Small molecule, T315 Promot of CBL-Dependent Degradation of EGFR through Ligand-Induced Y1045 Autophosphorylation

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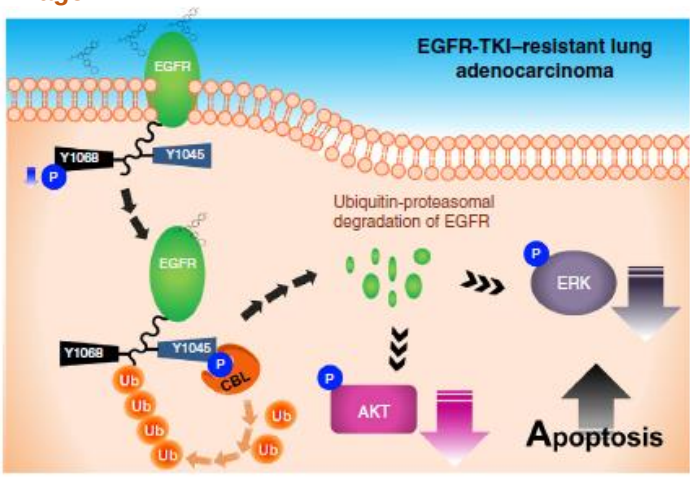
Abstract (300 word limit)

Several nature or synthetic small compounds can be helpful in improving the symptoms of diseases and treating patients. Post-translational modification (PTM) plays a vital role in various biological processes and disease progression such as cellular differentiation, signaling transduction, and protein stability and localization. Aberrant epidermal growth factor receptor (EGFR) signaling is one of the most critical oncogenic pathways in non-small-cell lung carcinoma (NSCLC) that triggers the tumor progression. However, suppression of the EGFR downstream signaling cascade has been considered a main therapeutic approach of intervention for cancer patients. In this thesis, we report that a therapeutically regulatory mechanism utilizing a new small compound T315-mediated EGFR degradation. Exposure to T315 induces apoptosis in lung cancer cell lines, including EGFR wild-type A549 as well as EGFR mutant PC9 and H1975 cells. T315 dose-dependently decreases the EGFR protein level and facilitates dephosphorylation of its downstream targets (AKT and ERK), and both of them play critical roles for lung cancer cell survival. We further demonstrate that T315 induces autophosphorylation at Tyr-1045 in the autophosphorylation domain of EGFR and boosts EGFR degradation through the ubiquitin proteasome pathway by increasing the interaction between the ubiquitin E3 ligase, Casitas B-lineage Lymphoma (CBL), and EGFR. The mass spectrometry implies that T315 may be bound to the extracellular domain of EGFR and subsequent triggers Tyr-1045 autophosphorylation. Finally, the combination of T315 with a commercial tyrosine kinase inhibitor of BIBW2992 additively suppresses in vitro NSCLC cell growth and the mouse xenograft model. Our evidences suggest that T315 is a next-generation of anticancer drug to inhibit the growth of EGFR TKI-resistant lung adenocarcinoma cells via EGFR degradation.

Image



Recent Publications (minimum 5)

1. Alsharedi M, Bukamur H, Elhamdani A. (2018) Osimertinib for the treatment of patients with EGFR mutation-positive non-small cell lung cancer. Drugs Today (Barc) 54(6):369-379.
2. Zhang H, Han B, Lu H, Zhao Y, Chen X, Meng Q, Cao M, Cai L, Hu J. (2018) USP22 promotes resistance to EGFR-TKIs by preventing ubiquitination-mediated EGFR degradation in EGFR-mutant lung adenocarcinoma. Cancer Lett 433:186-198.
3. Hong SY, Kao YR, Lee TC, Wu CW. (2018) Upregulation of E3 ubiquitin ligase CBLC enhances EGFR dysregulation and signaling in lung adenocarcinoma. Cancer Res. pii: canres.3858.2017.
4. Ménard L, Floc'h N, Martin MJ, Cross DAE. (2018) Reactivation of Mutant-EGFR Degradation through Clathrin Inhibition Overcomes Resistance to EGFR Tyrosine Kinase Inhibitors. Cancer Res.78(12):3267-3279.
5. Nukaga S, Yasuda H, Tsuchihara K, Hamamoto J, Masuzawa K, Kawada I, Naoki K, Matsumoto S, Mimaki S, Ikemura S, Goto K, Betsuyaku T, Soejima K. (2017) Amplification of EGFR Wild-Type Alleles in Non-Small Cell Lung Cancer Cells Confers Acquired Resistance to Mutation-Selective EGFR Tyrosine Kinase Inhibitors. Cancer Res. 2017 Apr 15;77(8):2078-2089.

Photograph

Biography (150 word limit)

Dr. Kuo-Yen Huang received his Ph.D. degree in the Graduate Institute of Life Science at National Defense Medical Center, Taiwan under the guidance of Prof. Pan-Chyr Yang in 2016. Currently, he is working as a postdoctoral research fellow at Prof. Yang's Lab in the Institute of BioMedical Sciences at Academia Sinica, Taiwan. His research interests are focus on cancer biology, cancer therapy and high throughput screening for identifying the potential reagents to overcome EGFR-TKI resistance.

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