐药细胞中的 Rb 磷酸化、细胞周期蛋白 D1 表达和 E2F 介导的 E2F1、CDC6、RAD51 等基因转录[69]。在临床试验中, BYLieve 研究评估了 AKT 抑制剂 BYL719 联合 Fulvestrant 对 CDK4/6 抑制剂治疗耐药的 PIK3CA 突变、HR+/HER2-复发性乳腺癌患者的影响, 结果证明该疗法显示出良好的疗效和可控的安全性[69]。

3.6. PI3K/AKT/mTOR 信号通路与乳腺癌免疫治疗耐药

肿瘤免疫治疗在肿瘤治疗中取得了显著的临床疗效。Atezolizumab 已被 FDA 批准与纳米粒子白蛋白结合型紫杉醇(nab-paclitaxel)用于治疗表达 PD-L1 的晚期转移性 TNBC 患者[70]。Durvalumab 和 Avelumab 正处在各种类型乳腺癌治疗的II/III期临床试验阶段。PI3K/AKT/mTOR 信号通路在转移性乳腺癌中对免疫抑制的维持具有重要作用, 该通路在转移性乳腺癌中的激活程度更高, 维持了更强的免疫抑制状态[71]。因此, 这些临床前研究数据表明, 联合使用 PI3K/AKT/mTOR 抑制剂可有效克服乳腺癌患者对免疫检查点阻断疗法的耐药性。然而, 要了解这些联合疗法的安全性和有效性, 还需要开展进一步

的临床研究。

4. 总结与展望

本综述阐述了 PI3K/AKT/mTOR 通路激活与乳腺癌治疗(如内分泌治疗、HER2 靶向治疗、CDK4/6 和 PARP 抑制剂、化疗及免疫治疗)耐药之间的关联。PI3K/AKT/mTOR 通路抑制剂与现有治疗手段联合方案展现出克服不同类型乳腺癌耐药性的潜力, 已成为一种应对耐药问题的新策略。展望未来, 该领域仍面临诸多亟待解决的问题。首要任务是研发更多高选择性的抑制剂, 以优化治疗效果并减少毒副作用; 其次, 需深入探索可靠的生物标志物, 以精准预测治疗反应及耐药情况, 从而避免不必要的治疗副作用; 此外, 还应致力于优化联合治疗方案, 以期实现最佳的协同增效作用; 同时, 针对 PI3K/AKT/mTOR 抑制剂耐药性的研究亦不容忽视。鉴于 PI3K/AKT/mTOR 通路在多种实体肿瘤中的广泛激活, 特别是乳腺癌, 开展更为高效的临床试验以充分验证或支持临床前研究结果, 对于进一步提升耐药乳腺癌患者的生存时间与生活质量具有至关重要的意义。

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