Targeting EHMT2 reverses EGFR-TKI resistance in NSCLC by epigenetically regulating the PTEN/AKT signaling pathway

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Background: Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) resistance is a major obstacle in the treatment of non-small cell lung cancer (NSCLC). Epigenetic alterations have been shown to be involved in NSCLC oncogenesis; however, their function in EGFR-TKI resistance remains uncharacterized.

Results: We found that an EHMT2 inhibitor, UNC0638, can significantly inhibit cell growth and induce apoptosis in EGFR-TKI-resistant NSCLC cells. Additionally, we also found that EHMT2 expression and enzymatic activity levels were elevated in EGFR-TKI-resistant NSCLC cells. Moreover, we determined that genetic or pharmacological inhibition of EHMT2 expression enhanced TKI sensitivity and suppressed migration and tumor sphere formation in EGFR-TKI-resistant NSCLC cells. Further investigation revealed that EHMT2 contributed to PTEN transcriptional repression and thus facilitated AKT pathway activation. The negative relationship between EHMT2 and PTEN was confirmed by our clinical study. Furthermore, we determined that combination treatment with the indicated EHMT2 inhibitor and Erlotinib resulted in enhanced antitumor effects in a preclinical EGFR-TKI-resistance model. We also found that high EHMT2 expression along with low PTEN expression can predict poor overall survival in patients with NSCLC.

Conclusion: Our findings showed that EHMT2 facilitated EGFR-TKI resistance by regulating the PTEN/AKT pathway in NSCLC cells, suggesting that EHMT2 may be a target in the clinical treatment of EGFR-TKI-resistant NSCLC.