IJMSRI
International Journal of Medical Science Research and Innovations

Volume 2 Special Issue 1 (Feb) 2025, Article 30 (pp.73-74)
ISSN-3048-9067

Original Investigation | Neurology

Therapeutic potential of ACAT1 inhibition to target metabolic pathways in glioblastoma: A Literature Review

Hamida El Malt[1], W.P.M. Sewmini[2]

MD, Ilia State University, Tbilisi, Georgia[1], MD, Tbilisi State Medical University[2]

Key Points

Question:
Can ACAT1 inhibition serve as a viable therapeutic target for glioblastoma (GBM) by modulating metabolic pathways?

Findings:
Potential Therapeutic Strategies: Chlorogenic acid (CHA), a natural compound, inhibits ACAT1 phosphorylation, offering a promising GBM treatment.
Ketone bodies (e.g., acetoacetate) reduce GBM cell viability and induce apoptosis, reinforcing metabolic reprogramming as a treatment strategy.

Meaning:
Targeting **ACAT1 and metabolic pathways** could provide **novel therapeutic strategies** for glioblastoma. Further research is required to **optimize ACAT1 inhibition** and evaluate its long-term effects in clinical settings.

Abstract

Importance:
Glioblastoma (GBM) is a highly aggressive brain tumor characterized by rapid growth and poor prognosis. Recent studies have emphasized the role of metabolic pathways, such as fatty acid oxidation and ketogenesis, in regulating GBM cell behavior and tumor progression. Acetyl-CoA acetyltransferase 1 (ACAT1) is an enzyme involved in these pathways and has been shown to influence GBM differentiation, growth, and mitochondrial function. Understanding the mechanisms by which ACAT1 modulates GBM metabolism could offer new therapeutic targets.

Methods:
A comprehensive review of current literature was conducted, focusing on studies examining the role of ACAT1 in glioblastoma metabolism and therapy. Data on the effects of ACAT1 inhibition, natural compounds like chlorogenic acid (CHA), and metabolic shifts involving ketone bodies in GBM were analyzed. The studies reviewed used both in vitro and in vivo models to explore ACAT1's influence on cell differentiation, tumor progression, and potential therapeutic interventions.

Results:
Inhibition of ACAT1 was found to promote the differentiation of GBM cells into astrocytes, delay tumor growth, and restore mitochondrial function (You et al., 2024). Furthermore, ACAT1 negatively regulates the choline metabolic pathway, which is crucial for GBM differentiation (Wang et al., 2023). CHA, a natural substance, has been shown to inhibit the phosphorylation of ACAT1, providing a promising approach for GBM treatment (Liu et al., 2021). Additionally, ACAT1 deficiency in myeloid cells was found to promote GBM progression by increasing the accumulation of myeloid-derived suppressor cells, which enhance tumor growth (Wang et al., 2023). Ketone bodies, such as acetoacetate, were shown to decrease GBM cell viability and induce apoptosis, further supporting the role of metabolic reprogramming as a therapeutic strategy (Vallejo et al., 2020).

Conclusion and Relevance
This review underscores the significant role of metabolic pathways, particularly ACAT1, in glioblastoma progression and therapy. Inhibiting ACAT1, using natural compounds like CHA, and targeting metabolic reprogramming with ketone bodies may offer effective strategies for treating GBM. These findings highlight the need for further exploration of ACAT1 and metabolic therapies as potential treatments for glioblastoma.

Volume 2 Issue 1 (Feb) 2025, Article 30 (pp.73-74)
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Article Information

Accepted for Publication: December 24-2024
Published: February 13-2025.

Corresponding Author: Hamida El Malt, MD, Ilia State University, Tbilisi, Georgia.
Acknowledgment: - MedVentures (CPD no.-#784331) for providing financial support for Publishing, Alte University.