Gefitinib Treatment-induced PTGIS Expression via IL-6/Stat3 Signaling Participates in Acquired Drug Resistance in Lung Cancer

Hsuan-Heng Yeh, Chien-Chung Lin, Wu-Chou Su
葉宣亨，林建中，蘇五洲

Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan.

Targeted cancer therapies promote tumor regression in clinical responses, however, most tumors develop resistance to these drugs. Stat3 activation is one of multiple mechanisms that cause acquired resistance to EGFR-tyrosin kinase inhibitor (TKI) in non-small cell lung cancer (NSCLC). However, the underlying molecular mechanisms are not well studied. In this study, we found that treatment of gefitinib (EGFR-TKI) in PC9 cells harboring EGFR-TKI sensitive mutation induced a feedback activation of Stat3 signaling. High levels of IL-6 were also detected in the conditioned medium of gefitinib-treated PC9 cells. We demonstrated that IL-6 could induce Stat3 activation in PC9 cells and the conditioned medium of PC9 cells treated with gefitinib could also induce Stat3 activation and this activation was suppressed by IL-6 neutralizing antibody. We also demonstrated that knockdown of Stat3 expression in PC9 cells could inhibit gefitinib treatment-induced IL-6 secretionby. Moreover, cell cytotoxicity of gefitinib was increased by pharmacological and genetic inhibition of Stat3 activation. Our data suggested that gefitinib treatment could activate IL-6/Stat3 signaling loop and modulate cell cytotoxicity to gefitinib. Using Microarray and Ingenuity Pathway Analysis (IPA) analysis, we revealed prostaglandin I2 synthase (PTGIS) as a downstream target gene of IL-6/Stat3 signaling. The induction of PTGIS by gefitinib via Stat3 feedback activation was confirmed in PC9 cells. Moreover, we showed that cotreatment of PTGIS inhibitor with gefitinib could improve cell cytotoxicity. Importantly, we found that gefitinib-resistant PC9 cells (PC9/gef) expressed more PTGIS then gefitinib-sensitive PC9 cells. Targeting PTGIS effectively increased gefitinib sencitivity of PC9/gef cells. Taken together, our study demonstrated that gefitinib-induced PTGIS expression via

IL-6 Stat3 signaling participates in modulating gefitinib efficacy and PTGIS targeting could potentially overcome acquired resistance to gefitinib in NSCLC.