Chapter 1

Introduction

1.1 Background

Glioblastoma multiforme or GBM is the most common primary brain tumor and the most pervasive glioma subtype. It is characterized by its rapid progression and poor prognosis, with a five-year survival rate of only 5.5% (Kanderi et al., 2024). The most effective and the first line of treatment for GBM is the drug Temozolomide (TMZ). TMZ functions as a methylating agent that exerts its killing effects on the activation of the DNA mismatch repair system (Ortis et al., 2021; Aasland et al., 2019). However, TMZ is only effective as an initial treatment. As the disease progresses and the tumor grows and mutates, cancer cells develop resistance towards the drug (Wu et al., 2021). This is worsened by the heterogeneous nature of GBM, as clusters of tumor cells each mutate into distinct resistance pathways that allow multidrug resistance and tumor recurrence even after treatment. Hence, novel alternative treatment is needed to further the progress in curing GBM.

A promising solution to this issue is targeting the cuproptosis pathway, a novel cell death pathway discovered by Tsvetkov et al. in 2022. The pathway induces cell death through proteotoxic stress and does not involve caspase activation or accumulation of reactive oxygen species (ROS) (Lou et al.,2024). This unique feature means that treatment utilizing the cuproptosis cell death pathway could be the answer to combating chemoresistance in cancer cells.

Although cuproptosis utilizes the activity of enzymes crucial in the Tricarboxylic (TCA) cycle, an energy production cycle that is constitutively expressed in every cell(Arnold & Finley, 2023), the effectiveness of cuproptosis as a treatment relies heavily on the expression of cuproptosis-related genes (CRG) that regulate the sensitivity as well as resistance towards the induction of cuproptosis (Chen et al., 2022). Therefore, the variability of GBM could potentially affect how these cells react to cuproptosis-based

treatment (Zhang et al., 2020). Yet, there is currently a lack in validation and comparative research regarding the effectiveness of cuproptosis and its ability to overcome GBM heterogeneity and pose as an alternative treatment.

1.2 Objective

The objective of this study is to compare the effectiveness of cuproptosis inducers (Es-Cu) in the treatment glioblastoma (GBM) against the effectiveness of TMZ. As well as determine if the effectiveness of cuproptosis inducers is affected by CGR levelheterogeneity of GBM and TMZ resistance.

1.3 Hypothesis

It is hypothesized that the induction of cuproptosis will have a significant cytotoxic effect in all GBM cell lines, with higher efficiency in non-resistant cell lines compared to TMZ resistant cell lines. Higher sensitivity of cuproptosis is hypothesized to be directly related to the expression CGR.