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HMG box-containing protein 1 (HBP1) participates in the antitumor effect of N-acetylcysteine (NAC) in invasive oral cancer

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Aberrant activation of the epidermal growth factor receptor (EGFR) gene is highly associated with poor prognosis and low survival in invasive oral cancer. Resistance to the EGFR-targeting antibodies or kinase inhibitors has been reported. Therefore, it becomes imperative to design alternative and/or additional agents to supplement the existing therapeutic means. N-acetylcysteine (NAC) has been shown to exhibit anti-EGFR function, but the underlying mechanism is not fully clear. Herein, we hypothesized that NAC might inhibit EGFR signaling through the induction of HBP1 in oral cancer. HBP1 is a known transcriptional suppressor of cyclin D1 and p47phox, a regulatory subunit of the NADPH oxidase complex, through which HBP1 regulates cell growth and redox homeostasis. NAC treatment suppressed cell growth, concomitantly with a reduction of the EGFR/Akt/cyclin D1 activation and an increase of HBP1 expression, in EGFR-overexpressing HSC-3 cells. When combined with AG1478, an EGFR inhibitor, NAC synergistically inhibited colony formation of HSC-3 cells, indicating that NAC is an effective anti-EGFR adjuvant. HBP1 disruption activated EGFR signaling as well as increased colony formation, cellular migration, and tumor growth in xenograft mice, and HBP1 knockdown also sensitized HSC-3 cells to AG1478, suggesting that HBP1 is a negative regulator of the EGFR signaling pathway. A significant overlap of the gene expression patterns between an HBP1-knockdown dataset and an existing EGFR signature was also identified. Finally, HBP1 silencing attenuated the anti-EGFR and anti-growth effects of NAC, and HBP1 knockdown also partially abolished NAC-inhibited p47phox expression and EGF-stimulated reactive oxygen species (ROS) generation. Taken together, our data indicate that HBP1 functions as a negative EGFR regulator, and NAC inhibits EGFR signaling presumably through HBP1 induction in invasive oral cancer.