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REVIEW

Expression and Function of Zinc-α2-Glycoprotein

Xin Wei[1] · Xi Liu[1] · Changhong Tan[1] · Lijuan Mo[1] · Hui Wang[1] · Xi Peng[1] · Fen Deng[1] · Lifeng Chen[1]

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Abstract Zinc-α2-glycoprotein (ZAG), encoded by the *AZGP1* gene, is a major histocompatibility complex I molecule and a lipid-mobilizing factor. ZAG has been demonstrated to promote lipid metabolism and glucose utilization, and to regulate insulin sensitivity. Apart from adipose tissue, skeletal muscle, liver, and kidney, ZAG also occurs in brain tissue, but its distribution in brain is debatable. Only a few studies have investigated ZAG in the brain. It has been found in the brains of patients with Krabbe disease and epilepsy, and in the cerebrospinal fluid of patients with Alzheimer disease, frontotemporal lobe dementia, and amyotrophic lateral sclerosis. Both ZAG protein and *AZGP1* mRNA are decreased in epilepsy patients and animal models, while overexpression of ZAG suppresses seizure and epileptic discharges in animal models of epilepsy, but knowledge of the specific mechanism of ZAG in epilepsy is limited. In this review, we summarize the known roles and molecular mechanisms of ZAG in lipid metabolism and glucose metabolism, and in the regulation of insulin sensitivity, and discuss the possible mechanisms by which it suppresses epilepsy.

Keywords Zinc-α2-glycoprotein · Metabolism · Glucose · Lipid · Insulin sensitivity · Neuron

Zinc-α2-Glycoprotein (ZAG)

ZAG is a 42-kDa secretory protein expressed in many animal species and is encoded by *AZGP1* gene, which is located on chromosome 7q22.1 [1, 2]. The *AZGP1* gene is 9.7 kb long and its organization and nucleotide sequence are highly similar to the first four exons of major histocompatibility complex (MHC) I genes, but the AZGP1 gene does not have sequences encoding transmembrane and cytoplasmic domains [1, 3]. In accordance with the *AZGP1* gene, the structure of ZAG protein is also very similar to MHC I molecules. The ZAG protein contains 3 domains, among which the α1 and α2 domains form a groove-like structure, and the α3 domain adopts a fold resembling immunoglobulin constant domains [4]. The groove-like α1–α2 superdomains of ZAG can bind to ligands and thus determine its specificity for its ligands, while the α3 domain links the α1–α2 superdomains and light chain of ZAG [4]. Unlike the MHC I proteins, the light chain of ZAG is a prolactin-induced protein [4].

ZAG binds to zinc and fatty-acids. It has been reported that ZAG has 2 strong and 15 weak binding sites for zinc, and zinc binding to these sites influences the binding of ZAG to fatty-acids and β-adrenergic receptors [5]. Zinc binding to the weak binding sites is considered to induce the oligomerization and precipitation of ZAG [6]. In the groove in ZAG formed by the α1–α2 superdomains, there are at least 2 sites that bind to the dansylated C^{11} fatty-acids 11-(dansylamino)undecanoic acid or 4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-hexadecanoic acid. And the binding of ZAG to the latter is competitively inhibited by zinc [6]. Interestingly, polyethylene glycol has also been identified as a ligand of ZAG. Polyethylene glycol displaces fatty-acids from ZAG binding sites, indicating that ZAG can bind to hydrophobic

Xin Wei and Xi Liu have contributed equally to this review.

✉ Lifeng Chen
lifen_chen@163.com

[1] Department of Neurology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China

molecules [7]. However, the effects of these ligands on the structure and function of ZAG need further investigation.

The Role of ZAG in Metabolism and Insulin Sensitivity

Lipid Metabolism

ZAG is known to be a lipid-mobilizing adipokine [8]. In humans, the ZAG level in serum has been shown to be positively associated with serum triglycerides and adipocyte fatty-acid-binding protein levels, and negatively associated with high-density lipoprotein-cholesterol levels [9]. In rats, AZGP1 mRNA is detectable in white and brown adipose tissues just 1 day after birth, and decreases rapidly thereafter in brown adipose tissue and after weaning in white adipose tissue, accompanied by an increase of adipose tissue amount [10]. ZAG treatment also reduces adipose tissue in rats by increasing lipolysis and the utilization of non-esterified fatty-acids; the plasma triglyceride level is decreased [11]. *In vitro*, ZAG stimulates the proliferation of 3T3-L1 pre-adipocytes and inhibits their differentiation [12]. ZAG treatment has also been found to increase the levels of adipose triglyceride lipase and hormone-sensitive lipase, which contribute to lipolysis [11]. While overexpressing ZAG in hepatocytes promotes the lipolysis and β-oxidation of fatty-acids, it also inhibits palmitic acid-induced lipogenesis and lipid accumulation in hepatocytes [13]. On the contrary, knockdown of ZAG expression significantly promotes lipogenesis and increases the lipid level in hepatocytes [13, 14]. All these studies suggest an important role of ZAG in lipolysis.

The mechanism by which ZAG influences lipid metabolism has not been clearly established, but increasing evidence shows that ZAG is involved in lipid metabolism in several ways. ZAG promotes the browning of white adipose tissue, and thus increase lipolysis [15]. The promoting effect of ZAG on white adipose tissue browning may be due to its stimulation of the expression of peroxisome proliferator-activated receptor γ (PPARγ) and early B cell factor 2, which may enhance the binding of these molecules to the promoter of PR/SET domain 16 (Prdm16) and the promoter of uncoupling protein (UCP) 1, while both Prdm16 and UCP1 are known to convert white adipose precursors into brown-like adipocytes and promote energy consumption [15]. In brown adipose tissue, ZAG enhances the expression of PPARγ and its coactivator 1α, and thus increases the expression of UCP1, which increases energy expenditure [15]. Interestingly, ZAG expression in SGBS (Simpson-Golabi-Behmel syndrome) adipocytes is enhanced by the PPARγ agonist rosiglitazone [16]. The ZAG-induced browning of white adipose tissue may also be mediated by PKA and p38 mitogen-activated protein kinase (MAPK) signaling, by which ZAG may enhance the expression of many lipolysis-related molecules, including UCP-1, Prdm16 and CIDEA, PPARγ coactivator 1α, nuclear respiratory factor-1/2, mitochondrial transcription factor A, adipose triglyceride lipase, hormone-sensitive lipase, carnitine palmitoyltransferase 1A, and p-acyl-CoA carboxylase [17]. The induction of UCP1 and UCP2 by ZAG is dose-dependent and *via* β3 adrenergic receptors, while the induction of UCP3 by ZAG is meditated by MAPK [11, 18]. Therefore, the increase in body temperature and decrease in body weight and adipose tissue induced by ZAG may be partly attributed to its promotional effect on UCP expression, which leads to increased energy expenditure [11, 15, 18]. The expression of ZAG is up-regulated by growth hormone, while silencing ZAG expression abolishes the lipolytic effect of growth hormone on adipocytes [19, 20]. Overexpression of ZAG also decreases the mRNA level of fatty-acid synthase (FAS), acetyl-CoA carboxylase, and acyl-coenzyme A: diacylglycerol transferase, and increases the mRNA level of hormone-sensitive lipase; these effects result in inhibition of lipogenesis and enhancement of lipolysis [21]. However, ZAG has also been reported to promote the proliferation of 3T3-L1 pre-adipocytes and inhibit their differentiation by inhibiting the expression of PPARγ and CCAAT-enhancer-binding protein α, and inhibit the activity of the promoter of FAS [12]. Therefore, ZAG has a pro-lipolysis effect, but the mechanism by which it influences lipid metabolism is controversial and needs further study (Fig. 1).

Glucose Metabolism

There has been little research on the effect of ZAG on glucose metabolism. It has been shown that intravenous administration of ZAG to mice decreases fasting blood glucose and improves glucose tolerance without changing the plasma insulin level 30 min after oral administration of glucose [22]. ZAG increases urinary glucose excretion and decreases the maximal plasma glucose and insulin levels in oral glucose tolerance tests in mice, as well as promoting the transfer of glucose into skeletal muscle and adipocytes [23]. These effects of ZAG on glucose metabolism are attenuated by the non-specific β adrenergic receptor antagonist, propranolol [23], indicating a role of β adrenergic receptors in ZAG-regulated glucose metabolism. ZAG binds to β2 and β3 but not β1 adrenergic receptors and activates them both in white and brown adipose tissues, which leads to an increase of cyclic adenosine monophosphate; it also inhibits the expression of β1 adrenergic receptor mRNA [20, 22]. However, ZAG has also been reported to decrease the circulating glucose level and increase the basal glucose intake into adipocytes and the

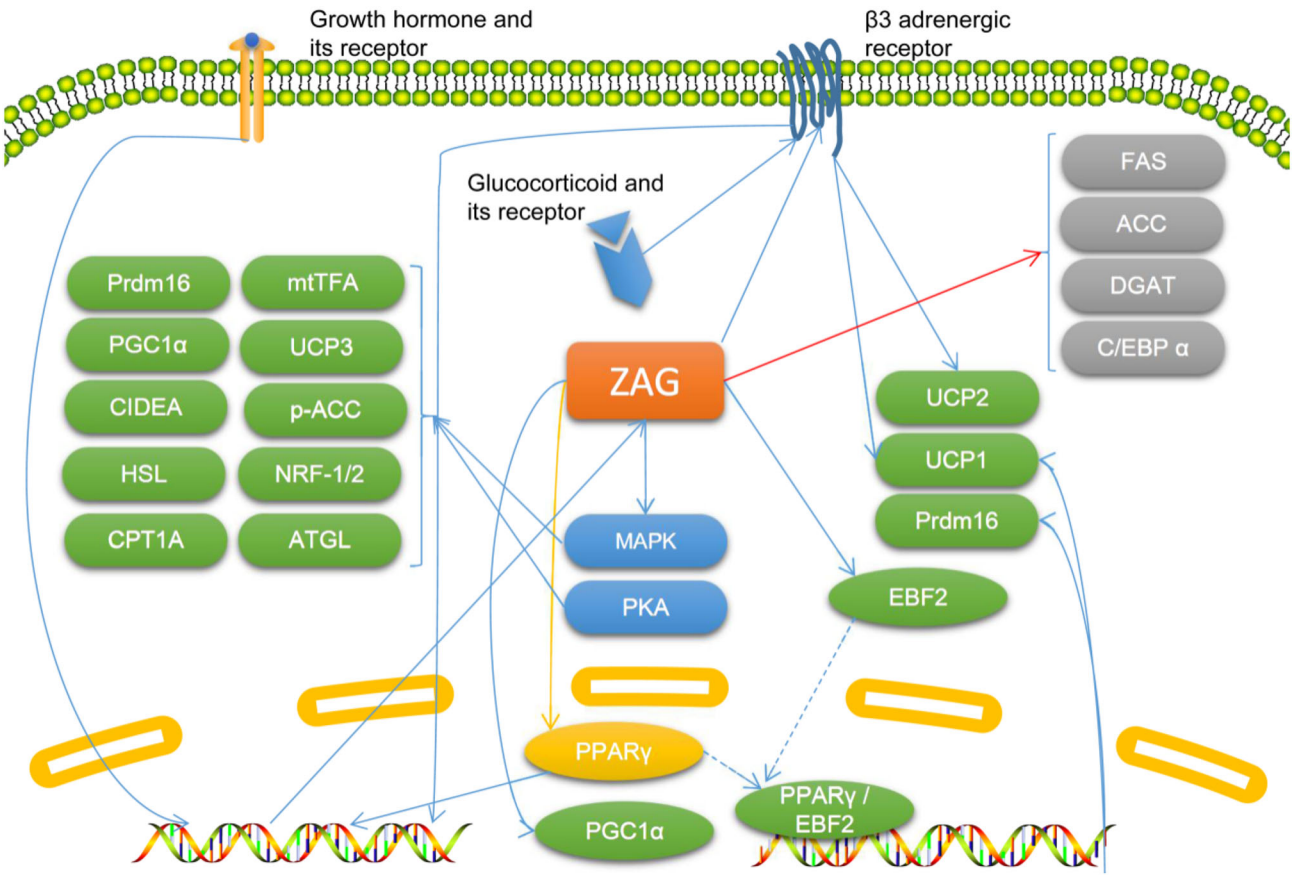

Fig. 1 The known molecular mechanisms by which zinc-α2-glycoprotein (ZAG) participates in lipid metabolism. Molecules colored in green are known to be upregulated by ZAG directly or indirectly, and those colored in grey are known to be downregulated by ZAG directly or indirectly. The molecule colored in yellow (PPARγ) is affected by ZAG but the results are controversial. Blue arrows indicate promotional effects, red arrow indicates inhibitory effects, and yellow arrow indicates controversial effects. ACC, acetyl-CoA carboxylase; ATGL, adipose triglyceride lipase; C/EBPα, CAAT-enhancer-binding proteins α; CIDEA, cell death-inducing DNA fragmentation factor alpha-like effector A; CPT1A, carnitine palmitoyltransferase 1A; DGAT, acyl-coenzyme A: diacylglycerol transferase; EBF2, early B cell factor 2; FAS, fatty-acid synthase; HSL, hormone-sensitive lipase; MAPK, mitogen-activated protein kinase; mtTFA, mitochondrial transcription factor A; NRF-1/2, nuclear respiratory factor-1/2; PGC1α, PPARγ coactivator 1α; PKA, protein kinase A; PPARγ, peroxisome proliferator-activated receptor γ; Prdm16, PR/SET domain 16; UCP, uncoupling protein.

expression of glucose transporter 4 (GLUT4) *via* β1 adrenergic receptors, while the plasma glucose level has also been found not to be associated with the plasma ZAG level [11, 24]. Silencing AZGP1 expression in adipocytes also decreases the expression of adiponectin, insulin receptor substrate 1 (IRS1), GLUT4, and PGC1α [25], indicating its role in glucose uptake, insulin action, mitochondrial biogenesis, and lipid oxidation. ZAG may promote glucose utilization, storage, and excretion, and β adrenergic receptors may play important roles in ZAG-regulated glucose metabolism, but the specific mechanism by which ZAG influences glucose metabolism needs further investigation (Fig. 2).

Insulin Resistance (IR)

ZAG has been associated with IR. In the subcutaneous adipose tissue of adults, a higher ZAG level is an independent predictor of better adipose tissue and whole-body insulin sensitivity [25]. Circulating ZAG levels in children, patients with polycystic ovary syndrome, and patients with type 2 diabetes mellitus are negatively associated with IR [26–28]. Similarly, a negative association between the AZGP1 mRNA level in adipose tissue and IR has also been verified [29]. Some researchers recommend a circulating ZAG index $[\ln(ZAG/HOMA-IR)]$ to identify IR, as it is negatively associated with IR and shows favorable diagnostic efficacy (sensitivity 88% and specificity 91%) [30]. However, it has also been reported that serum ZAG levels are positively associated with IR [9], and ZAG has also been reported to

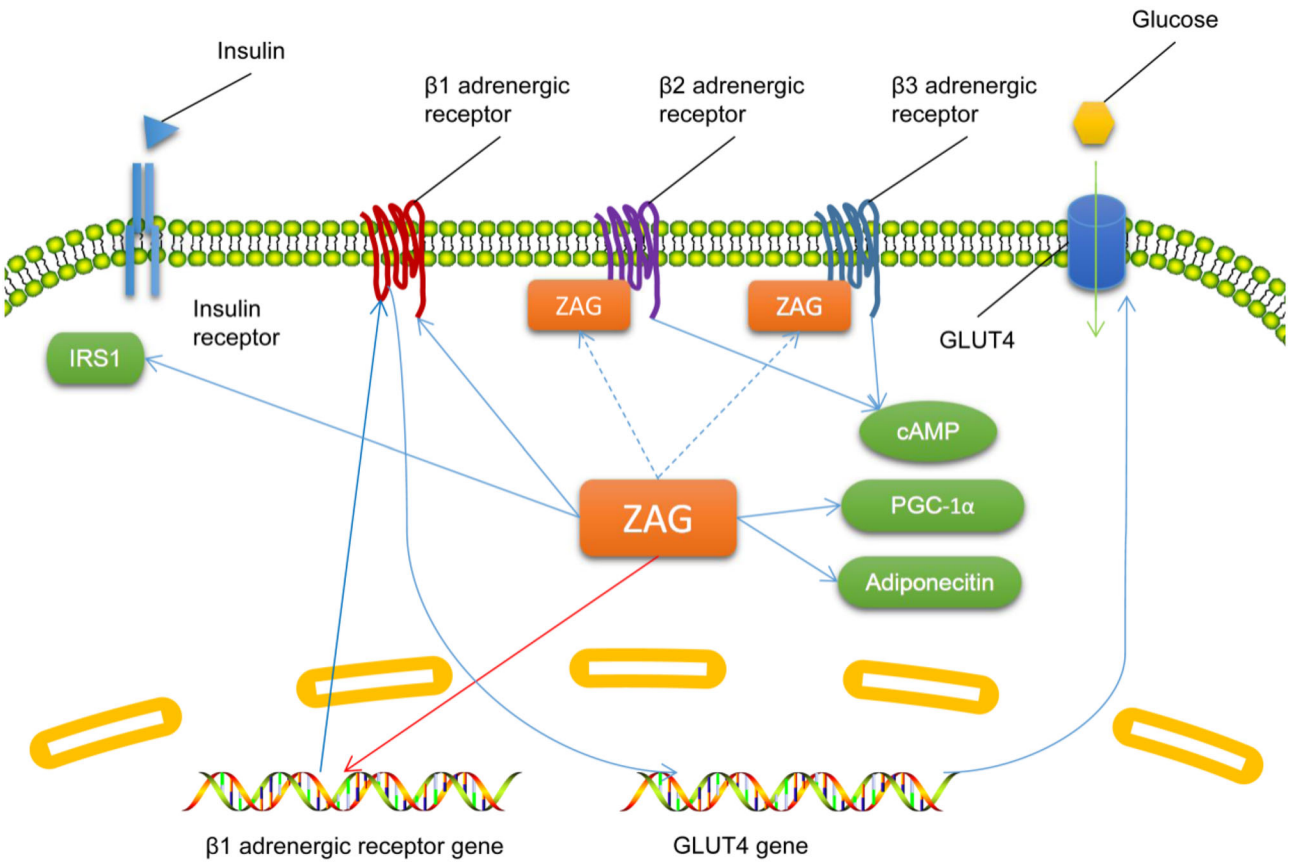

Fig. 2 The known molecular mechanisms by which zinc-α2-glycoprotein (ZAG) participates in glucose metabolism. Descriptions of molecules and arrows in different colors are as in Fig. 1. cAMP, cyclic adenosine monophosphate; GLUT4, glucose transporter 4; IRS, insulin receptor substrate; PGC1α, peroxisome proliferator-activated receptor γ coactivator 1α.

induce IR in adipocytes [24]. Interestingly, in cultured liver HPG2 cells, ZAG is not associated with IR, and insulin does not affect ZAG expression either [31]. Therefore, controversial results have been found in different studies on the relationship between ZAG and IR, but the majority of reports support a negative association between ZAG and IR.

The mechanism by which ZAG influences IR is not clear, and there are few reports on this topic. In type 2 diabetes mellitus patients, treatment with dapagliflozin, an antagonist of sodium-dependent glucose transporter 2 (SGLT2), increases serum ZAG and alleviates their IR [32]. The effect of dapagliflozin on ZAG and IR can be abolished by a PPARγ inhibitor (GW9662) [32], indicating that inhibiting SGLT2 or activating PPARγ increases ZAG and alleviates IR, and negatively associates ZAG with IR. However, ZAG has also been reported to induce IR in adipocytes by increasing the activity of protein phosphatase 2 (PP2A) in a β2 adrenergic receptor activation-dependent manner [24]. And ZAG also increases the phosphorylation of IRS1 at the Ser307 residue in gastrocnemius muscle, thus contributing to IR [33]. The limited research and the controversial findings make it difficult to outline the role of ZAG in IR; further study is needed (Fig. 3).

Other Molecular Mechanisms Involving ZAG

Besides its role in metabolism and insulin sensitivity, ZAG has also been shown to be involved in many other molecular mechanisms.

In both types of adipose tissue in mice, cultured human adipocytes, and SGBS pre-adipocytes, tumor necrosis factor α (TNFα) treatment decreases ZAG expression [6, 16, 34, 35]. And in patients receiving hemodialysis, the plasma ZAG level is negatively associated with plasma TNFα [36]. It has been reported that macrophage-treated human adipocytes show a significant decrease in ZAG expression, while TNFα treatment induces a similar decrease accompanied by a significant increase in inflammatory factors including interleukin 6 (IL6), leptin, IL8, monocyte chemoattractant protein 1, and RANTES (regulated upon activation, normal T cell expressed and

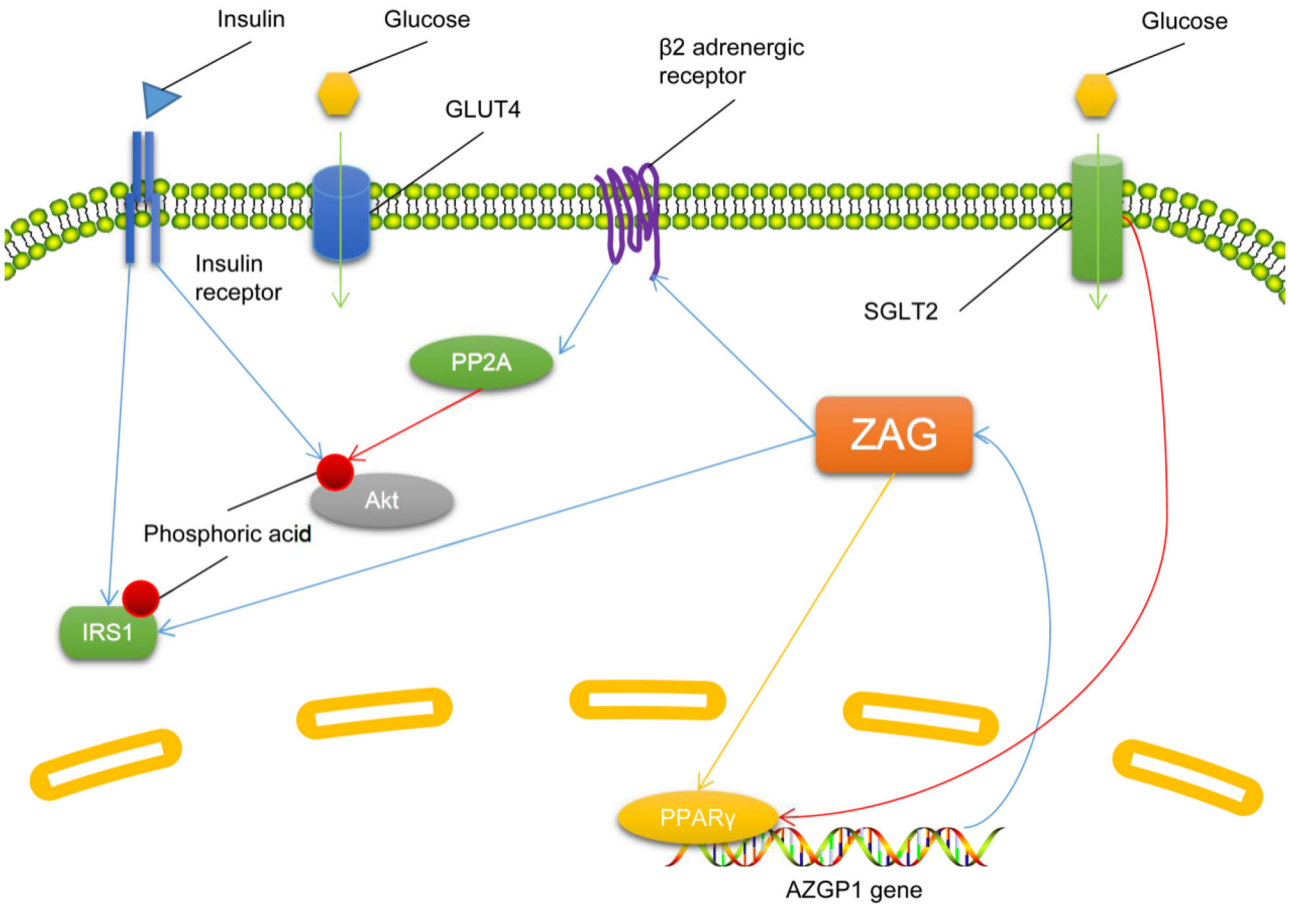

Fig. 3 Molecular mechanisms underlying the regulation of insulin sensitivity by zinc-α2-glycoprotein (ZAG). Descriptions of molecules and arrows in different colors are as in Fig. 1. GLUT4, glucose transporter 4; IRS, insulin receptor substrate; PP2A, protein phosphatase 2A; PPARγ, peroxisome proliferator-activated receptor γ; SGLT2, sodium-dependent glucose transporter 2.

presumably secreted protein) [35]. These findings suggest that macrophage-related inflammation plays important roles in the downregulation of ZAG expression, and TNFα is central in the molecular mechanism of such inflammation.

In malignant tumors such as ductal adenocarcinoma of the pancreas and hepatocellular carcinoma, ZAG acts as a tumor suppressor. It inhibits invasion and induces the mesenchymal-to-epithelial transdifferentiation of tumor cells by inhibiting the tumor growth factor β (TGFβ)-mediated extracellular regulated protein kinase (ERK) signaling pathway [37, 38]. ZAG has also been shown to have an antifibrotic effect in fibrosis of the kidney and heart induced by chronic kidney disease or heart stress *via* the negative regulation of TGFβ [39]. In LoVo cells, overexpression of ZAG inhibits the proliferation of tumor cells and their invasion, also leading to a reduction of FAS and phosphorylated mammalian target of rapamycin (p-mTOR), thus inhibiting the activity of the mTOR pathway and endogenous FAS-regulated fatty-acid synthesis [40]. On the contrary, ZAG increases the mTOR level in mouse gastrocnemius muscle [33]. ZAG also inhibits the proliferation, invasion, and metastasis of hepatocellular carcinoma both *in vivo* and *in vitro* by regulating the PTEN (phosphate and tension homology deleted on chromosome ten)/Akt and CD44 (cluster of differentiation 44) pathways [41].

ZAG expression is induced by hormones, including thyroid hormone, androgen, and glucocorticoid. In cultured hepatocytes, thyroid hormone induces ZAG expression dose-dependently, and there is a thyroid hormone-binding site in the proximal promoter of *AZGP1* [42]. In prostate cancer cells, *AZGP1* mRNA is induced by androgen stimulation, and this effect is inhibited by GATA-2 [43]. And in adipose tissue, dexamethasone induces a 6-fold increase in ZAG expression [44] (Fig. 4).

Presence and Distribution of ZAG in Brain

Only a few studies have investigated the presence and distribution of ZAG in brain, and their results are contradictory. In brain tissue from patients with Krabbe

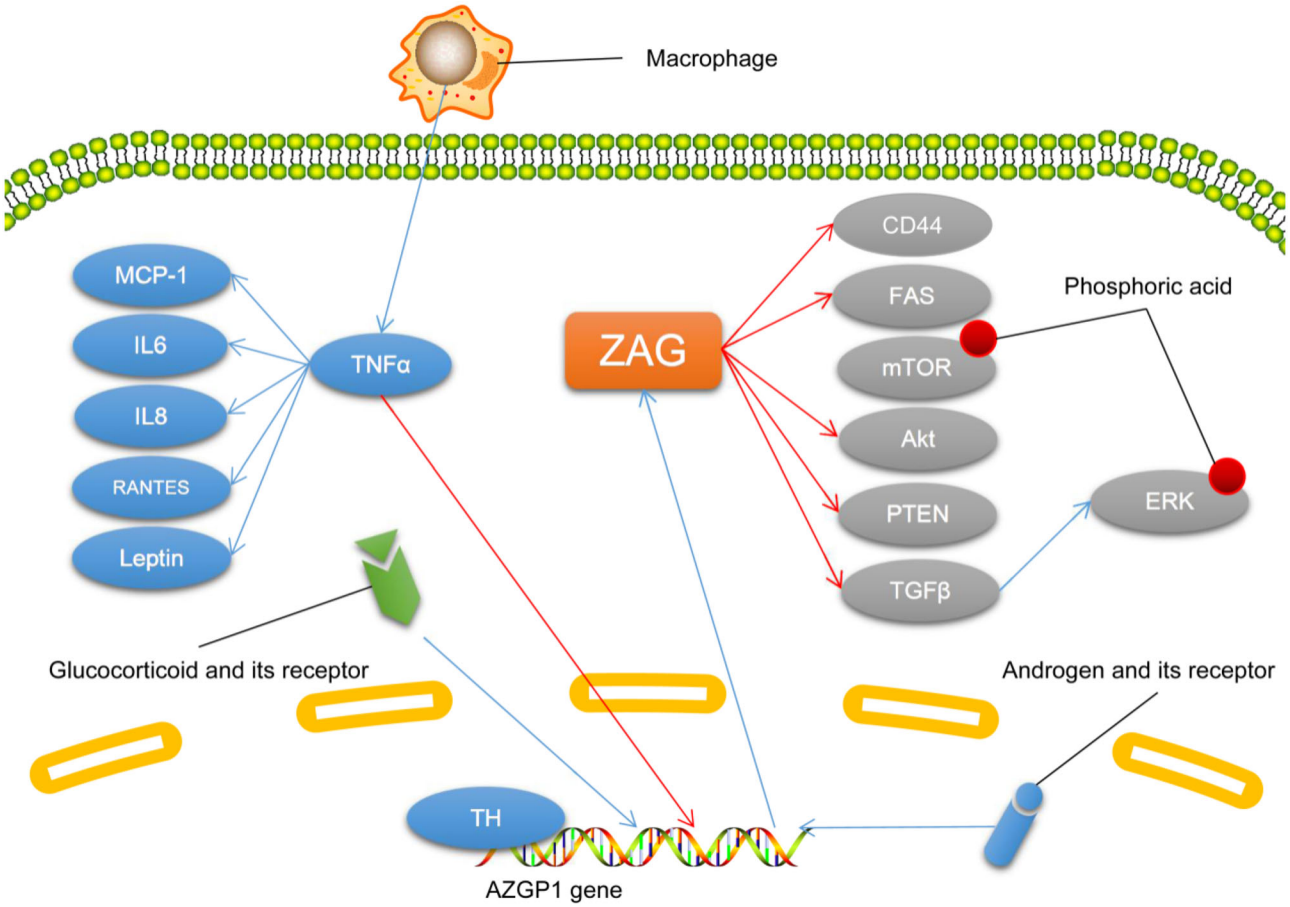

Fig. 4 The molecular mechanisms associated with zinc-α2-glycoprotein (ZAG). Descriptions of molecules and arrows in different colors are as in Fig. 1. CD, cluster of differentiation; ERK, extracellular regulated protein kinases; FAS, fatty acid synthase; IL, interleukin; MCP-1, monocyte chemoattracctant protein; mTOR, mammalian target of rapamycin; PTEN, phosphate and tension homology deleted on chromsome ten; RANTES, regulated upon activation, normal T cell expressed and presumably secreted protein; TGFβ, tumor growth factor β; TH, thyroid hormone; TNFα, tumor necrosis factor α.

disease, ZAG has been found in astrocytes and extracellular matrix surrounding capillaries, but not in neurons [45]. However, in brain tissue from epilepsy patients, ZAG was reported to be expressed in neurons but not astrocytes [46]. Besides, the former study did not identify ZAG in brain tissue from 7- to 25-month-old controls, while the latter study identified ZAG in the neurons of adult controls with brain trauma. This difference could be attributed to the different ages and disease conditions of the controls in these studies [46]. The synthesis of ZAG in brain may be age-dependent as it is for many other proteins [47–49]. While it is possible that ZAG is synthesized in the brain of adults but not infants, this hypothesis needs to be tested in further research.

In addition, ZAG has also been found in the cerebrospinal fluid of patients with Alzheimer disease, amyotrophic lateral sclerosis, and frontotemporal lobe dementia, and is considered a potential biomarker for these diseases [50–52]. But the role of ZAG in these diseases has not yet been clarified.

The source of ZAG in the brain is still debatable. Maślińska and colleagues speculated that, in brain tissue from patients with Krabbe disease, ZAG came from the plasma through a damaged blood-brain barrier [45], but in epilepsy patients, *AZGP1* mRNA and ZAG protein were both identified in brain tissues from patients and rats, and the authors speculated that ZAG may be synthesized in the brain, probably in neurons [46, 53]. In Alzheimer disease, the ZAG level in cerebrospinal fluid is not associated with its level in plasma [51], so the source of ZAG in cerebrospinal fluid remains controversial.

The Role and Mechanism of ZAG in CNS Diseases

Some studies have investigated the role and mechanism of ZAG in CNS diseases, most concerning epilepsy. In brain tissue from epilepsy patients, *AZGP1* mRNA and ZAG protein are decreased, and in brain from epileptic rat models, decreased *AZGP1* mRNA and ZAG protein in

neurons have also been identified [46, 50]. And in epileptic rat models, the decrease of *AZGP1* mRNA and ZAG protein exacerbates as seizures worsen [46]. Overexpressing ZAG in epileptic rat models has been found to alleviate seizures and epileptic discharges in the electroencephalogram [54]. Interestingly, liraglutide, a drug for diabetes which increases circulating ZAG, has been shown to suppress epilepsy in animal models and the comorbidity of epilepsy [55–57]. However, whether ZAG can alleviate epilepsy in the clinic is still unknown, and the mechanism by which ZAG alleviates epilepsy needs further investigation.

It is possible that ZAG suppresses epilepsy or seizures *via* several potential mechanisms. As a lipid-mobilizing factor, ZAG may affect the metabolism of fatty-acids in neurons. The traditional opinion is that neurons cannot use fatty-acids directly as fuel. However, it has recently been demonstrated that neurons can use fatty-acids for energy, and under either hypoxia or normal conditions, most of the fatty-acids consumed by neurons are metabolized into ketone bodies rather than CO_2 and water [58]. Astrocytes are also able to metabolize fatty-acids and produce ketone bodies, which are also considered to have a neuroprotective effect [59]. Meanwhile, ketone bodies have been shown to regulate the γ-aminobutyric acid (GABA) signaling pathway, vesicular glutamate transporter, norepinephrine signaling, potassium-adenosine triphosphate channels, the tricarboxylic acid cycle, and the mitochondrial permeability transition, and may exert an antiepileptic effect by these mechanisms [60]. ZAG expression is regulated by SGLT2 and PPARγ [31], while both are known to participate in epilepsy [61–63]. And both SGLT2 and PPARγ are known to participate in fatty-acid oxidation and ketogenesis [63, 64]. ZAG is known to promote fatty-acid metabolism [11], and in neurons, the catabolism of fatty-acids mainly produces ketone bodies [58]. Although whether SGLT2 and PPARγ regulate ketogenesis *via* ZAG is unclear, it is possible that ZAG affects ketogenesis by regulating fatty-acid metabolism in neurons. However, as there is no research on the effect of ZAG on ketogenesis, this hypothesis needs to be tested. Besides, ZAG affects the activity of mTOR [33, 40], which is known to participate in fatty-acid oxidation [40] and epilepsy [65, 66]. Therefore, it is possible for ZAG to promote fatty-acid metabolism and ketogenesis in neurons and astrocytes, and thus have a neuroprotective effect. However, no studies have investigated the effect of ZAG on fatty-acid metabolism and ketone body production in neurons and astrocytes.

The regulation of insulin sensitivity is another potential mechanism by which ZAG may act in epilepsy. Receptors for insulin are distributed widely in brain, and *via* these receptors, insulin modulates synaptic plasticity by regulating the release, uptake, and degradation of neurotransmitters [67, 68]. Evident IR occurs in patients with chronic epilepsy [69, 70], while in patients with type 1 diabetes mellitus who lack insulin, the risk of epilepsy is 3-fold that in normal controls [71]. And the H1085H C > T polymorphism of the insulin receptor gene is associated with drug resistance in refractory epilepsy patients [72]. Insulin recruits GABA receptors to the postsynaptic membrane and dendritic membrane, regulating the electrophysiological activity of neurons *via* GABA receptor-dependent and independent mechanisms [73, 74]. Insulin also regulates the expression and activity of dopamine transporters and GABA transporters, and plays a role in the antiepileptic mechanism of ketogenic diets [75]. A decrease of insulin receptors on membrane also leads to a reduction of dendrites in neurons [76]. All these findings indicate the involvement of insulin sensitivity in epilepsy. ZAG influences insulin sensitivity, but its specific role in the regulation of insulin sensitivity is still controversial based on current studies. ZAG has been positively associated with insulin sensitivity of the whole body and adipose tissue [25], and it has also been found to induce IR in adipocytes [24]. MHC I molecules are known to reduce insulin sensitivity by binding to insulin receptors [77]. As a member of MHC I molecules [3], it is possible that ZAG binds to insulin receptors and affect insulin sensitivity, but there is no direct evidence. As described above, SGLT2, PPARγ, PP2A, and Akt are involved in ZAG-related IR [31, 32]. Therefore, it is possible that ZAG participates in epilepsy by regulating insulin sensitivity.

Overexpressing ZAG suppresses the seizure-induced increase in inflammatory factors such as TNFα, IL6, and TGFβ, and the seizure-induced phosphorylation of ERK is decreased [54]. In addition, ZAG can be suppressed by TNFα [35]. Considering that these inflammatory factors have pro-epileptic effects [78–84], ZAG may suppress epilepsy by inhibiting neuroinflammation. Moreover, TNFα is known to suppress ZAG expression [35], while overexpression of ZAG inhibits TNFα expression [54], so there may be a circuit between ZAG and TNFα. Due to the limited number of reports on the interaction between ZAG and TNFα, it is difficult to dissect the specific mechanism by which these two molecules affect each other and the function of this potential circuit. Based on the literature, TNFα may inhibit ZAG expression by inhibiting PPARγ [35], because PPARγ activation increases ZAG expression [16]. The potential circuit between ZAG and TNFα indicates a possible interaction between inflammation and metabolic dysfunction, but more investigations are needed to confirm or deny its existence and function (Fig. 5).

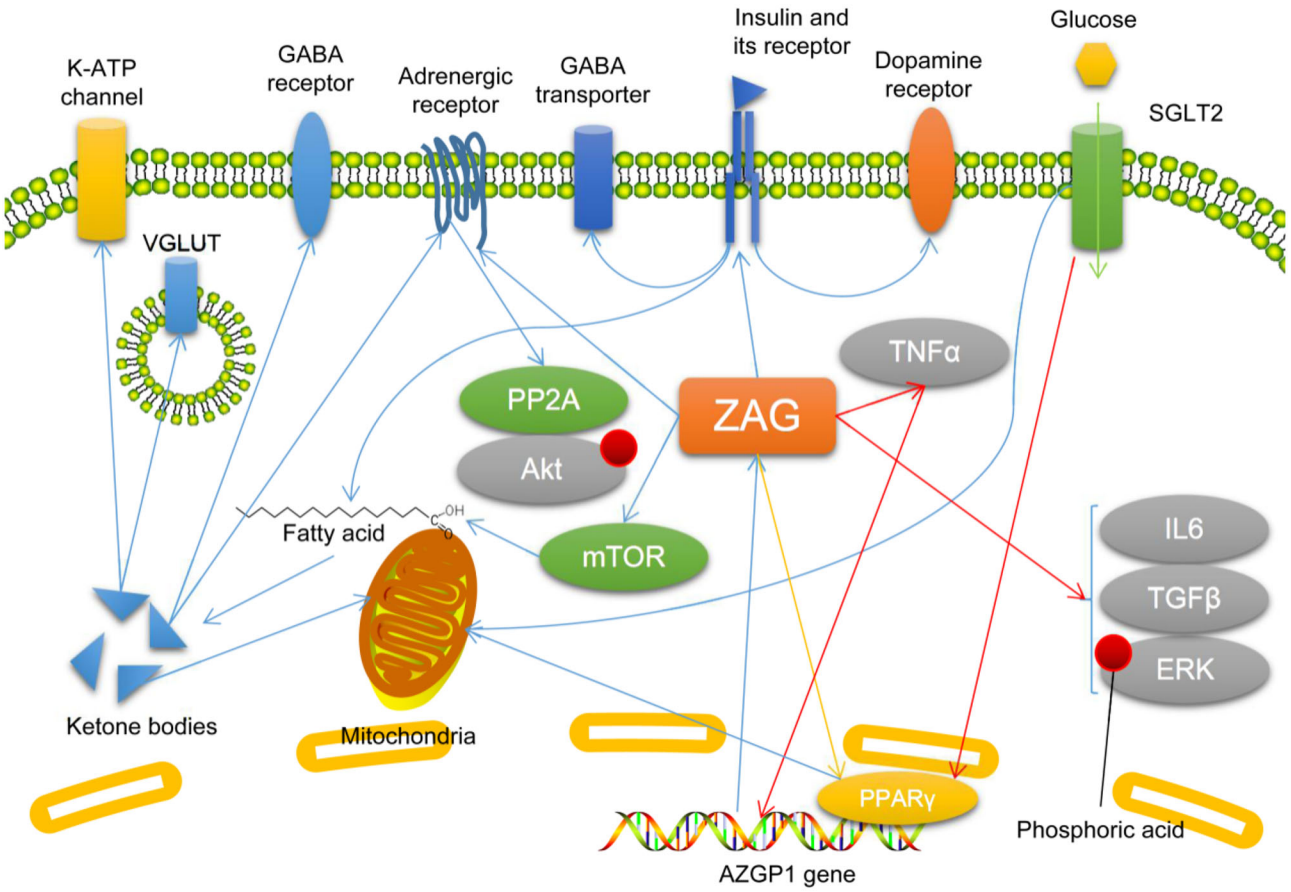

Fig. 5 Possible molecular mechanisms by which zinc-α2-glycoprotein (ZAG) participates in epilepsy. Descriptions of molecules and arrows in different colors are as in Fig. 1. ERK, extracellular regulated protein kinases; GABA, γ-aminobutyric acid; IL, interleukin; mTOR, mammalian target of rapamycin; PP2A, protein phosphatase 2A; PPARγ, peroxisome proliferator-activated receptor γ; SGLT2, sodium-dependent glucose transporter 2; TGFβ, tumor growth factor β; TNFα, tumor necrosis factor α; VGLUT, vesicular glutamate transporter.

Conclusion

ZAG is involved in lipid metabolism, glucose metabolism, and the regulation of insulin sensitivity. It may also participate in inflammation. ZAG is present in brain, but its distribution is still controversial. There are few studies on the role of ZAG in brain diseases, but it may suppress epilepsy by promoting ketogenesis, improving insulin sensitivity, and inhibiting neuroinflammation. The specific mechanism by which ZAG functions in epilepsy and other brain diseases, such as Alzheimer disease, needs further investigation. It is possible that research on ZAG in the CNS may discover new mechanisms of metabolic dysfunction in CNS diseases, especially considering the effectiveness of a ketogenic diet in many of these diseases. Furthermore, research on ZAG may also provide a means of reducing the adverse effects of a ketogenic diet, or develop new therapies with less adverse effects than a ketogenic diet. Besides, ZAG may regulate insulin sensitivity in brain, potentially participating in the mechanisms of CNS diseases with insulin signaling pathway dysfunction, and thus may provide new therapeutic targets for these diseases. In addition, ZAG may underlie an interaction between metabolic dysfunction and inflammation, and research on this may improve our understanding of this interaction. Finally, the physiological and pathophysiological roles of ZAG in the CNS are not clear, and research in this area, especially on regulation of the immune response, electrophysiology, and metabolism may be promising.

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Conflict of interest The authors declare that there is no conflict of interest.

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