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非小细胞肺癌吉非替尼耐药相关miRNAs的筛选鉴定

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Screening and Identification of miRNAs Associated with Gefitinib Resistance in Non-small Cell Lung Cancer

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摘要

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摘要 miRNA是一类通过结合mRNA调节基因表达的非编码单链小分子RNA，本研究目的是探讨非小细胞肺癌（NSCLC）中miRNA与吉非替尼耐药的关系。方法：CCK8法检测NSCLC吉非替尼耐药细胞PC9/GR相对于亲本细胞PC9的耐药倍数；miRNA芯片检测PC9/GR与PC9中miRNA的表达差异；RT-PCR验证miRNA芯片结果。将差异表达的miRNA模拟物/抑制剂转染至PC9/GR中，观察其对吉非替尼敏感性的影响。结果：吉非替尼对PC9和PC9/GR的IC50值分别为42.89 nmoL/L和3.87 μmoL/L，耐药倍数为90.23倍。miRNA芯片结果显示，PC9/GR与PC9比较55条有差异表达miRNAs（P<0.01），其中在PC9/GR上调的miRNAs有21条，包括miRNA-1 246、miRNA-125b等；下调的miRNAs有34条，包括miRNA-224、miRNA-125a～5p等。RT-PCR进一步验证其中9条miRNAs，有8条与芯片结果趋势一致。将上述8条miRNAs的模拟物/抑制剂转染至PC9/GR中，发现miRNA-125a～5p模拟物可降低吉非替尼敏感性。结论：PC9/GR与PC9的miRNA表达存在差异，miRNA可能与NSCLC吉非替尼耐药相关，miRNA-125a～5p可促进PC9/GR对吉非替尼产生耐药。

关键词： 非小细胞肺癌 吉非替尼 耐药 miRNA

Abstract: MiRNA is a kind of small non-coding RNAs that functions by regulating expression of the target gene after the genetic transcription. This study aims to analyze the differences of miRNAs expression between PC9 and PC9/GR cells, and to explore the relationship between miRNA and gefitinib resistance in non-small cell lung cancer (NSCLC). Methods: The gefitinib resistance on PC9/GR cells was evaluated using CCK8 assay. The total RNA of the two cell lines was isolated and examined. The miRNA expression of PC9/GR and PC9 was analyzed by microarray and the results were confirmed by real-time PCR method. Special miRNA was synthesized in vitro and was transfected into PC9/GR cells so as to observe the drug resistance of the model. Results: The values of IC50 of gefitinib on the PC9 and PC9/GR cells were 42.89 nmol/L, and 3.87μmol/L respectively (P < 0.01). The drug resistance index of PC9/GR cells related to the parental PC9 cells was 90.24. The microarray analysis showed that 55 human miRNAs were differentially expressed in the two cell lines (P < 0.01), of which 21 were up-regulated, including miR-1246 and miR-125b, and 34 were down-regulated, including miR-224 and miR-125a-5p. The expression of 9 miRNAs was further validated by real-time PCR, of which 8 were consistent with the microarray analysis, and one was not. MiR-125a-5p mimic was synthesized in vitro, and was transfected to PC9/GR. It promoted the effect of drug resistance. Conclusion: NSCLC resistantce to gefitinib is associated with a group of miRNAs. MiR-125a-5p can promote the effect of gefitinib resistance. This finding provides an experimental basis for further study of mechanism underlying the gefitinib resistance of NSCLC.

Key words: Non-small cell lung cancer Gefitinib Resistance miRNA

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