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Opinion Article

The Role of Ferroptosis Induction in Glioblastoma Therapy Resistance

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DESCRIPTION

Glioblastoma is the most aggressive primary brain tumor in adults, characterized by rapid proliferation, extensive invasiveness, and profound resistance to conventional therapies including surgery, radiation therapy, and chemotherapy. Despite aggressive treatment, the median survival remains less than two years, and recurrence is nearly universal. Therapy resistance in glioblastoma is multifactorial and arises from a combination of genetic heterogeneity, adaptive cellular responses, and microenvironmental factors. Ferroptosis, a regulated form of cell death driven by iron dependent lipid peroxidation, has recently emerged as a critical mechanism influencing tumor cell survival and therapy resistance. Understanding the role of ferroptosis induction in glioblastoma offers opportunities to overcome therapeutic barriers and develop innovative treatment strategies.

Ferroptosis is mechanistically distinct from apoptosis, necrosis, and autophagy. It is characterized by the accumulation of lipid peroxides in cellular membranes, iron dependent reactive oxygen species production, and irreversible membrane damage leading to cell death. In glioblastoma, tumor cells exhibit altered iron metabolism, elevated lipid content, and dysregulated antioxidant systems that collectively modulate susceptibility to ferroptosis. These adaptations allow tumor cells to survive oxidative stress induced by conventional therapies and contribute to treatment failure. Targeting ferroptosis pathways in these cells is therefore a promising approach to sensitize resistant tumor populations.

The induction of ferroptosis has been shown to interact with the efficacy of radiation therapy. Radiation therapy induces oxidative stress in glioblastoma cells, generating reactive oxygen species that damage Deoxyribonucleic Acid (DNA) and cellular components. However, tumor cells with enhanced ferroptosis defense mechanisms can neutralize lipid peroxides and evade death, resulting in radiation resistance. Pharmacological inhibition of glutathione peroxidase or suppression of cystine uptake sensitizes tumor cells to radiation by promoting ferroptotic cell death. Preclinical models have demonstrated that combining ferroptosis inducers with radiation therapy reduces tumor growth, increases DNA damage, and prolongs survival, suggesting that modulation of ferroptosis can overcome intrinsic radioresistance in glioblastoma.

Chemotherapy resistance in glioblastoma is also influenced by ferroptosis. Temozolomide, the standard chemotherapeutic agent, exerts cytotoxic effects primarily through DNA alkylation. Tumor cells resistant to temozolomide often display increased antioxidant capacity, iron sequestration, and lipid remodeling that mitigate ferroptotic death. By targeting ferroptosis pathways, it is possible to enhance chemotherapeutic efficacy and induce cell death in resistant tumor cells. Small molecules that deplete glutathione, inhibit system Xc minus transporters, or promote iron accumulation have shown synergistic effects with temozolomide in preclinical glioblastoma models. These findings underscore the potential of ferroptosis induction as an adjuvant strategy to overcome chemoresistance.

The tumor microenvironment in glioblastoma further influences ferroptosis susceptibility. Hypoxia, a hallmark of glioblastoma, can reduce ferroptotic sensitivity by stabilizing antioxidant defenses and altering lipid metabolism. Additionally, interactions with immune cells, astrocytes, and endothelial cells modulate oxidative stress and iron availability, shaping ferroptosis dynamics. Tumor associated macrophages secrete cytokines and growth factors that enhance antioxidant defenses in glioblastoma cells, further promoting resistance. Understanding these microenvironmental influences is critical for the rational design of ferroptosis based therapies that can effectively target resistant tumor niches.

Epigenetic and transcriptional regulation of ferroptosis related genes also contributes to therapy resistance in glioblastoma. Upregulation of genes involved in glutathione synthesis, lipid peroxidation repair, and iron sequestration supports tumor cell survival under therapeutic stress. Conversely, downregulation of ferroptosis promoting genes reduces sensitivity to oxidative damage. Therapeutic strategies that modulate gene expression, including epigenetic inhibitors or transcription factor modulators, may enhance ferroptotic susceptibility and overcome therapy resistance. Integrating these approaches with conventional treatment regimens could provide a multi layered assault on resistant tumor cells.

Emerging therapeutic strategies targeting ferroptosis in glioblastoma include small molecule inducers, gene therapy, and nanoparticle based delivery systems. Nanoparticles designed to

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deliver iron or reactive oxygen species in a controlled manner increase tumor selectivity and minimize systemic toxicity. Additionally, combination therapies that integrate ferroptosis inducers with radiation, chemotherapy, or immune modulation demonstrate synergistic antitumor effects. These strategies are currently under investigation in preclinical and early clinical studies, highlighting the translational potential of ferroptosis based approaches.

Challenges remain in translating ferroptosis induction into clinical practice. Tumor heterogeneity, adaptive resistance mechanisms, and potential toxicity to normal brain tissue pose significant obstacles. Precise biomarkers for ferroptosis susceptibility are required to identify patients most likely to benefit from these therapies. Furthermore, understanding the timing, dosing, and sequencing of ferroptosis inducers in combination with conventional treatments is essential to maximize efficacy while minimizing adverse effects. Ongoing research is focused on elucidating ferroptosis regulatory networks, identifying predictive biomarkers, and developing safe and effective delivery systems to bring ferroptosis based therapy into the clinical setting.

CONCLUSION

Ferroptosis plays a pivotal role in glioblastoma therapy resistance. Tumor cells exploit iron metabolism, antioxidant defenses, lipid remodeling, and microenvironmental interactions to evade ferroptotic cell death, contributing to resistance against radiation and chemotherapy. Targeting ferroptosis pathways offers a promising strategy to overcome this resistance and enhance treatment efficacy. Pharmacological inducers, gene therapy approaches, and nanoparticle based delivery systems are emerging as innovative therapeutic options. A comprehensive understanding of ferroptosis regulation, tumor heterogeneity, and microenvironmental influences is critical for translating these findings into effective clinical interventions. Incorporating ferroptosis based strategies into multimodal treatment regimens has the potential to improve outcomes for patients with glioblastoma, offering hope against a cancer type that has historically been refractory to therapy.