Lipid metabolic rewiring in glioma-associated microglia/macrophages (Review)

YIXUAN MA[1-3*], YIMIN HUANG[1-3*], FENG HU[1-3] and KAI SHU[1-3]

[1]Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China; [2]Sino-German Neuro-Oncology Molecular Laboratory, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China; [3]Hubei Key Laboratory of Neural Injury and Functional Reconstruction, Huazhong University of Science and Technology, Wuhan, Hubei 430030, P.R. China

Received June 28, 2024; Accepted September 2, 2024

DOI: 10.3892/ijmm.2024.5426

Abstract. Gliomas are the most prevailing brain malignancy in both children and adults. Microglia, which are resident in the central nervous system (CNS), are distributed throughout the brain and serve an important role in the immunity of the CNS. Microglial cells exhibit varying phenotypic and metabolic properties during different stages of glioma development, making them a highly dynamic cell population. In particular, glioma-associated microglia/macrophages (GAMs) can alter their metabolic characteristics and influence malignancies in response to the signals they receive. The significance of macrophage metabolic reprogramming in tumor growth is becoming increasingly acknowledged in recent years. However, to the best of our knowledge, there is currently a scarcity of data from investigations into the lipid metabolic profiles of microglia/macrophages in the glioma setting. Therefore, the present review aims to provide a thorough review of the role that lipid metabolism serves in tumor-associated macrophages. In addition, it outlines potential targets for therapy based on lipid metabolism. The present review aims to serve as a reference source for future investigations into GAMs.

Contents

Correspondence to: Professor Feng Hu or Professor Kai Shu, Department of Neurosurgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Qiaokou, Wuhan, Hubei 430030, P.R. China
E-mail: hufeng@tjh.tjmu.edu.cn
E-mail: kshu@tjh.tjmu.edu.cn

*Contributed equally

Key words: glioma, microglia, macrophages, cancer, lipid metabolism

1. Introduction

Gliomas are the most common type of brain malignancy in both children and adults. According to the World Health Organization (WHO), glioma can be classified into the low-grade (grades 1 and 2) and high-grade (grades 3 and 4) categories, based on the degree of malignancy from lowest to highest (1-3). The prognosis for gliomas remains poor despite the existence of multiple treatment strategies, including surgery, radiation, chemotherapy and targeted therapy. Specifically, glioblastoma (GBM) multiforme (WHO grade 4) has a 5-year survival rate of only 5.5% (4), which may be due to chemoresistance, heterogeneity and infiltrative properties, making the tumor difficult to remove completely (5). By contrast, low-grade gliomas (WHO grades 1-2) have a relatively favorable prognosis, with an overall survival of ~7 years (6).

Glioma tissues can consist not only of cancer cells but can also contain various non-cancerous cell types, such as resident microglia from the brain and monocytes (macrophages) from the circulating bloodstream. In particular, macrophages and microglia are highly heterogeneous and plastic, such that they become cells of different phenotypes after *in vitro* stimulation (7). Toll-like receptor 4 (TLR4) ligands and IFN-γ stimulation typically result in the pro-inflammatory M1 phenotype, whereas IL-4, IL-10 and IL-13 stimulation typically produce an anti-inflammatory M2 phenotype (8). In addition, macrophages can be selectively activated further and then subdivided into the M2a [type II T-helper cell (Th2) response, type II inflammation, pathogen killing and allergic response], M2b (Th2 activation, immunomodulation) and M2c (immunomodulation, matrix deposition and tissue remodeling) states (8,9). These macrophage subpopulations differ in their receptor expression, effector function, as well as cytokine and chemokine expression profiles. However, this phenotype definition was proposed based on data from mainly *in vitro*

research, meaning that they cannot be used to fully reflect the *in vivo* situation of the different pathological conditions.

Metabolic reprogramming refers to the process by which cells adjust their metabolic pathways and energy production methods to adapt to environmental changes under specific conditions. However, this process is not merely a simple metabolic change. Instead, it typically involves profound systemic adjustments aimed at meeting the specific physiological needs of the cells (10,11). Metabolic reprogramming in tumors will likely involve significant changes in the energy production and metabolic pathways being activated. Changes that have been previously reported include the Warburg effect, enhanced lipid synthesis and abnormal amino acid metabolism (12,13). However, the majority of such previous studies have mainly focused on tumor cells. Metabolic reprogramming in other cell types that reside in the tumor microenvironment, such as glioma-associated microglia/macrophages (GAMs), should also be considered. Tumor cell metabolic reprogramming can mediate macrophage phenotypic alterations through various mechanisms, such as epigenetic modifications, leading to altered macrophage metabolism and in turn tumor progression (14). Studies over the past decade have demonstrated that altered lipid metabolism in tumor-associated macrophages (TAMs) can serve an important role in tumor progression, though to the best of our knowledge, there have been few similar studies on GAMs. Therefore, the present review aims to systematically summarize the research progress on metabolic reprogramming in GAMs. Based on existing studies on TAMs (15), hypotheses regarding the role of GAMs in glioma are proposed, emphasizing their potential metabolic similarities. In addition, the complex regulatory mechanisms potentially driving these metabolic changes and their implications for tumor progression and immune evasion are summarized. The present review also explores potential therapeutic targets within lipid metabolism, aiming to facilitate future strategies for inhibiting glioma tumor growth by modulating GAM metabolism. The novelty of the present review lies in its comprehensive focus on the underexplored area of GAM lipid metabolism and integration of recent findings to propose novel research directions and clinical applications.

2. Metabolic microenvironment of glioma

Metabolic characteristics of glioma. Similar to other rapidly proliferating cells, glioma cells typically metabolize glucose into lactate even in the presence of oxygen (the 'Warburg' effect). This allows tumor cells to use glucose-derived carbon to synthesize essential cellular components whilst simultaneously producing sufficient ATP to support its substantial metabolic demands (16-18). In addition, glioma cells can increase their own intracellular stores of fats, amino acids and nucleotides through various pathways. These include extracellular uptake, *de novo* synthesis and the delivery of carbon or nitrogen via multiple routes (17,19).

Effect of cells in the tumor microenvironment on metabolism. The brain is a highly metabolically active organ that relies on glucose as its major energy substrate. However, lactate, ketone bodies, fatty acids (FAs) and amino acids can also serve as its energy source (20-22). In addition, astrocytes, neurons and microglia can all regulate the nutrient uptake processes of each other (18). Specifically, neurons can absorb lactate, cholesterol and FAs produced by astrocytes, whilst astrocytes can take up glutamate produced by neurons (20). Gliomas develop in a complex and frequently hypoxic environment, which significantly influences the metabolic decisions of glioma cells, driving tumor growth, reproduction and invasion (23-26).

3. GAMs

Sources. Microglia are macrophages that reside in the central nervous system (CNS) and are distributed throughout the brain. They serve as the key immune effector cell type in the CNS. GAMs typically originate from two cell types, namely brain-resident microglia (BRM) and bone marrow-derived monocytes (BMDM) (27). The debate over the origin of microglia remains to the present day after it was first proposed by del Rio-Hortega (28). It has been suggested that increased microglial density after CNS injury involves both BRM proliferation and active recruitment of BMDM progenitors from the bloodstream (29-32). By contrast, it has also been suggested that the increase in microglial density originates primarily from the BRM (33). The reason for this controversy may lie in the experimental methodology used. To avoid the influence of the blood-brain barrier, the method used to distinguish microglia from monocytes is to first destroy the hematopoietic system of the recipient's bone marrow with radiation and then transplant the labeled hematopoietic stem cells into the recipient, before observing the infiltration of the labeled monocytes into the tumor tissue of the brain. However, irradiation can damage the blood-brain barrier in mice whilst disrupting the immune system and non-specific infiltration of immune cells into the brain, compromising the accuracy of the experiment (34). This debate continued until it was resolved when a chimeric animal was generated by a form of heterologous symbiosis that required neither irradiation nor transplantation. Both axotomy and neurodegeneration models failed to recruit microglia from the circulation (33). In addition, similar results were observed in a mouse model of experimental allergic encephalomyelitis (35).

In high-grade gliomas, BMDM accounts for >85% of GAMs, whereas BRM is predominantly distributed in peritumoral tissues (36,37). In the past, the expression levels of CD45 were typically used to differentiate between BRM (CD45 high expression)-derived and BMDM (CD45 low expression)-derived GAMs (38). However, different views have emerged in recent years. A previous study has shown that although the expression level of CD48 can distinguish BRM-GAMs from BMDM-GAMs to a certain extent, the cell type-specific CD45 expression profiles of humans and mice are different. In addition, the differentiation effect of CD45 is not precise, necessitating the use of more sensitive and specific methods, such as RNA sequencing and flow cytometry, to accurately distinguish between BRM-derived and BMDM-derived GAMs (39).

A large-scale RNA sequencing analysis has previously revealed the existence of BRM-derived GAMs and BMDM-derived GAMs with distinct gene expression patterns. In particular, subpopulations of GAMs from different origins may perform different functions (36). Another previous study

found that transmembrane protein 119 (TMEM119) was stably expressed only in BRM-derived GAMs. Subsequently, RNA-sequencing was performed in this previous study based on the expression profile of TMEM119 and differences in the transcript fragments of BRM- and BMDM-derived GAMs were found. It was also observed that the gene expression pattern of BRM may differ at different stages of development, such that, as microglia mature, the expression of their specifically expressed genes (such as TMEM119, purinergic receptor P2Y12 and olfactomedin-like 3) increases, but their proliferative capacity decreases (40). Using genealogical tracer techniques and a mouse model of glioma, Bowman *et al* (39) previously found that the transcriptional profiles and epigenetic landscapes between the two major subgroups of GAMs differed markedly, whereby CD49d was proposed as a distinguishing marker. Furthermore, Müller *et al* (41) previously performed single-cell sequencing on clinical glioma specimens and found that the levels of immunosuppressive cytokines, M2 activation markers (IL-10 and TGF-βII), phagocytosis and tricarboxylic acid (TCA) cycle activity were all upregulated in BMDM compared with those in BRM.

Phenotypic changes. Macrophages and microglia belong to the same monocyte type. Therefore, they can have a high degree of diversity and plasticity, allowing them to exhibit various phenotypes when exposed to different *in vitro* stimuli (7). Stimulation with Toll-like receptor (TLR)4 ligands and IFN-γ typically produces the pro-inflammatory M1 phenotype, whereas stimulation with IL-4, IL-10 and IL-13 produces an anti-inflammatory M2 phenotype (8). In a previous study, RNA microarray was applied to compare the expression profiles of microglia, macrophages and control microglia obtained by CD11b antibody-mediated magnetic beads sorting. The results showed that ~1,000 transcripts were differentially expressed in GAMs twice or more compared with those in control microglia. This expression pattern overlapped only partially with the reported gene profiles of the M1, M2a, M2b and M2c phenotypes (42). It has also been shown that GAMs can exhibit a different expression profile from the M1 and M2 phenotypes whilst highly expressing glycoprotein non-metastatic melanoma protein B and secreted phosphoprotein 1.

According to previous histological investigations that focused on single cells, the characteristics of GAMs are not limited to only M1 and M2 phenotypes. Instead, a wide range of variations have been noted. At present, no one superior typing method has been found compared with M1/M2. Since the majority of the relevant studies have continued to concentrate on M1/M2, discussion of data related to this topic will also center around M1/M2. GAMs express a number of markers that characterize the M1 or M2 phenotype (7). It has been previously shown that glioma-derived macrophage colony-stimulating factor (CSF) can induce microglia and macrophages to shift into an M2 phenotype, thereby promoting tumor growth (43). Similarly, mTOR and CSF-1 was found to inhibit microglia transformation into the M1 phenotype (43,44). Dopamine, microRNA (miR)-142-3p, prolyl 4-hydroxylase subunit α 1 downregulation and anti-programmed cell death protein 1 also showed similar anti-tumor effects (45-48). Based on these previous aforementioned studies, it has been proposed that targeted therapy aiming at converting the M2 phenotype into the M1 phenotype is a potential therapeutic strategy to inhibit glioma growth. However, other previous studies have also shown that M1-specific markers or associated pathways (IL1-β) are positively associated with glioma growth (49). It has also been indicated that sterile α and HEAT/armadillo motif can inhibit glioma progression by inducing the M2 polarization of GAMs (50).

Effect of GAMs on glioma. In the glioma microenvironment, microglia act through two main mechanisms. Microglia first become active upon glioma stimulation, producing cytokines, growth factors and MMPs to promote tumor growth and invasion (51). Subsequently, tumor cells secrete chemotactic agents and chemokines to recruit another population of microglia for activation, creating a continuous cycle (7,52,53). It has been previously shown that several common chemokines and receptors are upregulated in gliomas, including monocyte chemoattractant protein-1 (MCP-1), granulocyte-macrophage (GM)-CSF and fractalkine (54). MCP-1 has been considered to serve a key role in recruiting microglia to gliomas, where IL-33 may also be involved (Fig. 1) (51,54,55). In addition, microglia can have an important effect on angiogenesis, an effect associated with VEGF, which stimulates angiogenesis and promotes tumor growth (8). It has also been shown that inflammation is a key factor in brain tumor progression. Inflammation leads to the production of chemokines, such as C-X-C-motif chemokine ligand (CXCL)12, CXCL18 and reactive oxygen species (ROS), which promote tumor development by damaging DNA, proteins and lipids (56). Another previous study showed that the programmed cell death 10 protein serves an important role in the CXCL2/C-X-C chemokine receptor type 2 signaling pathway (57).

4. Lipid metabolic reprogramming and tumor-associated microglia/macrophages

Lipid metabolic reprogramming is a major feature of tumorigenesis and progression, serving a crucial role in GAMs. Initially, during tumor development, GAMs exhibit an M1 phenotype. However, as the tumor progresses, GAMs predominantly show the M2 phenotype. This metabolic reprogramming has been indicated to be regulated by hypoxia-inducible factor 1α and its downstream components (58-64). However, due to the limited availability of pertinent studies on gliomas, this section will discuss lipid metabolic reprogramming in TAMs of other tumor types. From these insights, the potential impact of GAMs of gliomas will be speculated.

Reprogramming of lipid metabolism in TAMs

FA metabolism in TAMs. Altered FA metabolism in tumor cells increases lipid accumulation in the TAM, which in turn promotes TAM activation and polarization (65). It has been previously found that M2 polarization is associated with FA oxidation (FAO). The scavenger receptor CD36 is highly expressed in TAMs, through which they take up and accumulate lipids (66). Results from a previous *in vivo* experiment corroborated this finding, where TAMs from tumor-bearing mice were found to have a higher lipid content compared with macrophages from tumor-free mice (67). High levels of

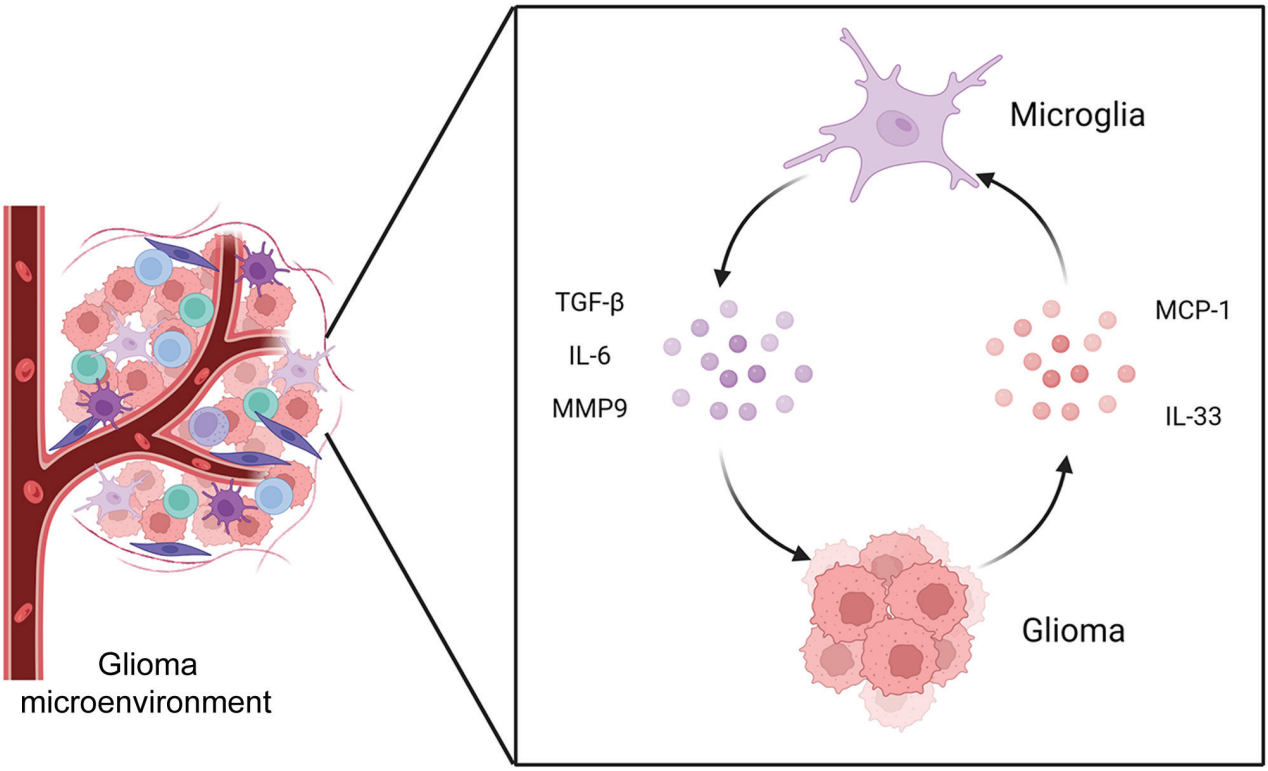

Figure 1. Interaction of glioma cells with microglia. First, microglia become activated by glioma stimulation, producing cytokines, growth factors and MMP, which promote tumor growth and invasion. Second, tumor cells secrete chemotactic agents and chemokines that recruit another population of microglia for activation, creating a continuous cycle. Created with BioRender.com. MCP, monocyte chemoattractant protein.

FAO can promote mitochondrial oxidative phosphorylation and downstream signaling, accompanied by activation of the TCA cycle, which in turn promotes the M2 polarization of TAMs (15,60,66,68-70). Other previous studies have also shown that the metabolic efficiency of FAO serves an important role in regulating the polarization of TAMs, whereby β-oxidation is closely associated with the phenotype of TAMs (60,70). The peroxisome proliferator-activated receptor (PPAR) system regulates FAO and significantly influences the metabolic reprogramming of TAMs and their polarization towards the M2 phenotype (71,72). Specifically, the PPAR system enhances FAO metabolic efficiency mediated by STAT6 and PPARγ coactivator-1β (73,74).

However, other potentially noteworthy pathways have not been intensively studied. In particular, IFN-γ, GM-CSF and lipopolysaccharide (LPS) are factors that can induce M1 polarization (75). Previous studies have shown that there may be associations between the aforementioned factors and the FAO (76,77). In addition, proposals of regulating FAO by targeting IFN-γ, GM-CSF and LPS to in turn achieve a desired anti-tumor effect have been made (78-81).

PPAR is an indispensable component in the FA metabolic pathway (82). To date, three PPAR isoforms have been identified, namely PPARα, PPARγ and PPARβ/δ. PPARγ serves an important role in lipid synthesis, whilst PPARα and PPARδ mainly regulate oxidative phosphorylation, substrate transport and energy homeostasis (83). PPAR can regulate the M2 polarization of TAM through multiple pathways, which in turn promotes tumor proliferation, angiogenesis and immunosuppression (84).

PPARβ/δ can promote TAM polarization toward M2, tumor invasion and angiogenesis. A previous lipidomic analysis of ovarian cancer ascites has revealed that high concentrations of polyunsaturated FAs (PUFAs), particularly linoleic acid, can function as potent PPARβ/δ agonists in macrophages, thereby promoting the M2 polarization of TAMs (85). Sirtuin 4 (SIRT4) is a member of the SIRT family that can regulate cell proliferation and metabolism. It has been previously shown that upon downregulation of SIRT4 in human hepatocellular carcinoma, TAMs can activate the FAO/PPARβ/δ-STAT3 signaling pathway, which leads to M2 polarization (86,87).

A series of studies have shown that the intact structural PPAR system is required for the regulation of FAO. Caspase-1 activation generates a 41-kDa PPARγ fragment by cleaving PPARγ on Asp64. This fragment can then enter the mitochondria and inhibit medium-chain acyl-CoA dehydrogenase activity, reducing the efficiency of FAO and leading to lipid droplet accumulation, which in turn promotes M2 polarization (88-90). In addition, receptor-interacting protein kinase 3 (RIPK3) is another key factor mediating macrophage necrosis. It has been shown that in human and mouse hepatocellular carcinoma tissues, downregulation of RIPK3 can inhibit caspase-1-mediated PPAR cleavage, promote FAO, polarize TAMs toward the M2 phenotype and enhance tumor immunosuppression (89).

In addition, the FA binding protein (FABP) family serves another important role in FA metabolism, where its intracellular localization is involved in glioma progression (91). It has been previously shown that epidermal FABP is significantly

overexpressed in mouse mammary carcinoma TAMs, which promotes the production of IFN-β by modulating lipid droplets, thereby recruiting immune effector cells and inhibiting tumor progression (92,93). By contrast, adipocyte/macrophage FABP is highly expressed in mouse and human breast cancer TAMs, where it promotes breast cancer cell proliferation and metastasis through the NF-κB/miR-29b/IL-6/STAT3 pathway (92,94). This suggests the different roles of different subtypes of FABP in cancer, where some types can promote tumor growth and metastasis, whilst others have oncolytic effects.

CD36 is a scavenger receptor that mediates lipid uptake, immune recognition, inflammation, molecular adhesion and apoptosis. This protein is a transmembrane glycoprotein and can bind to a variety of ligands, including FAs, to exert its effects (95). TAMs highly express CD36 and extensively utilize FAO for their energy supply. This process promotes mitochondrial oxidative phosphorylation and the production of ROS, leading to the activation of STAT6 and modulation of TAM polarization (66). S100A4 is another well-established pre-metastatic oncoprotein that is primarily expressed by macrophages in the tumor microenvironment. S100A4 has been shown to enhance CD36-mediated FA uptake through the PPARγ pathway, thereby promoting and polarizing TAMs towards the M2 phenotype (96).

Overall, the aforementioned previous observations have demonstrated that FA metabolism serves a role in promoting M2 polarization in TAMs to a certain degree. Therefore, it can be hypothesized that a comparable phenomenon may be present in GAMs. However, it must be emphasized that the existing body of experimental evidence on GAMs is insufficient to substantiate such a hypothesis. Further studies in this area are required for further advancement.

Phospholipid metabolism in TAM. Arachidonic acid (AA) is a membrane phospholipid produced by phospholipase A2 and is released into the cytosol. Known enzymes involved in AA metabolism include cytochrome P450, cyclooxygenase (COX) and lipoxygenase (LOX), which breaks AA down into hydroxyeicosatraenoic acids, prostaglandins and leukotrienes, respectively (97). In addition, AA or phospholipid metabolism in TAM mainly regulates the immune escape and proliferation of tumor cells.

A previous study has shown that TAMs can increase the expression of COX2 and prostaglandin E2 (PGE2) through the PI3K/Akt/mTOR pathway, leading to tamoxifen resistance and enhanced endocrine resistance in breast cancer (98). Meanwhile, PGE2 stimulates angiogenesis, suppresses immune function, promotes cancer cell migration and inhibits CD80 expression on tumor-associated phagocytes, thereby promoting cancer progression (99,100). TAM-derived osteopontin binds to α9β1 integrins, which upregulates COX2 expression, then increases the expression of PGE2 and MMP9 and accelerates angiogenesis (101). Another study showed that blocking the microsomal prostaglandin E synthase-1 and COX2 promoted TAM polarization toward M2 in colon cancer, thereby inhibiting tumor progression (102). Furthermore, it has also been previously shown that 5-LOX serves an important role in TAMs. In a metastatic lung cancer model, 5-LOX-expressing macrophages were observed to promote tumor cell proliferation by upregulating leukotriene B4 expression, whereas 5-LOX-suppressed macrophages exhibited reduced tumor proliferation (103,104). Similarly, reduced 5-LOX expression in human breast cancer TAMs can lead to decreased leukotriene synthesis and reduced effector T-cell recruitment, thereby promoting tumor progression (105).

Triglyceride metabolism in TAMs. Triglycerides are produced by the esterification of three hydroxyl groups on glycerol with three long-chain FA molecules and are involved in anabolism and catabolism. Anabolism is mainly regulated by diacylglycerol O-acyltransferases and monoacylglycerol O-acyltransferases, whilst catabolism is mainly regulated by hormone-sensitive lipase, abhydrolase domain-containing (ABHD)5, adipose triglyceride lipase and monoglyceride lipase (MGLL) (106,107). It has been shown that TAM can affect tumor development by regulating triglyceride metabolizing enzymes, where ABHD and MGLL serve a key role in this process.

ABHD is a key enzyme in triglyceride catabolism whilst also being able to inhibit autophagy and apoptosis in tumor cells (108). A previous study found that ABHD5 can promote the expression of spermine synthase (SRM) in TAMs of human and mouse colon cancer tissues. Spermine promotes apoptosis in tumor cells. Single-cell sequencing results also showed that high expression of ABHD5 in TAMs can promote tumor growth. Therefore, targeting the ABHD5/SRM/spermine axis in TAM may serve as a potential therapeutic strategy for colon cancer (109). Furthermore, it has been shown that ABHD5 in TAMs can increase MMP9 expression through the NF-κB pathway, thereby promoting the lung metastasis of colorectal cancer (110).

MGLL is another important component of the triglyceride catabolic pathway, which hydrolyzes triglycerides into free FAs. It has been previously found in mouse models of colon and breast cancer that MGLL deficiency can cause lipid accumulation in TAMs and promotes endocannabinoid receptor-2/TLR4 activation in TAMs, which enhances immunosuppression and promotes tumor progression (111).

Cholesterol metabolism in TAMs. Cholesterol is an important component of biological membranes. It regulates cell membrane fluidity and participates in various signaling pathways as a solubilizer of other lipids. Cholesterol metabolic reprogramming in TAMs has been previously shown to serve an important role in tumor development through TAM activation and recruitment, whilst promoting M2 polarization. It has been indicated that cholesterol metabolic reprogramming in TAMs mainly focuses on the alteration of the cholesterol efflux pathway. Therefore, targeting cholesterol efflux may be a potential method of controlling or treating cancer (112,113).

An ATP-binding cassette transporter (ABC) is a type of ATP-powered pump that consists of two transmembrane structural domains and two ATP-binding domains on the cytoplasmic side. ABC proteins scavenge surplus cholesterol within cells and regulate the balance of cholesterol to maintain homeostasis (84). Various cancers have been found to have elevated cholesterol levels (114). A recent study discovered that Apolipoprotein A (ApoA1) can enhance the removal of cholesterol from GAMs, decreasing intracellular cholesterol levels; this process was found to activate CD8+ T cells, enhancing anti-tumor immunity in a mouse GBM model (115). In another study, it was discovered that ABC-mediated

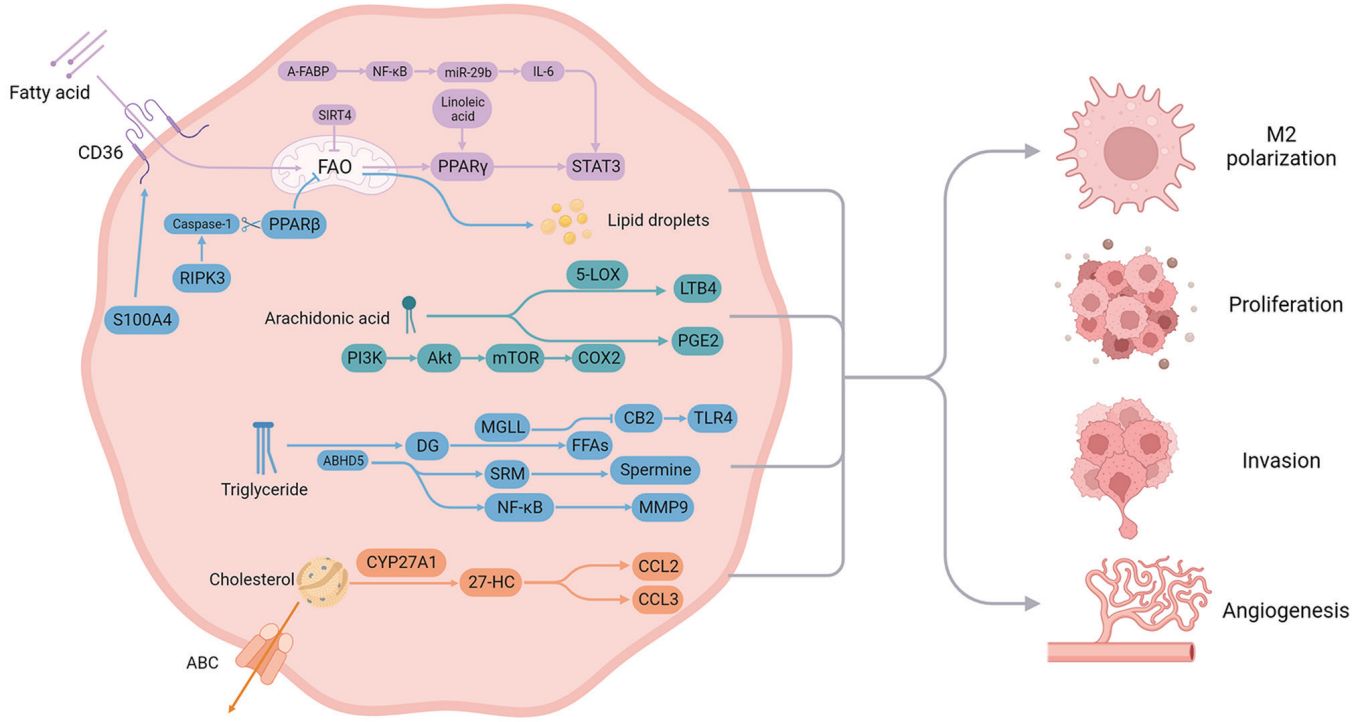

Figure 2. Reprogramming of lipid metabolism in tumor-associated macrophages and its regulatory mechanisms on tumor progression. Fatty acid metabolism regulates tumor progression mainly related to the PPARγ, PPARβ and NF-κB pathways. Arachidonic acid metabolism affects tumor progression mainly through the regulation of 5-LOX and COX2. Key enzymes in triglyceride metabolism associated with tumor progression include ABHD and MGLL. In addition, 27-HC production and catabolism, as well as ABC-mediated cholesterol efflux also have an impact on tumor progression. Created with BioRender.com. All abbreviations used in the figure legend and figure labels are defined in Table SI.

cholesterol efflux from TAM membranes facilitated M2 polarization in a mouse model of metastatic ovarian cancer; this in turn led to IL-4-associated immunosuppression and invasive metastasis, whilst also inhibiting the IFN-γ-induced antitumor effects (116). Studies on bladder cancer and melanoma mouse models have also revealed a similar phenomenon, whereby ABCG1 can facilitate the removal of cholesterol to control the balance of cholesterol within cells. The absence of ABCG1 in mice led to activation of the NF-κB pathway and a transformation of macrophages from M2 to M1, resulting in enhanced direct cytotoxic effects on tumors, which hinders the growth of malignancies (114). However, further studies are required to clarify the effects of cholesterol metabolism in a cell type-specific context.

27-Hydroxycholesterol (27-HC) is a major metabolite of cholesterol that is catalyzed by its cytochrome P450 oxidase (CYP27A1). CYP27A1 is highly expressed in M2 macrophages and activates M2 polarization, thereby promoting tumor progression (117). It has been previously found that CYP27A1 is highly expressed in mouse breast cancer TAMs, whilst the 27-HC catabolic enzyme CYP27B1 is not expressed at high levels in breast cancer cells, a setup that results in the accumulation of 27-HC in the tumor cells. This accumulation of 27-HC in turn promotes the proliferation of the tumor cells and facilitates the expression of several chemokines by the TAMs, including chemokine (C-C motif) ligand (CCL)2 and CCL3, which then recruit monocytes to the tumor site to promote tumor progression (118).

The lipid metabolic reprogramming in TAMs and its regulatory mechanism for tumor progression are shown in Fig. 2.

Metabolite-driven phenotypic changes in TAM

Short-chain FAs (SCFAs). The role of SCFAs in macrophages in inflammation has been extensively studied, but their role in TAMs has remained elusive. Therefore, this section will focus on their role in inflammation and, by extension, their role in tumor regulation.

During the inflammatory response, SCFAs can mediate both pro-inflammatory and anti-inflammatory effects. This phenomenon may be due to the expression and local concentration profiles of the different SCFA receptors and SCFAs themselves, respectively. It has been previously shown that in macrophages, SCFAs (namely butyrate) can bind to and activate free FA receptor (FFAR)3 to downregulate the levels of proinflammatory factors (including inducible nitric oxide synthase, TNF, MCP-1 and IL-6), thereby exerting anti-inflammatory effects (119,120). In addition, during airway inflammation, SCFAs can downregulate IL-8 expression by targeting FFAR2 and FFAR3 in macrophages, thereby exerting an anti-inflammatory effect and improving patient symptoms (121). These results suggest that SCFAs can exert potent anti-inflammatory effects that are realized through FFAR2 and FFAR3. Therefore, inhibitors of FFAR2/3 may mediate both proinflammatory and anti-tumor effects, to inhibit tumor progression. However, other studies have found that SCFAs can exert proinflammatory effects. It has been previously found that when FFAR2/3 is activated, it further activates mTOR, PI3K and MAPK signaling pathways downstream to mediate proinflammatory effects (122,123). In addition, SCFAs (acetate) were found to upregulate the production of proinflammatory cytokines and chemokines,

such as CXCL1/2 and IL-6, by activating FFAR3/FFAR2 and ERK1/2 downstream. These aforementioned studies suggest that SCFAs can have opposite roles in inflammation. This phenomenon is associated with the local concentration of SCFAs.

It has been demonstrated that SCFAs can also regulate inflammation through the binding of hydroxycarboxylic acid receptor 2 (GPR109A), a butyrate receptor present in intestinal epithelial cells and immune cells that serves an important role in inflammation and immunity. Stimulation with IFN-γ has been shown to upregulate GPR109A expression in macrophages (124). GPR109A activation is involved in IL-8 and IL-10 production downstream, which affects regulatory T cells to reduce inflammation (125-128). Therefore, GPR109A may exert anti-inflammatory and immunomodulatory effects. However, to the best of our knowledge, there are relatively few relevant studies in TAMs, meaning that the relationship between GPR109A and tumors requires further exploration.

SCFAs can not only exert anti-inflammatory effects through signaling but also participate in inflammatory regulation by inhibiting histone deacetylase (HDAC). In macrophages, SCFAs (propionate and butyrate) have been observed to exert anti-inflammatory effects by inhibiting the TNF and NF-κB signaling pathways, in addition to inhibiting HDAC and promoting IL-10 production (129-131). However, it remains elusive which HDAC is inhibited and further studies are warranted.

To conclude, SCFAs serve a role in controlling inflammation in macrophages mainly through two primary modes of behavior. One method likely involves attaching to G protein-coupled receptors (such as FFAR2/3 and GPR109A) to trigger signaling pathways further downstream. Another method may involve the inhibition of HDAC once it has entered the cell, resulting in anti-inflammatory effects. Therefore, it would be of benefit to study whether a similar mechanism exists in GAMs in future studies, where SCFAs can potentially exert anti-inflammatory effects in addition to promoting tumor growth.

Long-chain PUFAs. Omega-3 FAs are a family of long-chain PUFAs that also includes α-linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). G-protein coupled receptor 120 (GPR120) is a G-protein coupled receptor that is involved in the regulation of metabolic, endocrine and immune functions. GPR120 can be activated by long-chain PUFAs (132). It has been previously shown that GPR120 is highly expressed in adipose tissue and proinflammatory macrophages in mice fed a high saturated fat diet, where the use of fish oil containing DHA and EPA can exert anti-inflammatory effects through GPR120 (133). In addition, mice fed an omega-3 diet had a significant reduction in the number of M2-like TAMs and expression of M2-associated cytokines, chemokines and growth factors in tumor tissues, compared with those in mice fed on an omega-6 diet (134). Data from another previous study corroborated this finding, as DHA was found to combine with ethanolamine to generate DHEA in breast cancer cells, reducing the secretion of CCL5 and affecting TAM recruitment and tumor progression. In addition, omega-3 FAs have been found to inhibit prostate cancer progression through a variety of mechanisms, including inhibition of COX2-mediated PGE2 formation, LOX activity, TLRs, formation of pro-resolvin metabolites, activation of PPARγ and inhibition of NF-κB (135).

Fig. 3 briefly shows that SCFAs and long-chain PUFAs can drive phenotypic changes in macrophages, which in turn can regulate inflammation and tumor progression.

5. Possibility of lipid metabolic modulation-based therapy

Traditional views suggest that M1-like TAMs prefer glycolysis as an energy source, whilst M2-like TAMs favor FAO (66,136). Therefore, regulating FAO may offer a strategy to inhibit tumor progression.

S100A4 is a well-known pre-metastatic oncoprotein that is primarily expressed by macrophages in the tumor microenvironment. S100A4 can enhance CD36-mediated FA uptake through the PPARγ pathway, promoting the polarization of TAMs towards the M2 phenotype (96). Previous studies have shown that injecting S100A4-knockout macrophages can significantly reduce tumor growth in mice (71). Similarly, using VT1021 to block CD36 lipid uptake was found to inhibit the M2 polarization of TAMs, thereby suppressing cancer (137,138).

The caspase-1/PPARγ/FAO axis is another crucial target for cancer therapy. A study has previously found that the caspase-1 inhibitor (Tyr-Val-Ala-Asp) can inhibit breast cancer progression by blocking caspase-1-mediated PPARγ cleavage (90). In addition, RIPK3 deficiency was found to inhibit caspase-1-mediated cleavage of PPARα and PPARγ in TAMs, leading to increased FAO and promoting hepatocellular carcinoma. This process can be inhibited by using the RIPK3 agonist decitabine (90). It has also been shown that lipid metabolism can be reprogrammed and TAM polarization reversed by blocking FAO using etomoxir (66,139).

Rofecoxib, a specific COX-2 inhibitor, has been documented to restore the adhesion and antitumor activity of TAMs (140). Celecoxib was also observed to exert similar effects (141). Another study previously showed that a selective COX-2 inhibitor, LM-1685, significantly reduced the level of arginase 1 in M2 macrophages, thereby inhibiting tumor progression (142).

Zileuton, a 5-LOX inhibitor, was found to decrease MMP7 expression whilst reducing TAM migration and infiltration (143,144).

A recombinant tumor lysing adenovirus carrying ApoA1 was previously designed to overexpress ApoA1 in the tumor microenvironment. This led to an increase in cholesterol removal from GAMs and a significant decrease in cholesterol levels within GAMs. As a result, GAMs were able to regain their ability to engulf and present antigens, which enhanced the effectiveness of $CD8^+$ T cells in eliminating GBM. Furthermore, this treatment also induced a long-lasting immune response (115). In another study, ATR101, an inhibitor of ABC, was found to inhibit the M2 polarization of TAM by inhibiting cholesterol efflux from TAM, leading to cholesterol accumulation in cells (145).

Therapies that have been experimentally proven to be feasible through metabolic modulation are listed in Table I.

However, to the best of our knowledge, few therapies targeting the metabolic pathway of GAMs are available at

Table I. Possible therapies based on lipid metabolic modulation.

Target	Drug/intervention	Mechanism	Tumor type	(Refs.)
S100A4	S100A4-KO	Inhibition of IL-4/S100A4/PPARγ/CD36/FAO	Breast cancer	(71,96)
CD36	VT1021	Inhibition of FA intake/FAO	GBM	(137,138)
Caspase-1	YVAD	Inhibition of caspase-1/PPARγ/FAO	Breast cancer	(90)
RIPK3	Decitabine	Inhibition of caspase-1/PPARγ/FAO		(89)
FAO	Etomoxir; 25-HC	Inhibition of FAO	Hepatocellular carcinoma	(66,139)
COX-2	Rofecoxib/Celecoxib	Restoration of the adhesion and antitumor activity of TAM	Head and neck squamous cell carcinoma/Breast cancer	(140,141)
	LM-1685	Reduction of Arg1 levels in M2	Colon carcinoma	(142)
5-LOX	Zileuton	Reduction of migration and invasion of TAM	Lung cancer	(143,144)
ApoA1	AdV^{APOA1}	Increase of cholesterol removal from GAMs	GBM	(115)
ABC	ATR101	Inhibition of the efflux of TAM cholesterol	Lung cancer	(145)

TAM, tumor-associated macrophage. All abbreviations used in the table are defined in Table SI.

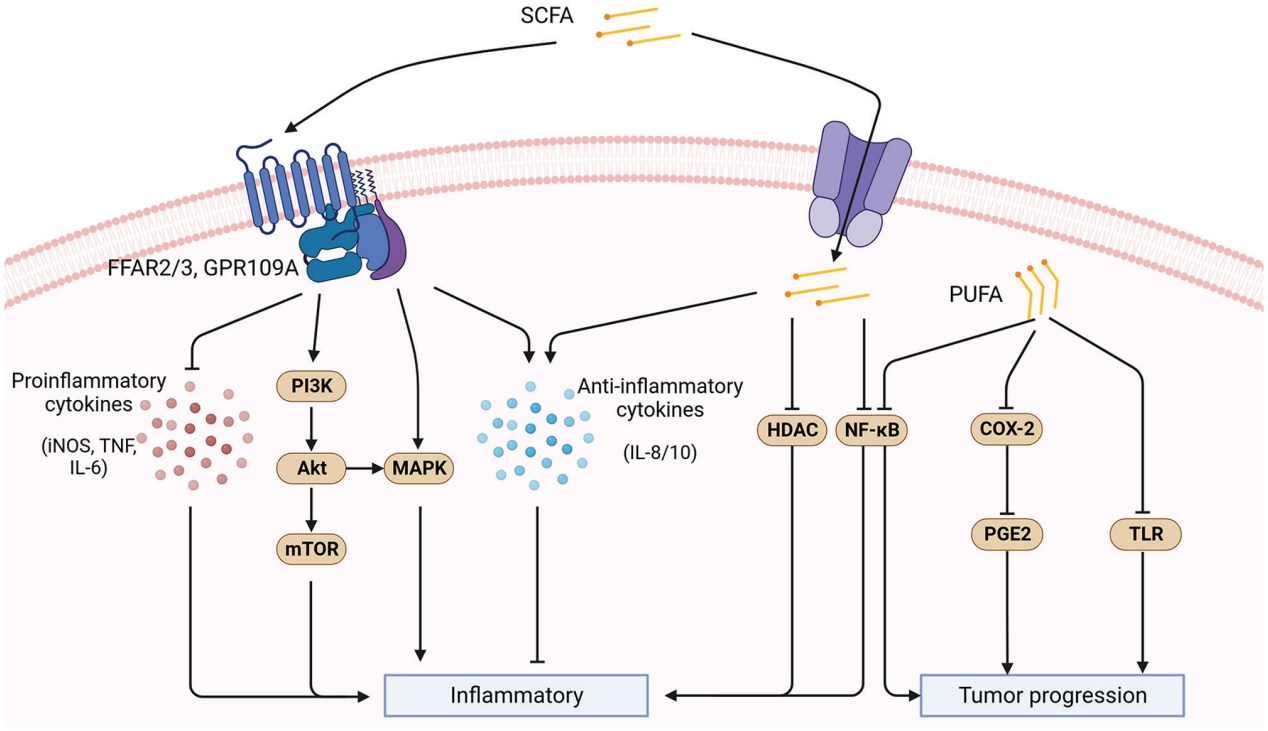

Figure 3. Metabolite-driven phenotypic changes in tumor-associated macrophages. SCFAs and long-chain PUFAs drive macrophage phenotypic changes that modulate inflammation as well as tumor progression. Created with BioRender.com. All abbreviations used in the figure legend and figure labels are defined in Table SI.

present and the aforementioned drugs have not yet been tested in clinical trials in patients with glioma or animal models of glioma. It remains speculative whether similar drugs may be effective in GAMs. Further research is needed to explore these possibilities.

6. Summary and prospect

GAMs play an important role in the tumor microenvironment, influencing glioma growth, invasion and angiogenesis through specific signaling molecules like MCP-1, GM-CSF and VEGF. They exhibit high plasticity, allowing them to differentiate into various phenotypes under different stimuli, adapting their metabolic pathways to support tumor progression.

While recent studies have highlighted significant alterations in lipid metabolism within TAMs, literature on lipid metabolic reprogramming in GAMs remains scarce. More in-depth studies focusing on GAMs are essential to understanding their unique metabolic adaptations and roles in glioma. Targeted therapies modulating lipid metabolism in GAMs hold promise for inhibiting tumor progression. Inhibiting FAO and targeting pathways involving COX-2 and

PGE2 have shown potential in preclinical studies. Developing drugs specifically modulating GAM metabolic pathways may provide more effective treatment options for glioma.

Future research should focus on specific drug development for GAMs, targeting lipid metabolism and other pathways unique to these cells. Testing potential metabolic modulation drugs in preclinical or clinical trials is urgently needed to evaluate their efficacy and safety. Considering the complexity of tumor metabolic pathways, multi-targeted therapeutic strategies may enhance therapeutic outcomes by disrupting the tumor's metabolic network comprehensively.

In addition, identifying and validating biomarkers for monitoring metabolic reprogramming and therapeutic response is crucial. Biomarkers will help optimize treatment regimens, improve efficacy and provide critical information for personalized therapy. Further research into GAM metabolic reprogramming mechanisms will provide a foundation for developing novel therapeutic approaches, potentially in combination with existing treatments like immunotherapy and chemotherapy.

By addressing these areas, future research can advance the understanding of GAM metabolism, leading to effective therapies for glioma, ultimately improving patient outcomes.

Acknowledgements

Not applicable.

Funding

This research was funded by the National Natural Science Foundation of China (grant no. 82203683), the National Key Research and Development Program of China (grant no. 2023YFC2510001) and the Chinese Society of Clinical Oncology Foundation-Zai Lab Cancer Treatment Research Foundation (grant no. Y-zai2021/qn-0217).

Availability of data and materials

Not applicable.

Authors' contributions

Writing-original draft preparation: YM and YH; writing-review and editing: FH and KS; visualization: YM and YH; supervision: FH and KS. All authors have read and agreed to the published version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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