Inhibiting the Escape: Unveiling the Potential of Type I PRMT Inhibitors in Targeting Lysosomal Exocytosis for Improved Cancer Therapy

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Epigenetic modifications exert a profound influence on gene expression, directing oncogenesis and resistance to drugs. Lysosomes, crucial for cellular signaling and component management, have recently emerged as pivotal players in cancer cell survival through lysosomal sequestration and exocytosis to evade programmed cell death. This study focuses on the epigenetic coordination of these processes, hypothesizing that epigenetic modifier drugs capable of suppressing lysosomal exocytosis could serve as effective therapeutics, thereby enhancing the efficacy of cisplatin.

Our study entailed screening a library of epidrugs, evaluating their impact on lysosomal exocytosis (β-hex assay), lysosomal content (LysoTracker staining), and combined cytotoxicity with cisplatin (cell viability assay). Remarkably, MS023, a type I PRMT inhibitor, emerged as a promising candidate, demonstrating reduction in exocytosis and enhancing cisplatin cytotoxicity.

Furthermore, silencing each PRMT targets (PRMT1, 6, and 8) was less effective in reducing exocytosis compared to the effect of MS023, suggesting the need for concurrent inhibition of multiple PRMTs or the involvement of an unidentified target. RNA-seq and gene ontology studies unveiled potential biological alterations and among the differentially expressed genes, three notable candidates—ABCA1, ABCA3, and SerpinE1—previously linked to drug resistance were identified. Focusing on ABCA3, which exhibited the highest fold change and lysosomal localization, we found that knocking down all MS023 target PRMTs led to a reduction in ABCA3 expression. Further investigation into other Type I PRMT inhibitors revealed that GSK3368715 also reduces exocytosis in addition to synergizing with cisplatin.

In summary, Type I PRMT inhibitors emerge as promising epidrugs impacting secretory pathways and drug efflux processes, with the aim of establishing future targets for cancer intervention and ultimately enhancing drug efficacy.