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TD1 AN INTEGRATIVE ANALYSIS OF THE PUTATIVE GEFTINIB-RESISTANT GENES IN A LUNG CANCER CELL LINE MODEL SYSTEM

X. Han1, M. Liu2, S. Wang1, X. Qian1, G. Lv1, L. Ma1, C. Zeng2, Y. Shi1
1Medical Oncology, Cancer Institute and Hospital, Chinese Academy of Medical Sciences (CAMS), Beijing, China
2The CAS Key Laboratory of Genome Variations and Precision Biomedicine, Beijing Institute of Genomics, Beijing, China

Aim: At present, the resistance mechanisms of epidermal growth factor receptor kinase inhibitor (EGFR-TKI) have not been fully elucidated, and seriously affects the process of individualized targeted therapy. Our study intends to obtain the molecular biomarkers associated with EGFR-TKI resistance in NSCLC, and get in-depth understanding of EGFR-TKI acquired resistance.

Methods: In this study, we established H1650 Gefitinib-resistant (H1650GR) cell line by exposing the cell to increasing concentrations of gefitinib. Using TruSeq RNA sample preparation kit v2 and HumanOmniZhongHua-8 BeadChip to investigate the transcriptome and genome alterations possibly involved in gefitinib resistance. Preliminary validation of drug resistance related gene variants were also conducted in vitro using real time quantitative PCR technique.

Results: By comparing the gene expression profiles of the gefitinib resistant H1650GR cell line to the gefitinib sensitive H1650 cell line, we identified 28 and 41 differently expressed genes in the MAPK and PI3K/AKT signaling pathways, respectively. In addition, other kinase, such as MAPK4, EIF2AK2, EPHB6 and MYLK were also high expressed in H1650GR. Meanwhile, 13 alkaline phosphatase down-regulated expression were detected in H1650GR. We also identified a total of 47 up-regulated genes located in the H1650GR unique amplification region of 3q13.1-3q19 (MUC13, LAMP3, HGD, MYLK and HEG1 were the 5 genes that had the highest variation ratio) and 61 down-regulated genes in the deletion region of 18q12.1-18q23 in H1650GR cells. TCF4, SERPINB7, SERPINB3, SERPINB4 and ALPK2 were the 5 genes that had the highest variation ratio. We verified 40 drug resistance related genes variants by detecting the mRNA relative expression level. ICK, MYLK, PTP4A1, MAP2K7, MAPK4 were high expressed, while ALPK2, TGFA, FZD4, KLF16, MAP2K2 were low expressed in H1650GR cell line.

Conclusions: Our results suggested that the up-regulation of genes in MAPK and PI3K/AKT signaling pathways, such as MAPK4, and amplification of MYLK might play important roles in the development of EGFR-TKI resistance. Further mechanistic studies are warranted to explore how these genes involved in the gefitinib resistance to NSCLC.

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