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EZH2-mediated up-regulation of *ROS1* oncogene promotes oral cancer metastasis

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Current anti-epidermal growth factor receptor (EGFR) therapy for oral cancer does not provide satisfactory efficacy due to drug resistance or reduced EGFR level. As an alternative candidate target for therapy, here we identified an oncogene, *ROS1*, as an important driver for oral squamous cell carcinoma (OSCC) metastasis. Among tumors from 188 oral cancer patients, up-regulated *ROS1* expression strongly correlated with metastasis to lung and lymph nodes. Mechanistic studies uncover that the activated *ROS1* results from highly expressed *ROS1* gene instead of gene rearrangement, a phenomenon distinct from other cancers. Our data further reveal a novel mechanism that reduces histone methyltransferase EZH2 leads to a lower trimethylation of histone H3 lysine 27 suppressive modification, relaxes chromatin, and promotes the accessibility of the transcription factor STAT1 to the enhancer and the intron regions of *ROS1* target genes, *CXCL1* and *GLI1*, for up-regulating their expressions. Down-regulation of *ROS1* in highly invasive *OSCC* cells, nevertheless, reduces cell proliferation and inhibits metastasis to lung in the tail-vein injection and the oral cavity xenograft models. Our findings highlight *ROS1* as a candidate biomarker and therapeutic target for *OSCC*. Finally, we demonstrate that co-targeting of *ROS1* and EGFR could potentially offer an effective oral cancer therapy.

Biography

Chien-Hung Shih is currently a PhD student at Institute of Molecular Medicine of National Tsing Hua University, Taiwan. He has his specialization in cell and molecular biology and epigenetics. His study focuses on investigating definite biomarkers and molecular mechanisms for oral cancer invasion and metastasis to find out potential therapeutic targets and strategies.

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