Assessing the use of UBC9 Inhibitors as chemotherapeutic enhancers against non-small cell lung cancer using integrated experimental and transcriptomic approaches

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Non-small cell lung cancer (NSCLC) is the leading cause of death by cancer in the United States, with a 5-year survival rate of only 21.7%. SUMOylation is a post-translational modification in which a Small Ubiquitin-like Modifier (SUMO) protein is covalently attached to a target protein, thereby regulating protein-protein interactions. SUMOylation regulates multiple cellular processes, including DNA repair, replication and cell cycle progression. Dysregulation of the SUMOylation pathway is well documented in cancer, where it contributes to carcinogenesis, DNA damage response and proliferation.

The SUMOylation pathway is driven by a cascade of enzymes in which UBC9 is the sole E2 conjugating enzyme. UBC9 is responsible for transferring activated SUMO proteins to their target substrates. UBC9 along with other pathway enzymes are upregulated in several cancers, including NSCLC. Therefore, targeting UBC9 represents a promising therapeutic target.

In this study, we assessed the selectivity and cytotoxicity of a set of newly developed UBC9 inhibitors in a NSCLC model cell line, A549. Immunoblot analyses confirmed a reduction in UBC9 and SUMO2/3 protein expression following treatment, indicating effective overall pathway inhibition. We also found that UBC9 inhibition reduced cell proliferation and induced cell death. Foremost, chemosensitizing effects were demonstrated by using treatment combinations with standard chemotherapeutic agents, etoposide and cisplatin.

To further explore transcriptional changes and confirm the specificity of our inhibitors, we performed RNA sequencing across multiple SUMOylation pathway enzyme inhibition treatments, including UBC9. An exploratory differential gene expression analysis was conducted using normalized counts, log2 fold change relative to our mock untreated sample of A549, and finally variance stabilizing transformation (VST) was used for visualization. These analyses revealed treatment specific transcriptional trends and identified possible genes associated with SUMOylation pathway dysregulation.

Together, these findings demonstrate that UBC9 and other pathway inhibitors disrupt SUMOylation and enhance therapeutic response in NSCLC cells. Current studies focus on including biological replicates to enable statistical validation of differential gene expression which will further idientify the molecular mechanisms underlying SUMO-targeted therapies and their chemosensitizing effects at the transcriptomic level.