Child Health Research Institute

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Iron Imbalance Can Potentiate Cisplatin Response in Pediatric Medulloblastoma by Regulating Ferroptosis

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Medulloblastoma (MB) is a rapidly invading malignant pediatric brain tumor and a leading cause of cancer-related childhood mortality. Metastases at diagnosis define the most aggressive tumors belonging to group 3. A novel tumor suppressor gene silenced in group 3 tumors, miR-1253, targets the iron-sulfur cluster transporter, ABCB7. Transcriptional inhibition of ABCB7 via miR-1253 led to iron overload and depletion of glutathione peroxidase 4 (GPX4), a central ferroptosis regulator. Ferroptosis regulator genes (FRGs) are highly expressed in aggressive cancers and maintain iron balance. The role of FRGs in group 3 tumors and their association with aggressiveness has not been explored. Group 3 MB are amongst the most aggressive, with 5-year survival <50%, in stark contrast to the 75-90% survival seen for the other MB subgroups. High recurrence fueled by drug resistance further reduces survival to <10%, highlighting a pronounced divergence in survivorship amongst subgroups and the dire need to elucidate mechanisms underlying tumor aggressiveness that can be targeted therapeutically. MiR-1253 induces iron imbalance in group 3 cancer cells. Cisplatin, a standard group 3 MB chemotherapy, induces cancer cell death not only by platinum-mediated DNA alkylation but also by promoting iron imbalance. Based upon these observations, we hypothesize that miR-1253 can potentiate cisplatin cytotoxicity in group 3 tumors by altering iron homeostasis and glutathione metabolism. We first compared the transcriptomes of a local cohort of pediatric MB patients for deregulated FRGs. Then, we examined the effect of miR-1253 overexpression or ABCB7 knockout on iron imbalance, oxidative stress, and lipid peroxidation. We rescued cells from iron imbalance via iron chelation (deferoxamine) or from ferroptosis using ferrostatin-1. Finally, we examined the potentiation of iron imbalance on cisplatin cytotoxicity in group 3 cancer cells. Our in silico interrogation revealed high expression of iron transport and glutathione metabolism, including mitochondrial iron transporters, ABCB6-8, and GPX4. Transient overexpression of miR-1253 in group 3 cell lines downregulated ABCB7 and GPX4. Consequently, cytosolic and mitochondrial labile iron pools rose, glutathione levels declined, and mitochondrial oxidative stress and lipid peroxidation were induced, resulting in higher cell death by ferroptosis. These effects were rescued by deferoxamine and recapitulated with ABCB7 knockdown. Treating miR-1253-expressing cancer cells with cisplatin compounded ferroptosis. Treatment with ferrostatin-1 rescued cells from combination therapy. Our studies highlight a novel mechanism for group 3 MB pathogenesis via ferroptosis regulation and provide a proof-of-concept for exploiting group 3 MB tumor vulnerability to iron imbalance as a novel treatment strategy.