FERROPTOSIS IN GLIOBLASTOMA MULTIFORME: a novel therapeutic approach

Literature review

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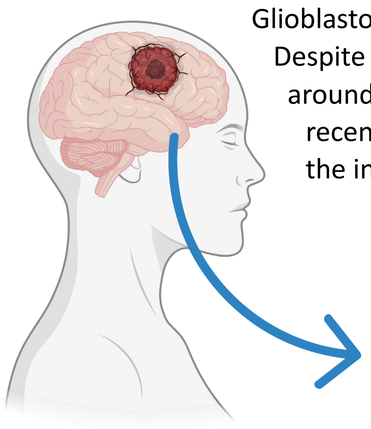
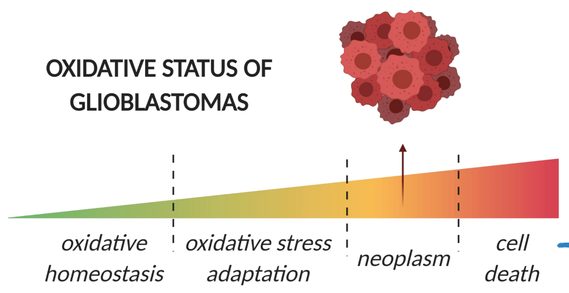
INTRODUCTION



Glioblastoma multiforme (GBM) is one of the most common and aggressive primary brain tumors. Despite the available therapies, life expectancy for patients is very poor, with a survival rate of around 14.6 months. Therefore, a definitive therapeutic strategy for GBM is urgently needed. It has recently become apparent that the oxidative features of GBM make this neoplasm susceptible to the induction of ferroptosis, a newly type of programmed non-apoptotic cell death.



- High oxygen consumption
- Elevated ROS concentration
- Increased iron uptake
- Enhanced lipid metabolism
- Less antioxidant activity

Figure 1. *Main oxidative features of GBM.*

OBJECTIVES

→ To determine the main oxidative features of GBM cells and ferroptosis.

→ To understand ferroptosis regulation in GBM cells.

→ To establish the main ferroptosis inducing compounds (FINs) that have been tested on GBM cell lines or murine xenografts.

METHODOLOGY

Extensive bibliographic search in Pubmed and Web of Science, according to the keywords listed on the right.

Article inclusion criteria:

✓ Original articles, most relevant reviews, relation with the reviewed topic, publication date (> 2012)

KEYWORDS
Glioblastoma
Oxidative stress
Ferroptosis
FINs

RESULTS

Ferroptosis

Ferroptosis is directly related to:

A Lipid Peroxidation

Lipid peroxidation is the triggering event of ferroptosis as it induces destabilization of the cell membrane. Lipid peroxidation is the result of:

B. High iron concentration (*Fenton reaction*)
C. Free radicals activity (*lipid oxidation*)

B Iron sources

Labile Iron Pool is the main source of Fe^{2+} to be considered in lipid peroxidation, and mainly derives from transferrin (extracellular uptake) or from ferritinophagy (ferritin degradation).

- Released Fe^{2+} will be able to react with membrane phospholipids by the **Fenton reaction**.

C Oxidative stress

It is the consequence of an imbalance between the production of free radicals and the antioxidant systems.

- Reactive oxygen species (ROS) are produced as a result of incomplete oxygen reduction, and its high concentration can induce lipid damage.

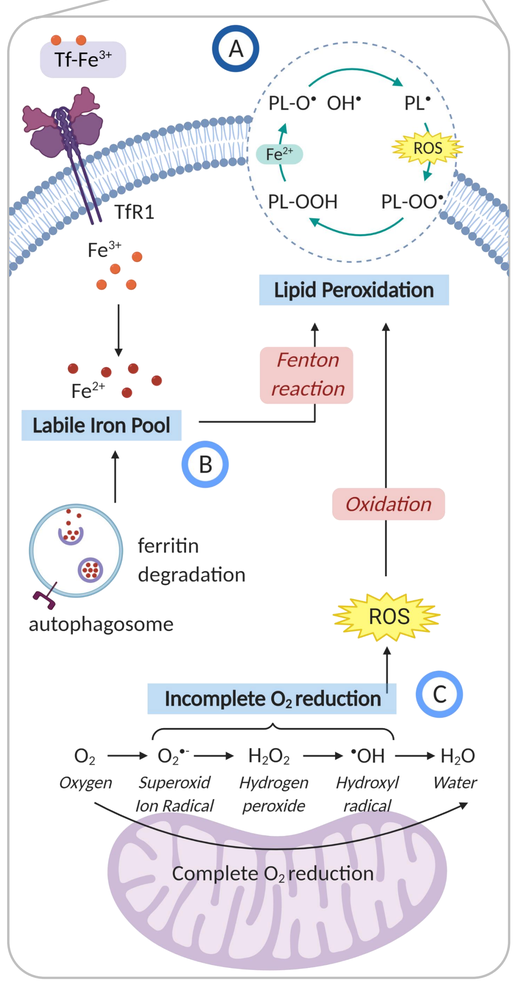
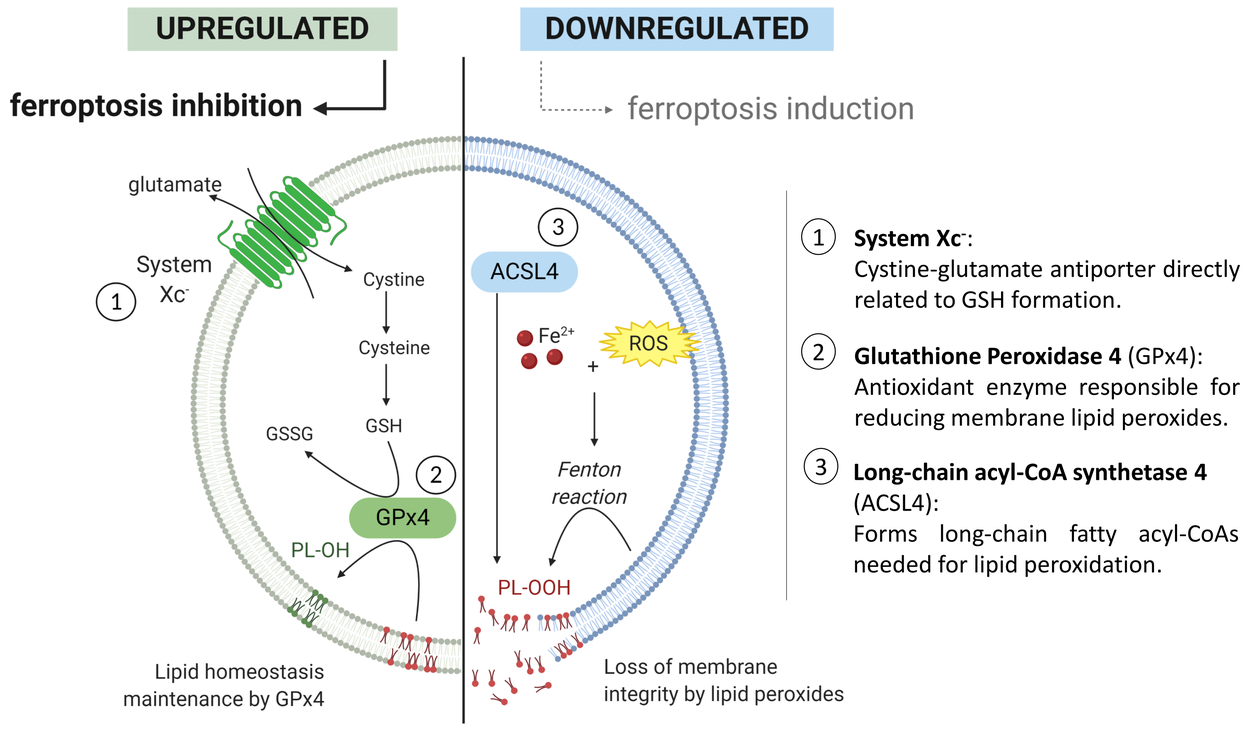


Figure 2. *Ferroptosis triggering events.* A| *Lipid peroxides formation by means of* B| *Labile Iron Pool and* C| *ROS production.*

Ferroptosis in GBM cells

GBM cells balance their sensitivity to the induction of ferroptosis by upregulating or downregulating the proteins involved in this cell death. Thus, they exhibit a distinctive ferroptotic protein profile that protects them from spontaneous ferroptosis.



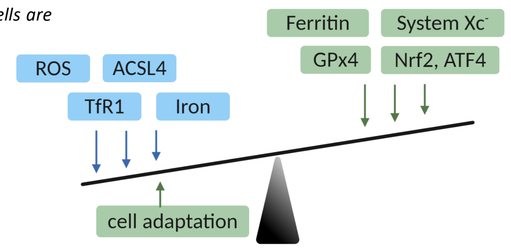
1 **System Xc⁻**: Cystine-glutamate antiporter directly related to GSH formation.

2 **Glutathione Peroxidase 4** (GPx4): Antioxidant enzyme responsible for reducing membrane lipid peroxides.

3 **Long-chain acyl-CoA synthetase 4** (ACSL4): Forms long-chain fatty acyl-CoAs needed for lipid peroxidation.

Figure 3. *The upregulated (green) and downregulated (blue) ferroptotic proteins in GBM cells are shown. The final effect is ferroptosis inhibition.*

→ Diagram on the right represents the imbalance that must be induced in order for the GBM cells to undergo ferroptosis. The **blue forces** must exceed the **green forces**.



Ferroptosis Inducing Compounds

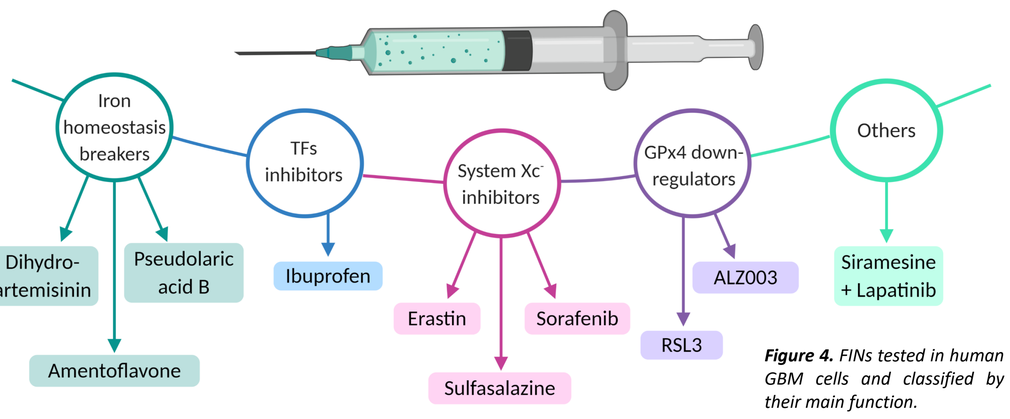


Figure 4. *FINs tested in human GBM cells and classified by their main function.*

Ferroptosis can be induced in GBM cells upon the administration of FINs. These substances can act through multiple mechanisms, all of them involving an increase in oxidative stress and iron accumulation, resulting in lipid peroxidation. Here those FINs tested in human GBM cells with significant results are presented, although some appear to be more potent than others.

→ **Still, they pose some challenges when used by themselves.**

Dual therapy

Further studies show more powerful effects when FINs are combined with pre-existing therapies for GBM:

- **Temozolomide:** alkylating agent that induces cell death by apoptosis and autophagy.
- **Radiation:** kills cancer cells by inducing cell cycle arrest and apoptosis.

Anticancer therapy is reinforced, as multiple types of cell death are triggered. There is a better chance of **eliminating the resistant clones**.

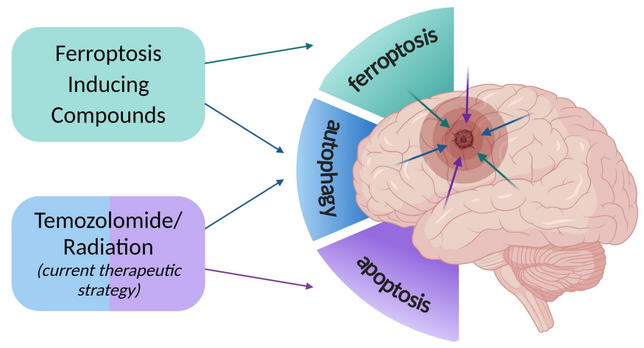


Figure 5. *The three types of cell death that are induced when combining ferroptosis inducing compounds with temozolomide (chemotherapeutic agent) and/or radiation.*

CONCLUSIONS

- ❖ The oxidative features of GBM are in line with the needed requirements for the ferroptosis induction.
- ❖ GBM cells modify their **ferroptotic protein profile**, establishing a defense mechanism in order to avoid spontaneous ferroptosis. This evidence confirms the importance of this non-apoptotic mechanism in GBM.
- ❖ **Dual therapies** are in the spotlight as they enhance anticancer effects, rather than delivering solely FINs.
- ❖ Future research at GBM should focus on precise operation of the ferroptotic pathways and on the dual therapies, in order to finally find the ***golden standard treatment*** for GBM.

RELEVANT BIBLIOGRAPHY

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