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·论著·

FGFR1 抑制剂 PD173074 经诱导自噬逆转人肺腺癌 HCC827 细胞对厄罗替尼耐药

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[摘　要]　**目的：**阐明人肺腺癌细胞HCC827厄罗替尼耐药后FGFR1的表达及其与自噬的关系，并探讨FGFR1抑制剂PD173074对肿瘤细胞厄罗替尼耐药的影响。**方法：**通过低剂量反复刺激法构建HCC827厄罗替尼耐药细胞株(HCC827/ER)；应用CCK-8法检测细胞增殖能力；PE Annexin V/7-AAD双染色法测定细胞凋亡率；RT-qPCR检测FGFR1表达水平；蛋白质印迹法检测FGFR1蛋白及自噬标志物含量。**结果：**HCC827细胞厄罗替尼耐药后增殖增强(P<0.001)、凋亡减弱(P<0.0001)；耐药细胞FGFR1及编码蛋白表达升高(P<0.0001)。FGFR1抑制剂PD173074可致HCC827/ER增殖减弱(P<0.001)、凋亡增多(P=0.0002)。HCC827/ER细胞LC3-II较HCC827降低(P<0.0001)、p62升高(P<0.001)；PD173074处理后HCC827/ER中LC3-II较处理前升高(P<0.0001)、p62较前降低(P<0.0001)。PD173074与自噬抑制剂HCQ共处理HCC827ER后细胞增殖增强(P=0.013)、凋亡减弱(P=0.0257)。**结论：** HCC827细胞厄罗替尼耐药后，FGFR1表达升高、细胞自噬下调；而FGFR1抑制剂PD173074可重新诱导肿瘤细胞自噬，从而逆转HCC827细胞对厄罗替尼耐药。FGFR1作为旁路激活是厄罗替尼获得性耐药的机制之一；同时应用厄罗替尼及FGFR1抑制剂可改善EGFR-TKIs耐药。

[关键词]　非小细胞肺癌；EGFR-TKIs；耐药；FGFR1；自噬

FGFR1 inhibitor PD173074 reverses HCC827 cells resistance to erlotinib via activating autophagy

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Abstract　**Objective:** To elucidate the expression of fibroblast growth factor receptor 1 (FGFR1) in human lung adenocarcinoma cell line HCC827 after erlotinib resistance and its relationship with autophagy and to explore the effect of the FGFR1 inhibitor PD173074 on erlotinib-resistant HCC827 cells. **Methods:** Erlotinib-resistant HCC827 cell lines (HCC827/ER) was established after low-dose chronic exposure of EGFR-mutant HCC827

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cells to erlotinib. Cell viability was detected by CCK-8 method. Cell apoptosis was measured by flow cytometry. The mRNA level of FGFR1 was evaluated by RT-qPCR, and FGFR1 protein and autophagic biomarkers were detected by Western blotting. **Results:** Erlotinib-resistant HCC827 cells showed increased proliferation (P<0.001), decreased apoptosis (P<0.0001), and up-regulated FGFR1 (P<0.0001). PD173074 inhibited the proliferation of HCC827/ER (P<0.001) and promoted apoptosis (P=0.0002). LC3-II in HCC 827/ER cells expressed lower (P<0.0001) and p62 higher (P<0.001), while after PD173074 treatment LC3-II increased (P<0.0001) and p62 decreased (P<0.0001). When co-treated PD173074 with autophagy inhibitor HCQ, HCC827ER cells proliferated more (P=0.013) and the apoptotic rate decreased (P=0.0257). **Conclusion:** Erlotinib-resistant HCC827 cells up-regulate FGFR1 to inhibit autophagy and then escape from erlotinib injury. FGFR1 inhibitor PD173074 can re-activate the autophagy of cancer cells, thus reversing the resistance of HCC827 cells to erlotinib.

Keywords non-small cell lung cancer cell; EGFR-TKIs; drug resistance; FGFR1; autophagy

肺癌仍是全球范围内病死率最高的恶性肿瘤[1-2]。肺癌5年生存率约为18.6%[3]，预后较前改善，主要归因于早期诊断及有效治疗策略的不断发展。当前，以吉非替尼、厄罗替尼等为代表的表皮生长因子受体-酪氨酸激酶抑制剂(epithelial growth factor receptors-tyrosine kinase inhibitors，EGFR-TKIs)可显著延长EGFR敏感突变的非小细胞肺癌患者的无进展生存期、提高生存质量；然而，治疗时间9~13个月[4-7]后患者可出现获得性耐药[8]、导致疾病进展，严重影响了非小细胞肺癌靶向治疗的效果。目前，针对非小细胞肺癌EGFR-TKIs分子靶向药物获得性耐药的机制研究已经成为热点，诸多研究试图从不同方向阐述获得性耐药发生的机制，进而为肺癌患者的基础研究与临床治疗提供新的思路。

EGFR-TKIs获得性耐药的可能机制包括EGFR基因原位变异(如T790M突变)与原位扩增、旁路激活(包括cMet扩增、PIK3CA激活)、细胞表型改变(小细胞肺癌转化、上皮间质转化)等，然而仍有超过30%的耐药机制不明[9]。The Cancer Genome Atlas Research Network(TCGA)数据提示非小细胞肺癌中成纤维细胞生长因子受体1(fibroblast growth factor receptor 1，FGFR1)出现突变或扩增，可作为潜在治疗靶点[10]；FGFR表达升高可能是吉非替尼、阿法替尼及贝伐单抗等耐药的分子机制之一[11-14]，然而具体机制尚待进一步明确。

自噬是高度保守的、调节非必需或失活细胞内组分降解的代谢过程[15-16]。细胞可通过自噬清除受损细胞器或有潜在危害的分子，从而维持细胞稳态；此外，自噬有助于细胞克服胞内外应激，包括饥饿、缺氧及药物等[17-19]。在肿瘤研究领域，FGFR1与自噬相关。FGFR1扩增的非小细胞肺癌细胞系中FGFR1激活可抑制自噬，抑制自噬可增强FGFR1抑制剂抗肿瘤作用[20]；在膀胱癌细胞系[21]、乳腺癌细胞系[22]中亦观察到类似现象。此外，调节自噬可克服慢性髓细胞白血病[23-24]、结直肠癌[25]、肝癌SMMC-7721细胞[26]等肿瘤TKI耐药。

因此，本研究旨在阐明人肺腺癌细胞HCC827厄罗替尼耐药后FGFR1的表达及其与自噬的关系，并探讨FGFR1抑制剂PD173074对肿瘤细胞厄罗替尼耐药的影响。

1 材料与方法

1.1 药物与试剂

Hyclone RPMI 1640培养基(SH30809.01B)购于美国GE公司，胎牛血清(900-108)购于美国GEMINI公司，青霉素-链霉素溶液(C0222)、CCK-8试剂盒(C0037)购于上海碧云天生物技术有限公司。厄罗替尼(S7786)、FGFR1抑制剂PD173074(S1264)、HCQ(S4430)购于美国Selleck公司。细胞凋亡检测试剂盒PE Annexin V Apoptosis Detection Kit I购于美国BD公司。FGFR1(9740S)，LC3A/B(12741S)，GADPH(5174S)，β-actin(4970s)购于美国Cell Signaling Technology公司；P62(ab91526)购于美国Abcam公司。RNAprep pure培养细胞/细菌总RNA提取试剂盒(DP430)购于天根生化科技(北京)有限公司。反转录试剂盒RevertAid First Strand cDNA Synthesis Kit(K1622)购于美国Thermo Scientific公司。UltraSYBR Mixture(CW0957M)购于康为世纪生物科技有限公司。

1.2 细胞株及细胞培养

人肺腺癌EGFR突变细胞株HCC827购于美国ATCC公司，给予10%胎牛血清RPMI 1640培养基常规培养。HCC827厄罗替尼耐药细胞株(HCC827/ER)由本课题组参考相关文献[12]采用低剂量反复刺激法构建：HCC827细胞置于厄罗替尼初始浓度为0.01 nmol/L的10%胎牛血清RPMI 1640培养基培养，浓度逐步增加至0.25，0.5，1，2，4 nmol/L，时间为6个月，构建HCC827/ER细胞系；并用含2 nmol/L厄罗替尼的10%胎牛血清RPMI 1640培养基常规培养。

1.3 细胞增殖检测

应用CCK-8法检测细胞增殖能力。参照CCK-8试剂盒说明书，将HCC827，HCC827/ER等细胞经处理后以2 000个/孔植入96孔板，每孔加入10 μL CCK-8溶液，37 ℃孵育1 h，酶联免疫检测仪(Thermo Electron Corporation Multiskan MK3酶标仪)450 nm测定吸光度，并绘制细胞生长曲线。

1.4 细胞凋亡检测

应用PE Annexin V/7-AAD双染色法测定细胞凋亡率。参照试剂盒说明书，常规消化对数生长期细胞，预冷的1×PBS洗涤2次后以1×结合缓冲液重悬细胞，加入PE Annexin V，7-AAD后室温下避光孵育15 min。加入1×结合缓冲液，应用流式细胞仪(Beckman Coulter FC500)检测细胞凋亡率。

1.5 RNA提取及反转录RT-qPCR检测

参照相应说明书，收集培养细胞标本后，使用总RNA提取试剂盒提取细胞总RNA；RevertAid First Strand cDNA Synthesis Kit进行cDNA合成。应用UltraSYBR Mixture制备PCR反应体系，放入Stratagene Mx3005P实时荧光定量PCR仪，设置反应条件为95 ℃ 10 min，95 ℃ 10 s，60 ℃ 30 s，循环40次，并于60 ℃设定荧光检测点。FGFR1引物序列：正向引物为5'-CCCGTAGCTCCATATTGGACA-3'，反向引物为5'-TTTGCCATTTTTCAACCAGCG-3'；内参β-actin序列为：正向引物为5'-GGCACCCAGCACAATGAAG-3'，反向引物为5'-CCGATCCACACGGAGTACTTG-3'。

1.6 蛋白提取及蛋白免疫印迹

培养细胞经4 ℃预冷PBS清洗后冰上裂解30 min，离心取上清液制备蛋白样本，并使用BCA法进行蛋白定量。各样本取等量蛋白行SDS-聚丙烯酰胺凝胶电泳、电转移至PVDF膜、一抗孵育4 ℃过夜、辣根过氧化酶标记二抗结合后，行ECL化学发光检测，并应用β-actin，GADPDH进行内参照。

1.7 统计学处理

所有实验均重复至少3次，并使用GRAPHPAD PRISM 7.0进行数据统计学分析。计量资料以均数±标准差($\bar{x}\pm s$)表示，应用方差分析比较各组总体差异、Bonferroni法比较各组间差异。P<0.05差异为有统计学意义。

2 结果

2.1 HCC827细胞厄罗替尼耐药后增殖增强、凋亡减弱；细胞FGFR1及编码蛋白表达升高

各细胞株与厄罗替尼共培养后行CCK-8法示：厄罗替尼耐药细胞株HCC827/ER培养96 h后细胞OD值为HCC827细胞的1.81倍(P<0.001；图1A)。流式细胞学分析示HCC827/ER细胞凋亡率低于HCC827细胞(13.3% vs 28.9%，P<0.0001；图1B，1C)。

RT-qPCR及蛋白质印迹法结果示：与HCC827细胞相比，厄罗替尼耐药细胞株HCC827/ER中FGFR1在mRNA及蛋白水平均表达升高(相对mRNA表达量4.31 vs 1，P<0.0001；相对灰度值1.12 vs 0.5，P<0.0001；图2)。

2.2 应用FGFR1抑制剂PD173074后HCC827/ER增殖减弱、凋亡增多

为研究FGFR1对厄罗替尼耐药细胞株HCC827/ER的影响，将HCC827/ER，HCC827细胞与厄罗替尼、FGFR1抑制剂PD173074共培养，并行CCK-8法检测示：应用PD173074后HCC827/ER细胞OD值较应用前降低(P<0.001，图3A)。流式细胞学分析示PD173074应用后HCC827/ER凋亡较前增多(19.5% vs 13.3%，P=0.0002；图3B，3C)。

2.3 HCC827/ER细胞自噬受抑制，PD173074处理后自噬增强

厄罗替尼耐药细胞株HCC827/ER中细胞自噬相关标志物LC3-II较HCC827降低(相对灰度值0.1971 vs 0.2535，P<0.0001)、p62升高(相对灰度值0.1205 vs 0.1129，P<0.001，图4)。而经PD173074处理后，HCC827/ER中LC3-II较处理前升高(相对灰度值0.2167 vs 0.1971，P<0.0001)，p62较前降低(相对灰度值0.0866 vs 0.1205，P<0.0001)。

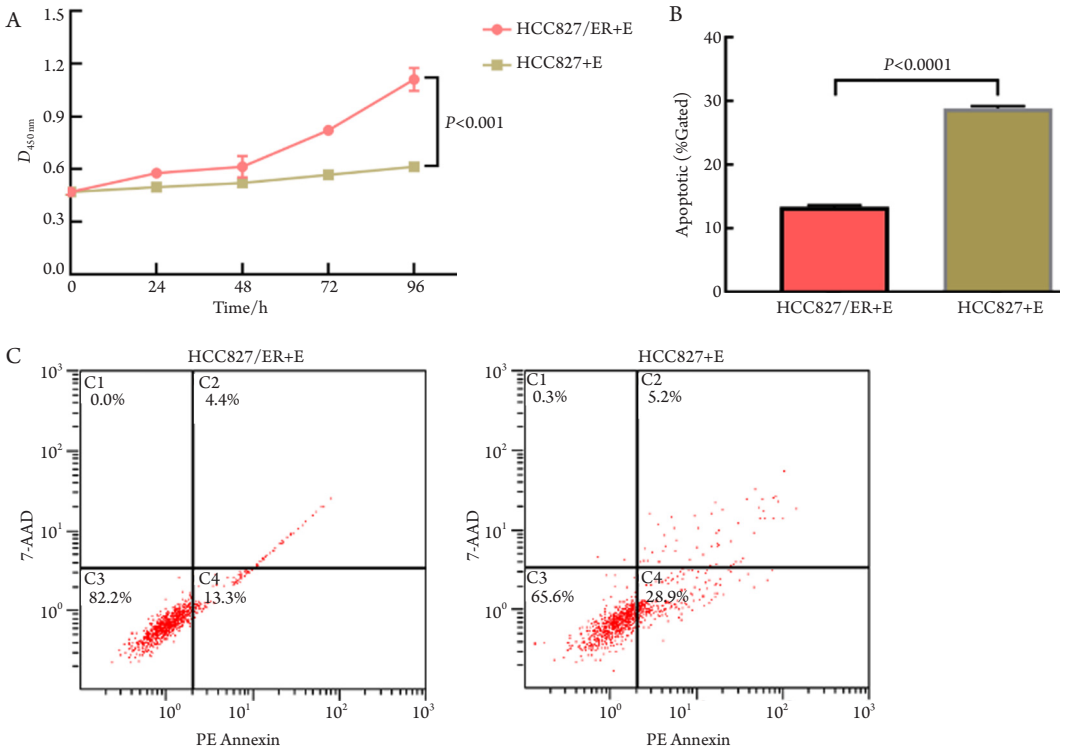

图1 HCC827/ER细胞增殖增强、凋亡减弱

Figure 1 HCC827/ER cells presented enhanced proliferation and decreased apoptotic rate

(A)HCC827细胞厄洛替尼耐药前后细胞活力变化；(B)HCC827细胞厄洛替尼耐药前后凋亡变化；(C)HCC827细胞耐药前后凋亡典型流式细胞分析图。

(A) HCC827 cell viabilities before and after erlotinib resistance; (B) HCC827 apoptotic rates before and after erlotinib resistance; (C) Typical images of FCM evaluating cell apoptosis.

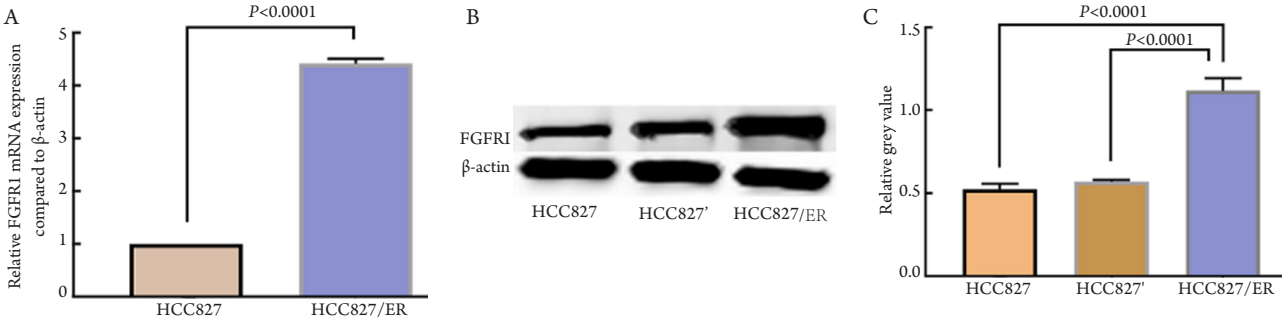

图2 HCC827/ER FGFR1表达升高

Figure 2 FGFR1 was upregulated in erlotinib resistant HCC827 cells

(A)HCC827细胞厄洛替尼耐药前后FGFR1 mRNA水平变化；(B)HCC827细胞厄洛替尼耐药前后典型FGFR1蛋白凝胶条带；(C)HCC827细胞厄洛替尼耐药前后FGFR蛋白相对灰度值变化。

(A) Relative FGFR1 mRNA expressions of HCC827 before and after erlotinib resistance; (B) Typical gel bands of FGFR1; (C) Relative gray values of FGFR1 proteins.

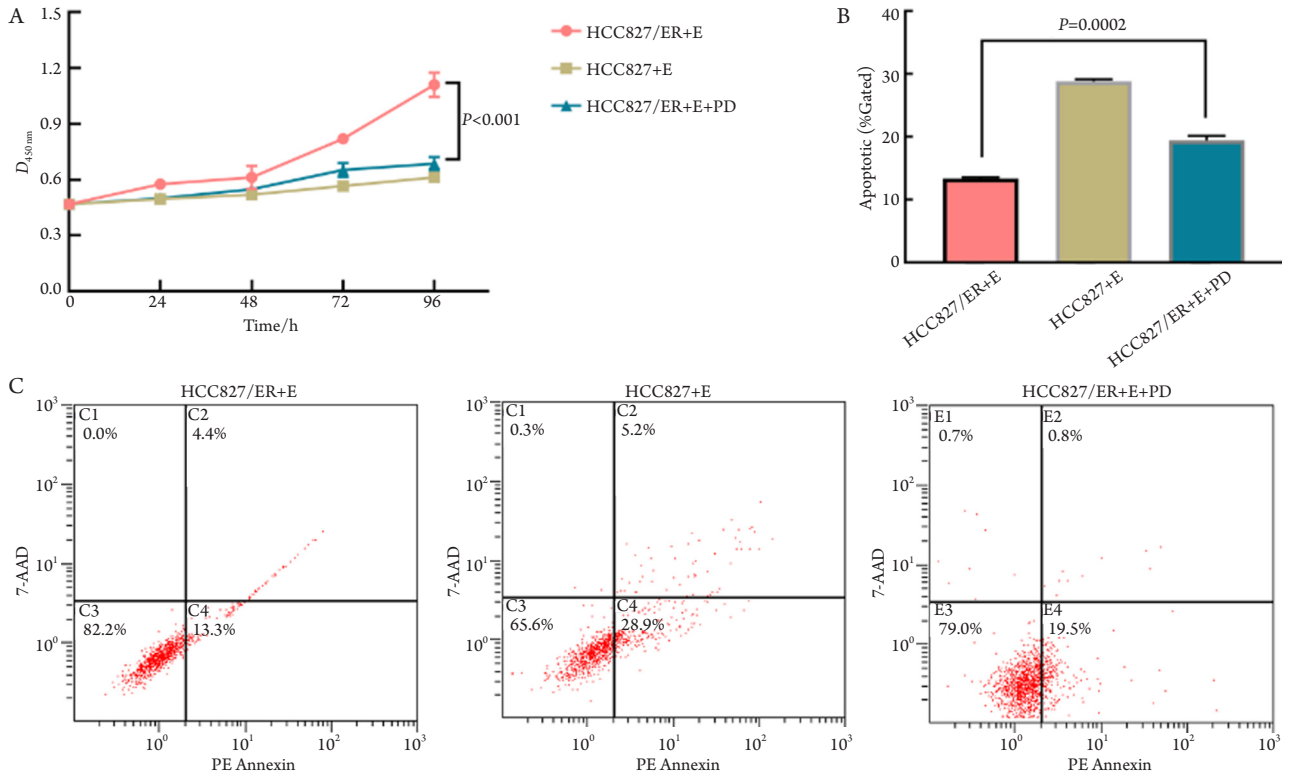

图3 PD173074处理后HCC827/ER增殖减弱、凋亡增多

Figure 3 PD173074 treatment weakened the proliferation and promoted the apoptosis of HCC827/ER cells

(A)PD173074处理前后厄洛替尼耐药细胞增殖变化；(B)PD173074处理前后厄洛替尼耐药细胞凋亡变化；(C)PD173074处理前后细胞凋亡典型流式细胞分析图。

(A) Viabilities of erlotinib-resistant cells before and after PD173074 treatments; (B) Apoptotic rates of erlotinib-resistant cells before and after PD173074 treatments; (C) Typical images of FCM evaluating erlotinib-resistant cells before and after PD173074 treatments.

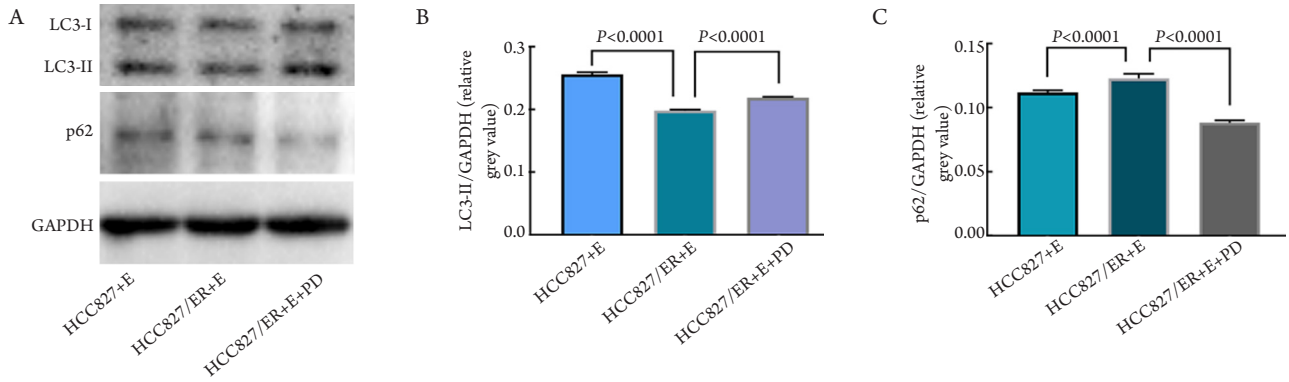

图4 HCC827/ER细胞自噬受抑制，PD173074处理后自噬增强

Figure 4 Autophagy was inhibited in HCC827/ER cells, whereas PD173074 treatment enforced autophagy

(A)厄洛替尼耐药前后、PD173074处理前后细胞LC3，p62蛋白凝胶典型图；(B)厄洛替尼耐药前后、PD173074处理前后LC3-II相对灰度值变化；(C)厄洛替尼耐药前后、PD173074处理前后p62相对灰度值变化。

(A) Typical gel bands of LC3 and p62; (B) Relative gray values changes before and after erlotinib resistance and PD173074 treatments; (C) Relative gray values changes of p62 before and after erlotinib resistance and PD173074 treatments.

2.4 自噬抑制剂HCQ可逆转PD173074的增敏作用

HCC827/ER与厄罗替尼、PD173074共培养体系中加入自噬抑制剂HCQ，以观察抑制自噬后PD173074对HCC827/ER细胞增殖及凋亡的影响(图5)。CCK-8法示：自噬抑制后HCC827/ER OD值为抑制前的1.36倍(P=0.013)，即PD173074对HCC827/ER增殖的抑制作用减弱；流式细胞学分析提示抑制自噬后HCC827/ER细胞凋亡率较抑制前减弱(17.6% vs 19.5%，P=0.0257)。

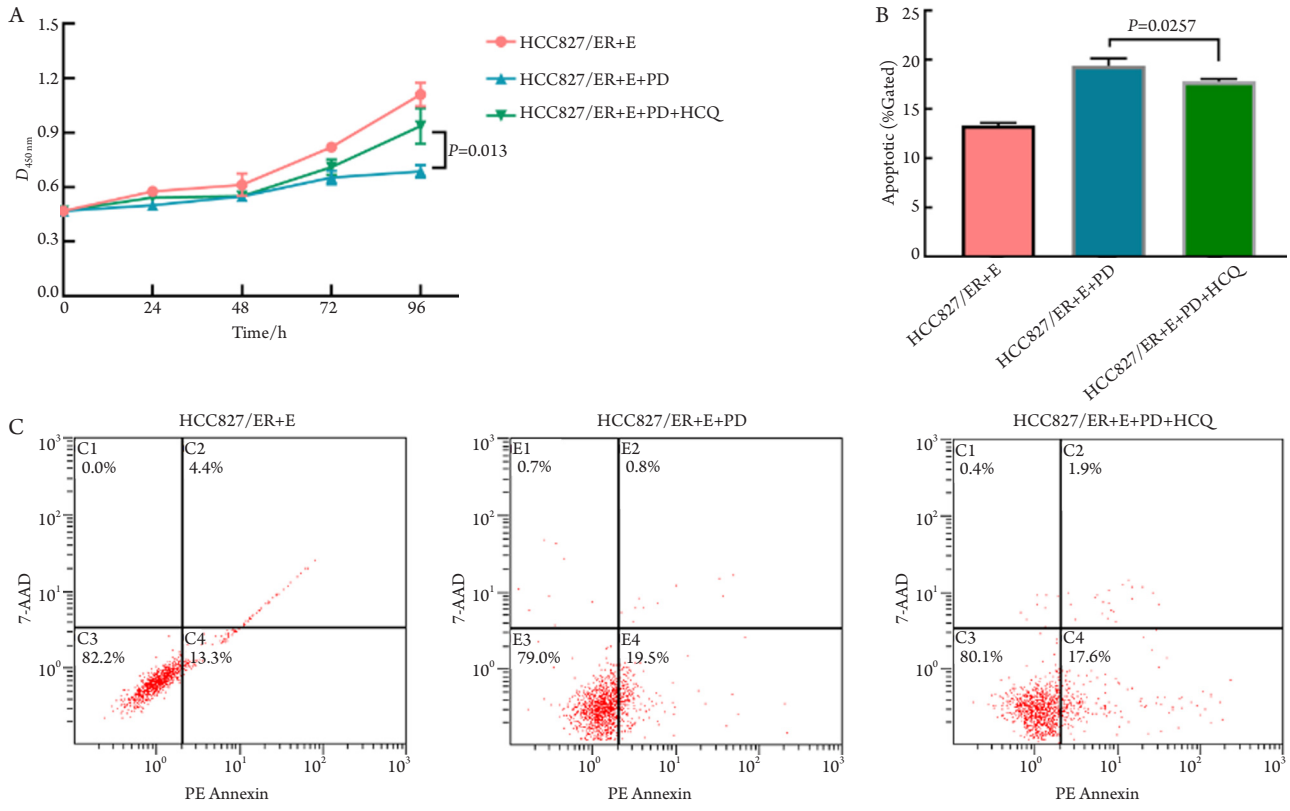

图5 PD173074与自噬抑制剂HCQ共处理HCC827ER后细胞增殖增强、凋亡减弱

Figure 5 PD173074 and HCQ co-treating HCC827ER enhanced cell proliferation and decreased apoptosis

(A) HCQ可逆转PD173074对耐药细胞的增殖抑制作用；(B) HCQ可逆转PD173074对耐药细胞的凋亡促进作用；(C) HCQ处理前后细胞凋亡典型流式细胞分析图。

(A) HCQ reversed the PD173074-induced proliferation inhibitory effect on erlotinib-resistant cells; (B) HCQ reversed the PD173074-mediated pro-apoptotic effects; (C) Typical images of FCM evaluating cell apoptosis.

3 讨论

EGFR，EML4-ALK，ROS1等肿瘤驱动基因陆续被发现，相应靶向治疗药物亦相继被开发，并与手术治疗、化学药物治疗、放射治疗等手段共同组成当前肺癌治疗体系，极大地改善了肺癌特别是驱动基因敏感突变非小细胞肺癌的预后[3]。然而药物治疗必然会导致获得性耐药[8]、导致疾病进展，妨碍了靶向治疗的效果。因此，探讨EGFR-TKIs获得性耐药机制并寻求相应抑制剂有重要意义。

本研究参照既往文献[12]中的方法构建了非小细胞肺癌HCC827厄罗替尼耐药细胞系，发现HCC827耐药后FGFR1在RNA及蛋白水平表达均升高，而应用FGFR1抑制剂PD173074可逆转人肺腺癌HCC827细胞对厄罗替尼耐药。因此，FGFR1作为旁路激活是厄罗替尼获得性耐药的机制之一，同时应用厄罗替尼及FGFR1抑制剂可改善TKI耐药。此与既往吉非替尼、阿法替尼等获得性耐药机制研究结果相符[11-14,27]。

本研究还发现：HCC827细胞厄罗替尼耐药后细胞自噬水平降低；这可能与耐药细胞FGFR1表达升高，激活MAPK/ERK[20]，PI3K/AKT/mTOR[22]等信号通路进而抑制自噬相关。而PD173074处

理后自噬增强、同时应用HCQ后FGFR1抑制剂对厄罗替尼的增敏作用减弱，提示FGFR1抑制剂PD173074通过诱导自噬发挥克服厄罗替尼耐药的作用。此与先前部分研究[23-26]抑制自噬、克服TKI耐药的结论略不相同。究其原因，其一可能是本研究体系中的自噬对肿瘤细胞的作用为杀伤性(抑癌)，而非相关研究中的保护性自噬。厄罗替尼处理HCC827细胞后，激活了抑癌性自噬并造成细胞杀伤；细胞耐药后FGFR1表达升高抑制了抑癌性自噬、细胞存活增多；而PD173074的应用则重新激活了耐药细胞株的抑癌性自噬。Nassour等[28]佐证了这种可能性，其最新发表于Nature的研究显示自噬性细胞死亡限制了染色体的不稳定性、是一种防止癌细胞生长的保护机制。原因之二为自噬缺失是EGFR-TKIs耐药机制之一。TKIs可诱导肿瘤细胞自噬[29-30]，而mTOR抑制剂雷帕霉素可增强吉非替尼效果[31]、依维莫司可恢复非小细胞肺癌耐药细胞系对吉非替尼的敏感性[32-33]，其作用可能通过重新激活耐药细胞缺失的自噬而实现。

本研究存在一定局限性。首先，研究仅在HCC827单株细胞系观察到上述现象；其次，研究未纳入临床水平相关检测及动物体外实验。但本课题组已有研究论证FGFR1在PC-9细胞系吉非替尼耐药的作用；而课题组正在收集EGFR-TKIs耐药后的非小细胞肺癌组织标本，且初步建立了耐药动物模型。课题组将尽快完善相关研究，以其更为全面地阐述FGFR1在肺腺癌EGFR-TKIs获得性耐药中作用及机制。

综上所述，HCC827细胞厄罗替尼耐药后，FGFR1表达升高、细胞自噬下调；而FGFR1抑制剂PD173074可重新诱导肿瘤细胞自噬，从而逆转HCC827细胞对厄罗替尼耐药。FGFR1作为旁路激活是厄罗替尼获得性耐药的机制之一；同时应用厄罗替尼及FGFR1抑制剂可改善EGFR-TKIs耐药。

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