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"Inhibition of PHF8 with Daminozide: Therapeutic Implications for Triple Negative Breast Cancer"

Breast cancer, as the world's most prevalent cancer, continues to pose significant global health challenges with 2.3 million women diagnosed and 685,000 deaths reported in 2020 alone. One of the most aggressive and treatment-refractory subtypes is triple-negative breast cancer (TNBC), characterized by the absence of estrogen receptor (ER) and progesterone receptor (PR), as well as lack of human epidermal growth factor receptor 2 (HER2) overexpression. These receptors can be effectively targeted in other subtypes of breast cancer with existing approved medications. Lack of these therapeutic targets in TNBC accentuates the need for the discovery of novel strategies to combat this disease.

The epigenetic regulator, Plant Homeodomain Finger protein 8 (PHF8), offers promise as a potential target for TNBC. PHF8, a histone demethylase, modulates histone methylation, a fundamental cellular process that contributes significantly to gene regulation and cancer development. Studies have shown that PHF8 is frequently overexpressed in various human cancers, including breast cancer, suggesting its potential role in the development of targeted treatments. Its involvement in gene regulation has been shown to play a crucial role in tumor progression. This is partly realized through the promotion of the epithelial–mesenchymal transition. This process contributes to metastasis as cells move beyond their surrounding microenvironment to eventually migrate away from their original location, worsening survival outcomes. Hence, the current study aims to investigate the therapeutic implications of inhibiting PHF8 in TNBC cell lines.

Our methodology encompasses a comprehensive suite of assays to evaluate the impact of PHF8 inhibition on TNBC cells. Daminozide served as the inhibitory agent for PHF8 in TNBC cell lines. Colony formation and MTS assays were utilized to assess cell viability and proliferation. Further, the extent of apoptosis in treated cells was evaluated using flow cytometry assays, providing a measure of the drug's efficacy in inducing programmed cell death. Reverse transcription-quantitative polymerase chain reaction was used to quantify and compare the gene expression levels. Additionally, Western blots were used to determine the changes in expression levels and activation of specific proteins following PHF8 inhibition. This includes key cell cycle regulatory proteins such as p27 and p21, as well as the histone markers: monomethylated lysine 20 on histone 4 (H4K20Me1), H3K27Me2, and H3K9Me1, which are the well-established substrates of PHF8.

Through this comprehensive study, we aim to elucidate the potential of PHF8 as a therapeutic target in TNBC, thereby paving the way for novel treatment strategies against this aggressive disease. Detailed findings will provide insights into the molecular interplay between

PHF8 and other proteins, aiding in the development of targeted therapies that could significantly improve outcomes for patients with TNBC.