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Targeting the ABCB7/GPX4 axis potentiates cisplatin response in pediatric Group 3 medulloblastomas by triggering ferroptosis

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Background: Medulloblastoma (MB), the most common malignant pediatric brain tumor and a leading cause of childhood mortality, is stratified into four primary subgroups, i.e. WNT (wingless), SHH (sonic hedgehog), group 3, and group 4, the latter two representing high-risk MB. Leveraging the chemosensitization property of ABCB7 as adjuncts to chemotherapy may provide a promising alternative to current therapeutic strategies.

Significance of the Problem: Group 3 tumors enrich iron transport genes to satisfy their high proliferative need. MiR-1253 targets iron transport by inhibiting the mitochondrial Fe-S transporter, ABCB7. Iron imbalance can lead to cell death by ferroptosis, characterized by iron overload leading to oxidative stress and inducing lipid peroxidation. This study elucidated the impact of targeting ABCB7 on cisplatin cytotoxicity in group 3 MB and whether these effects were mediated by ferroptosis.

Hypothesis, Problem OR Question: Inducing iron imbalance by targeting the ABCB7/GPX4 axis potentiate cisplatin response in MB

Experimental Design: Bioinformatics analyses were first utilized to identify deregulated oncoproteins that were targets of miR-1253 in group 3 MB, identifying the mitochondrial iron-sulfer transporter ABCB7. The effect of miR-1253 overexpression (miR-1253OE) or ABCB7 knockout (ABCB7KO) on cellular and mitochondrial iron levels, oxidative stress, lipid peroxidation, and glutathione levels was studied via confocal microscopy, immunostaining, and Western blotting. Impact of ABCB7 repression on cancer cell capacity for glycolysis and oxidative phosphorylation was assessed by Seahorse assays. Ultimately, an orthotopic mouse model was generated to illustrate that cisplatin cytotoxicity can be potentiated in group 3 tumors by repressing ABCB7

Results: In silico and in vitro analyses revealed specific enrichment of ABCB7 and GPX4, a critical regulator of ferroptosis, in group 3 MB cell lines and tumors. Restoration of miR-1253 resulted in downregulation of both ABCB7 and GPX4, concurrently increasing mitochondrial and cytoplasmic iron pools and, in turn, mitochondrial oxidative stress and lipid peroxidation, leading to cell death and abrogation of medullosphere formation. Seahorse studies showed that the bulk of ATP generation was occurring in the cytoplasm by glycolysis and not oxidative phosphorylation, suggesting mitochondrial toxicity with ABCB7 inhibition. In miR-1253OE cancer cells, cisplatin IC50 was reduced 2-fold. Resultantly, in miR-1253OE or ABCB7KO group 3 cells, concurrent treatment with cisplatin augmented oxidative stress and lipid peroxidation, depleted glutathione stores, and culminated in a higher index of ferroptosis. In a mouse model of group 3 tumors, ABCB7KO dramatically prolonged survival and potentiated cisplatin effects. The current study illustrates how targeting iron transport by a tumor suppressive miR can augment ferroptosis to potentiate cisplatin in group 3 MB tumors..