I. INTRODUCTION

1.1 Background

Glioblastoma multiforme (GBM) is a highly prevalent glioma that accounts for ≥ 60% of primary brain tumors. In addition to a high prevalence, the overall survival rates of GBM patients are low, averaging 14-15 months after diagnosis (Hanif et al., 2017; Grochans et al., 2022; Noch et al., 2018). This poor prognosis is attributed to the disease being commonly diagnosed at a high grade (stage IV) as well as the aggressive and highly invasive nature of GBM that promotes the rapid progression of the disease (Grochans et al., 2022; Noch et al., 2018). Another factor is its location in the brain, posing a challenge for invasive procedures, with surgery possibly leading to neurological damage (Gerritsen et al., 2022). Additionally, the presence of the blood-brain barrier (BBB) hinders access for most chemotherapy drugs into the brain, leading to a lack of effective treatments for the disease (Noch et al., 2018; Ou et al., 2021).

Currently, temozolomide (TMZ) is used as the main choice of chemotherapy for GBM due to its lipophilic nature that allows entry through the BBB to access the tumor. In the brain, TMZ is capable of producing methyl diazonium ions that can form DNA adducts, inducing double-strand breaks and halting the cell cycle which eventually leads to cell death (Arora & Somasundaram, 2019; Tong et al., 2021). Despite its pivotal role in GBM treatment, the efficacy of TMZ remains limited by the development of resistance which has been reported in at least 50% of patients treated with the drug, oftentimes leading to recurrence and a decrease in patient survival rate (Arora & Somasundaram, 2019; Lee, 2016).

A recent preliminary study by Xuan et al. (2023) suggests the possible involvement of glutamine and glutamate transport and metabolism in mediating TMZ resistance in GBM. Gene expression analysis of TMZ-resistant GBM patients and cell lines revealed the upregulation of several genes involved in glutamate transport and metabolism, with one of these genes reported to be Gene X (Xuan et al., 2023). This is notable considering gliomas are reported to experience glutamine addiction, a phenomenon in which cancer cells upregulate glutamine intake and metabolism to further drive tumorigenesis and metastasis (Oizel et al., 2020; Ekici et al., 2022). Our preliminary results revealed that Gene X knockdown in both the TMZ-sensitive glioblastoma cell line U87 and its TMZ-resistant counterpart U87R significantly attenuated cell proliferation. However, the current preliminary data is not sufficient to fully illustrate the mechanisms of gene X in tumorigenesis as well as the development of TMZ-resistant GBM. Hence, further study is needed to investigate the role and mechanism of Gene X in mediating tumorigenesis and TMZ resistance in GBM.

1.2 Objective

The current study aims to investigate the role of Gene X in mediating tumorigenesis and TMZ resistance in GBM, particularly in its proliferation and migration capabilities.

1.3 Hypothesis

It is hypothesized that Gene X knockdown will attenuate the proliferation and migration of both TMZ-sensitive and TMZ-resistant GBM cell lines *in vitro*.