



# **Metabolic Contrasts: Fatty Acid Oxidation and Ketone Bodies in Healthy Brains vs. Glioblastoma Multiforme**

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Abstract: The metabolism of glucose and lipids plays a crucial role in the normal homeostasis of the body. Although glucose is the main energy substrate, in its absence, lipid metabolism becomes the primary source of energy. The main means of fatty acid oxidation (FAO) takes place in the mitochondrial matrix through  $\beta$ -oxidation. Glioblastoma (GBM) is the most common form of primary malignant brain tumor (45.6%), with an incidence of 3.1 per 100,000. The metabolic changes found in GBM cells and in the surrounding microenvironment are associated with proliferation, migration, and resistance to treatment. Tumor cells show a remodeling of metabolism with the use of glycolysis at the expense of oxidative phosphorylation (OXPHOS), known as the Warburg effect. Specialized fatty acids (FAs) transporters such as FAT, FABP, or FATP from the tumor microenvironment are overexpressed in GBM and contribute to the absorption and storage of an increased amount of lipids that will provide sufficient energy used for tumor growth and invasion. This review provides an overview of the key enzymes, transporters, and main regulatory pathways of FAs and ketone bodies (KBs) in normal versus GBM cells, highlighting the need to develop new therapeutic strategies to improve treatment efficacy in patients with GBM.

Keywords: glioblastoma; fatty acids; ketone bodies; lipid metabolism; β-oxidation; carnitine

# 1. Introduction

Glucose is an essential nutrient, dependent on blood flow for a constant supply and normal homeostasis of the body. It is the substrate that enters tissue cells and is transformed into adenosine triphosphate (ATP). ATP occupies a key position both in the metabolism of normal cells and in the tumor microenvironment. To maintain the cellular function of the brain, an adequate and continuous supply of energy is necessary, because glycogen is stored in a limited amount at this level. During periods of limited glucose availability, tissues use fat-derived ketone bodies (KBs) as alternative fuel sources [1–4].

Ketones, the result of lipid metabolism, provide 5% to 20% of the total energy expended by the human body. In the liver, fatty acids (FAs) are transformed into KBs, which then circulate through the bloodstream to various organs, including the brain. When the insulin level is low and there is a high concentration of FAs in the blood, they are converted into KBs providing an alternative source of energy for the body and especially for the brain. Acyl-Coenzyme A (CoA) oxidation takes place in the mitochondria of organs with high energy requirements and generates KBs ( $\beta$ -hydroxybutyrate-BHB and acetoacetate-AcAc).



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**Copyright:** © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). BHB represents approximately 70% of circulating ketones, crossing the blood–brain barrier (BBB) and serving as fuel at this level when needed. At the same time, BHB also acts as a signaling molecule in many cellular functions, including the epigenetic regulation of gene transcription. The carnitine shuttle system facilitates the transport of fatty acyl-CoA in the mitochondria, being a particularly vital mechanism when the blood glucose level is low, ensuring a sustained energy supply of the body [5–12].

Growing evidence supports the link between disturbed lipid metabolism and cancer. Metabolic irregularities favor tumor proliferation. Identifying gene expression changes of enzymes involved in metabolic pathways could widen the range of cancer biomarkers and therapeutic approaches [13–15].

Mitochondria have recently been recognized as the "engine of cell death" due to their essential involvement in programmed cell death. Besides the essential role they have in the production of ATP, the generation of reactive oxygen species (ROS), and the facilitation of cell death pathways, mitochondria are involved in various pathological conditions, such as cancer, neurodegenerative diseases, obesity, or diabetes. Mitochondria are the point of convergence between the metabolism of glucose, glutamine, and lipids. The main function is to support the tricarboxylic acid cycle (TCA) and aerobic respiration through oxidative phosphorylation (OXPHOS) which generates ATP through the mitochondrial respiratory chain, thus satisfying the need for energy for cell survival [16–18].

Tumor cells undergo metabolic changes that cause these cells to use more glucose than normal cells, transforming glucose into lactate through aerobic glycolysis instead of metabolizing glucose through OXPHOS to produce ATP, a phenomenon known as the Warburg effect. This phenotype implies a high level of fermentation even when oxygen is abundant [19–22].

Gliomas are the most common primary brain tumors. The World Health Organization (WHO) has classified gliomas into four grades (I–IV), with higher grades indicating increased dedifferentiation and malignancy. Glioblastoma multiforme (GBM) constitutes a significant part (54.7%) and stands out as the most aggressive form, and is associated with high invasiveness, rapid growth, rapid spread in brain tissue, high recurrence rate, resistance to apoptosis, and an unfavorable poor prognosis. Although current treatment involves surgery, radiation therapy, and chemotherapy, the prognosis remains poor, with a median survival of approximately 12 to 18 months and a five-year survival rate of approximately 4.7% [23–27].

This treatment approach does not lead to long-term disease remission for the patients, in part due to the molecular heterogeneity and plasticity of GBM cells, seen present not only between different tumors but also within the same tumor. The metabolic alterations of GBM are attributed to mutations in tumor suppressor genes and oncogenes together with the impact of the surrounding microenvironment, so the interest in studying GBM metabolism as well as the metabolism of the surrounding microenvironment has increased in the last decade. Therefore, it is crucial to develop new therapeutic strategies for GBM patients, which are able to enhance the efficacy of existing treatment modalities while preserving the normal integrity of brain tissue. From this point of view, the knowledge about tumor metabolism and especially about lipid metabolism requires deepening [6,28–32].

In this review, we aim to provide an overview of the current knowledge of fatty acid oxidation (FAO) and its associated pathways in the normal brain versus changes in GBM.

### 2. Fatty Acid Homeostasis

FAO is a key catabolic pathway that occurs in the mitochondrial matrix for energy production in mammals (see Figure 1). This aerobic process begins with the activation of FAs by linking the thioester with CoA. Mitochondria use three primary enzymatic pathways for ATP generation, namely: TCA, OXPHOS, and FAO (Figure 1). The obvious interaction between these metabolic pathways leads to the maintenance of normal homeostasis of the body [33–36].



**Figure 1.**  $\beta$ -oxidation of FAs, Ketogenesis, and OXPHOS. Upon entering the cell, LCFA undergoes activation by binding with CoA. The initial reaction is catalyzed by ACoAD. This transformed molecule, now an acyl-CoA, is transported across the mitochondrial membrane through the carnitine shuttle system. The long-chain acyl-CoA produced is subsequently oxidized to generate acetyl-CoA, a process facilitated by MTP. Created in BioRender.

#### 2.1. $\beta$ -oxidation of Fatty Acids

β-oxidation of lipids in the mitochondrial matrix involves the removal of a hydroxyl group from FAs, with the formation of highly polar thioesters known as acyl-CoA molecules. Long-chain fatty acids (LCFAs) face a barrier to the free crossing of mitochondrial membranes. To overcome this, LCFAs require transport as carnitine derivatives, called acyl-carnitines or esterified carnitines, which facilitate their transport across the mitochondrial membrane (see Figure 2). The LCFA acyl-CoA produced is subsequently oxidized to generate acetyl-CoA, a process facilitated by the mitochondrial trifunctional protein (MTP). Short-and medium-chain fatty acids (SCFA and MCFA) passively diffuse across the mitochondrial membrane and are converted to acyl-CoA esters in the mitochondrial matrix [12,33,35,37].

Inside the mitochondria, the  $\beta$ -oxidation of FAs is carried out through a series of four catalysis reactions. Acyl-CoA dehydrogenase (ACoAD) catalyzes the first step by generating reducing equivalents that are transferred to the electron transfer flavoprotein, which serves as a shuttle between AcoAD and the respiratory chain. Enoyl-CoA hydrase catalyzes the second step, the hydration of 2-trans-enoyl thioesters in 3-l-hydroxyacyl-coA derivatives. In the third stage, the catalysis by Hydroxyacyl-CoA dehydrogenase takes place, obtaining the oxidation of 3-l-hydroxyacyl-coA esters into 3-ketoacyl-coA species. In the last step, under the action of ketoacyl-CoA thiolase, the thiolytic cleavage of the 3-ketoacyl-coA chain by the thiol group of a second molecule of coenzyme A occurs. This sequential process cleaves two carbon atoms from the acyl chain during each iteration, producing, finally, acetyl-CoA molecules. MTP located on the inner side of the mitochondrial membrane and composed of  $\alpha$  and  $\beta$  subunits, catalyzes the last three reactions in the  $\beta$ -oxidation of LCFA and MCFA acyl-coA esters. The  $\alpha$  subunit catalyzes two consecutive steps in LCFA oxidation, namely, enoyl-CoA hydration and 3-hydroxyacyl-CoA dehydrogenation, while the  $\beta$  subunit has long-chain 3-ketoacyl-CoA thiolase activity. In

some types of cancer, it has been shown that nonsteroidal anti-inflammatory drugs can inhibit the multiplication of tumor cells by binding and suppressing the  $\alpha$  subunit of MTP. Therefore, it is hypothesized that the selective inhibition of the  $\alpha$  subunit of MTP would be associated with the inhibition of tumor growth and therefore could offer new cancer therapies [11,33,38–41].



**Figure 2.** The Carnitine shuttle system for transporting LCFA acyl CoA into the mitochondrial matrix. LCFA is transported across the outer mitochondrial membrane with the assistance of carnitine. Facilitated by the enzyme CPT I located on the outer mitochondrial membrane, FAs bind to the hydroxyl group of carnitine, forming fatty acyl-carnitine. This complex is then transported into the mitochondrial matrix in exchange for carnitine via a carrier protein. Within the matrix, CPT II situated on the inner mitochondrial membrane facilitates the transfer of the acyl group from fatty acyl-carnitine to CoA, resulting in the formation of fatty acyl-CoA and free carnitine. The liberated carnitine is then transported back to the intermembrane space via a carrier protein, where it can be utilized for subsequent cycles. The fatty acyl-CoA within the mitochondrial matrix is now primed for  $\beta$ -oxidation by the enzymes present, ultimately yielding acetyl-CoA. Acetyl-CoA subsequently enters the Krebs cycle, contributing to energy production. OCTN2 is a carnitine-specific transporter found in the brain. Created in BioRender.

#### 2.2. Free Fatty Acids and Lipid Droplets

FAs serve as constituents of cell membrane phospholipids and as a fuel source for OXPHOS. Free fatty acids (FFAs) can enter the brain where they can be used as an energy source participating in various physiological processes such as cell transport, cell signaling and transduction, synaptic transmission, protein stabilization, and others, but they can also initiate various harmful activities inside brain cells. Brain FFAs also influence cell growth, development, and survival as well as the inflammatory response at the brain level by regulating the phosphoinositide 3-kinase (PI3K) pathways, the peroxisome proliferator-activated receptor, protein-coupled receptors, protein kinase C, or nuclear factor kappa-amplifying light chain of activated B cells. Active neuronal cells struggle to use FFAs for ATP production, but if neuronal mechanisms are overwhelmed, FFAs can become toxic to neurons. To prevent neuronal damage, FFAs will be stored in intracellular lipid droplets (LDs). Excess FFAs are transported by apolipoproteins in astrocytes, which are abundant in

LDs and less vulnerable to the damaging activity of ROS compared to neurons. Astrocytes are considered the primary sites for FFA storage and metabolism in the brain. LDs serve as energy reservoirs, transporting FAs to the mitochondria during nutrient deprivation, where they are used as an alternative energy source. Therefore, to protect neurons from FFA-associated lipotoxicity and to meet energy demands in specific situations, FA storage and oxidation processes appear to rely on a tightly interconnected metabolic relationship between neurons and astrocytes [42–45].

LDs contain neutral lipids, predominantly triacylglycerols, cholesterol esters, and sterol esters, which are found in most cell types, being synthesized at the level of the endoplasmic reticulum membrane. The process of composition and storage of neutral lipids in LDs serves as a protective mechanism against lipotoxicity induced by excessive lipid accumulation. Each step in the formation of neutral LDs is facilitated by a specific enzyme, with diglyceride acyltransferase I and II (DGAT1, DGAT2) playing an essential role in catalyzing the final step of the triglyceride formation pathways. The two enzymes are found mainly in the endoplasmic reticulum where they catalyze the conversion of diacylglycerol to triacylglycerol, but also in LDs during their growth. It has been shown that the suppression of DGATs promotes axon regeneration because FAs are redirected towards the synthesis of phospholipids at the expense of the synthesis of neutral lipids. DGAT1 also prevents mitochondrial dysfunction and lipotoxicity, which can occur in the case of brain pathology [42–44,46].

Physiologically, the formation of LDs is linked to the nutritional state of the cells. In the case of a high availability of exogenous lipids, LDs will form. Also, in case of a lack of an exogenous intake rich in fats, the cells change their energy source from glucose to FAs, so LDs will be formed. But besides these physiological states, LDs are also formed in case of cellular stress such as inflammation, hypoxia, endoplasmic reticulum stress, or mitochondrial dysfunction. The formation of LDs in certain pathological processes presented distinct functional phenotypes, depending on the context or the cell type involved [42,46–48].

#### 2.3. Carnitine Shuttle System in Normal Mitochondria

The carnitine shuttle represents a specialized mechanism that facilitates the transfer of LCFA through the inner mitochondrial membrane to the mitochondrial matrix for  $\beta$ -oxidation and energy production. FAs come from three main sources: exogenous FAs that enter cells from the bloodstream or intestinal lumen; FAs synthesized endogenously from acetyl-CoA by de novo synthesis; and FAs released inside the cell by hydrolysis of acylated proteins, phospholipids, and triglycerides [5,12,38,49,50].

Regardless of their origin (either exogenous, synthesized de novo, or by intracellular hydrolysis), intracellular FAs undergo thioesterification to CoA. Acyl-CoA synthases (ACoASs) catalyze this process, leading to the formation of acyl-CoA products, the activated form of intracellular FAs [51–53].

ACoASs typically associated with proteins and membranes are directed to or away from specific metabolic pathways depending on the cellular energy state. Their intracellular flow and destination are regulated by various proteins, including FA-binding proteins, sterol carrier protein 2, and acyl-CoA-binding domain proteins, which guide them to energy storage or generation processes [50,54,55].

When cells require energy, acyl-CoAs can be transported into mitochondria and peroxisomes, where they collaborate to maintain lipid homeostasis. Substrate transport, substrate specificity, end products, and energy production show variation between the mitochondrial and peroxisomal  $\beta$ -oxidation pathways [56,57].

The impermeability of mitochondrial membranes to acyl-CoA requires the conjugation of FAs to carnitine for their entry into mitochondria. The first component of the carnitine shuttle is Carnitine Acyltransferase I (CPT I) located in the inner part of the outer mitochondrial membrane with the role of converting acyl-CoAs into acylcarnitines and at the same time, a role in the rate-limiting stage of FAO. The second component of the carnitine shuttle, the inner mitochondrial membrane protein, is the Carnitine Acylcarnitine Translocase (carrier) which facilitates the exchange of acylcarnitines and carnitine between the outer and inner mitochondrial membranes. On the matrix side of the inner mitochondrial membrane, the third important component of the shuttle is located, namely, Carnitine Acyltransferase II (CPT II), which is responsible for converting acylcarnitine back into acyl-CoAs to allow subsequent oxidation processes. The carnitine released in this process is translocated back into the cytosol by the same carrier of the inner mitochondrial membrane through an acyl-carnitine /carnitine antiport reaction (see Figure 2) [12,38,58].

Carnitine transporters are encoded by two solute carrier (SLC) gene families, namely, SLC6 (SLC6A14) and several members of SLC22 (SLC22A1, A2, A3, A4, A5, A7, A16). OCTN2/SLC22A5 stands out as a high-affinity carnitine transporter. Carnitine Acylcarnitine Translocase is the A20 member of the SLC25 protein family, proteins that are mainly located in the inner mitochondrial membrane. In one-third of these, their transported substrates are unknown. The expression of Carnitine Acylcarnitine Translocase is found in tissues with high energy expenditure such as heart muscles or skeletal muscles, and, of course, in the liver when glycogen reserves have been exhausted, but also in the brain, even if at a lower rate [32,59–61].

The balance of carnitine homeostasis is maintained by a harmonious interplay of dietary absorption, endogenous biosynthesis, and efficient renal reabsorption. The brain does not directly use FAs for oxidative metabolism. Instead, it relies on KBs derived from acetyl-CoA and acetoacetyl-CoA, which are generated via FAO that occurs mainly in the liver [12,38,53,62].

#### 2.4. Ketogenesis

Ketogenesis, contrasting with ketolysis, is a biochemical process occurring in the mitochondria, where acetyl-CoA is utilized to produce KBs (see Figure 1) [1,63,64].

Acetyl-CoA acetyltransferase (ACAT) consisting of two metabolic enzymes, one cytosolic (ACAT2) and one mitochondrial (ACAT1), facilitates the reversible conversion of two molecules of acetyl-CoA to acetoacetyl-CoA (Figure 1). HMG-CoA synthetase, which is regulated by succinylation, desuccinylation for short-term control, and transcriptional regulation for long-term control, catalyzes the chemical reaction that leads to the formation of hydroxy-beta-methylglutaryl-CoA (HMG-CoA). Factors such as nutrition and hormones influence these mechanisms, explaining the prevalence of ketogenesis in conditions such as diabetes, starvation, or intense lipolysis [13,64–68].

After this, HMG-CoA lyase catalyzes the conversion of HMG-CoA to AcAc. AcAc can either undergo non-enzymatic decarboxylation in acetone or be converted to BHB by the action of BHB dehydrogenase (BHD). BHD shows the highest activity in the liver, followed by the kidney, heart, brain, and skeletal muscle. This variation in activity can be attributed to its role in catalyzing both the final stage of ketogenesis, predominantly in hepatocytes, and the initial stage of ketone oxidation in extrahepatic tissues [69–71].

AcAc and BHB serve as the body's two primary KBs for energy production. In extrahepatic tissues, including the brain, BHB is converted to AcAc by BHD, and AcAc is converted to acetyl-CoA by beta-ketoacyl-CoA transferase. Acetyl-CoA enters the citric acid cycle, leading to the production of ATP molecules through OXPHOS. However, acetone does not undergo conversion back to acetyl-CoA and is either excreted in the urine or exhaled (Figure 1) [72–77].

### 3. Ketone Body Metabolism

Energy is essential for normal brain function and constitutes approximately 20% of the body's total energy expenditure at rest, despite the brain comprising only about 2% of the total body weight [8,78]. Under typical physiological circumstances, the brain depends primarily on glucose for the production of ATP from the oxidation of glucose. When the availability of glucose is limited, KBs become the vital substrate for the brain, being able to provide up to 60% of the brain's energy needs. Together with lactate, it serves

as the primary alternative fuel for the brain. Both KDs and lactate can cross the BBB via monocarboxylate transporters (MCTs) present in endothelial cells and astroglia [8,79–81].

The use of ketones by the brain appears to be regulated mainly by their concentration in the bloodstream. Plasma ketone levels contribute to less than 5% of brain metabolism. Previous research suggests that, unlike healthy tissues, cancer cells are inefficient in using KBs for energy production. Several dietary approaches, such as ketogenic diets, ketogenic MCFA intake, or exogenous ketone supplementation, can produce substantial changes in normal brain metabolism but not in cancer metabolism [8,82].

Currently, very little is known about the regulation and use of KBs at the biochemical level.

# 3.1. Ketone Bodies Enter the Brain through MCTs

KB transport across the BBB is carrier-dependent and does not increase with neuronal activity, unlike glucose transport. Instead, it is correlated with circulating concentrations. MCTs are the known transporters exclusive to KBs and are widely distributed throughout the brain. MCTs are a group of 14 transmembrane proteins encoded by the SLC16A gene family, and eight of them are expressed in the brain. These conveyors can facilitate the movement of a wide range of substrates. MCT1, MCT2, MCT3, and MCT4 are the MCTs responsible for KB (AcAc and BHB) movement across the plasma membrane (see Table 1 for molecular aspects of the MCT family) [8,82–84].

Gene Name	Protein Name	Main Substrates		Main Role		
SLC16A1	MCT1	Lactate, ketone bodies, and pyruvate	-	Predominant expression in endothelial cells with a barrier role		
SLC16A2	MCT8	T2, rT3, T3, T4	-	High affinity to transport thyroid hormones = specific thyroid hormone transporters		
SLC16A3	MCT4	Ketone bodies, lactate, and pyruvate	-	Predominant expression presence in astrocytes		
SLC16A4	MCT5	-	-	Expression is elevated in certain GBM cells		
SLC16A6	MCT7	Ketone bodies	-	Transporter of ketone bodies		
SLC16A7	MCT2	Lactate, ketone bodies, and pyruvate	_ _ _	Predominant expression in neurons High susceptibility to hypoxia High sensitivity to intracellular pH		
SLC16A9	MCT9	Carnitine	-	Act a carnitine efflux transporter		
SLC16A14	MCT14	-	-	Hypothesis: MCT14 is a neuronal aromatic amino acid transporter		
Derived from references [48,83,85–89]						

Astrocytes express MCT4, which, similar to MCT1, has a relatively low affinity for BHB. In contrast, neurons predominantly express the MCT2 isoform, characterized by a high affinity for BHB. The effect of KBs on neurons could still be mediated by neuronal uptake. MCT2 expression in neurons is co-localized in mitochondria-rich postsynaptic density structures, suggesting its potential role in synaptic transmission. This implies that both neurons and, to some extent, astrocytes have the capacity to take up KBs (Figure 3) [8,90–92].



**Figure 3.** The transport of KBs and FFAs in the brain and the role of MCT. KBs are transported across the BBB via specialized carriers—MCTs, particularly MCT1, MCT2, MCT3, and MCT4. Neurons primarily express MCT2, while astrocytes mainly express MCT4. Within brain cells, KBs are converted back into acetyl-CoA to fuel ATP production in the mitochondria, without the need for ATP input. Created in BioRender.

## 3.2. The Catabolism of KBs in Glial and Neuronal Cells

After being transported into the brain, BHB and AcAc are converted back into acetyl-CoA, which then enters the TCA cycle for ATP generation (see Figure 3). This conversion takes place within the mitochondria, where BHB is transformed into AcAc by the reversible action of BHD using NAD+, leading to the formation of NADH. AcAc is then broken down to acetoacetyl-CoA by 3-oxoacid CoA-transferase 1 (OXCT1). mRNA levels of OXCT1 are detectable in all human tissues except the liver; hence, the liver cannot utilize KBs as an energy substrate. Acetoacetyl-CoA is subsequently converted back into two acetyl-CoAs, ready to enter the TCA cycle, by the reversible action of ACAT (the first enzyme of ketogenesis). Unlike glucose, this conversion of BHB and AcAc into an oxidizable form does not necessitate ATP. In the developing rodent brain, cultured neurons, astrocytes, and oligodendrocytes all demonstrated the ability to utilize KBs for oxidative metabolism at rates considerably higher than those for glucose. However, neurons and oligodendrocytes appeared to be more efficient at oxidizing ketones than astrocytes [8,93,94].

#### 4. Dysregulation of Fatty Acid Metabolism in GBM

Mitochondrial dysfunction in cancer leads to increased OXPHOS activity in these cells. Research has shown that in glioblastoma, mitochondria play a key role in inducing resistance to Temozolomide. Therefore, targeting the treatment of mitochondria could be effective in the treatment of cancer due to the dependence of tumor cells on mitochondria [34,75–77].

Remodeling of lipid metabolism through changes in FA transport, de novo lipogenesis, storage of LDs, and FAO in order to provide energy is a distinctive sign of cancer, including

GBM. Changes in lipid metabolism are associated with different aspects of tumor biology, such as proliferation, migration, and resistance to therapy, and are dependent on the type of tumor or the type of molecular subclass with which it is associated. FAs exert a significant impact on tumors, making disruption of their metabolism a potential strategy for tumor treatment. Consequently, targeting the reprogramming of FA metabolism in tumor cells has become an increasingly prominent focus of research [95,96]. Rapidly proliferating cells require a significant number of FAs to facilitate membrane synthesis and to generate phospholipids crucial for replication. FAs can serve as substrates for mitochondrial ATP synthesis, regulate post-translational modification of lipids, and modulate the function of signaling proteins. Through de novo lipogenesis or exogenous absorption from the surrounding microenvironment, tumor cells obtain FAs. CD36/AG translocase (FAT), plasma membrane AG-binding proteins (FABPpm), and FA transport protein family (FATP)/SLC27 are specialized transporters that facilitate the absorption of FAs from the surrounding microenvironment and are overexpressed in tumors. At the same time, the hypoxia-inducible factor (HIF)-1 $\alpha$  promotes FABP expression. Therefore, the tumor microenvironment shows an increased uptake of FAs and, secondarily, an increased number of LDs (Figure 4) [96–99].



**Figure 4.** Difference between a normal cell and a GBM cell. In GBM cell mitochondria: ROS levels increase, oxygen consumption is low, and ATP production occurs by glycolysis; FA synthesis and FAO are antagonistic pathways—in GBM both are activated. HIF1 plays a pivotal role in lipid metabolism. It can increase lipid uptake and trafficking, fatty acid synthesis, lipid droplet biogenesis, and lipid signal production, and suppress FAO. Lipid droplet accumulation may be the final result of HIF1 in lipid metabolism. Low expression of ketogenic enzymes in GBM leads to increased survival, proliferation, migration, and invasion of GBM cells. Created in BioRender.

As mentioned above, in the case of normal cells, and in the case of tumor microenvironment cells, LDs have the role of preventing lipotoxicity, thus maintaining lipid homeostasis. At the same time, under conditions of metabolic stress, LDs represent an important source of ATP and NADPH, following the  $\beta$ -oxidation pathways. Acetyl-CoA produced in TCA leads to the generation of NADH and FADH2 for the electron transport chain, with the secondary synthesis of ATP, a quantity six times higher than the oxidation of carbohydrates. Another important source of NADH is the oxidation of citrate diverted from acetyl-CoA under the action of isocitrate dehydrogenase I (IDH1). Thus, sufficient NADH, essential for anabolic metabolism and ROS detoxification, is generated. Thus, hypoxic cells through the overexpression of FABP3 and FABP7 benefit from an increased capture of FAs and a sufficient number of LDs to provide sufficient energy for the recovery of tumor cells, including GBM cells during reoxygenation. At the same time, GBM cells are protected from ROS toxicity by increasing NADPH levels. The in vivo inhibition of FABP3 and FABP7 inhibits the growth of the GBM cell line U87 by reducing the absorption of FAs and, secondarily, by the lack of formation of LDs. This interaction between tumor cells and lipids makes the latter play a crucial role in the preparation of the tumor microenvironment, and, therefore, favors tumor initiation and progression [96,100–102].

Analysis of metabolic profiles between low-grade gliomas (LGG) and patient-derived GBM revealed a prevalence of FA catabolism over synthesis in GBM. This observation demonstrates the dual nature of  $\beta$ -oxidation, which encompasses both anabolic and catabolic functions, providing metabolic plasticity to GBM cells, which allows tumor cells to adapt and grow in different microenvironmental conditions [103,104].

Increased de novo lipogenesis, characteristic of tumor metabolism dynamics, leads to overexpression of FA synthetase (FASN), which secondarily promotes the mobility and wound repair abilities of glioma cells. Activation of the phosphoinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway reveals positive feedback in maintaining high levels of FASN in GBM cells. It is well known that activation of the PI3K/Akt signaling pathway produces cell proliferation and invasion in malignant gliomas. In orthotopic GBM mouse models, FASN levels were reduced under Temozolomide and Metformin treatment [103,105–108].

The upregulation of FASN in GBM cells is likely attributable to increased expression of the essential transcriptional regulator sterol regulatory element-binding protein (SREBP) [103,109,110].

SREBP activation plays a crucial role in FA metabolism under hypoxic conditions. In addition, SREBP1 serves as a downstream target of tumor suppressor pathways, including the liver b1/AMP kinase-activated protein kinase (LKB-AMPK) and Akt pathways. AMPK phosphorylates SREBP1, inhibits its activity and, consequently, suppresses tumor growth. AMPK also phosphorylates acetyl-CoA carboxylase (ACC), which leads to the inhibition of FA synthesis. However, in GBM cells, AMPK activation increases ACC activity and levels. Activation of the PI3K/Akt pathway increases the expression of SREBP1 and genes associated with FA synthesis. Furthermore, PI3K hyperactivation and epidermal growth factor receptor (EGFR) mutations promote GBM growth and survival through SREBP-1 activation. These findings suggest that inhibition of SREBP activity could be a promising therapeutic approach [103,111,112].

#### 4.1. Carnitine Shuttle System Dysregulation in GBM

As mentioned above, an essential cofactor in lipid metabolic pathways is carnitine. It plays a key role in facilitating LCFA transport across the mitochondrial membrane (Figure 2). Consequently, a deficiency in the carnitine shuttle can lead to a reduced ability of tissues to use LCFA as an energy source. On the other hand, tumor cells grow in lipid-rich microenvironments that give them survival advantages. Therefore, inhibiting the factors involved in the carnitine shuttle could lead to the formation of a microenvironment not favorable to the development of tumor cells and therefore to the slowing down of tumor progression [49,113–115].

OCTN2, a membrane transporter of carnitine, is present in both brain cells and GBM cells. The expression of OCTN2 was found to be higher in primary GBM samples from patients, and even more pronounced in samples from patients with recurrent GBM, as compared to the healthy brain [32,116,117].

Fink et al. showed that increased OCTN2 expression in GBM patients correlates with unfavorable outcomes, as demonstrated by decreased tumor cell viability upon OCTN2 silencing by siRNA-mediated activity (preclinical studies using a GBM mouse model). Thus, increased expression of OCTN2 could be a potential prognostic factor for GBM. This in vivo study represents the first demonstration of the antitumor efficacy of the OCTN2/L-carnitine inhibitor Meldonium. Its peculiarity is that no significant side effects have been observed so far. Furthermore, this study suggests the possibility of optimizing GBM

therapy through targeted interventions, such as specific inhibition of OCTN2 or drug delivery by targeting OCTN2. It was also shown that L-Carnitine-conjugated nanoparticles promote permeation across the BBB to target glioma cells via OCTN2, resulting in improved antiglioma therapy [118,119].

Bogusiewicz et al. conducted a study aiming to gain a deeper understanding of intermediates in the carnitine transfer system by leveraging data obtained from untargeted lipidomic analyses of brain tumors. Particular attention is paid to factors such as tumor grade (WHO I-II, LGG; WHO III-IV, HGG), the presence of mutations in IDH, and 1p/19q coding. They demonstrated that carnitine levels were significantly increased in HGG compared to LGG, with a ratio of 4.21 in IDH wild-type tumors (IDHwt) compared to IDH mutant tumors (IDHm), with no statistically significant difference between cases with and without the presence of the 1p/19q co-deletion. The mean peak areas for short-, medium-, and long-chain acylcarnitines were greater in HGG compared to LGG, although statistical significance was observed only for short-chain acylcarnitines. Furthermore, their findings showed higher levels of these analytes in IDHwt samples compared to mutants, although the difference was not statistically significant. Carnitine and acylcarnitine levels tended to be higher in tumors with higher malignancy (HGG versus LGG) or in patients with poorer clinical outcomes (IDHwt versus IDHm and with 1p/19q co-deletion versus no co-deletion 1p/19q). The results of this study confirmed that changes in the carnitine transfer system could serve as a crucial factor in measuring the malignancy of gliomas and evaluating clinical prognosis [120].

Inhibition of carnitine transport by chemotherapeutic agents such as Vinorelbine and Vincristine resulted in suppression of FAO, which was further potentiated by Etomoxir—a CPT I inhibitor. Consequently, this led to decreased viability and increased apoptosis in glioma cells. Modulation of OCTN2 expression influenced glioma cell survival in an FAO-dependent manner. These results suggest that tumor cell survival is highly dependent on both FAO and OCTN2 activity, indicating that CPT I and OCTN2 could be potential drug targets. Vincristine, Vinorelbine, Cediranib, Verapamil, Oxaliplatin, and Etoposide inhibit OCTN2-dependent carnitine uptake in glioma cells (see Figure 5). Moreover, OCTN2 can transport anticancer drugs, such as Ectoposide or Oxaliplatin [32,118,121–123].



**Figure 5.** The alterations in FA metabolism in GBM. The metabolic changes in GBM result in increased FAO, LDs, and de novo lipogenesis due to the upregulation of enzymes in their metabolic pathways. Therefore, inhibiting (**X**) these enzymes is expected to enhance survival in patients with GBM. Created in BioRender.

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While the expression and enzymatic activity of proteins involved in this pathway have been investigated, the specific role and destiny of carnitine and its esters formed during the transport of FAs across the mitochondrial membrane remain poorly understood.

# 4.2. MCTs of KBs in GBM

MCTs are the only known transporters for ketone bodies and are widely distributed throughout the brain. MCT1/2/4 are recognized contributors to cancer development, operate through various mechanisms, and play a critical role in lactate transport. In GBM, maintaining an alkaline intracellular pH is essential to sustain glycolysis. Inhibition of MCT1 and MCT4, which are essential for this pH balance, would effectively prevent glucose metabolism through glycolysis. In vivo studies indicated an upregulation of MCT4 and MCT1 in GBM compared with normal brain parenchyma, oligodendrogliomas, and astrocytomas. Particularly remarkable was the significant increase in MCT4 levels observed in necrotic tissues of GBM tumors. These findings suggest the potential for strategies targeting MCT4 and MCT1 to provide new avenues for the development of new therapeutic targets. MCT1 inhibitors, including AZD3965, BAY-8002, and 7ACC2, bind to distinct conformations of MCT1, either outward or inward (Figure 5). However, all three inhibitors directly occupy the substrate binding site. Goldberg et al. showed that AZD0095 exhibits outstanding potency, high selectivity for MCT1, favorable secondary pharmacology, a welldefined mechanism of action, suitable properties for oral administration in clinical settings, and promising preclinical efficacy when used in combination with cediranib [124–128].

Current research on the role of MCTs in GBM is limited; however, the many implications associated with their function underscore the need for further investigation. Gaining a deeper understanding of MCTs in GBM is crucial for the development of new inhibitors. While there are several inhibitors targeting MCTs, there is currently a lack of research into potential therapeutic drugs specifically tailored for GBM.

#### 4.3. The Role of Ketogenic Enzymes in Glioblastoma

Given the dynamic and nutrient status-sensitive nature of ketone metabolism, there is considerable interest in exploring its biological connections to cancer. This interest stems from the potential for precision-guided nutritional therapies in cancer treatment [82].

Ketogenic enzymes, in turn, contribute to cell maintenance and energy supply, in order to prepare the microenvironment necessary for the development of GBM cells. This, together with the Warburg effect, underscores the importance of ketogenic metabolism in driving GBM progression. [52,93,129].

To obtain a clearer understanding of ketogenic enzymes in human gliomas and especially in GBM, in Table 2 we investigate the expression levels of several key enzymes involved in this metabolic pathway.

References	Aim	Analyzed Data	Suggested Mechanism of Findings	Significance and Future Research
ACAT1 & ACAT2				
Wang et al. [129]	<ul> <li>ACAT1 expression and myeloid cell ratio</li> </ul>	ACAT1 ITGAM * CXCL1 * MDSCs *	$\uparrow$ ACAT1 expression $\rightarrow \uparrow$ myeloid cell ratio $\uparrow$ myeloid marker ITGAM $\rightarrow \uparrow$ myeloid cell infiltration in tumor tissue CXCL1 = crucial role in the induction of MDSCs and accelerated tumor growth	<ul> <li>Manipulating MDSCs has emerged as a promising target for the development of anticancer therapies</li> <li>ACAT1 may play a potential role in the immune microenvironment</li> <li>CXCL1 contributes to the development of an immunosuppressive microenvironment and facilitates tumor progression. It is a potential prognostic biomarker and therapeutic target for patients with GBM</li> </ul>
Kou et al. [39]	<ul> <li>Suppression of ACAT and suppression of SREBP-1 = blocked GBM growth</li> </ul>	SREBP-1 LDs ACAT	<ul> <li>LDs ↑ in GBM patient tissues (infrequently in LGG, and undetectable in normal brain tissues)</li> <li>The formation of LDs is a signature feature of GBM</li> <li>↑ LDs = poor survival</li> <li>ACAT1 protein level is correlation with LD formation</li> <li>ACAT2 = no expression in GBM patient tumor tissues/ rarely expressed</li> <li>SREBP-1 = highly activated in GBM</li> </ul>	<ul> <li>SREBP-1 = a potential therapeutic target in malignancies</li> <li>Inhibiting ACAT1 to block cholesterol esterification represents a promising therapeutic strategy for treating GBM by suppressing SREBP-1</li> <li>LDs could potentially be mobilized when cancer cells encounter a harsh microenvironment</li> </ul>
Ohmoto et al. [130]	<ul> <li>Roles of ACAT1 in human GBM cell line U251-MG</li> <li>Role of K604</li> </ul>	ACAT1 K604 AKT ERK1/2*	<ul> <li>ACAT1 = expressed in human GBM tissues</li> <li>At low cell density, proliferation of GBM cell line U251-MG is significantly inhibited by K604 treatment</li> <li>At medium and high cell densities, K604 had no effect on the proliferation of GBM cell line U251-MG</li> <li>Phosphorylation of AKT and ERK1/2 = inhibited by K604 in a dose-dependent manner</li> <li>The activation of AKT and ERK1/2 may be associated with refractory GBM</li> </ul>	<ul> <li>ACAT1 may be a promising therapeutic target for GBM</li> <li>Further research is needed to elucidate the molecular mechanisms underlying the inhibition of ERK1/2 and AKT phosphorylation by K604</li> </ul>
Löhr et al. [131]	<ul> <li>ACAT1 and the GBM microenvironment</li> </ul>	ACAT1 GBM IDHw GBM IDHm-R132H SREBP-1 LD CD68	<ul> <li>ACAT1 = more pronounced in microglia and macrophages rather than in tumoral cells</li> <li>Expression of ACAT1 ↑ in GBM compared to LGG</li> <li>No expression of ACAT1 in normal brain tissues</li> <li>↑ LD in GBM</li> <li>IDHm status exhibited a near absence of LD accumulation, whereas GBM showed an abundance of LDs</li> </ul>	<ul> <li>The tumor microenvironment, including the macrophage/microglia may serve as a therapeutic target</li> <li>Mitotane could be particularly promising for GBM patients who have exhausted other treatment options</li> <li>The in vitro impact of ACAT1 inhibition on macrophage polarization holds significant interest</li> </ul>

# Table 2. The ketogenic enzymes and their role in cancer and in GBM.

Table 2. Cont.

Analyzed Data References Aim **Suggested Mechanism of Findings** Significance and Future Research The effect of Avasimibe on glioma is dose-dependent (was nearly abolished at 7.5 µM) ACAT1 expression is inhibited by Avasimibe in Inhibition of ACAT1 =  $\uparrow$  immunogenicity of tumor Expression of glioma cell lines ACAT1 in U87, cells. This finding suggests that such inhibition ACAT1 ACAT1 expression was unchanged in normal A172 and GL261 could be valuable in enhancing T-cell responses to CD80 human astrocytes Bemlih et al. [67] glioma cell lines tumors in vivo CD86 Avasimibe =  $\uparrow$  the expression of costimulatory and in normal Targeting cholesterol metabolism through the MHC \* class I molecules (CD80, CD86), and  $\uparrow$  MHC class I inhibition of ACAT-1 activity in GBM patients human astrocytes (characteristic of immunogenicity of glioma cells) presents a novel opportunity for controlling glioma progression HMG CoA Synthase & HMG CoA Lyase HMG CoA Synthase shows a positive correlation HMG CoA Synthase = play a oncogenic role Role of HMG with tumoral cell growth Ketogenic HMG CoA Synthase-HMG CoA CoA Synthase HMG CoA Synthase The dehydroacetic acid selectively inhibits the Lyase-acetoacetate axis is a promising therapeutic Zhao et al. [64] and HMG CoA BRAF<sup>V600E</sup> target in treatment of BRAF<sup>V600E</sup> positive proliferation and tumor growth of cells lvase in cancer expressing BRAF<sup>V600E</sup> human cancers HMG CoA Synthase = highly expressed and negatively correlated with the prognosis in cancer High HMG CoA Synthase 1 expression could Compared to adjacent control tissues, HMG CoA HMG CoA Synthase 1 reduce the sensitivity to drugs in cancer HMG CoA Syn-thase 1 Synthase 1 was underexpressed in GBM tissues Fibroblast Zhou et al. [132] HMG CoA Synthase 1 = had impacts on cell in cancer The infiltration levels of CD8+ T cell and cancer \_ CD8+ proliferation and immunity associated fibroblast = closely associated with HMG CoA Synthase 1 expression

	Table 2. Cont.			
References	Aim	Analyzed Data	Suggested Mechanism of Findings	Significance and Future Research
BHD & OXCT1				
– Chang et al. [66]	Expression of BHD and OXCT in glioma WHO grade III and in GBM	BHDOXCT GFAP	$\downarrow$ expression of BHD in GBM $\downarrow$ expression of OXCT in GBM	<ul> <li>Patients with low expression of BHD and OXCT in gliomas may respond better to adjuvant therapy, such as a ketogenic diet → further investigations utilizing animal models and/or conducting large-scale clinical trials are essential to validating these findings</li> </ul>
– Schwartz et al. [133]	Expression of BHD and OXCT in GBM patients and a Ketogenic diet	BHDOXCT	<ul> <li>Patient 1 (original tumor) = ↓ expression of OXCT and BHD in GBM, but still exhibits positive expression</li> <li>Patient 2 = The majority of tumoral cells are positive for OXCT and BHD → some GBM cells could metabolize ketone, thus obtaining energy for their continued growth</li> </ul>	Ketocal = $\downarrow$ the blood glucose and $\uparrow$ blood ketones, initially $\downarrow$ in weight (6%), but after then the patients' weight was stabilized $\rightarrow$ use an adjunctive therapy for GBM shows promise. The question arises whether GBM cells can utilize ketones for proliferation and growth?

\* ITGAM = integrin subunit alpha M; CXCL-1 = C-X-C motif chemokine ligand 1; MDSCs = myeloid-derived suppressor cells; ERK1/2 = extracellular signal regulated kinase  $\frac{1}{2}$ ; MHC = major histocompatibility complex;  $\uparrow$  = increase;  $\downarrow$  = decrease;  $\rightarrow$  = results.

# 5. Conclusions

The metabolic shifts observed in tumor cells are significant, primarily dictated by genetic factors. Our therapeutic aim revolves around altering these genetic determinants to enhance the cells' susceptibility to anticancer treatments.

The remodeling of lipid metabolism in GBM involves changes in FAO, FA transport, de novo lipogenesis, and LD storage. By increasing the expression of FA transporters and the transporters of the molecules involved in their supply, there is an increase in the content of FAs in the tumor microenvironment. The excess of FAs is stored in the form of LDs, which, in turn, will be split to generate energy. Thus, the hyperexpression of HIF-1 $\alpha$  in GBM leads to the hyperexpression of FAT, FABPpm, FATP, and, secondarily, the increase in the absorption of FAs and the formation of LDs in the tumor microenvironment. LDs prevent lipotoxicity and provide a source of ATP and NADPH in conditions of metabolic stress. The inhibition of FABP3 and FABP7 leads to the reduction of FA absorption and inhibits the growth of GBM cells.

Analysis of metabolic profiles between LGG and GBM reveals an increase in FA catabolism in GBM, providing metabolic plasticity for tumor adaptation and growth in different microenvironments. Through the PI3K/Akt signaling pathway, there is an over-expression of FASN with the promotion of de novo lipogenesis, which is associated with increased GBM cell invasion. At the same time, there is an increase in the expression of OCTN2, an important transporter of carnitine. Inhibition of OCTN2 has demonstrated antitumor efficacy in preclinical studies and could be a potential prognostic factor and therapeutic target for the treatment of GBM.

The role of KBs and ketogenesis enzymes in GBM metabolism is equally important, but still poorly understood, so new studies are needed regarding their expression and functions in GBM, as well as the potential of ketogenic therapies, such as ketogenic diets for this pathology. MCTs serve as key transporters for KBs across the BBB. Targeting MCTs, particularly MCT2 and MCT4, presents a novel approach in managing GBM cell metabolism.

The ongoing discovery of new therapeutic targets aimed at altering tumor metabolism underscores the importance of ongoing research in this area. In recent years, attention has been paid to metabolic reprogramming in GBM, as it has become increasingly evident that it plays a substantial role in the pathogenesis of these aggressive tumors. Investigations into the use of lipid metabolism for GBM have been limited, largely due to inadequate understanding of the physiological functions of lipids and lipid-related pathways in the brain and GBM. Therefore, future investigations focusing on therapeutic strategies targeting lipid metabolism pathways may provide new and practical concepts for GBM therapy.

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### References

- Ghimire, P.; Dhamoon, A.S. Ketoacidosis. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA; SUNY Upstate Medical University: Syracuse, NY, USA, 2024.
- Meidenbauer, J.J.; Mukherjee, P.; Seyfried, T.N. The glucose ketone index calculator: A simple tool to monitor therapeutic efficacy for metabolic management of brain cancer. *Nutr. Metab.* 2015, 12, 12. [CrossRef] [PubMed]
- Zhang, C.; Wang, M.; Ji, F.; Peng, Y.; Wang, B.; Zhao, J.; Wu, J.; Zhao, H. A Novel Glucose Metabolism-Related Gene Signature for Overall Survival Prediction in Patients with Glioblastoma. *BioMed Res. Int.* 2021, 2021, 1–13. [CrossRef]

- Henderson, L.R.; van den Berg, M.; Shaw, D.M. The effect of a 2 week ketogenic diet, versus a carbohydrate-based diet, on cognitive performance, mood and subjective sleepiness during 36 h of extended wakefulness in military personnel: An ex-ploratory study. J. Sleep. Res. 2023, 32, e13832. [CrossRef] [PubMed]
- 5. Kumari, A. Chapter 4—Beta Oxidation of Fatty Acids. In *Sweet Biochemistry*; Kumari, A., Ed.; Academic Press: Cambridge, MA, USA, 2018; pp. 17–19.
- 6. Woolf, E.C.; Syed, N.; Scheck, A.C. Tumor metabolism, the ketogenic diet and β-hydroxybutyrate: Novel approaches to adjuvant brain tumor therapy. *Front. Mol. Neurosci.* **2016**, *9*, 1–11. [CrossRef] [PubMed]
- 7. Newman, J.C.; Verdin, E. Ketone bodies as signaling metabolites. *Trends Endocrinol. Metab.* 2014, 25, 42–52. [CrossRef] [PubMed]
- 8. Jensen, N.J.; Wodschow, H.Z.; Nilsson, M.; Rungby, J. Effects of ketone bodies on brain metabolism and function in neurodegenerative diseases. *Int. J. Mol. Sci.* 2020, *21*, 1–17. [CrossRef] [PubMed]
- 9. Laffel, L. Ketone bodies: A review of physiology, pathophysiology and application of monitoring to diabetes. *Diabetes/Metab. Res. Rev.* **1999**, *15*, 412–426. [CrossRef]
- Dąbek, A.; Wojtala, M.; Pirola, L.; Balcerczyk, A. Modulation of Cellular Biochemistry, Epigenetics and Metabolomics by Ketone Bodies. Implications of the Ketogenic Diet in the Physiology of the Organism and Pathological States. *Nutrients* 2020, 12, 788. [CrossRef]
- 11. Tamas, C.; Tamas, F.; Kovecsi, A.; Serban, G.; Boeriu, C.; Balasa, A. The Role of Ketone Bodies in Treatment Individualization of Glioblastoma Patients. *Brain Sci.* 2023, *13*, 1307. [CrossRef]
- 12. El-Gharbawy, A.; Vockley, J. Inborn Errors of Metabolism with Myopathy: Defects of Fatty Acid Oxidation and the Carnitine Shuttle System. *Pediatr. Clin. N. Am.* 2018, 65, 317–335. [CrossRef]
- Firouzpour, H.; Shokrolahi, S.M.; Bourova-Flin, E.; Derakhshan, S.; Shahsavari, Z.; Karimi, A.; Sadeghi, H.M.M.; Goudarzi, A. The expression of ACAT1 in oral squamous cell carcinoma and the adjacent pre-tumour tissue. *Biomed. Pharmacother.* 2022, 12, 55–62. [CrossRef] [PubMed]
- 14. Sinkala, M.; Mulder, N.; Martin, D.P. Metabolic gene alterations impact the clinical aggressiveness and drug responses of 32 human cancers. *Commun. Biol.* **2019**, *2*, 4141. [CrossRef]
- 15. Vital-Lopez, F.G.; Wallqvist, A.; Reifman, J. Bridging the gap between gene expression and metabolic phenotype via kinetic models. *BMC Syst. Biol.* **2013**, *7*, 63. [CrossRef] [PubMed]
- 16. Guntuku, L.; Naidu, V.; Yerra, V.G. Mitochondrial Dysfunction in Gliomas: Pharmacotherapeutic Potential of Natural Compounds. *Curr. Neuropharmacol.* **2016**, *14*, 567–583. [CrossRef] [PubMed]
- Kaushik, B.; Arup, B.; Rakshamani, T.; Suman, K.S.; Bikas, C.P.; Chandrima, S.; Chitra, M. Mahanine, a novel mitochondrial complex-III inhibitor induces G0/G1 arrest through redox alteration-mediated DNA damage response and regresses glioblas-toma multiforme. *Am. J. Cancer Res.* 2014, *4*, 629–647.
- Luo, Y.; Ma, J.; Lu, W. The Significance of Mitochondrial Dysfunction in Cancer. Int. J. Mol. Sci. 2020, 21, 5598. [CrossRef] [PubMed]
- Liberti, M.V.; Locasale, J.W. The Warburg Effect: How Does it Benefit Cancer Cells? *Trends Biochem. Sci.* 2016, 41, 211–218. [CrossRef] [PubMed]
- Albayrak, T.; Scherhammer, V.; Schoenfeld, N.; Braziulis, E.; Mund, T.; Bauer, M.K.; Scheffler, I.E.; Grimm, S. The Tumor Suppressor cybL, a Component of the Respiratory Chain, Mediates Apoptosis Induction. *Mol. Biol. Cell* 2003, 14, 3082–3096. [CrossRef] [PubMed]
- 21. Strickland, M.; Stoll, E.A. Metabolic Reprogramming in Glioma. Front. Cell Dev. Biol. 2017, 5, 43. [CrossRef]
- 22. Luengo, A.; Li, Z.; Gui, D.Y.; Sullivan, L.B.; Zagorulya, M.; Do, B.T.; Ferreira, R.; Naamati, A.; Ali, A.; Lewis, C.A.; et al. Increased demand for NAD+ relative to ATP drives aerobic glycolysis. *Mol. Cell* **2021**, *81*, 691–707.e6. [CrossRef]
- Maher, E.A.; Bachoo, R.M. Glioblastoma. In Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease, 5th ed.; Elsevier: Amsterdam, The Netherlands, 2014; pp. 909–917.
- 24. Fabbro-Peray, P.; Zouaoui, S.; Darlix, A.; Fabbro, M.; Pallud, J.; Rigau, V. Association of patterns of care, prognostic factors, and use of radiotherapy–temozolomide therapy with survival in patients with newly diagnosed glioblastoma: A French national population-based study. *J. Neuro-Oncol.* **2019**, *142*, 91–101. [CrossRef]
- Seymour, T.; Nowak, A.; Kakulas, F. Targeting aggressive cancer stem cells in glioblastoma. *Front. Oncol.* 2015, 5, 159. [CrossRef] [PubMed]
- 26. Philips, A.; Henshaw, D.L.; Lamburn, G.; O'carroll, M.J. Brain tumours: Rise in glioblastoma multiforme incidence in England 1995-2015 Suggests an Adverse Environmental or Lifestyle Factor. *J. Environ. Public Heal* **2018**, 2018, 1–10. [CrossRef] [PubMed]
- 27. Bost, J.; Maroon, J.; Seyfried, T.; Donohue, J. The role of metabolic therapy in treating glioblastoma multiforme. *Surg. Neurol. Int.* **2015**, *6*, 61. [CrossRef]
- 28. Woolf, E.C.; Scheck, A.C. The ketogenic diet for the treatment of malignant glioma. J. Lipid Res. 2015, 56, 5–10. [CrossRef]
- Mashimo, T.; Pichumani, K.; Vemireddy, V.; Hatanpaa, K.J.; Singh, D.K.; Sirasanagandla, S.; Nannepaga, S.; Piccirillo, S.G.; Kovacs, Z.; Foong, C.; et al. Acetate is a bioenergetic substrate for human glioblastoma and brain metastases. *Cell* 2014, 159, 1603–1614. [CrossRef]
- Winter, S.F.; Loebel, F.; Dietrich, J. Role of ketogenic metabolic therapy in malignant glioma: A systematic review. *Crit. Rev. Oncol.* 2017, 112, 41–58. [CrossRef] [PubMed]

- Zagzag, D.; Esencay, M.; Mendez, O.; Yee, H.; Smirnova, I.; Huang, Y.; Chiriboga, L.; Lukyanov, E.; Liu, M.; Newcomb, E.W. Hypoxia- and Vascular Endothelial Growth Factor-Induced Stromal Cell-Derived Factor-1α/CXCR4 Expression in Glioblas-tomas: One Plausible Explanation of Scherer's Structures. *Am. J. Pathol.* 2008, *173*, 545–560. [CrossRef] [PubMed]
- 32. Juraszek, B.; Czarnecka-Herok, J.; Nałęcz, K.A. Glioma cells survival depends both on fatty acid oxidation and on functional carnitine transport by SLC22A5. J. Neurochem. 2021, 156, 642–657. [CrossRef]
- 33. Watson, K.S.; Boukhloufi, I.; Bowerman, M.; Parson, S.H. The relationship between body composition, fatty acid metabolism and diet in spinal muscular atrophy. *Brain Sci.* 2021, *11*, 131. [CrossRef]
- Nsiah-Sefaa, A.; McKenzie, M. Combined defects in oxidative phosphorylation and fatty acid β-oxidation in mitochondrial disease. *Biosci. Rep.* 2016, 36, e00313. [CrossRef] [PubMed]
- 35. Rovelli, V.; Manzoni, F.; Viau, K.; Pasquali, M.; Longo, N. Clinical and biochemical outcome of patients with very long-chain acyl-CoA dehydrogenase deficiency. *Mol. Genet. Metab.* 2019, 127, 64–73. [CrossRef]
- Ma, Y.; Wang, W.; Devarakonda, T.; Zhou, H.; Wang, X.-Y.; Salloum, F.N.; Spiegel, S.; Fang, X. Functional analysis of molecular and pharmacological modulators of mitochondrial fatty acid oxidation. *Sci. Rep.* 2020, 10, 1450. [CrossRef] [PubMed]
- Houten, S.M.; Wanders, R.J.A. A general introduction to the biochemistry of mitochondrial fatty acid β-oxidation. *J. Inherit. Metab. Dis.* 2010, 33, 469–477. [CrossRef] [PubMed]
- Longo, N.; Frigeni, M.; Pasquali, M.; Biophys, B. Carnitine transport and fatty acid oxidation. *Biochim. Biophys. Acta* 2016, 1863, 2422–2435. [CrossRef]
- Kou, Y.; Geng, F.; Guo, D. Lipid Metabolism in Glioblastoma: From De Novo Synthesis to Storage. *Biomedicines* 2022, 10, 1943. [CrossRef] [PubMed]
- Adeva-Andany, M.M.; Carneiro-Freire, N.; Seco-Filgueira, M.; Fernández, C.; Mouriño-Bayolo, D. Mitochondrial β-oxidation of saturated fatty acids in humans. *Mitochondrion* 2019, 46, 73–90. [CrossRef]
- 41. Liu, X.; Wu, L.; Deng, G.; Li, N.; Chu, X.; Guo, F.; Li, D. Characterization of mitochondrial trifunctional protein and its inactivation study for medicine development. *Biochim. Et. Biophys. Acta BBA Proteins Proteom.* **2008**, 1784, 1742–1749. [CrossRef]
- Lovatt, D.; Sonnewald, U.; Waagepetersen, H.S.; Schousboe, A.; He, W.; Lin, J.H.-C.; Han, X.; Takano, T.; Wang, S.; Sim, F.J.; et al. The transcriptome and metabolic gene signature of protoplasmic astrocytes in the adult murine cortex. *J. Neurosci.* 2007, 27, 12255–12266. [CrossRef]
- Ebert, D.; Haller, R.G.; Walton, M.E. Energy contribution of octanoate to intact rat brain metabolism measured by 13C nuclear magnetic resonance spectroscopy. J. Neurosci. 2003, 23, 5928–5935. [CrossRef]
- Ioannou, M.S.; Jackson, J.; Sheu, S.-H.; Chang, C.-L.; Weigel, A.V.; Liu, H.; Pasolli, H.A.; Xu, C.S.; Pang, S.; Matthies, D.; et al. Neuron-Astrocyte Metabolic Coupling Protects against Activity-Induced Fatty Acid Toxicity. *Cell* 2019, 177, 1522–1535.e14. [CrossRef]
- 45. Vesga-Jiménez, D.J.; Martin, C.; Barreto, G.E.; Aristizábal-Pachón, A.F.; Pinzón, A.; González, J. Fatty Acids: An Insight into the Pathogenesis of Neurodegenerative Diseases and Therapeutic Potential. *Int. J. Mol. Sci.* **2022**, *23*, 2577. [CrossRef]
- Valachovic, M.; Garaiova, M.; Holic, R.; Hapala, I. Squalene is lipotoxic to yeast cells defective in lipid droplet biogenesis. *Biochem. Biophys. Res. Commun.* 2016, 469, 1123–1128. [CrossRef]
- 47. Schmidt, C.; Ploier, B.; Koch, B.; Daum, G. Chapter 2—Analysis of Yeast Lipid Droplet Proteome and Lipidome. In *Methods Cell Biol.*; Academic Press: Cambridge, MA, USA, 2013; pp. 15–37.
- 48. Nguyen, T.B.; Olzmann, J.A. Lipid droplets and lipotoxicity during autophagy. Autophagy 2017, 13, 2002–2003. [CrossRef]
- 49. Longo, N.; Di San Filippo, C.A.; Pasquali, M. Disorders of carnitine transport and the carnitine cycle. *Am. J. Med. Genet. Semin. Med. Genet.* **2006**, 142, 77–85. [CrossRef]
- Zhan, T.; Poppelreuther, M.; Ehehalt, R.; Füllekrug, J. Overexpressed FATP1, ACSVL4/FATP4 and ACSL1 Increase the Cellular Fatty Acid Uptake of 3T3-L1 Adipocytes but Are Localized on Intracellular Membranes. *PLoS ONE* 2012, 7, e45087. [CrossRef]
- 51. Watkins, P.A.; Maiguel, D.; Jia, Z.; Pevsner, J. Evidence for 26 distinct acyl-coenzyme A synthetase genes in the human genome. *J. Lipid Res.* 2007, *48*, 2736–2750. [CrossRef]
- 52. Haley, W.E.; Freeman. HHS Public Access. Physiol. Behav. 2018, 176, 139–148.
- 53. Ren, J.; Lin, C.P.; Pathak, M.C.; Temple, B.R.S.; Nile, A.H.; Mousley, C.J.; Duncan, M.C.; Eckert, D.M.; Leiker, T.J.; Ivanova, P.T.; et al. A phos-phatidylinositol transfer protein integrates phosphoinositide signaling with lipid droplet metabolism to regulate a develop-mental program of nutrient stress–induced membrane biogenesis. *Mol. Biol. Cell* **2014**, *25*, 549–727. [CrossRef]
- 54. Huang, H.; Atshaves, B.P.; Frolov, A.; Kier, A.B.; Schroeder, F. Acyl-coenzyme A binding protein expression alters liver fatty acyl-coenzymeA metabolism. *Biochemistry* **2005**, *44*, 10282–10297. [CrossRef] [PubMed]
- 55. Jessica, M.; Ellis, J.M.; Lei, O.; Li, L.O.; Pei-Chi Wu, P.C.; Timothy, R.; Koves, T.R.; Olga Ilkayeva, O.; Robert, D.; Stevens, R.D.; et al. Adipose Acyl-CoA Synthetase-1 Directs Fatty Acids toward β-Oxidation and Is Required for Cold Thermogenesis. *Cell Metab.* 2010, 12, 53–64.
- Schrader, M.; Costello, J.; Godinho, L.F.; Islinger, M. Peroxisome-mitochondria interplay and disease. J. Inherit. Metab. Dis. 2015, 38, 681–702. [CrossRef]
- 57. Van Veldhoven, P.P.; Just, W.W.; Mannaerts, G.P. Permeability of the peroxisomal membrane to cofactors of beta-oxidation. Evidence for the presence of a pore-forming protein. *J. Biol. Chem.* **1987**, *262*, 4310–4318. [CrossRef]

- Hossain, F.; Al-Khami, A.A.; Wyczechowska, D.; Hernandez, C.; Zheng, L.; Reiss, K.; Valle, L.D.; Trillo-Tinoco, J.; Maj, T.; Zou, W.; et al. Inhibition of Fatty Acid Oxidation Modulates Immunosuppressive Functions of Myeloid-Derived Suppressor Cells and Enhances Cancer Therapies. *Cancer Immunol. Res.* 2015, *3*, 1236–1247. [CrossRef]
- Sekoguchi, E.; Norihiro, S.; Akihiro, Y.; Shinji, F.; Yuji, N.; Hiroyuki, A.; Kyoji, I.; Akira, M. A Novel Mitochondrial Car-nitineacylcarnitine Translocase Induced by Partial Hepatectomy and Fasting. J. Biol. Chem. 2003, 278, 38796–38802. [CrossRef]
- 60. Azzalin, A.; Brambilla, F.; Arbustini, E.; Basello, K.; Speciani, A.; Mauri, P.; Bezzi, P.; Magrassi, L. A New Pathway Promotes Adaptation of Human Glioblastoma Cells to Glucose Starvation. *Cells* **2020**, *9*, 1249. [CrossRef]
- 61. Agrimi, G.; Russo, A.; Scarcia, P.; Palmieri, F. The human gene SLC25A17 encodes a peroxisomal transporter of coenzyme A, FAD and NAD+. *Biochem. J.* **2012**, 443, 241–247. [CrossRef]
- 62. Wu, X.; George, R.L.; Huang, W.; Wang, H.; Conway, S.J.; Leibach, F.H.; Ganapathy, V. Structural and functional characteristics and tissue distribution pattern of rat OCTN1, an organic cation transporter, cloned from placenta. *Biochim. Biophys. Acta BBA Biomembr.* **2000**, 1466, 315–327. [CrossRef]
- Zahra, K.; Dey, T.; Ashish; Mishra, S.P.; Pandey, U. Pyruvate Kinase M2 and Cancer: The Role of PKM2 in Promoting Tumorigenesis. Front. Oncol. 2020, 10, 159. [CrossRef] [PubMed]
- 64. Zhao, L.; Fan, J.; Xia, S.; Pan, Y.; Liu, S.; Qian, G. HMG-CoA synthase 1 is a synthetic lethal partner of BRAFV600E in human cancers. *J. Biol. Chem.* **2017**, *292*, 10142–10152. [CrossRef] [PubMed]
- Vallejo, F.A.; Shah, S.S.; de Cordoba, N.; Walters, W.M.; Prince, J.; Khatib, Z.; Komotar, R.J.; Vanni, S.; Graham, R.M. The contribution of ketone bodies to glycolytic inhibition for the treatment of adult and pediatric glioblastoma. *J. Neuro-Oncol.* 2020, 147, 317–326. [CrossRef] [PubMed]
- 66. Chang, H.T.; Olson, L.K.; A Schwartz, K. Ketolytic and glycolytic enzymatic expression profiles in malignant gliomas: Implication for ketogenic diet therapy. *Nutr. Metab.* **2013**, *10*, 47. [CrossRef] [PubMed]
- 67. Bemlih, S.; Poirier, M.-D.; El Andaloussi, A. Acyl-coenzyme A: Cholesterol acyltransferase inhibitor Avasimibe affect survival and proliferation of glioma tumor cell lines. *Cancer Biol. Ther.* **2010**, *9*, 1025–1032. [CrossRef] [PubMed]
- Hegardt, F.G. Mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase: A control enzyme in ketogenesis. *Biochem. J.* 1999, 338, 569–582. [CrossRef]
- 69. Nelson, A.B.; Queathem, E.D.; Puchalska, P.; Crawford, P.A. Metabolic Messengers: Ketone bodies. *Nat. Metab.* 2023, *5*, 1–13. [CrossRef] [PubMed]
- Asif, S.; Kim, R.Y.; Fatica, T.; Sim, J.; Zhao, X.; Oh, Y.; Denoncourt, A.; Cheung, A.C.; Downey, M.; Mulvihill, E.E.; et al. Hmgcs2-mediated ketogenesis modulates high-fat diet-induced hepatosteatosis. *Mol. Metab.* 2022, 61, 101494. [CrossRef] [PubMed]
- Luo, W.; Qin, L.; Li, B.; Liao, Z.; Liang, J.; Xiao, X.; Xiao, X.; Mo, Y.; Huang, G.; Zhang, Z.; et al. Inactivation of HMGCL promotes proliferation and metastasis of nasopharyngeal carcinoma by suppressing oxidative stress. *Sci. Rep.* 2017, 7, 1–13. [CrossRef] [PubMed]
- 72. Morris, A.A.M. Cerebral ketone body metabolism. J. Inherit. Metab. Dis. 2004, 28, 109–121. [CrossRef] [PubMed]
- 73. Li, J.; Liu, Q.; Liu, Z.; Xia, Q.; Zhang, Z.; Zhang, R.; Gao, T.; Gu, G.; Wang, Y.; Wang, D.; et al. KPNA2 promotes metabolic reprogramming in glioblastomas by regulation of c-myc. *J. Exp. Clin. Cancer Res.* **2018**, *37*, 194. [CrossRef]
- Shivva, V.; Cox, P.J.; Clarke, K.; Veech, R.L.; Tucker, I.G.; Duffull, S.B. The Population Pharmacokinetics of d-β-hydroxybutyrate Following Administration of (R)-3-Hydroxybutyl (R)-3-Hydroxybutyrate. AAPS J. 2016, 18, 678–688. [CrossRef]
- Koopman, W.J.H.; Distelmaier, F.; Smeitink, J.A.; Willems, P.H. OXPHOS mutations and neurodegeneration. *EMBO J.* 2012, 32, 9–29. [CrossRef] [PubMed]
- Kim, S.-H.; Choi, J.-H.; Marsal-García, L.; Amiri, M.; Yanagiya, A.; Sonenberg, N. The mRNA translation initiation factor eIF4G1 controls mitochondrial oxidative phosphorylation, axonal morphogenesis, and memory. *Proc. Natl. Acad. Sci. USA* 2023, 120, e2300008120. [CrossRef] [PubMed]
- 77. Miki, K.; Yagi, M.; Yoshimoto, K.; Kang, D.; Uchiumi, T. Mitochondrial dysfunction and impaired growth of glioblastoma cell lines caused by antimicrobial agents inducing ferroptosis under glucose starvation. *Oncogenesis* **2022**, *11*, 59. [CrossRef] [PubMed]
- Rolfe, D.F.S.; Brown, G.C.; Merdzo, I.; Rutkai, I.; Sure, V.N.L.R.; Katakam, P.V.G.; Busija, D.W.; Karbowski, J.; Gordon, K.; Blondin, D.P.; et al. Cellular energy utilization and molecular origin of standard metabolic rate in mammals. *Physiol. Rev.* 1997, 77, 731–758. [CrossRef] [PubMed]
- 79. Pierre, K.; Pellerin, L. Monocarboxylate transporters in the central nervous system: Distribution, regulation and function. *J. Neurochem.* 2005, 94, 1–14. [CrossRef]
- Courchesne-Loyer, A.; Croteau, E.; Castellano, C.-A.; St-Pierre, V.; Hennebelle, M.; Cunnane, S.C. Inverse relationship between brain glucose and ketone metabolism in adults during short-term moderate dietary ketosis: A dual tracer quantitative positron emission tomography study. J. Cereb. Blood Flow. Metab. 2017, 37, 2485–2493. [CrossRef] [PubMed]
- 81. García-Rodríguez, D.; Giménez-Cassina, A. Ketone Bodies in the Brain Beyond Fuel Metabolism: From Excitability to Gene Expression and Cell Signaling. *Front. Mol. Neurosci.* **2021**, *14*, 732120. [CrossRef] [PubMed]
- Cunnane, S.C.; Courchesne-Loyer, A.; Vandenberghe, C.; St-Pierre, V.; Fortier, M.; Hennebelle, M.; Croteau, E.; Bocti, C.; Fulop, T.; Castellano, C.-A. Can Ketones Help Rescue Brain Fuel Supply in Later Life? Implications for Cognitive Health during Aging and the Treatment of Alzheimer's Disease. *Front. Mol. Neurosci.* 2016, *9*, 53. [CrossRef]

- Pérez-Escuredo, J.; Van Hée, V.F.; Sboarina, M.; Falces, J.; Payen, V.L.; Pellerin, L.; Sonveaux, P. Monocarboxylate transporters in the brain and in cancer. *Biochim. Biophys. Acta BBA-Mol. Cell Res.* 2016, 1863, 2481–2497. [CrossRef]
- 84. Halestrap, A.P.; Meredith, D. The SLC16 gene family? from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond. Pfl?gers Arch. *Eur. J. Physiol.* **2004**, *447*, 619–628. [CrossRef]
- 85. Ueno, M.; Chiba, Y.; Murakami, R.; Miyai, Y.; Matsumoto, K.; Wakamatsu, K.; Takebayashi, G.; Uemura, N.; Yanase, K. Distribution of Monocarboxylate Transporters in Brain and Choroid Plexus Epithelium. *Pharmaceutics* **2023**, *15*, 2062. [CrossRef]
- Roshanbin, S.; Lindberg, F.A.; Lekholm, E.; Eriksson, M.M.; Perland, E.; Åhlund, J.; Raine, A.; Fredriksson, R. Histological characterization of orphan transporter MCT14 (SLC16A14) shows abundant expression in mouse CNS and kidney. *BMC Neurosci.* 2016, 17, 43. [CrossRef]
- Hugo, S.E.; Cruz-Garcia, L.; Karanth, S.; Anderson, R.M.; Stainier, D.Y.; Schlegel, A. A monocarboxylate transporter required for hepatocyte secretion of ketone bodies during fasting. *Genes. Dev.* 2012, 26, 282–293. [CrossRef] [PubMed]
- Suhre, K.; Shin, S.Y.; Petersen, A.K.; Mohney, R.P.; Meredith, D.; Wagele, B.; Altmaier, E.; Gram, C.; Deloukas, P.; Erdmann, J.; et al. Human metabolic individuality in biomedical and pharmaceutical research. *Nature* 2011, 477, 54–60. [CrossRef] [PubMed]
- Halestrap, A.P. The SLC16 gene family-structure, role and regulation in health and disease. *Mol. Asp. Med.* 2013, 34, 337–349. [CrossRef] [PubMed]
- 90. Roosterman, D.; Cottrell, G.S. Astrocytes and neurons communicate via a monocarboxylic acid shuttle. *AIMS Neurosci.* 2020, 7, 94–106. [CrossRef]
- Achanta, L.B.; Rae, C.D. β-Hydroxybutyrate in the Brain: One Molecule, Multiple Mechanisms. *Neurochem. Res.* 2017, 42, 35–49.
   [CrossRef]
- Chiry, O.; Fishbein, W.N.; Merezhinskaya, N.; Clarke, S.; Galuske, R.; Magistretti, P.J.; Pellerin, L. Distribution of the monocarboxylate transporter MCT2 in human cerebral cortex: An immunohistochemical study. *Brain Res.* 2008, 1226, 61–69. [CrossRef]
- Puchalska, P.; Crawford, P.A. Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics. *Cell Metab.* 2017, 25, 262–284. [CrossRef]
- 94. Koppel, S.J.; Swerdlow, R.H. Neuroketotherapeutics: A modern review of a century-old therapy. *Neurochem. Int.* **2018**, 117, 114–125. [CrossRef]
- Sparks, L.M.; Moro, C.; Ukropcova, B.; Bajpeyi, S.; Civitarese, A.E.; Hulver, M.W.; Thoresen, G.H.; Rustan, A.C.; Smith, S.R. Remodeling lipid metabolism and improving insulin responsiveness in human primary myotubes. *PLoS ONE* 2011, *6*, e21068. [CrossRef] [PubMed]
- 96. Minami, J.K.; Morrow, D.; Bayley, N.A.; Fernandez, E.G.; Salinas, J.J.; Tse, C.; Zhu, H.; Su, B.; Plawat, R.; Jones, A.; et al. CDKN2A deletion re-models lipid metabolism to prime glioblastoma for ferroptosis. *Cancer Cell* 2023, 41, 1048–1060.e9. [CrossRef] [PubMed]
- Chen, H.; Yang, Z.; Sun, Y.; Yin, S.; Tang, M.; Zhang, F. Targeting the Key Enzymes of Abnormal Fatty Acid β-oxidation as a Potential Strategy for Tumor Therapy. *Front. Biosci.* 2022, 27, 95. [CrossRef] [PubMed]
- 98. Resh, M.D. Fatty acylation of proteins: The long and the short of it. Prog. Lipid Res. 2016, 63, 120–131. [CrossRef] [PubMed]
- Ehehalt, R.; Sparla, R.; Kulaksiz, H.; Herrmann, T.; Füllekrug, J.; Stremmel, W. Uptake of long chain fatty acids is regulated by dynamic interaction of FAT/CD36 with cholesterol/sphingolipid enriched microdomains (lipid rafts). *BMC Cell Biol.* 2008, 9, 45. [CrossRef] [PubMed]
- 100. Carracedo, A.; Cantley, L.C.; Pandolfi, P.P. Cancer metabolism: Fatty acid oxidation in the limelight. *Nat. Rev. Cancer* 2013, *13*, 227–232. [CrossRef] [PubMed]
- 101. Wahl, D.R.; Dresser, J.; Wilder-Romans, K.; Parsels, J.D.; Zhao, S.G.; Davis, M. Glioblastoma Therapy Can Be Augmented by Targeting IDH1-Mediated NADPH Biosynthesis. *Cancer Res.* **2017**, *77*, 960–970. [CrossRef] [PubMed]
- 102. Bensaad, K.; Favaro, E.; Lewis, C.A.; Peck, B.; Lord, S.; Collins, J.M.; Pinnick, K.E.; Wigfield, S.; Buffa, F.M.; Li, J.-L.; et al. Fatty acid uptake and lipid storage induced by HIF-1α contribute to cell growth and survival after hypoxia-reoxygenation. *Cell Rep.* 2014, *9*, 349–365. [CrossRef] [PubMed]
- 103. Zhao, H.; Heimberger, A.B.; Lu, Z.; Wu, X.; Hodges, T.R.; Song, R.; Shen, J. Metabolomics profiling in plasma samples from glioma patients correlates with tumor phenotypes. *Oncotarget* **2016**, *7*, 20486–20495. [CrossRef]
- 104. Jalbert, L.E.; Elkhaled, A.; Phillips, J.J.; Neill, E.; Williams, A.; Crane, J.C.; Olson, M.P.; Molinaro, A.M.; Berger, M.S.; Kurhanewicz, J.; et al. Metabolic Profiling of IDH Mutation and Malignant Progression in Infiltrating Glioma. *Sci. Rep.* **2017**, *7*, 44792. [CrossRef]
- 105. Colapietro, A.; Mancini, A.; Vitale, F.; Martellucci, S.; Angelucci, A.; Llorens, S.; Mattei, V.; Gravina, G.L.; Alonso, G.L.; Festuccia, C. Crocetin Extracted from Saffron Shows Antitumor Effects in Models of Human Glioblastoma. *Int. J. Mol. Sci.* 2020, 21, 423. [CrossRef] [PubMed]
- 106. Lee, J.E.; Lim, J.H.; Kil Hong, Y.; Yang, S.H. High-Dose Metformin Plus Temozolomide Shows Increased Anti-tumor Effects in Glioblastoma In Vivo Compared with Monotherapy. *Cancer Res. Treat.* **2018**, *50*, 1331–1342. [CrossRef] [PubMed]
- 107. Khwairakpam, A.D.; Shyamananda, M.S.; Sailo, B.L.; Rathnakaram, S.R.; Padmavathi, G.; Kotoky, J.; Kunnumakkara, A.B. ATP citrate lyase (ACLY): A promising target for cancer prevention and treatment. *Curr. Drug Targets* 2015, *16*, 156–163. [CrossRef] [PubMed]
- 108. Vanauberg, D.; Schulz, C.; Lefebvre, T. Involvement of the pro-oncogenic enzyme fatty acid synthase in the hallmarks of cancer: A promising target in anti-cancer therapies. *Oncogenesis* **2023**, *12*, 16. [CrossRef] [PubMed]
- 109. Douglas, H. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022, 12, 31-46.

- 110. Behrooz, A.B.; Talaie, Z.; Jusheghani, F.; Łos, M.J.; Klonisch, T.; Ghavami, S. Wnt and PI3K/Akt/mTOR Survival Pathways as Therapeutic Targets in Glioblastoma. *Int. J. Mol. Sci.* 2022, 23, 1353. [CrossRef] [PubMed]
- 111. Williams, K.J.; Argus, J.P.; Zhu, Y.; Wilks, M.Q.; Marbois, B.N.; York, A.G. An essential requirement for the SCAP/SREBP signaling axis to protect cancer cells from lipotoxicity. *Cancer Res.* 2013, *73*, 2850–2862. [CrossRef] [PubMed]
- 112. Cheng, C.; Geng, F.; Cheng, X.; Guo, D. Lipid metabolism reprogramming and its potential targets in cancer. *Cancer Commun.* **2018**, *38*, 1–14. [CrossRef]
- 113. Liu, J.; Head, E.; Kuratsune, H.; Cotman, C.W.; Ames, B.N. Comparison of the effects of L-carnitine and acetyl-L-carnitine on carnitine levels, ambulatory activity, and oxidative stress biomarkers in the brain of old rats. *Ann. N. Y. Acad. Sci.* 2004, 1033, 117–131. [CrossRef]
- 114. Trabjerg, M.S.; Mørkholt, A.S.; Lichota, J.; Oklinski, M.K.E.; Andersen, D.C.; Jønsson, K.; Mørk, K.; Skjønnemand, M.-L.N.; Kroese, L.J.; Pritchard, C.E.J.; et al. Dysregulation of metabolic pathways by carnitine palmitoyl-transferase 1 plays a key role in central nervous system disorders: Experimental evidence based on animal models. *Sci. Rep.* 2020, *10*, 15583. [CrossRef]
- 115. Wang, D.H.; Fujita, Y.; Dono, A.; Armendariz, A.G.R.; Shah, M.; Putluri, N.; Pichardo-Rojas, P.S.; Patel, C.B.; Zhu, J.-J.; Huse, J.T.; et al. The genomic alterations in glioblastoma influence the levels of CSF metabolites. *Acta Neuropathol. Commun.* 2024, 12, 1–13. [CrossRef] [PubMed]
- 116. Czeredys, M.; Samluk, Ł.; Michalec, K.; Tułodziecka, K.; Skowronek, K.; Nałęcz, K.A. Caveolin-1—A novel interacting partner of or-ganic cation/carnitine transporter (Octn2): Effect of protein kinase C on this interaction in rat astrocytes. *PLoS ONE* 2013, *8*, e82105. [CrossRef] [PubMed]
- 117. Korbecki, J.; Bosiacki, M.; Gutowska, I.; Chlubek, D.; Baranowska-Bosiacka, I. Biosynthesis and Significance of Fatty Acids, Glycerophospholipids, and Triacylglycerol in the Processes of Glioblastoma Tumorigenesis. *Cancers* 2023, 15, 2183. [CrossRef] [PubMed]
- Fink, M.A.; Paland, H.; Herzog, S.; Grube, M.; Vogelgesang, S.; Weitmann, K. L-Carnitine-Mediated Tumor Cell Protection and Poor Patient Survival Associated with OCTN2 Overexpression in Glioblastoma Multiforme. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* 2019, 25, 2874–2886. [CrossRef] [PubMed]
- Longfa, K.; Yanxian, H.Q.; Sun, J. L-Carnitine-conjugated nanoparticles to promote permeation across blood-brain barrier and to target glioma cells for drug delivery via the novel organic cation/carnitine transporter OCTN2. *Artif. Cells Nanomed. Biotechnol.* 2018, 46, 1605–1616.
- 120. Bogusiewicz, J.; Burlikowska, K.; Jaroch, K.; Gorynska, P.Z.; Gorynski, K.; Birski, M. Profiling of carnitine shuttle system in-termediates in gliomas using solid-phase microextraction (Spme). *Molecules* **2021**, *26*, 1–11. [CrossRef] [PubMed]
- 121. Jong, N.N.; Nakanishi, T.; Liu, J.J.; Tamai, I.; McKeage, M.J. Oxaliplatin Transport Mediated by Organic Cation/Carnitine Transporters OCTN1 and OCTN2 in Overexpressing Human Embryonic Kidney 293 Cells and Rat Dorsal Root Ganglion Neurons. J. Pharmacol. Exp. Ther. 2011, 338, 537–547. [CrossRef]
- 122. Hu, C.; Lancaster, C.S.; Zuo, Z.; Hu, S.; Chen, Z.; Rubnitz, J.E. Inhibition of OCTN2-Mediated Transport of Carnitine by Etoposide. *Mol. Cancer Ther.* 2012, *11*, 921–929. [CrossRef]
- 123. Console, L.; Scalise, M.; Mazza, T.; Pochini, L.; Galluccio, M.; Giangregorio, N. Carnitine Traffic in Cells. *Link. Cancer. Front. Cell Dev. Biol.* 2020, *8*, 583850.
- 124. Wang, N.; Jiang, X.; Zhang, S.; Zhu, A.; Yuan, Y.; Xu, H.; Lei, J.; Yan, C. Structural basis of human monocarboxylate transporter 1 inhibition by anti-cancer drug candidates. *Cell* **2021**, *184*, 370–383.e13. [CrossRef]
- 125. Park, S.J.; Smith, C.P.; Wilbur, R.R.; Cain, C.P.; Kallu, S.R.; Valasapalli, S.; Sahoo, A.; Guda, M.R.; Tsung, A.J.; Velpula, K.K. An overview of MCT1 and MCT4 in GBM: Small molecule transporters with large implications. *Am. J. Cancer Res.* 2018, *8*, 1967–1976. [PubMed]
- Lai, S.-W.; Lin, H.-J.; Liu, Y.-S.; Yang, L.-Y.; Lu, D.-Y. Monocarboxylate Transporter 4 Regulates Glioblastoma Motility and Monocyte Binding Ability. *Cancers* 2020, 12, 380. [CrossRef] [PubMed]
- 127. Miranda-Gonçalves, V.; Honavar, M.; Pinheiro, C.; Martinho, O.; Pires, M.M.; Pinheiro, C.; Cordeiro, M.; Bebiano, G.; Costa, P.; Palmeirim, I.; et al. Monocarboxylate transporters (MCTs) in gliomas: Expression and exploitation as therapeutic targets. *Neuro Oncol.* 2013, 15, 172–188. [CrossRef]
- 128. Goldberg, F.W.; Kettle, J.G.; Lamont, G.M.; Buttar, D.; Ting, A.K.T.; McGuire, T.M.; Cook, C.R.; Beattie, D.; Gutierrez, P.M.; Kavanagh, S.L.; et al. Discovery of Clinical Candidate AZD0095, a Selective Inhibitor of Monocarboxylate Transporter 4 (MCT4) for Oncology. J. Med. Chem. 2023, 66, 384–397. [CrossRef] [PubMed]
- 129. Wang, M.; Wang, W.; You, S.; Hou, Z.; Ji, M.; Xue, N.; Du, T.; Chen, X.; Jin, J. ACAT1 deficiency in myeloid cells promotes glioblastoma progression by enhancing the accumulation of myeloid-derived suppressor cells. Acta Pharm. *Sin. B* 2023, *13*, 4733–4747. [CrossRef] [PubMed]
- Ohmoto, T.; Nishitsuji, K.; Yoshitani, N.; Mizuguchi, M.; Yanagisawa, Y.; Saito, H. K604, a specific acyl-CoA:cholesterol acyl-transferase 1 inhibitor, suppresses proliferation of U251-MG glioblastoma cells. *Mol. Med. Rep.* 2015, *12*, 6037–6042. [CrossRef] [PubMed]
- Löhr, M.; Härtig, W.; Schulze, A.; Kroiß, M.; Sbiera, S.; Lapa, C. SOAT1: A Suitable Target for Therapy in High-Grade Astrocytic Glioma? Int. J. Mol. Sci. 2022, 23, 7. [CrossRef] [PubMed]

- 132. Zhou, C.; Wang, Z.; Cao, Y.; Zhao, L. Pan-cancer analysis reveals the oncogenic role of 3-hydroxy-3-methylgluatary-CoA synthase 1. *Cancer Rep.* **2022**, *5*, e1562. [CrossRef]
- 133. Schwartz, K.A.; Noel, M.; Nikolai, M.; Chang, H.T. Investigating the Ketogenic Diet As Treatment for Primary Aggressive Brain Cancer: Challenges and Lessons Learned. *Front. Nutr.* **2018**, *5*, 11. [CrossRef]

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