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The potential role and mechanism of STAT3 in acquired resistance to EGFR TKI in lung adenocarcinoma with EGFR mutation

Chao Ting-Ting and Kuo I-Hui
Cardinal Tien Hospital, Taiwan

Oncogene-addicted cancer cells generate a positive feedback loop leading to STAT3 activation after target drug therapy. The aim of this study was to suppress STAT3 pathway through elevating SHP-1 activity by SHP-1 enhancer. PC9 cell line is exon 19 deletion (746-750) of NSCLC and sensitive to TKI. PC9-Afatinib-resistance (PC9-AR) cell line is PC9 cell line treated with low dose Afatinib for more than 9 months. PC9-AR was resistant to Afatinib, but there was no T790M mutation in PC9-AR. SHP-1 enhancer, SC-43, was tested in PC9-AR and apoptosis and signal transduction was analyzed. By adding SC-43 caused growth inhibition and induced apoptosis in PC9-AR. SC-43 reduced STAT3 phosphorylation at tyrosine 705 in PC9-AR. PC9-AR expressed more EMT, which was also suppressed by SC-43. Ectopic expression of STAT3 in PC9 caused resistance to Afatinib. On the contrary, small interference RNA of STAT3 re-sensitized PC9-AR to Afatinib. Furthermore, SC-43 interacted with the N-SH2 domain of SHP-1 to enhance the activity of SHP-1 as its mechanism. SC-43 significantly reduced PC9-AR sphere formation and tumor growth in vivo through SHP-1/STAT3 pathway. SC-43 provides proof that targeting STAT3 signaling pathway may be a novel approach for the treatment in acquired resistance to EGFR TKI in lung adenocarcinoma with EGFR mutation.

Biography

Chao Ting-Ting is an Associate Researcher in the Medical Research Center at Cardinal Tien Hospital. She has received her PhD in Graduate Institute of Life Sciences from the National Defense Medical Center, Taiwan. She has subsequently completed Postdoctoral training at National Health Research Institutes and the Tri-Service General Hospital studying aging-related musculoskeletal disease and cochlear stem cell in hearing loss repairing. Her research interest focused on targeted therapies and is currently working on understanding the roles and mechanisms in small molecule drugs targeted therapies for lung cancer. She has published more than 28 papers in reputed journals.

chaotting@gmail.com

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