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Astrocyte, Lipid Metabolism in Alzheimer's Disease and Glioblastoma

Xu Zhang*, Ping Lu and Xiaorong Shen

Institute for Reproductive Health, Shanghai Institute for Biomedical and Pharmaceutical Technologies, Shanghai, China

Corresponding author: Xu Zhang, Institute for Reproductive Health, Shanghai Institute for Biomedical and Pharmaceutical Technologies, Shanghai, China

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Abstract

The brain is a central key organ of the body containing the second highest lipid content only after adipose tissue. Lipids as the main structural components of biological membranes play important roles in a vast number of biological processes within the brain such as energy homeostasis, material transport, signal transduction, neurogenesis and synaptogenesis, providing a balanced cellular environment required for proper functioning of brain cells. Lipids and their metabolism are of great physiological importance in view of the crucial roles of lipids in brain development and function. Astrocytes are the most abundant glial cells in the brain and involved in various processes including metabolic homeostasis, blood brain barrier maintenance, neuronal support and crosstalk. Disturbances in lipid metabolism and astrocytic functions may lead to pathological alterations associated with numerous neurological diseases like Alzheimer's Disease (AD) recognized as the most frequent cause of dementia leading to major progressive memory and cognitive deficits as well as Glioblastoma (GBM) known as the most aggressive malignant brain tumor with a poor prognosis. Herein, we not only review the level and role of altered lipid metabolism in correlation with astrocytic function and astrocyte-neuron crosstalk in AD and GBM, but also discuss important lipid-related metabolites and proteins participating in possible mechanisms of pathologically dysregulated lipid metabolism, offering potential therapeutic targets in targeted molecular therapies for AD and GBM.

Keywords: *Astrocyte, Lipid metabolism, Alzheimer's disease, Glioblastoma*

Introduction

The brain is a central and pivotal organ highly enriched in lipids (constituting 50% to 60% of brain dry weight) [1], the major biomacromolecules characterized with poor water-solubility and good solubility in non-polar organic solvent, and is regarded with the second highest lipid content next to the adipose tissue [2]. Lipids are a class of fatty substances differing in overall structure, molecular weight, head group configuration, carbon-carbon bond formation and other factors, among which fatty acids, phospholipids, sphingolipids, sterol lipids and triglycerides are the five main brain lipid classes [3], serving as basic structural components of biological membranes and participating in a broad variety of physiological events, including chemical energy generation and storage, substance transport, cellular signaling, neural differentiation, axonal regeneration, synaptogenesis, synaptic plasticity and brain development [4-14].

The brain consists of neurons and non-neuronal cells such as glial and vascular epithelial cells, of which astrocytes represent the most abundant glial cells [15,16]. Astrocytes mediate diverse biological activities under physiological conditions, including structural and energy support for neurons [17,18], neuronal development and maintenance [19,20], formation, function and plasticity of synapses [21,22], modulation of synaptic transmission [22], metabolomic homeostasis [23] as well as integrity of the Blood-brain Barrier (BBB) [24,25] which is a semipermeable membrane regulating solute exchange between blood and brain parenchyma to maintain CNS homeostasis and function and partially separating local lipid metabolism of the brain from that of the body [25-33]. Apart from the well-known enzymatic capacity of glycogenesis and glycolysis [34-38], equipment of lipid metabolism also exists in astrocytes, providing membrane components for neurons and other glial cells [39,40] and playing fundamental roles in astrocyte function including membrane fluidity, energy generation and intercellular signaling. Emerging evidence has shown that astrocytic usage of lipids stored in droplets via mitochondrial β-oxidation fulfills crucial energy-providing and neuroprotective roles in the brain [18,41], whereby disruption in lipid metabolism, structure and function of astrocytes may lead to pathogenic mechanisms underlying an array of neurological diseases.

Lipid Classification in the Brain

Fatty Acids

As one of the most well-known lipid class, Fatty Acids (FAs), the essential monomeric constituents of all lipids, account for almost 20% of the energy source through oxidation, for which astrocytes as the major provider of fatty acid β-oxidation may be the essential place [42-44]. Additionally, fatty acids can also be utilized by astrocytes for producing ketone bodies under particular conditions (e.g. ischemia), serving as a substrate for neuronal energy production-related Tricarboxylic Acid (TCA) cycle [45]. Fatty acids permeate the Blood-brain Barrier (BBB) via passive (dissociation from albumin carriers, binditheng to luminal membrane which belong to endothelia

cells, ATP-independent release and entrance into the cytosol) and/or protein-mediated transport (e.g. Fatty Acid Transport Proteins (FATPs), fatty acid translocase/CD36 (FAT/CD36), Fatty Acid Binding Proteins (FABPs) and caveolin-1) [46,47]. Fatty acids can be further divided into unsaturated and saturated fatty acids, from which the former subclass contains Monounsaturated Fatty Acids (MUFAs) and Polyunsaturated Fatty Acids (PUFAs), while the latter comprises palmitic acid, stearic acid and others [48,49]. PUFAs are highly enriched in the brain, with 3- to 4-fold level over other tissues [50,51]. What's more, essential PUFAs play key roles in brain activity and development [52,53], in which the ω-3 Docosahexaenoic Acid (DHA) are particularly involved in synaptogenesis, neurogenesis and neuroprotection in the brain [54-57].

Phospholipids

As the most abundant constituent of major categories of membrane lipids [58,59], Phospholipids (PLs) generally consist of two hydrophobic tails of fatty acids differing in length and a backbone-attached hydrophilic phosphate group [60-62].

Phospholipids, which are synthesized in the mitochondria and Endoplasmic Reticulum (ER) tracing from diacylglycerol and phosphatidic acid, spontaneously aggregate into the formation of bimolecular layers in aqueous environments on account of configuration and amphipathic property [63]. Phospholipids can be classified into glycerophospholipids and phosphosphingolipids, of which glycerophospholipids are the prominent glycerol-based class of lipid molecules which can be further subclassified into subtypes such as Phosphatidic Acid (PA), Phosphatidylcholine (PC), Phosphatidylethanolamine (PE), Phosphatidylglycerol (PG), Phosphatidylinositol (PI) and Phosphatidylserine (PS) on the basis of variation in hydrophilic head groups and participate in a variety of physiological activities in the brain [59,64,65]. Moreover, fates of brain cells are influenced by exposure to different phospholipids, such as differentiation of neural cells into astrocytes was promoted and inhibited with PE and PC treatment, respectively [66].

Sphingolipids

Sphingolipids containing sphingoid bases (also known as long-chain bases) and a set of aliphatic amino alcohols that includes sphingosine are mainly synthesized in Endoplasmic Reticulum (ER). Sphingolipids comprise a large group of lipid molecules through compounding with different functional groups, such as ceramide (functional group of single hydrogen atoms) and Sphingomyelin (SM) (functional groups including phosphocholine) with regards to structural composition, functioning as building blocks of membranes (e.g. lipid rafts) [67] and playing fundamental roles in formation and regulation of synapse structure and function [68], cell recognition, signal transmission and inflammatory regulation of astrocytes [69-72]. Besides, sphingolipid metabolites have also been discovered to exert regulatory roles in autophagy, cancer cell growth, response to DNA damage and inflammation [73-75].

Sterol Lipids

Sterol lipids include numerous organic molecules, of which cholesterol with four hydrocarbon rings is the main part. Cholesterol can be synthesized in ER by all nucleated cells, while over 70% of total body cholesterol are provided by the diet [76], namely the cholesterol absorbed in the gut transfers into the liver and then spreads through the body. What is noteworthy is that the brain, unlike other organs, makes its own cholesterol because of effective prevention of peripheral cholesterol exchange between brain tissue and plasma cholesterol-carrying lipoproteins by the BBB [77-79]. In brain tissue, *de novo* synthesis of cholesterol is mainly performed in astrocytes which are considered as the main cholesterol producer in the brain [80], though the majority of sterol is synthesized in oligodendrocytes in developing brain and has an association with myelination [81] and oligodendrocytes, besides, cholesterol can also be synthesized in many other cell types [82-84]. Apart from *de novo* synthesis [85], brain cells are able to acquire cholesterol from neighboring cells through the absorption of cholesterol-laden lipoproteins (e.g. Apolipoprotein E (APOE)) in a receptor-mediated way [86,87], in which lipoprotein synthesis for cholesterol transport occurs in astrocytes [88]. With abundant existence in myelin and lipid membranes [81], cholesterol fulfills vital roles in the brain, including BBB integrity, organization of lipid rafts (discrete microdomains present in the external leaflet of plasma membrane), regulation of cell membrane flexibility (through interaction with neighbouring phospholipids) and localization and activity of diverse membrane proteins (e.g. membrane receptor and transporter proteins), axonal guidance, formation and maintenance of synapses and dendrites, synaptic membranerelated fluidity and ion channel function, glucose transport, intracellular signaling and other important neuronal functions [84,89-103].

Triglycerides

As the major form of FA deposition and the optimal form of FA triesters of glycerol, Triglycerides (TGs) are essential ingredients of glycerolipid synthesis by assembling with other glycerol molecules [104]. Triglycerides mainly generated in the adipose tissue and liver can reach other tissues with the package into lipoproteins containing a hydrophilic exterior and a hydrophobic lipid core, including chylomicrons, Very-lowdensity Lipoproteins (VLDL), low-density lipoproteins (LDL), very-high-density lipoproteins (VHDL) and high-density lipoproteins (HDL) only which can cross the BBB [105-108]. Additionally, apolipoprotein E (ApoE) and apolipoprotein J (ApoJ), the most abundant apolipoproteins synthesized in astrocytes, serve as receptor ligands on HDL [109-111] and play fundamental roles in lipid metabolism-associated structural support, enzyme activity and substrate delivery [110,112-114].

Astrocyte-Neuron Coupling of Lipid Metabolism

In humans, the brain representing, on average, merely 2% of total body weight consumes approximately and over 20% of energy substrates during quiet waking and diverse tasks, respectively [115,116], which depends on relatively efficient metabolic coupling between astrocytes and neurons. Physiologically, astrocytes are considered primarily as glycolytic cells with a large enzymatic capacity for glycolysis [115,117,118], whereas neurons are predominantly oxidative [119-121]. Besides the glucose metabolism in which astrocytes participate in the delivery of blood-derived glucose to neurons as an obligatory energy fuel, glycogen storage and

activitydependent L-lactate production as a metabolic substrate for neurons during aerobic glycolysis [115,122-124], astrocytes-neuron coupling of lipid metabolism has also been suggested to occur as a response to neuronal activity in protection of neurons from lipotoxicity [125,126]. This is a mechanism proposing that L-lactate-derived *de novo* synthesis of free fatty acids (FFAs) in overstimulated neurons is triggered during astrocyte-neuron L-lactate shuttle (ANLS), resulting in excess FFAs in association to lipotoxicity-related reactive oxygen species (ROS) and lipid peroxidation chain reaction [127], peroxidized FAs with devastating effects [127] are then transferred from hyperactive neurons to astrocytes via apolipoprotein E-positive lipid particles, where they are directly stored in lipid droplets (LDs) [125,126,128] which are dynamic organelles possessing a core of neutral lipids (e.g. cholesterol esters (CEs) and triacylglycerides (TAGs)), influencing fatty acid breakdown for energy production [129] and buffering excess FFAs to prevent lipid accumulation [130] as well as utilized as an energy substrate in β-oxidation [126] (Figure 1).

AD

With the worldwide increase in longevity, Alzheimer's disease (AD) as the most common form of senile dementia is rapidly becoming a major health problem [131,133]. AD is a devastating irreversible neurodegenerative disease clinically defined by memory loss, neuropsychiatric abnormalities, cognitive impairment, behaviour deficits and progressive decline of self-care capacity [134-136] as well as pathologically characterized by extracellular amyloid-ß (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated microtubuleassociated protein tau [137-139]. Moreover, accumulation of lipid granules in glia, besides notorious Aβ deposition and tau aggregates, was noticed with the examination of Auguste Deter's brain (the first described AD patient), initially establishing a possible involvement of perturbations of lipid metabolism in AD pathology [140,141]. Altered lipid metabolism has also been further described with important roles in AD pathogenesis [142-151].

Recent AD pathology-related lipidome studies have demonstrated changes in content of numerous lipids (Table 1). Substantial differences in fatty acid levels were observed in AD brain tissues [152,153], including a decrease in levels of docosahexaenoic acid (DHA) present in frontal cortex gray matter [154] and hippocampus [155] to which damage correlates with impaired learning and memory [156], suggesting a dysregulation of fatty acid

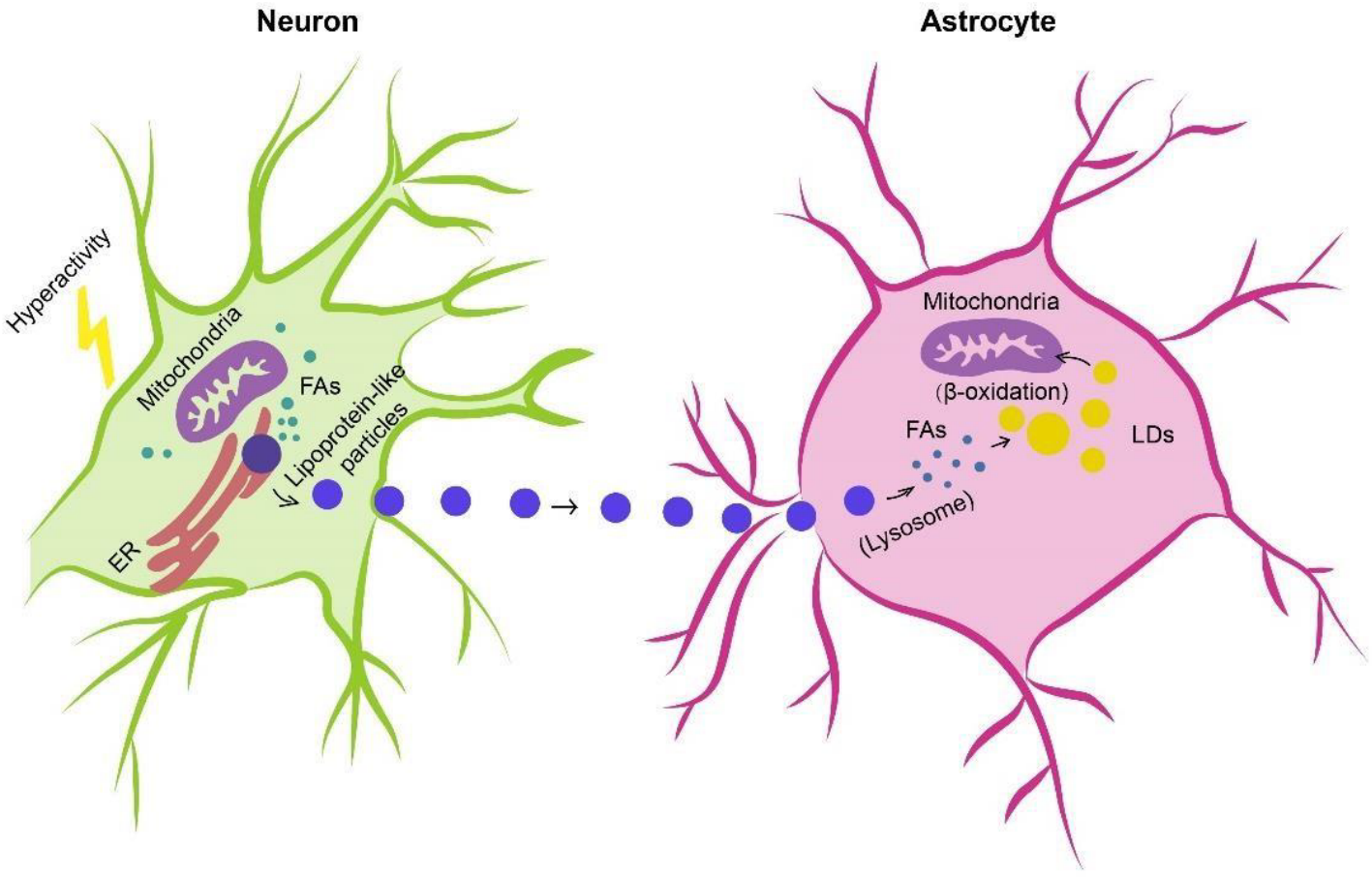

Figure 1: Astrocyte-Neuron coupling of lipid metabolism. Excess fatty acids produced in hyperactive neurons are transferred via lipid particles associated with APOE to astrocytes, where fatty acids are delivered to lipid droplets after endocytosis of neuron-derived lipid particles, detoxified as a means of neuron protection under conditions of enhanced activity as well as consumed by mitochondrial oxidation (e.g. β-oxidation). FAs, fatty acids; APOE, apolipoprotein E; LDs, lipid droplets.

Table 1: Summary of lipid changes in AD.

Lipids			Tissue	Changes in AD	Ref
Fatty acids	Omega-3 fatty acids	DHA	Brain; CSF; Circulation	↓	[176-180]
			MFG	↑	[179]
			FCx	↓	[181]
		EPA	Brain; Circulation	↓	[180]
			MFG	↓	[179]
		DPA	Brain	↑	[182]
		ALA	Plasma	↑	[183]
	Omega-6 fatty acids	AA	Brain; CSF	↑	[177,184,185]
			MFG	↓	[179]
			HPC	↓	[186]
		LA	Brain; Plasma	↓	[179,187]
	Saturated fatty acids		Brain; CSF	↑	[176]
	Eicosanoids	PG	Brain	↑	[188]
Phospholipids	Phosphatidylcholine (PC)	Total PC lipids	Brain	↓	[189]
		PC-EPA	CSF	↓	[190]
		PC-DHA	Plasma	↓	[191]
		PC-EPA	Plasma	↓	[191]
	Phosphatidylethanolamine (PE)	Total PE lipids	HPC	↓	[186]
		PE-SA	HPC	↓	[192]
		PE-OA	HPC	↓	[192]
		PE-AA	HPC	↓	[192]
		PE-DHA	HPC	↓	[192]
	Phosphatidylserine (PS)	Total PS lipids	Occipital lobe; Inferior parietal lobule	↓	[193]
Sphingolipids	Ceramides (CM)	Total CM lipids	Brain	↑	[194]
	Sphingomyelin (SM)	Total SM lipids	CSF	↓	[195]
Triglycerides		Total TG lipids	Serum	↓	[196]
		Polyunsaturated TG	Brain	↓	[197]
Sterol lipids	Cholesterol		Brain	↓	[198]
	Cholesterol precursors		Brain	↑	[198]
	Total oxidized cholesterol		Brain	↑	[199]

PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; CM, ceramides; SM, sphingomyelin; TG, triglyceride; AA, arachidonic acid; ALA, alpha-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; LA, linoleic acid; OA, oleic acid; SA, stearic acid; PG, prostaglandin; CSF, cerebral spinal fluid; FCx, frontal cortex; HPC, hippocampus; MFG, medial frontal gyrus;↑; increased from control ↓; decreased from control.

metabolism and may potentially marking this neurodegenerative disease [157]. Cholesterol accumulation observed in senile plaques and influenced brain regions from AD patients [158] has been reported in association with region-specific synapse loss [159]. A causal relationship between hypercholesterolemia and dysfunctional cholinergic system, cognitive impairments and pathology of amyloid and tau protein has been also demonstrated [160,161], further supporting important roles of disturbed cholesterol metabolism in AD. What's more, detection of elevated cholesterol esters was performed in lipid raft-like mitochondria-associated ER membranes (MAMs) [162] of which hyperactivity leads to cholesterol retention and synapse loss and correlates with cognitive deficits [163] and in which accumulated cleaved products of Amyloid Precursor Protein (APP) cause mitochondrial dysfunction, interruption of cellular lipid homeostasis and membrane lipid alterations generally observed in AD pathogenesis [164,165]. Mitochondrial dysfunction, accompanied with increased oxidative stress, in neurons induces a lipid transfer to nearby astrocytes in which lipid droplets accumulate, in turn, mitochondrial dysfunction in glial cells can be caused by accumulation of peroxidated lipids and oxidative stress, contributing to neurodegenerative processes [166-168]. Growing evidence has supported nonnegligible roles of phospholipids and sphingolipids in AD pathogenesis and progression, with studies reporting that phospholipids and sphingolipids, together with acylglycerols, fatty acids and sterol lipids, present significant content changes in AD brain tissues [154,169-175].

APOE

In comparison with early-onset familial AD (EOFAD), late-onset AD (LOAD) accounts for approximately 95% of all AD cases [200,201], in which genetic predisposition, after aging, plays major roles in the onset of AD. As the strongest risk factor for LOAD, apolipoprotein E (APOE) is the main lipoprotein in the brain and plays pivotal roles in brain lipid metabolism, membrane remodelling and neuronal growth and repair [202-206]. APOE mainly produced by astrocytes is released into extracellular space where essential lipids (e.g. cholesterol) are delivered to neurons adopting APOE-bound cargo through APOE receptors expressed on the neuronal surface [202]. In addition to the capacities of Aβ binding and influencing Aβ aggregation and clearance [204,207], APOE participates in indirect regulation of Aβ metabolism through interactions with receptors (e.g. low-density lipoprotein receptorrelated protein 1 (LRP1)) [206,208-213]. Critical and isoform-specific role of APOE has also been demonstrated in formation of intraparenchymal Aβ deposits in amyloid precursor protein (APP) transgenic mice [214-217]. APOE exists with 3 different alleles namely APOEε2, APOEε3 and APOEε4, translating to 3 protein isoforms termed APOE2, APOE3 and APOE4, of which APOE4 present in approximately 14% of worldwide populations [205,218] is the most prevalent genetic risk factor for AD [219-222]. A single amino acid difference between APOE3 and APOE4 (Cys 112 Arg) brings about a conformational change influencing the binding to Aβ, lipids and apolipoprotein receptors [223]. APOEε2 considered as a protective genetic factor associated with reduced risk for AD and late age at onset [219,224] has been reported to orchestrate differences in lipidome and transcriptome profiles of postmortem AD brain [218,225]. Conversely, APOEε4 markedly elevates AD risk [219,224], in which heterozygous and homozygous APOEε4 allele may increase AD risk by 3 and 12 times, respectively [223], accelerates disease course and worsens brain pathology [226-228]. A correlation between APOE4 genotype and increased expression of Serpina3n, a gene expressed by astrocytes and considered as a strong marker of reactive and aged astrocytes in the brain [229,230], has been reported with a possible contribution to the pathogenic role of APOE4 in AD [231]. Higher APOE4 level in Cerebral Spinal Fluid (CSF) of AD patients compared with that of control individuals has been connected to accelerated Aβ oligomer accumulation [232]. APOE4 may retard Aβ clearance and favour Aβ deposition via binding to Aβ after specific fragmentation [205,223]. APOE4 was reported to trap ATP-binding cassette transporters A1 (ABACA1) (a regulator of APOE4 lapidation in protection from lipidpoor ApoE4 aggregation) in late rather than recycling endosomes and alter ABACA1 membrane trafficking in astrocytes, which might result in reduced Aβ degradation [233]. Insufficient Aβ clearance also affects accumulation in synaptic cleft, contributing to disruption of hippocampal long-term synaptic plasticity related to learning and memory abilities [234]. APOE4 is internalized in APOE receptors such as low-density lipoprotein receptor-related protein 1 (LRP1) which is also a member of Aβ receptors including very low-density lipoprotein receptor (VLDLR) and apolipoprotein E receptor 2 (APOER2) [209]. Additionally, APOE4-induced reduction of dendritic spine density in mice [234,235] is consistent with pathological changes (dendritic spine density reduction and synapse loss) observed in brain tissues from AD APOEε4-carriers [236]. APOE4 causes widespread AD phenotypes-associated cellular and molecular alterations in brain cells derived from human induced pluripotent stem cells (iPSCs), among which increased Aβ secretion as well as impaired Aβ uptake and cholesterol accumulation occurred in neurons and astrocytes, respectively [237]. Astrocytic lipid metabolism is influenced by APOE4 [237,238], in which increased fatty acid unsaturation and lipid droplet (LD) accumulation were found in APOE4-expressing human iPSC-derived astrocytes, which can be restored to basal state through supplementation of culture medium with choline (a soluble phospholipid precursor) [238]. Furthermore, APOE4 can also impair astrocyte-neuron coupling of fatty acid metabolism via decreased fatty acid (FA) sequestering in LDs, reduced LD transport efficiency and lowered FA oxidation, resulting in lipid accumulation in astrocytes and hippocampus, diminished abilities of astrocytes in neuronal lipid elimination and FA degradation, accelerated lipid dysregulation and increased AD risk [239].

ACSBG1 and ACSL6

Cellular accumulation and activation of fatty acids (FAs) either synthesized *de novo* or taken up from diets require the ATP-dependent reaction catalyzed by acyl-CoA synthetases (ACSs), a family of enzymes initiating FA metabolism-related reactions through ligation to coenzyme A (CoA) [240]. ACS enzyme family contain various members differing in distribution and fatty acid substrate preference [241], among which only two show specific enrichment in the brain, ACSBG1 and ACSL6 [242,243], suggesting their potentially particular roles in modulation of brain fatty acid metabolism. ACSBG1, almost exclusively expressed in astrocytes, have preferences for a wide range of substrates containing long-chain saturated and unsaturated fatty acids [244,245]. ACSBG1 knockdown *in vitro* results in decreased ACS enzymatic activity and FA oxidation [245], indicating its participation in astrocytic FA oxidation, however, clear roles of ACSBG1 in brain function and/or dysfunction still remain poorly understood. ACSL6 showing high expression in the brain was reported to be downregulated in age-related neurodegenerative diseases [246,247] and in direct correlation with neurite outgrowth [248-252]. With high substrate preference for docosahexaenoic acid (DHA) of which low levels are associated with AD pathophysiology [253], ACSL6 has been revealed with key roles in regulating DHA incorporation into neuronal membranes using *Acsl6* deficient mice with significant reduction in DHA-containing phospholipids and impaired memory [254,255]. Critical roles of ACSL6 in brain DHA retention and neuroprotection are further supported by findings that ACSL6 depletion led to markedly reduced levels of brain membrane phospholipid DHA, spatial memory deficits, hyperlocomotion, increased cholesterol biosynthesis and age-related neuroinflammation [256]. What's noteworthy is that astrocyte-specific depletion had minimal influence on membrane lipid composition [256] in consideration of ACSL6 enrichment in astrocytes [240,257-261], possibly due to the expression of a DHA-nonpreferring variant [251,262-267] and enrichment of Y-gate domain rather than DHA-preferring F-gate domain in astrocytes [251].

ATAD3A

ATPase family AAA-domain containing protein 3A (ATAD3A), a nuclear-encoded mitochondrial membrane-anchored protein belonging to the AAA+-ATPase protein family and simultaneously interacting with inner and outer mitochondrial membranes, is implicated in a variety of biological processes including stability maintenance of mitochondrial DNA (mtDNA), regulation of mitochondrial dynamics and cholesterol metabolism [268-270]. ATAD3A deficiency led to neurodegenerative phenotypes in association with cholesterol elevation, downregulated expression of cholesterol metabolism-related genes [269], optic atrophy and axonal neuropathy [271]. Oligomerization and accumulation of ATAD3A at MAMs, lipid raft-like ER subdomain rich in sphingomyelin and cholesterol [272] and associated with diverse metabolic functions such as lipid metabolism, mitochondrial function and calcium homeostasis [273-277], have been discovered in both mouse models and postmortem human brain tissues of Alzheimer's disease [278]. Aberrantly oligomerized ATAD3A leads to cholesterol accumulation via expression inhibition of cholesterol clearancemediating cytochrome P450 family 46 subfamily A member 1 (CYP46A1) located on MAMs of which deficiency correlates with cholesterol disturbance, amyloid aggregation and cognitive impairments [279], AD-like MAM hyperconnectivity (e.g. impaired MAM integrity) [277] as well as synapse loss [278]. MAM-resident cholesterol imbalance facilitates amyloidogenic APP cleavage [165], in turn, retention of APP proteolytic fragments at MAMs interrupts cholesterol trafficking and homeostasis [280]. Additionally, blocking ATAD3A oligomerization by heterozygous knockout or pharmacological inhibition treated with DA1 peptide has been reported in causal relationship with cholesterol turnover normalization, MAM integrity enhancement, APP processing suppression, synapse loss mitigation and ultimate reduction of AD-like neuropathology and cognitive impairments [278], further revealing a role of ATAD3A in AD pathology and suggesting a potential therapeutic strategy of retarding AD progression through manipulation of abnormal ATAD3A oligomerization.

FoxO3

Forkhead box O transcription factor 3 (FoxO3) belonging to the forkhead box (FOX) family sharing an evolutionarily conserved forkhead DNA-binding domain composed of 80 to 100 amino acids [281]and possessing single nucleotide polymorphisms (SNPs) associated with human longevity [282,283] functions as a mediator of biological processes promoting lifespan and preventing aging-related diseases [284,285], of which alterations are involved in carcinoma, cardiovascular and neurodegenerative diseases [283,286-289]. FoxO3 plays a pivotal role in quiescence maintenance of neural stem cells (NSCs) in the brain, removal of which induces NSC differentiation and consequent NSC pool reduction [290-293]. Apart from capacities for neuronal survival promotion or neuronal apoptosis mediation [294,295], FoxO3 has also been shown with astrocyte proliferation controlling through inhibiting inflammatory cytokines (e.g. TNF-α and IL-1β) mediating reactive astrogliosis in neurodegenerative diseases [296-299]. Conditional knockout of FoxO3 in astrocytes was reported to impair consumption of excess fatty acids [300] which are cytotoxic and destructive to mitochondrial function [301]. FoxO3 reduction in aged mice was found to be specific to the cortex rather than the hippocampus, where FoxO3 deficiency caused cortical astrogliosis and dysregulated lipid metabolism [300]. In addition, lipid dysregulation, mitochondrial dysfunction together with Aβ uptake impairment were also observed in cultured astrocytes deficient in FoxO3, which could be reversed by astrocytic FoxO3 overexpression [300], potentially supporting the concept that FoxO3 elevation in astrocytes may retard or restore cortical astrogliosis and AD-associated impairments.

GSAP

Under typical conditions, Amyloid-β (Aβ) peptides as the products of body's cholesterol disturbance are cleaved from amyloid precursor protein (APP) which may occur in two cellular pools, namely lipid raft-associated pool preferentially favouring APP cleavage by β- and γ-secretase as well as non-raft pools where cleavage is performed by α-secretase in a non-amyloidogenic pathway [302] and rapidly eliminated to maintain normal Aβ levels [303]. γ-secretase activating protein (GSAP) was first reported for its regulatory roles in γ-secretase activity and specificity and its significant and selective enhancement of Aβ production through interactions with γsecretase and amyloid precursor protein carboxy-terminal fragment (APP-CTF) [304]. Significantly upregulated GSAP level has been demonstrated in both AD mouse models and postmortem brain tissues from AD patients [305-307]. Single-nucleotide polymorphisms (SNPs) at the GSAP locus have been shown association with AD diagnosis [308,309], of which one SNP was found to correlate with GSAP expression and AD risk [310]. Genetic knockdown and pharmacological inhibition of GSAP suppress Aβ generation and deposition and tau phosphorylation in AD mouse models [304,305,311]. Apart from the promotion of APP-CTF partitioning into Aβ production-favoring lipid rafts, GSAP has also been shown to be enriched in mitochondria-associated membranes (MAMs), an intracellular domain where amyloidogenic APP processing responsible for dysregulated lipid metabolism is performed [312,313]. GSAP depletion lowers APP-CTF accumulation in lipid rafts, reduces ER-mitochondrial contacts elevated in AD [313-316], and alters lipid profiles in a direction opposite to AD pathogenesis (e.g. GSAP depletion-raised levels of phosphatidylethanolamine (PE) and phosphatidylinositol (PI) showing consistent reduction in human AD brain) [310,317]. What's more, interactions between GSAP and multiple components related to ER-associated degradation (ERAD) regulating mitochondrial function through MAM and participating in AD pathogenesis have also been revealed, further supporting crucial roles of GSAP in attenuating AD-associated pathogenic process.

Glioblastoma

Glioma as a malignant primary brain tumor originating from astrocytes or other glial cells accounts for approximately 80% of all malignant brain tumors [318], of which glioblastoma (GBM) is the most aggressive type of brain tumor known with a 5-year survival rate below 5% [319-321]. Metabolic reprogramming has been recognized as a fundamental hallmark for carcinogenesis and progression of multiple tumors including GBM [322-324], through which tumor

cells meet the high-energy demands of rapid proliferation [325]. Except for the representative metabolic feature named the Warburg effect, a phenomenon in which GBM cells rely on glycolysis for energy production under oxygen-sufficient and oxygen-insufficient conditions [323,325-327], GBM cells can also be fueled by fatty acid oxidation (FAO) as an alternative crucial energy resource to meet high-energy consumption in GBM aggressiveness [328-332], of which inhibition negatively impacted GBM proliferation and progression [333]. Oxidation of fatty acids is achieved by two major pathways, namely enzymatic oxidation mediated by peroxidases (e.g cyclooxygenase (COX), cytochrome P450 (CYP450), lipoxygenase (LOX) and phospholipase A2 (PLA2)) [334] as well as nonenzymatic self-catalyzed peroxidation (Figure 2A) of which 4-hydroxynonenal (4HNE) is an end-product showing elevated expression proportional to the grade of brain tumor malignancy [335-337]. Moreover, lipid metabolism reprogramming in association with numerous pathophysiological processes such as tumor proliferation and development [338-343] has been further evidenced with the observation of large amounts of lipid droplets (LDs) in GBM [344-346] and other tumors [347-354]. Neutral lipid core of a single LD includes cholesteryl esters and triglycerides (TGs) composed of glycerol molecules with triple hydroxyl groups esterified by fatty acids [355-358]. TGs have been demonstrated to serve as an important energy reservoir for supporting GBM cell survival, in which LDs were rapidly broken down by GBM cells via autophagy, a pivotal cellular process degrading damaged organelles and protein aggregates and recycling nutrients via hydrolysis of cytoplasmic components to ultimately maintain cellular homeostasis [359-362], to release stored fatty acids for producing energy upon energetic stress like glucose deprivation (Figure 2B), in turn, inhibition of FAO or autophagy led

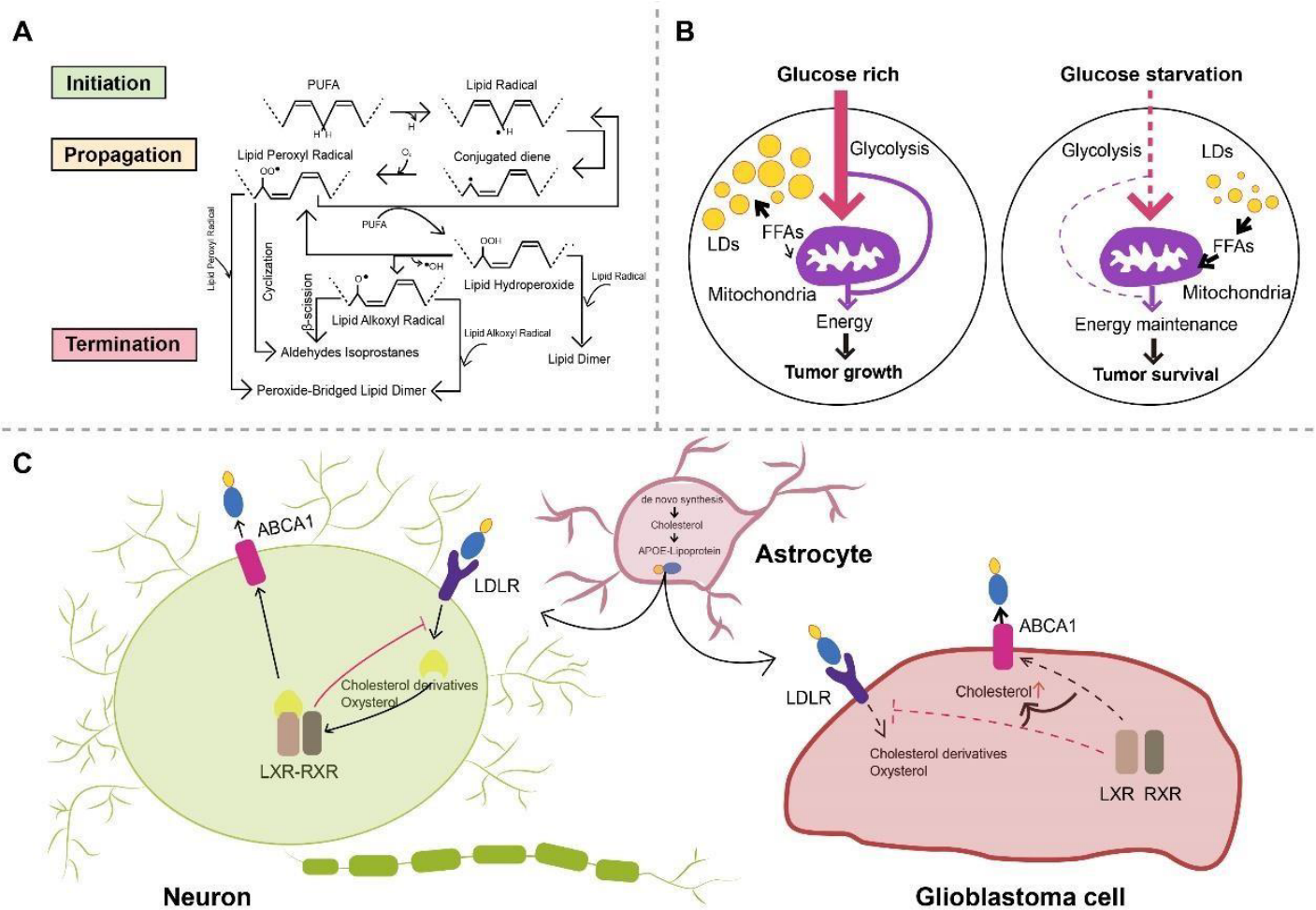

Figure 2: A. Scheme of non-enzymatic self-catalyzed lipid peroxidation. Abstraction of allylic hydrogen from PUFA induces lipid radical formation and initiates a chain reaction of lipid peroxidation, which is followed by conjugated diene-yielding molecular rearrangement. Conjugated dienes, in presence of molecular oxygen, are transformed to lipid peroxyl radical abstracting allylic hydrogen from another PUFA, forming lipid hydroperoxide and another lipid radical. Lipid hydroperoxide can be further catalyzed and transformed to lipid alkoxyl radical and lipid peroxyl radical. Lipid peroxidation is terminated when non-radical products are formed because of interaction with antioxidants. Reaction between two lipid peroxyl radicals or two lipid alkoxyl radicals will consequently form a peroxide-bridged lipid dimer, while lipid dimers can be formed by reaction between lipid hydroperoxides and lipid radicals. PUFA, polyunsaturated fatty acids. **B.** Schematic model of LDs hydrolysis maintaining GBM cell survival. GBM cells mainly utilize glucose to produce energy under glucose-rich conditions, while LDs can be rapidly broken down after autophagy activation upon glucose starvation, released FAs then enter mitochondria for energy production. FAs, fatty acids; LDs, lipid droplets; GBM, glioblastoma. **C.** Astrocytes are relied upon by neurons and GBM cells to provide *de novo* synthesized cholesterol. Neurons and GBM cells take up astrocyte-secreted cholesterol in APOE-containing lipoproteins. Following cholesterol uptake mediated by LDLR, oxysterol and cholesterol derivatives produced in neurons are physiological agonists for LXR of which activation leads to dimerization with RXR and subsequent elevation in ABCA1 expression. LXR activation also inhibits LDLR expression, resulting in decreased cholesterol uptake and regulating intracellular cholesterol level. On the contrary, mechanisms surveilling and regulating cholesterol are disrupted in GBM cells, in which oxysterol and cholesterol derivatives cannot activate LXR inducing intracellular cholesterol accumulation. ABCA1, ATP-binding cassette transporter A1; APOE, apolipoprotein E; GBM, glioblastoma; LDLR, low-density lipoprotein receptor; LXR, liver X receptor; RXR, retinoid X receptor.

to LD retention and significant potentiation of GBM cell death [363], suggesting that LDs may play critical roles in regulating GBM growth and limitation of LD usage might be indispensable in GBM treatment. What's more, cholesterol metabolism in GBM is different from that in healthy brain tissues where nearly all brain cholesterol is synthesized *de novo* [364-366]. Contrary to normal astrocytes mainly synthesizing cholesterol from glucose or glutamine [367,369] and converting excess cholesterol to oxysterol as an endogenous ligand of liver X receptors (LXRs) to consequently trigger efflux of surplus cholesterol via ATPbinding cassette transporter A1 (ABCA1) and suppression of cholesterol uptake by low-density lipoprotein receptors (LDLRs) [370-374], GBM cells are insufficient to *de novo* synthesize cholesterol and thus dependent on exogenously supplied cholesterol for survival through upregulated LDLR expression [364,375] (Figure 2C), in which LXR agonists could induce GBM cell death by lowering intracellular cholesterol content via ABCA1-dependent cholesterol efflux and LDLR inhibition [364]. Additionally, intracellular cholesterol level has been revealed to be involved in resistance against GBM cell death induced by temozolomide (TMZ), a blood-brain barrier (BBB) penetrant chemotherapy agent currently used in the standard therapy for patients with GBM [376,377]. Furthermore, sphingomyelins (SMs), an important group of phospholipids in cell membranes, together with their hydrolysis by sphingomyelinases (SMase) are crucial to effects of radio- and chemotherapy [378,381]. Ceramides which are generated by SMase-mediated SM hydrolysis caused by TMZ and radiation can induce cell apoptosis [382-384], which can be evaded through conversion of ceramides to sphingosine-1-phosphate (S1P) (Figure 3) [385-387] linked to tumor grade and implicated in GBM aggressive phenotypes [383,388].

S1PRs

GBM cells utilize exogenous source of S1P synthesized and exported by astrocytes and neuronal cells [389] and endogenous S1P production [390] for tumor progression. Involvement of S1P in tumor

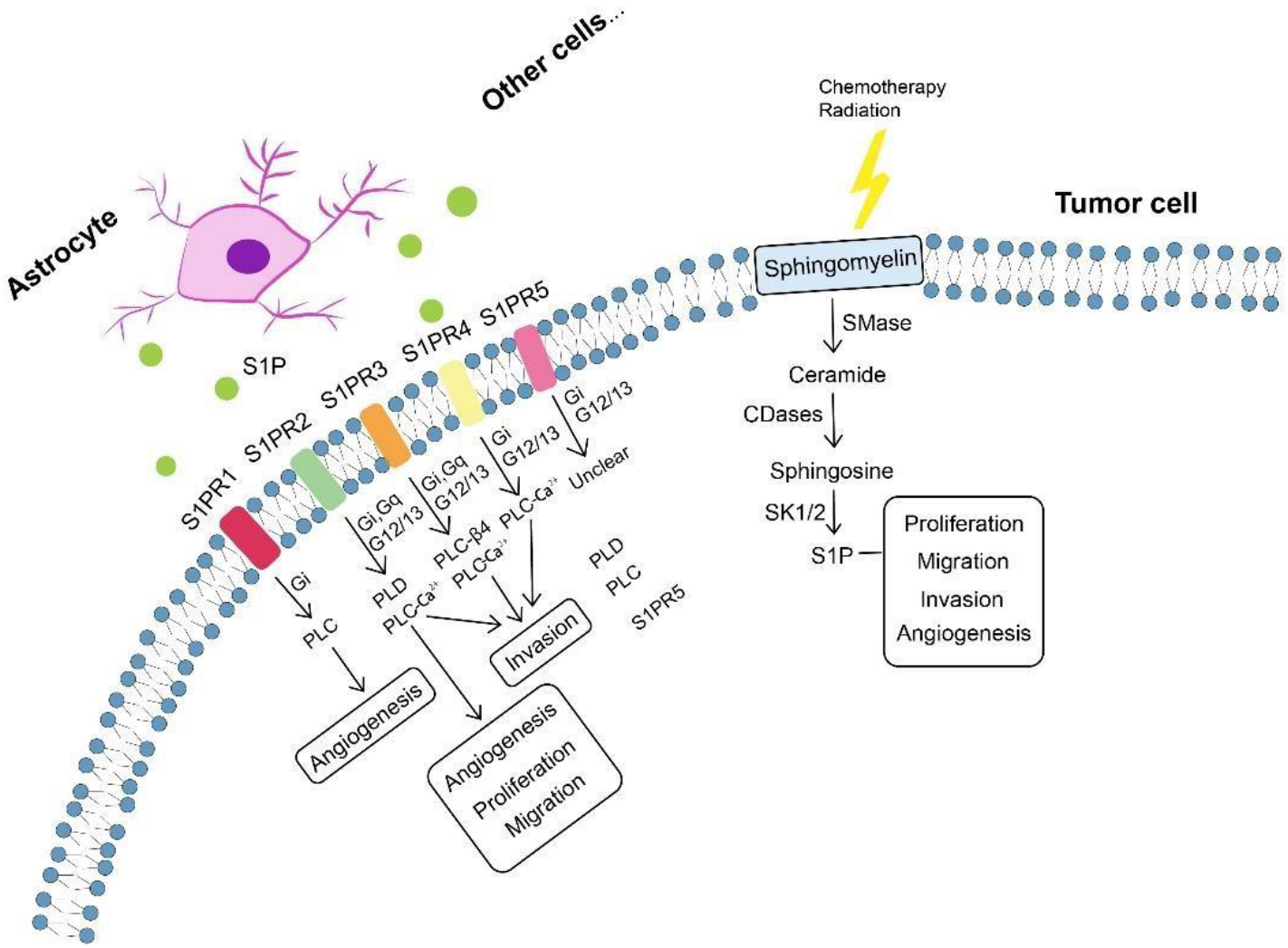

Figure 3: Sphingolipid metabolism in tumor progression. Sphingomyelin, after chemotherapy and radiation, is broken down into ceramide involved in blocking tumor progression. Ceramide can be converted by tumor cells to S1P (S1P can also be produced by astrocytes and other cells) exerting protumor effects including tumor proliferation, migration, invasion and angiogenesis. Involvement of S1P in tumor progression is specifically mediated by S1PRs (S1PR1-S1PR5) which can signal through phospholipase mechanisms. Each S1PR can couple to one or more GPCRs to signal through different phospholipases and induce phenotypes (e.g. angiogenesis, proliferation, migration and invasion). CDase, ceramidase; GPCRs, G protein-coupled receptors; SMase, sphingomyelinase; S1P, sphingosine-1-phosphate; S1PRs, S1P receptors.

growth, migration, invasion, survival and angiogenesis [391-394] is specifically mediated by the family of G-protein coupled receptors named S1P receptors (S1PRs, S1PR1-S1PR5) [395-400]. S1PR1, S1PR2, S1PR3 and S1PR5 are expressed in human GBM cells [401-403], and elevated levels of S1PR1, S1PR2, and S1PR3 have been detected in brain tissues from GBM patients compared with healthy tissues, while only S1PR1 and S1PR2 showed significant association with GBM survival rates [401,402]. S1PRs are essential for mediating diverse S1P functions, whereas orientations in which they influence cell phenotypes still remain unclear. S1PR1 inhibition was reported to promote GBM cell proliferation, which collides with studies suggesting increased GBM proliferation by S1PR1-3, of which S1PR1 showed the strongest effects [402,404]. S1PR2 was shown to both reduce GBM migration through Rho/Rho kinase signaling pathway and participate in promoting GBM invasion [405,406]. In addition, S1PR5 has also been identified as an independent prognostic factor of GBM patients' survival, aligning with reported role of S1PR5 in proliferation promotion [404,407]. Pharmacologically altered S1PR expression by fingolimod (FTY720), a sphingosine analogue leading to S1PR1 internalization, has been revealed to suppress astrocyte activation and change astrocytic secretion of C-X-C motif chemokine 5 (CXCL5) known to promote GBM proliferation and migration [408-410]. Furthermore, functions of individual S1P receptor subtypes are dependent upon activation of diverse downstream effector proteins, especially coupling to different G-proteins [399], such as binding of S1PR1, S1PR2 and S1PR5 with Gi, activation of Gq by S1PR2 and S1PR3 as well as signaling of S1PR2, S1PR3, and S1PR5 via G12/13 (Figure 3) [411], which alters signaling of phospholipases (particularly phospholipase C (PLC) cleaving proximal phosphodiester bonds of glycerophospholipids in production of phosphorylated headgroups and diacylglycerols [399,400]) and further activates downstream signaling molecules (e.g. extracellular signal-regulated kinase (ERK), phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MEK)) (Table 2). What's noteworthy is that a S1PR-targeted liposomal drug delivery system, named S1P/JS-K/Lipo, capable of blood-brain tumor barrier (BBTB) penetration and enhanced tumor-targeted delivery has recently been described, efficiently delivering a nitric oxide (NO) prodrug (JS-K, O_2-(2,4-dinitrophenyl) 1-[(4-ethoxycarbonyl) piperazin-1-yl] diazen-1-ium-1,2-diolate) to GBM tissues via specific interactions with S1PRs highly expressed on GBM cells [412], representing a promising targeted approach for GBM therapy.

FABP7

Fatty acid binding protein 7 (FABP7), a member of the multi-gene FABP family comprised of structurally related proteins with expression patterns specific to cell, tissue and development, binds to very long chain polyunsaturated fatty acids (VLCPUFAs) such as docosahexaenoic acid (DHA) with high affinity [422,423]. FABP7 abundant in astrocytes [424-426] is a lipid chaperone mediating cellular uptake, intracellular trafficking and subsequent oxidation of fatty acids (FAs), whose expression was reported to be elevated in GBM and GBM stem-like cells forming neurospheres (NS) and might accounting for GBM aggressiveness [427,428] and recurrence as well as associated with proliferation, migration and invasion of GBM cells, GBM histology and reduced survival time [429-434]. Under

Table 2: Summary of S1PR-mediated effects in GBM.

Models	Involved S1PRs	Signaling Pathways	Findings	Ref
LN18 GBM cells; U87MG GBM cells.	S1PR1 ↑ S1PR2 ↑ S1PR3 ↑	PI3K/AKT1 pathway	Demonstrated association between S1P1 and S1P2 with GBM patient's	[413]
			survival. S1PR1/2 inhibition reduces GBM migration.	
U373MG GBM cells	S1PR1 ↑ S1PR2 ↑ S1PR3 ↑	MAPK/ERK and PI3Kβ pathway	S1P promotes glioma cell proliferation.	[414]
U373MG GBM cells; GBM6 cells; GBM12 cells.	S1PR2	MEK1/2 and Rho/ROCK	S1P induces mRNA and protein expression of PAI-1 and uPAR, which are important for GBM invasiveness.	[415]
U373MG GBM cells; U118MG GBM cells.	S1PR1↑ S1PR2 S1PR3	MAPK-ERK Rho/ROCK	S1PR, S1PR2 and S1PR3 all positively contribute to S1P-stimulated glioma cell proliferation, of which S1PR1 makes the major contribution.	[416]
C6 glioma cells	S1PR2	MAPK/ERK, PKC, PLC, PLD and Ca^{2+} signaling	S1PRs are linked to at least two signaling pathways (i.e. PTX-sensitive Gi/Go-protein pathway and toxin-insensitive Gq/G11-PLC pathway).	[417]
C6 glioma cells; 1321-N1 astrocytoma cells.	S1PR2	PI3K/Cdc42/p38MAPK and PI3K/Rac1/JNK	S1PR2 mediates S1P-induced negative regulation of glioma cell migration.	[418]
U373MG GBM cells; U87MG GBM cells; M059K cells; U-1242 cells; A172 cells.	S1PR1 ↑ S1PR2 ↑ S1PR3 ↑	MAPK/ERK and PI3K	S1P potently enhances glioma cell motility by signaling through coupling of S1PRs to Gi proteins.	[419]
T98G glioma cells; G112 glioma cells.	S1P1, S1P2, S1P3 and S1P5	PTEN/AKT/Egr	S1PR1 is a significant prognostic factor for glioma;	[420]
			Downregulated S1PR1 expression increases glioma cell proliferation and enhances glioma malignancy.	
Human GBM specimens; U87 glioma cells; U251 glioma cells; T98G glioma cells; G112 glioma cells.	S1PR1↓		Downregulated S1PR1 expression in GBM patients with a poor survival. S1PR1 signaling negatively controls glioma cell proliferation.	[421]

AKT, v-akt murine thymoma viral oncogene homolog; Cdc42, cell division control protein 42 homolog; ERK, extracellular signal-regulated kinase; JNK, c-Jun Nterminal kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; PLC, phospholipase C; PLD, phospholipase D; PTEN, phosphatase and tensin homolog; PTX, pertussis toxin; Rac1, Ras-related C3 botulinum toxin substrate 1; ROCK, Rho-associated protein kinase.

metabolic stresses (e.g. hypoxia), fatty acids are stored as lipid droplets (LDs) and subsequently oxidized in a FABP-dependent manner for energy production in GBM cells [435]. Slowcycling cells (SCCs), a subpopulation of GBM cells preferentially utilizing mitochondrial oxidative phosphorylation (OXPHOS), showing elevated lipid contents specifically metabolized under glucose deprivation and displaying enhanced capabilities of migration, invasion and chemoresistance, have been revealed with the characterization of higher FABP expression and larger LD amounts in cultured conditions of normal oxygen levels or nutrients [436]. Additionally, resistance of SCCs against deprived glucose or inhibited glycolysis could be restrained by FA uptake blocking via genetic deletion or pharmacological inhibition of FABP7 [436].

Moreover, promotion effects of FABP7 on GBM cell migration can be mitigated with DHA supplementation through specific and dramatic inhibition of DHA supplementation in culture medium on plasma membrane lipid order of FABP7expressing GBM cells which positively correlates with GBM cell migration as well as DHA supplementation-mediated disruption of nanodomains formed by FABP7 on GBM cell membranes [437], further suggesting a critical role of FABP7 in lipid metabolism in GBM cells.

SCD

Stearoyl-CoA desaturase (SCD) is an endoplasmic reticulum (ER)-localized delta-9 fatty acid desaturase forming carbon-carbon double bonds at the 9th to 10th position from the COOH-terminus of saturated fatty acids (SFAs), stearic acid and palmitic acid and thus generating monounsaturated fatty acids (MUFAs), oleic acid and palmitoleic acid, respectively [438,439], whose expression correlates with the ratio of MUFA to SFA in which a disequilibrium contributes to alterations in cell growth and differentiation [438-441]. SCD has 4 isoforms in mice (SCD1, SCD2, SCD3 and SCD4), while only two paralogs are expressed in human, namely SCD sharing approximately 85% amino acid identity with mouse SCDs and SCD5 unique to primates [440,442]. SCD has been described as a hypermethylated gene member contributing to the CpG island methylator phenotype which defines a distinct glioma subgroup [443]. SCD expression in GBM, in contrast to SCD upregulation often observed in multiple human tumors [444-447], was reported to be lower than normal brain tissues because of hypermethylation and monoallelic deletion together with phosphatase and tensin homolog (PTEN) frequently deleted in GBM [448] in a subset of GBM patients [449]. In addition, GBM cells without epigenetic and genetic changes mentioned above were revealed to express elevated SCD levels on which tumor cells rely for their survival [449]. SCD inhibition by CAY10566, an inhibitor with a modest BBB penetration ability, has been demonstrated to not only significantly suppress intracranial GBM growth, but also obviously affect tumor vasculature including nearly complete blocking of intratumoral bleeding and possible normalization of blood vessels, potentially allowing enhanced delivery of combinedly used antitumor drugs such as temozolomide (TMZ) [449,450].

Conclusions

The brain is highly enriched in lipids where they are crucial for multiple physiological processes ranging from maintenance of structural integrity and metabolic homeostasis to brain function and development. Metabolism of lipids is a complicated process in which a wide range of lipid-related effector proteins are involved and whose alteration is strongly associated with brain dysfunctions and diseases such as Alzheimer's disease (AD) and glioblastoma (GBM). In this review, we throw light upon basic classes of lipids including fatty acids, phospholipids, sphingolipids, sterol lipids and triglycerides, of which dysregulated metabolism can be regarded as disease biomarkers. We also briefly discuss the role of lipids within the brain and altered lipid profile correlated with astrocytic function and astrocyte-neuron crosstalk in AD and GBM. Moreover, we have discussed lipid-related metabolites and proteins critical for disease-associated lipid dyshomeostasis and how these proteins together with lipids in correlation with astrocytic functions modulate disease pathogenesis and development, enlightening their therapeutic potential in preventing onset and progression of AD and GBM. However, there are still several lipids whose association with AD and GBM and availability as clinically valuable biomarkers for disease detection at early stages need further evaluation, which can be performed by newly-developed and improved techniques of gradually matured lipidomic platforms. What's more, there remains much to be discovered about benefits and risks of manipulation of compounds affecting effector proteins involved in lipid metabolism, and further characterization of pathways in which important lipid-related proteins participate along with clinical studies will aid the understanding of pathogenesis mechanisms behind AD and GBM and identification of novel therapeutic targets to help ameliorate disease courses, facilitate disease treatments and consequently benefit patients.

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