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MiR-155-Mediated Downregulation of FOXO3a involved in the Gefitinib-Resistance of Non-Small Cell Lung Cancer

Hsaio-Ching Wang, Jen-Liang Su

Institute of Cancer Biology, China Medical University, Taichung, Taiwan

Lung cancer is one of the most common malignancies worldwide. Epidermal growth factor receptor (EGFR) regulates many biological functions including proliferation, angiogenesis, anti-apoptosis and metastasis. A specific EGFR tyrosine kinase inhibitor, gefitinib (Iressa, ZD1839), has been developed to exhibit clinical efficacy in lung cancer patients. However, acquisition of resistance to gefitinib is also observed after treatment. It is critical and timely to understand the molecular mechanisms involved in gefitinib resistance. In this study, we found the expression level of FOXO3a was lower in gefitinib resistant PC9 (PC9/GR) cells than wild type PC9 (PC9/WT) cells. Kockdowned of FOXO3a in PC9/WT cells enhanced resistance of gefitinib ; consistantly, overexpression of FOXO3a make PC9/GR cells re-sensitize to gefitinib. MicroRNAs play critical role in multiple steps of cancer progression, including drug resistance. To define whether microRNAs involved in FOXO3a-mediated gefitinib-resistance, we predicted microRNAs which may target to FOXO3a by several softwares, such as miRWalk, DIANAmT , miRanda, miRDB and TargetScan. We further analyzed the expression of these candidate microRNAs in PC9/WT and PC9/GR cells by quantitative RT-PCR. We found that miR-155 was highly expressed in PC9/GR cells than in PC9/WT cells. Overexpression of miR-155 in PC9/WT cells downregulated FOXO3a and subsequently enhanced the resistance of gefitinib. Together, our study reveals a molecular link between miR-155 and FOXO3a and provides evidence that miR-155 and FOXO3a are potential therapeutic targets in gefitinib-resistant lung cancer.