ROLE OF FERROPTOSIS- A NOVEL PROGRAMMED CELL DEATH IN TEMOZOLOMIDE THERAPY FOR BRAIN CANCER:

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ABSTRACT:

GBMs are usually located in the brain, however they can also be found in the brain stem, cerebellum, and spinal cord. Sixty-one percent of all primary gliomas are found in the four brain lobes: frontal (25%), temporal (20%), parietal (13%), and occipital (3%).[1] TEMODAR (Temozolomide) is an alkylating medication used to treat adult patients with newly diagnosed glioblastoma multiforme (GBM) and resistant anaplastic astrocytoma who have progressed on a nitrosourea and procarbazine-containing treatment regimen.[2]

The molecular processes of ferroptosis, a new type of cell death that has been found to have an important role in the therapy of gliomas, are discussed in this review article. Ferroptosis is a new type of programmed cell death caused by cell membrane damage caused by mechanisms such as intracellular iron build-up, the creation of reactive oxygen species (ROS), lipid peroxidation, glutathione peroxidase (GPX) activity failure, and x-catenin (xCT).[3]

Ferroptosis is a specific form of cell death that is distinguished by mitochondrial shrinkage and increased membrane density. According to one study, temozolomide can cause ferroptosis in glioma cells by regulating DMT1 and Nrf2, two important iron transporters. As it increases sensitivity to iron toxicity and invasiveness, this might be a viable therapy for GBM.

The purpose of this article is to outline the molecular mechanisms of ferroptosis, introduce the application and challenges of ferroptosis and its role in the development and treatment of glioblastoma.

INTRODUCTION:

The most common primary malignant brain tumour in adults is called glioblastoma (GBM), a grade IV glioma and is also the most deadly tumours of the central nervous system. Only one chemotherapy medication, temozolomide (TMZ), has been shown to increase GBM patients' overall survival, yet only marginally.[4]

There is a need for immediate treatment due to the increase of glioblastoma instances. It is still difficult to get beyond the blood-brain barrier, even with modern anticancer medications. Target zones, drug concentration, duration of action, and safety are critical for achieving therapeutic results.

Using nano-transporters as carriers, scientists are creating vector delivery systems that maintain medication promise and safety.[5]

Animal cell death is largely triggered by certain signalling events. Apoptosis, autophagy cell death, and necrosis are the three kinds of cell death. Cell shrinkage, membrane blebbing, and chromatin condensation are all symptoms of apoptosis. Autophagy is a survival mechanism that is activated in response to metabolic crises or damaged organelles. Cell enlargement, plasma membrane rupture, and organelle structure loss are all symptoms of necrosis. There are other types of cell death that appear to need the cell's participation in its demise, ferroptosis being one of them.[6]

GBM cells have strong anti-apoptosis capacity and inhibitory tumor immune microenvironment (TIME), resulting in a poor response to immunotherapy. Recent bioinformatics studies have shown that ferroptosis-related genes (FRGs) can be used to predict treatment response in GBM.[7]

TEMOZOLOMIDE (TMZ) CHEMOTHERAPY IN GLIOBLASTOMA:

The oral alkylating drug TMZ, also referred to as 3-methyl-4-oxoimidazo [5, 1-d] (1-3, 5) tetrazine-8-carboxamide, possesses anticancer properties. It was initially identified in 1987 and, as of 2005, it was the primary chemotherapeutic drug for patients with gliomas. By methylation, DNA guanine residues at the O6 and N7 sites and causing nucleotide mispairing with thymine, TMZ causes cytotoxicity. This results in cell cycle arrest, single- and double-strand DNA breakage, and cell death.[8]

Temozolomide spontaneously hydrolyzes to produce the active metabolite 5-(3-methyl-1-triazen-1-yl) imidazole-4-carboxamide (MTIC). The efficacy of TMZ in tumours is strongly pH-dependent, with optimal efficacy achieved when tumour cell pH is close to physiological levels. Tumour cells have anti-TMZ defence mechanisms, which can be mediated by the DNA mismatch repair (MMR) system. TMZ has a high penetration capability in all tissues and is about 100% bioavailable. It is found in cerebrospinal fluid (CSF), which plays an important role in the treatment of glial tumours. The recently established technique of concentrated ultrasonic exposure in the presence of microbubbles causes a brief breakdown of the BBB, allowing TMZ to enter more easily.

RESISTANCE IN TMZ THERAPY:

According to the study, TMZ-induced DNA damage causes MGMT transcription to become active in at least certain tumours where the MGMT promoter is hypo methylated. This increased MGMT expression may play a significant role in the development of TMZ resistance.[9] TMZ resistance has remained a significant concern in the treatment of malignant gliomas. It is necessary to understand the complicated molecular basis of TMZ resistance and create viable treatments.

TMZ is a first-line chemotherapeutic medication for GBM that causes cytotoxicity via its metabolite MTIC. The resistance of TMZ is mostly due to O6-methylguanine-DNA methyltransferase (MGMT) repairing TMZ-induced DNA lesions, which allows cells to reverse TMZ cytotoxicity. Long-term TMZ therapy has been demonstrated to promote MGMT expression and minimise the susceptibility in a GBM cell line that lacks MGMT normally. MMR and DNA damage response (DDR), two DNA repair pathways, are also crucial to TMZ resistance. MMR gene deficiency or DDR inhibition is linked to TMZ tolerance, perhaps encouraging neoplastic development.[10]

Mechanism of ferroptosis:

The Cystine/glutamate transporter (System) is a crucial intracellular antioxidant molecule involved in ferroptosis, a cell death mechanism characterized by mitochondrial shrinkage, increased membrane density, and reduced mitochondrial cristae. It is triggered by intracellular glutathione depletion and reduced activity of glutathione peroxidase 4. The GPX4-catalyzed reduction pathway cannot metabolize lipid peroxides, and Fe2+ oxidizes lipids in a Fenton-like manner, producing reactive oxygen species (ROS) that promotes ferroptosis. Ferroptosis is distinct from necrosis, apoptosis, and autophagy in its appearance and function.[11, 12]

TEMOZOLOMIDE INDUCES FERROPTOSIS:

In patients with gliomas, methyltransferase can restore glucose-mediated methylation, which serves as a natural defence mechanism. Numerous processes, including as autophagy, apoptosis, caspase, transcriptional regulation, and Bcl-2 family members, can also induce TMZ resistance. Ferroptosis may represent a novel possible mechanism for TMZ resistance in gliomas, according to the latest research.[8]

The latest study investigates the role of DMT1 (divalent metal transporter 1; a major iron transporter and contributes non-heme iron uptake in various cell types.) overexpression in temozolomide-induced ferroptosis in glioma cells. Transfected TG905 cells with or without DMT1 siRNA were incubated with temozolomide. Temozolomide reduced DMT1 protein and mRNA expression, iron content, and intracellular ROS levels. The researchers also looked at the expression of DMT1, GPX4, Nrf2, and HO-1 protein, and discovered that temozolomide causes ferroptosis by upregulating DMT1.[13]

Nrf2, a key regulator of ferroptosis, was also discovered to be involved in this process. The study found that temozolomide caused ferroptosis in glioma cells via blocking the Nrf2/HO-1 pathway.[13] DMT1, a proton-coupled metal-ion transport protein, is an essential controller of iron homeostasis and iron absorption.[14] DMT1 knockdown elevated the expression of GPX4, Nrf2, and HO-1, indicating that temozolomide triggers ferroptosis in part through a DMT1-dependent mechanism.[13]

GBM invasiveness and treatment resistance may increase if ferroptosis is avoided. Because of the increased reliance on the antioxidant system and iron ions, changes in glucose, lipid, glutamine, and iron metabolism in GBM may increase vulnerability to ferroptosis. A potential treatment for GBM is to target ferroptosis. The molecular processes of ferroptosis include fatal phospholipid peroxidation caused by dysregulated redox homeostasis and cellular metabolism. The regulated cell death process is dependent on phospholipids containing iron, which are required for tumour cell viability. Utilising ferroptosis to kill GBM cells could be a novel and promising method.[7]

CONCLUSION:

GBMs are the most frequent primary malignant brain tumours in adults and can be detected in the brain stem, cerebellum, and spinal cord. Temozolomide (TMZ) is an alkylating agent that is used to treat adults with newly diagnosed glioblastoma multiforme (GBM) and resistant anaplastic astrocytoma who have progressed on a nitrosourea and procarbazine-containing therapy regimen. Ferroptosis, a new type of programmed cell death caused by cell membrane disruption, has been discovered to be important in glioblastoma therapy.

Intracellular iron buildup, reactive oxygen species (ROS), lipid peroxidation, glutathione peroxidase (GPX) activity failure, and x-catenin (xCT) are all molecular mechanisms involved in ferroptosis. GBM cells have a high anti-apoptosis capacity and a tumour immune microenvironment (TIME) that inhibits immunotherapy response. Ferroptosis-related genes (FRGs) have been found in recent bioinformatics research to predict treatment response in GBM.

Since 2005, TMZ, an oral alkylating medication with anticancer capabilities, has been the major chemotherapy treatment for patients with gliomas. TMZ resistance is primarily caused by O6-methylguanine-DNA methyltransferase (MGMT) mending TMZ-induced DNA lesions, allowing cells to reverse TMZ cytotoxicity. Long-term TMZ therapy has been shown to enhance MGMT expression and reduce vulnerability in a GBM cell line that normally lacks MGMT.

Unlike necrosis, apoptosis, and autophagy; Ferroptosis may provide a potential mechanism for TMZ resistance in gliomas. Targeting ferroptosis could be a promising method for treating GBM, as it involves fatal phospholipid peroxidation caused by dysregulated redox homeostasis and cellular metabolism. Ferroptosis, a new cell death form, has potential clinical applications in cancer treatment, with future research focusing on molecular mechanisms, inducers, and inhibitors.

The temozolomide has been shown to produce ferroptosis in glioma cells by disrupting the Nrf2/HO-1 pathway, which is important for iron homeostasis and absorption. This pathway is dependent on DMT1, which enhances GPX4, Nrf2, and HO-1 expression.

Finally, temozolomide suppresses tumour development by triggering ferroptosis via DMT1 expression. This work gives a better knowledge of how temozolomide impacts glioblastoma cells and may be useful in developing glioma treatment strategies.

REFERENCES:

1. Blissitt PA, American Association of Neuroscience Nurses. Clinical practice guideline series update: care of the adult patient with a brain tumor. *J Neurosci Nurs J Am Assoc Neurosci Nurses*. 2014;46(6):367-368. doi:10.1097/JNN.0000000000000088

2. fda.gov. TEMODAR label. Published online September 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021029s029lbl.pdf

3. Luo Y, Tian G, Fang X, Bai S, Yuan G, Pan Y. Ferroptosis and Its Potential Role in Glioma: From Molecular Mechanisms to Therapeutic Opportunities. *Antioxid Basel Switz*. 2022;11(11):2123. doi:10.3390/antiox11112123

4. Yin J, Wang X, Ge X, et al. Hypoxanthine phosphoribosyl transferase 1 metabolizes temozolomide to activate AMPK for driving chemoresistance of glioblastomas. *Nat Commun*. 2023;14(1):5913. doi:10.1038/s41467-023-41663-2

5. Petrenko D, Chubarev V, Syzrantsev N, et al. Temozolomide Efficacy and Metabolism: The Implicit Relevance of Nanoscale Delivery Systems. *Mol Basel Switz*. 2022;27(11):3507. doi:10.3390/molecules27113507

6. Green DR, Llambi F. Cell Death Signaling. *Cold Spring Harb Perspect Biol*. 2015;7(12):a006080. doi:10.1101/cshperspect.a006080

7. Zhuo S, He G, Chen T, et al. Emerging role of ferroptosis in glioblastoma: Therapeutic opportunities and challenges. *Front Mol Biosci*. 2022;9:974156. doi:10.3389/fmolb.2022.974156

8. Hu Z, Mi Y, Qian H, et al. A Potential Mechanism of Temozolomide Resistance in Glioma-Ferroptosis. *Front Oncol*. 2020;10:897. doi:10.3389/fonc.2020.00897

9. Kitange GJ, Carlson BL, Schroeder MA, et al. Induction of MGMT expression is associated with temozolomide resistance in glioblastoma xenografts. *Neuro-Oncol*. 2009;11(3):281-291. doi:10.1215/15228517-2008-090

10. Zhu Y, Chen Z, Kim SN, et al. Characterization of Temozolomide Resistance Using a Novel Acquired Resistance Model in Glioblastoma Cell Lines. *Cancers*. 2022;14(9):2211. doi:10.3390/cancers14092211

11. Pu F, Chen F, Zhang Z, et al. Ferroptosis as a novel form of regulated cell death: Implications in the pathogenesis, oncometabolism and treatment of human cancer. *Genes Dis*. 2022;9(2):347-357. doi:10.1016/j.gendis.2020.11.019

12. Li J, Cao F, Yin HL, et al. Ferroptosis: past, present and future. *Cell Death Dis*. 2020;11(2):88. doi:10.1038/s41419-020-2298-2

13. Song Q, Peng S, Sun Z, Heng X, Zhu X. Temozolomide Drives Ferroptosis via a DMT1-Dependent Pathway in Glioblastoma Cells. *Yonsei Med J*. 2021;62(9):843-849. doi:10.3349/ymj.2021.62.9.843

14. Hubert N, Hentze MW. Previously uncharacterized isoforms of divalent metal transporter (DMT)-1: implications for regulation and cellular function. *Proc Natl Acad Sci U S A*. 2002;99(19):12345-12350. doi:10.1073/pnas.192423399