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HGF诱导不同EGFR基因型非小细胞肺癌细胞对厄洛替尼的耐药

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摘要：

目的：探究肝细胞生长因子（hepatocyte growth factor，HGF） 体外诱导不同EGFR基因型非小细胞肺癌（non-small cell lung cancer，NSCLC）细胞对厄洛替尼的耐药及其可能的机制。方法：用HGF、厄洛替尼单独或联合处理人NSCLC细胞株PC9（EGFR突变型，敏感株）、H292（EGFR野生型，敏感株）、A549（EGFR野生型，原发性耐药株），实验分为四组：C组（不加药对照组）、H组（HGF处理）、E组（厄洛替尼处理组）、HE组（HGF+厄洛替尼联合处理组）。MTT法检测其对细胞增殖的影响，流式细胞术检测其对细胞周期和凋亡的影响，Western blotting检测其对细胞中c-Met、EGFR、ErbB3及其磷酸化蛋白表达的影响。结果：厄洛替尼对3种细胞增殖抑制的作用均呈浓度依赖性，HGF处理能够缓解厄洛替尼对瘤细胞增殖的抑制作用。3种细胞的HE组凋亡率均显著低于E组（均P<0.05）。厄洛替尼阻滞3种细胞周期于G 1期，对于H292、A549细胞，HE组G 0/G 1期比例显著低于E组（P<0.05）。HE组p-Met蛋白含量较E组显著升高（P<0.05），而p-EGFR和p-ErbB3表达无显著差异（P>0.05）。结论：在体外，HGF能够诱导不同EGFR基因型NSCLC细胞株对厄洛替尼耐药，其机制可能与其诱导c-Met磷酸化活化有关。

关键词：肝细胞生长因子 厄洛替尼 非小细胞肺癌 c-Met 耐药

HGF-induced resistance to erlotinib in EGFR-mutated and EGFR wildtype non-small lung cancer cells in vitro

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Abstract:

Objective: To assess differences in erlotinib resistance between EGFR-mutated and EGFR wildtype non-small lung cancer (NSCLC) cells following hepatocyte growth factor (HGF) in vitro. Methods: EGFR-mutated NSCLC PC9 cells and EGFR-wild type NSCLC H292 and A549 cells were left untreated (control) or treated with HGF, erlotinib or HGF plus erlotinib. Cell viability was assessed by MTT assays, cell appotosis and cell cycle progression by flow cytomety and protein contents of c-Met, EGFR and ErbB3 by Western blotting. Results: Erlotinib resulted in a significant proliferation inhibition in all three types of NSCLS cells in a dose-dependent manner and HGF effectively attenuated the erlotinib-induced proliferation inhibition. In all three types of cells studied, the apoptosis rate in the combination treatment (HGF plus erlotinib) group was lower than that in the erlotinib group (P<0.05), and erlotinib induced G 1 arrest. In H292 and A549 cells, the proportion of cells at G 0/G 1 phase was significantly lower in the combination treatment group than in the erlotinib group (P<0.05). Protein content of c-Met was significantly higher in the combination treatment than in the erlotinib group (P<0.05) whereas protein contents of p-EGFR and p-ErbB3 were not different between treatment groups (P>0.05) in all three types of cells. Conclusion: HGF may induce erlotinib resistance differentially in EGFR wildtype and EGFR-mutated NSCLC cells, possibly an Met activation-dependent mechanism.

Keywords:hepatocyte growth factor(HGF) erlotinib non-small lung cancer(NSCLC) c-Met resistance