[1]刘明,任敦强,郑丽霞,等.TGF-β1介导的上皮-间质转分化在Gefitinib耐药中的作用[J].第三军医大学学报,2013,35(15):1558-1561.

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Title: Role of TGF-β1-induced epithelial-mesenchymal transition in resistance to gefitinib in non-small cell lung cancer

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关键词: 肺肿瘤; TGF-β1; 上皮-间质转化; 表皮细胞生长因子受体; 耐药

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摘要: 目的 调查上皮-间质转化(epithelial-mesenchymal transition, EMT)在非小细胞肺癌(non-small cell lung cancer, NSCLC)患者接受吉非替尼（Gefitinib）治疗反应性中的作用及机制。 方法 突变富集PCR法检测NSCLC患者EGFR 突变状况；免疫组化法检测癌组织中上皮钙粘蛋白（E-cadherin）和纤维连接蛋白（Fibronectin）的表达情况，探讨EMT与表皮生长因子受体酪氨酸激酶抑制剂(epidermal growth factor receptor tyrosine kinase inhibitors, EGFR-TKIs)治疗敏感性的关系。体外选取人肺腺癌细胞系PC9细胞，经TGF-β1反复处理4周，观察细胞形态学变化；MTT检测TGF-β1处理后细胞对Gefitinib敏感性的影响；Western blot验证EMT相关标记蛋白表达变化并检测EGFR信号通路下游蛋白的变化。 结果 43例NSCLC标本中，EGFR 19、21外显子突变率为58.14%(25/43)。具有EGFR基因突变的肿瘤E-cadherin的表达水平显著高于EGFR 野生型(70.00% *vs* 30.00%, *P*<0.05)。接受Gefitinib总体有效率为46.51%(20/43)，具有E-cadherin阳性表达的患者治疗反应性明显好于Fibronectin阳性的患者(65.00% *vs* 30.43%，*P*<0.05)。TGF-β1可诱导PC9细胞向间质型细胞形态转化，上调Fibronectin的表达；与亲本PC9细胞相比，TGF-β1处理的细胞对Gefitinib的敏感性下降(*P*<0.05)；这

种敏感性的下降伴随着AKT和STAT3的持续活化。 结论 EMT在EGFR-TKI耐药中发挥着重要作用，TGF-β1诱导的EMT可影响PC9细胞对Gefitinib的敏感性，这种效应可能是通过持续活化AKT和STAT3而发挥作用。

Abstract: Objective To clarify the role and mechanism of epithelial-mesenchymal transition (EMT) in the sensitivity of non-small cell lung cancer (NSCLC) patients treated with gefitinib. Methods Epidermal growth factor receptor (EGFR) mutations were detected by mutant-enriched PCR assay, and the expression of E-cadherin and fibronectin were evaluated by immunohistochemistry (IHC). Cultured PC9 cells were treated with TGF-β1 for 4 weeks, and the morphological changes were observed by phase-contrast microscopy. MTT assay was used to detect the sensitivity of cells to gefitinib. In addition, the expression of EMT-related marker proteins (E-cadherin and fibronectin) and EGFR downstream signaling molecules (p-ERK, p-AKT and p-STAT3) were assessed by Western blotting. Results EGFR gene mutations were identified in 25 of 43 samples (46.51%). The frequency of E-cadherin-positive samples was significantly higher in the samples with EGFR mutants than in those with wild-type EGFR (70.00% *vs* 30.00%, $P<0.05$), and the overall response rate to gefitinib was 46.51% (20/43). The treatment responsiveness in the E-cadherin-positive patients was significantly higher than that in the fibronectin-positive patients (65.00% *vs* 30.43%, $P<0.05$). TGF-β1 could induce an EMT morphological alteration and up-regulate the expression of fibronectin in PC9 cells. The sensitivity to gefitinib was decreased in the PC9 cells treated with TGF-β1, and the activation of AKT and STAT3 were observed *in vitro*. Conclusion EMT plays an important role in the resistance to EGFR-tyrosine kinase inhibitors (TKIs). Induction of EMT by TGF-β1 may contribute to the decreased efficacy of gefitinib therapy through sustaining activation of AKT and STAT3.

参考文献/REFERENCES:

刘明，任敦强，郑丽霞，等. TGF-β1介导的上皮-间质转分化在Gefitinib耐药中的作用[J].第三军医大学学报,2013,35(15):1558-1561.

相似文献/REFERENCES:

[1]夏蕾,熊艳丽,罗维,等.染料木黄酮对辐射损伤小鼠肺纤维化的防护作用[J].第三军医大学学报,2012,34(21):2149.
Xia Lei,Xiong Yanli,Luo Wei,et al.Genistein protects mice against radiation-induced pulmonary fibrosis[J].J Third Mil Med Univ,2012,34(15):2149.
[2]刘卫金,邹利光,廖翠薇,等.胸膜凹陷征在肺外周结节CT诊断中的价值[J].第三军医大学学报,2006,28(01):9.
[3]田坤,李小玉,张定涛,等.射频技术治疗肿瘤性气道阻塞18例临床分析[J].第三军医大学学报,2013,35(02):182.
[4]陈寿松,肖同浩,陈昕薇,等.EGFR、COX-2及P63蛋白在非小细胞肺癌中的表达及其意义[J].第三军医大学学报,2008,30(07):628.
CHEN Shou-song,XIAO Tong-hao,CHEN Xin-wei,et al.Expressions of EGFR, COX-2 and P63 in non-small cell lung cancer and their significance[J].J Third Mil Med Univ,2008,30(15):628.
[5]宋仁刚,宋任强,柳大烈,等.不同浓度TGF-β1对大鼠骨髓内皮祖细胞体外增殖的影响[J].第三军医大学学报,2006,28(23):2306.
[6]王梅,葛明建.荧光定量RT-PCR法监测肺癌患者化疗前后外周血淋巴细胞mdr1 mRNA的变化[J].第三军医大学学报,2006,28(19):1979.
[7]刘文斌,刘晋祎,周紫垣,等.大鼠肺鳞癌癌变过程中细胞周期调控蛋白的动态表达[J].第三军医大学学报,2009,31(07):577.
LIU Wen-bin,LIU Jin-yi,ZHOU Zi-yuan,et al.Dynamic expression of cell cycle regulation related proteins during carcinogenesis of lung squamous cell carcinoma in rats[J].J Third Mil Med Univ,2009,31(15):577.
[8]王文献,王亚菲,文利,等.小肺癌的HRCT特征及其诊断价值[J].第三军医大学学报,2005,27(07):679.
[9]董必文,段凤英,段训凰.5-氮-2′-脱氧胞苷联合曲古抑菌素A对人肺腺癌细胞株A549增殖和凋亡的影响[J].第三军医大学学报,2010,32(17):1857.
Dong Biwen,Duan Fengyin,Duan Xunhuang.Effect of 5-aza-2-deoxycytidine and trichostatin A on proliferation and apoptosis of lung epithelial carcinoma A549 cells[J].J Third Mil Med Univ,2010,32(15):1857.
[10]李开龙,张建国,王慧民,等.甘草酸18α体调节梗阻性肾病大鼠肾间质中CTGF和TGF-β1表达的实验研究[J].第三军医大学学

报,2005,27(04):323.