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Lymphotoxin-b Interacts with Methylated EGFR to Mediate Acquired Resistance to Cetuximab in Head and Neck Cancer

Dennis Shin-Shian Hsu[1],Wei-Lun Hwang[2], Chiou-Hwa Yuh[3], Chen-Hsi Chu[4], Yang-Hui Ho[5], Pon-Bo Chen[6], Han-Syuan Lin[3,] Hua-Kuo Lin[3], Shih-Pei Wu[6], Chih-Yi Lin[6], Wen-Hao Hsu[6], Hsin-Yi Lan[6], Hsiao-Jung Wang[7], Shyh-Kuan Tai[8], Mien-Chie Hung[9,10,11,12], Muh-Hwa Yang[1,5,6,13]

許信賢，黃尉倫，喻秋華，朱真嬉，何仰惠，陳芃博，林涵軒，林華國，吳詩培，林知誼，許文豪，藍欣怡，王曉蓉，戴世光，洪明奇，楊慕華

[1]Genome Research Center, National Yang-Ming University, Taipei, Taiwan. [2] The Ph.D. Program for Translational Medicine, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan. [3]Institute of Molecular and Genome Medicine, National Health Research Institutes, Zhunan, Taiwan. [4]Department of Life Science and Institute of Bioinformatics and Structural Biology, College of Life Science, National Tsing Hua University, Hsinchu, Taiwan. [5]Genomics Research Center, Academia Sinica, Taipei, Taiwan. [6]Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan. [7]Division of Experimental Surgery, Department of Surgery, Taipei VeteransGeneral Hospital, Taipei, Taiwan. [8]Department of Otolaryngology, Taipei Veterans General Hospital, Taipei, Taiwan. [9]Department of Molecular and Cellular Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas. [10]The University of Texas Graduate School of Biomedical Sciences at Houston, Houston, Texas. [11]Graduate Institute of Cancer Biology and Center for Molecular Medicine, China Medical University, Taichung, Taiwan. [12]Department of Biotechnology, Asia University, Taichung, Taiwan. [13]Division of Medical Oncology, Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan.

Purpose: In head and neck squamous cell carcinoma(HNSCC), the incidence of RAS mutation, which is the major cause of cetuximab resistance, is relatively rare compared with the other types of cancers, and the mechanism mediating acquired resistance is unclear compared with the driver gene mutation– mediated de novo resistance. Here, we investigated the driver gene mutation–independent mechanism for cetuximab resistance in HNSCC. **Experimental Design:** We used the in vitro-selected and in vivoselected cetuximab-resistant sublines of HNSCC cell lines for investigating the mechanism of acquired resistance to cetuximab. Zebrafish model was applied for evaluating the synergistic effect of combinatory drugs for overcoming cetuximab resistance. **Results:** The cetuximab-resistant HNSCC cells undergo a Snailinduced epithelial mesenchymal transition. Mechanistically, Snail induces the expression of lymphotoxin-b (LTb), a TNF superfamily protein that activates NF-kB, and protein arginine methyltransferase 1 (PRMT1), an arginine methyltransferase that methylates EGFR. LTb interacts with methylated EGFR to promote its ligand-binding ability and dimerization. Furthermore, LTb activates the NF-kB pathway through a LTb receptor–independent mechanism. Combination of an EGFR tyrosine kinase inhibitor and a NF-kB inhibitor effectively suppressed cetuximab-resistant HNSCC and interfering with the EGFR–LTb interaction reverses resistance. **Conclusions:** Our findings elucidate the mechanism of driver gene mutations–independent mechanism of acquired resistance to cetuximab in HNSCC and also provide potential strategies for combating cetuximab resistance.