REDOX-MODULATORY AND MET-INHIBITORY TRIAD: SYNERGISTIC CYTOTOXICITY OF L-CYSTEINE, NAC, AND MET INHIBITION IN CERVICAL CANCER CELLS

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Background: The MET signaling pathway is a central regulator of tumor growth, epithelial-to-mesenchymal transition (EMT), and therapy resistance. However, MET inhibition alone may be insufficient due to compensatory signaling and intrinsic redox buffering. N-acetylcysteine (NAC) and L-cysteine, as thiol-based antioxidants, regulate intracellular glutathione pools and redox- sensitive signaling cascades. We investigated whether combining NAC and L-cysteine with MET inhibition could enhance anticancer efficacy without exogenous oxidative stress or chemotherapy.

Materials and methods: Human (HeLa, K562) and murine (B16, Myc-CaP) cancer cell lines were treated with L-cysteine, NAC, crizotinib (a clinically relevant MET inhibitor), or their combinations. Phospho-MET (pMET) expression was analyzed by confocal immunofluorescence microscopy with DAPI counterstaining. Cell death was quantified by flow cytometry using Hoechst and PI staining.

Results: L-cysteine/NAC alone did not reduce cell death, but in combination increased cytotoxicity across tested cell lines. The triple treatment (L-cysteine, NAC, crizotinib) significantly suppressed pMET activation, showing reduced fluorescence intensity and perinuclear redistribution. Flow cytometry demonstrated a robust increase in late apoptosis in the triple combination group compared with monotherapies or dual treatments ($p < 0.0001$). Mechanistically, redox stabilization appeared to sensitize cells to MET inhibition by limiting compensatory pro-survival pathways. Inhibitor screening suggested the involvement of AKT and p38 signaling in the NAC/L-cysteine–mediated ROS-independent mechanism.

Conclusion: The tri-modal strategy combining L-cysteine, NAC, and MET inhibition demonstrates robust and synergistic cytotoxicity in cancer cells, independent of exogenous oxidative or chemotherapeutic stress. These findings implicate a novel therapeutic paradigm in which redox modulation enhances oncogene-targeted interventions. This combinatorial framework holds promise not only for augmenting MET-targeted therapies but also for mitigating adverse effects such as chemotherapy-induced alopecia, given the known protective roles of NAC and METi in hair follicle stem cell maintenance.

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Key words: MET kinase, Redox regulation, Cysteine metabolism

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